Prakash Narain Tandon
Ravi Ramamurthi

Volume 1

Ramamurthi & Tandon's Textbook of NEUROSURGERY

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Ramamurthi and Tandon's

Textbook of
Neurosurgery

Ramamurthi and Tandon's

Vol 1

Textbook of Neurosurgery

Third Edition

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Prof B Ramamurthi (1922-2003)

Doyen of Indian Neurosurgery

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Preface

Since the publication of the second edition of this Textbook in 1996, phenomenal advances have been made towards improved understanding of the pathophysiology of various neurosurgical disorders, their diagnosis and therapy. Advances in molecular biology and genetics on one hand, the refinements of imaging technologies, introduction of image-guided techniques for neuronavigation, and refinements in endoscopic and minimally invasive procedures on the other hand have markedly reduced the morbidity and mortality of neurosurgery. Simultaneously, better availability of radiosurgery and safer endovascular approaches have led to the development of non-surgical therapy for a variety of lesions.

Recent years have witnessed a rapid increase in the number of well-equipped neurosurgical departments across the country providing both state-of-the-art services to the patients and training to specialists in the diverse subdisciplines of neurosurgery. It has been our endeavour to meet their needs for an updated account of the current knowledge of the subject.

The third edition of the textbook includes a comprehensive account of all the recent advances succinctly provided by a galaxy of outstanding contributors especially selected on the basis of their expertise and experience. Care has been taken to include relevant published literature both from India and abroad.

As in earlier editions, special attention has been given to tropical disorders not often adequately covered in publications of the West. This may be an additional attraction for neurosurgeons in other developing countries as also to those in the developed ones who often encounter such conditions in their practice.

The present editors deeply miss the invaluable, wise and experienced guidance of the Senior Editor Prof B Ramamurthi who was the moving spirit behind the earlier editions. The editors would like to thank all the contributors, their associates and the secretarial staff for their co-operation. The Jaypee Brothers Medical Publishers (P) Ltd, New Delhi, India deserve our special thanks for the excellent quality of the publication.

PN Tandon
Ravi Ramamurthi

Caraka Samhita

The early medical writer Caraka tells us that when setting out to learn about Indian medicine, we should have certain criteria in mind for choosing the texts we wish to study (Caraka. 3.8.3):

"A discerning person who wants to become a physician should start by selecting a text based on a consideration of his ability to cope with hard or easy tasks, the results he is after, the likely aftermath, the place and the time. After all, there are numerous physicians' manuals in circulation in the world, so he should apply himself only to a text which is extremely famous, which is used by scholars, which covers a lot of topics and is respected by qualified people. It has to be good for pupils of all three levels of ability, and it should not be flawed by repetitiousness. It should be derived from the tradition of the saints. The connection and the sequence of the text and commentary should be well organised. It should be solidly based, and have no corrupt or missing words. It should be full of significance, its ideas should follow in sequence and it should give importance to the exactness of what ideas really refer to. Its ideas should be coherent and its topics should not be haphazard. It should have both definitions and examples.

This type of text is like a flawless sun; it dispels darkness and throws light on everything."

The Roots of Ayurveda
Dominik Wujastyk

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SECTION

1

History

Thimmappa Hegde

1 Evolution of Neurosurgical Techniques

Thimmappa Hegde, Sarat Chandra P

INTRODUCTION

Medical Practice in Ancient India

The history of medical science in ancient India takes us back to antiquity. Recorded history of medical science is as old as the "Vedas". It is based on the practical experience and careful methods pursued by the sages in the olden days. The ancient writings of the Hindus, which give us an idea of the culture and traditions at that time, were classified as "Srutis" and "Smritis". Smritis are the scriptures, written by the sages, who have recorded the eternal truths as revealed by the Brahma, "The Creator". The Srutis stand as primary in point of authority, being taught through generations by word of mouth only and learnt by rote. The real systems of medicine which developed indigenously in India included "Ayurveda" and "Siddha". These are all pervasive health sciences and are not for medical purposes only. Ayurveda is considered as an essential part of the "Vedas". The primary aim of Ayurveda is to enable a person to maintain normal health by prescribing diet, medicine and a regimen of life. Ayurveda is a science of life and teaches mankind how to lead a healthy life and live long happily. Daily methods of good living known as "Dinacharya" are particularly emphasised. It also deals with physical and mental diseases and their cure. "Dhanavantri", "Charaka", "Atreya" and "Sushruta" have been considered the great masters in this science. The Siddha system of medicine is said to have originated in the days of Mohenjodaro, even thousands of years before the Vedic period, possibly between 3000 and 5000 BC. The word "Siddha" means the one who has attained perfection. According to the mythological sources, the origin of Siddha medicine is attributed to Lord Shiva, who gave the first discourse on this subject to Nandi Thevar, the celestial physician. These would indeed be valuable additions to our modern pharmacopoeia. Both Ayurveda and Siddha are similar and are based on the theory of "Tridosha". The third system of medicine—The Unani or the Greco-Arabian system—was introduced when Mohammedans came from Arabia and Persia. This includes blood as the fourth humour. The Siddha systems contain many valuable therapeutic agents, which should be studied scientifically. These three systems are taught and widely practiced in India and command much influence even today. The modern system of medicine was introduced in India by the Portugese and developed further by the British from the 16th and 17th century onwards.[7]

Medical Education in Ancient India

The educational system of ancient India was based on a personal relationship between the pupil and the teacher. The idea of organisation in education and its application to the methods of collectivism were emphasised by Buddhism. There were many Universities or "Viharas" in Ancient India that were famous, among which were Nalanda, Takshila and Kashi. The ruins of the ancient University of Nalanda are situated at Baragaon in Bihar. The best account of this university has been provided by two Chinese pilgrims, Yuon Chwang and I Tsing (5th to 6th century AD). Nalanda was known to be the largest residential university that India ever had and was a great centre for learning. Education was free, made possible by liberal grants by royal and private philanthropy. It had a large population of 8,500 pupils and 1,500 teachers. It was in such an academic atmosphere that Ayurveda was taught. The Takshila University was also a great centre of medical education, the remains of which can still be found in Rawalpindi, Pakistan. The course of training extended over a period of 7 years, at the end of which the student had a thorough severe test of his knowledge before he went into practice. The Banaras University (Kashi) flourished from 7th century BC to 12th century AD. The most outstanding feature of this university was its school of surgery.[7]

Medical Ethics in Ancient India

In admitting students to the study of medicine, as much importance was attached to moral fitness as to the intellectual and physical fitness of the pupils, for it was considered axiomatic that moral excellence was the basis of all true education. The object of education was not merely to prepare the student to earn a livelihood but also to infuse into him a strong desire to lead a good and virtuous life altogether. It was stressed that the study of medicine was solely for the purpose of showing compassion to all beings and not for selfish purposes. Various oaths have been described in "Charaka Samhita" and "Sushruta Samhita" to inculcate such habits amiably. For instance, one of such oaths in Charaka Samhita states "Thou shalt behave and act without arrogance and with

care and attention and with undistracted mind, humility, constant reflection and with ungrudging obedience."[7] Please note that this preceded the Hippocratic Oath by several centuries.

NEUROSURGICAL TECHNIQUES IN ANTIQUITY

Neurosurgery in Ancient India

Surgery had advanced a great deal in ancient India, the various wars being chiefly responsible as wounds and other injuries inflicted on the battlefield had to be treated effectively and expeditiously. The Indian people, generally speaking, possessed a progressive and enterprising mind and this along with their extensive knowledge of pharmacopoeia consisting of herbal, mineral and other drugs, helped a great deal in this process. The greatest name in the surgery of ancient India was that of Sushruta who probably flourished around 1000 BC that was in the pre-Buddhist period. This is supported by the fact that the "Atharva Veda", which is pre-1000 BC, agreed with Sushruta's system of describing the bones of the human body. The Mahabharata, the great Indian Epic, also refers to Sushruta as one of Vishwamitra's sons. At that time, surgery was taught at Banaras (Kashi) and medicine by Punarvasan Atreya at University of Takshila (Taxila). It was in Banaras where Indian surgery reached its highest point. "Sushruta Samhita" was written here by Sushruta, who for the first time brought together the existing knowledge of surgery.[7] Sushruta (Fig. 1), unlike his Greek contemporaries who were morbidly reluctant to perform human dissections, has vividly described the cranial nerves, including the optic and vestibulocochlear nerves in cadavers. He also described various surgical procedures like excising, probing, puncturing, suturing and evacuating fluids. His method of management of spinal injuries in itself reflects his great knowledge on the subject. For instance, on treatment of dislocation of the neck and downwards, the surgeon was instructed to grasp the head at the nape of the neck along with the angle of the jaw and lift it up. On the whole, however, he believed that the treatment of fractures of the spine was hopeless.[4,60]

Fig. 1: Sushruta—The practice and teaching of medicine by Sushruta from an Indian print of the 18th century AD

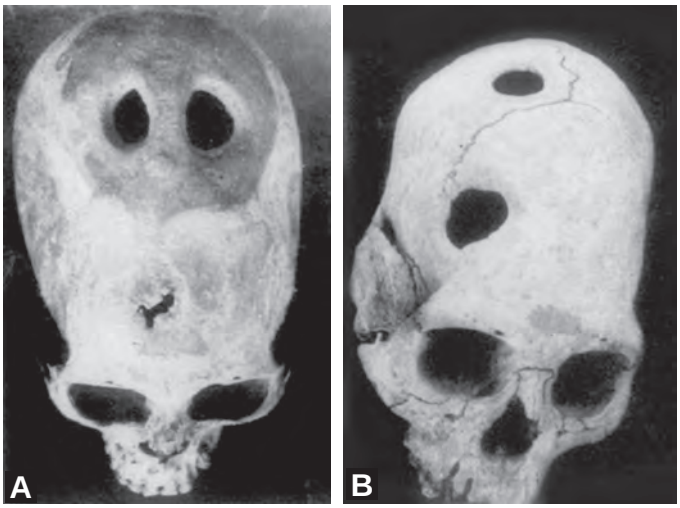
Charaka was another master of ancient Indian medicine. He was said to be the incarnation of Shesha, the serpent God with thousand heads, who is supposed to be the repository of all sciences, especially medicine. He was the son of Visudha, a learned sage, and is said to have been born at Banaras around 320 BC. His book Charaka Samhita is still used as the standard book on Ayurvedic medicine. Buddhist tradition makes him a contemporary of the great Indo-Scythian King Kanishka, to whose court he was attached in the capacity of a physician. He described various ailments like hemicranial headache, facial paralysis, spasm of the throat, and diseases of the mouth, nose and eyes. Management of all these was based usually on correcting the humors of the body.[7]

Atreya, Dhanvantri, Agnivesa and Vagbhata are a few other names of famous physicians of antiquity. Jivaka, the personal physician of Gautama Buddha, is reported to have removed intracranial masses using trephine holes. In the 10th century AD, two physicians were asked to attend King Bhoja of Dhar. All medical therapy for his severe headache had failed. The physicians advised surgery. A drug called "Sammohini" rendered the King unconscious. The head was then trephined and a pearly tumour was removed from the brain. He made a complete recovery.[7]

Trephining in Neolithic Period

In 1875, two historians of great repute, Prunières and Brocard, discovered that trephining of the skull was frequently carried out in the Neolithic period, many millennia before our historic period (Figs 2A and B). Trephining was then probably performed to remove foreign bodies, as well as splinters of fractured skull, and also perhaps for mystic reasons, e.g. to release evil spirits from the skull, which were thought to unbalance the humors in the body and ultimately lead to diseases. Graveyards from the Paracas and Parachamac regions in Peru provide ample evidence that pre-Incan surgeons were performing trephination in great numbers as early as in 3000 BC. Neolithic Celtic remains have revealed the presence of round or oval skull pieces, presumably removed by trephination. Trephination was also performed in England as discovered in a skull excavated at Crichel Down in 1938.[71]

Such trephined skulls were found in all parts of the world demonstrating the similarity of medicine of ancient civilisations. New growth of the bone about the edges of the trephines proved that these procedures were often followed by survival. The patient was usually, perhaps always, dulled or made unconscious

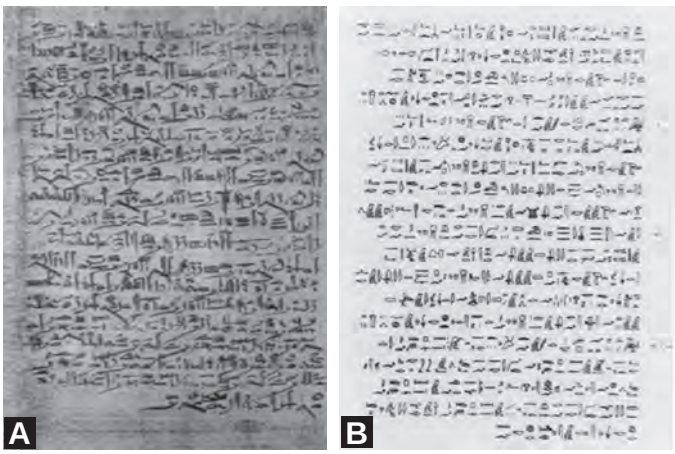


Figs 2A and B: Skull trephine as performed during Neolithic period (Anthropologic Institute of Florence)

with soporific potions. Trephining is still practiced among some primitive races for instance, the Kabyles of Northern Africa, the hill tribes of Dagestan and in many parts of Melanesia. All these operations owe their origin more from a demonical or magical concept rather than rational therapy.[4,47]

The Edwin Smith Surgical Papyrus

The Edwin Smith surgical papyrus, dating from the 17th century BC, is one of the oldest of all known medical papyri (Figs 3A and B). Edwin Smith was an Egyptologist who bought this ancient manuscript roll at Luxor, Egypt, in 1862, from unknown sources. Though he understood the importance of this manuscript, it was not until 1930 that James H Breasted, then Director of the University of Chicago Oriental Institute, translated the treatise and established its importance. More interestingly, this ancient composite manuscript, as discovered by Breasted, was a copy made by an Egyptian scribe from a still earlier document based on the contributions probably of several earlier authors dating to perhaps as early as 3000–2500 BC.[8]



Figs 3A and B: Edwin Smith papyrus—case 47 and 48 taken from Edwin Smith papyrus along with hieroglyphic interpretation shown on the right side (Plate XVII from Breasted)

The papyrus, apart from being the oldest one of its kind in existence, has many more unique features. It contains actual cases and not recipes. The treatment of cases is rational and mostly surgical. Each case had been given one of the three different verdicts: (a) favourable, (b) uncertain, and (c) unfavourable. It is of special interest to neurosurgeons because it contains the first descriptions of the cranial sutures, the meninges, the external surface of the brain, the cerebrospinal fluid and intracranial pulsations. Also of great interest are the different modes of treatment described for various types of head injuries. The frustration in treating spinal injuries was recognised even then.[8]

Hippocrates and Neurosurgery (460–377 BC)

Hippocrates is considered the father of Western medicine and his writings have influenced the practice of medicine for more than 20 centuries. Littre, who is an authority on the work of Hippocrates and his students, had collected more than 53 subjects in 72 books.[1,4] Surprisingly, most of the Hippocratic workers seem ignorant of structural anatomy and most of their writings prove to be confusing, if not wrong. The observations of Hippocrates on head injuries and their treatment are recorded in the work "On injuries of the head". The clinical acumen of Hippocrates is well demonstrated by his descriptions of aphasia, unconsciousness, pupillary inequality and ophthalmoplegia. He was aware of the fact that a blow on one side of the head could lead to convulsions and paralysis of the limbs on the opposite side. It is very interesting to note the meticulous instructions he gave for surgery of head injuries. His instructions for the use of the trephine were the most precise. ".....The opening should not be made over the cranial sutures, for the dura being adherent, was likely to be damaged", "... the trephine should repeatedly be removed from the skull and cooled with water during the procedure and the incision examined to be sure that the dura mater was not reached".[57]

Celsus (30 BC) further described the treatment of head injuries and pointed out the occurrence of contrecoup fractures and advised trephining for fractures.[4] Galen (130–201 AD) was a disciple of Hippocrates and went far beyond his master. Unlike his master, who had great humility and would often say, "I don't know", Galen had an explanation for almost everything.[4]

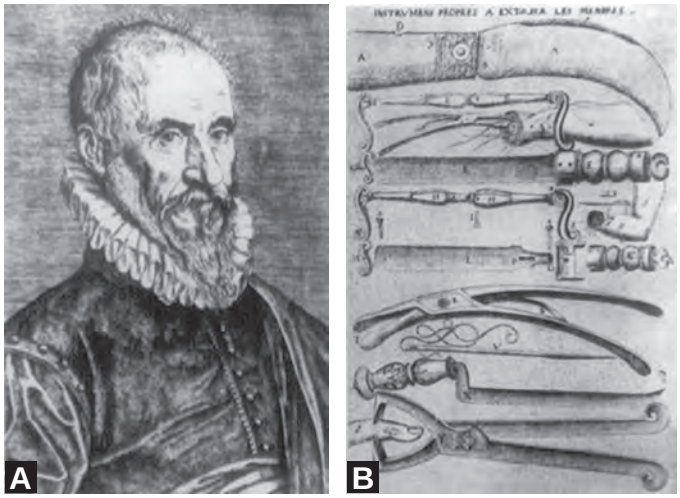
Galen's descriptions for trephination were similar to that of Hippocrates, e.g. ".....the trephine should be rotated slowly and carefully, with frequent inspections so as not to breach the dura mater.....". He emphasised upon the description of the 5 types of skull fractures listed by Hippocrates. He described dressings in great detail, including a dressing of wool with oil of roses, with a warning not to put pressure on the dura. Other Greeks who further added to knowledge, during this period were, Aretaeus the Cappadocian (150 AD), Oribasius (325–403 AD) and Heliodorrus.[1,4,57,60]

Neurosurgical Techniques in the Medieval Period (500–1500 AD)

During this period, not much was added to the techniques of management of skull fractures than what was already known. However, significant contributions were made during the later part. Paul of Aegina (625–690 AD) advocated exploration and extraction of broken pieces of bone in spinal fractures. Roger of Saleron (1170 AD) described in detail the surgical management of skull fractures. Lanfrane compiled his textbook of surgery in 1296 and was the first surgeon who advocated suturing of divided peripheral nerves. Guy de Chauliac (1300–1360 AD), who has been called "the father of modern surgery", described repair of peripheral nerve injuries, and classified head injuries according to their management very much similar to present day management. Jacopo Berengano da Carpa (1470–1530 AD) described cranial fractures in detail and advised early surgical intervention.[4,17]

Neurosurgical Techniques in the Renaissance (1500–1700 AD)

Two key figures deserve mention during this period. Ambroise Pare of the French army (1510–1590 AD) described elevation of depressed fractures and debridement of wounds in detail (Figs 4A and B). He described the use of traction for spinal injuries and like his predecessors realised the futility of treatment of cord injuries. He, however, advised removal of splinters of broken vertebra impinging on the cord as a last resort. Fabricus Hildain (1560–1634) perhaps gave the earliest description of laminectomy.[4,17]



Figs 4A and B: (A) Ambroise Pare was unquestionably one the greatest surgeons of the Renaissance. He was born in 1510 at Bourghersent in Meyenne and acquired his initial surgical skills from a barber shop. He knew no Latin and thus wrote in French to the considerable opposition of the Professors of Sorbonne, who could not conceive of a member of the college not knowing Latin. He was surgeon to Henry II, Francis II and Charles IX who also protected him during the massacre of St Bartholomew. He has been described as a man of genius, an infatiguable worker and being honest to the highest degree. He introduced various radical changes in surgical procedures like giving up the method of hot iron cautery used by Arabians, marked improvement of amputation surgery, surgery for hare lip, etc. (B) Here shown on the right are some of the instruments being used by him

Neurosurgical Techniques in the Pre-Listerian Period (1700–1846 AD)

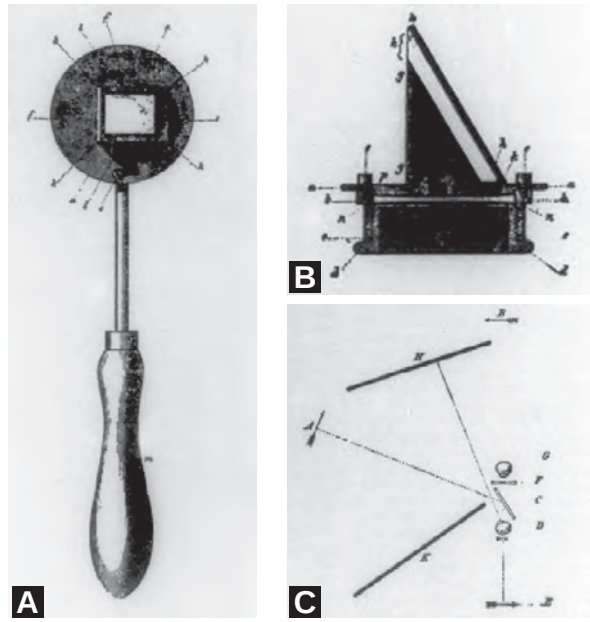
Neurosurgery was still limited to head injuries till the beginning of the pre-Horsley era in view of the lack of knowledge of antisepsis in the Western world and of anaesthesia. There were, however, a few surgeons who cannot be ignored. Jean Louis Petit (1674–1750 AD) advised trephining in all cases of scalp wounds with fractures. SF Morand in 1792[10] was the first to operate successfully upon a temporal abscess. Sir Percival Pott (1713–1788 AD) used a trephine for treatment of brain abscesses. Gurthrie (1785–1856 AD) realised the importance of epidural haematoma and advocated its urgent management.[4,17]

Neurosurgical Techniques in the Pre-Horsley Period (1846–1890 AD)

Dramatic developments started to take place in this era. Various discoveries laid down a strong foundation for the development of contemporary neurosurgical techniques. The era of painless surgery was ushered in with the discovery of chloroform and ether (1846–1848 AD). The antiseptic principles described by Lister in 1867 reduced the infection rate significantly and gave a boost to the surgeons to proceed beyond the dura mater (Fig. 5). Almost simultaneously, clinical localisation was improved markedly by neurologists like Fritsch, Hitzig, Ferrier, Gowers and Hughlings Jackson.[34]

In 1884, Sir Rickmann Godlee operated upon a brain tumour for the first time solely on the basis of clinical localisation by Hughes Bennet.[30] The patient unfortunately died a month later due to meningitis. This, however, did not discourage the other surgeons and only increased their determination to cross the last frontier. Sir William Macewen carried out his first surgery on a brain abscess in 1881.[31] He published his monograph on "Pyogenic Infective Diseases of the Brain and Spinal Cord" in 1893, where he reported 94 cases of "infective intracranial lesions". Of the 19 cases of cerebral and cerebellar abscesses in total, 18 had total recovery, a record that remains unparalleled even today.[10] In 1887, Van Bergmann, an outstanding German surgeon published a monograph on cerebral surgery containing case histories, diagnosis and operative management of over 189 patients most of them with brain abscesses.[4,10,59] PC Knapp and EH Bradford in 1889 finally summarised the situation in an article that documented 23 cases of brain tumours, which were operated upon based on purely clinical localisation.[4,10,60]

Fig. 5: Joseph Lister (1827–1912 AD) was born at Upton in the county of Essex and is considered as one of the greatest figures in the history of surgery. He is best known for his antiseptic principles, including introduction of carbolic acid spray in the operating room, the results of which were published in the Lancet in 1867. He was the first physician to sit in the House of Lords. Part of the Glasgow ward where he carried out his work and most of his publications are still preserved at Welcome Historical Medical Museum in London



Figs 6A to C: Helmholtz's ophthalmoscope—Photographic reproduction of the original illustration of ophthalmoscope published in German in 1851, and later translated into English by Shastid TH in a monogram titled "The Description of an Ophthalmoscope—Being an English translation of von Helmholtz's—Beschreiburg lines Augenspiegels" in 1916

DEVELOPMENT OF CONTEMPORARY NEUROSURGICAL TECHNIQUES

Before proceeding on this fascinating journey, it would be useful to look at the development in other branches of medicine, which have made this journey possible.

In 1851, Hermann von Helmholtz invented the ophthalmoscope (Figs 6A to C). To quote from his work on visualising the retina "... I had the great joy of being the first who saw before him a living human retina".[84]

The Development of Techniques for CSF Access and Analysis

The puncture of the subarachnoid space for a therapeutic purpose was made for the first time in 1885 by Corning when he injected cocaine for anaesthesia. Six years later, Quincke described lumbar puncture for relief of raised intracranial pressure.[22]

The first edition of Keen's "An American Textbook of Surgery" described the use of ventricular puncture using the landmarks outlined in 1890. However, the usefulness of ventricular puncture was fully realised in 1918 when Walter Dandy described pneumoencephalography and ventriculography for the purpose of localisation of cerebral masses.

Development of Neuroradiology

Roentgen discovered X-rays in 1896 and within a year, its use in medicine was well established. This constituted the main tool for diagnosis based on bony erosion, sutural diastases and pineal shift and calcification.[35,70]

Diagnostic radiology took a great leap forwards in 1918 with the introduction of pneumoventriculography and pneumoencephalography by Dandy. This discovery came about when Dandy noticed air under the diaphragm in the X-ray film of a patient with intestinal perforation.[13]

In 1921, myelography was introduced when Jean Sicard, a French clinician, and his pupil, Jacques Forestier, injected analgesics into the spine of a patient suffering from low back pain and subsequently found that the oil they used as a carrier for the analgesic, lipiodol, was radiopaque.[72]

The invention of myelography encouraged the outstanding Portuguese neurologist, Egas Moniz, to develop "Arterial Encephalography".[48]

Neuroimaging attained its pinnacle with the invention of the CT scan and MRI. In 1967, Godfrey Hounsfield of EMI Laboratories working on the interpretation of data derived from X-ray transmission hit upon the idea of simplifying data by sectioning the object into a series of "slices" for a complete diagnostic picture.[33]

The MRI scan was based on the Nobel Prize winning work of Block and Purcell in the 1940s, which was applied to medical imaging in the 1970s.[59]

More recently, functional imaging, like positron emission tomography (PET), functional MRI and SPECT, has been introduced. It may be noted that though the principle of PET was suggested as early as in 1951 by Wrenn and his colleagues, it was introduced in clinical

practice in 1970. All these inventions collectively gave a tremendous boost to the development of neurosurgical diagnosis and techniques, which also evolved more or less simultaneously.[75,85–87]

Patient Positioning

Victor Horsley was the first to stress the need for proper cranial immobilisation. Harvey Cushing (Fig. 7) was the first surgeon to devise a horse shoe shaped head rest which kept the patient's eyes, nose and mouth free and provided access for administration of anaesthetics. He also introduced the practice of shaving just prior to surgery.[60]

De Martel, in 1913, introduced the sitting position. He constructed a special chair in which the patient's head could firmly be fixed. The hazards of the sitting position were later described by Bailey.[4,60] Frank Henderson Mayfield (Fig. 8) introduced the three pinhead clamp, which made patient positioning safer and easier.[76] Victor Horsley was the first surgeon to use the operator worn headlight to illuminate the operating field.[60]

Surgical Gloves

As late as 1900, operations were performed with bare hands, asepsis being achieved by continuously dipping the hands in a bucket of carbolic acid. Halsted (Figs 9A and B) was the first surgeon to introduce the use of gloves during operations. There is a romantic edge to the story of its origin. Halsted's scrub nurse was allergic to carbolic acid and he devised the gloves primarily for her. She later on became his wife.[4]

Fig. 7: Harvey Cushing (1869–1939) was perhaps the greatest neurosurgeon of all times. Results in neurosurgery before him were dismal. As found out by Cushing at Johns Hopkins, ten years before 1901, antemortem diagnoses were made in only 32 cases of 36,000 admitted. Of these, only two cases were operated with fatal results. From this stage, Cushing introduced most painstakingly, various methods like maintenance of ether chart, absolute haemostasis, gentle use of cotton pledgets, use of silver clips and electrocautery for haemostasis and above all slow and gentle handling of tissues, which he inherited from Halsted, all of which reduced the mortality significantly. His operative mortality during the last years of his practice was only 8.7% for a total of 635 surgeries. He was also the author of a series of brilliant monographs: The pituitary body (1912), Tumours of nervus acousticus (1917), A classification of the tumours of the Glioma group (1926, with Percival Bailey) and so on down to Meningiomas (1938). His "Life of Sir William Osler" (1925) obtained the Pulitzer Prize, which was a classic in medical biography and a best seller

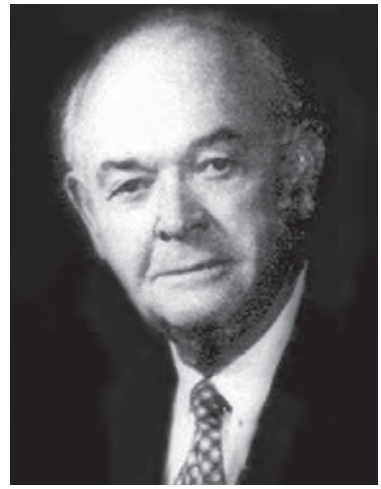
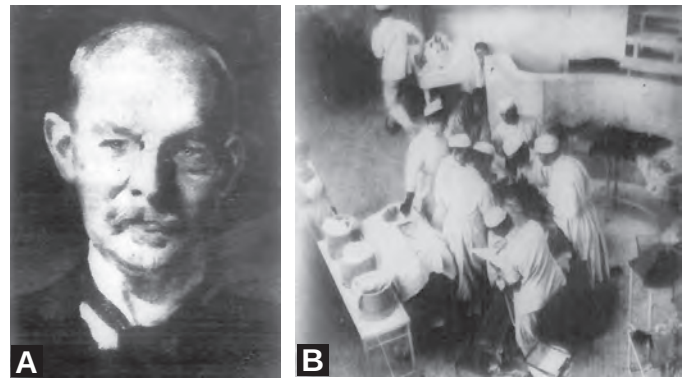


Fig. 8: Frank H Mayfield was born in 1908 in South Carolina and underwent his medical graduation from The College of Virginia. He was fortunate to have had the guidance of the eminent surgeons of that time, Drs Cushing, Dandy and Coleman. Apart from designing the three pin head clamp to which his name is attached, he is also known for this pioneering work in lumbar disc surgery, development of aneurysm clips and many surgical instruments. He was the first recipient of The Harvey Cushing Medal in 1977 by the American Association of Neurological Surgeons



Figs 9A and B: (A) WS Halsted (1852–1922) was the first professor of surgery at Johns Hopkins. He was a quiet but effective force in transforming surgery from a series of dramatic events into a less conspicuous, painstaking and scientific study of disease. In addition to introduction of surgical gloves, use of silk ligatures and of infiltration anaesthesia with cocaine, he also devised numerous operative procedures and technical improvements often based on previous experiments on animals. (B) Photograph of Halsted in the so called "All star operation theatre" being assisted by Cushing and Finney (opposite), Bloodgood (at his right), Young (at the instruments) and Follis (leaving the theatre). Note the use of gloves and caps but no masks. The technique of handling tissues gently and slowly formed the basis on which Cushing developed neurosurgical techniques to set a standard for the future generations of neurosurgeons

Craniotomy

Earlier, the skull was opened with a trephine and the opening was enlarged with a mallet and chisel to the extent required. It was traumatic to the brain and often produced unacceptable deformities.[4,5]

In 1889, Wilhelm Wagner introduced the osteoplastic craniotomy, which allowed access to large areas of the brain without a disfiguring cranial defect. This was introduced after several years of painstaking studies on cadavers. Taison, in 1894, suggested that the bone be divided from within outwards using a chainsaw between burr holes. Almost simultaneously, Leonardo Gigli described an ingenious yet simple instrument for sawing the bone, which was initially intended to perform symphysiotomy in obstetrical surgery (Fig. 10).

D'Vilbiss, in 1896, designed a bone cutting forceps for making linear cuts in the bone from within outwards. De Martel, in 1908, introduced the metal guide for introducing the Gigli saw between burr holes. He also introduced a power-driven perforator with an automatic disengaging gear, which stopped the motor as soon as the perforator penetrated the skull. Poirier, in 1891, advocated that the dural flaps should be cut with the base towards the midline to reduce bleeding from dural emissary veins.[4,5,11,84]

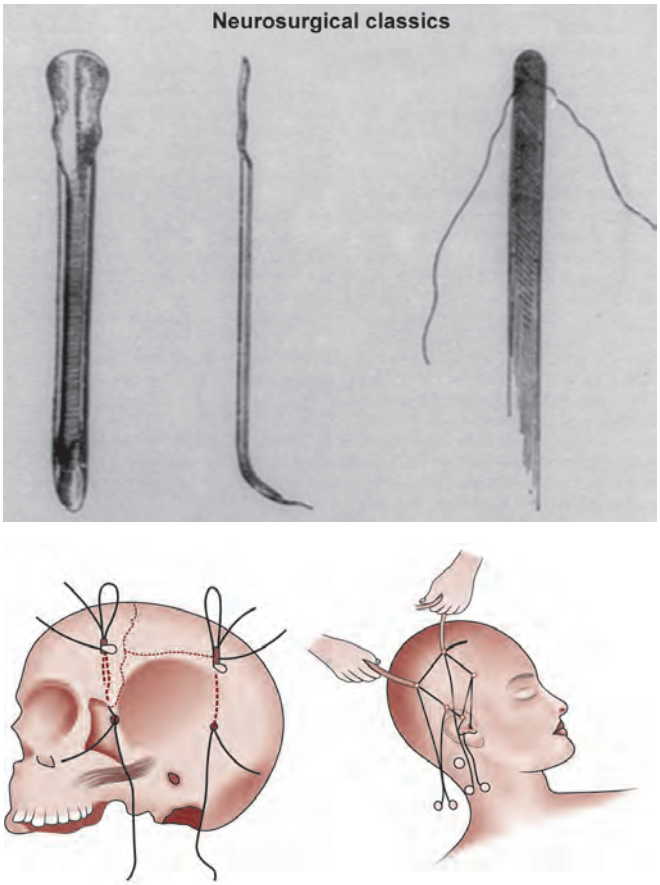


Fig. 10: The Gigli saw was devised by Leonardo Gigli in 1898. He devised a grooved probe, which he named as a "whalebone" to introduce the wire between burr holes

Suction and Irrigation

Cushing was the first surgeon to utilise a hand bulb syringe attached to a rubber catheter to cleanse the tracts of brain wounds in the First World War.[11] Power suction was introduced many years later by Herbert Olivecrona.[60]

Brain Retractors

The malleable self-retaining retractor fixed to the edge of the cranial defect was introduced by De Martel.[11] Yasargil later introduced the currently popular Leyla retractor. He named the retractor after his daughter when he saw her playing with a doll, which maintained its new position whichever way it was twisted. Many modifications and improvisations were made later by various innovative neurosurgeons like Suzuki, Rhoton, etc.[11,60]

HAEMOSTASIS

One of the most important reasons why early surgeons were discouraged from performing neurosurgery was bleeding and the difficulty of controlling it. Cushing himself, after having witnessed Victor Horsley, perform one of the surgeries, seriously contemplated against continuing this profession.[3,24,42]

Scalp Haemostasis

Brown, in 1909, introduced the practice of infiltrating the scalp with a mixture of local anaesthetic and diluted adrenaline solution. Cushing advocated the use of firm digital pressure along the edges of the proposed incision and the technique of everting the galea with artery clamps—a practice followed even today.[3,11,42]

Victor Horsley, in 1892, invented bone wax, which was initially made of bee's wax and had haemostatic qualities by virtue of its tamponade effect on bone bleeding.[3,42] Later, absorbable gelatin sponge (Gelfoam) was also found to be useful in controlling bleeding from the bone.

Cerebral Haemostasis

Various ingenious methods were devised in the past including packing with cotton, wool, oil of olive and caustics. Presently, three basic methods are used.

Thermal Methods

Galen popularised the use of hot irons for cautery as a primary method of haemostasis. Pare abandoned this method around 1500 years later. Thermal cautery was reintroduced by Cushing and Bovie in 1928 in the form of electrocautery (Fig. 11). Greenwood introduced the bipolar forceps in 1930 and this was further modified by Malis. More recently, a variety of lasers which were initially introduced by Maimman in 1960 have been used for haemostasis.[3,42,60,84]

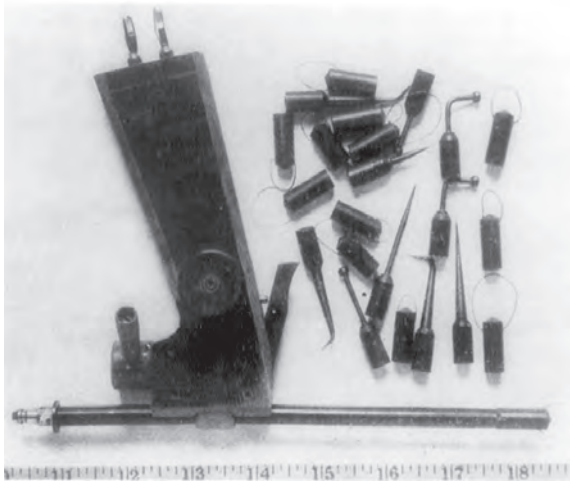


Fig. 11: Photograph of original hand-made model of the pistol-grip with pencil attached and a cluster of terminal electrodes of various types. This was initially devised by Bovie in 1927 and later modified by Cushing in the form of only a pencil to improve the precision

Mechanical and Chemical Methods

Since the time of Hippocrates, the use of caustics, like copper sulphate, was in vogue but these fell out of favour as they caused indiscriminate destruction. Horsley, and later Cushing, introduced the use of crushed muscle. Correll and Wise first introduced Gelfoam (absorbable gelatin sponge) in 1945. Yackel and Kenyon of Eastman Kodak Laboratories first produced oxidised cellulose (Oxycel) and oxidised regenerated cellulose (Surgicel) in 1942, but these came into clinical use much later. The use of microfibrillar collagen (Avitin) as a haemostatic agent was first demonstrated by MR Hait in 1969.[3,42,85]

OPERATING MICROSCOPE IN NEUROSURGERY

The operating microscope was used by otologists to perform middle ear surgery as early as 1921. For the use of the microscope in neurosurgery, it required many adaptations in the form of improved illumination, manoeuvrability and magnification. Hans Littmann of Carl Zeiss Company was one of the pioneers in developing such a suitable model. Since then many more models have been introduced. Almost simultaneously micro instruments have been developed by neurosurgeons, including Yasargil, Rhoton, Maroon, Hardy, Suzuki and many others.[85]

DEVELOPMENT OF NEUROSURGICAL TECHNIQUES IN SURGERY FOR BRAIN TUMOURS

Gliomas

Bailey and Cushing were among the first to classify gliomas according to their histological features. Cushing and Eisenhardt started the practice of examining the biopsy specimen during surgery. Early efforts by Horsley in 1893 and Cushing in 1909 consisted of external decompression with or without partial removal and this soon proved to be unrewarding.[12,33] Dandy, in 1921, advocated radical internal decompression.[14] Cushing (Fig. 7) later greatly improved the operating techniques in glioma surgery. His methods of achieving haemostasis with cotton pledgets, reducing brain swelling by increasing head elevation and painstaking closure of the dura, greatly contributed to reduce the morbidity and mortality in such patients. He also stressed the importance of excision of the mural nodule to achieve a permanent cure for cystic gliomas. The use of intravenous hypertonic solutions was introduced by Sachs and Bailey to reduce intracranial pressure before the dural opening.[11,24,80]

Meningiomas

William Macewen probably performed the first surgery for meningioma in 1879. However, Franceso Durante performed the first successful surgery for an intracranial tumour in 1885 when he removed an olfactory groove meningioma.[2] The principle of replacing the diseased bone after autoclaving was first introduced by Naffziger.[2]

Pineal Tumours

Krause (1926) was the first surgeon to explore this ominous territory. He described his supracerebellar infratentorial approach in three patients and surprisingly all patients did well.[37] Van Wagenan, in 1931, described a transventricular approach, which never gained wide acceptance.[78] Walter Dandy used the parafalcine supratentorial interhemispheric approach, which was the culmination of extensive studies on experimental animals. He used either the sitting or lateral position to allow the hemisphere to fall by gravity. However, in the absence of steroids, operating microscope and advanced anaesthesia, the surgical mortality was quite high.[16] James L Poppen, in 1966, described his classical paraoccipital supratentorial approach (Fig. 12).[21,58] The introduction of the operating microscope greatly improved the quality of outcome.

Acoustic Tumours

Sir Charles Ballance was the first to successfully remove an acoustic neuroma in 1894. He used a suboccipital craniectomy and removed the tumour with a finger. The patient surprisingly survived.[6] Cushing subsequently developed the technique of subtotal internal decompression, which reduced the operative mortality significantly. Based on his experience and that of previous authors, Cushing felt that total excision should not be attempted.[11] Dandy, in 1925, developed the technique of internal decompression followed by total excision. He also described the importance of unroofing the internal acoustic meatus for complete excision. His techniques laid down the principles for contemporary acoustic surgery [Figs 13(A and B) and 14].[15] Givre and Olivecrona, in 1949, developed the technique for preservation of the facial nerve.[26] Rand and Kurze, in 1968, described preservation of both facial and cochlear nerves.[61] The

Fig. 12: James L Poppen was born in 1903 at Drenthe, Michigan. He embarked on his neurological career in 1933 at the Lahey Clinic after having completed his 2 years surgical residency at the Illinois Research and Educational Hospital. Apart from having described numerous surgical techniques and also publishing his well-known "Atlas of Neurosurgical Technique", he was highly regarded by his colleagues and residents for his unique and exceptional operative skill. He was very much appreciated for his mark of character that he had always treated the most minor operation or procedure with just as much care and dignity. One of his favourite quotes was "The same challenge exists to complete a lumbar puncture accurately and painlessly as to clip an intracranial aneurysm"

use of the middle cranial fossa approach for acoustic tumours was described by William F House in 1961.

The translabyrinthine approach for cerebellopontine angle tumours was first suggested by Panse in 1904 and then subsequently first performed by Quix in 1911 and later by Schmieglow. However, it lost its popularity after Cushing discouraged this procedure in 1921. With improvement in instrumentation and magnification, it was reintroduced by House and Hitselberger in 1960.[33]

Fig. 14: Walter Dandy

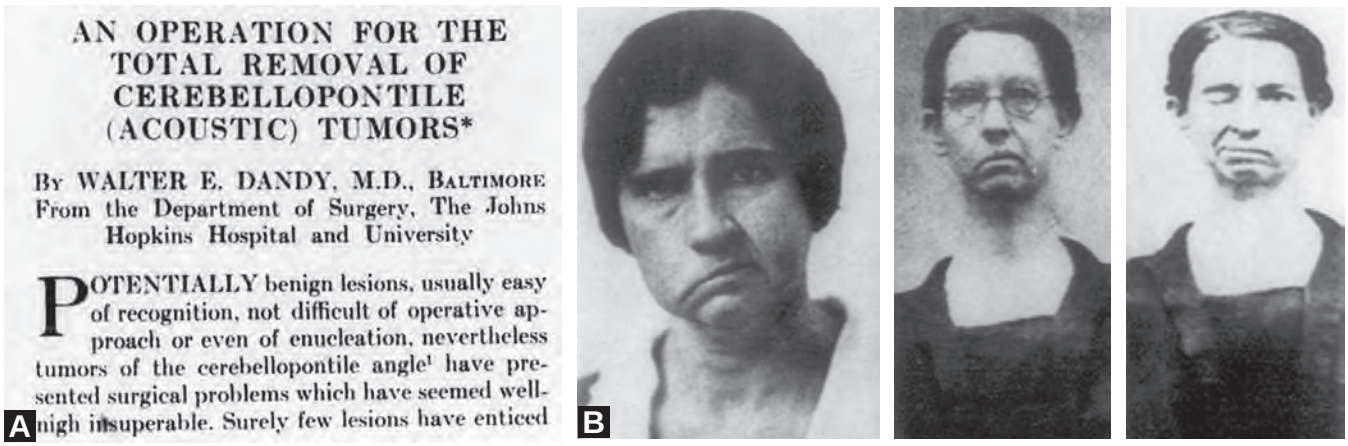
Pituitary Tumours

Harvey Cushing was the first to coin the terms hypopituitarism and hyperpituitarism. He mentioned these in his monograph on the subject in 1912. In 1932, he wrote an exhaustive review on basophilic adenomas.[11]

Trans-sphenoidal Surgery

The first successful removal through the transsphenoidal route was performed by Schloffer in 1907. Hirsch from Vienna pioneered an inferolateral endonasal approach in 1909. Harvey Cushing modified this surgery and standardised an oronasal rhinoseptal transsphenoidal approach. He used this approach for the next 20 years.[80] Norman M Dott (Fig. 15) used the same approach, which he learned from Cushing throughout his career.

Guiot from Paris learned this method, from Dott, and popularised it in Europe in the 1960s.[27] Per-operative fluoroscopy in transsphenoidal surgery was introduced by Guiot. In 1962, Jules Hardy, after having learned


AN OPERATION FOR THE TOTAL REMOVAL OF CEREBELLOPONTILE (ACOUSTIC) TUMORS*

By WALTER E. DANDY, M.D., Baltimore
From the Department of Surgery, The Johns Hopkins Hospital and University

POTENTIALLY benign lesions, usually easy of recognition, not difficult of operative approach or even of enucleation, nevertheless tumors of the cerebellopontile angle[1] have presented surgical problems which have seemed well-nigh insuperable. Surely few lesions have enticed

A

B

Figs 13A and B: (A) Photograph of the article by Dandy published in Surgery, Gynaecology and Obstetrics in 1925, advocating total excision of acoustic tumours. Prior to this, most of the surgeons were following Cushing's method of intratumoural decompression, as total excision was associated with high morbidity and mortality. (B) Photograph of the patient who underwent total excision of tumour by Dandy. Note the improvement of facial palsy in the photograph on the right following a spinofacial anastomosis

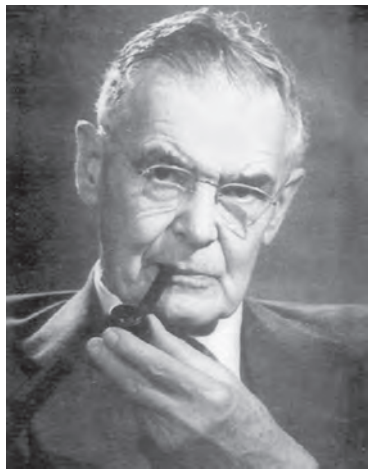


Fig. 15: Norman M Dott was born in Edinburgh in 1897 and graduated from The University of Edinburgh. He came under the influence of Harvey Cushing in 1923, when he had the opportunity to work under him at Boston under the Rockfeller Travelling Fellowship. It is interesting to note that in the initial years, he began practicing neurosurgery privately as this speciality was not recognised at Edinburgh Hospital. Among his many contributions include performing the first angiogram in the United Kingdom using Thorotrast to demonstrate a saccular aneurysm, he also worked on cerebrospinal fluid and its circulation, study of brain displacements, cerebral ischaemia, spinal cord compression, the treatment of facial paralysis by extrapetrous nerve graft and use of hypothermia during surgery. He also invented many instruments and designed operating tables and theatres

this procedure from Guiot, re-introduced it in North America. He further improved the technique by introducing per-operative fluoroscopy, the operating microscope and micro-instrumentation. He was also the first to recognise small intrapituitary lesions, which he later named as microadenomas.[27,82]

Transcranial Surgery

The subfrontal approach to pituitary tumours was devised by Krause and subsequently modified by Frazier in 1913.[23] Cushing, in later years, favoured this approach. Bronson S Ray popularised a midline subfrontal approach. The consequences of heavy retraction led Ray and Patterson to devise the pterional approach.[67,68] The subtemporal approach, initially suggested by Horsley, is used today though not frequently.[85] A large number of skull base approaches are based on this subtemporal approach.

Spinal Cord Tumours

Credit goes to Victor Horsley for having excised an intradural extramedullary tumour in 1887 at the young age of 30 years. The surgery was performed on the basis of clinical localisation by William Gowers.[17] Elsberg in his masterpiece monograph "Tumours of Spinal Cord: The Symptoms of Initiations and Compression of the Spinal Cord and Nerve Roots: Pathology, Symptomatology, Diagnosis and Treatment", emphasised on the importance of careful neurological examination and the use of spinal manometric study to establish the presence and location of intraspinal blocks. He also described a case of central cervical disc herniation usually misnamed as a "chondroma". In subsequent publications, he described in detail the clinical localisation of spinal cord and extradural tumours.[18-20] The first operative description of these tumours was accompanied by a beautiful colour illustration in Fedor Krause's masterpiece, "Surgery of the Brain and Spinal Cord". Krause referred to the mass as an "enchondroma" also a misnomer.[36] Although Cushing is given the credit for the first successful removal of an intramedullary ependymoma, the technique of intramedullary spinal cord surgery along with the management of other spinal tumours was described in detail by Charles Elsberg.[19] Rasmussen, in 1940, described the pathological features of intramedullary tumours along with surgical considerations in great detail.[65]

CEREBROVASCULAR SURGERY

Hutchison was the first physician to diagnose a saccular, non-traumatic intracranial aneurysm clinically in 1875. This was confirmed at autopsy 11 years later.[80] The development of cerebrovascular surgery would not have been possible but for the various developments which took place, including haemostatic clips by Cushing, angiography by Egas Moniz, and the use of the operating microscope.

Norman Dott performed the first planned surgery for an aneurysm in 1933. He used a muscle patch and achieved a good long-term outcome.

Walter Dandy, in 1937, clipped an aneurysm for the first time using a metal clip and shrivelled the sac with electrocautery. He also reported, in 1939, treatment of an intracavernous aneurysm by ligating the internal carotid artery in the neck, as well as intracranially, thus trapping it. However, carotid insufficiency and hemiplegia were soon noted to be the major complications of carotid ligation. Matas emphasised the importance of testing the efficiency of collateral circulation. Surgery for aneurysms developed by leaps and bounds, thanks to innovative neurosurgeons. Yasargil of Zurich, Drake of London, Ontario and Norlen of Goteborg are prominent amongst them.[49,80]

The first successful surgery for intracranial AVM was performed by Olivecrona in 1932 (Fig. 16). Results improved with the use of magnification and increased illumination provided by the operating microscope, making surgery more refined and accurate. Haemostasis improved with the introduction of bipolar forceps.[80]

In 1960, Julius Jacobson, a vascular surgeon, produced a very important paper "Microsurgery in anastomosis of small vessels". In 1967, guided by the inspiration of Prof. Donaghy, MG Yasargil of Zurich performed the first extracranial to intracranial bypass. Pool, in 1966, reported on the use of the microscope for the first

Fig. 16: Herbert Olivecrona (1891–1980) was one of the eminent students of Cushing. He was the chief founder of Swedish Neurosurgery and trained many outstanding neurosurgeons, to name a few; Wilhelm Tonnis, Sjoquist Lundberg, Lars Leksell and Edward Bucsh. Apart from doing pioneering work in vascular surgery, he developed numerous neurosurgical techniques. He was the first to excise an acoustic schwanomma, preserving the eighth nerve. Sjoquist developed medial tractotomy for trigeminal neuralgia under his guidance

Fig. 17: Wilder Graves Penfield born in 1897 at Spokane, Washington, was a man of many facets, and an excellent academic record. He graduated from Johns Hopkins Medical School in 1918. He was selected as the head of the Department of Neurology and Neurosurgery in 1928 at the McGill University at Montreal on the formation of its Neurological Centre. Apart from his numerous contributions and his pioneering work on epilepsy and brain mapping, he was the author of the novel "No Other Gods", a fictionalised version of Abraham's search for a monotheistic religion

time in aneurysm surgery. Rand had, however, used the microscope for aneurysm surgery in 1964 but had reported it only in 1967.[69,80]

SURGERY FOR EPILEPSY

Victor Horsley was the first surgeon who demonstrated that excision of a lesion responsible for focal epilepsy could lead to cure. Foerster and Penfield did creditable work in defining the structural basis of traumatic epilepsy and, in 1930, published their results with radical operations. Gibbs, Davis and Lennox, in 1935, established for the first time the correlation of clinical epileptic seizures with EEG studies. Electrocorticography was first performed in humans by Foerster in 1935 and Penfield and Jasper in 1941. Penfield was one of the chief pioneers for the development of epilepsy surgery (Fig. 17). He outlined the motor and sensory homunculus using stimulation studies in awake patients and described in detail the various types of seizure phenomenon. However, the most intriguing observation, both laudatory to reviewers and to Penfield himself, was the production of "psychical hallucinations" in the form of vivid recollections of past events on stimulation of certain areas of the temporal cortex, which threw light on the symptomatology and pathophysiology of temporal lobe seizures. He was responsible for establishing the value of cortical excision in the treatment of medically refractory focal epilepsy, especially that due to temporal lobe lesions. Falconer developed the technique of en bloc temporal lobectomy along with excision of the uncus, the hippocampus and amygdala.[32,50–55,62-64,66] In the early 1970s, B Ramamurthi introduced the concept of making lesions in the medial temporal epileptogenic areas, stereotactically.[40] Rasmussen introduced a series of modifications of the surgical technique to reduce the morbidity and mortality and improve the outcome of epileptic surgery.

SURGERY FOR MOVEMENT DISORDERS

Parkinson's observation of a patient in whom tremor disappeared following a stroke on the same side provided the idea of surgically interrupting the motor system at various levels. Victor Horsley, at the beginning of the 20th century, resected the pre-central gyrus of a boy with hemiathetosis and achieved dramatic results. Paul Bucy (Fig. 18) and his colleagues, in 1930, acquired considerable experience in unilateral subpial resection of areas 4 and 6 of the cortex in patients with various types of dyskinesias. Earl Walker was the first to suggest pedunculotomy as a mode of treatment for Parkinson's disease. In 1952, Irving Cooper, while performing a pedunculotomy, accidentally damaged the anterior choroidal artery. The surgery was terminated, but surprisingly, the patient had an excellent result. Following this, clipping of the anterior choroidal artery became an accepted form of treatment for some time, but the results were variable, as the anterior choroidal artery had a variable distribution, and it was realised that lesions in the basal ganglia may be more useful. This experience encouraged Cooper to develop chemopallidotomy.[60,80]

In 1948, Spiegel and Wycis modified Horsley's animal stereotactic apparatus and made a great advance in providing a suitable and stable stereotactic technique applicable to humans. Thus, stereotactic thalamotomy as a mode of treatment was laid on firm grounds for functional neurosurgery.[25] The globus pallidus was

Fig. 18: Paul C Bucy was born in 1904 at Hubbard, Iowa. He earned his MD and MS degrees in Neuropathology from State University of Iowa and later in 1928 joined Bailey's newly created neurosurgical staff at University of Chicago. He became in charge of Neurological Surgery at the same institute in 1939. Among his various contributions include writing of the classic volumes, "Intracranial tumours of Infancy and Childhood" and "The Precentral Motor Cortex and Neurology". He described the Kluver-Bucy syndrome in monkeys

the stereotactic target of choice for the treatment of Parkinsonian tremors in the early 1950s.[38] In 1954, Hassler and Reichert reported dramatic mitigation of Parkinsonian tremor after a lesion was made in the ventrolateral thalamus.[28] In 1949, Leksell described his stereotactic apparatus. He also developed stereotactic radiosurgery with the gamma knife.[41]

More recently, transplantation of neural tissues within the brain was described as a mode of treatment for Parkinson's disease though the concept was an old one.[43,77] Mammalian neural transplant was attempted by Thomson as early as 1890. Le Gros Clark successfully transplanted embryonic neocortical tissue in the cerebral ventricle of a six-week-old rabbit.[39] Since then, there has been an explosion of research in this field all over the world, and successful transplants into practically every region of the central nervous system have been reported both in lower mammals and primates. In India, the Department of Science and Technology[73,74] established a National Neural Transplantation Unit at the All India Institute of Medical Sciences in 1986 under Tandon and Gopinath. Bjorklund et al.[9] and Perlow et al.[56] first suggested neural transplantation for Parkinson's disease. Suspensions of chromaffin cells of the patient's own adrenal medulla were stereotactically implanted into the caudate nucleus. The transitory improvement, though it established the validity of the approach, dictated a review of strategy. Madarazo et al. from Mexico carried out open surgery where they implanted the adrenal medulla into a cavity made in the caudate nucleus and demonstrated excellent results.[46] Only a few others could duplicate the same results. After a critical review of adrenal medullary transplants in humans, Lindvall et al. concluded that there was not enough evidence to justify the claims made earlier.[44,45] For all practical purposes, this procedure has been given up now, owing to the unpredictable nature and unacceptable surgical risks. More recently, foetal substantia nigra transplants in the striatum have been shown to relieve at least partly the manifestations of Parkinson's diseases.[79,83] The latest trend is a trial of implantation of stem cells into the brain for various neural disorders. This is still experimental.

SURGERY FOR INTRACTABLE PAIN

Section of the posterior spinal roots was first performed by Bennet in 1888 for relief of pain. Foerster subsequently performed the same surgery for relief of tabetic pain. Cushing transected the spinal cord in a patient suffering from intractable pain due to metastatic malignancy.[29] Martin performed the first cordotomy in 1911. Van Wagenen and Earl Walker performed the first frontal lobotomy for relief of intractable pain.[80,85]

SURGERY FOR TRIGEMINAL NEURALGIA

Since 1880s, the standard operative approach for trigeminal neuralgia was retrogasserian neurotomy. In fact for many years, Victor Horsley used to perform the surgery at the patient's residence itself. In 1891, Frank Hartley devised an extradural temporal approach to the Gasserian ganglion. About 6 months later, Fedor Krause, unaware of Hartley's surgery, performed the same operation. Cushing modified both the techniques and reduced the mortality considerably. In 1901, Charles Frazier performed a rhizotomy using the Hartley-Krause approach. This was subsequently modified so that only differential sectioning of the sensory root was done sparing the motor root. Walter Dandy used the suboccipital approach for rhizotomy which, however, did not become very popular. Dandy, however, made a very interesting observation of the nerve being frequently compressed by a blood vessel. In 1937, Sjoquist introduced trigeminal tractotomy for relief of facial pain. In 1930, Kircshner developed the technique of percutaneous electrocoagulation of the Gasserian ganglion. Various other authors have modified and perfected this approach. Gardner, in 1959, reported treatment of neuralgia by separating the compressing blood vessel over the nerve. Jannetta subsequently developed and popularised the technique of microvascular decompression.[80,85]

PSYCHOSURGERY

The idea of psychosurgery first came to Egas Moniz in 1935 while attending the Second World Congress of Neurology. He had come there to present his pioneering work on angiography when he heard from John Fulton and his associates the effects of brain lesions on animals. On his advice, his young neurosurgical colleague, Almeida Lima, began performing frontal lobotomies. Very soon psychosurgery became an accepted mode of therapy. This work earned Moniz the Nobel Prize in 1949.[25,80,85]

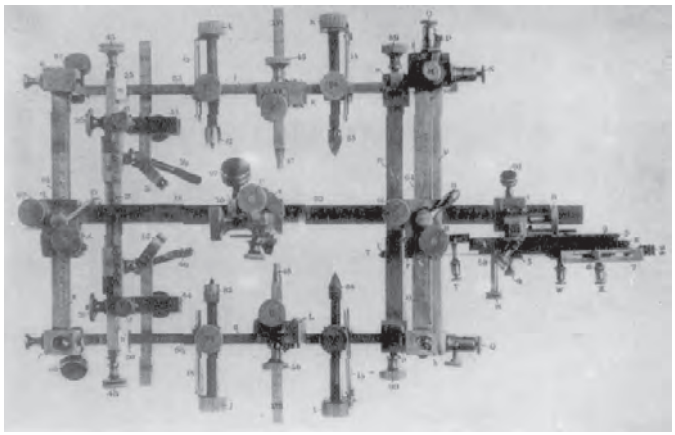


Fig. 19: Clarke and Horsley's stereotaxic apparatus—This was being used on Rhesus monkeys. Accuracy was not very good as the direction of the probe depended on the calvarial measurements, rather than in relation to the ventricles. The apparatus (only part of which is shown here) was bulky and cumbersome

STEREOTACTIC SURGERY

The concept for development of stereotaxy was born in 1908 when Horsley and Clarke (Fig. 19) designed a frame for laboratory experiments that would direct a probe to a pre-determined location in the animal's brain with the help of a previously designed brain atlas.

Even earlier to this Zernov, a Russian neurosurgeon built a guidance frame to aspirate intracranial abscesses, which he called as an encephalometer. However, stereotaxy came of age only with the pioneering work of Spiegel and Wycis who designed an apparatus, which measured distances in relation to the ventricular anatomy rather than to the calvarium. This markedly improved the accuracy. Based on the same principle, a large number of frames were created, to name a few those designed by Leksell, Riechert, Talairach, Bertrand and Narabayashi.[25] In India, Arjun Sehgal developed his own machine.

With the introduction of CT and MRI, the technique of stereotactic surgery was modified avoiding invasive investigations. With CT and MRI compatible machines, the localisation of a point in space was directed by coordinates given by computer applications. Stereotactic surgery has further advanced with the introduction of stereotactic radiosurgery and frameless stereotaxy.[25]

ENDOSCOPIC NEUROSURGERY

The concept of neuroendoscopy is not new. L'Espinasse, a virologist from Chicago, in 1910, used a small rigid cystoscope to cauterise the choroid plexus for the treatment of congenital hydrocephalus. This encouraged Walter Dandy in 1918 to develop a technique to treat communicating hydrocephalus by extirpating the choroid plexus using cystoscopes. The results were disastrous but he predicted with great foresight that this would evolve into a useful diagnostic and therapeutic tool with improvement of imaging techniques. Fay and Grant in 1923, using a small cystoscope, photographed the ventricle and choroid plexus for the first time. They also attempted to create a fistula through the corpus callosum to permit the escape of ventricular fluid into the subarachnoid space. The first successful endoscopic third ventriculostomy was reported in 1923 by Jason Mixter. Over the next few years, Putnam and Scarff reported better results with endoscopic plexus coagulation although this procedure had been abandoned earlier as a primary treatment for hydrocephalus. Renewed interest in neuroendoscopy developed with improvement of illumination, magnification and computer software along with the development of a flexible fiberoptic apparatus.[85]

DEVELOPMENT OF HIGH SPEED DRILLS

The use of drills in medical practice in fact dates back to 100 AD when Romans used a finger-operated drill to treat painful teeth. In the 18th century, a French dentist developed a drill turned by a bow, similar to the bow of a violin. A foot-powered drill for dental procedures was developed by George Greenwood in 1790. About 70 years later, George Harrington developed the first motor-driven drill for dental work, which was operated by a windup spring. George Green, a dentist in Kalamazoo, developed the first electrical dental drill and later developed an air-powered drill operated by foot bellows. In neurosurgery, Victor Horsley and William MacEwen were the first to experiment with various drills with mixed success. De Martel, in 1925, designed a cumbersome but effective drill. Jordan and Day later developed an electric drill, which operated up to 50,000 rpm. A water turbine drill, which eliminated the use of belts and gears of earlier electrical devices was devised by Nelson in 1953 at the National Bureau of Standards, this reached up to speeds of 61,000 rpm. Air-driven turbines were built independently by Iseman in 1941 and Borden in 1950. This led to the development of even higher drill speeds. Barber developed the "turbobit" in 1962 and the Robert Hall drill was introduced in 1963. After many modifications of the "turbobit", a vane-type motor was introduced in 1967 by the Midas Rex Company, which remains the standard against which all other high-powered pneumatic drills are measured.[81,85]

Neurosurgery is a rapidly evolving speciality today. Many people have contributed various developments painstakingly over many years. Its development is still very much in the steeper part of the learning curve and we are fortunate to have been born to witness this era of change. Let us experience, enjoy and contribute towards this change.

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2 History of Microneurosurgery

Thimmappa Hegde, Sarat Chandra P

Modern neurosurgery came of age with the advent of microneurosurgery. The development of the operating microscope opened a whole new world of anatomy. The history of microneurosurgery is not complete without mentioning the pioneering work of various anatomists whose painstaking work laid down the foundations for the development of microneurosurgery.[33]

Galen and Vesalius were the first to mention about the membranes over the brain. Vieussen, in 1690, described in detail the pia and arachnoid membranes. Ruysch, in 1697, showed that the arachnoid extended over the convexity of the brain. Pacchioni (Fig. 1), in 1729, recognised the fluid around the brain, but this was considered to be pathological until 1770, when Cotuguo showed that its presence was physiological. In 1802, Bichat showed that the arachnoid formed a serous cavity similar to the peritoneal cavity. Magendie (1822) gave the first detailed description of the subarachnoid space containing cerebrospinal fluid that circulates under pressure and perfuses the entire surface of the brain. Various anatomists like Kolliker (1850), Virchow (1854) and Luschka (1855) later confirmed this.[33] In 1875, Key and Retzius published a monumental work in which there are detailed diagrams of the subarachnoid space injected with a blue dye, Berliner-Blau. Much more surprisingly, they demonstrated that even the subarachnoid space was compartmentalised and demonstrated the relationship of cerebral vessels to the arachnoid and numerous trabeculae suspending these vessels from the walls of the cisterns. The importance of such intricate anatomy was only realised after the development of microsurgical techniques.

Fig. 1: Antonio Pacchioni was an Italian anatomist who described the dura mater, along with small bodies adjacent to the sinuses which bear his name. He published many anatomical plates in collaboration with Malpighi and Eustachius. He believed that the dura mater was a muscular tissue which served to push the nervous fluid to the periphery and considered cerebrospinal fluid as pathological

In the contemporary period, the contribution of Albert L Rhoton cannot be ignored. Even though a neurosurgeon, he is best known for his articles along with excellent drawings on microsurgical anatomy demonstrated on cadavers.[3,7,10,15,17,18,22,24-29] Bisaria from India gave a detailed description of the microsurgical anatomy of the posterior communicating artery along with its anomalies.[1] His work was among the first from our country to provide a detailed study on cerebral microsurgical anatomy.

In the mid 1950s Leonard Malis found the microscope helpful in experiments on the cerebral cortex of cats.[5] He observed that surgical trauma was much less when he used a microscope. Also, along the way, he modified the bipolar coagulator developed by James Greenwood and this later came to be known as Malis bipolar coagulator.[9]

Loughead and Tom, in 1960, began using a microscope for experimental studies on the effect of subarachnoid blood on blood vessels of dogs.[16] Almost simultaneously, Theodore Kurze along with William House demonstrated the importance of the microscope in operating on acoustic schwannomas.[5] Julius Jacobson, in 1960, published a landmark paper "Microsurgery in anastomosis of small vessels" in Surgical Forum, which outlined the importance of the use of the surgical microscope in neurosurgery.[12] Nothing can overstate the contribution of MG Yasargil to the cause of microneurosurgery. He was instrumental in popularising the concept of total microsurgery and in the development of microscopes and microsurgical instruments.

In India, microneurosurgery had a late start. Although Dr Ramamurthi was well versed with microsurgical techniques (having attended the microvascular workshop in 1969 at Burlington arranged by Dr Donaghy), he concentrated more on the development of stereotactic surgery without actually realising the enormous future possibilities of microsurgery in India. The other

problems facing our country included the difficulty of procuring a good microscope and the resistance by other practicing physicians to accept microneurosurgery. In 1973, Huw Griffith of Bristol demonstrated the transethmoidal approach to the pituitary fossa at the Institute of Neurology, Madras, using a locally manufactured operating microscope. Professor HW Pia and Professor E Grote from Giessen W Germany, conducted workshops at New Delhi and Mumbai in 1978 to strengthen microneurosurgery for more regular use. Several years before this, a beginning of microsurgery, using an indigenously built microscope, had already been made at the AIIMS. The first Indian paper on the subject was published in 1977.[22] Since then, there has been a slow but steady progress.

DEVELOPMENT OF VARIOUS MICRONEUROSURGICAL TECHNIQUES

Aneurysms

Perhaps in no other area were microsurgical techniques more effectively applied. Pool and Cotton, in 1966, published their encouraging experience with the use of the operating microscope during aneurysm surgery.[21] Even earlier to this, Robert Rand operated on an aneurysm under the microscope in 1964.[23] Adams and Witt published their experience on intracranial aneurysm surgery with the use of the microscope.[5] Charles Drake published his experience with aneurysms of the posterior circulation in 1965 and excellently documented his subsequent improvement[6] (Fig. 2). In 1965, Yasargil (Fig. 3), then Assistant Professor of Neurosurgery, along with his teacher Professor Krayenbuhl (Fig. 4), started performing microsurgery in the laboratory.[4] The magnitude of initial difficulties can be comprehended by Yasargil's frustration and conclusion at one time that microsurgery was not practical and more time should not be wasted on it! From this stage, he moved towards perfection. In 1973,

Fig. 2: Charles G Drake was born in 1920 at Windsor, Ontario and received his medical education from The University of Western Ontario. He received his neurosurgical training at Toronto General Hospital, under the supervision of McKenzie and Botterell, who encouraged him to focus his energies on management of aneurysms and arteriovenous malformations. Since then, he operated on more than 1000 aneurysms, 60% of which were in the vertebrobasilar territory. In collaboration with Allcock and Aitken he did pioneering work on vasospasm and stressed the usefulness of magnification and illumination. He openly shared his failures and successes which provided useful learning for others

Fig. 3: M Gazi Yasargil was born in 1925 at Lice, a village in Eastern Turkey. He did his medical schooling from Frederick Schiller University in 1944 and later transferred to Basel, Switzerland, from where he obtained his medical degree in 1950. He was very much influenced by Professor Hugo Krayenbuhl who headed Neurosurgery at University of Zurich. His interest in microvascular surgery encouraged Krayenbuhl to send him to the Microvascular Laboratory at the University of Vermont where he painstakingly learned the methods of various microvascular techniques. He will be perhaps ever be remembered for his excellent study on various subarachnoid cisterns[3]

Fig. 4: Hugo A Krayenbuhl was born in 1902 at Zihlschlacht, Switzerland and received his neurological training under the guidance of the outstanding German neurologist Karl Bonhoeffer and later worked under Sir Hugh Cairns, the eminent pupil of Harvey Cushing. In addition to the large number of publications, he was the author of the book "The Cerebral Angiography" along with Yasargil and undoubtedly neurological surgery in Switzerland owes its high level of competence to this surgeon

upon Krayenbuhl's retirement, he was elected Professor Ordinarius of neurosurgery at University of Zurich and director of the Neurosurgical Clinic at Kantonsspital in Zurich. From then onwards, he continued to amass the largest experience on microneurovascular surgery in the world. His monographs on microneurosurgery, along with his excellent anatomical description of the various subarachnoid spaces are considered as classics in contemporary neurosurgical literature.[33]

Arteriovenous Malformations

In 1965, Yasargil invited Robert Rand to join him in an operation upon a patient harbouring an arteriovenous angioma of the spinal cord.[5] This surgery was performed with the aid of the surgical microscope and the Malis bipolar coagulator, which greatly increased the precision and ease. Since then, a large number of microsurgeons from Europe, Japan and America have contributed in evolving the various techniques in surgery of arteriovenous malformations. Malis was one of the surgeons who suggested the useful technique of following a venous structure back to its origin at the centre of an arteriovenous malformation.[5]

Arteriovenous Fistulas

Carotico-cavernous fistulas were being treated in the 1930s by simple ligation of the cervical carotid artery. This was obviously not always successful. Subsequently, embolisation with a number of materials including skeletal muscle, gelatin sponge and plastic was tried. Serbinenko[31] and Mullan[19] reported balloon embolisation. In 1973, Dwight Parkinson reported his famous case of direct surgical closure of the rent under conditions of cardiac arrest.[20] Dolenc has performed this surgery by temporarily interrupting the carotid intracranially, thus making cardiac arrest unnecessary.[5]

Occlusive Cerebrovascular Surgery

Attempts to revascularise areas of ischaemic brain dates back to the 1930s. From then onwards, various surgeons performed surgical procedures, consisting of placing pedicled muscle grafts or omental patches over the cortical surface.[8,11,14] This met with limited success.[5]

In 1960, Jacobson and colleagues performed the first embolectomy in a patient using the operating microscope.[13] Patency was, however, not established adequately. Over the next few years, more than half a dozen cases of embolectomy were reported with only limited successes. Shelly Chou[2] performed the first totally successful embolectomy at the University of Minnesota in 1963. In the same year, Woringer and Kunlin sutured a saphenous vein graft between the internal carotid artery in the neck and the supraclinoid carotid artery.[32] Since then, many authors have performed this procedure. In 1965, Yasargil performed for the first time successful anastomosis between the superficial temporal artery and the middle cerebral artery in a dog. Donaghy and Yasargil performed this procedure for the first time on a human being in 1967. In both the patients the anastomosis remained patent.[5] Speculative debate regarding the rationale for and against EC-IC bypass has been reduced sharply by the emergence of data from the EC-IC bypass multicentric study in 1985. There has been widespread criticism that this study has been biased in many ways and that the conclusions are not fully relevant and that ST-MC or EC-IC bypass surgery has unfortunately been not practised enough to help deserving patients.

Peripheral Nerve Surgery

In 1964, Chaffee and Numoto demonstrated a more complete return of motor units, when the sciatic nerve of rats was sutured under the microscope, rather than with the naked eye.[5] Exceptional work was done in peripheral nerve injuries by Madjid Samii who demonstrated very high recovery rates.[30] David Kline from America, in collaboration with various plastic and orthopaedic surgeons, reconfirmed the usefulness of the microscope.[5]

Microneurosurgery is not just limited to the areas mentioned above but has also been effectively applied to surgeries for acoustic tumour, para-third ventricular tumours, sellar/suprasellar areas, anterior cervical microdiscectomy, intramedullary spinal tumours and skull base surgery, to mention a few. The techniques have developed and evolved from surgeon to surgeon and from generation to generation. Over the course of time microneurosurgery developed its own unique methods, standards and rules different from any other surgical branch.

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SECTION

2

Diagnostics

Santhosh Joseph

3 Electrodiagnosis

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As of today, there are a number of diagnostic procedures available both outside as well as inside the operating room utilising electrodiagnostic techniques. As these techniques are more commonly used, it becomes imperative for the practising neurosurgeon to be at least familiar with the basic techniques, their indications and interpretations. This chapter provides a brief review of all the existing techniques.

MUSCLE AND NERVE ELECTROPHYSIOLOGIC STUDIES

Electromyographic evaluation in combination with nerve conduction studies is the gold standard for assessing the neurophysiologic characteristics of neuromuscular diseases.

Electrodiagnosis, as an extension of the neurologic examination, employs the same anatomic principles of localisation, and searching for evidence of motor and sensory compromise.

Nerve Conduction Studies

Physiologically, the nerve transmits an electrical impulse across its axon both antidromically and orthodromically. Each stimulus has a proximal as well as distal transmission. This property is used to assess compound muscle action potential (CMAP), sensory nerve action potential (SNAP), F response, H reflex and SSR. Each potential is described by its latency, amplitude, area and configuration. To obtain the velocity, the nerve is stimulated at two different sites and recording is done on the same muscle, and the difference in response latency is multiplied by the distance between these two stimulation sites.

Definition of Related Terms

Latency: This is the time in milliseconds from the application of a stimulus to the initial deflection from the baseline either positive or negative, and is the time required for the action potentials in the fastest conducting fibres to activate the muscle fibres (Fig. 1).

Conduction velocity: It is calculated by measuring the difference in distance and latency between sites of stimulation in metres per second.

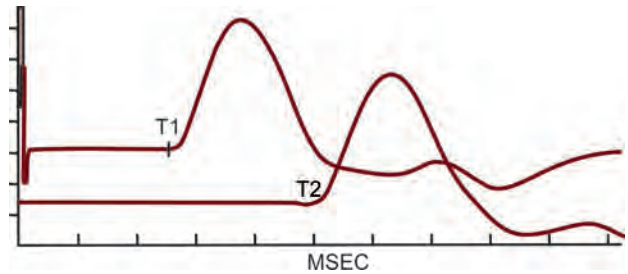


Fig. 1: Response latencies from stimulation of the median nerve at the wrist (T1) and elbow (T2)

Amplitude: It is measured in height in millivolts from the baseline to the peak of the negative phase (upwards deflection). It is proportional to the number of muscle fibres activated and gives an estimate of the amount of functioning nerve and muscle.

F response: It results from the backfiring of antidromically activated anterior horn cells. It is especially helpful in assessment of motor conduction of the proximal segment of a stimulated axon along with the entire length of the peripheral axon (Fig. 2).

H reflex: It is an electrically elicited spinal monosynaptic reflex and bypasses the muscle spindles. The group 1A sensory fibres and alpha motor neurons form the respective afferent and efferent arcs of this reflex. The H reflex latency and amplitude are helpful in diagnosis of mild S1 radiculopathy (Fig. 3).

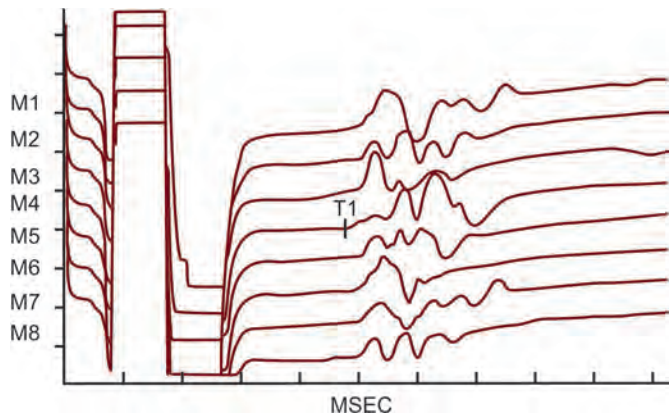


Fig. 2: Typical F-wave responses recorded from the abductor pollicis brevis with median nerve stimulation at the wrist

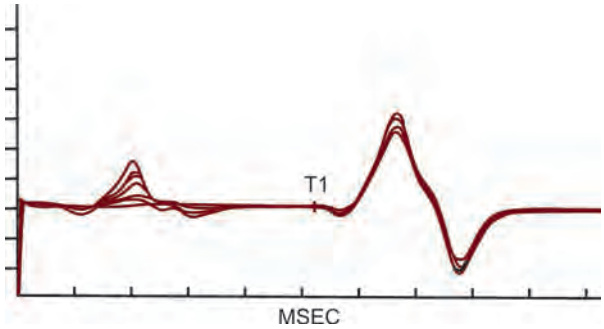


Fig. 3: Typical H-wave reflex (second peak)

Types of Neuropathy

The following are the types of neuropathy:

- *Demyelinating neuropathy criteria*: Distal latency (DL) greater than 125% of upper limit of normal (ULN) and nerve conduction velocity (NCV) less than 80% of lower limit of normal (LLN).
- *Axonal neuropathy*: Decreased CMAP/SNAP amplitude with either normal or mild prolongation of DL, and normal or mild slowing of NCV.
- *Mixed demyelinative/Axonal neuropathy*: Demyelination is present if—
  NCV < 80% (LLN) if amplitude > 80% (LLN)
  NCV < 70% (LLN) if amplitude < 80% (LLN)
  Distal latency > 125% if amplitude > 80% (LLN)
  Distal latency > 150% if amplitude < 80% (LLN)

Technical Limitation while Interpreting Nerve Conduction Study (NCS)

- *Nerve conduction study (NCS) adds to the clinical diagnosis*: It means if there were no symptoms or definite signs then most of the time NCS should be normal, and if it is abnormal in the absence of signs of any disorder the findings should be interpreted only after correcting technical limitations.
- *Age*: Decreased amplitude of sural SNAP is seen in almost 25% of individuals older than 65 years. The CMAP amplitude may also be in the lower range of normal.
- *Temperature changes the latency and conduction velocity*: Lower temperatures slow down impulse propagation, thus increasing distal latency and increase the amplitude of nerve and muscle potential. The conduction velocity increases almost linearly, by 2.4 m/s, or approximately 5% per degree, as the temperature measured near the nerve increases from 29°C to 38°C. Conduction velocity changes nonlinearly with increase in skin temperature, showing a more pronounced effect in the lower temperature range.[47]
- Inappropriate placement of recording electrodes can change the waveforms, e.g. mixing of ulnar-related waveforms while recording on APB for the median nerve.
- *Submaximal stimulus*: Usually a motor potential requires 200–300 mV of stimulus and sensory 150–250 mV and submaximal stimulation can lead to decreased amplitude of CMAP/SNAP.
- In case NCS shows axonal neuropathy of the common peroneal (CP) or posterior tibial (PT) nerves in an asymptomatic individual then always look for atrophy of the extensor digitorum brevis (EDB) or abductor hallucis brevis (AHB).
- In bare foot persons, there is atrophy of the EDB and CP-CMAP amplitude is thus reduced. In such cases, CP-CMAP on the tibialis anterior should be performed.
- Presence of fat, oedema and an open wound interferes in the recording and leads to false values.
- Normal anatomical variations, e.g. Martin Gruber anastomoses (MGA), may, in some individuals, lead to decreased amplitude in NCS in the hypothenar muscles on stimulation of the ulnar nerve at the wrist and elbow.[35]

Important Points to Remember

- Do not trust electrophysiological studies (EPS) if they do not match your clinical examination finding.
- The role of EPS is to corroborate clinical history and examination, and is not a substitute for the latter.
- While interpreting NCS, normative data of the concerned laboratory should be available before interpretation.

Electromyography

The pattern of electrical activity in muscle [i.e. electromyography (EMG)], both at rest and during activity, may be recorded from a needle electrode inserted into the muscle. The nature and pattern of abnormalities relate to disorders at different levels of the motor unit. Before planning to start EMG, the clinician should have relevant NCS and clinical details of the patient.[34]

Electromyography Findings

At rest:

- Insertion activity
- Spontaneous activity.

At voluntary movements:

- Assessment of individually recruited motor unit action potential (MUAP)
- Size
- Shape
- Stability
- Assessment of activation pattern of MUAPs
- Recruitment
- Interference pattern (IP).

Insertional Activity

It is a single burst of activity arising when the needle is inserted, slightly outlasting the moment of the needle insertion. It is thought to occur due to mechanical stimulation or injury of the muscle fibres. It lasts for a few hundred milliseconds, usually 300–500 ms. They appear as a cluster of positive or negative repetitive

high-frequency spikes, which make a crisp static sound over the loudspeaker.

Increased insertional activity indicates instability of the muscle membrane indicating:

- Denervation, usually an early finding 1–2 weeks after nerve injury
- Myotonic disorders
- Necrotising myopathies, such as inflammatory myopathies.

Decreased insertional activity suggests either fibrotic or severely atrophied muscles or functionally unexcitable muscles (e.g. during attacks of familial periodic paralysis).

Spontaneous Activity

Normal

- Normally no spontaneous activity is seen except at the motor endplate region.
- Two types of normal endplate spontaneous activity are present. (1) Endplate noise and (2) Endplate spikes.

Abnormal

- Fibrillation potentials
- Fasciculation potentials
- Complex repetitive discharges
- Myotonic discharges
- Myokemic discharges
- Neuromyotonic discharges
- Cramps.

Endplate noise: These are extracellularly recorded miniature endplate potentials and non-propagating depolarisations. It is caused by spontaneous release of acetylcholine quanta. These are negative potentials, irregular in rhythm, with amplitude of 10–50 uV and duration of 1–2 milliseconds (sounds like a "sea shell held to the ear").

Endplate spikes: These are discharges of single muscle fibres generated by activation of intramuscular nerve terminals irritated by the needle. They may originate in the intrafusal muscle fibres. They are irregular having an initial negative deflection, firing at 5–50 impulses per second, with amplitude of 100–200 pV with duration of 3–4 milliseconds (sounds like "clacking or buzzing").

Fibrillation potentials: These are spontaneous action potentials of denervated single muscle fibres. They result from the resting membrane potential of the denervated fibre and usually appear 10–21 days after muscle denervation. They are brief spikes (usually triphasic with initial positivity) or positive waves (initial positivity with slow negativity, sawtooth appearance), fire regularly at 1–30 Hz, with an amplitude of 20–200 pV; gradually decreasing with time, with a duration of 1–5 milliseconds (sounds like "crisp and clicking" and "tick-tock of a clock").

Causes

- *Common*: Denervation; Based on their distribution, useful in localising lesions affecting motor neurons, spinal roots, plexus or peripheral nerves; late in the course of denervation, muscle fibres that are reinervated, fibrotic or severely atrophied show no fibrillation potentials.
- May persist in paraspinous muscles for years after surgery.
- Inflammatory myopathy.

A grading system is used (from 0 to 4) to semiquantitate fibrillation potentials as their density is a rough estimate of the extent of denervated muscle fibres:

0 no fibrillations
+1 persistent single trains of potentials (> 2 seconds) in at least two areas
+2 moderate number of potentials in three or more areas
+3 many potentials in all areas
+4 abundant spontaneous potentials nearly filling the oscilloscope.

Fasciculation potentials: Fasciculation potentials are spontaneous discharges of a motor unit. They originate from the motor axon anywhere along its length. Their size and shape are like MUAPs, have an irregular rhythm and a lower firing rate than voluntary MUAPs (sounds like "corn popping").

Causes

1. Diseases of anterior horn cells (MND)
2. Radiculopathies
3. Entrapment neuropathies
4. Peripheral polyneuropathies
5. Cramp fasciculation syndrome
6. *Others*: tetany, thyrotoxicosis and overdose of anticholinesterase medication.

They may also occur in healthy people. Benign discharges tend to fire more quickly, whereas grouped fasciculation potentials from multiple pairs are more common in MND.

The association of fasciculation potentials with fibrillation potentials or other neurogenic MUAP changes is strong evidence of a lower motor neuron disorder.

Complex repetitive discharges: These result from the nearly synchronous firing of a group of muscle fibres. One fibre in the complex serves as a pacemaker, driving one or several other fibres so that the individual spikes in the complex fire in the same order as the discharge recurs. One of the late-activated fibres re-excites the principal pacemaker to repeat the cycle. They are shaped containing 10 or more distinct spikes, regular in rhythm, firing at 5–100 Hz, typically begin abruptly, with an amplitude of 50 pV–1 mV, with a duration of 50–1000 milliseconds (sounds like "machine gun" on the loudspeaker).

Complex repetitive discharges are non-specific and seen in many chronic disorders, including chronic neuropathies and myopathies. They may also be found in the iliopsoas or cervical paraspinal muscles of apparently

healthy people, probably implying a clinically silent neuropathic process.

Myotonic discharges: Abnormal insertional activity of recurring single-fibre potentials wax and wane in the range of 10 LIV–1 mV, varying inversely with the firing rate of 20–150 Hz (accelerating or decelerating motorcycle or chainsaw). Myotonic discharges may occur with or without clinical myotonia in the myotonic dystrophies (types I and II) and other myopathies.

Myokymic discharges: These originate ectopically in motor nerve fibres and result from complex bursts of grouped repetitive discharges in which motor units fire repetitively, usually with 2–10 spikes with a firing rate of 30–40 Hz, each burst recurs at regular intervals of 1–5 seconds (sounds like "marching soldiers" on the speaker).

Neuromyotonic discharges: Here, the muscle fibres fire repetitively at high frequency (150–250 Hz) and produce a pinging sound on the speaker. They continue during sleep and diminish in intensity with distal nerve blocks.

Cramp discharges: These include sustained involuntary muscle contraction during cramps. The discharge consists of MUAPs, with a firing rate of 40–60 Hz, with abrupt onset and cessation.

Motor Unit Action Potentials

The MUAP is the extracellular electrode recording of a small portion of a motor unit. They are triphasic in shape, measured as total peak-to-peak amplitude. It normally varies from several hundred microvolts to a few millivolts.

Duration: It is measured from the initial signal's deviation away from the baseline to the final return to baseline. It indicates the degree of synchrony among many individual muscle fibres and is a rough indicator of the number of fibres in a motor unit. It normally varies 5–15 milliseconds.

Long-duration MUAPs with high amplitude are best indicators of reinnervation.

Short-duration MUAPs with low amplitude are seen in disorders associated with loss of muscle fibres, like myopathies.

Phase: This is the deviation of the signal from its beginning until its return to the baseline. The phases equal the number of negative and positive peaks extending to and from the baseline, or the number of baseline crossings plus one. A MUAP having more than four phases is considered polyphasic. Around 5–15% of MUAPs may have five or more phases and proximal muscles may have around 25% MUAPs with five or more phases. Increased polyphasics is a nonspecific abnormality seen both in myopathies and neuropathies.

Late component (satellite or linked potential): This is a time locked waveform to the main MUAP, but separated from it by an isoelectric interval. (The duration measure does not include such potentials.) It implicates early reinnervation of muscle fibres by collateral sprouts from adjacent motor units.

Complexity: The MUAP with greater than 4 phases or a satellite potential is said to be complex.

Variability: These include changes in shape of the MUAP on consecutive discharges. It indicates deficient neuromuscular transmission. They may indicate NMJ disorder, MND, polyneuropathy or radiculopathy and early stage of reinnervation.

Characteristics of Activation Pattern of Motor Unit Action Potentials

Recruitment

Normally only 1 or 2 motor units excite semirhythmically during constant contraction. At greater muscle force, additional units are recruited and previous units fire more rapidly. The firing frequency of a motor unit, when additional units are being recruited, is known as *Recruitment frequency*. In normal muscles, mild contraction induces isolated discharges at a rate of 5–10 Hz. *Recruitment ratio* is the average firing rate divided by the number of active units, which should not exceed five. *Reduced recruitment* is seen in lower motor neuron weakness and advanced myopathies with extensive muscle loss. *Early recruitment* is seen in myopathy.

Interference pattern (IP): It is the pattern of discharge of motor units firing rapidly on applying increasing force so that individual MUAPs are not recognisable. It depends upon descending inputs from the cortex, number of motor neurons capable of discharging, firing frequency of each motor unit, waveform of individual potentials and phase cancellation. Incomplete interference pattern is seen in poor voluntary effort or upper motor neuron disorder, and with reduced recruitment.

Electrodiagnostic Findings in Nerve Injury

The electrodiagnostic findings (EDX) provide information about:

- Site of the injury
- Underlying pathophysiology
- Rate of recovery.

Timing of the Test is Important

If performed too soon after the injury, there may not have been sufficient time for EDX signs of axon damage to develop so it cannot be determined whether a nerve lesion is caused primarily by demyelinating conduction block or axon loss.

In the case of a severe axon loss injury (axonotmesis and neurotmesis), CMAPs and SNAPs are entirely normal for the first 2 days despite the presence of an obvious clinical deficit and an inability of the patient to voluntarily recruit motor units during EMG.

By day 3, wallerian degeneration starts causing some loss of the distal CMAP amplitude.

By day 9, the CMAP is further diminished and may even disappear.

By days 11–12, the SNAP amplitude is also diminished (the reason for the earlier loss of CMAP amplitude relates to the early failure of neuromuscular junction transmission).

Finally, after a few weeks, there is evidence of active denervation in the form of fibrillation potentials and positive sharp waves during EMG.

If the lesion is caused by conduction block (neuropraxia), significantly (e.g. > 50%) lower proximal as compared with distal CMAP amplitude, with abnormal neurogenic MUAPs or even their complete absence can be seen.

The distal CMAP amplitude (if stimulating and recording beyond the site of conduction block) should be within normal limits in cases of conduction block. There may be a limited amount of axon loss if injury has occurred to some axons at the site of the conduction block. Therefore, there may be some positive sharp waves or fibrillation potentials on NEE. It is important to remember that many nerve injuries involve components of both conduction block and axon loss.

There is no way to clearly differentiate a predominantly demyelinating conduction block process from an axon loss lesion on the basis of clinical symptoms, signs or of an EDX performed within 7 days of the injury.

An avulsion injury that involves both anterior and posterior preganglionic segments may produce a characteristic EDX pattern involving loss of CMAP amplitudes but preservation of SNAP amplitudes. This is because the lesion affects the dorsal root proximal to the ganglion that lies outside the spinal canal in the intervertebral foramen.

A repeat examination should always be performed to assess for electrophysiological recovery or worsening. One must assess for recovery of SNAP and CMAP amplitudes; during regeneration the SNAP amplitude characteristically recovers before the motor amplitude.

Furthermore, one may appreciate some degree of normalisation of motor unit recruitment and morphology. One particularly important EMG feature is the appearance of low-amplitude, polyphasic, unstable nascent motor unit potentials, which is important EDX evidence of early motor unit reinnervation. Some of the important features of the various types of nerve damage are discussed here.

Neuropraxia

- No axonal degeneration, only conduction block: focal site of demyelination.
- Aetiology: Compression or traction injury.
- Large myelinated fibres are more susceptible to compression and ischaemia (motor).

EDX

- Nerve conduction is normal distally, but altered across the injury site (consider axonal loss if amplitude decreased proximally and distally).
- Needle EMG shows decreased recruitment, but no abnormal spontaneous potentials.
- Normal conduction returns in days/weeks (due to remyelination of the damaged segment).

Axonotmesis

- Axonotmesis implies axon damage with preservation of the endoneurium, perineurium and epineurium, and there will be wallerian degeneration of the axon.
- Motor NCS lost day 4–7 (NMJ fragmentation).
- Sensory NCS lost day 8–10.
- Preservation of endoneurium allows for regeneration with reinnervation.
- Recovery time dependent on distance for reinnervation.

EDX

- Day 0–3: same as neuropraxia.
- Day 4–7: decreased motor amplitude.
- Day 8–10: decreased sensory amplitude.
- Day 10–14: abnormal spontaneous potentials on EMG (PSW, Fibs).
- Month 6–12: "nascent pot's (S > M) and "jitter".
- Performing EDX too early may lead to misleading information (wait 2–4 weeks).
- An early sign of axonotmesis is decreased CMAP amplitude (30–40% lower than the contralateral side).
- Repeat testing will be required in about 2–3 weeks.

Neurotmesis

- Disruption of axon, endoneurium and connective tissue (perineurium and epineurium).
- Poor prognosis for reinnervation.
- EDX finding are same as above.
- Findings for entrapment neuropathy [carpal tunnel, thoracic outlet syndrome (TOS)] are discussed elsewhere.[25,58,61]

EVOKED POTENTIALS

Sensory Evoked Potentials

Recording of spinal or cerebral potentials elicited by stimulation of specific afferent pathways helps in monitoring the functional integrity of these pathways although it does not indicate the pathologic basis of lesions involving them.

Somatosensory-Evoked Potentials

The somatosensory-evoked potentials (SEPs) are obtained by multiple electrical stimulations of peripheral nerves. The electrical signals generated are measured at the level of the peripheral nerves (over the brachial plexus or popliteal fossa), spinal cord (lumbar as well as high cervical), and cortex (scalp). These recordings are made over the scalp and skin on the neck and the back (over the spinous processes of the vertebrae) to monitor these signals in the cortex and the spinal cord.

This method relies mostly on the stimulation of the large myelinated somatosensory fibres, which transmit the impulses to the spinal cord by the posterior column system.

Median nerve stimulation at the wrist or posterior tibial nerve stimulation at the popliteal fossa or medial malleolus (ankle) is commonly used.

These evoked potentials (EPs) are so small compared to the background EEG activity that the responses to a number of stimuli have to be recorded and averaged with a computer in order to permit their recognition and definition. The background EEG activity, which has no fixed temporal relationship to the stimulus, is averaged out.

Methodology[1]

- Electrode sites on the scalp are marked using the 10–20 international system (Figs 4A and B). The recording sites preferred by the authors are C3, C4, CZ, FPZ, FZ, A1 and A2.
- The recommended stimulus is a monophasic pulse of 10–20 mA and 100 μs duration.
- The stimulus is applied to the median nerve at the wrist or the posterior tibial nerve at the ankle near the site where the nerve passes posterior to the medial malleolus. Spinal cord intra-operative SEP monitoring often involves the posterior tibial nerve; but, when surgery is above the eighth cervical spinal cord level then median nerve intra-operative SEP monitoring is used.
- Rates of stimulation of 5 Hz for median nerve and 2 Hz for the posterior tibial nerve have been used. Each limb should have evoked potential testing separately. Generally, 350–500 repetitions are generated, but up to 2,000 repetitions may be necessary.
- An analysis time of 30–120 ms is sufficient for this type of testing.
- The filter settings undertaken are 30 Hz (low pass) and 3,000 Hz (high pass).

Role of Somatosensory-Evoked Potential in Neurosurgical Diseases

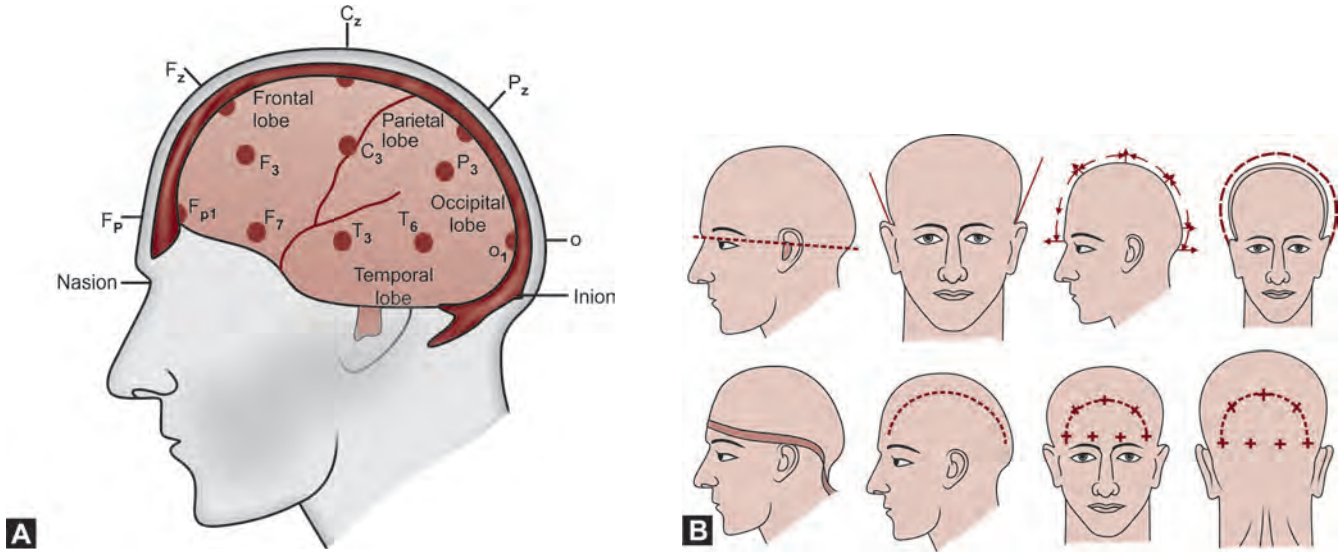
- Disorders of the peripheral nerves
- Plexus lesion
- Radiculopathy
- Thoracic outlet syndrome
- Cervical myeloradiculopathy
- *Malingering*: Some patients have sensory symptoms but no objective clinical deficits, suggesting that symptoms may not be organic in origin. In such a circumstance, an abnormal SEP indicates that symptoms have an organic basis.[43]
- Intra-operative assessment of the functional integrity of neural pathways.

Intra-Operative Monitoring

This consists of monitoring and continuous 'on-line' assessment of the functional integrity of neural pathways and mapping (functional identification and preservation of anatomically ambiguous nervous tissue) techniques.

Intra-operative SEPs are obtained by repetitive measurement of SEPs in order to monitor functionality of the posterior spinal cord tracts, resulting in detection of spinal cord damage during surgery and prevention of post-operative neurologic deficits.

Monitoring provides services beyond simply warning of ensuing complications. It offers insight towards prompt intervention. A surgeon can feel reassured about the integrity of the spinal cord and can, therefore, extend



Figs 4A and B: (A) Actual representative areas of the brain in the 10-20 system. (B) Landmarks and measurements of the 10-20 system

the procedure to a greater degree. Further, some patients may receive procedures that would have been avoided in the absence of such feedback about the status of the nervous system. Surgical correction of scoliosis is the most common procedure for which intra-operative SEP monitoring is used.

Limitations of intra-operative SEP monitoring include its monitoring only the posterior-column somatosensory system and the input being provided when the actual damage may have already taken place.

Abnormality Criteria

It is important to obtain baseline data, including pre-incision tracings and early (surgical site preparation) intra-operative data. All subsequent data, as collected, are then compared to the baseline findings. The subjects serve as their own 'internal' control.

The patient's underlying condition may prevent the recording of intra-operative SEPs in 5% of the cases. The most frequent conditions leading to the problem of poor data acquisition are neural tube defects and severe spastic quadriparesis with atrophy of the lower extremities.

Other disorders associated with unrecordable intra-operative SEPs include:

- Sequelae of spinal cord trauma
- Advanced spondylosis with myelopathy
- Scoliosis with myelopathy
- Peripheral neuropathy
- Spinal cord tumour.

Abnormality criteria for intra-operative SEPs include: (1) potentials to be monitored (cervical and cortical); (2) increase in latency equals more than 10% of the baseline value and (3) decrease in amplitude is greater than 50%.

Transient and relatively less significant changes in the amplitude (30–50% of baseline) or latency (< 2 ms) of intra-operative SEPs may be seen during surgery due to hypotension, haemodilution, hypothermia or irrigation with cold saline. Return to the baseline values is seen when these alterations are corrected. These alterations often occur gradually over a period of 30–60 minutes.

More significant changes, such as intra-operative SEP amplitude reductions of greater than 50% of baseline or increases in latency of less than 2 ms, tend to be acute and not associated with any change in temperature, blood pressure or the amount of anaesthetic administered.

It is important to note that increasing concentrations of halothane can quickly produce a decrease in the amplitude of the cortical potentials, which is directly proportional to the end tidal concentration of that gas. Patients less than 10 years old are particularly susceptible to the effect of high concentration or boluses of general anaesthetics producing attenuation of the cortical potentials. Cortical potentials in children are also more likely to be attenuated by a combination of anaesthetics, such as isoflurane and nitrous oxide, especially in high doses.

The best scalp recordings are obtained by avoiding the combination of anaesthetics or keeping the concentration of nitrous oxide at less than 50% and isoflurane at less than 0.6% when these agents are used together.

When one uses the latter range of anaesthetic doses and adds narcotics (i.e. fentanyl) during the induction, intra-operative SEPs remain unaltered.

When interpreting intra-operative SEP abnormalities, one has to be attentive to the factors that can cause recording artefacts. These include electrical stimulator failure, electrode problems (high impedance, detachment from the skin) and electrical or magnetic interference from other equipments in the operating room. Additionally, certain physiological factors, such as obesity, diabetes with neuropathy, peripheral vascular disease, seizure disorders and closed head injuries, have been associated with less than optimal responses.

Somatosensory-Evoked Potentials (SSEPs) in Peripheral Nerve Trauma

It gives information about the integrity of the posterior sensory tracts in the spinal cord and is therefore useful in evaluating suspected posterior nerve root avulsion.

However, the presence of an intact SSEP does not reliably indicate satisfactory nerve root function. The SSEPs are so sensitive that they may yield positive waveforms in the presence of only a few hundred intact nerve root axons. Furthermore, they do not provide enough localising information to be of great assistance in post-ganglionic peripheral nerve injuries and do not provide information about injury to anterior (motor) rootlets in the spinal canal.

Brainstem Auditory-Evoked Potentials

Brainstem auditory-evoked potentials (BAEPs) are elicited by monaural stimulation with repetitive clicks and are recorded between the vertex of the scalp and the mastoid process or earlobe (Fig. 5). The presence, latency

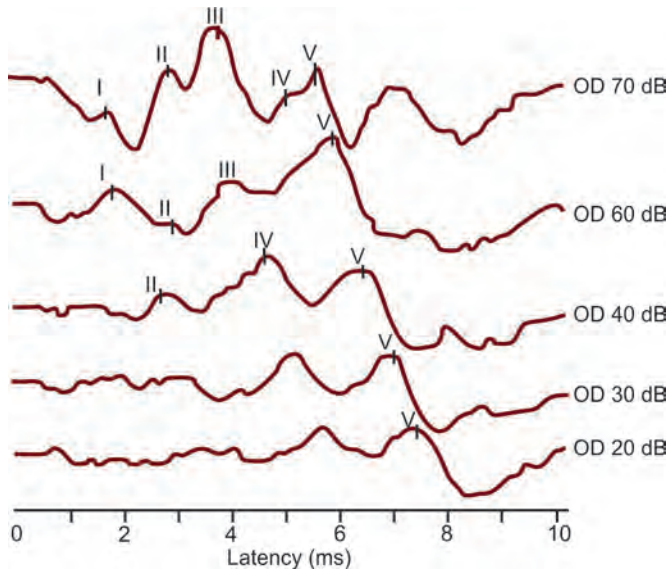


Fig. 5: Normal brainstem auditory-evoked potential wave

and interpeak latency of the first five positive potentials recorded at the vertex are evaluated.

Brainstem Auditory-Evoked Potential Wave Generators

Wave I: Distal acoustic nerve
Wave II: Proximal acoustic nerve/cochlear nucleus
Wave III: Superior olivary complex at the level of the lower pons
Wave IV: Lateral lemniscus
Wave V: Inferior colliculus or upper pons

The findings are helpful in screening for acoustic neuromas, detecting brainstem pathology and evaluating comatose patients. The BAEPs are normal in coma due to metabolic/toxic disorders or bihemispheric disease, but abnormal in the presence of brainstem pathology. Intra-operative BAEP monitoring has been shown to be useful for preservation of hearing and vestibular nerve function during the resection of acoustic neuroma and other posterior fossa surgeries.[30]

The types of surgeries in which BAEPs are used include not only acoustic neuroma resections but also posterior fossa and petroclival skull-base tumours, arteriovenous malformations, aneurysms and decompressive procedures in patients with Chiari malformation.

Intra-Operative Brainstem Auditory-Evoked Potential Monitoring

As in the non-intra-operative approach, the patients receive auditory stimulation delivered by a series of clicks at intensities of 60–70 dB hearing level keeping the frequencies of the clicks at 5–50 per second.

Earphones, transducers or even direct middle ear inserts deliver the sounds. The signals from several stimuli are averaged due to the low amplitude of each individual auditory-evoked response, which is often less than 0.1 μv. The recording can be done on the scalp during the non-operative BAEPs or directly from the acoustic nerve with special cotton wick electrodes. The scalp electrodes are placed on both ears or mastoids and vertex, and ground. A contralateral (to the side of stimulus) ear-mastoid to vertex montage can help differentiate the waveform IV and V peaks that may be fused in the ipsilateral channel.

The signal phase (rarefaction, condensation or mixed) should be chosen to maximise BAEP waveforms. Overall, the goal should be the identification of the most important components of the BAEPs, namely wave I and wave V in the shortest time possible. The effects of surgery on BAEPs are interpreted noting the generators of the waveforms to help localise where the problem is taking place.[12]

The BAEP changes seen during surgery can be divided into three types:

- *Type 1*: Gradual and persistent prolongation of the waveforms of 1 ms or more. This type of abnormality may or may not be followed by a return to the baseline values. Post-operative type 1 BAEP abnormalities are not accompanied by clinically significant hearing deficits, but careful audiological testing may reveal some minor hearing loss.
- *Type 2*: When there is a sudden loss of wave I through wave V ipsilateral to the side of the surgery without return to the baseline. Hearing impairment is often observed post-operatively on the same side of the surgery when type 2 changes are seen during surgery.
- *Type 3*: When the contralateral BAEP waveforms become abnormal during posterior fossa surgery, the prognosis is poor. Type 3 changes are often associated with other signs of brainstem dysfunction. When this pattern is not accompanied by return to the baseline, it has been correlated with poor outcome, such as death or post-operative survival with severe neurologic deficit, including hearing impairment.

Visual Evoked Potentials

The visual evoked potential (VEP) is an evoked electrophysiological potential that can be extracted using signal averaging from the electroencephalographic activity recorded at the scalp. The VEP can provide important diagnostic information regarding the functional integrity of the visual system.

Elicited by monocular stimulation with a reversing checkerboard pattern they are recorded from the occipital region in the midline and on either side of the scalp.

The VEP peak latency, amplitude and waveform are age dependent. The VEP peak latency refers to the time from stimulus onset to the maximum positive or negative deflection or excursion; thus, the term VEP peak latency corresponds to the term implicit time used to describe the time from the stimulus to the maximum deflection of electroretinograms. The VEP peak latency may also be referred to as 'time to peak' or 'peak time'.

The component of major clinical importance is the so-called P100 response, a positive peak having a latency of approximately 100 ms. It's presence, latency and symmetry over the two sides of the scalp are noted. Amplitude may also be measured, but changes in size are much less helpful for the recognition of pathology (Fig. 6).

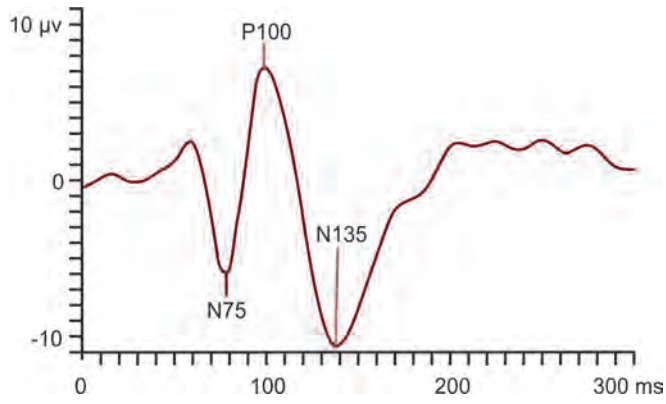


Fig. 6: Normal pattern reversal visual evoked potential

The VEPs are most useful in detecting dysfunction of the visual pathways anterior to the optic chiasm. In patients with acute severe optic neuritis, the P100 is frequently lost or grossly attenuated; as clinical recovery occurs and visual acuity improves, the P100 is restored but with an increased latency that generally remains abnormally prolonged indefinitely. The VEP findings are therefore helpful in indicating previous or subclinical optic neuritis. They may also be abnormal with ocular abnormalities and with other causes of optic nerve disease such as ischaemia or compression by a tumour. Normal VEPs may be elicited by flash stimuli in patients with cortical blindness.[58]

ELECTROPHYSIOLOGY FOR SOME CLINICAL CONDITIONS OF INTEREST TO NEUROSURGEONS

Carpal Tunnel Syndrome

Electrophysiology

Aim of nerve conduction study (NCS) and EMG:

1. To demonstrate a distal lesion of the median nerve.
2. To exclude other peripheral conditions that can result in similar symptoms like high median neuropathy, C6-C7 radiculopathy, lesions of the brachial plexus or even polyneuropathy.
3. To assess severity of carpal tunnel syndrome (CTS) and for therapeutic decisions.
4. Baseline to assess the outcome after intervention.

Electrodiagnostic Grading of Carpal Tunnel Syndrome

Grade 1: Very mild CTS—normal standard tests, abnormal comparative tests.
Grade 2: Mild CTS—abnormal sensory with a normal motor response.
Grade 3: Moderate CTS—abnormal median sensory and motor response.
Grade 4: Severe CTS—absence of sensory response, abnormal distal motor latency.
Grade 5: Extreme CTS—absence of median motor and sensory responses.

Electrophysiological Findings

Sensory Latency

- Most important, most sensitive and earliest indicator of CTS is prolonged sensory latency.
- May show diminished amplitude and is often absent.
- Latencies of 1–2 ms are considered mild, whereas latencies more than 6 ms are considered severe.

Distal Motor Latency

- Prolonged, but is not as sensitive an indicator as sensory latency.
- Motor latency abnormalities tend to occur later in the course of the disease.
- Latencies of 1–2 ms are considered mild, whereas latencies more than 6 ms are considered severe.

EMG may show loss of motor units and presence of denervation potentials in the thenar muscles. Although these abnormalities are present before clinically evident muscular atrophy sets in, they usually occur after distal motor latency is prolonged. Insertional activity may be increased in CTS. The EMG/NCS is incomplete unless the ulnar nerve of the same arm is also evaluated to rule out the possibility of peripheral neuropathy.

Post-Operative Changes

There is an immediate increase in motor conduction velocity following release of the carpal tunnel. After one week this value decreases to an intermediate value and then gradually returns to normal in the next 8–12 weeks.

Criteria for the Electrodiagnostic Evaluation of Unilateral Neurogenic Thoracic Outlet Syndrome[61]

All three of the following criteria must be found in the affected limb:

1. Amplitude of median motor response is reduced.
2. Amplitude of ulnar sensory response is reduced.
3. EMG evidence of denervation in muscles innervated by the lower trunk of the brachial plexus.

Details Regarding the Above Criteria

Criterion 1:

a. Using standard surface electrodes with active pick up over the APB, the amplitude of the median motor response on the affected side should be less than 50% of that obtained on the unaffected side.

Criterion 2:

a. Using standard ring electrodes on the fifth digit, the ulnar sensory amplitude on the affected side should be less than 60% of the amplitude on the unaffected side.

Criterion 3:

a. Muscles innervated by the lower trunk of the brachial plexus include the APB, pronator quadratus, flexor pollicis longus, first dorsal interosseous, abductor digiti minimi, flexor carpi ulnaris, extensor pollicis brevis and extensor indicis.
b. The EMG abnormalities in TOS are most commonly seen in median and ulnar innervated intrinsic muscles of the hand, especially the APB.
c. Positive waves and fibrillations may be found, but chronic denervation changes are more common, i.e. increased motor unit amplitude, increased motor unit duration, and decreased recruitment with rapid firing of motor units are activated.

The electromyographer should rule out neuropathic conditions that might mimic TOS, specifically cervical radiculopathy, CTS, ulnar neuropathy and polyneuropathy.

Acoustic Neuroma

The results of pre-operative brainstem auditory-evoked response (BAER) studies were useful in predicting the outcome of hearing preservation attempts. Patients with intact BAER waveform morphology and normal or delayed latencies had a higher probability of hearing preservation in comparison to those with abnormal pre-operative BAER morphology.[25]

A characteristic finding on ABR in a person with an acoustic neuroma would be a wave I with nothing after it—no waves 3 or 5 (10–20% of cases). A wave I–III interval delay is common, and a wave V delay occurs in 40–60% of cases.

The place of intra-operative BAER audiometry in improving hearing outcomes is still uncertain, largely due to the known difficulties in obtaining reliable recordings. However, on empirical grounds, it is likely that if hearing preservation rates are to improve, BAER audiometry will play a significant part in this improvement. The only pre-operative factor that may predict a favourable hearing preservation outcome is the presence of normal pre-operative BAER morphology.[29]

ELECTROENCEPHALOGRAPHY

The electroencephalogram (EEG) was developed by the German psychiatrist, Hans Berger, in 1929. Its potential applications in epilepsy rapidly became clear, when Gibbs and colleagues in Boston demonstrated 3 per second spike wave discharge in what was then termed petit mal epilepsy. The EEG continues to play a central role in the diagnosis and management of patients with seizure disorders—in conjunction with the now remarkable variety of other diagnostic techniques developed over the last 30 or so years—because it is a convenient and relatively inexpensive way to demonstrate the physiological manifestations of abnormal cortical excitability that underlie epilepsy (Smith, 2005).[50]

The electroencephalograph records spontaneous electrical activity generated in the cerebral cortex. This activity reflects the electrical currents that flow in the extracellular spaces of the brain, and these reflect the summated effects of innumerable excitatory and inhibitory synaptic potentials upon cortical neurons. This spontaneous activity of cortical neurons is influenced and synchronised by subcortical structures, particularly the thalamus and upper brainstem reticular formation. Afferent impulses from these deep structures are probably responsible for entraining cortical neurons to produce characteristic rhythmic brain wave patterns such as alpha rhythm and sleep spindles.

The EEG provides confirmation of Hughlings Jackson's concept of epilepsy—that it represents a recurrent, sudden, excessive discharge of cortical neurons; but like other ancillary tests, it must be used in conjunction with clinical data.

How Can Electroencephalography Help in Epilepsy?[47]

Diagnosis of Epilepsy

- Differential diagnosis of paroxysmal neurological events.
- Distinction between a focal and generalised seizure disorder.
- Identification of specific epilepsy syndromes.
- Recognition of photosensitivity and reflex epilepsies.

Management of Epilepsy

- Assessing risk of recurrence after an unprovoked seizure.
- Selection of antiepileptic treatment.
- Likelihood of seizure relapse if medication is withdrawn.
- Identification of irritative zone in epilepsy surgery candidates.
- Investigation of cognitive decline, especially when rapidly progressive.
- Monitoring in the management of status epilepticus.
- Detection of non-convulsive status.

Although the diagnosis of seizures and epileptic syndromes is primarily made from careful history and examination, the EEG remains an important investigative tool. The EEG often provides supportive evidence of seizure disorder and assists in classification of seizures and epilepsy. Moreover, EEG findings are important for determination of seizure focus and may also help with prognosis under certain circumstances.[53]

Minimum Technical Standards

Digital recording machines are rapidly replacing the traditional "paper" systems.

Advantages

- Digital EEG is particularly useful for detecting and analyzing epileptic discharge (ED) as the waveforms in question can be reformatted in various montages after the recording is completed.
- Very little storage space requirement; elimination of paper costs; automatic event detection and the ability to network different recording stations.
- Filter and paper speed settings with digital recordings are accurate and automatic, thereby avoiding technician oversight.
- Problems due to pen alignment and curvilinear effect are not seen with digital systems.

Disadvantages

- The incompatibility of systems made by different vendors, often forcing one to resort to paper printouts for transmission of EEG data between two centres.

- Comparing two separate epochs is somewhat cumbersome, as only limited data can be observed simultaneously on the monitor.[34]

Standardising Electroencephalography Recording, Lab Infrastructure and Electroencephalography Reporting

The International Federation of Clinical Neurophysiology (IFCN) has certain standards for recording of clinical EEG. These recommendations are discussed under the following headings:[42]

Patient Information

Patient's demographic details, such as name, age and clinical diagnosis, state of the patient, medications, test number and other remarks, have to be entered.

Documentation during Recording

Prior to starting the recording, square wave calibration signals of 100 μV, of 1–2 sec duration in the referential derivation must be carried out to assess the integrity of the amplifiers and analog-to-digital (A-D) conversion. The technologist should be able to annotate comments, such as eye opening and closing, hyperventilation (HV), photic stimulation (PS), drowsiness, sleep, artifacts, etc., and there must be provision for entering free text.

Recording

Amplification and channel acquisition must be available for at least 24 channels and preferably 32 channels of recording EEG along with artifact channels. The sampling rate must be at least 200 samples and preferably more. The low-frequency filter (high-pass filter) should be set at 0.16 Hz or less for recording. The low frequency filter function can also be expressed as a time constant in seconds. The high-frequency filter is good at 70 Hz. The 50 Hz notch filter must be available to cut off external electrical disturbances, but should not be used routinely, as it distorts sharp waves. Proper earthing and positioning of equipment and checking impedances eliminate this artefact. Recording should be made on a referential montage. Digitisation with 12 bits will provide a dynamic range from 0.5 μV to ± 1023 μV. Electrode impedances must be below 5k ohms and preamplifier input impedances must be more than 100 mohms. Common mode rejection ratio must be at least 110 dB for each channel.

Display

Digital EEG equipment must be able to display the EEG with the same temporal and spatial resolution traditionally used for paper recordings. Remontaging with bipolar and referential montages should be possible. Digital low frequency (high pass) filters of 0.5, 1.0, 2.0 and 5.0 Hz and digital high-frequency (low pass) filters of 15, 35 and 70 Hz must be available. For the majority of EEG investigations, the recorded signal ranges 1–70 Hz. The screen display scaling should be set such that 1 sec occupies 30 mm with a minimum display resolution of 120 data points per second, per channel. Varying the time scale should also be available, e.g. 5, 15, 30 or 60 mm/s. For 60 mm/sec display, at least 200 data points per second should be presented for each channel. The standard inter channel separation is 10 mm. The standard video screen must have a minimum resolution of 4 pixels per vertical millimetre. For paper printouts at least 300 dots per inch (dpi) resolution are needed.

Electrode Nomenclature

When additional scalp sites are required, these must be placed between the traditional 10–20 electrode system sites and are named the 10% system or the extended 10–20 electrode system[4,32] (Figs 4A and 4B). In the coronal row, AF lies midway between rows Fp and F; FC between F and C; CP between C and P; PO between P and O and so on. Thus, CP1 will be between CPz and CP3; C5 will be between C3 and T3. Extra electrodes increase the yield of the EEG. Sphenoidal electrodes are particularly useful for detecting mediobasal temporal discharges and are inserted under the mandibular notch (approximately 2.5–3 cm anterior to the tragus) and directed posterosuperiorly towards the foramen ovale.[18,46] Anterior "cheek" electrodes (placed on the maxilla approximately 2 cm anterior to the site of entry of the sphenoidal electrode) and anterior temporal electrodes (placed 1 cm above one-third the distance from the external auditory meatus to the external canthus) are also useful for demonstrating epileptiform discharges (EDs) from the temporal lobe, and the yield appears comparable to that from sphenoidal electrodes.[36]

Montages to Be Used?

Montages are different connections and combinations of electrodes.

Bipolar Derivation

In this widely used method, rows of electrodes are connected to consecutive channels, such that an electrode is attached to lead 2 of 1 channel and lead 1 of the next channel (e.g. Fp2-F4 in channel one and F4-C4 in channel 2, F4 is connected to lead 2 of channel 1 and lead 1 of channel 2). This arrangement is good for seeing phase reversals.

Common Reference Derivation

Every electrode is connected to one input of the amplifiers (usually lead 1) and all the lead 2 inputs are joined together and connected to another electrode. The common reference electrode is thought to lack electrical activity, but this assumption is not true, because no area over the scalp can be totally inert. This can be made

out in the recording, as an active reference will have its potential appearing in many channels.

Common Average Reference Derivation

A common average reference should be used to circumvent the problem generated by an active reference. This uses the average of the electrical activity at all electrodes as reference against which individual activities are compared. The average reference will be near zero in its activity. No single method of derivation is ideal and each has its upside and downside. Unipolar derivations are good to view small potentials which get amplified due to the distance between the electrodes. CZ and PZ can be used as the average reference.

Sensitivity and Specificity of the Electroencephalography

The diagnostic sensitivity of a single awake EEG with PS and HV is about 50% in adults with epilepsy. This increases to 92% after four EEGs. A single awake plus sleep record will be positive in about 80%. The diagnostic specificity of the EEG depends on the proper interpretation of the EEG. Misinterpretation of normal variants, such as benign sporadic small spikes (BSSS), 14 and 6 positive spikes, wicket waves, 6 Hz phantom spikes as well as artifacts, can lead to a wrong diagnosis of epilepsy and unnecessary antiepileptic drug therapy. It is also important to understand that a normal EEG does not exclude epilepsy. The EEG may remain normal despite repeated EEG recordings in 5–10% of patients. Such patients usually have only simple partial seizures (sensory more than motor).

Reading the EEG should be unbiased, but interpretation of the EEG must always be done in the clinical context. To summarise, the interictal EEG cannot exclude epilepsy, and the amount of epileptiform activity does not provide a guide to seizure frequency or therapeutic response despite widespread belief to the contrary.

Role of Brain Mapping

Brain mapping is a frequently misused tool but, when judiciously used, can display electrical fields that can be understood more easily than the primary EEG. It cannot however replace careful analysis of the primary EEG data by the epileptologist. Every effort must be made to get an awake and sleep EEG. Patients should be asked to be sleep deprived too.

Activation Procedures

Hyperventilation

Forster,[21] in 1924, first demonstrated that hyperventilation (HV) may precipitate absence seizures in children and this method of activation has since become routine during EEG recordings. Although HV is particularly useful for demonstrating generalised EDs, it may also activate focal ED in up to 10% of patients with partial epilepsies.[40] The neuronal irritability during HV is considered to be due to brainstem mediated cerebral vasoconstriction induced by hypocapnia.

HV should be avoided in patients with potential for brain damage from further vasoconstriction, e.g. malignant hypertension, subarachnoid haemorrhage, sickle cell disease or trait and myocardial infarction.

Photic Stimulation

Photic stimulation (PS) is useful for activation of generalised EDs. Testing is generally done with stepwise increase of frequencies up to 30 Hz with a strobe light at a distance of 20–30 cm from the eyes. At low frequencies, PS is recommended with eyes open and then closed. At medium and higher frequencies, stimulation should start with the eyes open, and the patient is asked to close the eyes during PS, thereby continuing with PS for a few more seconds with the eyes remaining closed. Eye closure during PS is particularly useful for augmenting ED and should routinely be used. The ED outlasting PS strongly suggests generalised seizure disorder, whereas those confined to the train of PS may be an incidental finding in non-epileptic subjects, especially in the setting of drug withdrawal or toxic metabolic encephalopathy, or simply represent a genetic trait.[41]

PS is particularly useful in the diagnosis of primary generalised epilepsy and ED may occur during PS in up to 40% of these patients.[23] Recent evidence indicates that approximately a quarter to a third of EEGs with photic related ED also contain spontaneous focal or generalised ED elsewhere in the records.[24]

Sleep Deprivation

When the first EEG fails to show ED in patients with epilepsy, sleep deprived recording often helps. Several studies have convincingly documented that the chances of finding ED increase with sleep deprived recordings in both partial and generalised seizure patients of all ages.[16] The ED following sleep deprivation occur both in the awake and sleep portions of the EEG.

Clinical Significance of Interictal Epileptiform Discharges

Epileptiform Discharges in Non-Epileptic Subjects

Although the presence of interictal ED generally supports the diagnosis of seizure disorder, caution is necessary in interpreting the clinical significance as ED may occur in subjects without seizures. Among healthy adults without seizure history, the frequency of ED is approximately 0.5%.[45] Practically none of these healthy subjects subsequently develop seizures. "Incidental" ED occur slightly more often (approximately 2%) in subjects with a history of previous neurological insults such as trauma, stroke, craniotomy, infections, cerebral palsy or during migraine.[62] Up to 14% of these patients

subsequently develop seizures. In children without prior seizures, ED may occur in up to 5% and this may be as high as 8% if adequate sleep is recorded;[44] these tend to be benign Rolandic or occipital spikes or generalised 3 Hz spike-wave discharges and likely represent an incidental genetic trait. Risk of subsequent seizures in these children is around 6%.[11] Certain EEG patterns, however, almost always indicate associated clinical seizures and these include Hypp's arrhythmia and 1 or 2 Hz generalised slow spike-wave complexes.

Epileptiform Discharge in the First and Serial Electroencephalograms

First standard EEGs in patients with a reasonably certain diagnosis of seizure disorder contain ED in approximately 50%.[2] Yield from the first EEG in children with absence seizures, however, is higher, around 75%.[27] Apart from sleep, several other factors have been shown to increase the likelihood of ED and these include: (i) recording within 48 hours of a seizure and (ii) ongoing seizure frequency of at least one attack per month. The yield, however, is not significantly altered by neurological status, aetiology of seizures, age of the patient and antiepileptic drug therapy. Serial EEGs are often necessary for demonstrating ED. Most patients who eventually show ED do so by the fourth EEG. Recordings are persistently negative in only 8% of epileptics although there is evidence that a higher proportion of patients with partial seizures may have persistently negative serial EEGs.

The above observations suggest that:

- The ideal time for obtaining an EEG is the first day or two after a seizure;
- Long-term monitoring should be considered if four routine recordings have remained negative in patients with ongoing "seizures".

Ictal Video-Electroencephalography (Long-Term Monitoring)

While interictal ED generally provide support for the diagnosis of seizure disorder, electrographic or clinical seizures during EEG confirm seizures and suggest their localisation. Although the EEG remains the gold standard for confirming seizures, an actual attack or event is rare during a standard 20–30 minute recording. Even serial EEGs may fail to reveal ED in up to 10% of epileptics. When the nature of attacks or the exact seizure focus cannot be ascertained with several routine EEGs, video-electroencephalogram (VEEG) monitoring often provides necessary additional information. With current systems, EEG data may be collected continuously for several days or even weeks.

Indications for Video-Electroencephalography Monitoring

Diagnosis

- Identification of epileptic paroxysmal electrographic and/or behavioural abnormalities. These include epileptic seizures, overt and subclinical, and documentation of interictal ED and in the differential diagnosis between epileptic disorders and conditions associated with intermittent symptoms due to non-epileptic mechanisms (e.g. syncope, cardiac arrhythmias, transient ischaemic attacks, narcolepsy, other sleep disturbances, psychogenic seizures and other behavioural disorders).
- Verification of the epileptic nature of the new "spells" in a patient with previously documented and controlled seizures.

Classification/Characterisation

- Classification of clinical seizure type(s) in a patient with documented but poorly characterised epilepsy.
- Characterisation (lateralisation, localisation, distribution) of EEG abnormalities, both ictal and interictal, associated with seizure disorders. Characterisation of epileptiform EEG features, including both ictal discharges and interictal transients, is essential in the evaluation of patients with intractable epilepsy for presurgical evaluation.
- Characterisation of the relationship of seizures to specific precipitating circumstances or stimuli (e.g. nocturnal, reflex, catamenial, situation-related and activity-related). Verification and/or characterisation of temporal patterns of seizure occurrence, either spontaneous or with respect to therapeutic manipulations (e.g. drug regimens).
- Characterisation of the behavioural consequences of ED as measured by specific tasks.

Quantification

- Quantification of the number or frequency of seizures and/or interictal discharges and their relationship to naturally occurring events or cycles.
- Quantitative documentation of the EEG response (ictal and interictal) to a therapeutic intervention or modification (e.g. drug alteration).
- Monitoring objective EEG features are useful in patients with frequent seizures, particularly with absence and other seizures having indiscernible or minimal behavioural manifestations.[28]

Partial Seizures

Partial seizures, in scalp EEGs, are metamorphic, i.e. they show two or more distinct phases.[48] The most common patterns consist of a series of rhythmic waves, sequential spikes/sharp waves, a mixture of spikes and rhythmic waves or regional voltage attenuation. Most often the initial frequency of temporal lobe seizures is in the alpha or theta range with slower frequencies occurring in a lesser proportion. Extratemporal seizures, however, often start in the beta frequencies rather than slower frequencies. With scalp EEG, the frequency may diminish or augment, but as the seizure ends, rhythmic waves or sequential spikes change to a slow spike-wave pattern

that gradually decreases in frequency. Focal electrodecremental events are of excellent localising value, reflecting intense neuronal depolarisation or high-frequency firing. Following metamorphic seizures, there is often postictal delta slowing and suppression or activation of focal spikes. These postictal changes also have good localising value for seizure origin and should be carefully sought.[33]

It is important to recognise that simple partial seizures, especially those with sensory rather than motor symptoms, may not be associated with discernable changes in routine scalp EEG in up to 80% of patients.[17] However, the yield in these patients may be augmented by using additional closely spaced electrodes.[5]

Generalised Seizures

Typical absence seizures are characterised by isomorphic and stereotyped patterns that do not evolve as partial seizures. However, the spike-wave discharges may change from 3.5 or 4 Hz at the onset to 2 or 3 Hz as the seizure progresses. Also, the spike amplitude may decrease during the later part of the seizure. Atypical absence attacks frequently show gradual onset and offset with spike-wave discharges occurring at frequencies less than 3 Hz.

Generalised tonic-clonic seizures may be preceded by diffuse polyspike-wave complexes. Ictal recordings during the tonic phase typically show generalised attenuation with or without high-frequency rhythmic waves that gradually increase in voltage ("epileptic recruiting rhythm") and evolve into polyspikes. The clonic phase is characterised by paroxysmal spike activity mixed with slow waves and the postictal period shows generalised attenuation followed by gradual recovery of rhythms.[22]

Myoclonic seizures are associated with 10–15 Hz polyspikes with or without slow waves, whereas tonic seizures show generalised paroxysmal fast activity or diffuse voltage attenuation preceded or followed by sharp and slow wave complexes. Generalised atonic seizures may show 2–3 Hz spike-wave discharges or may not be associated with any scalp EEG change.

Can Electroencephalography Help in the Prognosis of Epilepsy?

Routine EEG is useful for prognostic purposes in at least the following three situations:

1. Assisting in epilepsy syndrome classification.
2. Predicting recurrence after the first seizure.
3. Providing information on seizure relapse after anticonvulsant withdrawal.

Classification of Epilepsy

The EEG provides important information for classification of various epileptic syndromes and thereby assists in predicting the natural history of the syndrome. For example, a child with normal neurological examination and Rolandic spikes in EEG has a high probability of "outgrowing" seizures and may not even need treatment following isolated, infrequent seizures. Similarly, generalised 4–6 Hz spike-wave and polyspike discharges in an adolescent with seizures suggest juvenile myoclonic epilepsy of Janz: a condition with a high-response rate to valproic acid.

First Seizure

Prediction of recurrence after a single seizure is clinically important and many studies have addressed this question. However, differences in methodology make comparison of these studies difficult and the results still remain somewhat controversial. A meta-analysis of sixteen published reports suggests that EEG abnormalities may increase the risk of recurrence after the first seizure.[8]

A recent large prospective study of children with single unprovoked seizure in those without obvious aetiology ("idiopathic"), showed that the presence of ED in the EEG was associated with a recurrence rate of 54% whereas the rate was only 25% when the first EEG was normal.[49] In the above study, the EEG was not of any predictive value in children with remote symptomatic seizures.

Several prospective studies suggest that the EEG is useful in adults with first seizure, especially among those with idiopathic seizures.[57] The Italian first seizure trial group (1993)[20] also showed a 1.7-fold increase in seizure recurrence when the EEG contained ED. Some controversy still exists in this area as some authors maintain that the EEG findings are of no predictive value after the first seizure.[31]

Anti-Epileptic Drug Withdrawal

The role of EEG in predicting relapses after anti-epileptic drug withdrawal remains more controversial. A recent meta-analysis discussing in depth about various factors in predicting relapses after anti-epileptic drug withdrawal indicates that any EEG abnormality (epileptiform activity or slowing) is associated with a relative relapse risk of 1.45.[7] Other factors found to increase the relapse rate in the above meta-analysis were adolescent or adult epilepsy onset (rather than childhood onset) and known remote aetiology.

Summary

After almost 80 years since Hans Berger showed the usefulness of EEG in man, this procedure still remains the "gold standard" for the diagnosis of seizures and epilepsy. The role of EEG has expanded in recent years and the test now plays an important role in predicting seizure recurrence among patients with newly diagnosed epilepsy and during anti-epileptic drug withdrawal. Rapid advances in technology have made digital equipment and continuous monitoring more widely available and at the same time providing better quality recordings than ever before.

ELECTROCORTICOGRAPHY

This is a technique of placing grids or strips directly on the brain for recording EEG activity to localise the epileptogenic focus during surgery for epilepsy. Electrocorticography (ECoG) along with cortical stimulation mapping was first described by Penfield in 1939. Using this procedure, they demonstrated that stimulation of the supplementary area resulted in simultaneous movements and tonic posturing of both proximal and distal muscles along with speech arrest.

The hypothesis for successful epilepsy surgery is based on the principle that removal of both lesional as well as the surrounding epileptogenic area is necessary for achieving seizure freedom.[37,38] Hence, it is important that both should be delineated before surgery. However, epileptogenic zones are often difficult to identify, because they may be found in and around the margin of, or remote from a lesion.[10] The scalp EEG is helpful but may not be precise enough to localise the epileptogenic area.[59] For greater precision either intra-operative or extra-operative subdural ECoG is often used to guide surgical resection of both the lesion and the epileptogenic zone. The area of interictal spiking or the irritative zone is often wider than the ictal onset zone (area where the seizure originates) which is considered as a gold standard for localising the epileptogenic zone.[38]

Intra-operative ECoG is widely utilised for electrical mapping of the epileptogenic zone during epilepsy surgery. It is useful to delineate the margins of the epileptogenic zone, guides the surgeon in achieving resection and is also of value to evaluate the completeness of resection. It has been found to be particularly useful in resective surgeries of neocortical foci (especially developmental lesions like cortical dysplasias) and for tailored resections in hippocampal sclerosis.[13,14,51] The ECoG can be a valuable tool during multiple subpial transections (MST).

The obvious advantages of intra-operative ECoG are: (i) they allow placement of recording and stimulation electrodes; (ii) recordings can be performed before and after each stage of resection to assess the completeness of surgery; (iii) it allows direct electrical stimulation of the brain so that the regions involved in functions may be spared by the resection (e.g. eloquent cortex); (iv) no risks associated with long-term placement, e.g. infection.

The major limitations of ECoG are: (i) the limited sampling time; (ii) spontaneous epileptiform activity consists exclusively of interictal spikes and sharp waves, and seizures are rarely recorded. Thus, in most of the cases, localisation of the ictal focus is based on a hypothesis that it corresponds to the interictal activity, which is yet to be proven; (iii) it is difficult to distinguish primary ED from secondarily propagated discharges arising at a distant epileptogenic site; (iv) both the background activity and the ED may be altered by the anaesthetics, narcotic analgesics and by the surgery itself. About 80–84% of epilepsy surgery centres around the world still perform ECoG in some or all of their patients with partial epilepsy.[19]

The ECoG in all cases should be performed under standard anaesthetic conditions with induction using isoflurane. After craniotomy and dural opening, anaesthesia must be maintained with nitrous oxide and intravenous narcotics with reduction (0.5% of isoflurane) of inhalational agents. Core body temperature should be maintained above 35.5°C. The low-frequency filter is set at 1 Hz, the high-frequency filter at 70 Hz, and sensitivity should be between 300 and 5,000 μV/mm depending on the amplitude of the background and discharges.[54-56]

ECoG score 1: Normal background of mixed gamma, beta and alpha frequencies of moderate to low amplitude (i.e. usually < 20–30 mV). A few low-amplitude spikes are observed.

ECoG score 2: Loss of fast (> 20 Hz) background frequencies, but otherwise a background of mixed alpha, beta and delta frequencies of low to moderate amplitude. Repeated but non-continuous, spikes, polyspikes or paroxysmal fast activity of medium amplitude are often observed.

ECoG score 3: Mostly 6–20 Hz background frequencies with some localised nearly continuous interictal epileptiform features of moderate amplitude or persistent repetitive spiking. Very rarely, electrographic seizures are captured.

ECoG score 4: Slow (< 6 Hz) background frequencies with continuous synchronous features of moderate to high amplitude. Multiple independent epileptiform abnormalities (polyspikes, paroxysmal fast activity and electrographic seizures) are recorded.

ECoG score 5: Slow, rhythmic, usually synchronous background (< 4 Hz), often of high amplitude. Continuous synchronised or independent high-amplitude epileptiform abnormalities in multiple cortical sites are observed.

An ECoG score of 2–5 is considered abnormal and these areas should always be included within the resective zone.

An ECoG score 1 is considered relevant depending on its relation to the lesion. For instance, if there is widespread activity consistent with ECoG score 1 activity, then "chasing the spikes" is avoided and the maximally abnormal area is resected. If this activity is more focal and amenable to surgical resection, then it is utilised to guide surgical resection. Surgery always includes wide resection, making sure that the subcortical white matter is also included in the resection. A post-resection ECoG should always be performed as, often, significant activity may be noted from the margins.

Potential Advantages of Electrocorticography

ECoG recordings are more magnified: The ECoG activity is similar to that recorded from the scalp EEG, consisting of isolated spikes, brief bursts of spikes or runs of sharp waves. However, they look more magnified as they are recorded directly from the surface of the brain. They are often multifocal with a wide distribution and have been commonly recorded from the temporal cortex. More

commonly, the ED were reported to have been recorded from the hippocampal structures and inferiomesial surfaces of the temporal tip. To a much lesser extent, they were recorded from the lateral temporal cortices and more so from the posterior temporal cortices.[51,52]

New information is often seen on ECoG: Devinsky et al.[18] found new ED on ECoG in 24% of temporal lobe epilepsy, which were not previously found by scalp EEGs even with the use of sphenoidal electrodes. On the other hand, Engel et al.[19] did not obtain any additional information from the ECoG compared to the pre-operative scalp EEG.

The interictal zone recorded on ECoG correlates with the 'ictal zone': The ECoG seldom records ictal events, but rather interictal epileptiform activity. The relationship between the epileptic zone (area of origin of the epileptic seizure) and the irritative zone (area of maximum interictal ED) is not completely understood. In particular, the degree to which the two zones overlap, especially on the ECoG recording is unclear. It has been hypothesised that the frequency of this activity is proportional to the proximity to the "epileptogenic area". Alarcon et al.[3] found that the removal of this area leads to a good surgical outcome, even if areas of less frequent discharges were left untouched. If the area of maximal discharging was not completely resected, the surgical outcome was more likely to be poor. An earlier study[55] had found no such association. However, it should be noted that the latter study has used visual analysis of the ECoG as compared to the former study which used a computerised spike detection program.

In our own study of 165 patients,[56] 73% of the patients who have a good clinical outcome showed improved ECoG scores in 90%. The ECoG seemed to correlate better in temporal lesions with regard to clinical outcome (95%). It should, however, be noted that most of the patients in the present series were lesional epilepsies.

Electrical stimulation of the cortex further increases localisation: Electrical stimulation of the cortex at the time of ECoG is useful for further localisation of the epiletogenic zone.[26] The area of brain producing an aura on electrical cortical simulation has been reported to have strong correlation with the epileptic zone. This was, particularly the case when the area from which the responses matched closely with the area exhibiting the greatest ED, seen on ECoG.[9,60] However, this hypothesis was not agreed upon in a study,[26] where they proposed that the clinical symptomatology may not be related to this area of stimuli, but reflects a distant area to which the discharge has spread.

Post-resection ECoG abnormality may have a correlation to outcome: Bengzon et al.[6] noted a significant difference in the surgical outcome between patients with residual spikes compared to spike-free post-resection recordings. Around 36% of patients who were seizure-free post-surgery had residual spikes; whereas 75% of patients who were not seizure-free had residual spikes on post-resection ECoG. These findings were similar to those reported by others.[15,39,54]

Concluding, ECoG, though being widely used in epilepsy surgery, there is controversy regarding its efficacy and utility. This is particularly so as there are no prospective randomised studies. Despite its limitations, it remains a necessary tool in epilepsy surgery. In our study,[56] of a total of 73% (116/157) who had a good outcome following resective surgeries, 90% showed electrical improvement in post-resection ECoG.

CONCLUSION

Electrodiagnostic studies, both intra-operative and pre-operative, have become an integral part of the diagnostic armamentarium for both neurosurgeons and neurologists. Thus, it becomes important for every neurosurgeon in training to be familiar with their principles, techniques and interpretations.

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4 Intracranial Pressure

Ravi Ramamurthi, Nigel Peter Symss

HISTORY

The mechanics of intracranial pressure (ICP) has intensively been studied over the last 100 years or so. Quincke, in 1891, first reported the measurement of ICP through the lumbar route. Later studies by Quickenstedt, Ayala and Ayer established the range of normal ICP and demonstrated the effect of changes in position and respiration, especially the Valsalva manoeuvre. Quickenstedt also described the discrepancy between cranial and spinal pressures in the presence of a spinal block, with higher pressures being recorded above a spinal block. In 1951, Guillaume and Janny carried out the first continuous recordings of ICP on a strip chart recorder. Lundberg,[42] in 1960, published his classic monograph on the continuous recording of ICP using an indwelling intraventricular catheter in a large series of 130 neurosurgical patients (Fig. 1). He described three waveforms and sought to correlate the clinical features with changes in the pressure wave pattern. His work established the usefulness of ICP monitoring in clinical neurosurgery. However, it was not before the 1970s that ICP monitoring came to be routinely used in clinical neurosurgery. It is presently accepted as an important basic technique in the management of patients with a variety of intracranial diseases.

ANATOMY AND PHYSIOLOGY

The cranium can be likened to a rigid sphere. The three main components of this sphere are brain, blood and cerebrospinal fluid (CSF) occupying 1400 ml, 75 ml and 75 ml of space, respectively.[59] The contents of the intracranial space are bound by the dura and communicate with the spinal canal through the foramen magnum. Since the thick bones of the calvarium are essentially

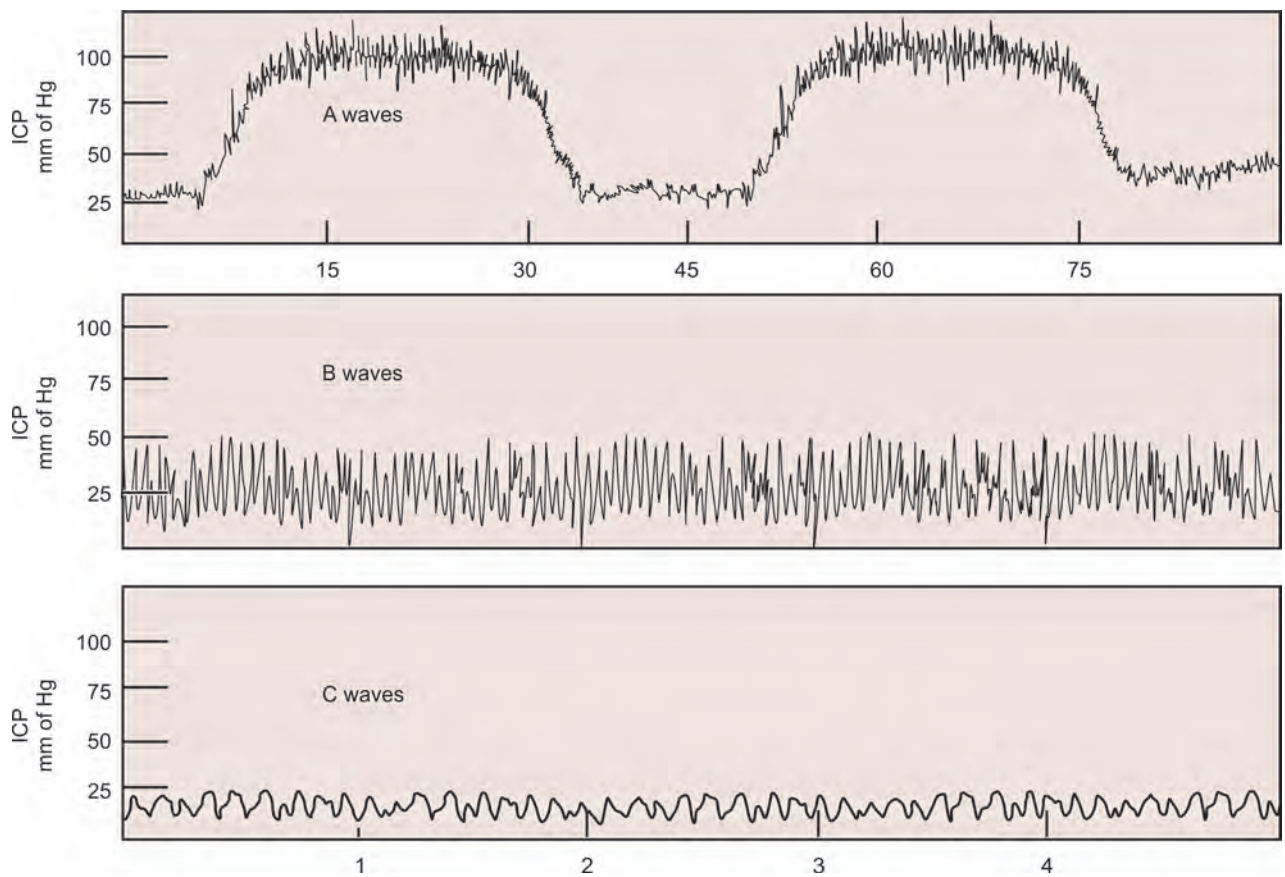

Fig. 1: Lundberg's CSF pressure waves

non-distensible, the volume of the intracranial space is virtually constant regardless of the pressure generated within it. Therefore, any change in the volume of the brain causes a reciprocal change in the volume of other intracranial components, i.e. either blood or CSF. This is the basis of the modified Monro-Kellie doctrine introduced into neurosurgery by Cushing. However, the Monro-Kellie doctrine does not hold true in infants because the skull is not rigid.

The normal ICP is pulsatile due to the respiratory and cardiac cycle. The cardiac pulsations are reflected in the ICP through pulsations of the choroid plexus, and the cerebral and spinal arteries. The variations in venous return and cardiac output with respiratory excursions possibly account for changes in the ICP with the respiratory cycle. The normal CSF pressure measured through the lumbar route ranges from 50 to 200 mm of H_2O in the lateral decubitus position. The amplitude of the pressure wave can be as much as 5 cm of H_2O due to the combined effect of the cardiac and respiratory cycles.[2,10] As the ICP increases, the pulse pressure generally increases. A transient increase in lumbar CSF pressure occurs on shifting from the lateral to the sitting position. This is due to an auto-regulatory dilatation of the cerebral blood vessels in response to a transient drop in cerebral arterial blood pressure on assuming the sitting position. Once the cerebral arterial blood pressure returns to normal, the resistance vessels constrict leading to a decrease in the cerebral blood volume and the lumbar CSF pressure.[43] In patients with raised ICP, this transient rise in CSF pressure can be prolonged.

In addition to the pulsatile character of the ICP wave, rhythmic oscillations in the pressure also occur. Lundberg[42] described three pressure waves namely: A waves; B waves and C waves (Fig. 2).

A waves are pathological and develop over a background of raised ICP. There is a rapid rise in ICP up to 50–100 mmHg followed by a variable period during which the ICP remains elevated followed by a rapid fall to the baseline. The A waves that persist for longer periods (usually 5–20 minutes) are called plateau waves. A study of patients with raised ICP due to various pathological causes suggested that plateau waves are closely associated with disturbances of CSF circulation or absorption.[24] Smaller A waves termed "atypical" or "truncated" A waves,[31,80] that often do not exceed an elevation of 50 mmHg, are also clinically important early indicators of neurological deterioration. The A waves are accompanied by clinical features of raised ICP, e.g. headache, vomiting, decerebrate posturing, pupillary changes, bradycardia and hypertension, and respond to CSF drainage, hyperventilation and osmotic diuretics.

B waves occur at the rate of 0.2–2 per minute and are related to respiration. From the studies of patients being monitored by transcranial Doppler and ICP, it appears that B waves may be vasomotor in origin.[56] Lundberg[42] initially described them in patients with intracranial hypertension, though they can also occur in normal individuals. B waves are said to be one of the best predictors of outcome after surgery for normal pressure hydrocephalus. Raftopoulos et al. suggested that the presence of B waves may have positive prognostic value in deciding if a patient being evaluated for occult hydrocephalus would benefit from a CSF diversion.[63]

Stephensen et al. analysed the relationship between the percentage of B waves and their diurnal variations and outcome in patients with hydrocephalus. They found no linear correlation between improvement after surgery in 55 patients and the total percentage B waves, but a correlation was found between improvement and percentage of B waves during sleep ($r = 0.39$, $p = 0.04$). The percentage of B waves was the same during sleep and wakefulness, and patients with NPH had the same proportion of B waves as the non-communicating patients. They concluded that B waves are commonly observed in patients with both communicating and non-communicating hydrocephalus, but are only weakly related to the degree of post-surgical improvement.[71]

C waves are of low amplitude with a frequency of 4–8 per minute. These waves are thought to be related

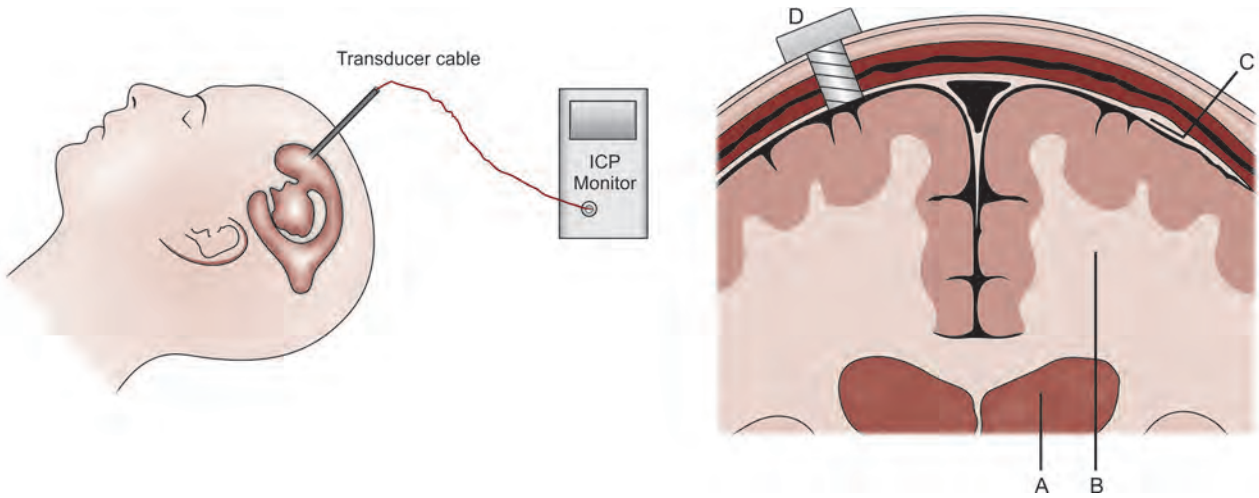

Fig. 2: Diagrammatic representation of ICP monitoring. Figure showing various methods of monitoring the ICP. (A) Intraventricular catheters. (B) Intra-parenchymal catheters. (C) Epidural catheters. (D) Subarachnoid bolt

to Traube-Hering-Mayer waves. These waves are of little clinical significance. Increased ICP is indicated by a sustained elevation in pressure above 15 mmHg or when intermittent A or B waves are recorded.

VOLUME-PRESSURE RELATIONSHIP

The cranium being rigid and non-distensible, any increase in the volume of a component would be accompanied by a reciprocal decrease in the volume of the other two components. Once the volume buffering capacity is exhausted, the ICP would begin to rise. During gradual expansion of a mass lesion, the volume displaced may be CSF, intravascular blood or brain tissue water. Of the three components, CSF appears to be the main buffer and is the first to be displaced as evidenced by compressed ventricles and obliterated subarachnoid spaces. Reduction in cerebral blood volume may occur, but is accompanied by serious sequelae. Longstanding compression of the brain can produce atrophy and loss of volume, as seen in large meningiomas, but changes in solid brain contents are very small in terms of total volume.

The rate of expansion of an intracranial mass is also important. A rapidly growing intracranial mass lesion may outpace the compensatory shift of CSF and then even the smallest increase in mass could produce a life-threatening increase in ICP. Foldes and Arrowood[15] infused the spinal subarachnoid space with saline and found that pressure remained constant at elevated levels during continuous infusion, indicating that at higher pressures, fluid infusion was being matched by fluid egress from the subarachnoid space. Their observations suggest that as much as 1 ml of CSF per minute, or 60 ml per hour, can be expressed out of the intradural space in the presence of elevated ICP. Thus, a large haematoma could be accommodated within a few hours without a dangerous rise in ICP. Langfitt et al.[38] studied the volume-pressure relationship in the rhesus monkey (Fig. 3). The ICP was measured by means of subarachnoid catheters during controlled gradual expansion of an extradural balloon. As the balloon was expanded at a rate of approximately 1 ml per hour, there was no increase in ICP during infusion of the first few millilitres of water (horizontal limb of the curve). With further expansion of the balloon, the ICP began to rise and at a volume of approximately 6 ml in the monkey, it began to rise very rapidly (vertical limb of the curve). The flat portion of the curve was termed the period of spatial compensation, and the vertical portion was called the period of spatial decompensation. In other words, in the presence of an expanding intracranial mass lesion, a rapid rise in the ICP would occur once the amount of displaceable volume within the intracranial space has been reduced to the point that any additional volume added to the cranium exceeds the volume of fluid displaced. The curve may shift to the left if the intracranial mass expands very rapidly or if there is a pre-existing pathology in the brain reducing the amount of displaceable volume. The classical pressure-volume curve is exponential. In a semi-logarithmic co-ordinate system, the curve would be linear.

Various mathematical models have been described to define the volume-pressure relationship (Fig. 4). Compliance is defined as change in volume per unit change in pressure (dV/dP). It is a measure of the distensibility of the intracranial space. The higher the compliance, the larger is the extra volume that the cranium can accommodate without a precipitous rise in pressure. Elastance is inversely related to compliance (dP/dV). It is a measure of the resistance offered to an expanding intracranial mass.[41] The slope of the volume-pressure curve is the elastance. In the horizontal limb of the volume-pressure curve, compliance is high and the elastance is low while in the vertical limb, compliance is low and the elastance is high. Volume-pressure response (VPR) is the change in ICP on injection or withdrawal of 1 ml of fluid from the ventricle in 1 second.[49] The normal VPR is 2 mmHg/ml. This response is a measure of the elastance and increases in parallel with the ICP in experimental animals and in human patients with intracranial disorders.[48] It is not certain if measurement of brain elasticity would provide useful clinical information pertinent to the management

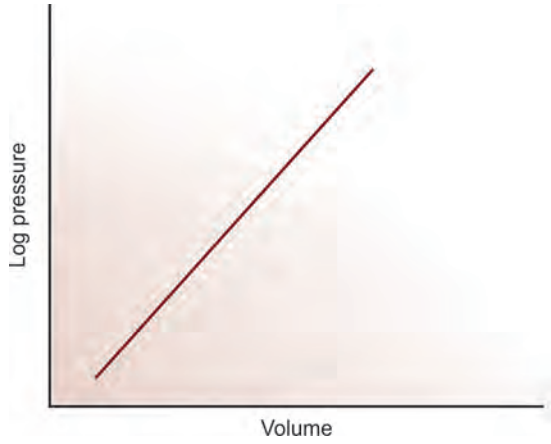

Fig. 3: The lineal relationship between the volume and the pressure semi-logrithmic co-ordinate systems

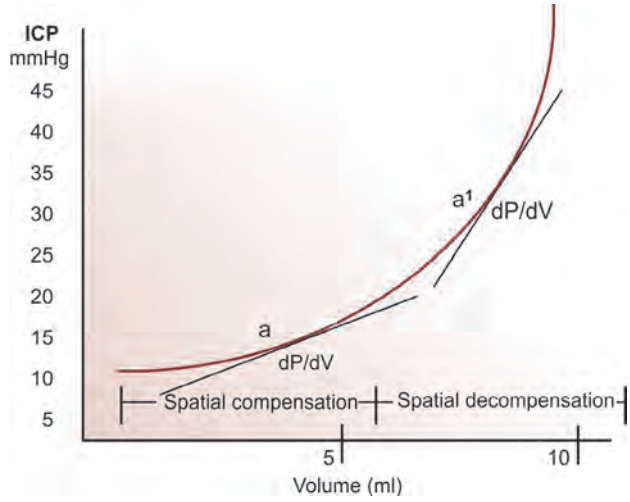

Fig. 4: Intracranial volume-pressure relationship. Note that the elastance at point 'a¹' is more than at point 'a'

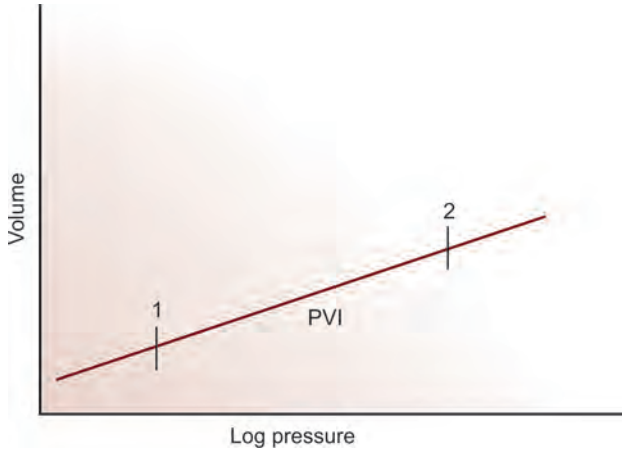

Fig. 5: The pressure-volume index is the slope of the curve between log pressure (abscissa) and volume (ordinate) between points 1 and 2

of critically ill neurosurgical patients, as such measurement provides information about only a small part of the pressure-volume curve, and gives no indication of the remaining compensatory capacity.[70] The pressure-volume index (PVI) is the volume in millilitres that is necessary to raise the ICP to a level 10 times the opening pressure.[45] The slope of the curve drawn between log ICP (abscissa) and volume (ordinate) is the PVI (Fig. 5).[33] As originally described, the test could potentially be dangerous for use in humans and a series of variations of the PVI have been described by various authors. Tans and Poottvliet[72,73] studied PVI in a heterogeneous group of 40 neurosurgical patients and concluded that measurement of the PVI is useful only in patients with normal or minimally elevated ventricular fluid pressures who do not exhibit A waves or runs of B waves. Patients with abnormal waveforms can be assumed to have abnormal pressure-volume indices. They further concluded that a PVI of less than 10 always required measures to reduce the ICP. Wilkinson et al.[78] described the ICP reserve test. A maximum of five 1 ml aliquots of fluid are injected into the subdural space over 5 minutes. The fluid aliquots are infused rapidly at 60-second intervals, with the pressure response defined as the mean ICP 60 seconds following each bolus injection. This test attempts to quantify the overall capacity of the brain to adapt to increased intracranial mass ("reserve") more than simply to determine the elastance of the brain. Guertin et al.[22] reported that abnormalities of the ventricular reserve test were as accurate as the baseline mean ICP elevation in identifying patients at risk of subsequently developing severe intracranial hypertension. Furthermore, when both observations were abnormal, they observed an 80% risk of the patient developing severe intracranial hypertension within 4 hours. Robertson et al.[66] have described a computerised frequency analysis of the ICP waveform. Any change in the shape of the waveform would indicate changes in the compliance of the brain. According to the authors, this method is a safe substitute for the fluid injection techniques to measure the PVI.

PATHOLOGY OF INCREASED INTRACRANIAL PRESSURE

Intracranial hypertension can lead to secondary changes by interfering with the cerebral blood flow (CBF) and by producing brain herniation and pressure on critical structures. Transtentorial herniation with brainstem compression can lead to clinical deterioration even when the blood flow through the cerebral hemispheres is still adequate for tissue oxygenation. A critically located temporal lobe mass may produce uncal herniation and compression of the brainstem without a rise in ICP sufficient to reduce blood flow in the cerebral hemispheres. Similarly, a frontal mass can cause sufficient axial distortion to impair perfusion of brainstem structures.

The average normal CBF is 50 ml/100 g/min. The CBF is influenced by a host of factors like arterial pressure, ICP, arterial blood gases and metabolic demands of the brain. A complex interaction between these variables determines the CBF. Ischaemic changes can develop when the CBF drops to 20 ml/100 g/min. The ICP influences the CBF through changes in the cerebral perfusion pressure (CPP). The CPP is defined as the difference between mean arterial pressure (MAP) and ICP, i.e. CPP = MAP – ICP. A rise in ICP would lead to a fall in CPP unless buffered by a rise in MAP. In a patient with intracranial hypertension, it is important to complement decongestive measures with maintenance of adequate MAP so as to continuously obtain a CPP of 50 mmHg or more. ICP and CPP monitoring are important in the management of head injury patients. However, there are other brain-related measures defined as 'pressures', such as cerebral intra-tissue pressure, critical closing pressure, 'optimal' CPP, non-invasive CPP (nCPP) and non-invasive ICP (nICP), and interhemispherical pressure gradients, which currently draw more attention in the management of head injured patients. Czosnyka et al. found that "Optimisation" of CPP provides a rational compromise between the "Critical Closing Pressure-oriented protocol" and the "Lund concept", thereby allowing individualised tailoring of cerebral haemodynamics. The nICP and nCPP are practical alternatives for invasive monitoring, especially in the early stages of trauma management, and CCP and pressure gradients are prognostic tools.[9]

Raised ICP can cause arterial hypertension (the Cushing response), bradycardia and respiratory changes. There are still a number of uncertainties about the origin of the Cushing response. Traditionally, it has been attributed to an increase in systemic vascular resistance produced by either ischaemia of or pressure on the brainstem. Hoff and Reis[28,29] postulated that ischaemia of the cerebral hemispheres could also elicit the Cushing response. According to them, cerebral ischaemia secondary to intracranial hypertension results in removal of supratentorial inhibition of brainstem vasopressor

centres, resulting in the release of sympathomimetic factors, which in turn cause peripheral vasoconstriction. Increased cardiac output may also be a factor responsible for intracranial hypertension.[19] Severe bradycardia may be the principal alteration in vital signs in patients with acutely expanding lesions such as an extradural haematoma.* The bradycardia produced by intracranial hypertension in experimental animals is unaffected by denervation of the carotid sinuses, is abolished by section of the vagi and is independent of the rise in blood pressure.[11] The occurrence of respiratory irregularities is due to release of the respiratory centres in the medulla as a result of damage to the supramedullary mechanisms. The changes in respiratory pattern depend upon the level of involvement of the brainstem. Damage to the midbrain is associated with Cheyne-Stokes or, rarely, normal respiration. As the pressure head increases to affect the midbrain and upper pons, the patient develops sustained hyperventilation. When the level of dysfunction reaches the upper medulla, breathing becomes more rapid and shallow, and in the final stages of medullary involvement breathing becomes ataxic.[47] The changes that occur in experimental animals in response to an expanding supratentorial mass are a decrease in respiratory rate, bradycardia, cardiac arrhythmias, pupillary constriction followed by unilateral dilatation, increase in pulse pressure and finally an increase in arterial blood pressure.[26] Neurogenic pulmonary oedema is a rare but serious complication of raised ICP. It seems to be mediated by the effects of intracranial hypertension on the hypothalamus, medulla or cervical spinal cord with a resultant increase in sympathetic activity with beta and alpha adrenergic discharge.[4,37,44] The former leads principally to increased cardiac output and decreased systemic hypertension, and plays little role in the production of neurogenic pulmonary oedema. On the other hand, alpha receptor stimulation leads to systemic and pulmonary arterial constriction with an increase in the pressure gradient across the alveolar membrane.

Brain injury biomarkers may have clinical uses in classifying injury severity level, predicting adverse secondary events and monitoring the effectiveness of therapeutic measures. Hergenroeder et al. analysed pooled serum samples obtained from severely injured traumatic brain injury (TBI) patients [Glasgow Coma Scale (GCS) ≤ 8] and age, sex and race-matched volunteers. Samples were immunodepleted for 12 highly abundant serum proteins, and then labelled with mass-balanced isobaric tags (iTRAQ), and analysed by liquid chromatography-tandem mass spectrometry (LC-MS/MS). Their study revealed 31 biomarkers whose serum abundance was altered after head injury. Changes in three candidate biomarkers [serum amyloid A, (SAA), C-reactive protein (CRP) and retinol binding protein 4 (RBP4)] were verified using independent TBI and healthy volunteer serum samples. Receiver operating characteristic (ROC) curve analysis of CRP and SAA indicated they were potent indicators of injury even at very acute time points. Analysis of serum RBP4 levels at 24–36 hours post-injury may predict subsequent increases in ICP with a sensitivity of 86% and specificity of 88% at 11.6 mμg/mL (n = 7, ICP <20 mmHg; n = 8, ICP >25 mmHg). Their results support the use of serum as a source for identifying TBI biomarkers, and indicate that these biomarkers may have uses for predicting secondary pathologies such as elevated ICP associated with TBI.[27]

*It may be mentioned that in clinical practise severe bradycardia is infrequently observed in patients with rapidly increasing ICP.

INTRACRANIAL PRESSURE MONITORING

Intracranial hypertension commonly precedes clinical deterioration.[77] ICP monitoring can forewarn the clinician of impending deterioration and remedial action can be taken before severe or irreversible brain damage can take place. In neurosurgical patients who are paralysed for elective ventilation, it is a reliable method of assessing the neurological status (see Fig. 2). Continuous ICP monitoring, where indicated, helps to optimise brain protection. ICP monitoring has extensively been used in patients with head injury. It is most useful in neurologically stable (GCS 9 or more) patients with a traumatic intracranial haematoma, in whom the decision to surgically evacuate the haematoma is equivocal. A patient with persistently high ICP or a progressively rising ICP not responding to decongestants would merit surgical intervention. According to Galbraith and Teasdale,[18] patients with an ICP of more than 30 mmHg often require surgery. ICP monitoring is also indicated in patients undergoing elective ventilation for traumatic brain swelling. Today, ICP monitoring is only a part of CNS monitoring. CBF studies, continuous transcranial Doppler studies and jugular arteriovenous oxygen difference help to give a better understanding of cerebral perfusion and brain metabolism in TBI.[3]

Lobato et al. studied the incidence of pathological and ICP changes during the acute post-traumatic period in patients with severe head injuries. The aim was to define the most appropriate strategy of serial CT scanning and ICP monitoring for detecting new intracranial mass effect and improving the final outcome. Considering the high incidence of ICP and CT deterioration through the clinical course, along with the absence of strong predictors and the discordances between CT and ICP changes (which were seen in 30.3% of their cases), they recommended ICP monitoring after admission in all patients and serial CT scanning at 2–4, 12, 24, 48 and 72 hours after injury with additional controls as indicated by clinical or ICP changes in all cases.[65] The current Brain Trauma Foundation recommendation of ICP monitoring in those patients presenting with a GCS score <8 with an abnormal CT scan or a normal CT scan with age >40 years, systolic blood pressure <90 mmHg or exhibiting posturing should be followed.[51]

Some neurosurgical centres monitor ICP in patients with aneurysmal subarachnoid haemorrhage (SAH).[1]

A rise in ICP may indicate aneurysmal re-bleed, while neurological deterioration without initial increase in ICP or even an initial reduction in pressure, should alert the neurosurgeon to the likelihood of development of vasospasm rather than an intracranial mass lesion.[75] Continuous ICP monitoring in patients with suspected arrested hydrocephalus and normal pressure hydrocephalus can help to choose patients who may benefit from a CSF diversionary procedure. The detection of transient periods of intracranial hypertension or pathological pressure waves suggests the presence of symptomatic hydrocephalus and a greater likelihood of a successful outcome.[7,20,23]

Torbey et al. reported on the uses of continuous pressure CSF monitoring in establishing the diagnosis of idiopathic intracranial hypertension without papilloedema (IIHWOP) in patients with chronic daily headache (CDH). Pcsf was measured via a lumbar catheter and analysed for mean, peak, highest pulse amplitude and abnormal waveforms. A 1–2 day trial of continuous controlled CSF drainage (10 cc/h) followed Pcsf monitoring. Response to CSF drainage was defined as improvement in headache symptoms. Patients with abnormal waveforms underwent a ventriculoperitoneal shunt (VPS) or lumboperitoneal shunt (LPS) insertion. All patients had normal resting Pcsf (8 ± 1 mmHg) defined as ICP <15 mmHg. During sleep, all patients had B waves and 90% had plateau waves or near plateau waves. All reported improvement of their headache after surgery. Demonstration of pathological Pcsf patterns by continuous Pcsf monitoring was necessary to confirm the diagnosis of IIHWOP, and provided objective evidence to support the decision for shunt surgery. They concluded increased Pcsf was seen mostly during sleep and was intermittent, suggesting that Pcsf elevation may be missed by a single spot-check LP measurement.[74]

Neurosurgical patients who are paralysed and are being electively ventilated in the post-operative period should undergo ICP monitoring. Even in patients who are not being artificially ventilated, post-operative ICP monitoring can be beneficial if the haemostasis was difficult or the brain was not lax at the end of surgery. Constantini et al.[5] in a heterogeneous group of 514 neurosurgical patients reported an average time gap of 5 hours between a rise in the ICP and subsequent clinical deterioration in the post-operative period. In certain non-neurosurgical conditions, like Reye's syndrome and fulminant hepatic failure, ICP monitoring and control can be beneficial. ICP monitoring can also provide an additional objective measurement in assessing brain death.[77] The ICP drops and the waveform dampen. Contraindications to ICP monitoring include widespread scalp infection, any intracranial infection, open compound injury and bleeding diatheses.

Monitoring systems can be divided into fluid coupled and non-fluid coupled systems.[34] The former involves a fluid-filled catheter or a hollow bolt placed in the ventricle, subarachnoid space or the subdural space, connected to a pressure transducer through a fluid-filled line. The transducer converts the hydraulic pressure into an electrical signal which can be displayed digitally or on an oscilloscope. In the non-fluid filled systems, the transducer is mounted on the monitoring device itself. The monitoring devices have variously been designed for use in the ventricle, brain parenchyma, subdural and epidural space. Wheatstone bridge, inductive and capacitate-coupled oscillating circuits and optical transducers have been used. Optical transducers sense changes in the amount of light reflected off a pressure-sensitive diaphragm located at the tip of the catheter. The mean pressure is then displayed digitally. This design has the advantage of being solid state and can be used in the ventricle, parenchyma or in the subdural space. It compares favourably with the fluid-filled ventriculostomy catheter in terms of the pressure recordings; however, it cannot be recalibrated once inserted and needs to be changed every 5 days because the zero drift increases significantly after this period.[8] The cost of this system is high.

The telemetric system consists of an implanted transducer which is telemetered through the intact scalp. This system should particularly be useful for long-term ambulatory monitoring.[21]

Long-term monitoring of ICP is limited due to the lack of an implantable sensor with low drift. Kroin et al.[35] demonstrated a new capacitative transducer system which will produce accurate and stable ICP records over extended periods. The mean ICP and cisterna magna (CM) pressure were compared for months to demonstrate that the transducer system produced minimal drift over time. The change in the ICP sensor record closely duplicated that of the CSF waveform in the CM in response to well-known physiological stimuli. Mean ICP remained within 3 mmHg of CM pressure for months, with a mean difference of less than 0.3 mm Hg. Histological examination of the dog brains revealed only minimal tissue reaction to the presence of the sensor. They advocated the clinical use of this sensor and its telemetry for long-term monitoring of patients with head injury, mass lesions and hydrocephalus.[35] Advancements are being made for developing sensor systems based on microtechnologies and nanotechnologies which allow continuous monitoring and control of therapeutic procedures using wireless pressure monitoring systems.[17]

Efforts have been made at non-invasive monitoring. Totally nICP monitoring would avoid many of the risks of monitoring. Heifetz and Weiss[25] have used modified skull tongs with sensitive strain gauges to measure the ICP by detection of minute skull expansions. They have been able to demonstrate changes in skull expansion that correlate with the results of jugular compression or intraventricular fluid administration. Several devices have been described for measuring ICP through the open fontanelle of infants.[61] However, variable artifacts can be produced by the interposed tissues, depending on the pressure used to apply the sensing device to the

scalp.[30] Newer design modifications have been claimed to have overcome this problem.[69]

The ICP is normally transmitted to the perilymph of the cochlea via the cochlear aqueduct. Tympanic membrane displacement, due to changes in perilymphatic pressure, has been found to correlate with changes in the ICP. This technique is not suitable, if the cochlear aqueduct is not patent or the stapedial reflex is absent. In a clinical study, the tympanic membrane displacement measurement technique was reported to be useful in young patients with hydrocephalus and idiopathic intracranial hypertension.[65] It may prove to be a useful tool in the assessment of acute and chronic shunt malfunction in children.[54]

Although the ICP can be monitored from the ventricle, brain parenchyma, subarachnoid space, subdural space, epidural space and the operative cavity itself, it is important to realise that the pressure is not equal throughout the intracranial space. It is unclear if acute changes in the posterior fossa would be reflected in supratentorial monitoring as surgery, brain shifts and occlusion of the basal cisterns may radically alter the equilibration of the two compartmental pressures and the compliance of the supratentorial and infratentorial compartments may differ.[67] Similarly, the type of pathology producing intracranial hypertension can also influence the distribution of pressure in the cranium.[40] Pressures that involve CSF dynamics are more likely to alter the intraventricular pressure, compared to rapidly forming masses that tend to increase tissue pressure near the mass more than the intraventricular pressure.[50]

Eide described a new method for processing of continuous ICP signals. The amplitude and latency values of the accepted single ICP waves were determined. For accepted 6 second time windows, the mean ICP wave was computed as mean ICP wave amplitude and mean ICP wave latency. The mean ICP wave parameters provide information about the single ICP waves that is not given by mean ICP. Their method has been implemented in software to be used during online ICP monitoring, revealing mean ICP wave amplitude, mean ICP wave latency and mean ICP as numerical values every 6 seconds. The clinical significance of their method was illustrated in four patients by observations that mean wave amplitudes corresponded better to the acute clinical state than the mean ICP; mean wave amplitudes could be elevated despite a normal mean ICP. They suggested that the mean ICP wave parameters are related to ICP-volume compensatory reserve capacity (compliance).[12]

Eide also simultaneously compared continuous ICP signals from two different sensors: Codman ICP MicroSensor; Johnson and Johnson, and Camino OLM ICP; Camino Laboratories, San Diego. They were placed within the brain parenchyma in three patients as part of the management of severe SAH. For each 6 second time window mean ICP was computed, showing large differences in mean ICP values between the signals. Differences above 5 mmHg were observed in 13% of the 128,425 time windows derived from 24 hours ICP recordings in these three patients. Comparisons of 675,503 individual single pressure wave pairs of these 128,425 time windows revealed marginal differences in single wave amplitude (dP, i.e. pulse pressure) and latency (dT, i.e. rise time) values, suggesting that differences in mean ICP were caused by differences in baseline pressure. He concluded that changes in baseline pressure affect mean ICP but not single pressure wave characteristics such as amplitude (dP) and (dT) latency values.[13]

Epidural Monitoring

This is performed by placing the device in the epidural space via a burr hole. These are simple to insert with a low infection rate. It is relatively safe in conditions, like fulminant hepatic failure, where haemostatic abnormalities may coexist and insertion of a parenchymal or ventricular device could be dangerous.[32] However, in this system, there is no provision for CSF drainage and epidural pressures tend to be inaccurate. In a study carried out in a canine model, Sahay et al.[68] found that during continuous intraventricular fluid infusion, the ventricular pressure (VP) initially rises followed by a fall (the latent phase) and again begins to rise (the monotonic phase). The latent phase is not reflected in the extradural pressure (EDP), which remains constant during this phase and begins to rise during the monotonic phase, but remains consistently less than the VP. Some studies in the 1970s have reported that EDP is often lower than that recorded from subdural or intraventricular sites.[6,64] On the other hand, there have also been reports of higher recordings from the epidural sites as compared to the intraventricular pressure.[39] The inelasticity of the dura may be responsible for this discrepancy. More recently, epidural pressures have been reported to be systematically higher than ventricular fluid pressures. This has been attributed to the characteristics of the sensor and to the anatomy of the epidural space. Poca et al. studied these two causes and better explained higher epidural readings. They compared pressure values obtained during simultaneous epidural and lumbar pressure monitoring in 53 patients and during simultaneous subdural and lumbar pressure monitoring in 22 patients. The same non-fluid coupled sensor device was used in all compartments. Their conclusion with epidural ICP monitoring produces artifactually high values not related to the type of sensor used, but to the specific characteristics of the epidural intracranial space.[62]

A permanently implanted epidural sensor permitting long-term telemetric ICP monitoring, consisting only of an inductance and a pressure-sensitive capacitance, has been implanted in 127 patients by Güçer et al. Of these 127 patients, 13 continued to have the sensor in place for 4–9 years. The remaining patients were lost to follow-up or the sensor was removed. The sensor has been evaluated on the basis of accuracy, longevity, safety and

stability. Longevity was proven by successful monitoring over periods of years (in one patient, at least 9 years). They found the sensor to be a safe tool; the only morbidity has been two asymptomatic peri-sensor blood clots in two patients. There have been no infections in any of the 127 cases. The stability of the sensor was evaluated by measuring baseline drift over time. This rate was 1.0 +/- 0.2 mm H_2O/day.[21]

Subarachnoid and Subdural Devices

The subarachnoid and subdural devices are similar. The most commonly used devices for fluid coupled subdural pressure monitoring are the hollow screw or bolt devices, the "subdural cap catheter" and simple catheters placed in the subdural space. The first subdural subarachnoid device was introduced by Vries et al.[76] in 1973, and is also called the Richmond screw. This is a hollow self-tapping screw that is inserted into the skull through a 1/4 twist drill hole after the dura has been incised. The screw is inserted until it protrudes just under the dura in the subarachnoid space but not in contact with the brain. The screw is easy to insert and has an infection rate of about 2% after an average 5 days monitoring.[79] This device can be difficult to insert in very young infants and CSF drainage is possible only occasionally. It has a higher rate of osteomyelitis at the twist drill site (I) and may underestimate the ICP at higher levels as brain tissue may herniate into the device and dampen the waveforms.[57] The failure rate is about 8% over a 5-day period of monitoring.[79] Occasionally, CSF leakage from the twist drill site may develop after removal of the bolt.

The cup catheter is a ribbon-shaped device with a larger and shallower opening on its face for pressure transmission. The design seems to offer a smaller chance of cortical injury, and the choice of exiting the device remotely from the site of monitoring reduces the potential for post-removal spinal fluid leakage or infection compared to the subarachnoid bolt.[57,77] Being fluid coupled, this device is also dependent on frequent fluid flushing to maintain an adequate volume for pressure transmission.

Intracranial pressure can also be measured from a subarachnoid catheter. A subarachnoid catheter has been reported to be more reliable compared to the subarachnoid bolt and has a lower failure rate.[52] However, the method does not permit removal of the CSF.

The use of the Camino fibreoptic subdural device for the measurement of ICP in patients has been found comparable with recordings from the intraventricular fluid-filled catheter. Studies have also demonstrated accuracy for the Codman MicroSensor ICP Transducer, a miniature strain gauge mounted on a flexible nylon catheter.[53] Fernandes et al. conducted a comparative study in patients between the Codman MicroSensor and a Camino Transducer which was fitted immediately adjacent to it. A computerised system was used to continuously record both ICP readings. The readings from the two ICP transducers were compared on time series, logistic regression and Altman-Bland plots. Drift of the ICP, recorded by the Codman MicroSensor, was noted in two patients, one in the positive direction (maximum 30 mmHg) and one negative (maximum 20 mmHg). In both cases, the Camino ICP recording was relatively stable. In 24% of the readings, the Codman MicroSensor recorded ICP as 5 or more mmHg greater than the Camino, this difference was 10 mmHg or greater in 9% of readings. Conversely, the Camino recording was 5 mmHg or more than the Codman in 5% of all recordings, and 10 mmHg or more in 3%. They concluded that these differences, in the majority of cases (excepting the negative drift), could be explained by a constant offset of the Codman transducer.[14]

Parenchymal Monitoring

This has become popular in some centres since the availability of non-fluid filled devices, like the fibreoptic system and the piezoresistive microtransducers[60] which can easily and safely be implanted into the brain parenchyma. A parenchymal fluid-filled catheter coupled with a transducer frequently gets clogged with brain matter and clots.[8] Parenchymal monitoring has been reported to be useful in patients with small ventricles or large shifts, in large craniectomies or open compound injuries with dural loss where placement of an epidural or subdural device may be difficult.[8,60] Parenchymal monitoring is again handicapped by the inability to drain CSF.

Intraventricular Monitoring

This remains one of the most popular techniques and is probably the procedure of choice in patients with ventriculomegaly. It is very accurate, and is the current gold standard against which other methods are compared. A variety of sets are available commercially, but basically they all consist of a ventricular catheter which is fluid coupled to a strain gauge transducer. The placement of the catheter is simple and the standard landmarks for a ventricular tap are followed. It is usually placed in the frontal horn and tunnelled from its site of exit from the skull to the point of exit from the scalp. Placement of the catheter is verified by the drainage of fluid and an adequate waveform on the monitor. It offers the added advantage of therapeutic drainage of CSF to lower the ICP, and can also be used to perform CSF dynamic studies. The major disadvantage is that it may be difficult to insert in patients with small ventricles or significant shifts. The risk of infection varies from 8% at 5 days to 40% at 12 days.[46] Other studies have also shown that the risk of infection increases if the catheter remains at the same site beyond 5 days, and therefore it is advisable to change the site every 5 days if the patient requires a ventriculostomy catheter for a longer period. Intracranial haemorrhage was seen in about 2% of the cases in a large series.[55] The failure rate is considerably lower than with the subarachnoid bolt.[57]

ICP monitoring from the operative cavity in the posterior fossa using a fluid-filled catheter has been reported to be safe and more accurate than supratentorial monitoring after posterior fossa surgery.[67] It also has the added advantage of allowing drainage of CSF or collected blood whenever required.

Catheter tip transducer systems using strain gauges or fibre-optical pressure sensing techniques are currently in clinical use. With these devices, zero drift and calibration cannot be checked *in vivo*. All the present ICP monitoring devices in clinical use require a physical connection between the brain and the external environment. This becomes a source of infection, limiting the duration of monitoring. A number of telemetric monitoring devices, in which data is transmitted transcutaneously, have been developed over the last two decades. All the present ICP monitors are temporary percutaneous implanted devices. Placement of these devices carries significant morbidity, particularly infection. Apart from decreasing the risk of infection in patients with severe head injury, the clinical value of an accurate telemetric ICP monitoring system which maintains its reliability over a long period of implantation is high.[16]

O'Neill et al. conducted a survey, sent to 3,100 practicing neurosurgeons and a similar survey to 720 neurosurgery residents, to assess the current practice patterns of these procedures. Basic demographic information and estimated rates of proper ventriculostomy placement were sought. A total of 934 practicing neurosurgeons and 100 neurosurgery residents responded to their survey. Their study revealed a mean of 1.4 passes per ventriculostomy procedure for practicing neurosurgeons, 1.4 for senior residents and 2.4 for junior residents, with a rate of successful cannulation of the ipsilateral ventricle ranging from 72% to 84% for these groups. Both residents and practicing neurosurgeons admit to frequently using multiple passes and frequent catheter placement outside the ipsilateral frontal horn. Despite these imperfections, survey respondents were reluctant to embrace technology that could improve placement accuracy if it increased procedure time.[58]

Lumbar Monitoring

Kusaka et al. reported a new lumbar method for monitoring ICP in rats. A PE10 catheter connected to a pressure transducer is placed into the subarachnoid space of L5 through the dura following laminectomy to record lumbar CSF pressure (lumbar-ICP). Simultaneously, ICP at the CM (cisterna-ICP) was recorded using a catheter placed in the subarachnoid space at the CM. Anaesthetised adult male rats were subjected to baseline recording followed by experimentally induced SAH or intracerebral haemorrhage. Baseline lumbar-ICP and cisterna-ICP varied between 6 mm and 8 mmHg, and respiratory variation could be detected. Then an acute response to SAH was recorded in both the lumbar-ICP and the cisterna-ICP in all rats. They found that the lumbar catheter continuously and accurately monitored lumbar-ICP, and reliable pressure tracings were obtained for up to 24 hours after SAH. They concluded this new lumbar-ICP method is simple, safe, easy and reliable in rats.[36]

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5 Neuro-Ophthalmology

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It has been said that the eye is the window to the brain. Neuro-ophthalmology, which includes examination of the optic nerve, fundus, ocular movements, pupillary and corneal reflex, along with charting of the visual fields, contributes a great deal to the neurological evaluation. In this chapter only the examination of the visual field is discussed with particular reference to the various types of field defects that can occur with brain tumours.

Brain tumours may affect the visual pathway by direct compression or indirectly, through various mechanisms (Table 1).

THE NORMAL FIELD OF VISION

The visual field is a three dimensional area which is visible through each eye when fixating at a central target. The field of vision is centred at a fixation point of each eye, as an asymmetric oval shape extending maximally on the temporal side for about 90 degrees. The superior and inferior fields have an extension of 40 and 60 degrees, respectively. Nasally it is restricted by the nasal bridge and measures up to 40 degrees. There is binocular representation of the visual fields for 60 degrees to the right and left of a common fixation point.

THE NORMAL VISUAL PATHWAY

The visual pathway begins with stimulation of photoreceptors of the retina and processing in the ganglion cells. The axons of the ganglion cells converge to form the optic nerve. The nerve then travels through the optic canal and emerges in the intracranial cavity at the sellar region. At this juncture the nasal fibres of the optic nerve cross to form the optic chiasm. The contralateral nasal fibres and ipsilateral temporal fibres continue together as the optic tract, which provides for one-half of the binocular visual field. The optic tract is relayed in the ipsilateral lateral geniculate body (LGB) where sorting of fibres occurs. The third order neurons commence from the LGB and continue as the optic radiation that terminates in the visual cortex (area 17) of the occipital lobe (Fig. 1).

Table 1: Effect of brain tumours on visual pathways

Brain tumours	
Direct effects	*Indirect effects*
• Direct compression	• Papilloedema • Impact of tumour resection • Post-radiation neuropathy • Toxic effects due to chemotherapy • Metastatic lesions to retina or infiltration of optic nerve • Haematological effects like ischaemia, venous engorgement

ASSESSMENT OF VISUAL FIELD

Any form of deviation or loss in extension and pattern of the field from normal is considered a defect and has

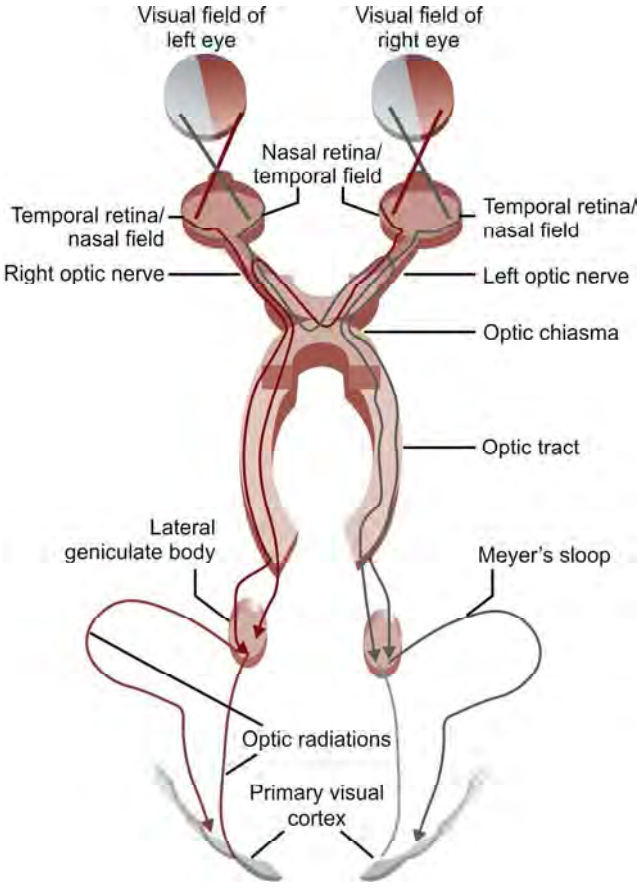


Fig. 1: Visual pathway

clinical implications in the management of brain tumours. The pattern of field defect can give information regarding the localisation of lesions along the visual pathway, while monitoring of field defect would help in determining the progression or recurrence of a brain tumour.

The process of estimating and mapping the field of vision is called perimetry. The field of vision of a patient can be assessed by various methods; the easiest and convenient for bed side examination is confrontation examination. This is a crude and subjective evaluation, wherein the examiner compares the visual field of the patient to his own field of vision. More sophisticated methods used routinely in clinical practice include Goldmann perimetry and automated perimetry, which are objective and hence more reliable methods. These techniques can precisely map and record the peripheral (full extent) as well as central (central 30°) field of vision, respectively (Figs 2A to D).

INTERPRETATION OF VISUAL FIELD

Terminologies

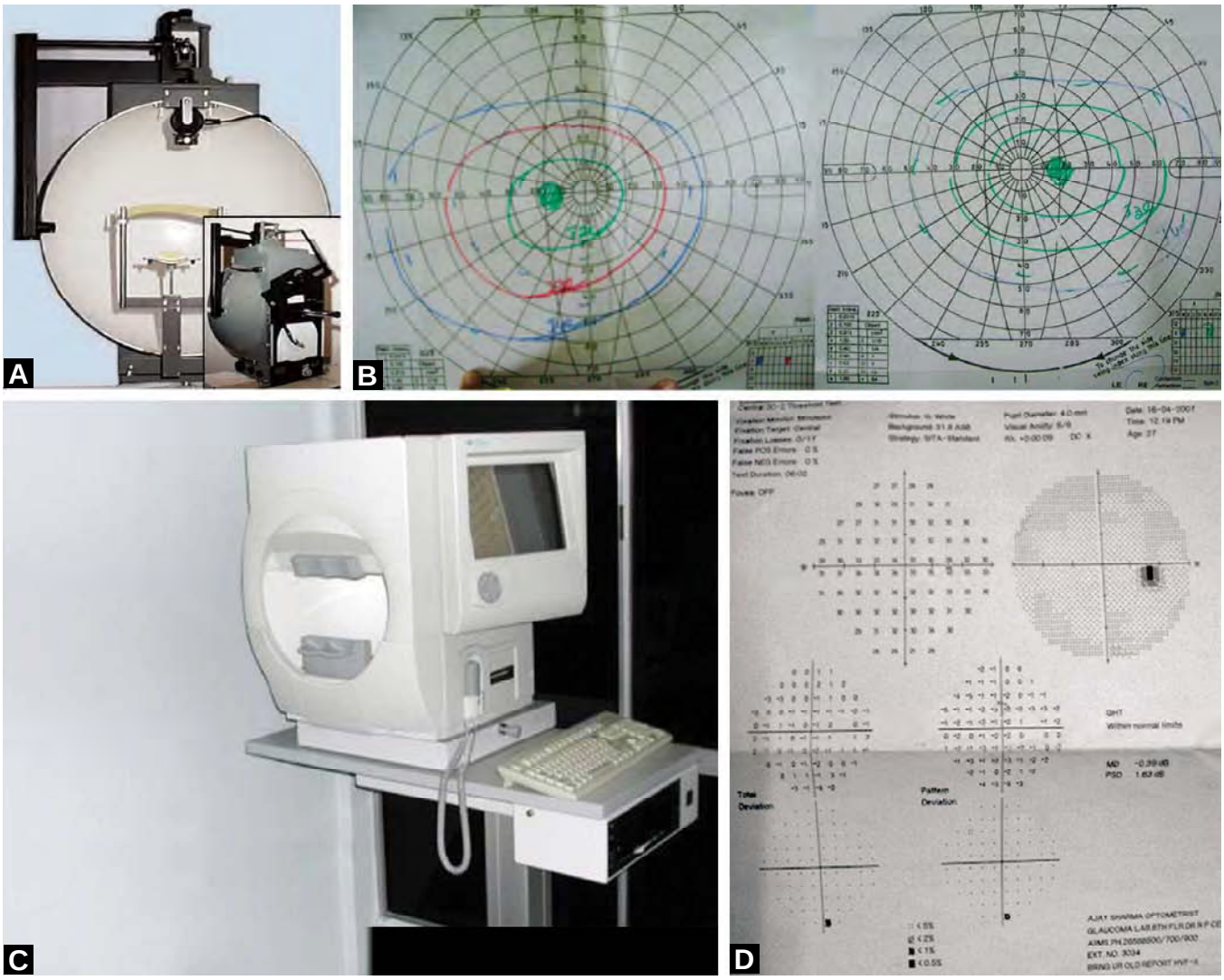
Isopter: It is a line joining the retinal points of the same sensitivity.

Constriction: Implies that there is generalised decrease in sensitivity of the retina and on kinetic perimetry it encloses a smaller area than normal.

Hemianopia: When one-half of the visual field is involved either in one or both eyes.

Homonymous: When the defects are present in the visual fields of both eyes and are on the same side of the vertical meridian.

Heteronymous: When the defects are present in the visual fields of both eyes but are on the opposite sides of the vertical meridian.



Figs 2A to D: (A) Goldmann perimetre. (B) Extent of normal visual field on Goldmann perimetry. (C) Automated perimetre. (D) Extent of normal field of vision on automated perimetry

Scotoma: It is a localised area of decreased sensitivity. It may be absolute, when the patient cannot see even the brightest possible stimulus or it may be relative if some of the stimuli are seen. They can be classified either by their location or by shape.

Congruency: The extent to which the homonymous field defect in one eye resembles that in the other eye in terms of shape, size, depth and slope of the margins.

VISUAL FIELD DEFECTS

The arrangement of visual fibres in a particular region of the visual pathway determines the characteristics and shape of visual field defects. In general, lesions anterior to the optic chiasma produce monocular defects, while lesions affecting the chiasma and beyond are always bilateral. Heteronymous defects are seen in chiasmal lesions, while all lesions affecting the visual pathway beyond the chiasma produce homonymous lesions. The more posterior a lesion is in the visual pathway, the more congruent field defect it will produce. For example, a lesion of the occipital lobe will produce a more congruent field defect than that of the optic tract. Table 2 summarises the pattern of field defects produced by various brain tumours.

Retina

Anatomy

The visual field and the retina have an inverted and reversed relationship. Thus, light rays from the temporal visual field stimulate the ganglion cells of the nasal retina. The axons of these ganglion cells form the nerve fibre layer and finally converge at the optic nerve head and exit as the optic nerve.

Organisation of Retinal Nerve Fibre Layer

The inner most layer of the retina; retinal nerve fibre layer (RNFL) bundles converge in a specific pattern to form the optic nerve head. The papillomacular bundle is formed by macular fibres that enter the temporal aspect of the disc. The arcuate nerve fibre bundle contains the axons that arise temporal to the fovea and arch superiorly and inferiorly to the fovea, to enter the superior and inferior poles of the disc, respectively. The axons from the nasal retina enter radially in to the optic nerve head, as the nasal nerve bundle. Thus, the macular fibres are centrally placed, while fibres from the upper part of the retina lie superiorly and those from the lower retina are placed inferiorly in the optic nerve (Fig. 3).

Table 2: Visual field defects according to the location of the tumour

Location of tumours	*Structure involved*	*Type of field defect*
Orbit • Optic nerve glioma • Optic nerve meningioma	• Optic nerve	Total field loss (early lesions may present with central or centrocecal field defect)
Sella • Pituitary adenoma • Craniopharyngioma • Meningioma	• Chiasma • Chiasma • Willebrand's knee	• Bitemporal field defect • Bitemporal field defect • Junctional scotoma
Mid brain • Craniopharyngioma • Meningioma • Large pituitary adenoma • Aneurysms • Hamartomas	• Optic tract • Lateral geniculate body	• Homonymous hemianopia (macular splitting) • Sectoral defects
Parietal lobe • Meningiomas • Gliomas • Metastasis • Vascular	• Superior part of optic radiation	• Inferior quadrantic field defect • Homonymous hemianopia (macular splitting)
Temporal lobe • Gliomas • Metastasis • Vascular	• Inferior part of optic radiation	• Superior quadrantic field defect (usually incongruous in nature)
Visual cortex • Gliomas • Meningiomas • Metastasis • Vascular	• Occipital lobe	• Homonymous hemianopia sparing macula. (Complete or Partial depending upon the size of the tumour)

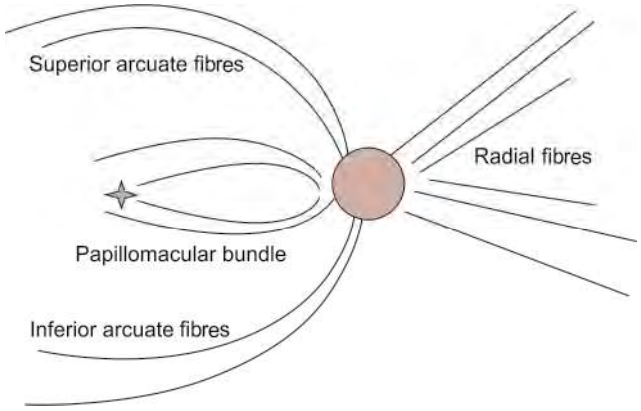


Fig. 3: Arrangement of nerve fibres as RNFL

Fields Defects

The layer of the retina that is affected by the disease process determines the pattern of field defect. Lesions in the outer retina have no particular definite boundaries, so they can produce field defects of varying shapes and sizes, while involvement of the RNFL produces a field defect corresponding to the particular pattern of the nerve fibre bundle affected (Fig. 4). The field defects produced by the involvement of RNFL are well demarcated and respect the horizontal meridian. They characteristically either involve the blind spot or point towards it. These defects should be differentiated from the sectoral defects and quadrantic defects produced by the LGB and the cortex, which respect the vertical meridian and start from the fixation point.

Papillomacular bundle involvement results in a central scotoma (Fig. 5A), centrocecal scotoma or paracentral scotoma.

Arcuate nerve fibre bundle lesions may cause a variety of field defects like: Bjerrum or arcuate scotoma, Seidel scotoma, Nasal step of Ronne, depending on the site of the lesion. Arcuate field defect (Fig. 5B) is seen in many conditions, apart from anterior optic nerve lesions (see the following box):

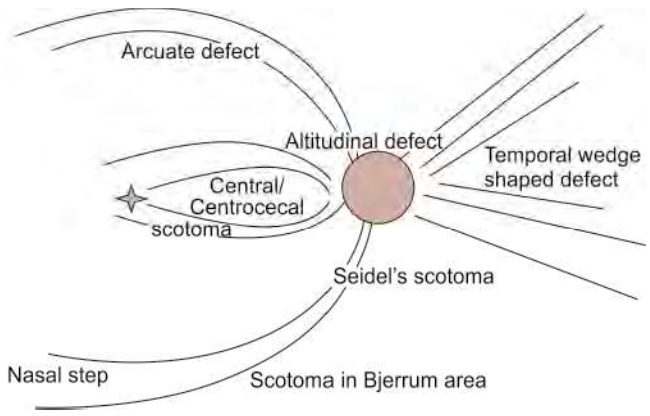


Fig. 4: Field defects produced by involvement of a specific nerve fibre bundle

1. Glaucoma
2. Chorio-retinal lesions
3. Juxtapapillary choroiditis
4. Myopia with peripapillary atrophy
5. Central retinal artery occlusion
6. Branch retinal artery occlusion
7. Ophthalmic artery or carotid artery occlusion
8. Drusen
9. Optic nerve pit
10. Chronic papilloedema
11. Anterior optic nerve lesions

Involvement of the nasal fibre bundle leads to temporal wedge shaped defects.

Optic Nerve

Anatomy

The optic nerve is formed by the axons of retinal ganglion cells that converge to form the nerve fibre bundles. It is about 50 mm in length and can be divided into four parts: optic nerve head (intraocular part 1 mm), intraorbital (25 mm), intracanalicular (10 mm) and intracranial (15 mm).

Organisation

The above described arrangement of the nerve fibres is maintained throughout the optic nerve, such that even lesions involving the posterior part of the optic nerve produces a pattern corresponding to the nerve fibre bundle involved (Fig. 6).

Field Defects

In addition to the field defects described above, the involvement of axons at the superior or inferior pole of the optic disc produce *altitudinal defects* (Fig. 7).

The Chiasma

Anatomy

The chiasma is formed by the crossing of the nasal fibres of each optic nerve. It is located over the diaphragm sella and is posteriorly related to the wall of the third ventricle. There may be variations in the location of the chiasma that have important clinical significance for localisation of the lesion. In 80% of the population, it is located directly over the sella (central); in such cases, pituitary lesions involve the chiasma first. In about 10% of the normal population, it is located more anteriorly over the tuberculum sellae (prefixed); here pituitary lesions will involve the optic tract first. In the remaining 10% of cases it is located more posteriorly over the dorsum sella, where pituitary lesions involve the optic nerve first.

Anteriorly, the chiasma is related to the anterior cerebral arteries and their communicating branches. Posteriorly, it is related to the hypophyseal stalk and the pituitary body. It is immediately inferior to the floor of the third ventricle and lies above the hypophysis.

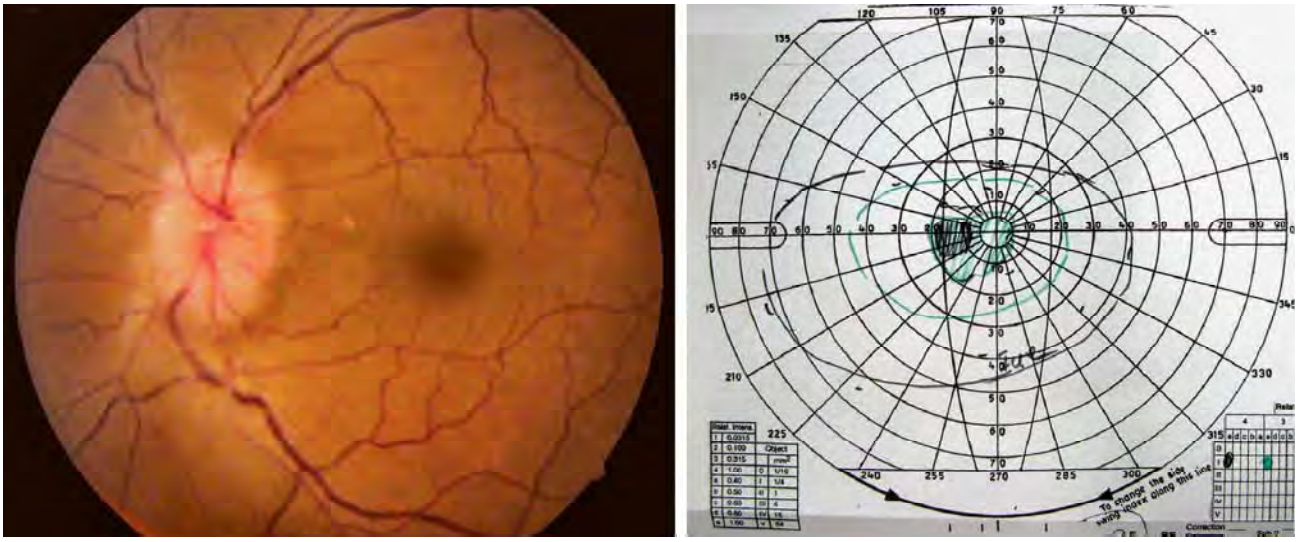


Fig. 5A: Fundus picture. Central scotoma in case of optic neuritis

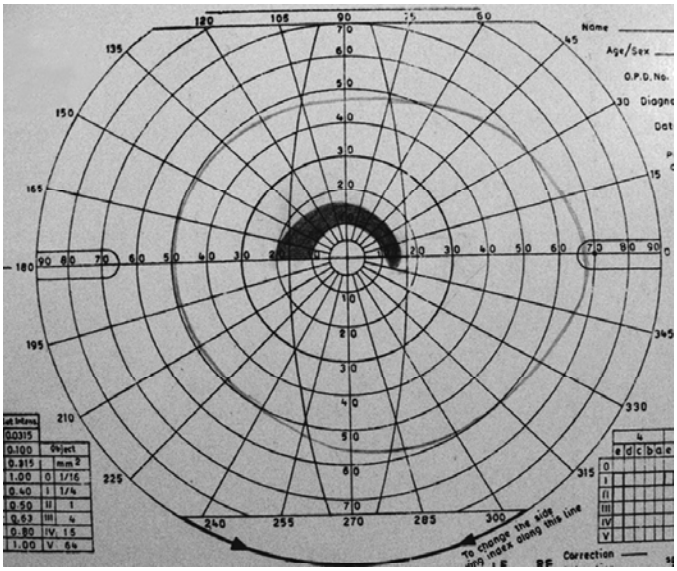


Fig. 5B: Arcuate field defect

Laterally, it is related to the internal carotid artery and the cavernous sinus.

Organisation

At the chiasma, the fibres representing the nasal visual field (temporal fibres) are present in the lateral part. The

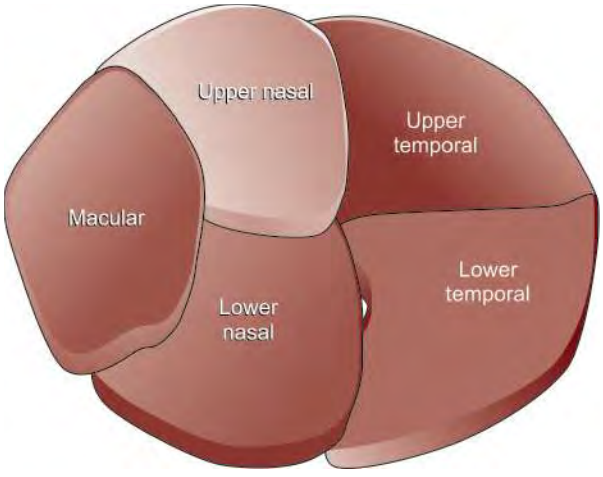


Fig. 6: Arrangement of nerve fibres in optic nerve

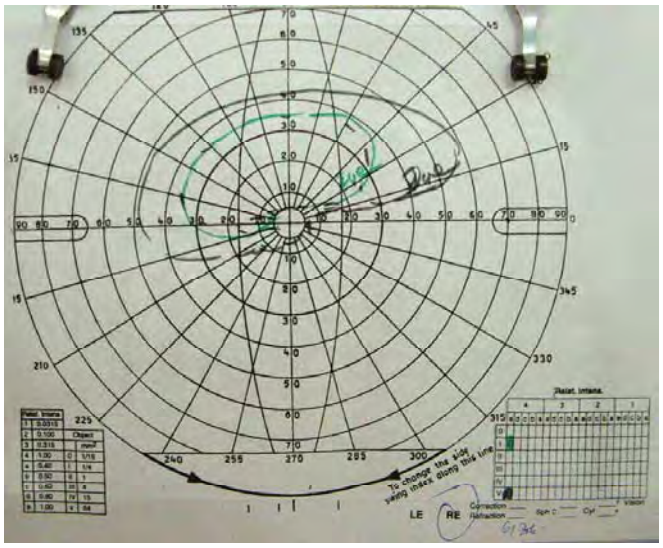


Fig. 7: Altitudinal field defect in a case of non-arteritic ischaemic optic neuropathy

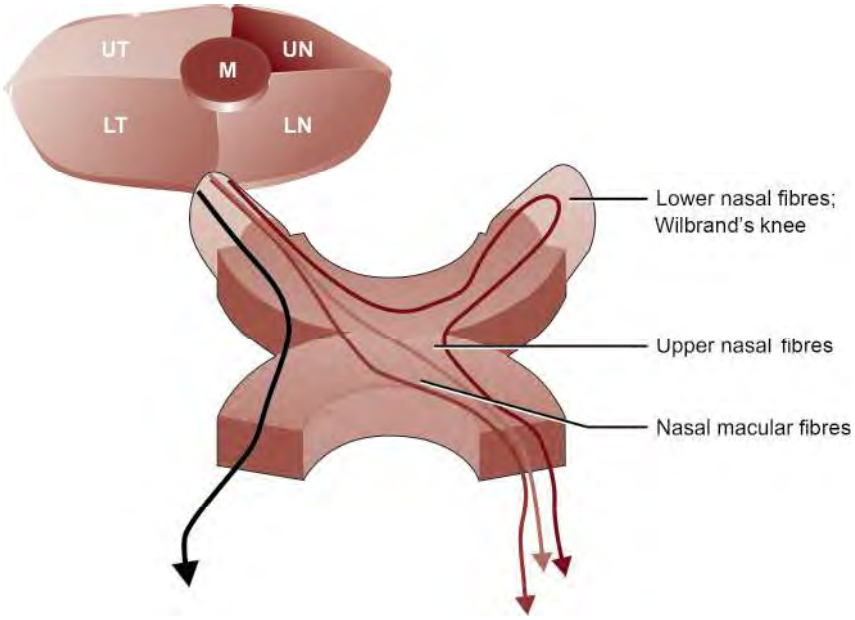


Fig. 8: Decussation of optic nerve fibres at the chiasma

inferonasal fibres (superior temporal field) cross anteriorly in the chiasma and loop forward into the contralateral optic nerve, forming von Willebrand's knee and then continue in the contralateral optic tract. The nasal macular fibres decussate most posteriorly. The upper nasal fibres (inferior temporal field) cross in the middle (Fig. 8). Thus, the right optic tract constitutes the right nasal field (right temporal axons) and the left temporal field (left nasal decussated fibres) representing the left half of the visual space.

Clinical Features

A patient with a chiasmal lesion presents with varying signs and symptoms, depending upon the type, size and site of the lesion. Pituitary adenoma presents with signs of compression of the visual pathways, as well as other features of hormonal disturbance. There may be unilateral or bilateral loss of vision, as a result of concurrent compression of the optic nerve by the tumour. Relative afferent pupillary defect may be present in unilateral lesions. Lesions of the cavernous sinus and large pituitary adenomas compress the motor nerves of the eye, leading to ocular motility disorders. See-Saw nystagmus and oscillopsia are features of tumour or trauma.

Field Defects

The axons in the chiasma are arranged in such a way that they are limited by a vertical meridian, which passes through the fovea of each eye. Thus, a lesion of the chiasma and the proximal visual pathway will have the following features:

- Hemianopic defect (bilateral defect)
- Originates from the fixation point
- Respects the vertical meridian
- Patients with retrochiasmatic lesions do not have decreased visual acuity

The field defect produced by a lesion involving the chiasma depends upon the location of the chiasma, site of the lesion and part of the chiasma affected.

Bitemporal hemianopia: Lesions that affect the body of the chiasma produce bitemporal hemianopia (Fig. 9A). Lesions of the pituitary gland, i.e. tumours, inflammation or haemorrhage are the common conditions that can affect the body of the chiasma and produce classical bitemporal

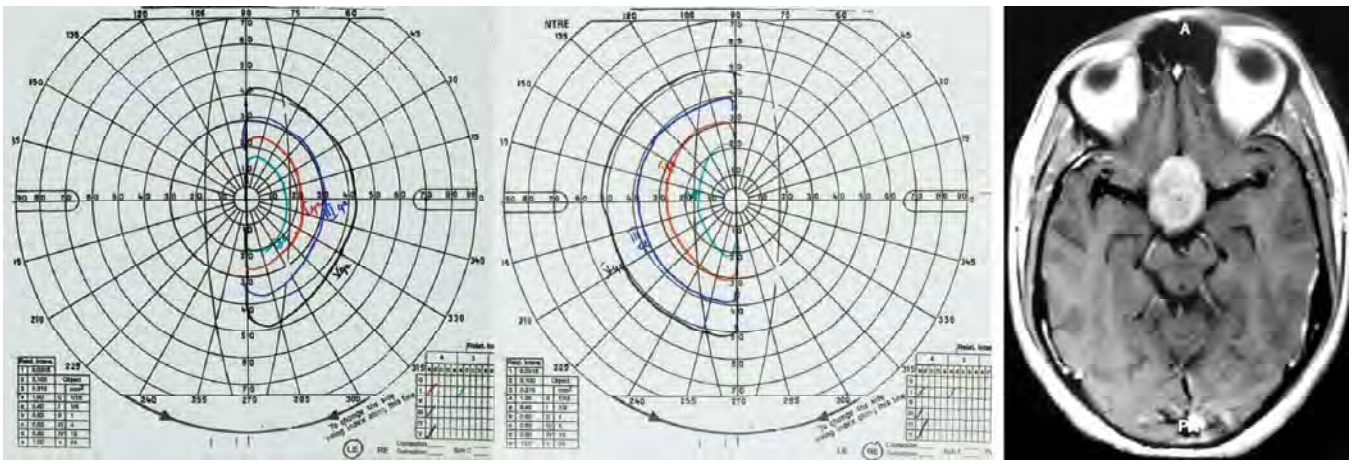


Fig. 9A: Bitemporal hemianopia in a case of pituitary adenoma. MRI of large pituitary adenoma

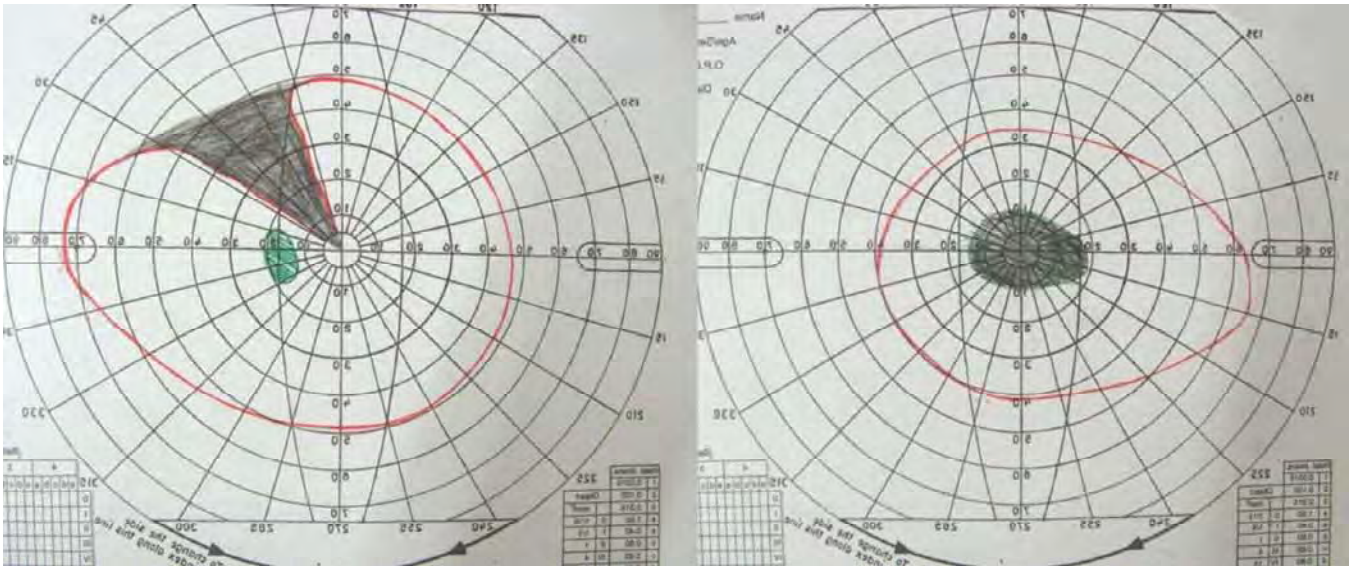


Fig. 9B: Junctional scotoma

hemianopia. Inferior bitemporal hemianopia is characteristic of craniopharyngioma. Saccular aneurysms of vessels in the circle of Willis can also lead to bitemporal hemianopia. Other ophthalmic conditions that can cause a similar field defect are bilateral glaucoma and other optic neuropathies, disc anomalies and psychogenic visual loss.

Junctional scotoma: It is produced when a lesion involves the junction of the optic nerve and chiasma, leading to an optic nerve defect in the ipsilateral eye and superior temporal (involvement of von Willebrand's knee) defect in the contralateral eye (Fig. 9B). A lesion involving the hemichiasma would cause total blindness in one eye (optic nerve of ipsilateral eye) and temporal hemifield defect in the contralateral eye (decussating nasal fibres of the contralateral eye). Lesions like meningioma, that arise from the dura of the tuberculum sellae and adjacent structures compress the optic nerve, as well as the chiasma. Depending upon their site and size they may lead to asymmetric involvement of both eyes. Craniopharyngiomas can also lead to asymmetric visual field defects. Meningiomas and craniopharyngiomas, when small in size, lead to compression of the posterior part of the optic nerve or anterior part of the chiasma, leading to mono-ocular field defect in the ipsilateral eye, most commonly in the superotemporal quadrant (inferonasal decussating fibres). A proper and careful field evaluation will expose the subtle involvement of the contralateral eye.

Binasal field defects: A large mass lesion compressing one side of the optic chiasma, on further enlargement, causes a midline shift of the chiasma with subsequent compression of the other side as well, leading to a binasal field loss presentation (Fig. 9C). This pattern of field loss can also be seen with empty sella syndrome, arachnoiditis and after surgery for pituitary tumours.

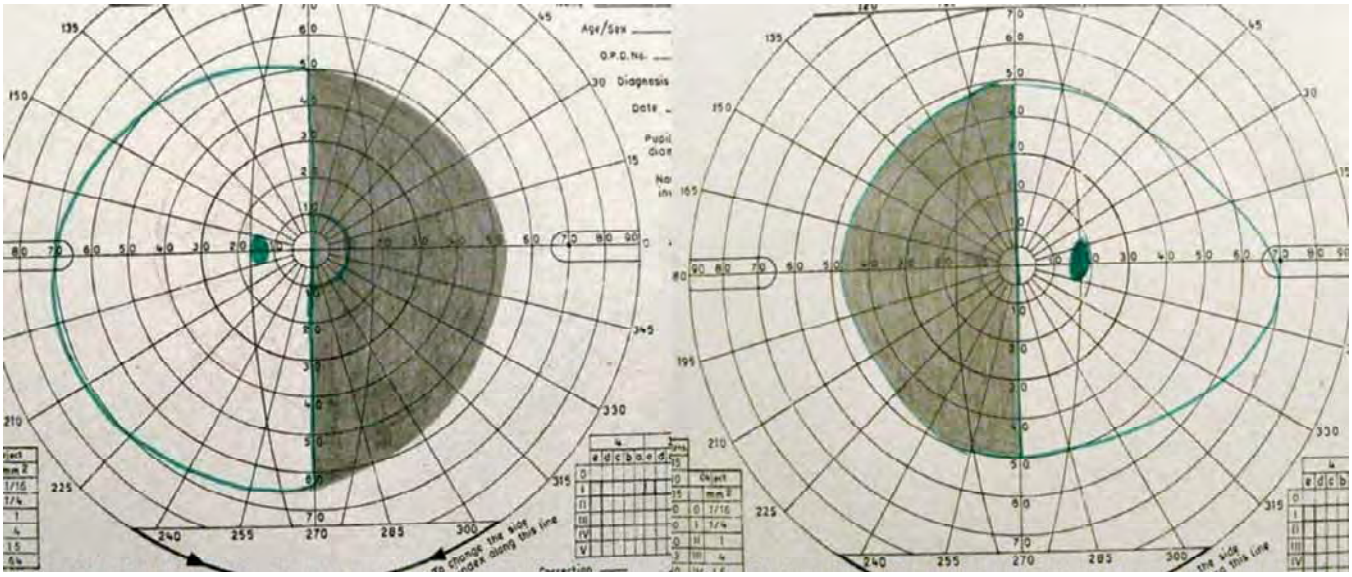


Fig. 9C: Binasal defect

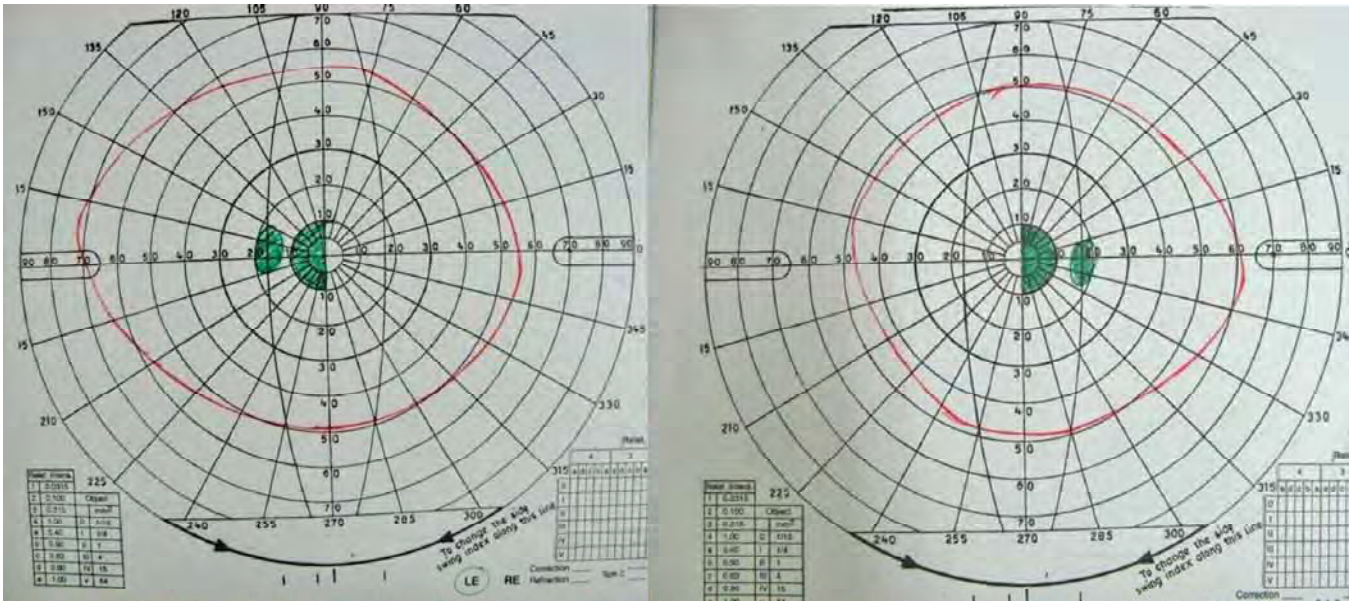


Fig. 9D: Central bitemporal hemianopia

Homonymous hemianopia: This type of field defect is commonly seen in cases where the chiasma is prefixed. Thus, any lesion which affects the chiasma can also affect the optic tract, leading to homonymous hemianopia. Large pituitary adenomas and craniopharyngiomas are the most common causes.

Lesions that affect the posterior part of the chiasma cause *central bitemporal hemianopia* (Fig. 9D).

Optic Tract and Lateral Geniculate Body

Anatomy

The optic tract runs superiorly and posteriorly from the optic chiasma and curves around the brainstem to terminate in the LGB. The LGB is a part of the thalamus and is situated along the lateral aspect of the midbrain. Each geniculate body consists of six layers of neurons and second order fibres, travelling through the optic tract, are relayed in different layers of the LGB. It receives dual blood supply from the anterior and lateral choroidal arteries, which nourish the fibres from the superior and the inferior homonymous quadrants of the retina, respectively. The optic tracts lie between the tuber cinereum and the anterior perforated substance.

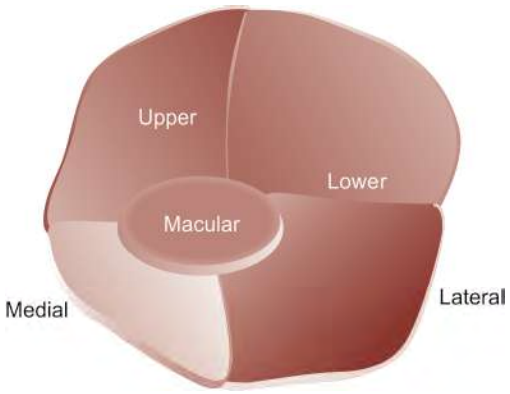


Fig. 10: Arrangement of fibres in the right optic tract

Organisation

Each optic tract is formed by the temporal fibres of the ipsilateral eye and the nasal fibres from the contralateral eye. Thus, each optic tract represents the contralateral half of the binocular visual field. The arrangement of axons present in the optic nerve takes a 90 degree turn through the chiasma into the optic tract (Fig. 10). Thus, the axons from the lower retina lie in the lateral aspect; the axons from the upper lie in the medial aspect, while the macular fibres lie in the dorsolateral aspect.

The axons from the ipsilateral eye are relayed in nuclei layer 2, 3 and 5, while the axons from the contralateral side relay in 1, 4 and 6 nuclei layer. The fibres from the upper part of the retina occupy the medial half of the anterior one-third of the LGB. The lower retinal fibres occupy the lateral half of the anterior one-third of the LGB, while the macular fibres are relayed in the posterior two-third of the LGB (Fig. 11).

Clinical Features

The characteristic hemianopic atrophy or Bow tie pattern of optic atrophy is seen in longstanding lesions of the optic tract and LGB. The most useful sign of localising a lesion between the optic tract and LGB is involvement

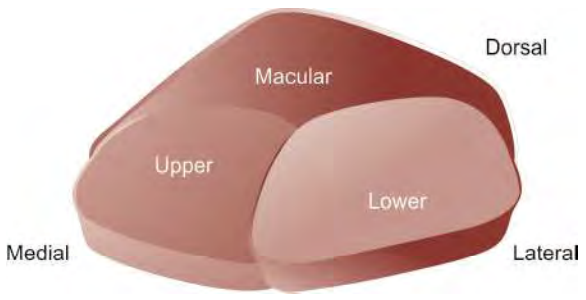


Fig. 11: Arrangement of fibres in the lateral geniculate body

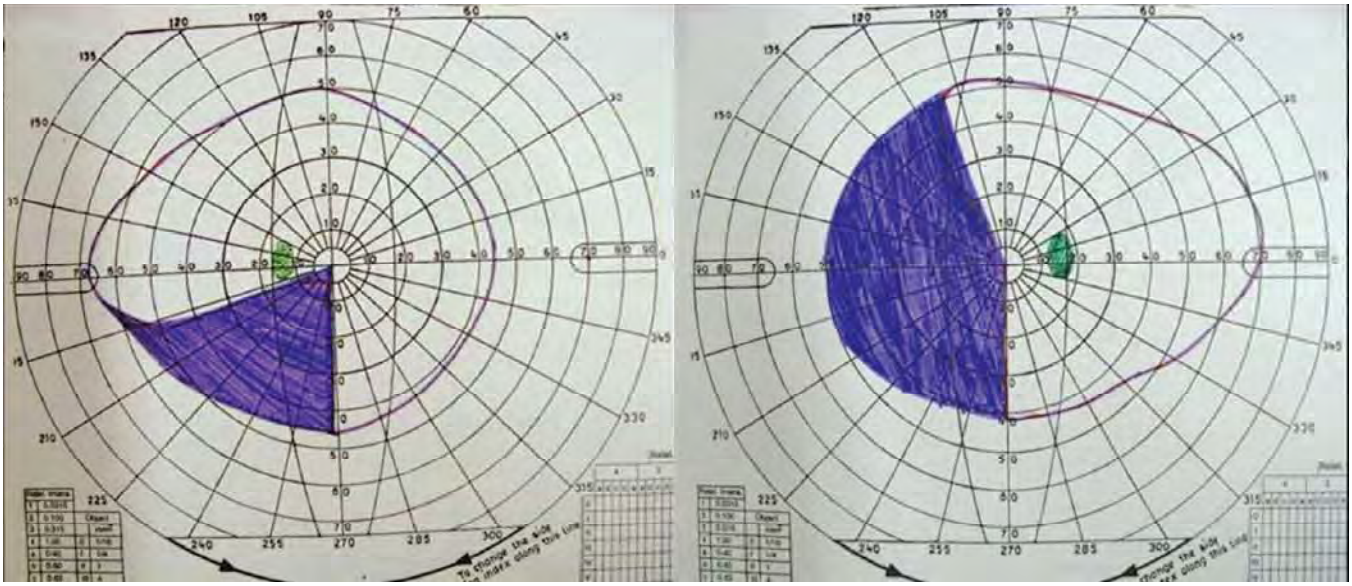


Fig. 12: Incongruous field defect in optic tract lesion

of the pupil. Optic tract lesions are associated with various pupillary abnormalities including RAPD on the contralateral side, Wernicke's hemianopic pupil[1] and Behr's pupil[2], while in lesions of the LGB, pupillary reactions are spared.

Lesions affecting the optic tracts are craniopharyngiomas, meningiomas, and large pituitary adenomas, demyelinating diseases, vascular lesions such as aneurysms, arteriovenous malformations and hamartomas. Lesions affecting the LGB include infarction, tumours, trauma and inflammatory disorders.

Field Defects

Complete optic tract disruption on one side leads to complete macular splitting homonymous hemianopia, while partial involvement will cause an incongruous field defect (Fig. 12). Similarly, a defect in one LGB will produce complete homonymous hemianopia, while partial lesions of the LGB cause a sectoral field defect (Fig. 13).

Optic Radiations

Anatomy

The optic radiations are geniculocalcarine pathways that extend from the LGB to the visual cortex. They cross the Wernicke's area as optic peduncles and travel in the retrolenticular part of the internal capsule.

[1]Wernicke's hemianopic pupil refers to the condition when the pupil does not react to the light projected from the direction of hemianopic field defect.

[2]Behr's pupil refers to the larger pupil seen in an optic tract lesion. It is seen on the contralateral side of the lesion and is usually associated with hemiparesis, particularly in cerebrovascular accidents.

Organisation

The fibres, after exiting from the LGB, rotate by 90 degrees again to regain their original arrangement. Thus, the superior fibres lie in the upper part of the radiation, the inferior fibres in the lower part and the macular fibres lie in the centre (Fig. 14).

Arrangement of fibres in the temporal lobe: The inferior fibres from the corresponding superior visual fields of both eyes commence from the anterolateral part of the LGB, sweep anteriorly and then laterally along the temporal horn of the lateral ventricle to form Meyer's loop, then extend posteriorly to end in the area below the calcarine fissure of the occipital cortex (Fig. 15).

Arrangement of fibres in the parietal lobe: The superior fibres that carry the inferior field travel directly through the lower portions of the parietal cortex to the occipital lobe area above the calcarine fissure (Fig. 15).

Clinical Features of Temporal Lobe Involvement

The clinical features of temporal lobe lesions are seizures, paragnosia, involuntary movement of the mouth, and visual and auditory hallucinations. Aphasia is characteristic of left temporal lobe lesions. The most common temporal lobe lesions are tumours which include glioma and metastasis. Surgical resection of the tumour (when more than 8 cm), itself may produce field defects. Anterior choroidal artery occlusion may affect the optic radiation in the temporal lobe and LGB. In such cases, hemianaesthesia along with contralateral hemiplegia occurs. Other lesions are trauma, demyelination and abscess.

Clinical Features of Parietal Lobe Involvement

The two most important localising signs of a parietal lobe lesion are loss of normal optokinetic response and

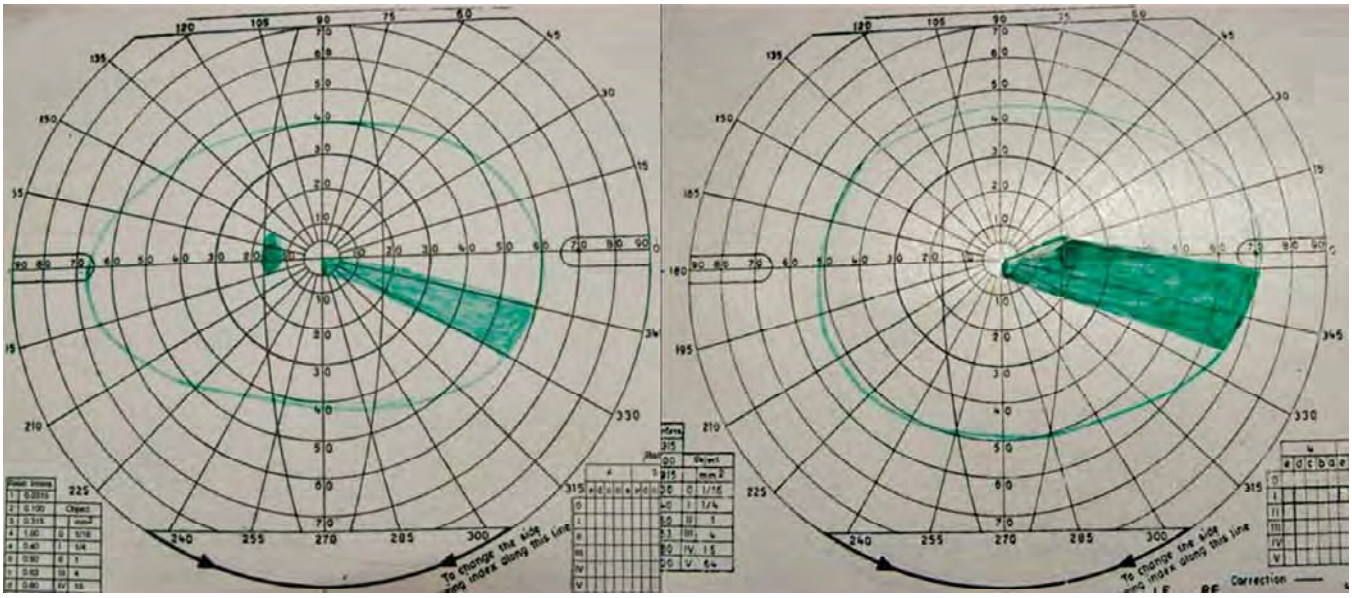


Fig. 13: Right sectoral homonymous defect in left lateral geniculate body lesion

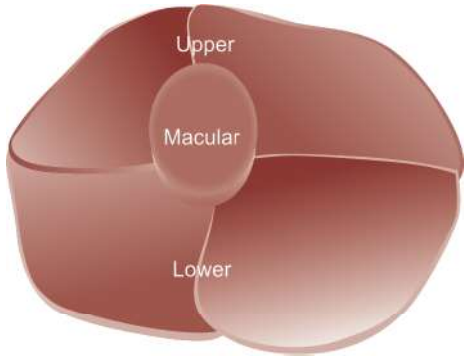


Fig. 14: Arrangement of fibres in optic radiations

conjugate deviation of the eyes. The involvement of the right parietal lobe leads to deficit of spatial orientation of the left space, thus the patient may neglect the left half of the body. Involvement of the left parietal lobe is associated with Gerstmann's syndrome (agraphia, acalculia and visual agnosia). The differential diagnosis of lesions involving the parietal lobe, include infarction, haemorrhage, AVM and tumours.

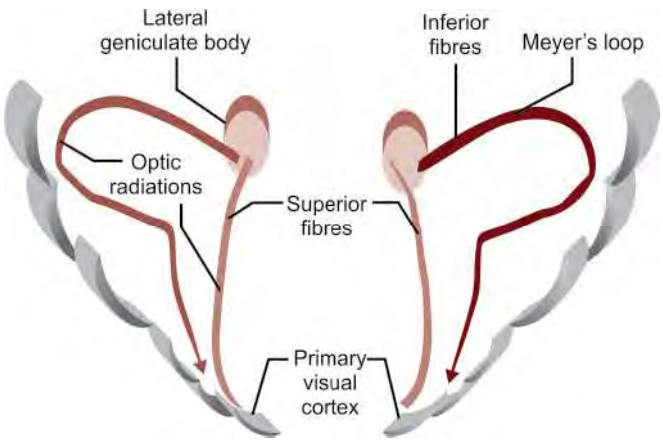


Fig. 15: Arrangement of optic radiations

Field Defects

Lesions involving the optic radiations produce field defects which are homonymous and more congruous. The involvement of the anterior temporal lobe will produce contralateral homonymous superior quadrantanopia (Fig. 16). In more extensive lesions, the defect may extend inferiorly but the hemianopia will be denser superiorly. The defects are wedge shaped defects of varying sizes and are homonymous and incongruous.

Lesions involving the parietal lobe produce an inferior homonymous field defect that is classically described as pie on floor (Fig. 17). These defects are usually more extensive and more congruous than temporal lobe defects. The homonymous hemianopia of the parietal lobe is always associated with macular splitting (Fig. 18).

Visual Cortex

Anatomy

The primary visual cortex (area 17) is located on the medial surface of the occipital lobe near the calcarine fissure. Brodmann's area 18 and 19 are associated visual areas which help in further processing of visual information.

It is now a well established fact that from the primary visual cortex, the visual pathways extend forward into two branches, a dorsal via the parietal lobe to the frontal lobe and a ventral to the temporal lobe. These sub-serve distinct cognitive functions. These are, however, not directly relevant for visual field testing.

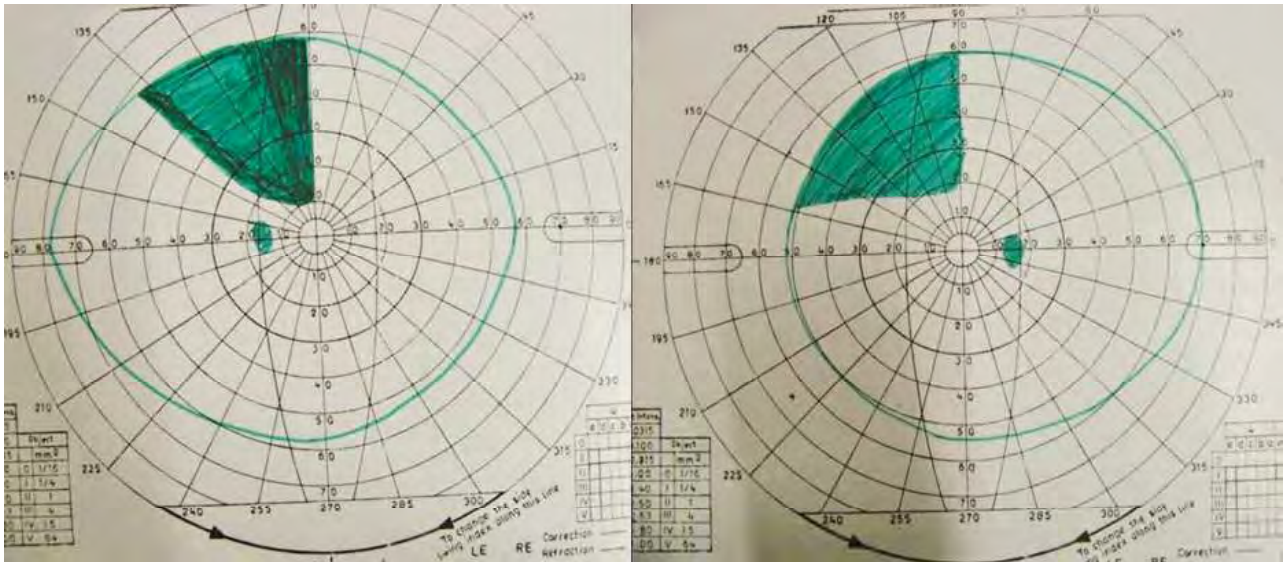


Fig. 16: Left homonymous superior field defect in right temporal lobe lesion

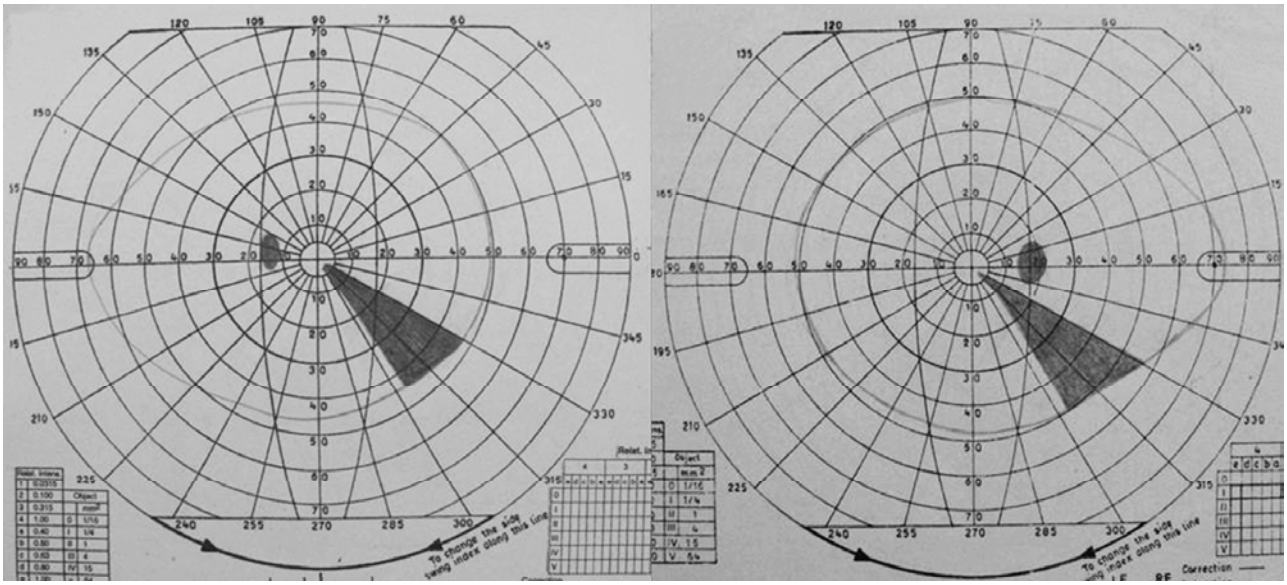


Fig. 17: Right homonymous inferior field defect in a left parietal lobe lesion

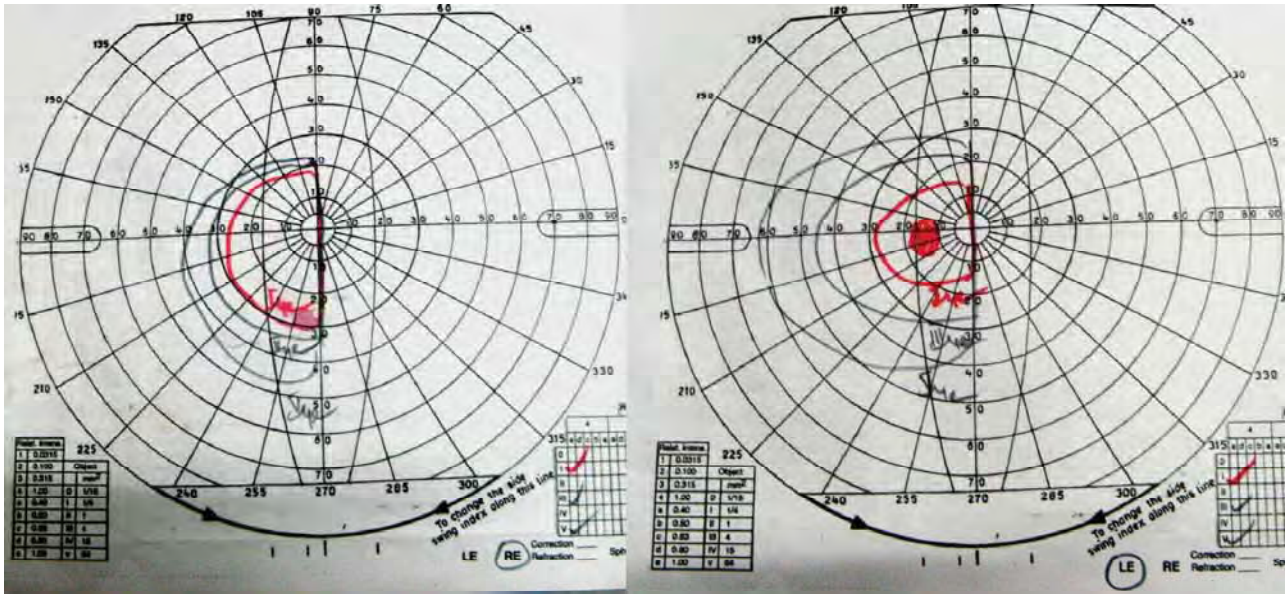
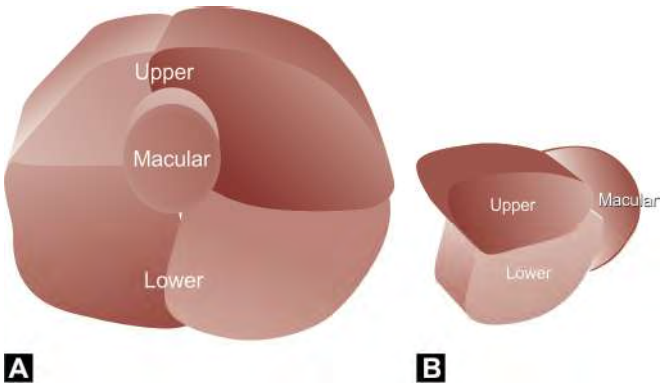


Fig. 18: Right homonymous hemianopia in a left parietal lobe granuloma



Figs 19A and B: Arrangement of fibres in occipital lobe

Organisation

The right visual cortex receives impulses from the left temporal field and the right nasal field. The orientation of fibres in the optic radiation is maintained in the visual cortex (Fig. 19A). The central field is represented at the occipital tip and is separated from the representation of peripheral fibres. The superior fibres (representing inferior field) are relayed in the area superior to the calcarine fissure while the inferior fibres (superior field) are projected to the area inferior to the fissure (Fig. 19B). In each eye there is an isolated temporal crescent in the visual field, for which there are no overlapping points in the other eye. This temporal crescent perceived by the nasal retina is represented in the anterior most portion of the calcarine cortex.

Clinical Features

Occlusion of the left posterior cerebral artery causes infarction of the left calcarine cortex, along with the splenium of the corpus callosum, which produces field defects in the right side and alexia without agraphia. Other signs include headache, visual agnosia and dyschromatopsia, which are mainly secondary to the infarction. Tumours lead to isolated visual field defects and palinopsia. Tumours affecting the occipital lobe are gliomas, meningiomas and metastasis. Bilateral occipital disease is usually due to vascular lesions which include thromboembolism, haemorrhage, hyperviscosity syndromes and vasculitis. This is also a feature following bilateral tentorial herniation, which results in bilateral occipital infarct resulting in blindness.

Fields Defects

Occipital lobe lesions produce field defects that are homonymous and highly congruous.

Complete homonymous hemianopia sparing the macula: The macular area is a watershed zone of anastomoses between the middle and the posterior cerebral arteries. Ischaemia of the occipital lobe results in sparing of the central 3–5 degrees of the visual field due to its dual blood supply (Fig. 20).

Central homonymous hemianopia: A lesion affecting the tip of the occipital lobe would produce a field defect in the macular area which is homonymous (Fig. 21). In such cases, at least 5 degrees of the central field is spared in both eyes on the side of hemianopia.

Quadrantic field defects: Lesions of the area below the calcarine fissure would give rise to a homonymous superior quadrantic defect. Similarly, a lesion involving the area above the calcarine fissure would lead to an inferior homonymous defect. Because of their anatomical and vascular separation, these defects always respect the horizontal meridian and they should not be confused with optic nerve related visual field defects. The former are always homonymous and congruous and respect the vertical meridian as well.

There could be asymmetry in field defects in cases with bilateral occipital lobe involvement. Involvement of the occipital lobe bilaterally may lead to *bilateral*

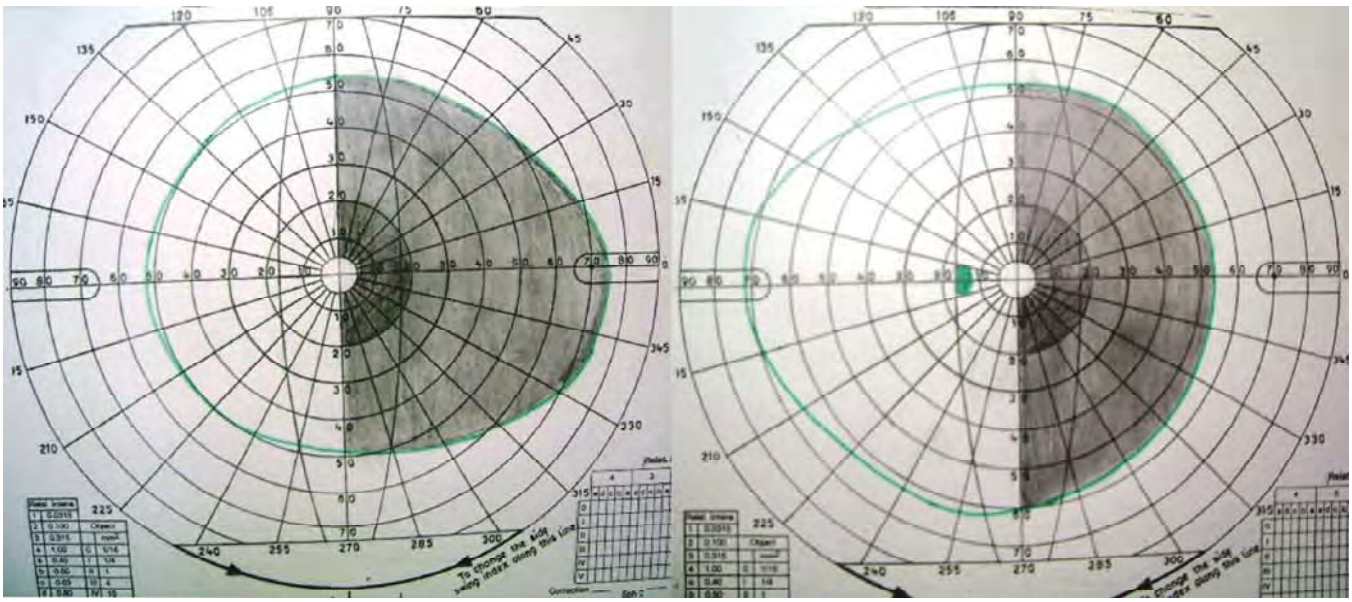


Fig. 20: Right complete homonymous hemianopia sparing macula

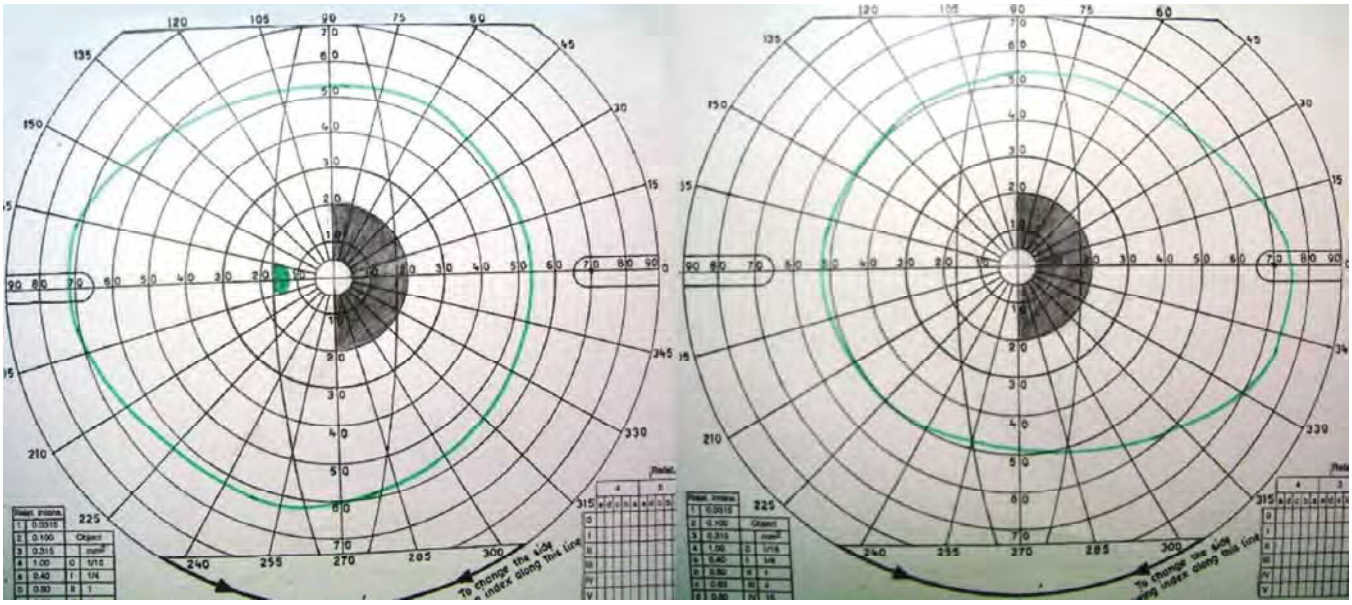


Fig. 21: Right central homonymous hemianopia

homonymous hemianopia with sparing of central tubular vision. This should be differentiated from other causes of constricted visual field like malingering, glaucoma and retinitis pigmentosa.

Lesions involving the occipital pole bilaterally would cause *bilateral central homonymous hemianopia*.

A checkerboard pattern field defect results from involvement of the occipital lobe below the calcarine fissure on one side and above the fissure on the opposite side.

Temporal crescent: The binocular field of vision is formed by superimposition of corresponding visual points of the central 60 degrees visual field of both the eyes but, then, in each eye there is a peripheral area which has no corresponding points in the other eye. This area is perceived by the nasal most retina of the eye and is represented in the anterior most portion of the calcarine cortex. Any lesion involving the anterior most part of the calcarine cortex leads to monocular temporal crescentric field defect in the contralateral eye.

SPECIAL VISUAL FIELD DEFECTS

Baring of Blind Spot

When a small degree of field is mapped, the isopter may be constricted and any scotoma outside the isopter may be continuous with the blind spot causing true baring of the blind spot. False baring of the blind spot is seen when the isopter is just outside the blind spot.

Pseudobitemporal Hemianopia

They are field defects that do not respect the vertical meridian.

Binasal Hemianopia

They are bilateral nasal defects usually caused by involvement of arcuate fibres of both eyes. Rarely, it may be caused by pressure upon the temporal aspect of the optic nerve or anterior portion of the chiasma, as in cases of aneurysm, pituitary tumour and vascular infarction.

CONCLUSION

Binocular visual field charting is an important part of ocular as well as neurological examination. It not only aids in differentiating an ocular lesion from a neurological lesion, but serves as an important diagnostic tool for localising the site of lesion and assessing the extent of damage.

6 Neuro-Otology

Sathiya Murali, Srividya, Mohan Kameswaran

Investigations for neuro-otological systems may broadly be classified into investigations for the vestibular system and investigations for the auditory system.

QUANTITATIVE TESTS FOR VESTIBULAR FUNCTION

Quantitative tests of physiologic processes under vestibular control can be useful in identifying the cause of a patient's symptoms, confirming a finding noted on clinical examination, planning a therapeutic intervention and monitoring the response to that intervention.

Electronystagmography

Electronystagmography (ENG) remains the most useful laboratory test in the evaluation of patients with complaints of dizziness or vestibular disturbance.[17] ENG can provide diagnostic information when there is a suspicion of unilateral or bilateral vestibular hypofunction.

Electro-Oculography

Electro-oculography (EOG) is typically used to record eye movements during ENG testing based on the corneo-retinal potential (electrical charge potential between cornea and retina). The eye acts as an electrical dipole along its long axis. Movement of this dipole relative to the surface electrodes produces an electrical signal corresponding to eye position. Horizontal eye movements can typically be resolved to an accuracy of 0.5°C. The sensitivity of EOG is less than that of direct visual inspection (approximately. 0.1°C). Visual inspection of small amplitude eye movements directly or with Frenzel's lenses or an ophthalmoscope is important for documentation of low amplitude nystagmus. Vertically aligned electrodes sense voltage associated with eye and lid movements, so EOG cannot be used in the quantitative assessment of vertical eye movements. Torsional eye movements cannot be measured with EOG. For this reason it is important for the person performing the study to look at the eyes either directly or with Frenzel's lenses in place, during positioning testing so that vertical torsional nystagmus caused by posterior canal "Benign Paroxysmal Positional Vertigo" is not missed. Calibration is accomplished by asking the patient to look at targets that are placed at the centre of the oculomotor range and at 10° and 15° eccentrically in the horizontal plane. Errors can occur if there is a restriction of ocular motility on calibration testing or if the patient is unable to follow instructions for the calibration tasks. The corneo-retinal potential, which provides the basis for EOG, varies with the amount of light striking the retina and necessitates keeping the room illumination constant. Surface impedance of the skin, which has an influence on recorded electrical potentials, changes with perspiration and the calibrations have to be checked frequently.

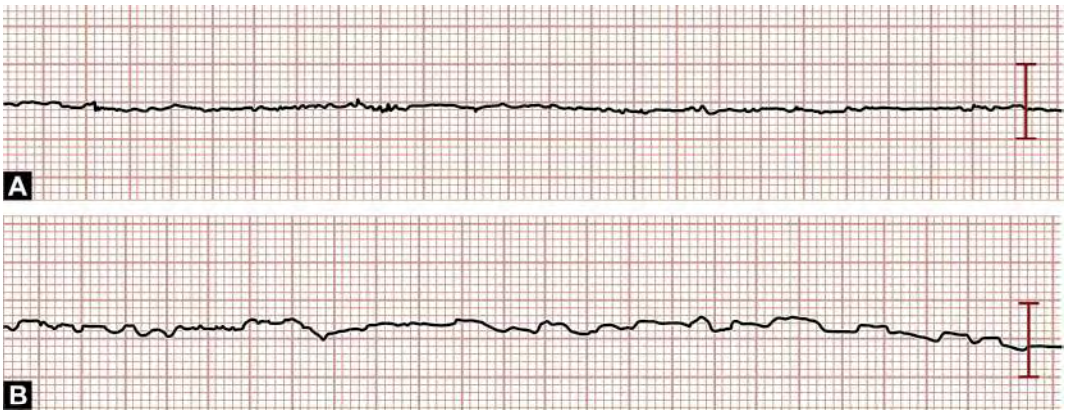
Video-Oculography/Videonystagmography

Video-oculography (VOG) is infrared (IR) imaging analysis which uses the conventional black and white camera. The eyes are illuminated with IR light. Eyes are not reactive to IR light, and hence can be viewed while in total darkness, thus eye fixation is eliminated. The eye movements are recorded by an IR video camera and converted into a digital format through software that documents the eye movements (Fig. 1). Horizontal and vertical tracings of eye movements are produced by the camera tracking the pupil of the eye.

Advantages of VOG include accuracy of 0.1–0.5°, contact free recording of eye movements and ease of handling. Rotatory eye movements in benign paroxysmal positional vertigo (BPPV) can be detected only in VOG.

Static tests include spontaneous nystagmus and gaze nystagmus. Spontaneous nystagmus is suitable for recording non-evoked eye movements with eyes closed

Fig. 1: Video-oculography



Figs 2A and B: Electronystagmography showing spontaneous nystagmus with (A) Eyes open. (B) Eyes closed

and with eyes open (Figs 2 and 3). The effects of fixation suppression can be determined.

Gaze Nystagmus

Here the eye movements are measured while the patient is fixating on a target. Nystagmus caused by CNS lesions can be differentiated from that caused by peripheral vestibular lesions. CNS nystagmus may be horizontal, vertical or rotatory. It often shows considerable variations in amplitude and tends to decline slowly, if at all, with time. If horizontal, CNS nystagmus usually beats to the right in rightwards gaze and to the left on leftwards gaze, and is usually not suppressed by ocular fixation. This is in contrast to nystagmus caused by a peripheral lesion (Fig. 4). Here it is horizontal, always beats in one direction (usually towards the normal side and suppressed by ocular fixation).[24] Nystagmus is named after the direction of the fast component which is the corrective movement of the eyes generated by the CNS. The vestibular system generates the slow phase of nystagmus which is directed to the opposite side (Table 1).

DYNAMIC TESTING

Saccade Testing

The patient is instructed to fixate a series of randomly displayed dots or lights at eccentricities of 5–30° saccades. Saccades typically begin with a latency of 180–200 milliseconds after presentation of a target. Saccade velocity increases linearly with amplitude up to about 20° but remains relatively constant for higher amplitudes. Healthy subjects consistently undershoot the target for saccades more than 20° (Fig. 5). Asymmetries in saccade amplitude or peak velocities can provide localising

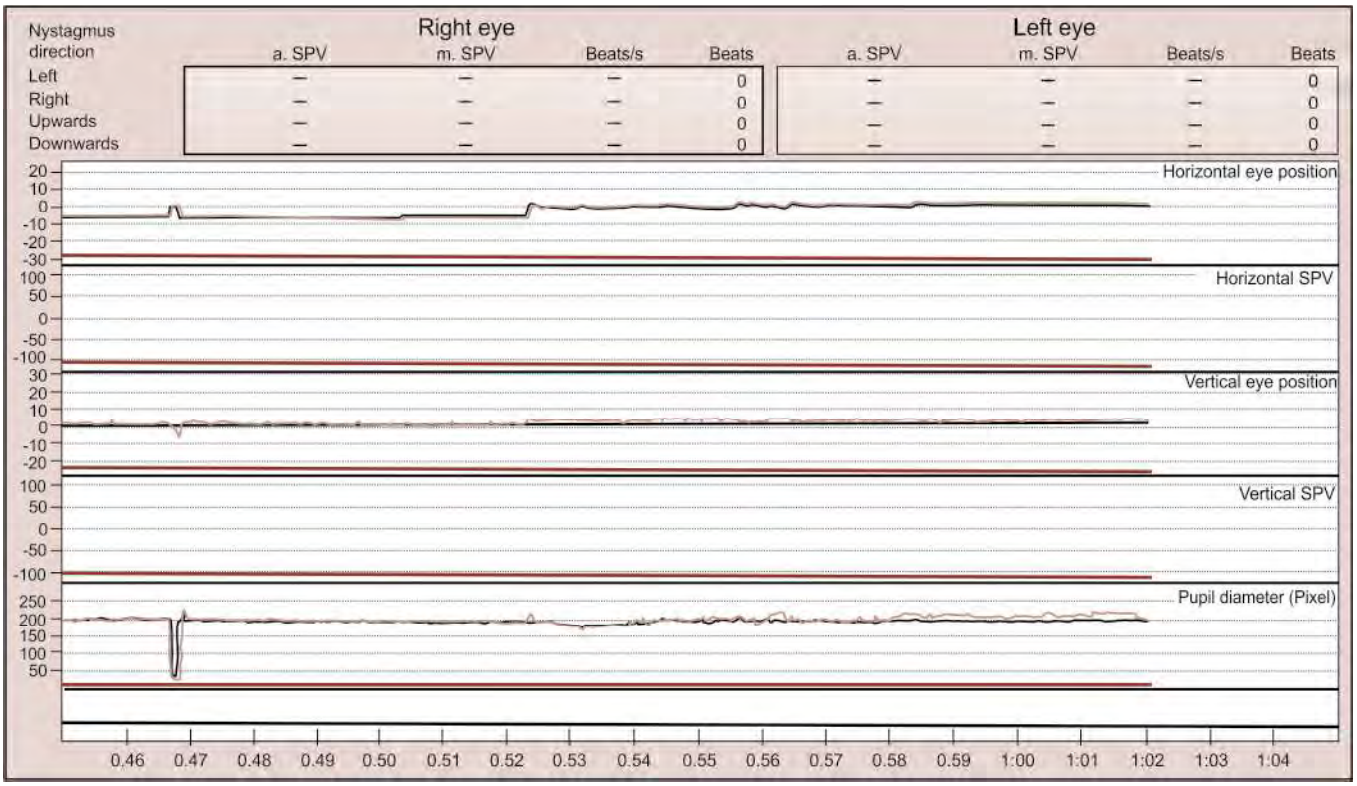


Fig. 3: Video-oculography showing absence of spontaneous nystagmus

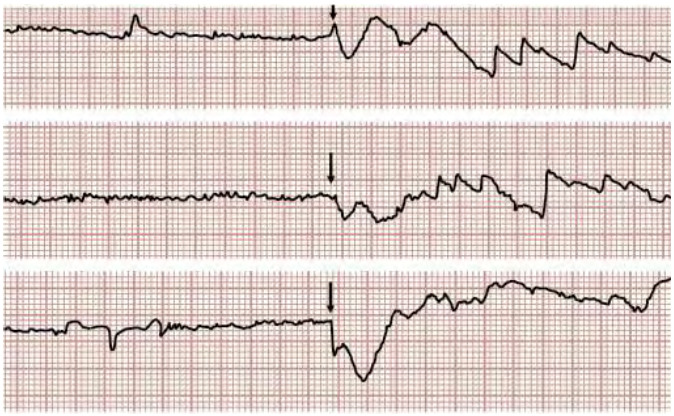


Fig. 4: Left acute vestibular neuronitis

Table 1: Features differentiating central from peripheral causes of vertigo

Features	*Central*	*Peripheral*
Imbalance	Severe, mostly constant	Mild to moderate, mostly episodic
Neurologic symptoms	Frequent	Rare
Nystagmus	- Changes direction in different gaze positions - No change with visual fixation	- Unidirectional in all gaze positions - Decreases with visual fixation
Hearing loss	Rare	Frequent
Nausea	Variable, may be absent	Severe
Recovery by central compensation	Slow	Rapid

information (Fig. 6). With EOG, the speed of abducting saccades seems to be lower than that of adducting saccades, although recordings with search coil and IR technique suggests that the opposite is actually the case.

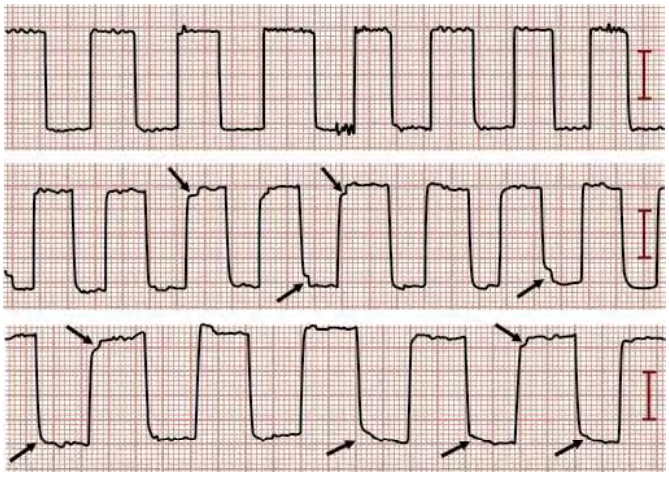


Fig. 5: Normal saccades

Smooth Pursuit

The patient is asked to watch a target that moves horizontally in a sinusoidal fashion at a low frequency with position amplitude of 20° in each direction (Fig. 7). Inspection of the waveform of the tracking eye movement is often of greater diagnostic use than absolute measure of gain and phase. "Catch up" saccades are typically made when pursuit responses are decreased. Saccadic pursuit is characterised by the occurrence of these saccades in a "stair-step" pattern. Such patterns are seen in cerebellar disease and also may occur with decreases in pursuit gain that occur with ageing.

Saccadic substitution of smooth pursuit is seen in neurological lesions (Fig. 8).

Disorganisation of pursuit eye movements with wandering slowed inaccurate tracking is seen in brainstem lesions (Fig. 9).

Optokinetic Testing

Testing is often performed with the subject surrounded by a visual scene that moves completely in one direction at

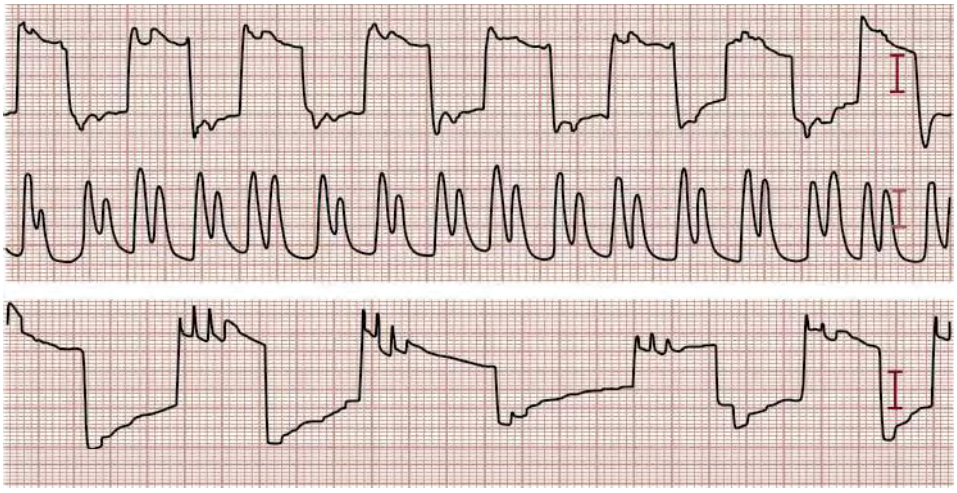


Fig. 6: True overshoots in brainstem encephalitis

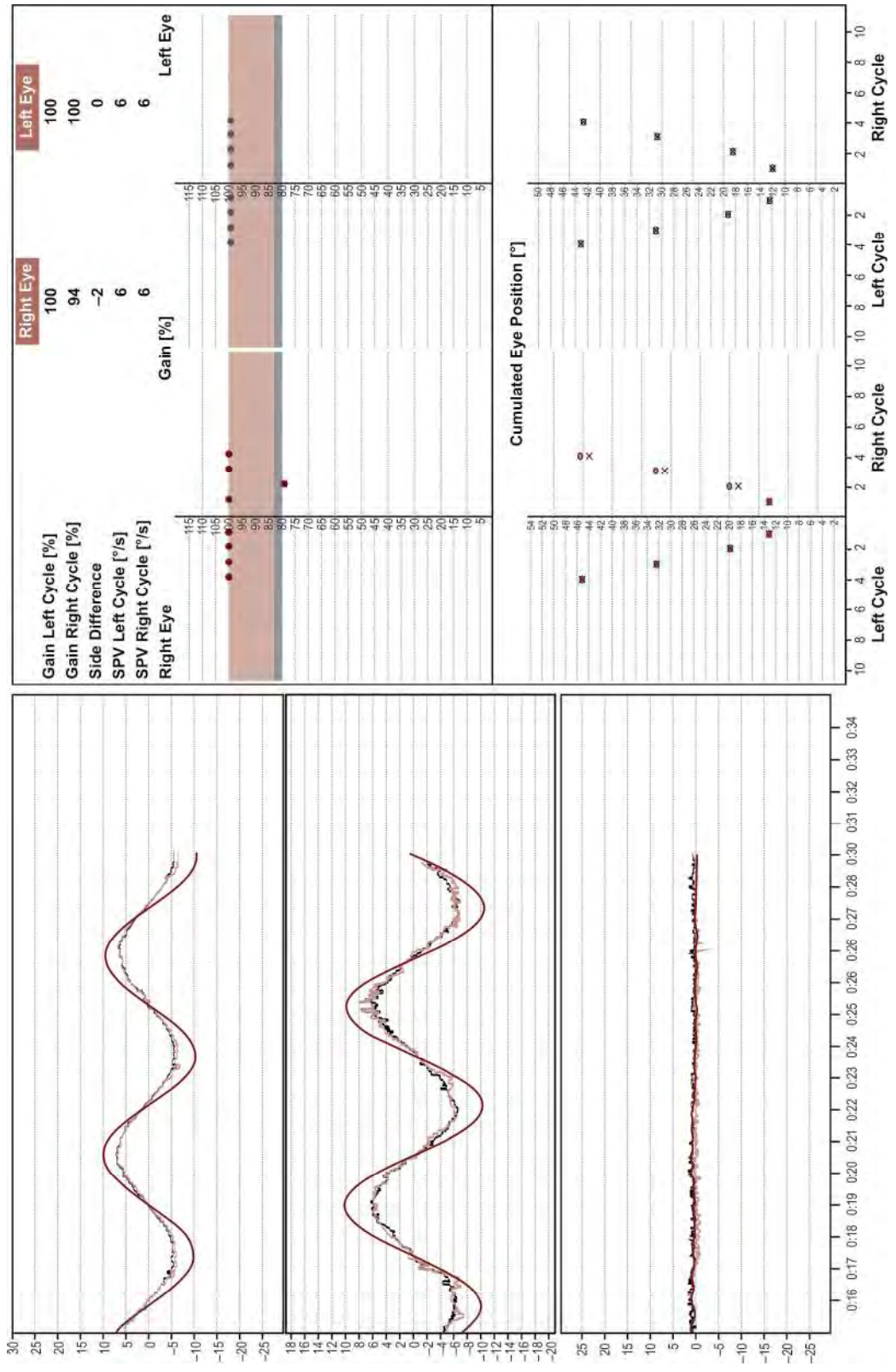


Fig. 7: Normal smooth pursuit—video-oculography recording

velocities of 30–60° per second (Fig. 10). The optokinetic tracing response is a nystagmus in the plane of motion of the visual scene (Fig. 11). Response gain (slow-phase eye velocity/velocity of the visual scene) is measured, and the profile of slow-fast component interaction is assessed. In general, slow-phase abnormalities on optokinetic tests parallel those detected with smooth pursuit testing, whereas fast-phase abnormalities are correlated with those detected on saccade testing. OKAN is a nystagmus that persists immediately after the room lights and illumination of optokinetic stimulus are extinguished. It is attributable to central velocity storage mechanisms that perseverate vestibular and optokinetic responses. Asymmetries in OKAN have been reported

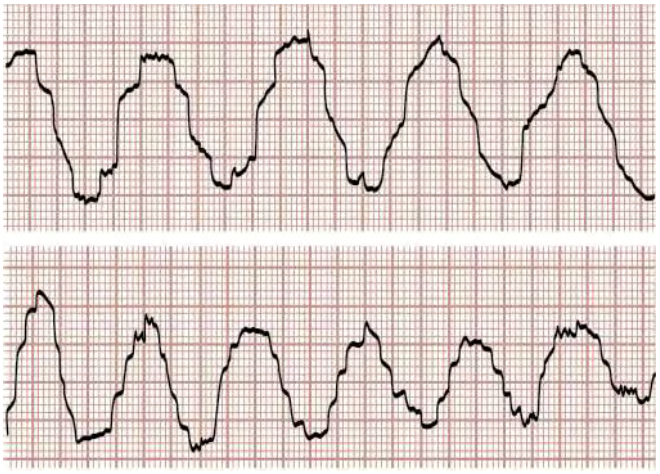


Fig. 8: Saccadic substitution of smooth pursuit

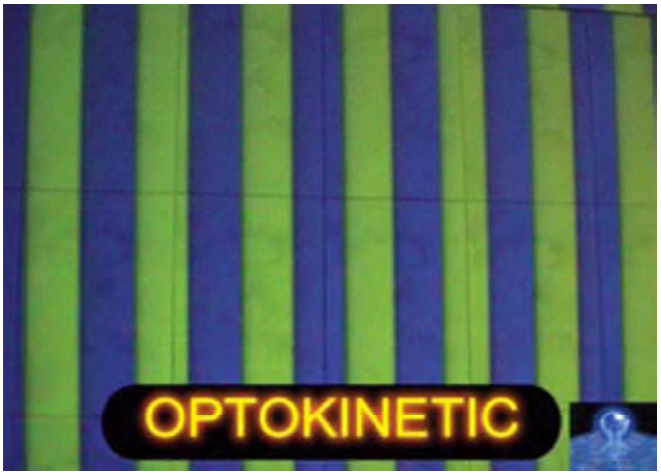


Fig. 10: Optokinetic stimulus in video-oculography

in patients with unilateral vestibular hypofunction induced by removal of an acoustic neuroma and other CNS lesions (Figs 12 and 13). Responses are greater in amplitude and longer in duration for stimulus and eye movement towards the side of the lesion.[23] Although a true optokinetic stimulus requires full-field movement of a visual surround, similar diagnostic information can usually be obtained from motion of a drum or bars of light that occupy only a portion of the visual field.

Caloric Testing

Caloric testing remains the most useful laboratory test in determining the responsiveness of a labyrinth. It is one of the few tests that allow one labyrinth to be studied independently of the other. The stimulus can be applied relatively easily with techniques that are commonly available. Caloric testing relies on stimulating or cooling the vestibular system by alternately heating and cooling the external auditory canal with water or air. The horizontal canal is affected most by such temperature effects, because it is located closest to the external auditory canal and is oriented in the plane of the temperature gradient

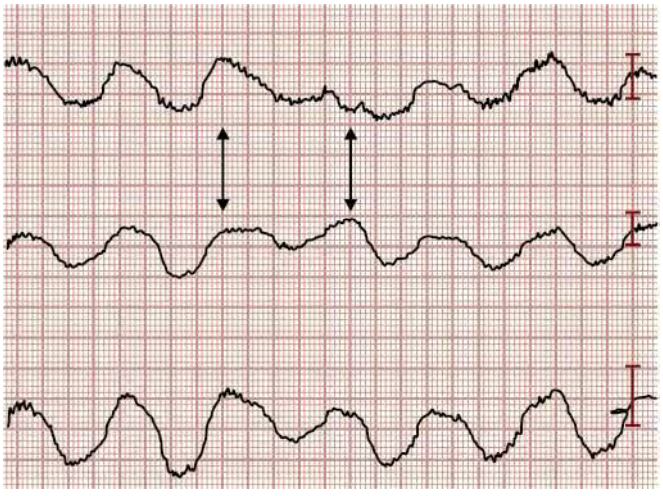


Fig. 9: Wandering slow inaccurate tracking in brainstem lesion

that is produced in the temporal bone from irrigation with water.

Calorics cause a response in two ways. The first is a convective component, with the temperature gradient across the horizontal canal resulting in a density difference within the endolymph of the canal. When the horizontal canal is oriented in the plane of gravity, the more dense fluid falls to the lower position in the canal, whereas the less dense fluid falls to the upper portion in the canal. In the presence of gravity, there is a flow of endolymph from the cooler (more dense) region to the warmer (less dense) region. This movement of fluid within the canal deflects the cupula, thereby leading to a change in discharge rate of vestibular nerve afferents. Endolymph flows towards the ampulla for warm irrigation and away from the ampulla for cold irrigation. This effect depends on head position.

The second component does not vary with head position and results in an excitation of the horizontal canal when the ear is warm and in an inhibition when it is cooled. The non-convective component may be a result of a direct temperature effect on hair cells or vestibular nerve afferents[9] or cupular displacement resulting from pressure changes in the membranous duct.[20]

Alternate binaural caloric testing as pioneered by Fitzgerald and Hallpike[19] is the most commonly used testing protocol. Cool water (30°C) and warm water (44°C) are administered for 60–90 seconds to each ear in a set order such as right warm, left warm, right cold and left cold. Such a stimulus results in heating effect in the temporal bone that lasts for 10–20 minutes, although nystagmus frequently decays over a much shorter time course (2–3 minutes) because of the effects of adaptation.[5] The prolonged heating effect of a single temperature irrigation requires that at least 10 minutes be allowed between successive irrigations. Biphasic caloric irrigations can reduce nausea and shorten the wait between stimuli for about 2 minutes by irrigating with water at 43.5°C for 45 seconds, 30.5°C for 65 seconds and 43.5°C for 23 seconds.[30]

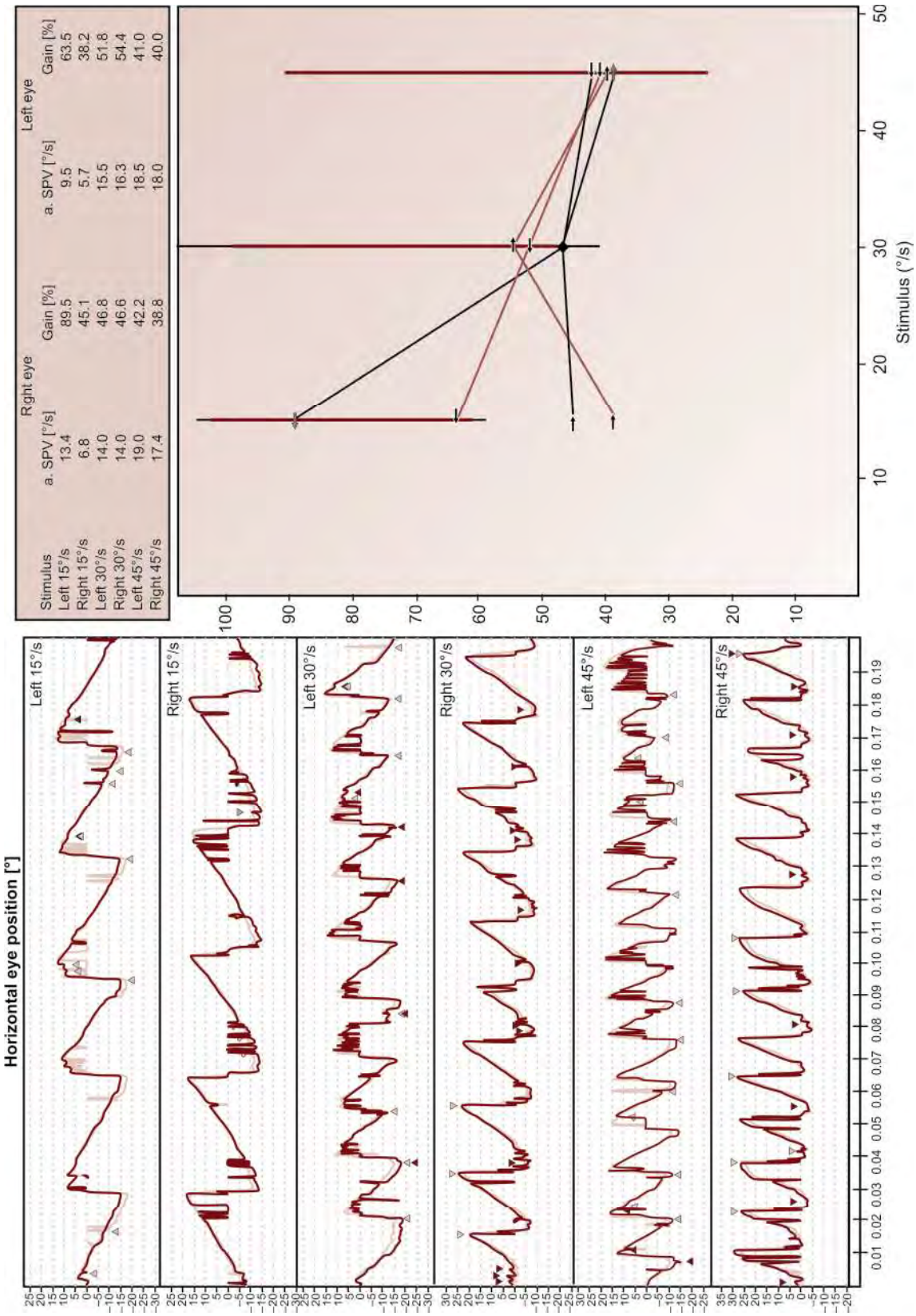


Fig. 11: Normal OKAN on video-oculography

Interpretation

In the normal vestibular system, adequate, equivalent responses should be obtained from each ear. A normal caloric response does not rule out a vestibular pathology however, since this test only measures a response from part of the labyrinth at a very low frequency of stimulation.

Slow-phase velocity is determined for each recording for use in the following calculations:

- Unilateral weakness (UW) is used to evaluate symmetry. In many clinics, a UW greater than 25% is significant.

  % UW = [((RC + RW) – (LC + LW))/(RC + RW + LC + LW)] × 100[27]

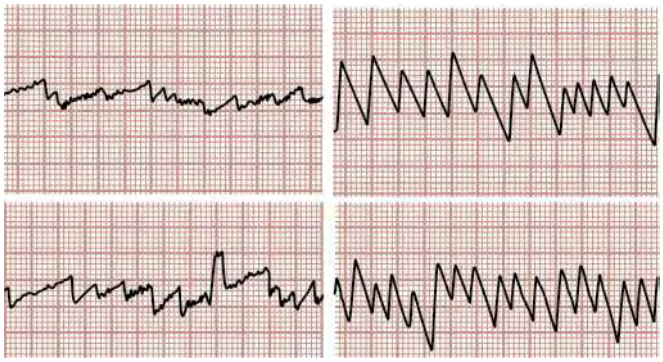


Fig. 12: Asymmetric optokinetic nystagmus in medullary compression—Arnold-Chiari malformation

Where RC is right cold; RW is right warm; LC is left cold and LW is left warm.

A negative number indicates right unilateral weakness, and a positive number indicates left unilateral weakness. Unilateral weakness is indicative of a peripheral vestibular lesion that involves the nerve or end-organ on the side of the weakness.

- Bilateral weakness: Average caloric responses of 6° per second or less are consistent with a bilateral weakness. Borderline bilateral weakness is noted when the average responses are between 7° and 9° per second. Abnormally weak bilateral responses may be due to bilateral peripheral vestibular pathology or central interruption of the vestibulo-ocular reflex (VOR).[22] When a borderline bilateral weakness or bilateral weakness is observed, drug effects should be excluded.
- Directional preponderance (DP): If the patient has spontaneous nystagmus, DP is evident. In general, a DP greater than 20–30% is considered significant. In the absence of a spontaneous nystagmus, DP may be a central sign indicating asymmetric sensitivities of central vestibular neurons to inhibitory-excitatory stimuli or asymmetries in the inputs from these central vestibular neurons to extraocular motor neurons.

  % DP = [((LC + RW) – (RC + LW))/(RC + RW + LC + LW)] × 100.[27]

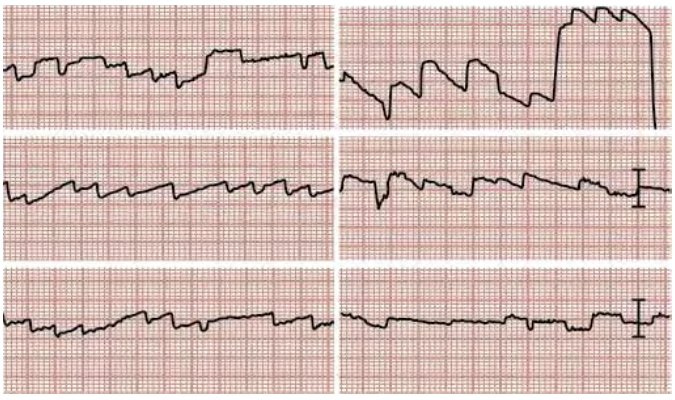


Fig. 13: Multiple sclerosis

Rotatory Chair

Unlike caloric tests, rotational tests analyse the responses of both labyrinths together. They require a high torque motor-driven chair and relatively advanced software to analyse the results. Rotatory chair testing is useful in assessing vestibular function in patients with suspected bilateral vestibular hypofunction, in patients receiving vestibulotoxic medications and in children who may not tolerate caloric testing. Clinical situations in which findings on rotatory chair may provide useful information in paediatric patients include determining whether a failure to achieve normal developmental milestones is in part based on absent vestibular function, evaluating vestibular function after meningitis and determining the presence or absence of vestibular function in patients undergoing genetic evaluation for hearing loss. Cerebellar abnormalities produce specific changes that can be evaluated with rotatory chair testing. Velocity storage mechanisms that are responsible for prolonging the VOR time constant compared with that of vestibular nerve afferents are sensitive to the orientation of the head with respect to gravity. In healthy subjects, tilting the head downwards at the onset of post-rotatory vertigo results in an immediate suppression of the stored velocity response, but patients with midline cerebellar lesions near the uvula and nodulus have VOR time constants that are normal in the upright position and are not affected by post-rotatory tilt.[10] Patients with cerebellar lesions caused by Arnold-Chiari malformation have tilt suppression that is intermediate between that of healthy patients and patients with midline cerebellar lesions. Abnormally high gain on rotational testing also has been noted in cases of cerebellar atrophy.[4]

Parameters that are commonly examined include gain, phase and symmetry. Gain is the ratio of the amplitude of eye movement to the amplitude of head movement (stimulus). Phase is a parameter that describes the timing relationship between head movement and reflexive eye response. When the head and eyes are moving at exactly the same velocity in opposite directions, they are said to be exactly out of phase or 180°. If the reflex eye movement leads the head movement, a phase lead is present, and if the compensatory eye movement trails the head movement, a phase lag is present. Symmetry is a comparison of the slow component of the nystagmus when rotated to the right compared with rotation to the left. A fourth parameter that may be studied is the time constant. This is a measure of the time (in seconds) required for the VOR gain to exponentially decrease by 63%. It is measured in step-velocity testing after the chair is rapidly stopped and is reduced in patients with vestibular dysfunction. Note that the time constant and gain may be reduced in inattentive patients as well.

Each of these parameters is useful in diagnosing and localising vestibular lesions. Studies have shown that patients with a unilateral peripheral vestibular lesion may exhibit asymmetric responses to rotation. On the other hand, patients with a compensated unilateral

lesion show a characteristic pattern of decreased gain and increased phase lead at low-frequency stimulation. Bilateral peripheral vestibular lesions are characterised by low gain and phase lag with sinusoidal testing. Rotational chair testing is ideal in the assessment of these patients because, unlike caloric testing, higher frequencies are also tested and both labyrinths are stimulated spontaneously.

This allows for accurate determination of remaining vestibular function. In fact, Arriaga et al. determined that rotational chair testing has a sensitivity of 71% for diagnosing peripheral vestibulopathies, as opposed to only 31% sensitivity for caloric testing/ENG.[3] Although it is a more sensitive test for peripheral vestibular disorders, rotational chair testing has a specificity of only 54%, compared with the 86% specificity of ENG. Both tests are, therefore, complementary and should be used in the diagnosis of peripheral vestibular dysfunction. Finally, abnormalities may be observed with central vestibular deficits. Thurston et al. showed that gains may be increased in some individuals with cerebellar deficits.[37] Cerebellar atrophy, on the other hand, may result in a disorganised nystagmus pattern with beat-to-beat variability in the amplitude.

Shortcomings of Conventional Vestibular Function Tests

- Only assess lateral semicircular canal function
- Do not assess overall balance
- Relatively insensitive
- Lack of correlation with symptoms.

Vestibular Evoked Myogenic Potentials

Vestibular evoked myogenic potentials (VEMP) is a sound-evoked muscle reflex, or sonomotor response that can be recorded using evoked potential techniques by acoustical stimulation of the saccule (Fig. 14). VEMP has become an important investigative modality in the evaluation of patients with balance disorders.

Recent studies have demonstrated that healthy subjects exhibit a burst of activity in the ipsilateral sternocleidomastoid (SCM) muscle in response to auditory

Fig. 14: Vestibular evoked myogenic potentials

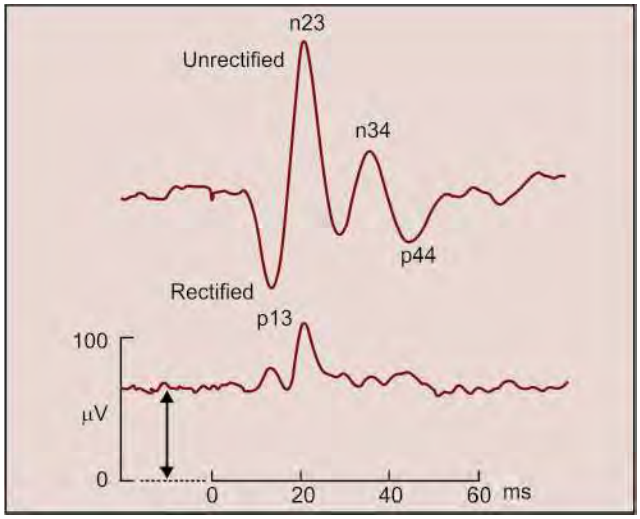


Fig. 15: Normal vestibular evoked myogenic potential recording

stimulation [100–200 msec rarefaction clicks, 95 dB sound pressure level (SPL)].[10] These click evoked responses are recorded with electromyography (EMG) and occur at a short latency (12 msec) relative to the onset of the click stimulus (Fig. 15).

The responses are abolished on the side of surgery after unilateral vestibular neurectomy.[11] In a study of patients who had previously experienced an episode of vestibular neuritis, Murofushi et al.[28] identified 10 of 47 patients who went on to experience an episode of posterior canal BPPV on the side with vestibular hypofunction. These patients had intact sound evoked myogenic responses whereas many of the patients who did not have BPPV developed no responses to the click stimuli on the affected side. Since, the posterior canal receives innervation from the inferior vestibular nerve, these investigators interpret this study in conjunction with electrophysiologic evidence of click evoked activation of saccular afferents,[29] to indicate that responses are a result of selective activation of vestibular nerve afferents innervating the sacculus. In addition to aiding the diagnosis of otolith function, patients with superior canal dehiscence syndrome also seem to have an approximately 20 dB increase in sensitivity to VEMPs.[35]

VEMP may be absent in basilar artery migraine, Ménière's disease, idiopathic bilateral vestibulopathy (IBV) and vestibular schwannoma. VEMP may be increased in superior semicircular canal dehiscence syndrome (Fig. 16) and perilymphatic fistula. Asymmetrical amplitudes may be seen in Tullio's phenomenon and spasmodic torticollis. Delayed VEMP is seen in cases of technical error, central lesions like brainstem stroke, multiple sclerosis (Fig. 17), spinocerebellar degeneration and migraine.

Computerised Dynamic Posturography

Computerised dynamic posturography (CDP) is a series of vestibulo-spinal tests for quantitatively assessing balance function in different set-ups which simulate

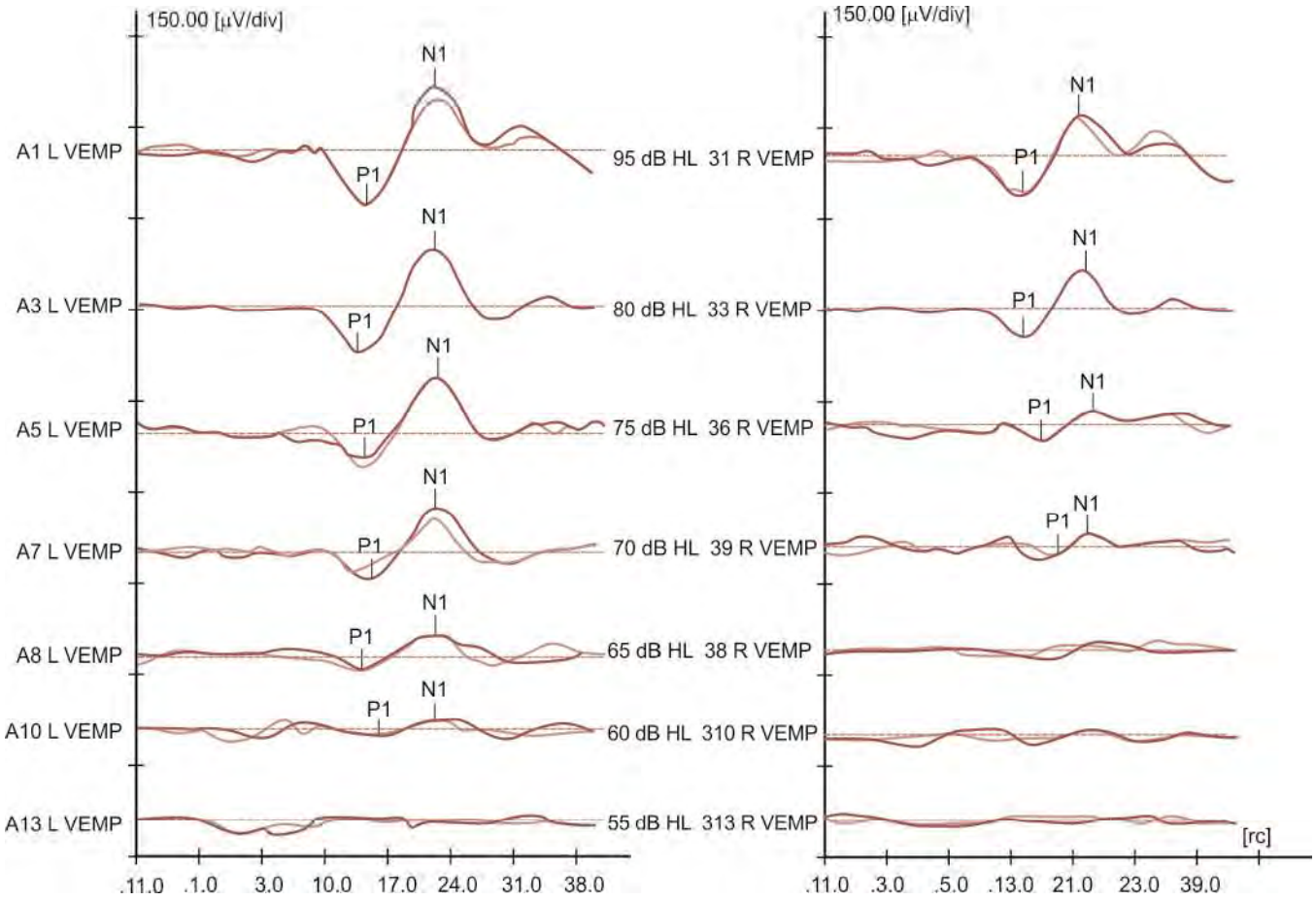


Fig. 16: Increased vestibular evoked myogenic potential in superior semicircular dehiscence

conditions encountered in our day-to-day life. In our daily life we come across various circumstances in which our vestibular system is assaulted and challenged. A person with a normal balance function can effectively counteract these challenges and maintain equilibrium, whereas a person with a deranged balance function fails to do so. For this, our balance system must be able to do two things:

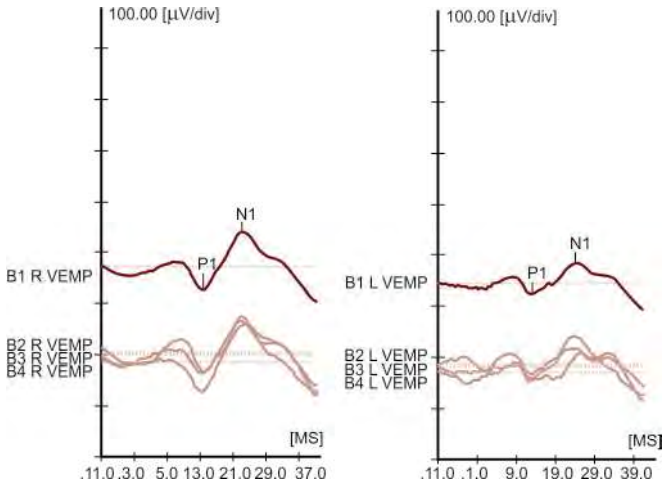


Fig. 17: Delayed vestibular evoked myogenic potential in multiple sclerosis

- To determine the position of centre of gravity relative to the base of support.
- To execute automatic movements in the body muscles such that the centre of gravity is brought back to a balanced position in a timely manner and effectively.

CDP tests these two faculties of the balance system separately. The first portion is tested by the Sensory Organisation Test (SOT) and the second portion by Motor Coordination Test (MCT).

The functional integrity of the sensory system (i.e. the inputs to the balance system, viz. the visual, proprioceptive and vestibular) is assessed by the SOT. This test detects any defect in the subject's ability to effectively use the somatosensory/visual/vestibular inputs to maintain balance and the ability of the CNS to select the appropriate input when contradictory and conflicting information is sent through these three input systems.

The second part of the CDP test is the Motor Coordination Test or Motor Control Test (MCT). It is useful in assessing the integrity of efferent motor pathways in the control of balance. That is, whether the requisite motor activity for the maintenance of balance is being properly executed after sensory information from the somatosensory/visual/vestibular senses have been received by the CNS.[1]

Cranio-Corpography

Cranio-corpography (CCG) basically consists of photographically recording the patient's head and body movements as he or she performs the Unterberger's stepping test and the Romberg's test.[1] CCG is a very quick, non-invasive and very simple objective test of vestibular and balance function. It is totally physiological, easily repeatable and provides a photographic and quantifiable record, and can even be done in children and in patients with perforated ear drums.

It was, however, found that CCG too has some inherent limitations, and though CCG helped to partially widen our view of the balance system, CCG was found to be a crude test of the vestibulo-spinal system and quite fallacious at times. It was due to these shortcomings of ENG and CCG that posturography became relevant. However, posturography or its present modification called computerised dynamic posturography is a test of systemic balance function and it does this by examining the vestibulo-spinal reflex mechanism.

INVESTIGATIONS FOR THE AUDITORY SYSTEM

Investigations for the auditory system aim to evaluate the integrity of the auditory system from the peripheral organ which is the ear to the auditory cortex. Audiological investigations have recently gained sophistication both with the accuracy as well as in their use as a neuro-otological tool. The tests that are currently available aim to answer the following questions:

- Is there a defect in the auditory system?
- What is the quantity of the defect?
- What is the site of the defect?
- Are multiple levels involved?

Answering these questions will eventually help the clinician understand prognosis. The tools in the armamentarium include:

- Bedside tests (see chapter on Acoustic Schwannoma)
- Puretone audiogram
- Impedance audiometry
- Electrophysiological tests:
  - Otoacoustic emissions (OAE)
  - Electrocochleography (ECoG)
  - Auditory brainstem response (ABR)
  - Auditory steady state response (ASSR)
  - Middle latency responses (MLR)
  - Long latency response (LLR)

Puretone Audiogram

Puretone audiogram is a subjective test, which is used to detect if there is definite hearing loss, the type (sensorineural/conductive) and quantity of the hearing loss. It helps in measurement of hearing threshold at various frequencies. Hearing threshold is the minimum sound that a subject may hear for a given frequency. The disadvantages of the test are that it is purely subjective, cannot be performed in a child, a patient who is not co-operative and in unconscious patients.

Impedance Audiometry

Impedance audiometry has been one of the major advancements in the field of otology and neuro-otology in recent times. The uses of impedance can briefly be summarised as:

- Objective differentiation between conductive and sensorineural hearing loss.
- Measurement of middle ear pressure (tympanometry) and evaluation of Eustachian tube function.
- Differential diagnosis of whether the lesion is cochlear or retrocochlear.
- Identification of site of lesion in facial palsy and certain brainstem pathologies (stapedial reflex test).

Impedance audiometry being a very useful objective test, it is mandatory to include this test in the routine diagnostic test battery.

ELECTROPHYSIOLOGICAL TESTS

Otoacoustic Emissions

Otoacoustic emissions (OAE) are biological sounds from the normal cochlea. This sound is generated in the outer hair cells of the cochlea. This is another objective test for hearing screening in neonates and young children which has now become popular.

Electrocochleography

Auditory evoked potentials are classified according to the time window within which they are recorded. Electrocochleography (ECoG) is a short latency evoked potential that reflects the summed activity of a large number of peripheral auditory nerve fibres as well as the response of generators located within the cochlea itself. The ECoG consists of three distinct evoked potentials:

1. The cochlear microphonic (CM)
2. The summating potential (SP)
3. Compound action potential (AP)

The CM and the SP are both intracellular potentials. The CM is a potential that mirrors the stimulus and it reflects the instantaneous displacement of the basilar membrane[6] (Fig. 18).

The SP is characterised by a baseline shift in the CM and it is also thought to originate from within the hair cells of the organ of Corti.[13,14,36]

The AP is the third evoked potential of the ECoG complex. It is a recording of the synchronous response of a large number of auditory nerve fibres to the acoustic stimulation. It is an onset response that is recorded using click stimulus.

Procedure

The ECoG is recorded either extratympanically or intratympanically. It is rerecorded extratympanically via an active electrode placed within the ear canal or on the drum itself and a reference electrode placed on the contralateral mastoid process. Intratympanically the

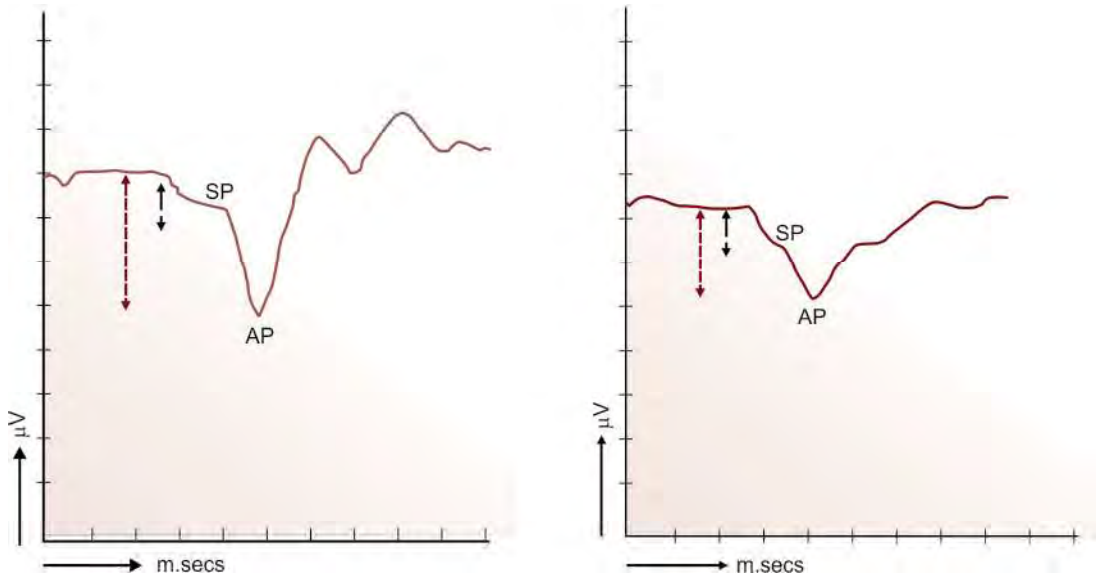


Fig. 18: Normal ECoG and ECoG in Ménière's disease—comparative increase of summating potential

ECoG is recorded using a transtympanic needle electrode placed on the promontory of the middle ear.

Clinical Applications

- To assess hearing in the paediatric age group.[12,18]
- Tool to assess auditory status in patients suspected of having Ménière's disease.
- As a part of retrocochlear assessment.
- During otoneurologic surgery.

Auditory Brainstem Response

Auditory brainstem response (ABR) is a recording of the synchronised response of a large number of neurons in the lower portions of the auditory pathways. While first described by Sohmer and Feinmesser in 1967,[31] later Jewette and colleagues gave detailed descriptions of ABR (Fig. 19).[25,26] Origin of various waves has been described in Table 2.

The ABR is recorded using differential amplification with the active electrode positioned at the vertex or high forehead with reference electrodes positioned at the mastoids or the ear lobes. It requires brief acoustic stimulus with a relatively rapid onset. The most common stimulus used to evoke the ABR is a 100-msec rectangular pulse or click. A click is the ideal stimulus for eliciting the ABR as it results in a large number of auditory nerve fibres firing at approximately the same time.

Table 2: Origin of various waves of auditory brainstem response[2]

Wave	*Site of origin*
I	Cochlear nerve (distal end)
II	Cochlear nerve (proximal end)
III	Cochlear nucleus
IV	Superior olivary complex
V	Lateral lemniscus/inferior colliculus
VI and VII	Neural generators, not definitely known

Clinical Applications

It is a tool for estimating auditory sensitivity as well as for a range of otoneurologic applications.

It is by far the most commonly used of the auditory evoked potentials, due to the fact that it can be recorded by non-invasive techniques and is easy to record, not strongly affected by attention, sleep state, sedation and anaesthesia or age.

Neuro-otological Applications

Historically, the recording of ABR has been to assist with detection of lesions affecting the auditory pathways between the cochlea and the inferior colliculus. Such lesions include space occupying lesions,[15] such as vestibular schwannomas and pathology, caused by factors such as multiple sclerosis, stroke or trauma. Generally, this is accomplished by examining the morphology of the click evoked ABR measures using a high-level stimulus.

Assessing Neurological Disorders

There are several different ways in which the click-evoked ABR is altered by the presence of retrocochlear pathology (Table 3). In some cases, the ABR recorded in the ear with retrocochlear pathology will have absent or distorted components. For example, an ABR that is absent in an ear with audiometric thresholds in the normal to moderate range, an ABR that is characterised only by early peaks or an ABR with a wave V amplitude that is smaller than the amplitude of wave I have all been interpreted as evidence of potential abnormality.[32] Such grossly abnormal ABR morphologies are thought to reflect partial conduction block or significant loss of cross fibre synchrony along the neural pathways between the cochlea and the inferior colliculus.

A second measure which is commonly used to diagnose potential retrocochlear pathology is prolonged

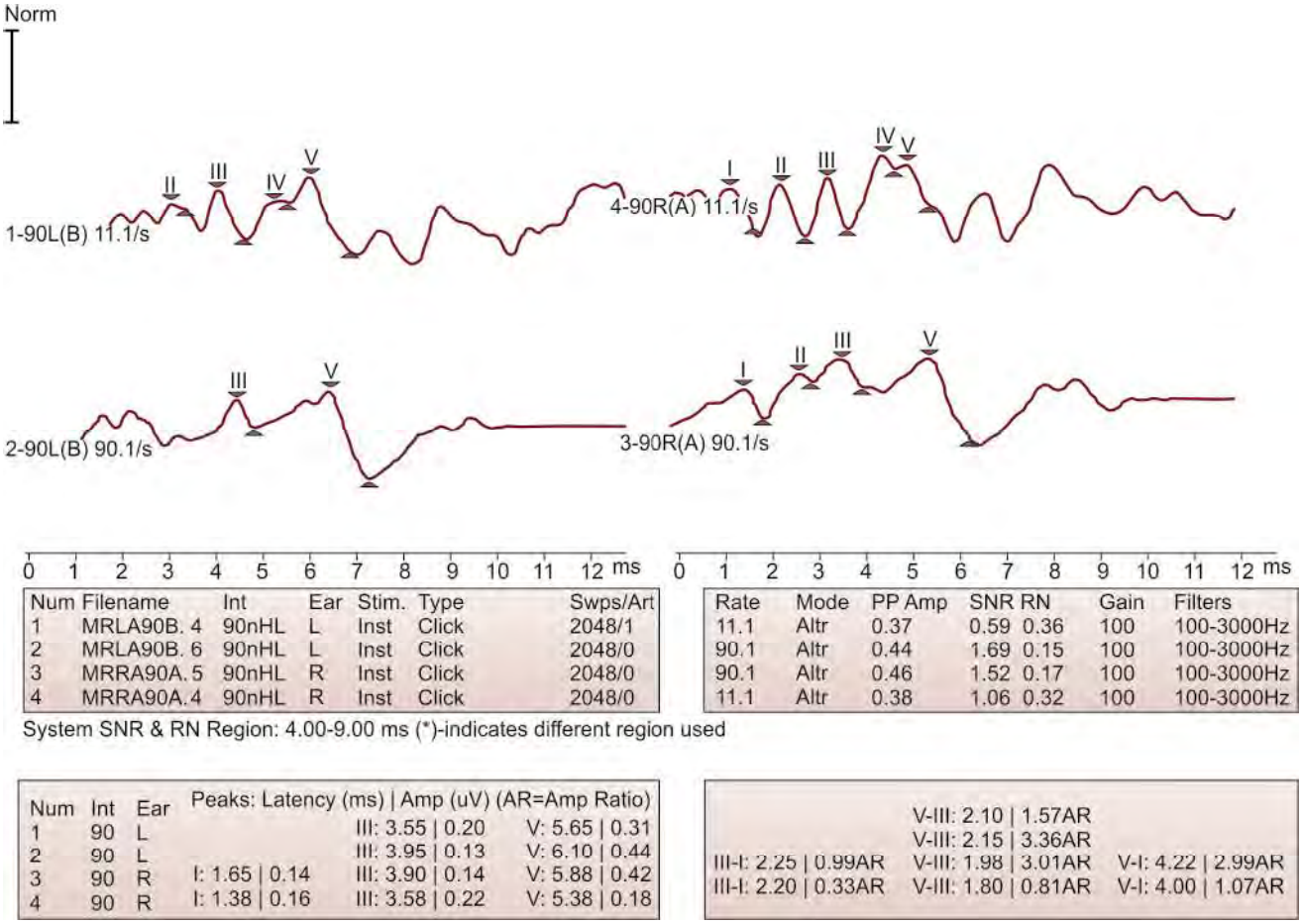


Fig. 19: Normal BERA tracing showing I to V waves

Table 3: Different parameters of auditory brainstem response for abnormality criteria

Parameter measured	*Normal value (millisecond)*	*Criteria for abnormality (millisecond)*
1. I-III IPL	2	More than 2.2
2. III-V IPL	2	More than 2.2
3. I-V IPL	4	More than 4.4
4. Interaural latency difference of wave V	Less than 0.3	More than 0.3
5. Morphology of wave V	Present	Absent

inter-peak or absolute latencies. In most persons, a high level click stimulus will generate an ABR with a wave V latency of approximately 5.5 msec and with an I-V latency of approximately 4.0 msec.[34] The presence of a tumour growing within the internal auditory canal may be slow neural conduction velocities. When the absolute latency of wave V is longer than 6.3–6.4 msec or when the interval between wave I and wave V of ABR is longer than 4.4–4.5 msec, the presence of retrocochlear pathology must be suspected.

Finally, since tumours occurring on the auditory nerve are typically unilateral, a very commonly used technique for identifying potential retrocochlear lesions is to compare the latency of wave V and the length of the inter-peak latency between ears.

A difference of more than 0.3–0.4 msec between the latency of wave V of ABR in the two ears or an interaural difference in the length of the I-V interval of greater 0.3 msec can also be considered indicative of potential retrocochlear pathology.

Several investigators have attempted to quantify the sensitivity and relative specificity of ABR as a tool for identifying ears with vestibular schwannomas.[8,21,33,38] The results of these studies vary. Some of these variants can be attributed to the choice of parameters used to categorise the ABR as normal or abnormal. Additionally, recent studies have revealed lower degrees of sensitivity. This trend may reflect the fact that the increased resolution and availability of imaging techniques allow for the identification of tumours while they are still small. There is some indication that the accuracy of ABR as a predictor of retrocochlear status may be related to tumour size,[8,21] and some authors have proposed a derived response technique that they call a stacked ABR that may be able to identify small tumours with a greater degree of accuracy than is possible using conventional techniques.[16]

It is used to monitor the status of the auditory nerve during skull base surgery, because ABR is not strongly affected by anaesthesia. It provides continuous feedback

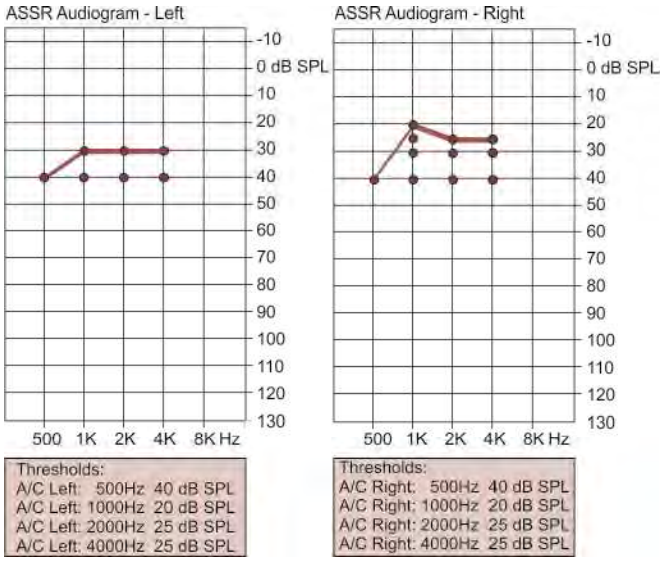


Fig. 20: Auditory steady state response

about the status of the auditory nerve during surgery. The major drawback to using ABR as a monitoring device is that it has a small amplitude potential that cannot clearly be identified in the on going electroencephalographic activity. Rather, resolutions of ABR require averaging. Thus, even in ideal situations, where the ABR is relatively robust and the noise levels are manageable it is not possible to provide the surgeon with instantaneous feedback relative to auditory nerve function.

Auditory Steady State Response

Auditory steady state response (ASSR) is a far-field auditory potential that is evoked using continuous stimulation. As a potential clinical tool, it has several advantages over the more commonly used ABR. For example, with ASSR it is easier to distinguish between severe and profound hearing loss as opposed to ABR (Fig. 20).

ASSR is a reasonable alternative to the ABR as a tool for estimating frequency-specific thresholds in paediatric populations.[7]

Middle and Long Latency Evoked Potentials

Although the ABR and the ASSR reflect neural activity at the level of the brainstem, there are a series of responses that can be recorded which reflect the synchronous activity of large groups of neurons located at the level of the auditory midbrain and cortex. Two of these responses are the auditory middle latency response and long latency responses. They can be elicited using more frequency specific stimuli and are not as dependent on neural synchrony as are the ABR and ECoG, hence MLR may be used for estimating low frequency sensitivity or to evaluate auditory function in persons in whom auditory dys-synchrony/neuropathy is suspected to be present. The LLR has an additional advantage that it can be evoked using speech rather than tonal stimuli. The disadvantages of these are that, the responses are adversely affected by sedation/ anaesthesia and responses are not fully developed until or after 10 years of age.

The audiological test battery which includes the above mentioned tests is mandatory rather than a single test to arrive at a reasonable correct diagnosis.[7]

Editorial Comments

Vestibular Function Test in Unconscious Patients

Vestibulo-ocular reflex elicited by irrigating the external auditory canal with ice cold water has proved to be a very reliable bed-side investigation to evaluate unconscious patients. It not only provides objective indication of the depth of unconsciousness, evidence of ocular nerve palsies, internuclear ophthalmoplegia but is also a guide to prognosis.

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Cochlear and Brainstem Implants

Mohan Kameswaran, Kiran Natarajan

Auditory neural prostheses, such as cochlear implants and brainstem implants, have proved to be extremely significant innovations in neuro-otology in the last decade. This has been made possible due to advances in biomedical engineering and the development of materials that are biocompatible. These neural prostheses are devices, which help to restore lost or deficient neural function by integration of external circuitry with neuronal circuitry. Cochlear and auditory brainstem implants offer safe and effective hearing habilitation and rehabilitation for profoundly deafened adults and children.[21] Rather than repairing diseased organs, the emphasis has changed to bypassing them using bionic prosthetic devices. Auditory neural prosthetic intervention must be done as early as possible due to the phenomenon of neural plasticity. Neural plasticity is the ability of the central nervous system to be programmed to learn a new task. This fades between 6 years and 8 years of age.

Electrophysiological tests and imaging modalities are now available to accurately pinpoint the level of lesion in the auditory pathway. In 99% of sensorineural hearing loss, including congenital hearing impairment, the primary pathology is in the cochlea. In the past, patients with profound sensorineural hearing loss unresponsive to amplification with hearing aids had to cope by lip-reading or learning sign language. The first attempt to electronically stimulate the auditory system occurred nearly two centuries ago. The auditory system is unique in its organisation which gives it the opportunity to receive and integrate external electronic circuits. This is due to the low rejection potential of the inner ear as well as the nervous system.

COCHLEAR IMPLANTS

A cochlear implant is a surgically implantable device that helps restore hearing in patients with severe or profound hearing loss, unresponsive to amplification by hearing aids. Cochlear implants are electronic devices designed to detect mechanical sound energy and convert it into electrical signals that can be delivered to the cochlear nerve, bypassing the damaged hair cells of the cochlea. The cochlear implant represents the most successful attempt by man, till date, to interface a prosthetic device with the nervous system. The implant helps convert sound into electrical signals. These signals are then sent to an array of electrodes implanted surgically in the cochlea. The implant system preserves the tonotopic map of the cochlea (Fig. 21).

History of Implants

Djourno and Eyries published the first description of cochlear implants in 1957. In 1961, House used a single channel cochlear implant and in 1984, Clark developed a multichannel implant. Initially, 22 channel implants were used which have now been replaced by 24 channel straight arrays followed by the 24 channel contour implants. The first paediatric cochlear implantation was done in the United States in 1987.[14]

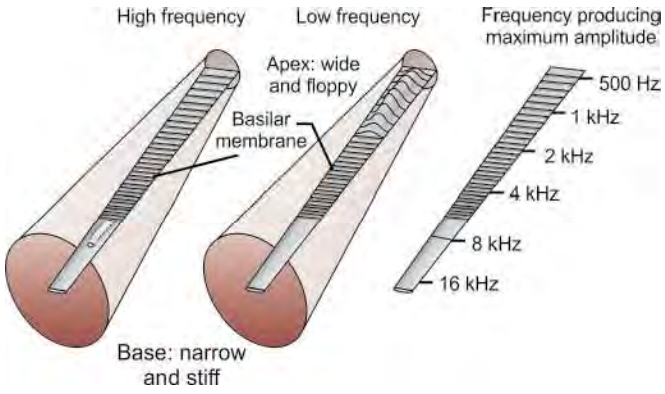

Fig. 21: Tonotopicity of the basilar membrane

Components

The implant has external components consisting of a microphone which receives sound and transduces it into an electrical waveform, a speech processor which divides the signals into components for each of the electrodes and a transmitting coil which sends the signals across the scalp to the internal components. The internal components include a receiver-stimulator which receives the signals from the transmitting coil and sends it to the electrode array which is implanted in the scala tympani of the cochlea. Speech processors are currently available as body worn and ear level speech processors (Fig. 22).

Selection Criteria

Bilateral profound cochlear hearing loss unresponsive to amplification by the most powerful hearing aids is the indication for an implant. All children below the age of 10 years who have congenital or acquired profound hearing loss and who will not benefit from conventional hearing aids and all adults who have lost hearing after acquisition of language are candidates.[9] The only true pre-requisite is an intact auditory nerve (Fig. 23).

Post-lingual candidates do extremely well with an implant and in pre-lingual and per-lingual candidates, an important factor influencing candidacy is neural plasticity and the emphasis is now on implantation as early as possible to maximise speech understanding and perception. In very young children, language acquisition is easier, hence the need for early implantation. Owing to the loss of neural plasticity in older pre-lingually deaf

Fig. 22: Components of cochlear implant

people, the response to implantation may not be optimal and extensive pre-operative counselling regarding realistic expectations is crucial. Candidacy criteria have changed and benefit has increased as cochlear implant technology has advanced.[1] Today not only patients with profound deafness, but also patients with severe hearing loss are considered candidates for implantation.

The expanded indications for implantation are related to age, additional handicaps, residual hearing and special aetiologies of deafness. The minimum age for implantation in children has come down and children as young as 6 months of age have been implanted. As the cochlea is at full size at birth, there is no anatomic difficulty with electrode insertion in very young children.[2]

Medical and radiological criteria have expanded to include significant cochlear abnormalities, including additional handicaps, as in syndromic deafness.

A multi-disciplinary approach is required involving the surgeon, audiologist and speech therapist and auditory verbal habilitationist. The patient and his family must highly be motivated for the implant.

Contraindications

Cochlear aplasia (Fig. 24), absence of auditory nerves, retro-cochlear cause of deafness, central deafness, presence of external or middle ear infections and co-existent severe medical illness are contraindications.

Pre-Operative Evaluation

Pre-operative evaluation includes a complete ENT and head and neck examination, including assessment for additional handicaps, haematological tests, TORCH serology, if required, and skiagram of chest and ECG for assessing fitness for surgery.

An audiologic assessment is the primary means of determining implant candidacy.[12] Audiological and electrophysiological investigations include pure tone (Fig. 25) and impedance audiometry (Fig. 26), otoacoustic emissions (OAE) (Fig. 27), brainstem evoked response audiometry (BERA) (Fig. 28), auditory steady state response (ASSR) (Fig. 29), aided audiometry (Fig. 30) and a hearing aid trial. Promontory stimulation testing can be done in older children and adults to assess the response of the cochlea to electrical stimulation.

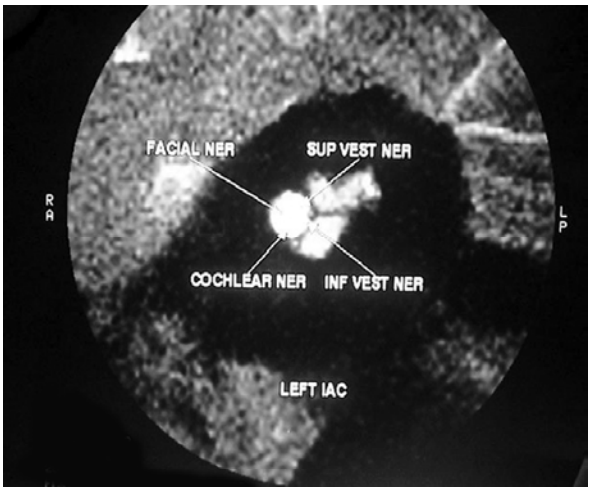

Fig. 23: MRI of the internal auditory meatus showing intact cochlear nerve

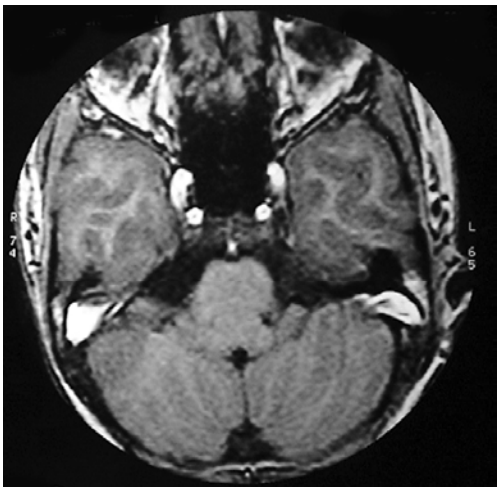

Fig. 24: Michel's aplasia—absent cochlea

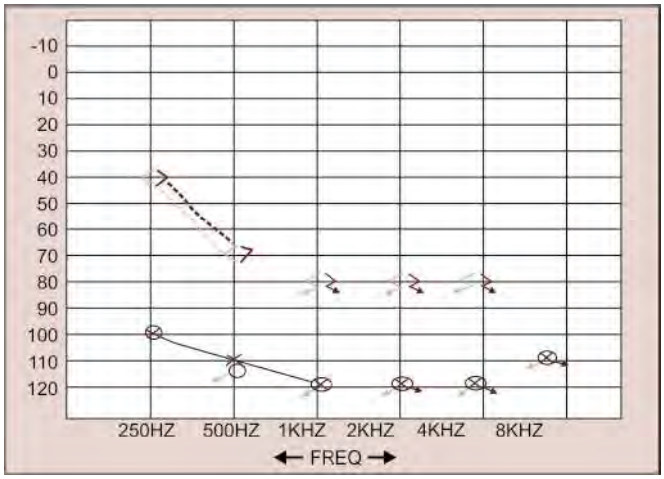

Fig. 25: Puretone audiometry showing profound hearing loss in both ears

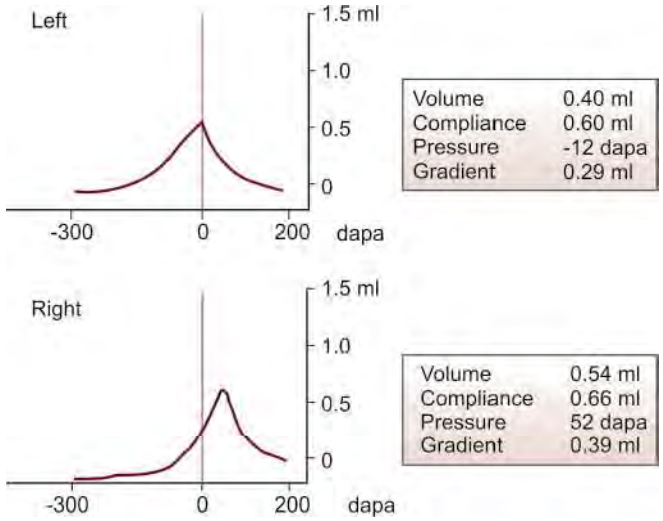

Fig. 26: Impedance audiometry showing bilateral 'A' type with absent reflexes

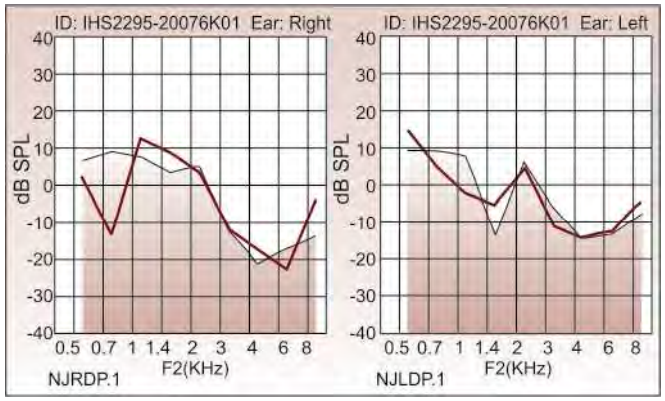

Fig. 27: Absent otoacoustic emissions

Magnetic resonance imaging is the gold standard investigation for the assessment of cochlear anatomy and the vestibulocochlear bundle (Figs 31 and 32). It reveals anomalies like Mondini's and Michel's aplasia, labyrinthitis ossificans and absent eighth nerve. Specialist referral, e.g. to an ophthalmologist or cardiologist, may be required in case of an additional handicap or syndrome where cochlear implantation involves a number of unique issues. Rapid advances in genetics and molecular biology are revolutionising our understanding of congenital deafness and genetic counselling should play an important role in prevention.[19] Pre-operative rehabilitation is important before surgery. Counselling patients and parents, prior to implantation to develop realistic expectations of the likely outcome, is vital.

Surgery of Cochlear Implantation

The goal of cochlear implant surgery is to insert the entire electrode array into the scala tympani with as little damage as possible to the structure of the inner ear.[23] The success of cochlear implantation depends on scrupulous attention to technique at all the various steps of the procedure. Implantation is a 1.5–2.5 hour procedure performed with strict aseptic precautions and is done under general anaesthesia. Surgery is essentially the same in children and adults because the anatomic

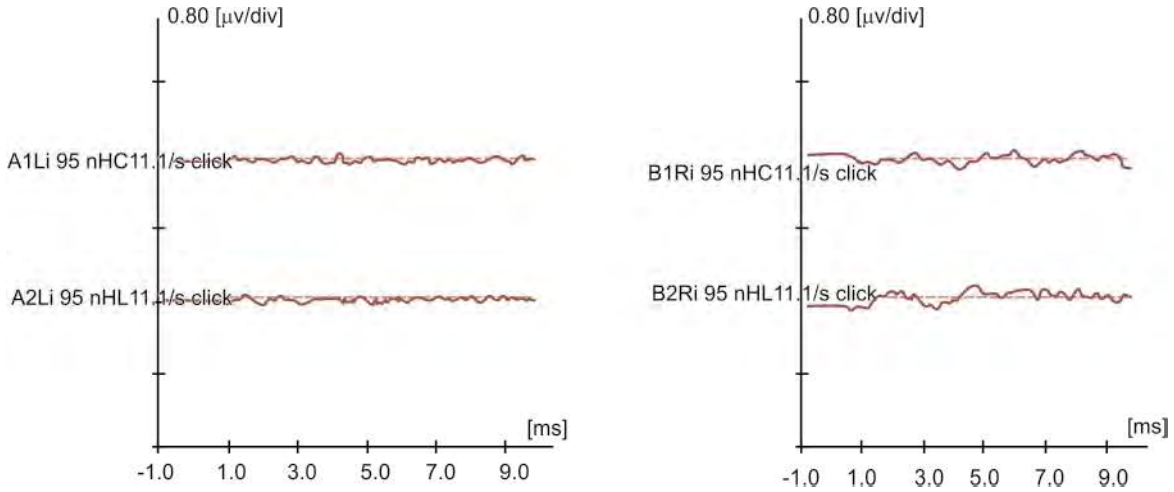

Fig. 28: Brainstem evoked response audiometry showing no peak at maximum intensity in both ears

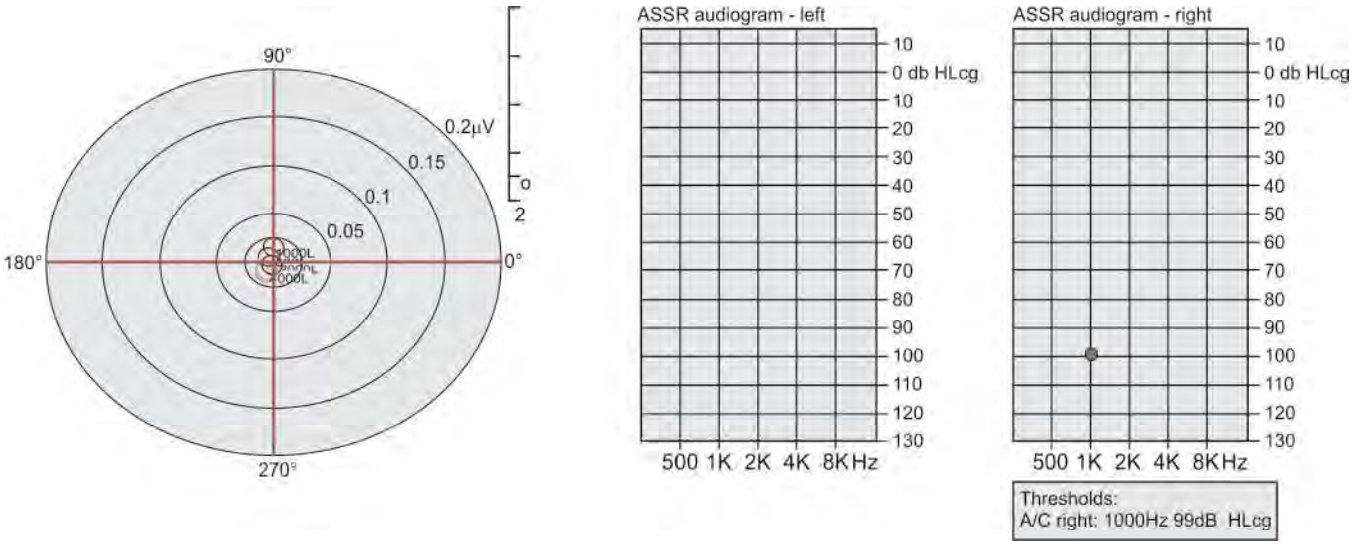

Fig. 29: Auditory steady state responses

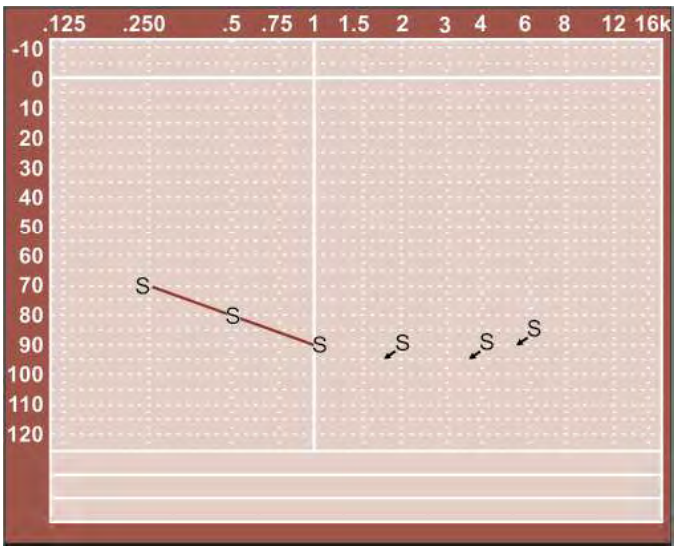

Fig. 30: Aided responses out of speech spectrum

structures are of adult configuration at birth. However, in very young children, there is a slightly increased risk of facial palsy.

The steps of surgery are:

- *Incision*: Usually an extended post-auricular incision is made to expose the mastoid cortex. The incision should be made more than 1 cm from the body of the implant.
- *Simple mastoidectomy*: The mastoid is drilled out to expose the mastoid antrum. Saucerisation of the cavity is not done (Fig. 33).
- *Posterior tympanotomy*: The facial recess is opened and the promontory and round window niche are exposed without exposing the facial nerve (Fig. 34).
- *Well for receiver-stimulator*: This is fashioned in the skull behind the mastoid cavity using a template as a guide and a groove is made to connect it to the mastoid cavity. Tie-down holes are made on either side of the well for securing the implant.

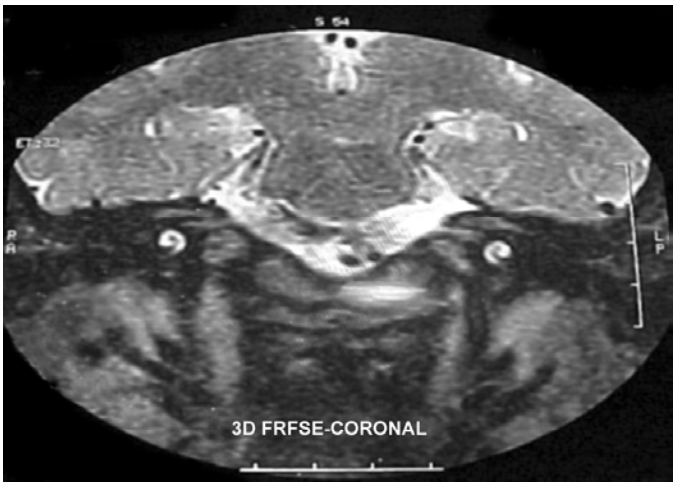

Fig. 31: MRI showing bilateral normal fluid-filled cochlea—comma sign

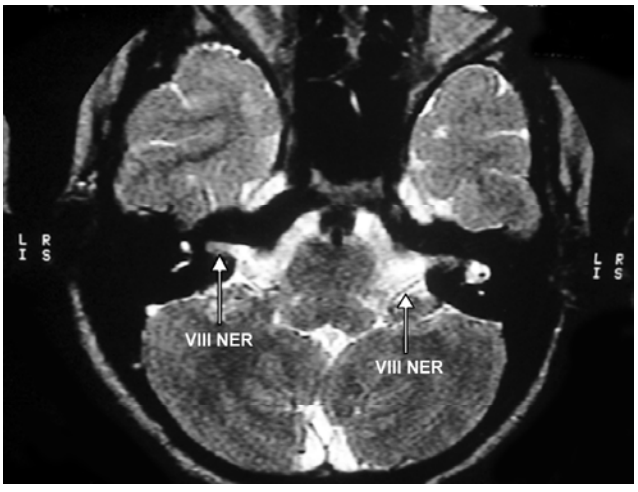

Fig. 32: MRI showing bilateral vestibulocochlear bundles

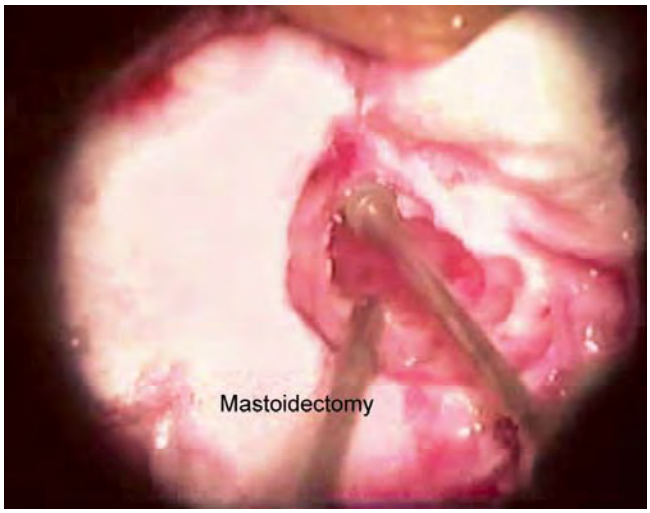

Fig. 33: Cortical mastoidectomy

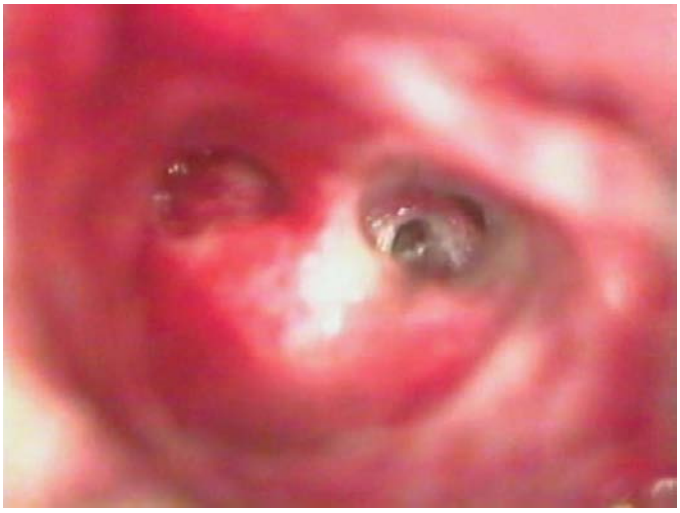

Fig. 35: Cochleostomy in progress

- *Cochleostomy*: The basal turn of the cochlea is opened anterior to the round window to make the axis of introduction of the electrode array straighter (Fig. 35).
- *Insertion of electrode array*: The electrode array is inserted atraumatically into the scala tympani using a claw (Fig. 36). Once the electrodes are inserted, diathermy should not be used.

Fixation of the device and electrode array and wound closure is done.

Electrophysiologic Testing or Neural Response Telemetry

Neural response telemetry (NRT) is performed after implanting the electrode array. This assures the team that the device is functioning and that the patient is receiving an auditory stimulus and responding appropriately.[4]

Post-Operative Care

A pressure dressing is applied for 3–4 days. Antibiotics and analgesics are administered in the post-operative period. The patient is called for review three weeks post-operatively for switch-on of the device (Fig. 37). Frequent mapping sessions are required and prolonged and intensive rehabilitation after implantation is essential. Rehabilitation aims at improving receptive language skills and expressive skills. Post-implantation rehabilitation can be important for some adult recipients, but appears critical for children to optimise the usefulness of an implant.[15]

With increasing experience in cochlear implantation, the indications for implant surgery have widened to include cochlear anomalies and multiple handicapped individuals. Implantation is beneficial in such situations. However, the surgeon must anticipate challenges during implantation and also the subsequent habilitation may be challenging.

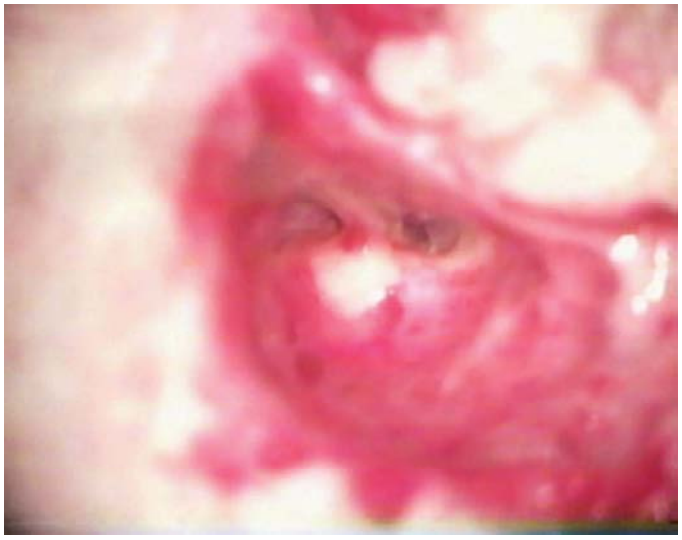

Fig. 34: Posterior tympanotomy

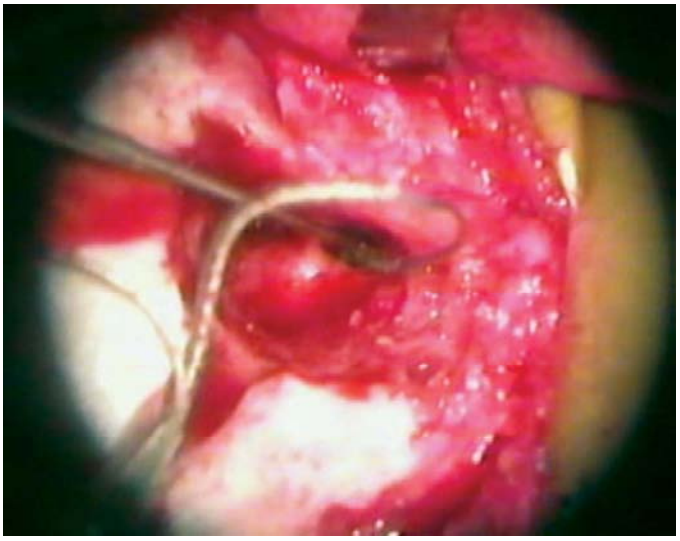

Fig. 36: Insertion of electrode array into the scala tympani of the basal turn of the cochlea

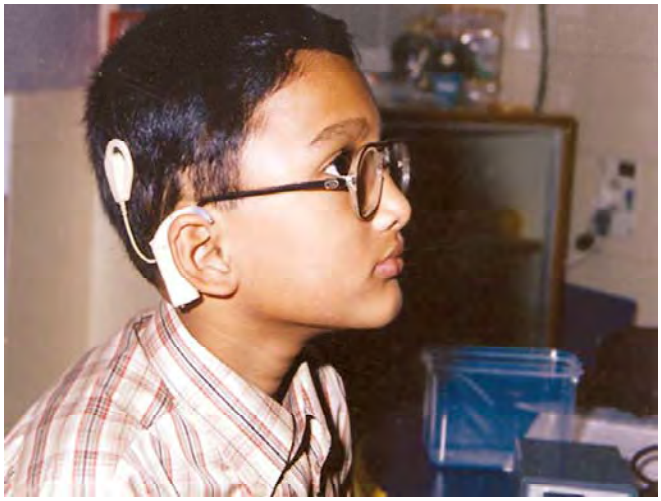

Fig. 37: Cochlear implantee

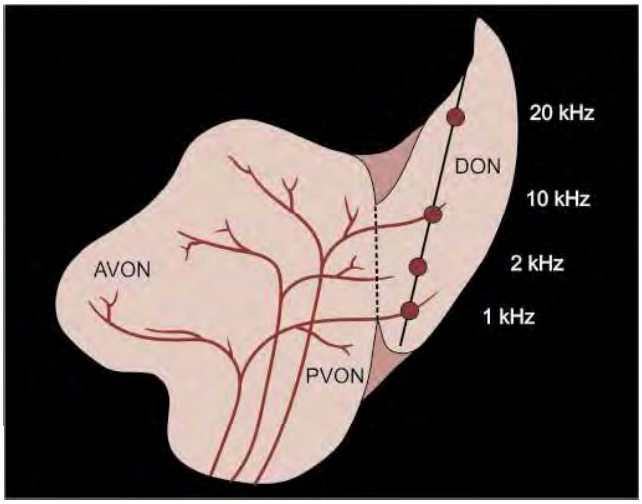

Fig. 39: Tonotopicity of the cochlear nucleus

Complications of Cochlear Implantation

Major complications include facial palsy, and implant exposure due to flap loss and wound infection. Other complications include facial nerve stimulation, device failure, deterioration of hearing, tinnitus, temporary balance problems, numbness of the scalp, loss of taste, electrode/device extrusion, CSF leak and meningitis.

The Future

Cochlear implant surgery and technology continue to evolve.[22] In the future, fully implanted devices, improved speech coding strategies, and cochlear hair cell and nerve growth factors used in conjunction with an implant may be available.[17]

AUDITORY BRAINSTEM IMPLANTATION

Auditory brainstem implant (ABI) is an effective means of hearing rehabilitation in patients with neurofibromatosis type 2. In such patients with damaged cochlear nerves on both sides, the brainstem implant bypasses the cochlear nerves and directly stimulates the cochlear nucleus[16] (Fig. 38). The cochlear nucleus has tonotopicity (Fig. 39).

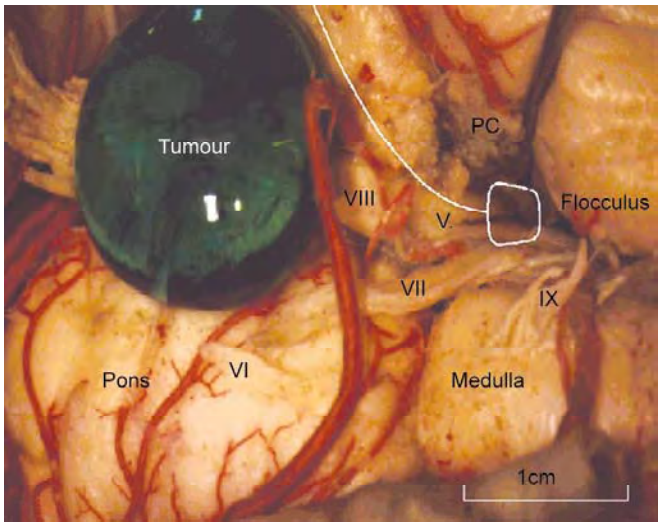

Fig. 38: Auditory brainstem implant placement in the lateral recess

Components

The ABI system commonly used is the Nucleus 24 ABI, which can be used with the Sprint body worn/Esprit behind the ear speech processor. It consists of a receiver-stimulator that receives and decodes the electrical signal from the speech processor and an electrode array, which delivers the signal to the surface of the cochlear nucleus within the brainstem. It has 21 electrodes, arranged in three of seven rows over a silicone electrode carrier. There are two ground electrodes; one plate electrode on the receiver-stimulator package and one ball electrode attached to a separate electrode lead. The receiver-stimulator is placed at least 10 mm behind the edge of the auricle and above the canthomeatal line and is angled 30–45 degrees posterosuperiorly. The stimulus is delivered by an external component comprising a microphone, a signal processor and a transmitter coil similar to a cochlear implant (Figs 40 and 41).

Indications for Auditory Brainstem Implant

Multichannel ABIs are currently indicated for patients with neurofibromatosis type 2 (NF2) and schwannomas involving the internal auditory canal or cerebellopontine angle.[10] Increasingly, ABI is being considered for non-tumour patients and even in children with congenital hearing loss before the loss of neuronal plasticity. In the near future, it may be used in bilateral temporal bone fractures and demyelinating diseases affecting the eighth cranial nerves, but sparing at least one cochlear nucleus.[18] Auditory brainstem implantation has also been recommended for use in cases of bilateral totally ossified cochleae in which a cochlear implant cannot be used.[8] It has also been reported to be useful in cases of bilateral absence of auditory nerves.[5,6]

The current criteria for ABI include evidence of bilateral seventh and eighth cranial nerve tumours involving the IAC or cerebellopontine angle, language competency, age > 12 years or older, psychologic suitability, willingness to comply with research follow-up protocol and realistic expectations.[18] Several factors can affect the

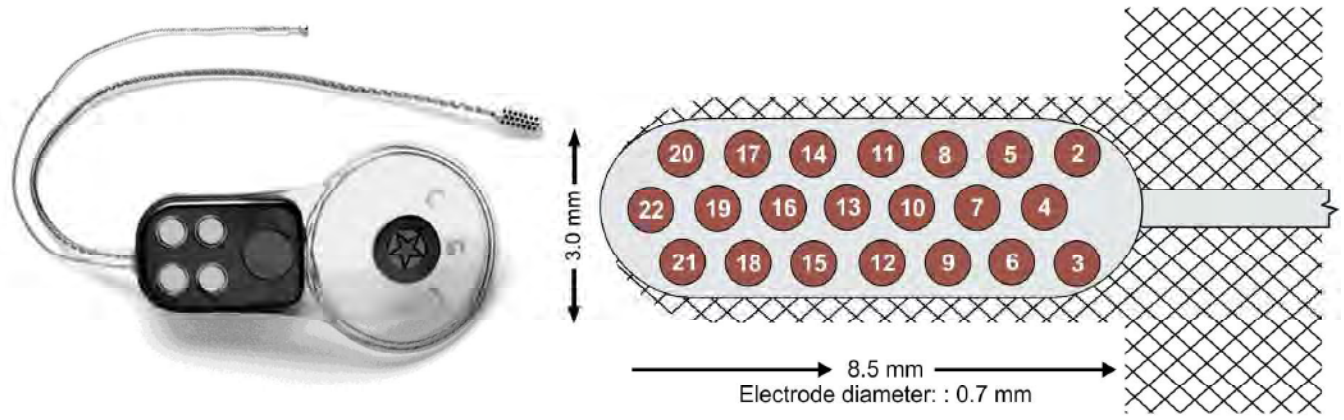

Fig. 40: Internal components of auditory brainstem implant

Fig. 41: External components of auditory brainstem implant

benefit received from an ABI. These factors may include size and location of auditory nerve tumours, degree and duration of hearing loss prior to surgery, and commitment and motivation to use the ABI.

Pre-operative counselling regarding the importance of such factors as expectations, personal motivation and family support is invaluable and the importance of regular use of the implant has to be stressed in order to maximise the benefits from the implant.

Pre-Operative Evaluation

Extensive pre-operative evaluation prior to ABI surgery is essential and a multi-disciplinary approach involving neurotologists, neurosurgeons, audiologists and anaesthetists is required. Prior to planning the surgery, assessment of the tumour and the hearing is vital. Comprehensive audiological tests, including pure tone audiometry, brainstem evoked response audiometry, otoacoustic emissions and auditory steady state response (ASSR), are required. Pre-operative MRI is very important because it may signal potential problems leading to non-stimulation such as a large lateral recess or tumour damage to the cochlear nucleus region and also helps to rule out other intracranial and spinal tumours (Fig. 42).

Auditory Brainstem Implant Surgery

For successful ABI surgery, a few important issues, such as patient selection, choice of device, choice of approach, technique of tumour removal, knowledge of micro-anatomical variations, intra-operative identification of the cochlear nucleus and prevention of complications, have to be considered.[20]

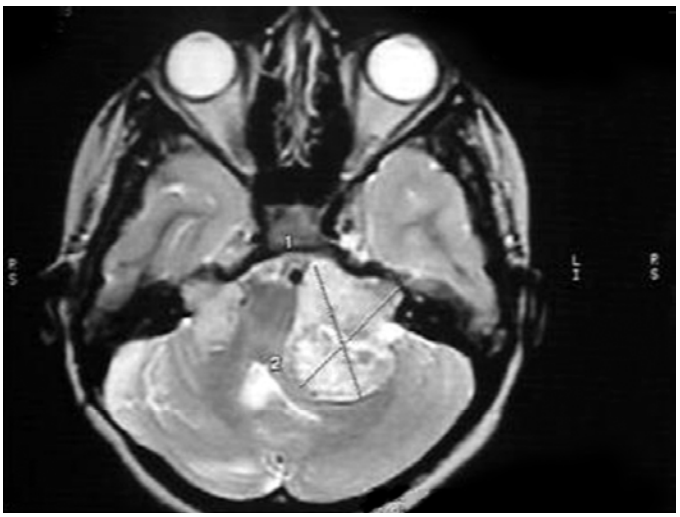

Fig. 42: MRI of neurofibromatosis type 2

During surgical removal of small NF, preservation of auditory nerve has to be attempted not only for auditory preservation but also to retain the option of using a CI in cases of total hearing loss.[13] Nerve monitoring is required and neuromuscular blocking agents should be avoided during monitoring. EMG monitoring of V, VII and IX nerves is done.

There are several approaches described for tumour removal and placement of ABI. Trans-labyrinthine approach provides optimal access for both removal of the tumour and placement of the electrode array. A trans-labyrinthine approach is used by ENT surgeons and has the advantage of offering the best lateral angle to the exit of the cochlear nerve, which allows the early identification of the facial nerve and does not require cerebellar retraction. Disadvantages with trans-labyrinthine approach are limited exposure of cranial nerves and vessels in the posterior fossa. The lateral suboccipital approach is preferred by most neurosurgeons as it is fast, safe and offers very good exposure of the lateral posterior fossa. The problems are cerebellar retraction and late identification of the facial nerve. The angle to the lateral recess and direct vision of the entrance are more difficult in comparison to the trans-labyrinthine approach.[20] The middle cranial fossa approach is only possible with angled endoscopes; however, it is technically the most difficult and places the facial nerve at greatest risk.

After craniectomy is performed, a seat for receiver-stimulator is created in the area postero-superior to the craniectomy. Tie-down holes are then placed on either side of the receiver-stimulator for securing the implant. During tumour removal, a stump of the cochlear nerve is preserved to aid in identification of the cochlear nucleus. After tumour removal, the cochlear nerve is followed medially as it enters the lateral recess of the fourth ventricle. The ABI is inserted in the lateral recess of the fourth ventricle, which is adjacent to both cochlear nuclei.

Knowledge of micro-anatomy of the cochlear nucleus complex and its variations is essential for successful implantation. Constant anatomical landmarks are very helpful in finding the cochlear nucleus. The exits of the cranial nerves 7, 8 and 9 form a triangle of about 5–6 mm (Fig. 43). If the first of these nerves is identified, the others and the entrance of the lateral recess will be found within an area of 6 mm. Between the bulging of the cochlear nucleus and the ponto-bulbar body, a small straight vein is a constant finding and an important landmark. The typical straight vein at the cochlear nucleus heading to the entrance of the foramen of Luschka is found in 76%.[11] Its positive identification gives the best security for an optimal implantation. Normally, an intact choroid plexus marks the entrance to the lateral recess (foramen of Luschka) and the taenia obliquely traverses the roof of the lateral recess, marking the surface of the ventral

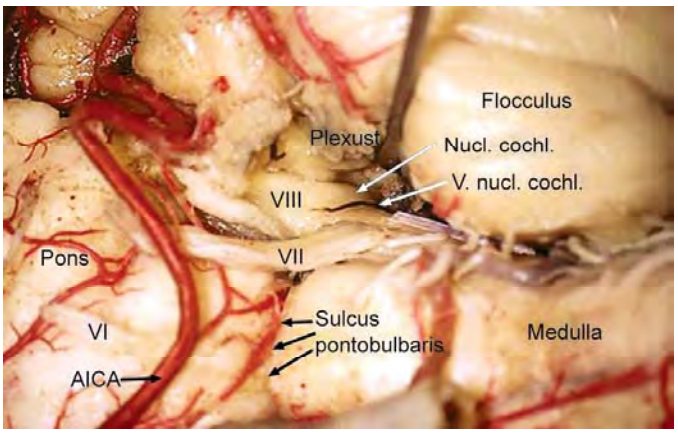

Fig. 43: Cochlear nucleus

cochlear nucleus. Location of the lateral recess can be confirmed by noting the egress of CSF during Valsalva manoeuvre.[18]

The taenia of the choroid plexus at the entrance of the fourth ventricle is dissected and the device is advanced into the lateral recess of the fourth ventricle over the surface of the cochlear nuclei (Figs 44 and 45).

Placement of the electrode completely within the recess gives the fewest side effects and preserves auditory stimulation. After placement, the electrodes are stimulated to confirm their position over the cochlear nucleus and electrically evoked brainstem responses (EABRs) are recorded (Fig. 46).

Activity in adjacent cranial nerve nuclei and vital sign changes are also noted. After the electrode array and receiver-stimulator are secured, the dura is re-approximated. The patient has to be under constant neurologic monitoring in the post-operative period.

Activation of the device is done 3–6 weeks later. The device position may be verified by X-ray/CT scan (Fig. 47). The switch-on is done with monitoring of vital signs and also non-auditory effects (tingling, jittering of the visual field, facial movement, vertigo, motor responses) are specifically looked for. Several programming sessions are required before the most suitable setting is achieved. At each follow-up visit, the patient undergoes an extensive neurologic examination to monitor any changes in neurologic status.

Penetrating ABI (PABI) electrodes have also been tried on the cochlear nucleus. This implant has the

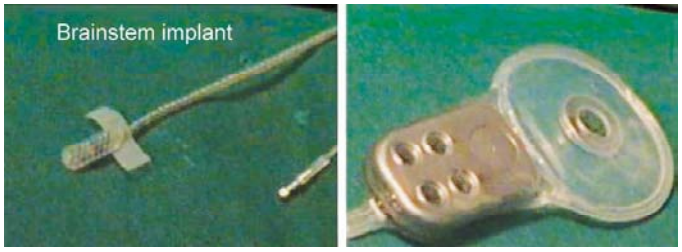

Fig. 44: Two ends of the auditory brainstem implant

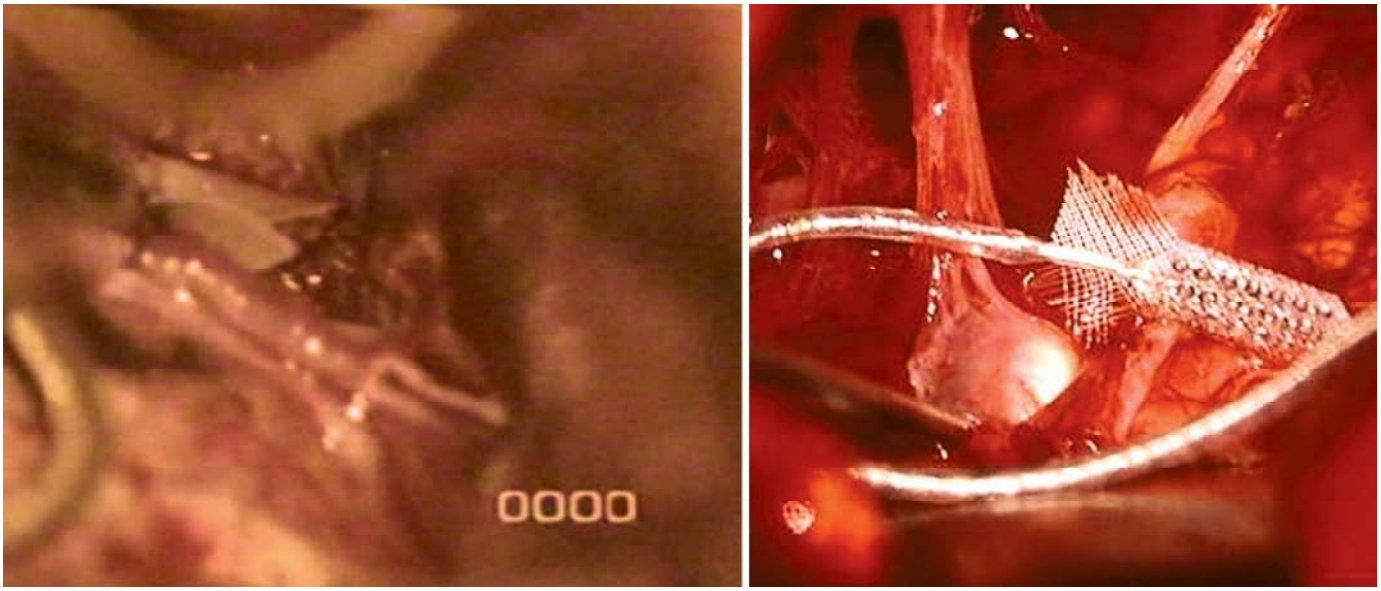

Fig. 45: Intra-operative picture of auditory brainstem implant electrodes

potential of offering improved performance due to better access to the complex tonotopic organisation of the cochlear nucleus.[18] Endoscopic-guided placement of electrodes through the retro-sigmoid approach may also be helpful in reducing the morbidity of surgery.[7] Sleeper implants may be placed at the time of removal of the first tumour and activated after removal of the second side tumour.

Contraindications to ABI include previous stereotactic radiotherapy which has the risk of radiation necrosis of the cochlear nucleus region and anatomic distortion and fibrosis. ABI may not be possible in very large tumours which cause distortion of the brainstem.

Auditory Midbrain Implants

The auditory midbrain implant (AMI) is a new hearing prosthesis designed for stimulation of the auditory midbrain, particularly the inferior colliculus central nucleus (ICC).[3] AMIs are placed in the ICC. They may prove to be a safe and potential alternative for hearing restoration in NF2 patients and may help in enhancement in lip-reading capabilities and environmental awareness and some improvement in speech perception performance.

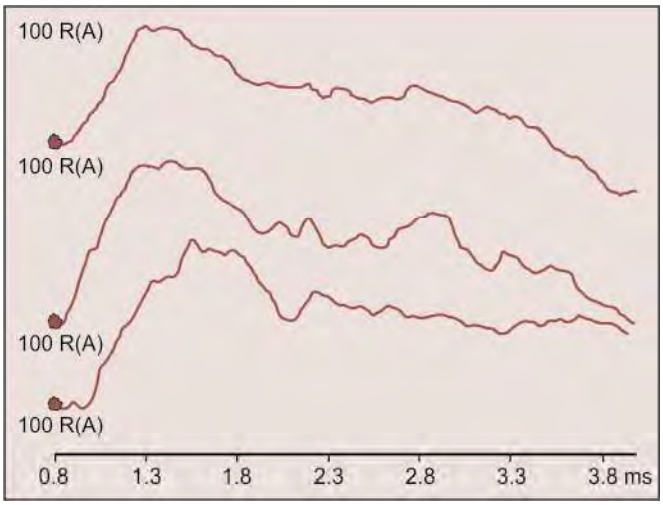

Fig. 46: Intra-operative electrically evoked brainstem responses

CONCLUDING REMARKS

Advances in biotechnology and the development of materials that are biocompatible have resulted in development of prostheses that help in rehabilitation of hearing loss unresponsive to conventional amplification. Cochlear implantation represents the single most important advancement in the rehabilitation of unaidable sensorineural deficits. Early identification and intervention, careful patient selection, and counselling of families regarding realistic expectations are crucial.

In retro-cochlear disorders in which a cochlear implant is contraindicated, the auditory brainstem implant is the only option available for hearing rehabilitation. The primary aim of treatment of patients with NF2 is the recovery of hearing after reducing or extirpating the tumour. The ABI has few side effects and allows most patients with NF2 to experience improved communication as well as access to environmental sounds. Patient selection is important and appropriate pre-operative counselling regarding realistic expectations is necessary and the importance of regular usage must be emphasised. The biosafety of cochlear and brainstem implants has been established and no long-term deleterious effects have been reported with their usage. Developments in technology will expand the benefit of these devices and offer new treatment for otologic disorders.

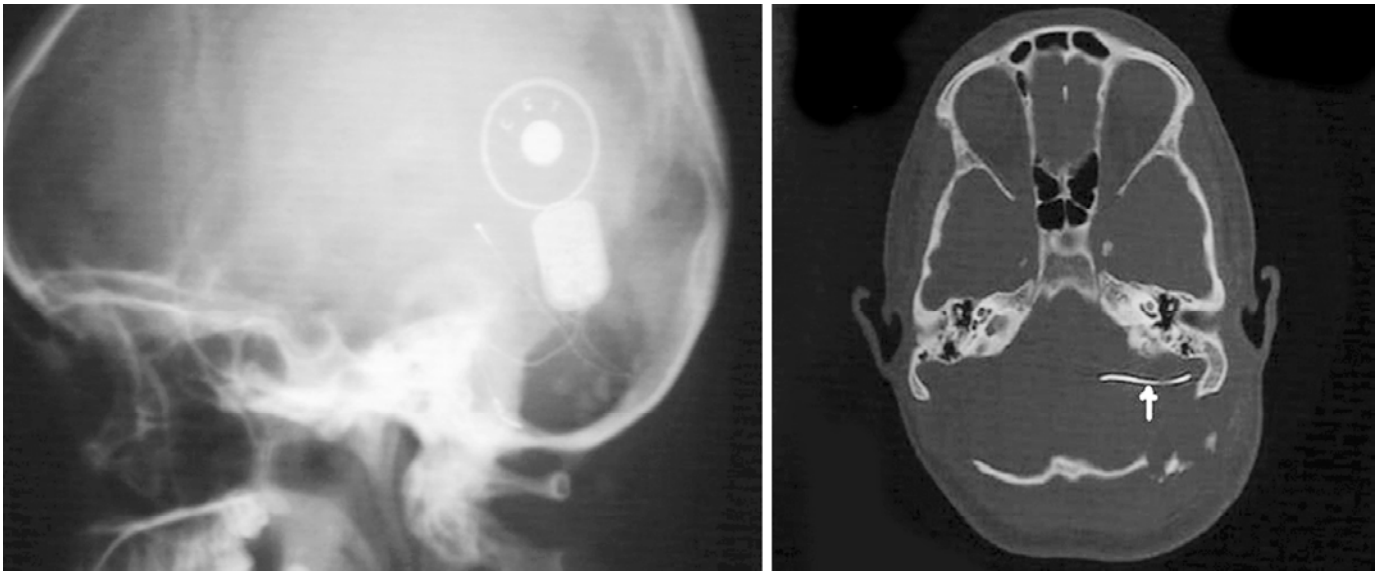

Fig. 47: Post-operative X-ray and CT scan showing auditory brainstem implant

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7 Neuroendocrinology

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INTRODUCTION

The anterior pituitary secretes the following hormones: (1) prolactin (PRL), (2) growth hormone (GH), (3) adrenocorticotropic hormone (ACTH), (4) thyroid-stimulating hormone (TSH), (5) gonadotrophic hormones which are follicle stimulating hormone (FSH) and luteinising hormone (LH). The posterior pituitary secretes the antidiuretic hormone (ADH or vasopressin) and oxytocin.

Pituitary hormones are measured by radioimmunoassay (RIA), immunoradiometric assay (IRMA) or enzyme-linked immunosorbent assay (ELISA). It is necessary to measure the levels of these hormones and also some substances released from the target organs, in patients suspected of harbouring a pituitary or a parasellar lesion. The reserve capacity of the pituitary gland, in its response to stress, must be tested with provocative tests (dynamic testing). The basal levels of the circulating hormones may be normal even with very little functioning pituitary tissue. The normal basal levels are given in Table 1.

PROLACTIN

Prolactin is secreted by lactotrophic cells located in the lateral wings of the anterior pituitary. These cells constitute 20% of adult anterior pituitary cells and are derived from acidophilic stem cells, which are also the precursor cells for somatotrophs. Physiological hypertrophy of lactotroph cells occurs in states where there is excess oestrogen as in the foetus and in women during the second and third trimester of pregnancy.

Prolactin contains 198 amino acid residues which were identified in 1977.[53] Different molecular forms have been recognised, the commonest being the monomeric (21.5 kd) accounting for 90% of circulating PRL. There is a "big" form with a molecular weight of 45–50 kd and a "big-big" form weighing more than 100 kd.[12,15,55,69] The polymeric forms have very little biologic activity as compared to the monomeric form. Prolactin receptors are present in the ovaries, mammary glands, pituitary gland, heart, thymus, lung, spleen, liver, pancreas, kidney, adrenal gland, uterus, skeletal muscle and areas of the central nervous system. PRL causes activation of Janus Kinase 2, a tyrosine kinase that initiates the JAK-STAT pathway and also activation of mitogen-activated protein kinases and Src kinase.[35]

The secretion of PRL is spontaneous in the absence of hypothalamic or hypophysiotropic influences. The following substances inhibit the release of PRL: dopamine, gamma-aminobutyric acid (GABA), gonadotropin-releasing hormone (GnRH)-associated peptide and somatostatin. There is also a negative autoregulatory effect of PRL itself.[29,51] The predominant control of PRL is inhibitory, but three substances, thyrotropin releasing hormone (TRH), vasoactive intestinal peptide (VIP) and serotonin are PRL releasing substances. Oestrogens increase the secretion of PRL and are responsible for the increase in pituitary size and PRL production during pregnancy.[14] T3 and glucocorticoids inhibit PRL release. Epileptic seizures can also increase the PRL levels.[38]

The basal level of PRL is 5–20 ng/ml. The average is 10 ng/ml in women and is 20–25% lower in men and in postmenopausal women. PRL levels vary through the day with a circadian rhythm and the highest levels are noted during sleep.[66] Stress induces variations in PRL levels. Physical activity, general anaesthesia, surgery, myocardial infarction, seizures, and nipple and chest wall stimulation may increase PRL levels. During pregnancy and lactation, PRL levels increase to 200–300 ng/ml.

Routine dynamic testing of PRL levels is not of much use, except in the research setting. The TRH stimulation test is the most effective. Baseline fasting TSH and PRL levels are measured and 500 ng of TRH is given intravenously over 30 seconds. The serum levels are measured at 15-minute intervals up to an hour. Any rise of over 100% is normal. Anything less is indicative of inadequate lactotroph reserve. The other substances that can be used for dynamic testing are chlorpromazine and metoclopramide to increase PRL secretion and L-dopa and nomifensine to reduce PRL secretion.

GROWTH HORMONE

This is a 191 amino acid polypeptide with a molecular weight of 22,124 daltons. It is secreted in a pulsatile fashion with surges of secretion occurring at 3–5 hour intervals[39] and the serum levels vary with the time of day.[39] The normal serum level of growth hormone is up to 5 ng/ml. Young adolescents secrete human growth hormone (HGH) at the rate of about 700 μg/day, while healthy adults secrete HGH at the rate of about 400 μg/day.[18] It is secreted by the somatotroph cells within the

lateral wings of the anterior pituitary gland. The most predictable levels of these GH peaks occur about an hour after the onset of sleep.[58]

Growth hormone secretion is controlled by two polypeptides which are secreted by the hypothalamus and reach the pituitary through the hypothalamo-hypophyseal portal circulation. Growth hormone-releasing hormone (GHRH) stimulates the secretion of GH, while somatostatin (SRIF) suppresses the release.[37] The pulsatile release of GH is controlled by SRIF rather than GHRH.[60] The hypothalamic control of these peptides is regulated by the brainstem and the limbic system. The effects produced by GH are due to stimulation of insulin-like growth factor 1 (IGF-1), which is also known as somatomedin C. IGF-1 stimulates chondrocytes and induces replication of epithelial cells. In the circulation it is bound to a protein (growth hormone binding protein, GHBP) which is a subunit of the growth hormone receptor, and an acid labile subunit (ALS).

Substances that stimulate GH secretion are encephalin, glucagons, alpha melanocyte stimulating hormone, vasopressin, diazepam, oestrogens, norepinephrine, L-Dopa, clonidine, apomorphine and ghrelin. In human corticotroph cell cultures, interleukin-1(IL-1) and tissue necrotic factor (TNF alpha) stimulate the release of GH in GH3 cells.[16,21,22] Stress, hypoglycaemia and exercise also stimulate GH secretion. Serotonin precursors, such as L-tryptophan or 5-hydroxytryptamine (5HT), enhance GH secretion. The substances that suppress GH secretion are SRIF from the periventricular nucleus,[23] hyperglycaemia,[34] isoproterenol, glucocorticoids and elevated levels of free fatty acid.

GH levels are measured in the serum in the basal state as well as after provocative tests. The basal level is tested in a fasting patient at 8.00 am. The blood may also be drawn at 12 noon, 4 pm and 8.00 pm. Normally all values must be below 2 ng/ml. The normal range is 0–5 ng/ml.

The dynamic tests used to determine GH reserve are:

1. *Insulin-induced hypoglycaemia*: After overnight fasting, hypoglycaemia is induced by a bolus injection of human insulin at a dose of 0.15 IU per kg body weight. Blood samples are taken at 30-minute intervals. A normal response is said to occur when the GH level increases to more than than 7 ng/ml, but there is absolute proof of adequate reserves only when the value reaches 20 ng/ml and above.[11] The insulin-induced hypoglycaemia test has to be done under closely monitored conditions, especially in patients in whom the adrenal reserve is low. It is contraindicated in patients with ischaemic heart disease, cerebrovascular disease, seizures and adrenal insufficiency.
2. *The arginine test*: This is used when there is a contraindication to the insulin-induced hypoglycaemia test. A 500 ml of 6% solution of arginine is infused intravenously over a 30-minute period. Blood samples are taken, initially, at 15-minute intervals and then at 30-minute intervals up to 2 hours. The glucose level should increase to more than 20% of the original value and the GH level to more than 7 ng/ml to conclude that the test is normal. L-Dopa is another substance that can be used.

The dynamic tests that are used when there is acromegaly are:

1. *Oral glucose tolerance test (OGTT)*: After overnight fasting, 75 grams of glucose is given orally. Blood samples are taken at 30-minute intervals for up to 2 hours. The glucose, GH and somatomedin C levels are measured. In normal persons, the GH is suppressed to undetectable levels. Failure of suppression indicates acromegaly. This is true in 93% of acromegalics.[62] For practical purposes, if the GH is below 2 ng/ml acromegaly can be excluded.
2. *TRH test*: The test is done between 8.30 am and 10.00 am. A basal sample is drawn and then 200 ug of TRH is injected. Two samples are taken at half-hourly intervals and the GH levels are measured. Normally there is no increase of GH. A more than twofold increase above the basal levels is called an "inappropriately high response" and is often associated with active acromegaly. Dopaminergic agents, such as laevodopa and bromocriptine, normally cause a rise in GH, but in about two-thirds of acromegalics they cause a reduction.

Somatomedin C estimation is done by RIA. The normal fasting value is 0.67 u/ml (range 0.31–1.4) and the mean in acromegalics is 6.8 u/ml (range 2.6–21.7). This assay is useful in the post-treatment follow-up of acromegalics.

ADRENOCORTICOTROPIC HORMONE AND CORTISOL

Cortisol is essential for the physiological and biochemical response to stress, both endogenous and exogenous. Cortisol is secreted from the zona fasciculata, the second layer of the adrenal cortex. Cortisol secretion is controlled by ACTH, which is secreted by the anterior pituitary and is in turn controlled by corticotropin-releasing hormone (CRH) from the paraventricular nucleus of the hypothalamus. Corticotrophs in the anterior pituitary produce ACTH and these constitute 10–20% of the cells. They are concentrated in the central portion of the gland, though some cells are also present in the lateral wings and in the pars intermedia.[2]

Corticotropin-releasing hormone secretion is modulated by positive influences from other parts of the brain and negative feedback from circulating glucocorticoids.[17] The afferents to the paraventricular nuclei arise from the nucleus of the tractus solitarius, the hypothalamus, the nucleus of the subfornical region, the medullary reticular formation, the locus ceruleus and the limbic system, especially the lateral septal region.

Adrenocorticotropic hormone secretion is stimulated by CRH and vasopressin and inhibited by negative

feedback from circulating cortisol.[28] CRH, ACTH and cortisol are secreted in a periodic and rhythmic manner with the maximum secretion at 8.00 am and the least at midnight. This diurnal variation is due to the transfer of information about the light/dark cycle from the retina to the paired suprachiasmatic nuclei in the hypothalamus. The pattern is not present at birth.[6] In normal humans, bursts of ACTH and cortisol secretion occur about 15 times in a 24-hour period.[64] ACTH levels can vary 10-fold in a day and cortisol is actively secreted only during one-fourth of a day. ACTH secretion is modulated by many neurotransmitters.[32] ACTH is stimulated by acetylcholine, serotonin and IL-1 and is inhibited by catecholamines, beta-endorphin and dopamine.[5]

It is difficult to measure ACTH in the serum as its half-life is only 20 minutes. Generally, basal levels of plasma and urinary cortisol are measured. Since there is a lot of diurnal variation, the average of 4–6 samples taken over a 24-hour period should be measured. Cortisol secretion is highest in the morning and lowest at midnight. The mean plasma cortisol level should be 5–25 ug/dl. The urinary-free cortisol level should be less than 100/ug per 24 hours and 17-hydroxysteroids should be 3–8 mg per 24 hours. Dynamic tests are used to evaluate the status of the hypothalamic-pituitary-adrenal (HPA) axis, in its response to stress and in hyper-functioning states.

Measurements of cortisol in serum, saliva and urine reflect systemic cortisol levels at the time of sample collection, but cannot assess the past cortisol levels. Hair cortisol levels may be increased in patients with Cushing's syndrome, and, as hair grows about 1 cm/month, measurement of hair cortisol can provide historical information on the development of hypercortisolism.[59]

Urinary-free Cortisol Excretion Rate

It is one of the best methods for quantifying hypercortisolism in which unmetabolised cortisol is measured. Urinary-free cortisol (UFC) is measured in a carefully collected 24-hour urine sample. The normal range is between 30 nmol/day and 150 nmol/day. The sensitivity of the UFC method in the diagnosis of Cushing's syndrome is between 95% and 100%.

The tests used for assessing normal function are:

1. *Insulin-induced hypoglycaemia (Insulin tolerance tests, ITT)*: The blood glucose levels should drop to below 40 mg/ml. An increase in cortisol level to more than 12 ug/ml is considered an adequate response and demonstrates an intact hypothalamic-pituitary-adrenal axis.[1]
2. *ACTH stimulation test*: The test is done in the morning and fasting is not necessary. After drawing blood for a basal sample, 0.25 mg of ACTH is injected and another sample is drawn after 30 minutes. Plasma cortisol should be more than 18 ug/ml and the increment should be more than 7 ug/ml.
3. *Metyrapone test*: Metyrapone inhibits 11-beta hydroxylase in the adrenal cortex and blocks the conversion of 11-deoxycortisol to cortisol. The drop in serum cortisol stimulates ACTH secretion which in turn stimulates the synthesis of 11 deoxycortisol and the metabolites of this compound can be measured in the urine. In normal people, 24-hour urinary 17 hydroxycorticoid levels are two or three times above the baseline level in 1 or 2 days after the administration of metyrapone.

The dynamic tests used in hypercortisolaemia are:

1. *Low-dose dexamethasone test*: The low-dose dexamethasone suppression test is a good screening procedure. A 9.00 am blood sample is drawn and 2 mg of dexamethasone is given at 10.00 pm. Blood is again drawn at 9.00 am the next day. Cortisol is measured in both the samples. The cortisol should normally be suppressed to below 2/ug/ml. This response practically excludes Cushing's syndrome. This test is also useful in postoperative assessment. A positive dexamethasone test and a markedly increased UFC are diagnostic of Cushing's syndrome in patients who are not under severe stress.[27]
2. *High-dose dexamethasone test*: This is used in the differential diagnosis of Cushing's syndrome and where the low-dose dexamethasone test is abnormal. The test is carried out similar to the low-dose test except that 8 mg of dexamethasone is given instead of 2 mg. Cortisol will be suppressed to less than 50% of the basal value in Cushing's disease, but not in ectopic ACTH syndrome or adrenal tumours.
3. *CRH stimulation test*: This is also a test for differential diagnosis of Cushing's syndrome. After overnight fasting and taking a baseline sample, 100 ug of bovine or human CRH is injected intravenously as a bolus and blood samples are taken at 15-minute intervals up to 90 minutes. Normally the cortisol levels should rise to 15–30 ug/ml and ACTH levels to 28–230 pg/ml. Patients with Cushing's disease exhibit a normal or exaggerated response, whereas there is no response with ectopic ACTH syndrome or adrenal tumours.
4. *Venous sampling for ACTH gradient*: This is done when the results of other tests are not definitive and computed tomography (CT) and magnetic resonance imaging (MRI) images do not reveal a microadenoma. If an ectopic source of ACTH cannot be excluded, then venous sampling is done at various levels including the internal jugular vein, the right ventricle and the inferior vena cava at the level of the diaphragm and the coeliac, the renal and the femoral veins. Simultaneously, two catheters are placed in the inferior petrosal sinus on either side and if this is not technically possible they are placed in the internal jugular vein as high as possible. A bolus injection of 100 ug of CRH is given intravenously and blood samples are collected from various sites at 5-minute intervals for 25 minutes. The source of ACTH can

be reliably identified from the elevation of ACTH in various samples. Inferior petrosal vein sampling also helps in locating the site of a pituitary microadenoma when there is a doubt.

Tests for Hypocortisolism

Morning Plasma Cortisol Level (Between 8 am and 9 am)

Cortisol levels more than 500 nmol/l at this time practically exclude adrenal insufficiency, while a level less than 100 nmol/l is almost diagnostic of adrenal insufficiency.

In a patient with such a low plasma cortisol, measurement of ACTH in the same blood sample allows the distinction between primary (elevated ACTH) and secondary (normal or low ACTH) adrenal insufficiency.[46]

All patients who are suspected to have adrenal insufficiency with morning plasma cortisol levels between 100 nmol/l and 500 nmol/l require "dynamic" testing in which 250 μg of synthetic corticotropin or less is injected intravenously or intramuscularly, and plasma cortisol is determined before injection and 30 or 60 minutes after injection. If the cortisol rises to a level more than 550 nmol/l, primary adrenal insufficiency is excluded.[46]

THYROID

Tetraiodothyroxine (T4) is the major hormone secreted by the thyroid gland, but tri-iodothyronine (T3) is the metabolically active hormone.[52] Thyroid hormones control development, growth and metabolic rate. Thyroid hormone secretion is controlled by TSH secreted by the anterior pituitary. TSH was first identified by Crew and Weisner.[4] It is a glycoprotein with two subunits, alpha and beta.[47] The alpha subunit is common to other glycoprotein hormones, LH, follicle-stimulating hormone (FSH) and human chorionic gonadotropin (HCG). Thytrophin releasing hormone tonically stimulates the release of TSH.[20] Dopamine, SRIF, neurotensin, serotonin, norepinephrine, cholecystokinin, oestrogens and cortisol directly or indirectly affect the release of TSH.

Thytrophin releasing hormone is synthesized in the paraventricular nucleus of the hypothalamus. TRH is also found in other neuronal and non-neuronal tissue. The hypothalamic-pituitary-thyroid axis is controlled primarily by the circulating thyroid hormone in a negative feedback system.

Hypothyroidism and hyperthyroidism are diagnosed on the basis of determination of T3 and T4. Free T4 is a good screening test of thyroid function, because it takes into account both T3 uptake and total T4 in the serum. Radioactive iodine uptake should not be used as a screening test of thyroid function. When T3 and T4 are low, TSH stimulation will enable differentiation between primary and secondary hypothyroidism. This differentiation is also possible by the TRH stimulation test. Mass spectrometry is a new advanced technique by which the hormones can be quantitatively assessed in biological fluids.[57]

Thyrotropin-releasing hormone stimulation test: Blood is drawn for basal levels and then 200/ug of TRH is injected and blood samples are drawn 30 and 60 minutes later. TSH assay is done on the blood samples. The normal basal values range from 0.3 IU/ml to 3.5 IU/ml. The increment should be more than 2.7 IU/ml after 30 minutes. In a patient with low thyroid hormones, impaired TSH response to TRH indicates deficient TSH at the pituitary level. A delayed TSH response to TRH, i.e. when the TSH level is higher at 60 minutes than at 30 minutes, is characteristic of hypothalamic dysfunction. It may also be seen in pituitary disease or primary hyperthyroidism. In primary hyperthyroidism, the basal TSH level is suppressed and fails to rise after TRH administration.

Basal TSH level in the upper normal range, or slightly elevated in the presence of raised T3 and T4, is called inappropriate secretion of TSH and is characteristic of TSH secreting pituitary adenoma. The TSH alpha subunit is measured by a specific RIA. This is elevated in TSH secreting pituitary adenoma.

Newer Methods

Index Methods

These are free hormone estimate tests.[24] They are of two types. The first test is a total hormone measurement (TT4 or TT3) and the other is an assessment of the thyroid hormone binding protein (THBP) concentration. These tests use either an immunoassay for thyroxine-binding globulin (TBG) or a T4 or T3 "uptake" test called thyroid hormone binding ratio (THBR).

Alternatively, indexes may be calculated from a TT4 measurement paired with an estimate of the free T4 fraction determined by isotopic dialysis. The quality and purity of the tracer (radiolabelled T3 or T4) used impacts the accuracy of the index.[31,43,45]

Indexes Using a Thyroid Hormone Binding Ratio or "Uptake" Test

"Classical" uptake test is a method in which a trace amount of radiolabelled T3 or T4 is added to the specimen and it is allowed to distribute across the thyroid hormone binding proteins like the endogenous hormone.[24,30]

"Classic" T3 uptake or THBR tests are dependant on the endogenous T4 concentration in the specimen. Currently used THBR tests produce normal FT4I and FT3I values when TBG abnormalities are mild (i.e. pregnancy). However, some of these tests may produce inappropriately abnormal index values when patients have grossly abnormal binding proteins [congenital TBG high or low, familial dysalbuminaemic hyperthyroxinaemia (FDH), thyroid hormone autoantibodies or NTI] and in the presence of some medications that influence thyroid hormone protein binding.

Ligand Assays

Types: Types of legend assays are as follows:

1. Two-step, labelled-hormone/back-titration methods

2. One-step, labelled hormone-analogue methods
3. Labelled antibody methods.

One-step ligand assays attempt to quantify free hormone in the presence of binding proteins whereas two-step assays use a physical separation of free hormone from protein-bound hormone before measuring the free hormone by a sensitive immunoassay, or by using an antibody to immunoextract a proportion of ligand out of the specimen before quantification.

One-step methods may become invalid when the specimen and the standards differ in their affinity for the assay tracer[7,9,54] whereas two-step methods are less prone to non-specific artifacts. The physical isolation of free from protein-bound hormone is accomplished with either a semi-permeable membrane using a dialysis chamber, an ultrafiltration technique, or a Sephadex LH-20 resin adsorption column.[10,42,56,61,67]

Labelled antibody methods measure free hormone as a function of the fractional occupancy of hormone antibody binding sites. This competitive approach uses specific immunoabsorbents to assess the unoccupied antibody binding sites in the reaction mixture.

The only reason to select a free thyroid hormone method (FT4 or FT3) in preference to a total thyroid hormone test (TT4 or TT3) is to improve the diagnostic accuracy for detecting hypothyroidism and hyperthyroidism in patients with thyroid hormone binding abnormalities that compromise the diagnostic accuracy of total hormone measurements.[24] Free hormone tests should be performed at 37°C since tests performed at ambient temperature show falsely increased values when specimens have a very low TBG concentration.[50,65]

GONADOTROPINS

Luteinising hormone and FSH are the gonadotropins and they are synthesised by gonadotrophs in the anterior pituitary. They have a common alpha subunit with TSH and HCG. The beta subunits confer the biologic specificity of all these four hormones.[21] LH and FSH are controlled by the hypothalamic-pituitary-gonadal axis.[48] LH and FSH release is controlled by GnRH, which is a decapeptide synthesised in the hypothalamus. GnRH release is regulated by several molecules including neurotransmitters, glial cell factors, sex steroids,[25,26] kisspeptin (Kp) and neuropeptide.[3] Plasma FSH levels also increase after Kp stimulation.[40,41] LH and FSH travel through the systemic circulation and in turn stimulate the gonadal steroids testosterone, oestradiol and progesterone. They also stimulate the peptides, inhibins and activins, as also gametogenesis. A negative feedback is exerted on the pituitary and hypothalamus by the gonadal hormones.

LH and FSH are secreted in a pulsatile fashion over 24 hours. The pattern in men is fairly constant at 90–120 minutes whereas, in women, it changes with changes in the menstrual cycle.[13,36,63] This pulsatile secretion is due to the pulsatile release of GnRH from the hypothalamic neurons.

Various other substances also regulate the hypothalamic-pituitary-gonadal axis. Prolactin inhibits GnRH secretion and causes hypogonadism.[63] Exogenous and endogenous opiates reduce GnRH secretion and produce hypogonadism. The other substances that decrease gonadotropin release are corticosteroids, dopamine and SRIF.

The normal values of FSH, LH, oestrogen, progesterone and testosterone are shown in Table 1. In a premenopausal woman, low serum oestradiol with elevated gonadotropin levels is suggestive of gonadotropin deficiency. In post-menopausal women serum oestradiol is low and LH and FSH may be high. In men, if the testosterone is low and there is no corresponding increase in gonadotropins, then there is gonadotropin deficiency.

Gonadotropin-releasing Hormone Stimulation Test

After drawing blood for a basal sample, 100 ug of GnRH is injected intravenously and a sample of blood is drawn after 30 minutes. LH and FSH estimations are done. A normal response is when the basal values of LH rise fourfold or fivefold and FSH values rise twofold. Utilising the LH RIA 2nd HMG-IRP, a cut-off of 10 IU/l was used as a marker for evidence of activation of the reproductive axis.[31,68] A reduced response is suspicious of pituitary failure. A normal response of gonadotropin secretion is sometimes seen in patients diagnosed to have gonadotropin deficiency based on low values of sex steroids and basal gonadotropins.

Gonadotropin-releasing Hormone Analogue Stimulation Tests

Recently stimulation tests were conducted using leuprolide. The dose of leuprolide is 20 μg/kg SQ. Leuprolide is about 20 times more potent than GnRH. A dose response curve showed that maximum peak LH is reached roughly about 4 hours after the leuprolide dose is given; and by 24 hours, peak sex steroid is reached.[19]

The Buserelin Stimulation Test

This is a highly specific and sensitive GnRH agonist test. It is used for investigating males with delayed puberty.[8]

ANTIDIURETIC HORMONE (VASOPRESSIN)

The prohormones, a neurophysin and a glycopeptide, which are enzymatically converted into ADH are synthesised in the hypothalamus. This occurs in the magnocellular neurons of the supraoptic and paraventricular nuclei.[49] The prohormones are contained in neurosecretory granules and transported to the posterior pituitary through the axons in the infundibulum. The neurophysin and glycopeptide are secreted along with ADH and have no known biological activity.

Table 1: Normal basal levels

Free Tri-iodothyronine (T3)		2.2–5.0 pg/ml
Free Thyroxine (T4)		0.7–2.2 ng/dl
Thyroid stimulating hormone		*ND–9 u IU/ml
17 OH Progesterone		50–180 ng/dl
Progesterone	Post-ovulatory	Above 5 ng/ml
Testosterone	Male	360–990 ng/dl
	Female	15–110 ng/dl
Prolactin	Male	ND–15 ng/ml
	Female	ND–20 ng/ml
Growth hormone	Fasting adults	ND–5 ng/ml
	Fasting children	ND–10 ng/ml
Cortisol	Morning sample	5–25 ug/dl
	Evening sample	2.5–12.5 ug/dl
17 Ketosteroids	Male	9–24 mg/24 hrs
	Female	5–17 mg/24 hrs
DHEA	Male	80–560 ug/dl
	Female	35–430 ug/dl

	Follicle stimulating hormone (m IU/ml)	*Luteinising hormone (m IU/ml)*	*Oestradiol (pg/ml)*
Male	ND–20	ND–20	5–50
Female			
Follicular	5–20	2–15	20–200
Luteal	2–10	5–25	20–120
Mid cycle	15–30	50–200	80–375
Menopausal	Above 40	Above 20	Below 30

*ND: Not detectable

Antidiuretic hormone secretion is controlled by osmotic as well as volume regulation. Osmotic regulation is most sensitive.[33,44] These receptors are located in the anterior part of the hypothalamus. ADH is released even if there is a 1% increase in the plasma osmolality. The normal plasma osmolality is 285–295 mOsm/kg water. The osmotic receptors respond mainly to extracellular sodium. The volume regulation receptors are found in the aorta, carotid sinus and left atrium. The impulses reach the brainstem through the glossopharyngeal and vagus nerves and ascend through multisynaptic pathways to end in the magnocellular neurons of the hypothalamus. ADH is released only when there is a 10–15% reduction in blood pressure.

Through the blood stream, ADH reaches the kidneys and binds to the receptors in the renal collecting ducts. Adenyl cyclase is activated and cyclic adenosine monophosphate (AMP) is generated that acts as a second messenger. This leads to increased reabsorption of water from the nephron back into the circulation.

The substances that reduce the action of ADH are endogenous prostaglandins, hypocalcaemia, hypokalaemia, lithium, demeclocycline, water, ethanol, phenytoin and anticholinergic drugs. The conditions and substances that stimulate the release of ADH or enhance its action are hypothyroidism, hypoadrenocortisolism, nicotine, chlorpropamide, cholinergic drugs, clofibrate, barbiturates, morphine, carbamazepine and anaesthetic agents.

The two syndromes that are produced by disorders of ADH secretion are syndrome of inappropriate ADH secretion (SIADH) caused by excessive ADH and diabetes insipidus (DI) caused by diminished secretion of ADH. These are dealt with in detail in the chapter on "Fluid, Electrolyte and Metabolic Disturbances".

The water deprivation test is used in suspected DI. Reduced water intake should normally reduce the urine output and increase the urine osmolality. This test should not be done in established DI and when the serum osmolality is high. The patient is made to pass urine as completely as possible and samples of urine (10 ml) and blood (8 ml) are collected and stored after centrifugation at 4 degrees Celsius. The weight of the patient is noted. Water is not ingested by the patient from 7.00 pm to 12 noon the next day. Three blood and urine samples are drawn 13, 15 and 17 hours into the water deprivation. The osmolality is measured in all the samples.

In central DI, the urine osmolality does not rise and the urine output remains high. The plasma osmolality becomes higher than 295 mOsm/kg. Urine osmolality below 400 mOsm/kg is diagnostic of DI and if it is more

than 700 mOsm/kg in any of the morning samples of urine, it rules out DI.

Administration of deamino-delta-d-arginine vasopressin (DDAVP) can also help in differentiating central and nephrogenic DI. In nephrogenic DI there will be no changes in the urine output and serum and urine osmolality on administration of DDAVP, whereas in central DI changes will occur.

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8 Intra-Operative Monitoring

Babu KS, Rajasekar V

It is just over a century since the first brain tumour was resected successfully. Since then, diagnosis, imaging, and management of brain tumours have improved, in large part due to technological advances. Similarly, the operation theatre (OT) for brain tumour surgery has increased in complexity and specificity with multiple types of equipment, now considered necessary as technical adjuncts. It is evident that advanced image-guidance techniques and sophisticated technologies (e.g. robotics and nanotechnology) will drive changes in the current OT environment for the foreseeable future.[9]

Our body generates many electrical signals. Heart, skeletal muscles, peripheral muscles and different segments of the central nervous system generate these electrical signals, while the brain generates spontaneous electrical activity, which is recorded as an electroencephalogram (EEG). The central nervous system also produces an electrical response to specific stimuli. The type of stimulus varies depending on the sensory modality that is being stimulated. Flashes of light are used to evoke visual evoked potentials (VEP), auditory clicks for auditory evoked potentials (AEP) and electrical stimulation of the peripheral nerves to evoke sensory responses, along their ascending pathway called somatosensory evoked potentials (SEP). Motor evoked potentials (MEP) are evoked by transcranial electrical or magnetic stimulation of the cortex. These are the most common types of intra-operative monitoring (IOM) techniques used in the OT.

Evoked potentials (EP) have been used in the OT for the past three decades. Many centres routinely use IOM of neurosurgical cases. However, this has not become popular in our country for many reasons, such as finding suitable personnel for IOM, added cost to the patient, technical problems associated with electrical interference, reproducible wave forms, lack of equipment and IOM training centres. IOM is a dynamic process where the status of the neural structures needs to be continuously monitored and correlate the changes with the status of the patient. This would require a considerable amount of practical experience than what is needed in the electrophysiology laboratory. Having dedicated personnel will go a long way in understanding EP changes and fixing technical problems that arise during surgery. As Nuwer pointed out, false positive type of changes in the potentials are bothersome in the OT.[32] They are substantially more common for inexperienced monitoring teams who have not yet learnt how to minimise the causes of technical and clinical variability. False negative monitoring cases are those in which the potentials remain relatively stable, but the patient wakes up with a new neurological deficit. At other times, there are considerable changes during monitoring and these are wrongly interpreted. There have been cases where the monitoring team has followed just background noise or artefacts throughout the course of surgery (Fig. 1). Reliance on equipment without experienced personnel may result in failure or even worse, lead to inaccurate and misleading feedback to the surgeon. Inappropriate application of monitoring techniques has potentially catastrophic consequences. IOM is a means to monitor peripheral nerves, spinal cord, brainstem, optic nerves and cerebral cortex during the course of surgery. The prime objective of IOM is: (1) to identify new neurological dysfunction early and prevent it before it becomes irreversible and (2) to provide reassurance to the surgeon that no damage has occurred till that point in surgery, so that more radical excision of masses can be performed.

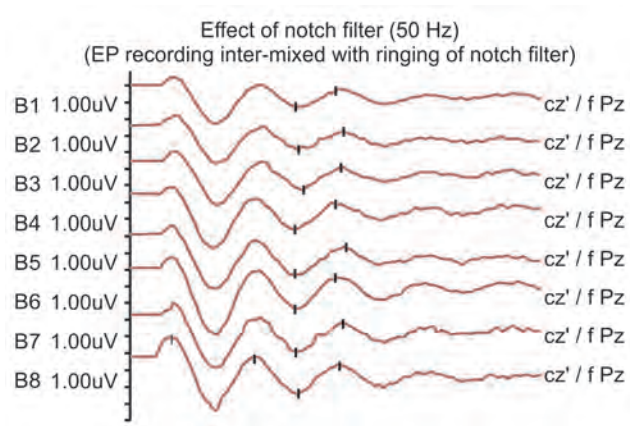

Fig. 1: Effect of 50 Hz notch filter. Notch filter caused ringing that has been erroneously followed throughout the course of surgery

CHOOSING AN INTRA-OPERATIVE MONITORING MACHINE

The majority of models which are currently available in the market for IOM have facilities to do AEP, VEP, SEP, EEG and electromyography (EMG). Some of them have

specialised features for microelectrode recording during pallidotomy and thalamotomy. However, to be cost effective, some companies give the choice of choosing certain features like SEP and AEP only or other combinations. It is important to remember that machines can malfunction if used improperly. Hence, it must be ensured that the IOM machine that is used in the OR is isolated from the wall current and from the patient in several ways. Each type of IOM machine has its own features. Users must be familiar with their own equipment and follow the safety instructions prescribed by the manufacturers (Table 1).

HARDWARE

It is to one's advantage to have a number of channels for recording. We have two dedicated machines for IOM; one has a twenty channel recording system and another an eight channel recording system. These machines are very similar to the ones that one sees in the EEG and EP-diagnostic labs. However, one must remember that the operation theatre is a hostile environment for electrophysiological recordings. The EP voltages that one records in the operation theatre are of the order of a few microvolts. The sources of high voltage interference in the OR are many, such as bipolar and monopolar cautery, AC mains, ECG, patient table, etc. Hence, amplifiers are the most important part of the IOM machine. These amplifiers must be able to withstand high electrical voltage fluctuations. The machines that one sees in the diagnostic labs are not designed for such a purpose. It is important to have amplifiers that have good rejection of noise occurring at both the inputs (common mode rejection). They should be able to withstand diathermy frequencies. A signal (wave form or trace) of interest will comprise of many different frequencies hence, one must not set filters too severely, as it will result in rejection of need frequencies and would lead to attenuation of the responses and may even result in abolishing it completely. Digital filtering is better than analog filtering, as the latter can change latency and distort the signal. A compromise must be reached between rejecting unwanted frequencies from the EEG and other sources and allowing only the signals of interest.

Ideally, the IOM machine must have its own electrical outlet. The outlet should have a separate ground that is not linked with other OT equipments. This way, the machine will have its specific place in the OT. Since, the OT is always crammed with equipment, it will not be possible to keep the machine close to the operation table. So, it is important to consider the length of the cables between the machine and the amplifiers, stimulators, etc. that are placed close to the patient before purchasing the equipment.

SOFTWARE

A feature, which enables the operator to change the electrodes or channels through the software, is useful. During surgery, the electrodes that are hooked on to the

Table 1: Intra-operative monitoring in various surgeries and their parameters

Types of surgeries/ monitoring		*Stimulus*	*Intensity*	*Rate*	*Montage*			*Low filter*	*High filter*	*Window*	*Repetition*
					Active	*Reference*	*GND*				
Spinal cord, aneurysm	SEP median nerve	Electrical 300 msec	1 ma above motor threshold	4.7/sec	C'3,4	Fpz	Non-cortical	10 Hz	1.5 KHz	40 ms	300
Spinal cord, aneurysm	SEP posterior tibial nerve	Electrical 300 msec	1 ma above motor threshold	4.7/sec	C'Z	Fpz	Non-cortical	10 Hz	1.5 KHz	60 ms	300
CP angle, MVD	BAEP	Insert ear phones clicks	70 dB	11.1-19.1/ sec	Cz	A1, A2	Fz	100 Hz	3000 Hz	10 ms	2000
Pituitary tumours	VEP	LED flashes	Constant output over closed eyes	1.9 Hz	O1, O2 or Oz	Cz	Fz	10 Hz	100	500 ms	150
Direct nerve/ nucleus stimulation	Facial nerve, brainstem motor nuclei	Electrical 50 msec	< 2.5 ma	4.7 Hz	Bipolar electrodes at frontalis, oculi, oris tongue, soft palate, posterior pharangeal		Fz	10 Hz	3000 Hz	20 ms	Triggered stimulation
Spinal cord-corticospinal pathways	MEP cathode C'z, anode Fpz	TES 50 msec	150-400 V	1.9 Hz	Bipolar electrodes in peripheral muscles as required		Spinal cord	10 Hz	3000 Hz	60 ms	<25

patient will be buried under the drapes and would be out of reach. If there are standby electrodes, it will be possible to switch to these electrodes and, similarly, the active and reference electrodes can be switched through the software. The software must also have the facility to display the averaged data (e.g. SEP), triggered data (identification of nerve roots, etc), free running format (e.g. EEG, EMG) and also to be able to visualise the raw data. It will be useful to view the raw data to understand any technical difficulties or artefacts. Some manufacturers provide for display of either the raw or the averaged data but not both simultaneously. This will definitely be a disadvantage to the user. The facility to display all the previously averaged traces is an important feature. Changing the time base, rescaling the amplitude of the traces, performing simple digital filtering, such as smoothening, correct baseline shifts due to DC potentials, ability to measure peak and inter peak latencies and amplitudes are important. The facility to enter comments such as anaesthetic changes, stage of surgery or any other events that occur during the course of surgery is also a very important feature.

Very often, it may be necessary to perform multimodality monitoring, e.g. monitor AEP and SEP at the same time. This would also mean that the machine must have the ability to run dual time bases. Similarly, it may be desirable to monitor both the right and left sided responses at the same time (e.g. left and right median nerve stimulation where the stimulus is given at the same time and responses are also recorded at the same time). This is possible, as the cortical responses are recorded from different electrodes on opposite hemispheres. On the other hand, if the posterior tibial nerve is stimulated for the right and left leg, where the responses for both are recorded from the same spot, it will be necessary for a time interval between right and left leg stimulation to record individual responses. Similarly, for localisation of eloquent areas where subdural strip electrodes can be used for bipolar stimulation, it may be necessary to switch the stimulating points to localise the functional areas. All these features should be software controlled.

Modern machines have ready-made protocols to perform a wide variety of monitoring procedures. However, many electrophysiologists develop their own protocol; hence the software should have a facility to store such customised protocols. Each vendor offers certain advantages in their machine over others. Hence, one must take into account these various features before choosing the machine.

RECORDING ELECTRODES

Standard 8 mm EEG reusable gold disk electrodes are the most popular, as they are non-corrosive and need less maintenance. These electrodes need to be properly anchored to the patient, as most of these electrodes will be out of reach during surgery. Therefore, skin preparation and proper application of electrode cream is very important. We keep the electrodes in place by putting

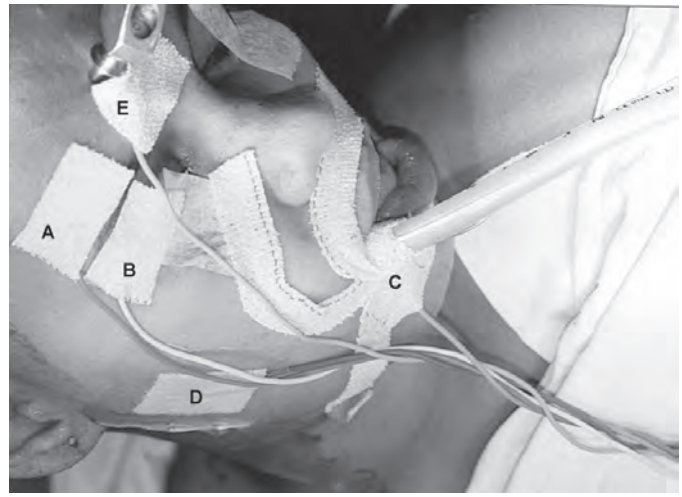

Fig. 2: Photograph showing electrode placement for facial nerve monitoring. Subdermal needle electrodes are placed in the (A) Frontalis muscle. (B) Orbicularis oculi. (C) Oris, with a common reference electrode in (D) The masseter. (E) Ground electrode in the Fpz. Note how the cables are twisted together to reduce artefacts. The electrode close to cleaning area is covered with transparent adhesive

an adhesive on top of the electrode and covering it with a sterile transparent sheet (Fig. 2). This is important as, during cleaning of the surgical area, the cleaning fluids will drip down and the electrodes will get soaked and get dislodged. Many centres also use collodion for sticking electrodes. The collodion needs to be applied in a well-ventilated room before surgery, as it has an obnoxious smell (acetone solvent). Once the electrodes are stuck with collodion, the electrode cream is injected through the hole in the middle of the disc electrode; this acts as the conducting material between the scalp and the electrode. It is cautioned not to use an electrode gel or paste that contains calcium chloride, as it can cause a type of chemical burn called calcinosis cutis, particularly in children.[43] For a corticogram, subdural strip electrodes are used. They are useful in epilepsy surgery, cortical localisation of the central sulcus, recording "after discharge" during cortical stimulation of eloquent areas, particularly the speech areas during awake craniotomy. They come in different shapes and sizes. They could be custom made, depending on personal needs, such as the number of electrodes, density, inter-electrode distance and shape of electrode array. These electrodes could be made of silver/silver chloride (Fig. 3, SLE Electronics and Accessories, UK) or platinum discs (Fig. 4, Ad Tech, Wisconsin, USA).

Similarly, depth electrodes are also commercially available; again they vary in the number of electrode points and the inter-electrode distance. They are usually made of platinum (Fig. 5, Ad Tech, Wisconsin, USA). For spinal cord surgeries epidural electrodes are very useful for recording over the scalp electrodes. These are commercially available as thin wires, usually ranging from one pole to five poles for recording. These are inserted into the epidural space through a 16 gauge catheter. Some labs have used a blunted stainless steel

Fig. 3: Silver/silver chloride plate array of 25 electrodes (5 × 5 cm). These are used for corticograms to localise central sulcus or epileptic foci

Fig. 4: Strip electrodes: platinum electrodes used for localising central sulcus and also for monitoring after-discharge during cortical stimulation

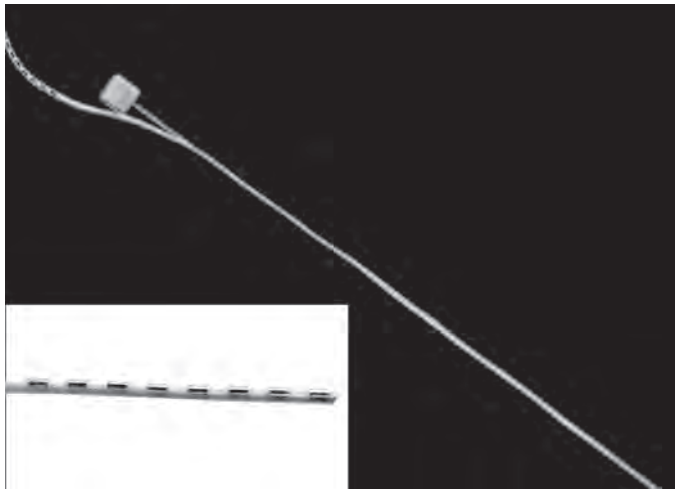

Fig. 5: Depth electrodes: these are eight contact 5 mm spacing platinum electrodes used for epilepsy surgery. The stylus with the electrodes is introduced into the brain. Once the site is determined the stylus is withdrawn so that the tube attached to the electrode will be flaccid and out of the surgeon's operating area

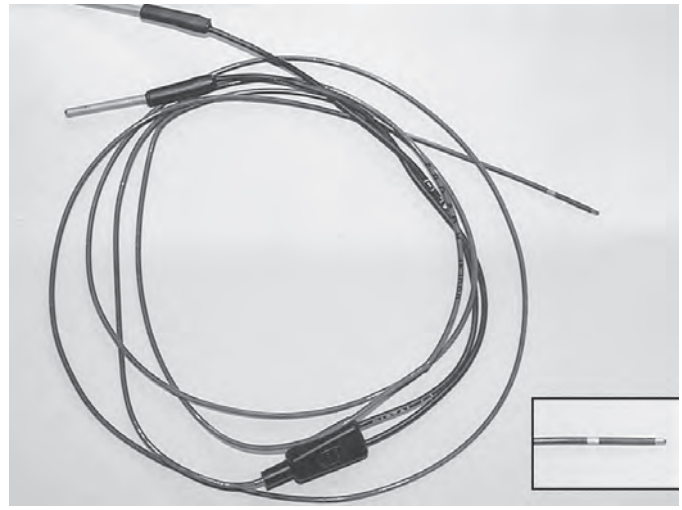

Fig. 6: Epidural electrodes: used for spinal cord surgery. These recording electrodes are introduced into the epidural space. Interelectrode distance is 1 cm

needle 0.9 X 3 mm connected to a fine wire[15] for epidural recording. We use a two pole intra-cardiac electrode (Fig. 6, Bard, Galway, Ireland). They are easy to insert directly into the epidural space without the need for a catheter (Fig. 7). These are held in place by stitching the cable at the exit to the exposed muscle and covering it with a cotton strip, such that it is out of the surgeon's operating area. They are insulated, except at the tip. These are available as a single wire or as a pair. A hypodermic needle is used to introduce the hook wire into the target muscle. Subdermal needle electrodes (Fig. 8, Nicolet, Wisconsin, USA) of 27 gauge are also very useful for recording EEG, EP and compound muscle action potentials (CMAP). They are inserted tangentially into the skin. Needles have inter-electrode impedances, which are about five to ten times that of stick-ons and, because of this they are more liable to produce noise-contaminated records in electrically hostile environments. Needle electrodes distort waveforms below 5 Hz if the input impedance of the amplifiers is less than 1 Mohms. Because of differences in both electrode potential and

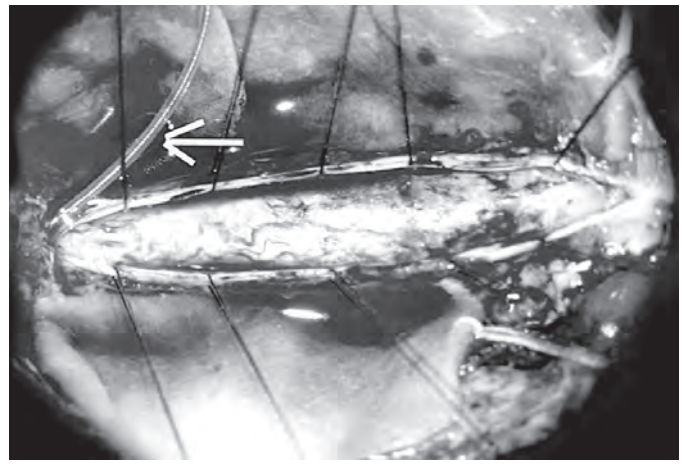

Fig. 7: Placement of epidural electrodes: photograph shows operating area with the epidural electrode moved out of the operating field

Fig. 8: Subdermal needle electrode: 1 cm steel electrodes used for EEG, EP and AMAP

recording characteristics, one should avoid recording between electrodes made of different metals.

BIPOLAR AND MONOPOLAR ELECTRICAL STIMULATION

Both bipolar and monopolar electrical stimulation are popular and they have their advantages and disadvantages. In bipolar stimulation, the spread of the stimulating current is limited between the two electrodes, which are adjacent to each other, while, in monopolar stimulation, one probe is placed on the neural structure that is to be identified, while the second electrode is placed indifferently, which is usually the exposed muscle at the operating site. In contrast to monopolar stimulation, bipolar stimulation requires orientation of the probe tips longitudinally along the nerve.[28] Therefore, in cases in which the course of the nerve is not known (i.e. nerve encased by tumour), a monopolar stimulus design is useful. Bipolar probes are useful to know which nerve it is rather than to know if it is a nerve or connective tissue. We have successfully employed monopolar stimulation for facial nerve stimulation, brainstem mapping of the motor nuclei,[29] spinal nerves in tethered cord and cortical stimulation under general anaesthesia.[27] We employed bipolar stimulation in awake craniotomy cases for mapping of the eloquent areas, so that the spread of the current is local and specific responses could be obtained and determined.

VISUAL EVOKED POTENTIAL

Flashes of light emitting diode (LED) fixed in goggles are the most common type used for intra-operative stimulation of the eyes. In these, the contours of the rubber edges fit well against the bony structures surrounding the orbit and a strap around the head can help to hold the goggles in place. The patient's eyes are kept closed with an adhesive and the light is flashed on to the closed eyelids. These are found to be convenient even for transsphenoidal surgeries. However, care must be taken to avoid the goggles slipping out of place and pressing against the eye. Contact lenses have also been used for stimulating devices. Contact lenses are fitted with a fibre optic cable that delivers light from a remote source.[39,45] In some devices the LEDs are implanted into special contact lenses and these are connected by a fine wire to a remote electrical source.[17,44]

VEP is used in patients with a tumour or aneurysm pressing on the optic nerve or chiasm. We have used VEP monitoring for pituitary tumours.[12] However, intraoperatively, we found that VEP is not as useful as other EPs and, hence, have abandoned it over time. For VEP monitoring, the active electrodes are placed at O1 and O2 with a common reference at Cz. In this, the low filter is set at 10 Hz and the high filter is set at 100 Hz. The rate of stimulation is 1.9/sec. The time base is set at 500 msec. The number of trials is set at 150. The principle peaks lie between 75 msec and 100 msec. Due to a longer recording time, these recordings are very easily susceptible to artefacts. Monitoring during trans-sphenoidal surgery for pituitary tumours showed a drop in VEP amplitude during infiltration of the nose (during which there is rise in BP), suggesting that VEP is susceptible to cerebral blood flow changes (Fig. 9).

Intra-operative monitoring of visual evoked potentials (VEPs) has been regarded as having limited significance for the preservation of visual function during neurosurgical procedures, mainly due to its poor spatial resolution and signal-to-noise ratio. Cortically recorded VEPs, instead of the usual scalp VEPs, as intra-operative monitoring, focusing on the posterior visual pathway is better. Direct recording from the visual cortices under general anaesthesia achieved satisfactory detectability of the visual response to a light-emitting diode flashing light. Intra-operative cortical VEP monitoring is a potentially useful procedure to monitor the functional integrity of the posterior visual pathway.[33]

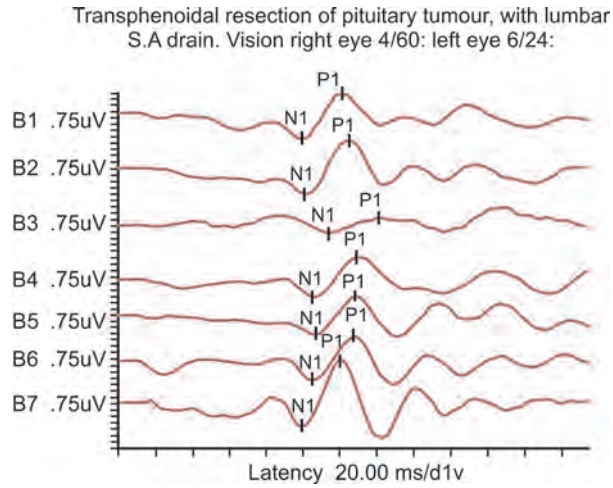

Fig. 9: Visual evoked potential (VEP) recordings taken during the course of trans-sphenoidal surgery. When the BP increased, VEP showed drop in amplitude during nasal infiltration (B3) which recovered in due course of time when BP returned to normal

BRAINSTEM AUDITORY EVOKED POTENTIAL

Neurophysiologic intra-operative monitoring of brainstem auditory evoked potentials (BAEPs) is a widely used method to assess the functional integrity of the central auditory system, during surgery involving the brainstem or the cranial nerves. The stimulus is a brief click delivered through tubal insert earphones. The stimulator is connected to silicone tubes, to which are attached disposable polyurethane foam tips, which are inserted into the ear. For better recording of wave one, gold TIPtrodes serve a dual purpose: they are used for delivering the sound and as a recording electrode.

BAEP is useful in surgery for CP angle tumours, brainstem surgery, microvascular decompression and in stereotactic biopsy of some brainstem tumours. In these, the active electrode is placed on the CZ and the reference electrodes are placed on the ear lobes. The rate of stimulation is 11.1/sec. The filter settings are set for low filter at 100 Hz and high filter at 3000 Hz. At least 2000 trials are averaged. The time base is set as 10 msec. The principle peaks are wave I, III and V. We monitored BAEP in 21 cases during stereotactic biopsy of brainstem tumours. We found only in two cases transient changes in BAEP, suggesting that stereotactic biopsy of intrinsic brainstem masses does not cause significant disruption of the auditory pathways.

Brainstem auditory evoked potentials (BAEP) monitoring is a useful tool to decrease the danger of hearing loss during cerebellopontine angle surgery, particularly in microvascular decompression (MVD). Critical complications during MVD surgery are the stretching of the VIII nerve—the main cause of hearing loss—labyrinthine artery manipulation, direct trauma with instruments or a nearby coagulation and at end of the surgery neocompression of the cochlear nerve by the prosthesis positioned between the conflicting vessel(s) and the VIIth-VIIIth nerve complex. All these dangers warrant the use of BEAP monitoring during the surgical team's training period.

Based on delay in latency of peak V, establishing warning thresholds that can provide useful feedback to the surgeon to modify the surgical strategy is essential. The initial signal at 0.4 ms is considered the safety limit. A second signal threshold at 0.6 ms (warning signal for risk) corresponds to the group of patients without resultant hearing loss. The third threshold characterised by the delay of peak V is at 1 ms (warning signal for a potentially critical situation). BAEP monitoring provides the surgeon the information on the functional state of the auditory pathways and should help avoid or correct manoeuvres that can harm hearing function. BAEP monitoring during VIIth-VIIIth complex surgery, particularly in MVD of facial nerves for HFS, is very useful during the learning period.[36]

SOMATOSENSORY EVOKED POTENTIAL MONITORING

SEPs are used for spinal cord monitoring, in surgery for cortical masses and cerebral aneurysms, cortical localisation of the central sulcus and in surgeries in and around the brainstem. The stimulating electrodes can be discs, bars or needles. Care must be taken when needles are used to ensure that they are not inserted into the nerve itself. It will be sufficient if the needles are placed subcutaneously. Needle electrodes have certain advantages in that they do not dry out during surgery, as compared to surface stimulation. Percutaneous stimulation is non-invasive and easy to use for peripheral nerve stimulation. The surface area is larger allowing a more even delivery of current. Drying of the electrode paste is a problem to be considered during long surgeries. For surgeries less than five hours, we found that percutaneous stimulation is adequate.

SEP monitoring is more commonly employed than AEP and VEP monitoring. SEP monitoring is used for spinal cord surgery, surgery in and around the brainstem and in aneurysm surgery.[25] Depending on the location of the lesion and type of surgery, either the median nerve at the wrist or the posterior tibial nerve at the ankle is stimulated at a rate of 4.7/sec. The filters are set between 10 Hz and 1500 Hz. For the median nerve, the time base is set at 40 msec, while for the tibial nerve it is set at 60 msec. Recordings are obtained from scalp electrodes; C3′ or C4′ for median nerve, Cz′ for tibial nerve and referenced to Fpz. Three hundred trials are averaged. The principle cortical peaks for median nerve are N20 and P30 and for tibial nerve are P37 and N45. In some spinal cord surgeries, we have used epidural electrodes. Epidural electrodes are not useful below the L1 level. Whenever scalp recordings are found to be unreliable, either due to artefacts or amplitudes are of low magnitude, epidural electrodes are used (Fig. 10). Bipolar epidural electrodes provide certain advantages over the scalp electrodes. Epidural electrodes are less susceptible to cerebral blood flow changes and anaesthesia. The rate of stimulation can be higher (10.7/sec), as compared to scalp recording. An average of 100 responses is more than adequate. This would drastically reduce the time. Besides this, the faster ascending EPs are from the spinocerebellar tract and not from the

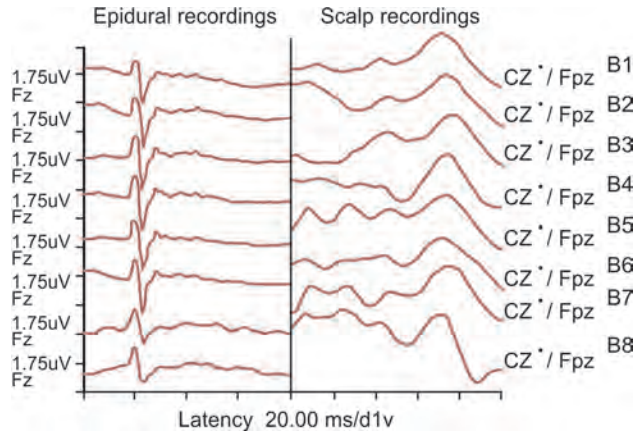

Fig. 10: Comparison of epidural and scalp recordings during spinal cord surgery of intramedullary tumour. Note scalp recordings intermixed with artefacts

posterior column. Using epidural electrodes, it would be possible to record from both these tracts and, hence, may reflect any damage or ischaemia to the cord more reliably than the scalp recordings.

MOTOR EVOKED POTENTIAL

Intra-operative motor evoked potential (MEP) monitoring in patients with spinal and cranial lesions is thought to be a valuable tool for prevention of post-operative motor deficits. MEPs provide the possibility for monitoring anterior and lateral spinal cord tracts. Responses can be recorded directly from the motor tracts or muscle. Recently, transcranial electrical stimulation (TES) and transcranial magnetic stimulation (TMS) techniques were introduced for IOM of the corticospinal pathways. For intra-operative monitoring we found TES is more convenient than TMS. In TES, the stimulus is delivered through a silver disc of 2 cm diameter, which is the cathode and the FPz is the anode. For TMS, the coils are big and difficult to position in the OT. Besides this, for TMS, care must be taken to see that there is no metal close to the coil. However, some centres have successfully used TMS for intra-operative monitoring. For both TES and TMS, a proper anaesthetic regime plays a major role in obtaining stable and reproducible waveforms.

Sustained vascular dynamics (vasospasm, congestive oedema) may cause delayed paresis which are missed or hardly reflected by intra-operative MEP changes. Even minor MEP changes must therefore be observed to prevent impending motor deficit.[31]

MEP monitoring, as opposed to SEPs, is a valid indicator of corticospinal function in brainstem-related surgery, independent from the type of lesion operated on. New deficit occurs only after more pronounced MEP changes than in supratentorial surgery, but complete loss, as in spinal surgery, is not seen. MEPs may help to prevent permanent new paresis.[30]

Intra-operative monitoring of facial nerve motor evoked potentials (FNMEPs) elicited by transcranial electrical stimulation during skull base tumour surgery is useful for predicting facial nerve function outcome.[18]

Intra-operative neurophysiological monitoring (IONM) with motor-evoked potentials (MEP), elicited by transcranial electrical stimulation and somatosensory-evoked potentials (SSEP) used in pregnant women, did not lead to any changes in either uterine muscle tone or foetal heart rate. Hence, IONM can be safely used in pregnant women.[35]

MOTOR NUCLEI AND NERVE STIMULATION

During brainstem surgery it is important to identify various nuclei, so that the surgeon can avoid manipulating or cause injury to them.[14,15] Identifying the facial nerve and mapping the course of the nerve fibres during cerebellopontine angle (CP) tumour surgery is also very important. We have used custom-made platinum monopolar electrodes. The indifferent electrode is stitched to the exposed muscle near the operating area. The tip of the platinum electrode is made into a ball that can be bent. We found this to be useful, particularly for CP angle tumours during drilling of the porus acousticus, where the facial nerve is out of view and under the bone. The electrode can be bent into a hook and the surgeon can "feel" for the nerve. We employ the same technique for spinal nerves in patients with a tethered cord. Here again, the indifferent electrode is stitched to the exposed muscle. Our starting current strength is 2.5 mA and we usually go down to 0.2 mA, keeping the rate of stimulation at 4.7/sec. The filters are set between 30 Hz and 3000 Hz. The time base for these is set at 20 msec for recording CMAP.

MAPPING ELOQUENT AREAS

Central sulcus mapping is done using somatosensory evoked potentials.[4,5,7,8,13] This is followed by cortical stimulation for further confirmation of the eloquent areas under general anaesthesia.[6] This technique is useful in planning the course of surgery for subcortical lesions. For a corticogram, subdural electrodes are used (Fig. 11). The contralateral median nerve is stimulated at 4.7/sec. The filters are set between 10 Hz and 1000 Hz, time base at 40 ms and 200 responses are averaged. The sulcus, where a phase reversal (Fig. 12) occurs, is considered the central sulcus.[11] This is further confirmed by monopolar cortical stimulation.[6] Monophasic square pulses of 300 microseconds duration at a rate of 50 Hz are used. The indifferent electrode is placed on the exposed muscle in the operating area. Current strength in steps of 1 mA starting from 3 mA is used. A maximum of 15 mA of current strength is used.[21] In awake craniotomy, bipolar stimulation is used. The stimulus is a monophasic square pulse of 1 msec duration stimulated at the rate of 50 Hz.[20] Subdural strip electrodes are placed in the vicinity of the stimulating area to record after discharge. Current strengths, starting from 2 mA to a maximum of 10 mA, are used. However, we could get responses within 4 mA of current strength. The strip electrodes are used to record after-discharge. Usually current strengths

Fig. 11: Photograph showing placement of an array of plate electrodes across the identified central sulcus. To ensure contact wet cotton strips are placed over the array of electrodes

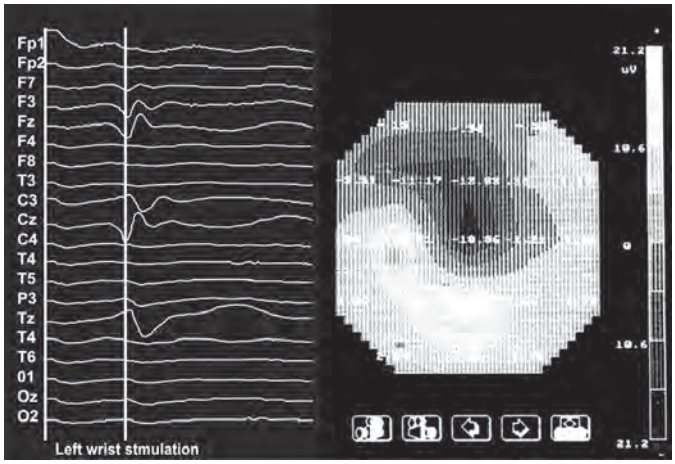

Fig. 12: Corticogram: using grid electrodes twenty channels recordings are obtained. Channels F7, F3, Fz, Cz show negative responses N20 (sensory gyrus), while Channels C3, Pz show positive responses P20 (motor gyrus) at 19.75 ms. In between them is the central sulcus. The gray scale on the right indicates voltages at 19.75 ms

are maintained 1 mA below the level of after-discharge. In our series, we have not used higher current strengths to see the after-discharge; this is to avoid any seizures that can occur due to stimulation.

INTRACRANIAL MONITORING USING ELECTROENCEPHALOGRAPHY

Intracranial monitoring using electroencephalography (IC-EEG) continues to play a critical role in the assessment of patients with medically intractable localisation-related epilepsy. Intracranial monitoring using EEG allows detailed definition of the region of ictal onset and defines the epileptogenic zone, particularly with regard to adjacent potentially eloquent tissue. Recent developments of IC-EEG include the co-registration of functional imaging data, such as magneto-encephalography to the frameless navigation systems. IC-EEG remains the gold standard for localisation of the epileptogenic cortex. Intracranial electrodes take a variety of different forms and may be placed either in the subdural (subdural strips and grids, depth electrodes) or extradural spaces (sphenoidal, peg and epidural electrodes). Each form has its own advantages and shortcomings, but extensive subdural implantation of electrodes is most common and is most comprehensively used.[10]

INTRA-OPERATIVE ELECTROMYOGRAPHY

Intra-operative monitoring, by stimulated electromyography (EMG) of the facial nerve to predict the completeness of microvascular decompression (MVD) for hemifacial spasm (HFS), is useful. The disappearance of an abnormal muscle response in the facial nerve EMG indicates the completeness of MVD. Intra-operative facial nerve EMG provides a real-time indicator of successful MVD during an operation, while BAEP monitoring may provide an early warning of hearing disturbance after MVD.[23]

INTRA-OPERATIVE DOPPLER ULTRASONOGRAPHY AND ULTRASOUND ANGIOGRAPHY

In treatment of brain arteriovenous malformations (AVMs), there is a correlation between the change of resistive index (RI) of the feeding artery and the completeness of resection of brain AVMs. The resistive index (RI) of the feeding artery was recorded so as to identify residual AVM. Intra-operative Doppler ultrasonography is a reliable tool for intra-operative localisation and complete resection of AVMs. Providing real-time flow pattern of AVMs, intra-operative ultrasound angiography combined with RI effectively indicates the completeness of resection of AVMs.[27,47]

NEURONAVIGATION

Currently, neuronavigation is an indispensable part of neurosurgical procedures in the majority of centres. The history of neuronavigation is quite short (less than three decades). The advent of neuronavigation would be unimaginable without the development of imaging technology, electronics, robotics and space technology.[16]

Intra-operative neuromonitoring includes motor mapping by direct cortical stimulation (CS) and subcortical stimulation (sCS) and localisation of the central sulcus, by using cortical multipolar electrodes and the N20 wave inversion technique. The location of all cortically and subcortically stimulated points with positive motor response is stored in the navigator and correlated with the cortical and subcortical motor functional structures, defined pre-operatively. Multimodal navigation allows integration and correlation among pre-operative and intra-operative anatomical and functional data. Cortical motor functional areas are anatomically and functionally located pre-operatively, thanks to MR and fMR imaging and subcortical motor pathways with DT imaging and tractography. Intra-operative confirmation is done with CS and N20 inversion wave for cortical structures and with sCS for subcortical pathways.[37]

Frameless stereotactic neuronavigation provides tracking of surgical instruments on radiographic images and orients the surgeon to tumour margins at surgery. Bipolar electrical stimulation mapping (ESM) delineates safe limits for resection of brain tumours adjacent to eloquent cortex. These standard techniques could complement the capability of intra-operative MR (iMR) imaging to evaluate for occult residual disease during surgery and promote more complete tumour removal. The presence of residual neoplasm is evaluated using iMR imaging; resection is continued until eloquent areas are encountered or iMR imaging confirms complete removal of any residual tumour.[42]

Preservation of motor function is very important in patients who require resection of tumours adjacent to the primary motor cortex and pyramidal tract. Electrical stimulation of the tumour cavity is necessary to prevent post-operative neurological deterioration in these cases.

A NY Tract Finder bipolar needle electrode, which enabled the identification of motor pathways by inserting it into the white matter, was developed and has been used. Motor-evoked potentials are induced by electrical stimulation with this electrode, when it is inserted toward the estimated motor pathway from the resected tumour cavity, with guidance by a neuronavigation system. The scale on the needle indicates the approximate distance from the tumour cavity wall to the pyramidal tract. This technique may be a feasible method to detect and spare the motor pathways. However, further studies are needed to determine reliability and limitations.[46]

NAVIGATED BLOOD FLOW IMAGING

Blood flow imaging (BFI) is a new 2-dimensional ultrasound modality that offers angle-independent visualisation of flow. When integrated with 3-dimensional (3D) navigation technology, BFI can be considered as a first step toward the ideal tool for surgical needs: A real-time, high-resolution, 3D visualisation that properly portrays both vessel geometry and flow direction. The neurovascular flow direction is properly visualised in all cases using BFI. Navigation technology allowed for identification of the vessels of interest, despite the presence of brain shift. BFI allows for quality control of sufficient flow in all distal arteries during aneurysm surgery and makes it easier to discern between feeding arteries and draining veins, during surgery for arteriovenous malformations. BFI seems to be a promising modality for neurovascular flow visualisation that may provide the neurosurgeon with a valuable tool for safer surgical interventions.

FLUORESCENCE-GUIDED RESECTION

Fluorescence-guided resection (FGR) of brain tumours is an intuitive, practical and emerging technology for visually delineating neoplastic tissue exposed intra-operatively. It detects surface fluorescence as a biomarker of the current surgical margin. Implementation of deformation modelling for brain shift compensation in protoporphyrin IX FGR and updated MR image information provide maximal surgical benefit.[41]

INTRA-OPERATIVE MAGNETIC RESONANCE IMAGING IN NEUROSURGERY

Intra-operative MRI (iMRI) has been incorporated into modern neurosurgical operating theatres as a guide for neurosurgical interventions. This technology has been shown to be a useful modality in brain tumour surgery and biopsy. Its use in spine, vascular and epilepsy surgery has been evolving. It is particularly useful in low-grade gliomas, pituitary adenomas and paediatric tumours.[2,3]

The addition of iMRI to the surgical armamentarium for treatment of patients with GBM improves the degree of tumour resection while minimising complications and thus may positively impact survival in this patient population. However, even with such technology, complete resection may not always be possible because of tumour location near critical brain structures or involvement of surrounding vascular structures.[26]

The intra-operative combination of an open magnetic resonance imaging (MRI) system with neurophysiological localisation and continuous monitoring techniques allows for the best available anatomic and physiological orientation, as well as real-time functional monitoring. MRI-compatible platinum/iridium electrodes for intra-operative neuromonitoring are attached to the patient's head. All other electrodes located outside the magnet are stainless steel needle-electrodes for recording of motor evoked potentials and for stimulating somatosensory evoked potentials. Intra-operative magnetic resonance scanner, neurophysiological monitoring for evoked potentials and direct cortical stimulation can be performed with standard quality within a low-field intra-operative MRI system. Electrodes fixed to the head should be of low magnetic susceptibility to guarantee optimal imaging quality. The combined use of an open ultra low-field MRI system and intra-operative monitoring allows for resection control and continuous functional monitoring.[40]

The use of the intra-operative ultra low-field MRI scanner helps to evaluate the extent of resection in glioma surgery. Further, tumour resection after intra-operative scanning leads to an increased rate of complete tumour resection, especially in patients with contrast-enhancing tumours. However, in non-contrast- enhancing tumours, the intra-operative visualisation of a complete resection seems less specific, when compared with post-operative 1.5 T MRI.[38]

Precise identification and preservation of the pyramidal tract during surgery for parenchymal brain tumours is of crucial importance for the avoidance of post-operative deterioration of motor function. The technique of intra-operative diffusion-weighted imaging (iDWI) using an intra-operative MR scanner of low magnetic field strength (0.3 T) has been developed. iDWI is very useful for localisation of the pyramidal tract and for clarification of its spatial relationships with the tumour. The use of iDWI, in addition to structural iMRl and subcortical functional mapping with electrical stimulation, can potentially result in a reduction of the post-operative morbidity after aggressive surgical removal of lesions located in the vicinity of the motor white matter tracts.[34]

INTRA-OPERATIVE MONITORING OF CEREBRAL BLOOD FLOW BY LASER SPECKLE CONTRAST ANALYSIS

Laser speckle contrast analysis (LASCA) is performed in patients undergoing cerebral revascularisation procedures for the treatment of haemodynamic compromise and complex aneurysms. LASCA offers non-invasive and rapid intra-operative assessment of relative CBF,

which can be used for optimising neurovascular procedures. The portable LASCA device is centred over the surgical field and continuous 5 minutes recordings of relative CBF are obtained. In the case of flow augmentation for haemodynamic compromise, CBF monitoring is performed before and after completion of the anastomosis. LASCA allows immediate visualisation and measurement of relative CBF in excellent spatiotemporal resolution.[22]

WIRELESS INSTANTANEOUS NEUROTRANSMITTER CONCENTRATION SYSTEM

Wireless Instantaneous Neurotransmitter Concentration System (WINCS), which couples digital telemetry with fast-scan cyclic voltametry (FSCV) is used to measure extracellular concentrations of dopamine. With the extended capability of the WINCS to use fixed potential amperometry (FPA), it is possible to measure extracellular concentrations of dopamine, as well as glutamate and adenosine. FPA offers superior temporal resolution and in combination with enzyme-linked biosensors, the potential to monitor non-electroactive analytes in real-time. The WINCS design incorporates a transimpedance amplifier with associated analog circuitry for FPA, a microprocessor, a Bluetooth transceiver and a single, battery-powered, multilayer, printed circuit board. The WINCS was tested with 3 distinct recording electrodes: 1) a carbon-fibre microelectrode (CFM) to measure dopamine; 2) a glutamate oxidase enzyme-linked electrode to measure glutamate and 3) a multiple enzyme-linked electrode (adenosine deaminase, nucleoside phosphorylase and xanthine oxidase) to measure adenosine. Because many neurotransmitters are not electrochemically active, FPA in combination with enzyme-linked microelectrodes represents a powerful intra-operative tool for rapid and selective neurochemical sampling in important anatomical targets during functional neurosurgery.[1]

INTRA-OPERATIVE ELECTROCORTICOGRAPHY

Wilder Penfield and Herbert Jasper, in the 1950s, developed the technique of intra-operative electrocorticography for localisation and surgical treatment of epilepsy. It has been used in the surgical management of medically refractory epilepsy to localise anatomic areas of focal seizure onset, guide the extent and completeness of resective epilepsy surgery, aid in functional mapping of cortical anatomy and predict epilepsy surgery outcome. The usefulness is often dependent on the underlying pathology and type of resective surgery.

It seems to be valuable in the following circumstances: (1) tailoring the extent of hippocampal resection during temporal lobectomies; (2) guiding resection of cortical brain malformations, low-grade tumours and other neocortical lesions, especially those involving eloquent cortex and (3) monitoring for after discharges during functional cortical mapping. Cortical stimulation can identify cortex with reorganised function secondary to congenital lesions and cerebral plasticity. These lesions include brain tumours, cortical dysplasia resulting in intractable epilepsy and cavernous angioma causing epilepsy. It has the disadvantage of being invasive but the advantage of being highly accurate, allowing for surgical tailored resections. The weight of the uncontrolled data at this stage is such that in children, electrocorticography remains to be a useful test in some cases of cortical resection and that cortical stimulation is usually indicated when resection in or near eloquent cortex is needed.[19] Electrocorticography (ECoG) monitoring in the microsurgical treatment of cavernous angiomas can direct the surgical procedure and control the post-operative epileptic seizure.[24]

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9 Conventional Radiology

Ravi Ramamurthi, Goutham Cugati

PLAIN X-RAY OF THE SKULL

Careful examination of well-exposed plain radiographs often helps to give a clue to the possible diagnosis and points to the line of further investigation. It is useful to have anteroposterior (AP) and lateral views. Special views like posteroanterior (PA), Towne's, perorbital, tangential or stereoscopic are required for special indications. An inspection of the plain radiograph of the skull includes the examination of the vault with its outer table, the diploe, the inner table and the structures at the base. The thickness of the vault varies in different areas and in different individuals. Anteriorly, the frontal sinuses extend into the frontal bone on both sides to a varying extent. In some, the frontal sinuses extend high up into the frontal bone and also laterally almost to the outer margin of the orbit. This is more common in acromegaly and has to be taken note of when planning surgery. Occasionally, the air sinuses may extend along the orbital plate on either side. Similarly, pneumatisation of the mastoid may be so extensive as to include the squamous part of the temporal bone or even the petrous tip.

Arterial markings in the skull are usually visible as thin wavy lines and may become well marked when the external carotid branches supply a vascular lesion like a meningioma or an arteriovenous malformation. The venous channels of the skull are usually more prominent. The confluence of veins in the parietal bone has been termed the "parietal spider". At times, this is strikingly prominent and should not be mistaken for a vascular lesion of the skull. The foramina of the emissary veins may be well visualised in some X-rays, but this happens more often in patients with increased intracranial pressure.

In the base of the skull, the pituitary fossa is one of the most important structures. In the lateral view, the anterior clinoid process, the planum sphenoidale, the chiasmatic sulcus, the tuberculum sella and the posterior clinoids are usually recognisable. It is important to be aware of the normal variations in the shape and size of the sella. Zagga et al. found three types of sella namely oval, round and flat among which oval shaped sella was seen in 83%. Among the three types of sella floor namely the concave, flat and convex, the concave type of sella floor was seen in 75% of the Nigerian population.[11] Occasionally, the pituitary fossa may be deep and extend more in the vertical than in the AP direction. This has been termed "J-shaped sella" and has no special pathological significance.

In the lateral view, it is also possible to visualise the floor of the middle cranial fossa; a difference in the level of the floor on either side may indicate hypoplasia or a space-occupying lesion dating from early childhood.

Posteroanterior View

The greater and lesser wings of the sphenoid bone and the anterior clinoid processes are seen through the orbit in the PA view. As normal variations are often present in the thickness of these structures, care is necessary before diagnosing any pathology. The anterior clinoids and the planum sphenoidale may be eroded by carotid aneurysms or thickened by a meningioma. Occasionally, the sphenoid wings may be so thin, as to suggest their absence.

Fronto-Occipital

In the AP view the frontal bone, frontal and ethmoid sinuses, crista galli, ridge of the petrous bone, the posterior clinoid processes, the sides of the sella turcica and the foramen magnum can be inspected.

Caldwell View

The petrous bones are projected through the orbits and along with the internal auditory canals are well visualised in the Caldwell view (Per-orbital view) (Fig. 1).

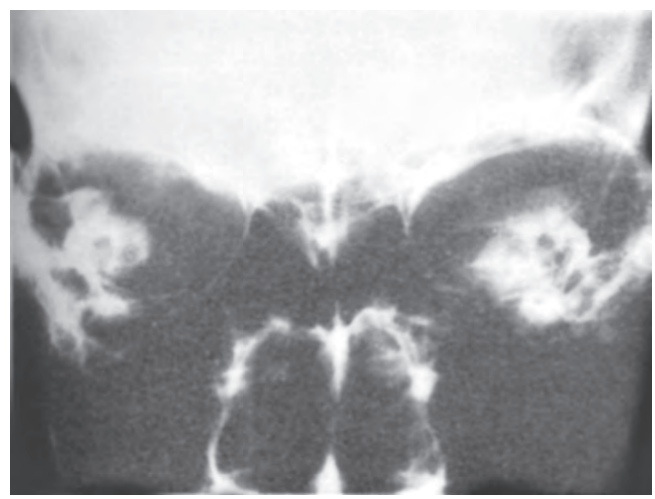

Fig. 1: Per-orbital view of the skull showing erosion of the apex of the right petrous bone

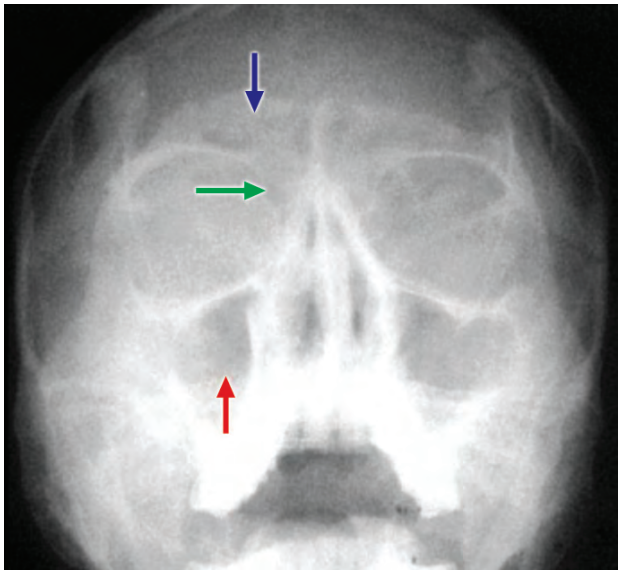

Fig. 2: X-ray Towne's view showing frontal (blue), ethmoidal (green) and maxillary (red) sinuses

Towne's View

The occipital bone, petrous pyramids, foramen magnum, dorsum sellae and posterior clinoids are seen well in this projection (Fig. 2).[5] Normal variations in the thickness of the petrous ridge must be remembered before diagnosing an erosion of the petrous bone or an enlargement of the internal auditory canal in the Towne's view.

Submento-Vertical View

Lesions involving the base of the skull can be demonstrated by a special basal view (submento-vertical view) (Fig. 3). The floor of the anterior, middle and posterior cranial fossa may be outlined. Erosion of the orbital roof, the lesser wing, the floor of the middle cranial fossa and the petrous bone are well seen. Although unilateral enlargement of the foramen spinosum would indicate an enlargement of the middle meningeal artery and the presence of a meningioma, normal variations do occur in the size of the foramen spinosum on either side. Occasionally, the foramen spinosum and the foramen ovale may coalesce and present as a single large foramen. Nasopharyngeal growths, chordomas and chondromas show appropriate changes in the base of the skull. The basal view is also used to visualise the foramen magnum and the odontoid process.

Plain X-rays of the skull may also reveal signs of systemic disorders. In hyperparathyroidism, there appears a peculiar but characteristic granular demineralisation of the vault, along with accentuation of the temporal line (the marginal line for the attachment of the temporal muscle to the skull) on frontal radiographs.[3] In Paget's disease, thickening of the bone is characteristic. In haemolytic anaemias, the diploic space widens with thinning of the tables of the skull vault (especially the outer table) and a radial disposition of the diploic trabeculae, giving rise to the so-called "hair-on end" appearance.

Multiple, rounded radiolucent areas suggest deposits of multiple myeloma or osteolytic metastases (Fig. 4). Larger well-defined areas of radiolucency may indicate deposits occurring in reticulosis which, in older children and adults, usually manifests as the solitary "eosinophilic granuloma" (Fig. 5). In very young patients, these areas may be confluent as in the Letterer-Siew disease or the Hand-Schuller-Christian syndrome. An important cause of multiple, rather ill-defined radiolucent areas in the skull of an infant or a child, is metastases from a neuroblastoma. As in this condition intracranial metastases are also fairly common, the combination of multiple rather ill-defined radiolucencies in the skull vault with signs of raised intracranial pressure, strongly favours the diagnosis of neuroblastoma.

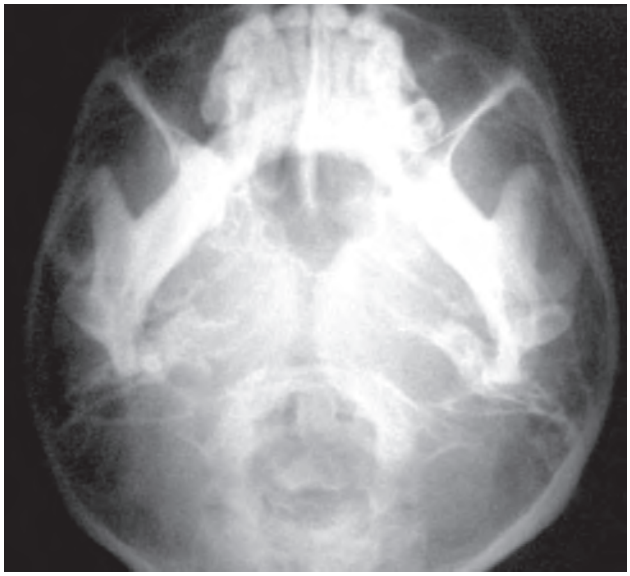

Fig. 3: X-ray submento-vertical view

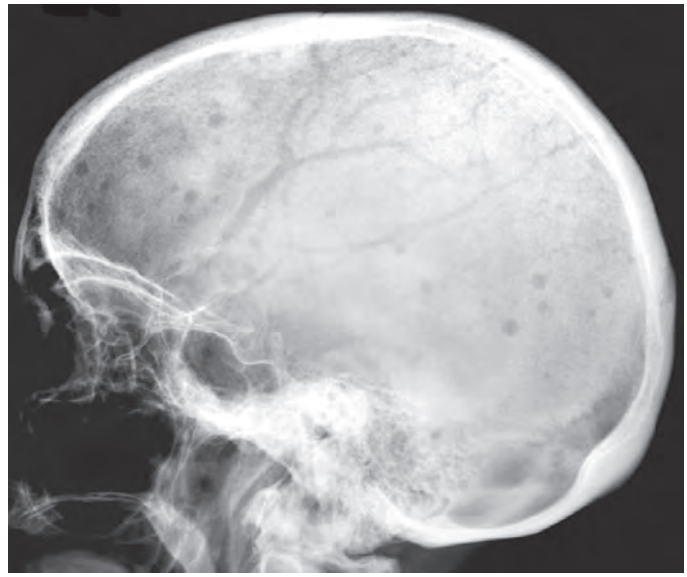

Fig. 4: Multiple, rounded radiolucent areas suggestive of deposits of multiple myeloma or osteolytic metastases

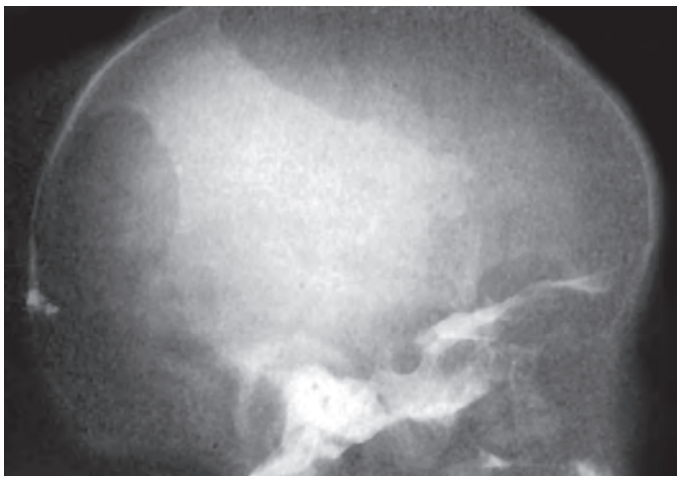

Fig. 5: Geographic skull—large osteolytic areas with irregular shape but sharp margins—findings typical of histiocytosis

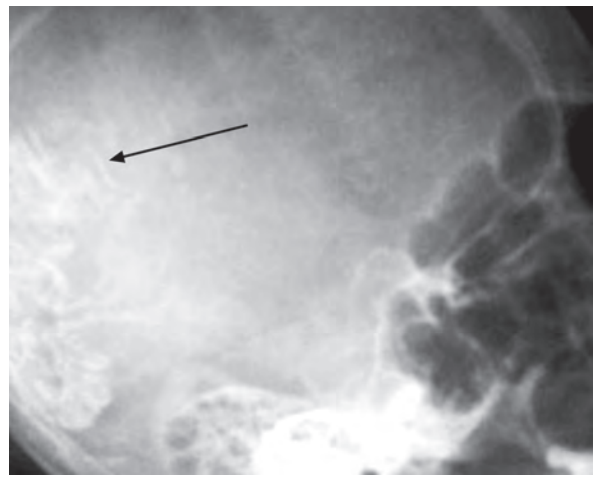

Fig. 6: Sturge-Weber Syndrome: characteristic, thin, parallel lines of gyral calcification ("rail-road") involving the atrophic occipital cortex

Intracranial Calcification

Calcification within the skull may be normal or abnormal. The structures in the midline that calcify are the pineal body, the falx cerebri, the Pachionian granules and the habenular commissure. The normal structures away from the midline that do so are: the choroid plexus, the petroclinoid ligament, the lateral edge of the diaphragma sellae and the carotid artery. The carotid siphon may show calcification in arteriosclerosis and may simulate a suprasellar calcification and is identified by its curvilinear shape and parallel streaks. Calcification of the midline structures is of clinical importance as they may be shifted to the opposite side by a space-occupying lesion in the supratentorial region, thus providing an important lateralising sign. Of the three, pineal and habenular calcifications are of much greater importance, as these structures shift readily, whereas the much more rigid falx cerebri does not lend itself very easily to a shift. Apart from a lateral shift, the pineal shadow may be shifted superiorly in the lateral radiograph of the skull by a space-occupying lesion near the dorsum of the midbrain, e.g. a tentorial meningioma. According to McRae,[4] the habenular commissure is calcified almost as often as the pineal gland and its location may be more precisely determined.

The incidence of calcification of normal intracranial structures is low in India compared to figures from Western countries. Pillai,[6] Varadarajan and Ramamurthi[10] and Shrivastava[9] reported the incidence of pineal calcification to be 5.8% and that of the choroid plexus 0.5–3%. It is suggested that this low incidence of calcification may perhaps be related to the type of nutrition. It is interesting to note that Pillai[6] reported an incidence of 23.5% from Kerala State in the south western corner of India. In general, abnormal calcification tends to be less dense in our patients, as compared to patients from developed countries. Contrary to popular belief, tuberculomas show radiologically visible calcification only in 6–7% of cases.[7] Dense irregular calcification is more often seen in healing brain infarcts that result from vascular occlusion in tuberculous meningitis and should not be mistaken for a tuberculoma. In some instances of abnormal calcification, the shape and type of calcification may be diagnostic, as in the case of the double-line wavy ("rail-road") calcification, seen in the Sturge-Weber-Dimitri syndrome (Fig. 6); or its position and shape may suggest the nature of the lesion, as in the case of the suprasellar oval or speckled calcification seen characteristically in a craniopharyngioma. Other instances of abnormal calcification occur in tuberose sclerosis, toxoplasmosis, oligodendroglioma, an aneurysmal sac, chronic subdural haematoma and dermoids. Of all brain tumours, oligodendrogliomas show the highest incidence of calcification. In the vast majority of cases, however, the type of calcification is not pathognomonic.

Increased Vascularity

An increase in vascularity, as indicated by increased and widened diploic vascular markings, is of clinical significance only if found to be localised or unilateral. Such vascularity may point to an underlying vascular neoplasm such as a meningioma, an arteriovenous malformation or a metastatic deposit.

Localised Areas of Bony Erosion or Sclerosis

Irregular areas of hyperdensity in the inner table of the frontal bone, as seen in hyperostosis frontalis interna, are not of any pathological significance. Erosion is associated with increased vascularity in the bone, whereas sclerosis occurs with decreased blood supply or as a reaction to tumour tissue infiltrating the bone. Direct pressure may also expand or erode the bone, as happens at the internal auditory meatus in an eighth nerve tumour or the tip of the petrous bone in a trigeminal neurinoma (Fig. 1) or in the pituitary fossa due to an intrasellar tumour. Local areas of bony erosion may be caused by an adjacent surface tumour like a meningioma. The inner table is more widely affected and there may be an associated increase in the local vascularity. A

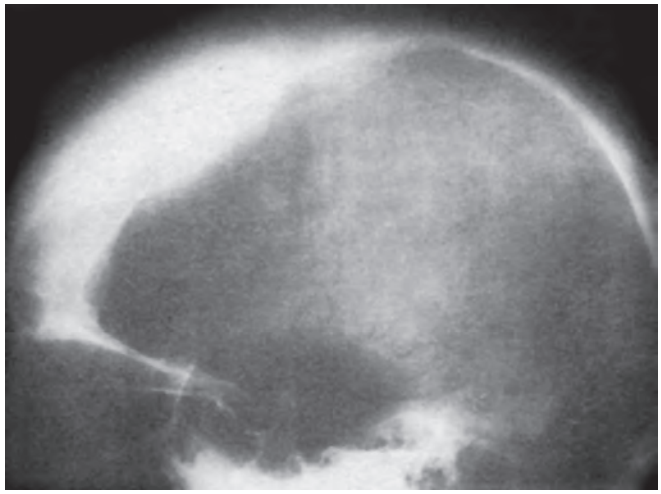

Fig. 7: Increased density of both tables of the frontal bone due to fibrous dysplasia

combination of sclerosis and erosion or sclerosis alone may occur, e.g. reactive sclerosis produced by a meningioma of the sphenoid ridge. Another condition that causes localised changes in the cranial vault is fibrous dysplasia of the bone (Fig. 7). This condition, usually seen in young patients, is of obscure aetiology. In the skull vault, it commonly presents as a cystic expansion of the diploic space, usually in the direction of the outer table, with a coarsening of the diploic pattern. Lesions in the base of the skull, however, present as a diffuse fairly dense, sclerotic thickening of the bone which is often bilateral. The sclerosis often extends to the infratemporal and maxillary regions, giving rise to the condition described as "leontiasis ossea". When unilateral, it may closely mimic a meningioma of the sphenoidal ridge. It can be differentiated from the latter by the more diffuse bone formation and associated cystic expanding lesions, seen in other parts of the skeleton.

Raised Intracranial Pressure

In infants and children, raised intracranial pressure is manifested by separation of the sutures and increased convolutional markings with thinning of the bone. Although the sutures in infants normally tend to be somewhat wide in the neighbourhood of the fontanelles, any separation beyond 2 mm is indicative of raised intracranial pressure. Such sutural diastasis may also be seen in young adults, occasionally up to the age of 20 years. Prominent convolutional markings with premature fusion of the sutures are seen in craniosynostosis. By contrast, the fully ossified skull of adults, with sutures partly or completely fused, does not allow sutural separation. Likewise, abnormal convolutional markings also fail to develop in adults even with marked increase in intracranial pressure.

Under these circumstances, the changes occurring in the sella turcica constitute by far the most important manifestation of raised intracranial pressure. In the earliest phase, there is demineralisation of the subcortical bone leading to a loss of the normal "lamina dura" (white line) of the sellar floor. This is followed by a thinning of the dorsum sellae and the posterior clinoid processes. The dorsum sellae later becomes foreshortened and pointed, resulting in a shallow sella turcica. In extreme cases, the sella becomes very shallow and flattened with its floor and anterior wall demineralised and the posterior clinoid processes and the dorsum sellae destroyed. The pituitary fossa may balloon-out in some cases of increased intracranial pressure associated with hydrocephalus. In such cases, the infundibular recess of the enlarging third ventricle acts like an expanding intrasellar lesion and the X-ray appearances resemble those of a pituitary adenoma. Another useful sign of increased pressure is the enlargement of the emissary foramina of the occipital region. This is due to increased intracranial venous pressure which is transmitted to the exterior, through the emissary and diploic veins. When there is a localised increase in pressure inside a portion of the intracranial cavity, in children and young adults, the skull may show localised thinning with a bulge. This may happen in a cystic lesion in the temporal region or in unilateral or loculated dilatation of the ventricles. Superficial expanding intracranial lesions like a congenital cyst or a chronic subdural haematoma may cause a localised thinning and bulging of the overlying bone.

Craniostenosis syn. Craniosynostosis

In craniostenosis, one or more sutures of the skull fuse prematurely during infancy or early childhood. This requires early recognition and treatment. Craniosynostosis is classified into the complete or partial types. In the complete variety all the sutures are fused, the head assumes a rounded (oxycephalic) or pointed or tower-like (turricephalic) shape. There is a marked increase in the convolutional markings due to the pulsation effect of the normal brain on the vault of the abnormally small skull. Deformity resulting from a combination of complete craniostenosis and hypertelorism, proptosis and hypoplasia of the maxillary antra is called "craniofacial dysostosis" or Crouzon's disease. The growth at the fused sutures is arrested, whereas it continues normally at the open sutures in partial craniostenosis. When the sagittal suture is prematurely fused, the growth occurs at the coronal and lambdoid sutures and the skull grows in an anteroposterior direction, resulting in a dolicocephalic or scaphocephalic type of craniosynostosis. If the coronal or lambdoid sutures fuse abnormally, the skull is foreshortened in its AP diameter, resulting in brachycephaly. In another variety of incomplete craniosynostosis, fusion of one half of the coronal or lambdoid sutures results in an asymmetrical skull, i.e. plagiocephaly.

Microcephaly

The skull is small due to an under-developed brain. The sutures are normal and the fontanelles closed. There are virtually no convolutional markings on the skull vault. There is usually some degree of "shelving" of the frontal

bone. In a few cases due to lack of growth stimulus, the sutures fuse prematurely leading to "secondary craniosynostosis". From the point of view of treatment, early differentiation between the small skull due to primary premature craniosynostosis and microcephaly with or without secondary craniosynostosis is of vital importance. The former needs surgical intervention, whereas surgery has no role for true microcephaly. An early decision is necessary, as the operation should be undertaken in the first year of life when the brain has its maximum rate of growth. The differentiation is easy if the sutures are normal, the small skull then obviously being secondary to the underlying microcephaly. If, however, secondary craniosynostosis has supervened, the absence of convolutional impressions in microcephaly differentiates it from the characteristic excessive convolutional markings seen in primary cranisynostosis.

"Hemiatrophy" of the Skull

In infantile hemiplegia when one cerebral hemisphere fails to develop fully, the skull on the affected side appears smaller than the opposite side and the bones are thicker. The crista galli is also shifted to the atrophic side. In the AP view, the atrophy of one half of the skull is well seen and is commonly known as "hemiatrophy of the skull".

Platybasia and Basilar Invagination

Platybasia is the term applied to the condition in which the base of the skull is flat. This is assessed by measuring "Welcker's angle", i.e. an angle subtended by the lines joining the nasion to the tuberculum sellae and that joining the tuberculum sellae to the anterior margin of the foramen magnum. The normal limit of the angle is 125 degrees. If the angle measures more than 140 degrees, platybasia is said to exist.

Basilar invagination and basilar impression are terms used to indicate elevation of the median part of the floor of the posterior cranial fossa; this condition may coexist with platybasia and developmental anomalies of the craniovertebral junction, such as occipitalisation of the atlas and atlanto-axial dislocation.

A number of radiological lines and measurements are available to determine the presence and degree of basilar invagination.[8] A few of the more important ones are mentioned here: 1) Chamberlain's line extends from the posterior end of the hard palate to the posterior lip of the foramen magnum. If more than one-third of the odontoid process extends above this line, basilar invagination is present; 2) McGregor's line joins the posterior end of the hard palate to the lower margin of the occipital squama. If the tip of the odontoid process extends more than 5 mm above this line, basilar invagination is suggested; 3) Bull's angle is subtended between the line extending the hard palate backwards and the line joining the centre of the anterior and posterior arches of the atlas extended forwards. If this angle measures more than 13 degrees, basilar invagination is indicated and 4) the clivus-canal line is a line which is extended along the plane of the clivus into the spinal canal. The odontoid tip normally lies anterior and inferior to this line and if the tip of the odontoid projects superior and behind this line, basilar invagination is present. For all the above, a strict lateral view of the skull is necessary.

In the AP projection, basilar invagination may be diagnosed by the use of Fischgold's line or the interdigastric line which joins the digastric grooves of the two sides. If the atlanto-occipital joint lies less than 7 mm below this line, basilar invagination is suggested. McRae's line joins the anterior and the posterior margins of the foramen magnum. Basilar invagination is said to exist if the upper margin of the occipital squama on either side of the foramen magnum is convex upward or if it lies above the line of the foramen magnum or if the condyles are above the foramen magnum. It may also be observed in the AP projection that the petrous pyramids are directed medially and upwards, instead of medially and slightly downwards as seen in the normal skull.

Sellar and Parasellar Neoplasms

The size and dimensions of the sella are quite variable in the normal skull X-ray. It is more useful if careful examination of the sella is done, rather than taking elaborate measurements. The upper limits of normality are: a) A-P diameter 17 mm; b) depth 14 mm and c) width 15 mm.

The dorsum sella is markedly thinned (but not destroyed) and is concave forwards and the anterior clinoid processes are thinned and sharpened by erosion from below (undercutting). The sella is deepened; a depth of more than 15 mm and an AP diameter of 20 mm are definitely abnormal.[1] The floor may be so demineralised that the tumour actually appears to project into the sphenoid sinus. Irregular growth may cause a step to be visible in the floor of the sella, "Double floor" in a "strict lateral" view (Fig. 8). The enlargement of the sella in some cases of raised intracranial pressure may simulate a pituitary

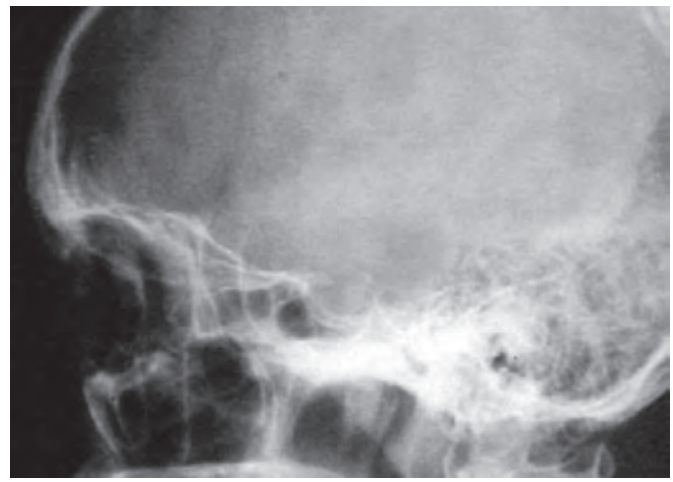

Fig. 8: X-ray lateral view in a patient with pituitary adenoma showing double flooring of the sella

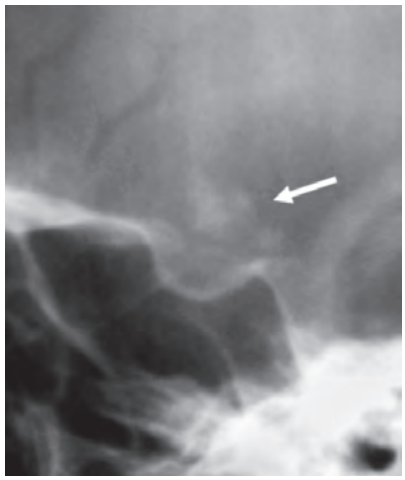

Fig. 9: X-ray lateral view in a patient with craniopharyngioma showing suprasellar calcification

tumour due to the infundibular recess of the third ventricle acting like an intrasellar lesion.

The X-ray changes in pituitary tumours have been graded by Hardy.[2] Grade I: The sella turcica is normal in size, although there may be a lowering of the floor on one side as revealed by strict lateral X-rays of the skull. Grade II: The sella turcica is enlarged to various degrees but the floor remains intact. Grade III: When the erosion is well localised to an area of the floor of the sella. Grade IV: When all the boundaries are barely visible and the entire floor of the sella is diffusely eroded or destroyed, having the aspect of a 'phantom' sella.

In addition to the sellar changes, however, there may be radiological changes, characteristic of gigantism or acromegaly. In acromegaly, the paranasal sinuses are large, the bones thick and coarsely trabeculated and the bony prominences and ridges accentuated. The skull vault is usually thick and the mandible is also thick, with everted edges. There is fairly well-marked prognathism with malocclusion of the teeth. There is also a 'tufting' of the terminal phalanges of the fingers and toes.

Craniopharyngiomas are usually suprasellar and about two-thirds of them show some calcification. (Fig. 9) Classically, the calcification is of the curvilinear or "egg-shell" variety situated just above the sella. More often one sees a diffuse speckled calcification. The majority of these tumours enlarge the sella to some extent with some truncation of the dorsum sellae.

IMAGING OF THE SPINE

Plain X-rays

Plain X-rays of the spine are valuable in all cases of suspected spinal cord lesions. Different techniques are necessary for proper visualisation of the various components of the spinal column at different levels of the spine. Special views are necessary to demonstrate changes in the atlas and the odontoid process. In the cervical region, in addition to the AP and lateral views, oblique views are necessary to show clearly the intervertebral foramen. Lateral views in flexion and extension help in determining minor subluxations between the cervical vertebrae and may also demonstrate abnormal mobility. Obliteration of the cervical lordosis itself is a useful sign. Proper visualisation of the lowermost cervical and upper four thoracic vertebrae is often difficult, especially in obese patients. The AP view alone is not informative because of the cervicothoracic curvature.

While viewing radiographs of the spine, the structures to be examined are the upper and lower borders of the body, the trabeculae in the body, the intervertebral disc space, the pedicles, the inter-articular joints, the laminae, the transverse processes and the spinous processes. One should also look at the paravertebral shadow, the head, neck and the body of the ribs and other shadows like that of the lateral border of the aorta, etc. The interpedicular distance varies from the cervical to the lumbar spine, with an enlargement in the cervical and lumbar regions corresponding to the origin of the brachial and lumbosacral plexuses. The interpedicular distance increases from C2 to C6 and then narrows from C6 to T4, below which there is a progressive increase. In the lateral view, a progressive narrowing of the AP diameter of the spinal canal may be seen from above downwards. The capacity of the spinal canal varies in different individuals according to its shape. In developing countries with resource constraints, a careful study of plain radiographs of the spine still occupies an important place in diagnosis. Congenital, traumatic, inflammatory and other abnormalities are dealt with in detail in the concerned chapters.

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10 Basic Principles of CT Scan and MRI Scan

Veena Norhona

Basics of Computed Tomography

INTRODUCTION

The first computed tomography (CT) scanner was developed by Sir Godfrey Hounsfield in 1972; since then this modality has become an important tool in diagnostic radiology. Since the first scanner to the present day multislice helical scanner, CT technology has revolutionised the world of imaging and enhanced patient management.

BASIC PHYSICS

Computed tomography uses X-rays to obtain cross-sectional, two-dimensional (2-D) images of the body. The cross-sectional image is produced by 360° rotation of the X-ray tube around the patient. The transmitted radiation is measured by the detectors located inside the gantry like a ring around the patient. The final image is generated from these measurements. The gantry of the CT machine houses the X-ray tube and the detectors (Fig. 1).

TYPES OF SCANNING TECHNIQUES

Axial (Sequential) Scanning

In sequential scanning, a single slice is obtained with a single 360° rotation of the tube (Fig. 2A). The disadvantage is that the time taken for an individual study is long, hence prone to motion artifacts and the quality of reformations is suboptimal.

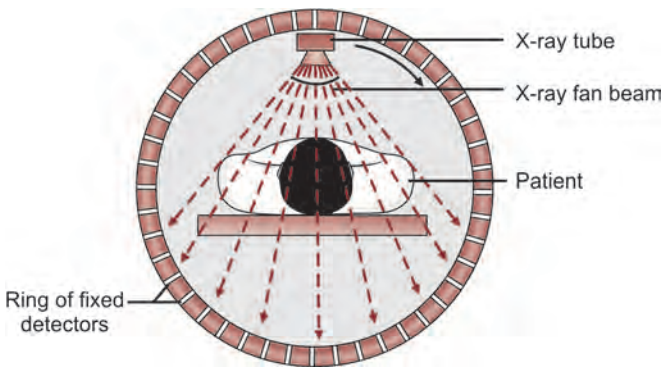


Fig. 1: Cross-sectional view of the gantry showing the orientation of the X-ray tube and detectors in a fourth generation CT scanner

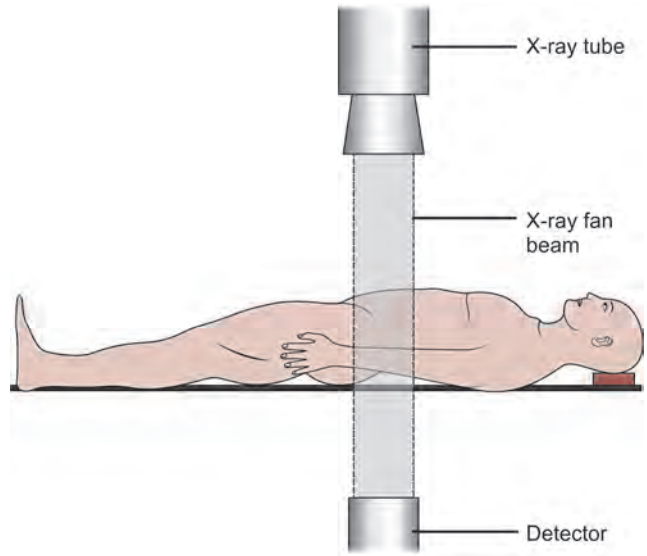


Fig. 2A: Sequential scan—single cross-sectional slice of the patient in a single rotation

Helical (Spiral) Scanning

With the advent of slip ring technology, the continuous rotation of the X-ray tube around the patient is made possible during continuous patient table movement. This led to the development of helical scanning (Fig. 2B). The transmitted radiation thus, takes the form of a helix or spiral around the patient acquiring a large volume of data. This allows larger anatomical regions of the body to be imaged during a single breath hold, thereby reducing the

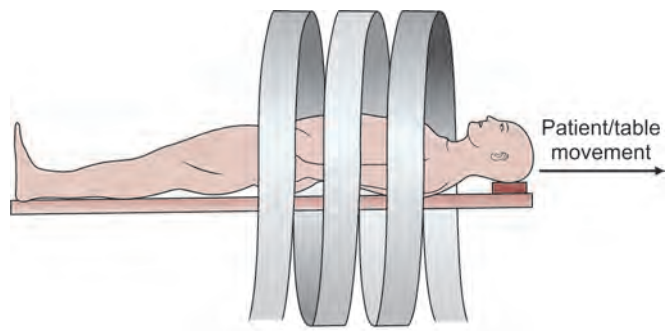


Fig. 2B: Helical scan—rotation of the tube around the patient with continuous table movement

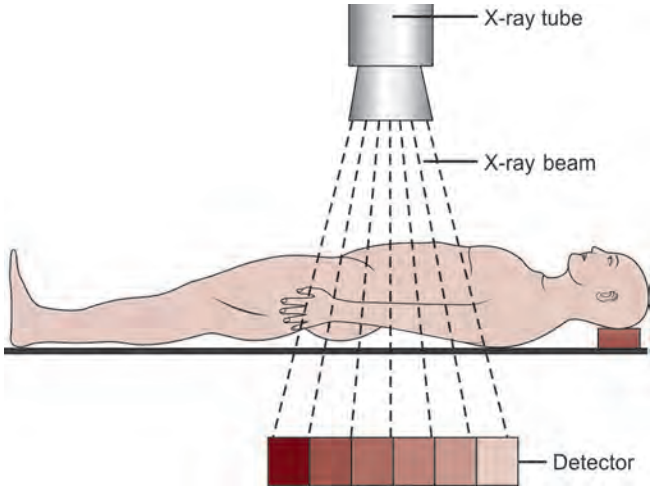


Fig. 3: Multi-slice imaging—generation of six slices per rotation of the tube in a multi-detector scanner

possibility of artifacts caused by patient movement. Faster scanning also increases patient throughput.

Multi-slice or multi-detector machines utilise the principles of the helical scanner but incorporate multiple rows of detector rings. They can therefore acquire multiple slices per tube rotation, thereby increasing the anatomical coverage in a shorter time (Fig. 3).

COMPUTED TOMOGRAPHY TERMINOLOGIES

Pixel and Voxel

Every CT image is made up of a square of picture elements called the pixel and volume element called the voxel (Fig. 4). The obtained CT image is subdivided into a matrix of up to 512 × 512 or 1024 × 1024 elements. The pixel width is determined by the field of view (FOV) and matrix size, i.e. FOV/matrix. The voxel volume = pixel area × slice thickness.

Hounsfield Unit or Computed Tomography Number

Each voxel is traversed during the scan by numerous X-ray photons and the intensity of the transmitted radiation is measured by the detectors. From these

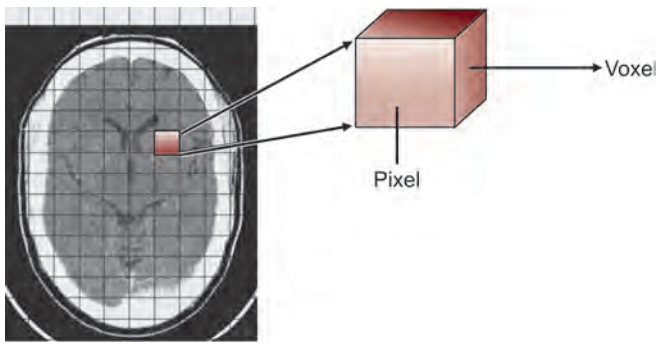


Fig. 4: Pixel—represents the matrix and voxel represents the slice thickness

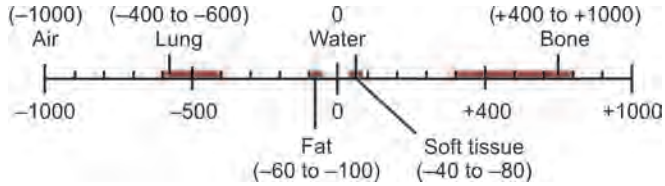


Fig. 5: Scale representing the range of Hounsfield numbers of the tissues seen in the body

intensity readings, the density or attenuation value, viz. Hounsfield unit (HU) or CT number is calculated and assigned to every tissue.

Each pixel is assigned a numerical value (CT number), based on the attenuation of X-rays by the tissue. This number is compared to the attenuation value of water and displayed on a scale of arbitrary units named HU after Sir Godfrey Hounsfield. This scale assigns water an attenuation value (HU) of zero. Each number represents a shade of grey with +1000 (white) and –1000 (black) at either end of the spectrum (Fig. 5).

The CT number of various tissues in the body is as follows:

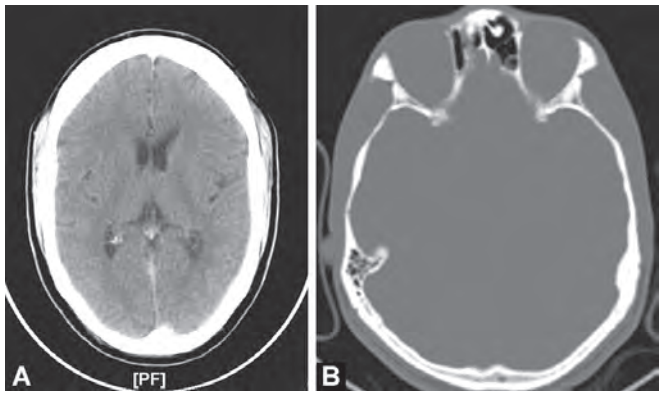
- Brain grey matter — 35–40 HU
- Brain white matter — 30–35 HU
- Blood—Flowing blood — 40 HU
- Acute haematoma — 70–90 HU (density depends on the haemoglobin concentration and coagulation profile)
- Calcification — + 80 and above
- Fat — – 100
- CSF — 0–10 HU
- Bone — + 800–1000 (depends on the type of bone).

WINDOW LEVEL AND WINDOW WIDTH

The term "window level" (WL) represents the central Hounsfield unit of all the numbers within the window width (WW). The WW covers the HU of all the tissues of interest and these are displayed as various shades of grey. Tissues with CT numbers outside this range are displayed as either black or white. Both the WL and WW can be set independently on the computer console and their respective settings affect the final displayed image (Figs 6A and B).

SLICE THICKNESS

It is the collimation of the X-ray beam as it emerges from the X-ray tube. The slice thickness can be varied depending on the anatomical region to be covered by varying the beam collimation. For example orbit scanning is done using 2–3 mm slice thickness, posterior fossa 4–5 mm slice thickness and supratentorial brain parenchyma 10 mm slice thickness.



Figs 6A and B: (A) Soft tissue window settings of an axial CT scan of the brain (WW = 100, WL = 30). (B) Bone window setting of an axial CT scan of the brain (WW = 2,000, WL = 220)

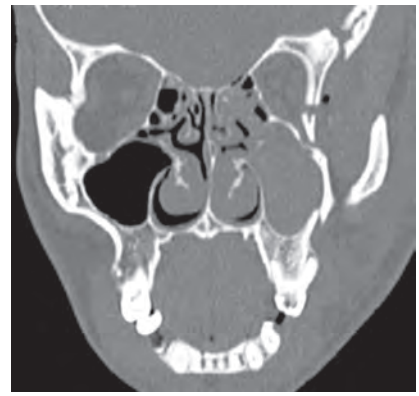


Fig. 8: Coronal reformations of the face showing fractures involving the lateral wall of the left maxillary sinus, zygoma, lateral wall of the left orbit and frontal bone

PITCH

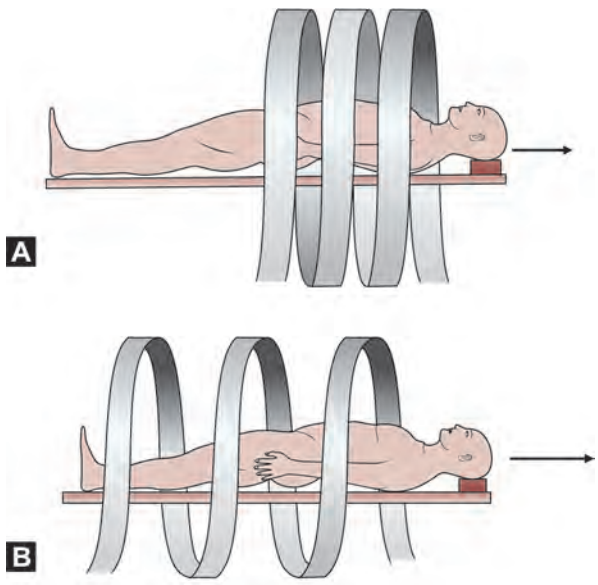
Pitch is the terminology used in helical scanning and denotes the distance travelled by the table (in millimetres) during one complete rotation of the X-ray tube, divided by the slice thickness (millimetres). Increasing the pitch by increasing the table speed reduces dose and scanning time, but at the cost of decreased image resolution (Figs 7A and B).

$$\text{Pitch} = \frac{\text{Table distance per } 360^\circ \text{ rotation (mm)}}{\text{Slice thickness (mm)}}$$

IMAGE POST PROCESSING

Post processing the acquired volumetric data during spiral CT is done in ways appropriate to the clinical situation such as:

- *Multiplanar reformatting*: After obtaining the serial axial volumetric data, the computer reconstructs the data in sagittal and coronal planes. With the current multi-slice CT scanner it is possible to obtain isotropic sagittal and coronal reconstructions. These are useful in paediatric and trauma patients who cannot be positioned for direct coronal scans (Fig. 8).
- *Three-dimensional (3-D) imaging*: The acquired data can also be post processed to obtain a 3-D model to display spatial information or surface characteristics (volume and surface rendering). This is useful in paediatric craniofacial anomalies and maxillofacial injuries to guide the surgeon in treatment planning (Fig. 9).
- *CT angiography (CTA)*: This involves injection of 100–120 ml of contrast medium, rapidly, using a pressure injector at a predetermined rate of injection. Serial axial images are obtained. These images are then used for reconstruction of the data using maximum intensity projection to get a display of the vascular tree. By altering the time of image acquisition and contrast injection, we can obtain only the arterial or venous phases (Figs 10A and B).



Figs 7A and B: (A) Shows a low pitch—tight helic. (B) A pitch of more than 1 – loose helic – shorter scan time at the cost of image resolution

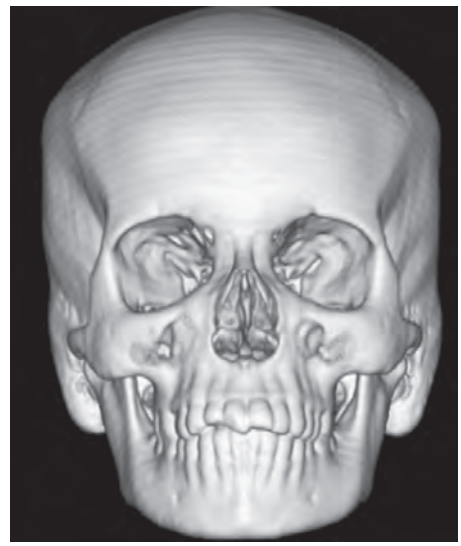
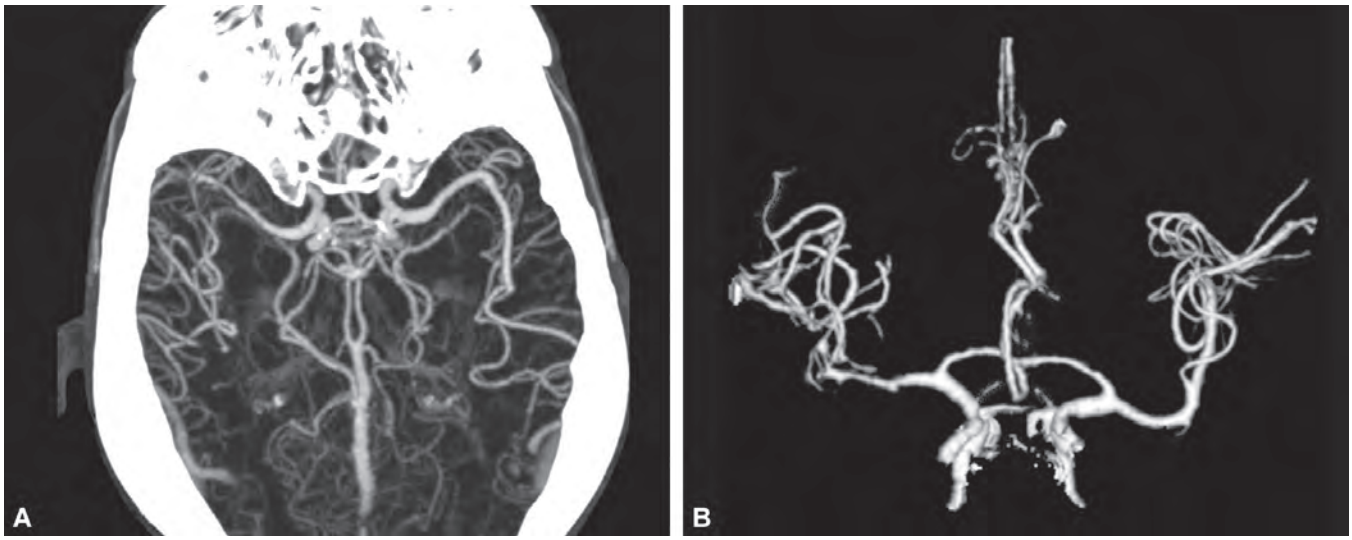


Fig. 9: CT of the skull



Figs 10A and B: CT angiogram of the brain showing. (A) Axial MIP image. (B) Volume rendering

COMPUTED TOMOGRAPHY CONTRAST MEDIA

These are iodine containing compounds. Iodine absorbs X-rays within the CT range (120 KVp) since iodine has an atomic number of 53 and atomic weight of 127.

There are two types of contrast agents used:

1. *Ionic contrast*: These are sodium or methylglucamine combined with a tri-iodinated benzene ring to form soluble salts. These are hyperosmolar and hence are likely to cause severe contrast reactions. These are contraindicated intrathecally.
2. *Non-ionic contrast*: These are near iso-osmolar and hence tend to produce fewer side effects and considered relatively safe for patients.

Absolute contraindication for contrast:

1. Previous contrast sensitivity
2. Abnormal renal parameters

Patients with diabetes and multiple myeloma are more likely to develop altered renal function post IV contrast injection. Patients with myasthenia gravis, sickle cell anaemia and pheochromocytoma are at risk of developing contrast-induced symptoms.

ADVANTAGES AND CLINICAL USE OF COMPUTED TOMOGRAPHY

- CT is readily available in most hospitals and is cost-effective.
- It is a rapid imaging modality with excellent image resolution, hence useful in trauma, paediatric and uncooperative patients.
- Patients in whom magnetic resonance imaging (MRI) is contraindicated.

DISADVANTAGES OF COMPUTED TOMOGRAPHY

- Radiation—The effective doses from diagnostic CT procedures are typically estimated to be in the range of 1–10 mSv.

FURTHER READING

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Physical Principles of Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is based on the principles of nuclear magnetic resonance (NMR).

BASIC PRINCIPLES OF MAGNETIC RESONANCE IMAGING

Magnetic resonance imaging is based on the absorption and emission of energy in the radiofrequency (RF) range of the electromagnetic spectrum. The human body is primarily made up of fat and water, which have many hydrogen atoms (almost 63%) (Fig. 11). The hydrogen atom (1H) consists of a single positively charged proton that spins around its axis. These charged particles create an electromagnetic field, similar to that of a bar magnet.

The proton possesses a property, called spin, which has a small magnetic field. These spinning particles have a net magnetic moment which has both magnitude and direction. In the absence of an external magnetic field, these protons are randomly oriented.

When placed in a magnetic field of strength B, the protons align themselves parallel or antiparallel to the external magnetic field. There is a low energy state where the poles are aligned N-S-N-S and a high energy state N-N-S-S. This particle can undergo a transition between the two energy states by the absorption of a photon. A particle in the lower energy state absorbs a photon and ends up in the upper energy state. The energy of this photon must exactly match the energy difference between the two states.

Application of a RF pulse of appropriate duration and amplitude excites these protons from the lower energy state to the higher energy state.

The MRI signal results from the energy difference of the spins emitted during transition from the higher energy state to the lower energy state. The signal is thus proportional to the population difference between the states (Figs 12A and B).

When the RF pulse is applied, the protons are tipped into the horizontal or X-Y plane by an angle termed as the flip angle or tip angle depending on the type of RF pulse. The rate at which the protons precess is termed as frequency and the angular position of the precessing spin is called the phase of the spin.

The frequency of precession (f) is called the Larmor frequency and is characteristic of the specific nucleus and strength of the external magnetic field and is expressed as:

$$f = \gamma B$$

Where f = mHz/sec, B is expressed in Tesla and ã is the gyromagnetic ratio of the specific nucleus and expressed as mHz/T. Hydrogen has the highest gyromagnetic ratio and is the most abundant body element, hence is the natural choice for H signal.

Radiofrequency Field

Every nucleus in the body precesses at its own Larmor frequency and will produce an MR signal only when the RF energy is delivered at the correct frequency. The excitation RF pulses are delivered by coils that produce an RF field perpendicular to the external magnetic field. The RF is absorbed by the nuclei and the magnetic moment is tipped away from the Z axis, i.e. axis of the external magnetic field depending on the duration and amplitude of the RF pulse.

Free Induction Decay

When the RF pulse is switched off, the magnetic momentum of the nuclei begins to return to its original position, thereby transferring the absorbed energy and inducing alternating current signal in the receiver coil. This is termed as free induction decay (FID). As this occurs immediately after the RF pulse, this signal is not used for image data. The magnetisation is manipulated to generate a useful signal termed as echo, which produces the image.

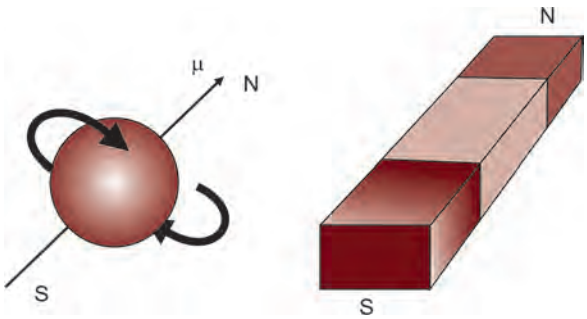
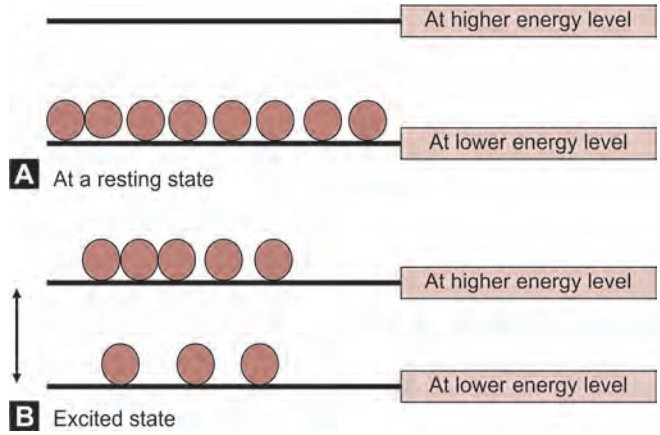
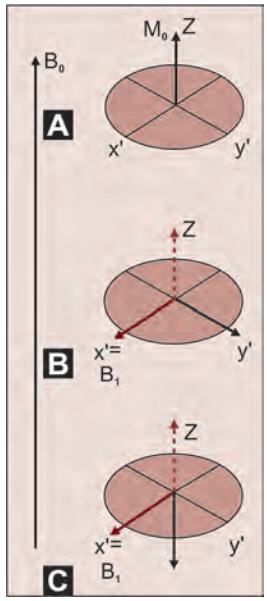


Fig. 11: Every spinning particle possesses a magnetic moment (μ) and creates a magnetic filed similar to a bar magnet



Figs 12A and B: (A) Showing protons outside a magnetic field. (B) showing excited protons in a magnetic field moving from a lower energy level to a higher energy level with two distinct energy levels. The population difference is directly proportional to the magnetic field strength



Figs 13A to C: (A) Alignment of the protons along the direction of the external magnetic field (B_0) in the z-axis. (B) After applying the RF pulse of an appropriate frequency, the magnetisation (M_0)/ protons are tipped away from its equilibrium in the x-y plane. (C) If a longer pulse lasting twice as long is applied, the magnetisation is inverted

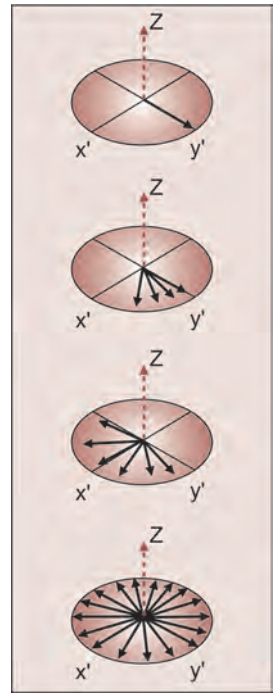


Fig. 15: Spin – spin relaxation–T2 relaxation-Loss of magnetisation in the x′-y′ plane is faster than the loss of magnetisation in the z- direction due to loss of phase coherence of the microscopic components

T1 and T2 Relaxation

When the RF pulse is switched off, two processes take place simultaneously

A. Recovery of the net magnetic moment in the Z axis—termed as longitudinal or T1 relaxation. T1 is the time required for the buildup of 63% of the original magnetisation along the Z axis (Figs 13A to C).
B. Loss of phase coherence in the X-Y plane or transverse plane—termed as T2 relaxation.

The nuclei while returning to the ground state dissipate their excess energy to their surroundings, which is called the lattice. This process is named as spin-lattice relaxation (Fig. 14). Smaller molecules reorient more rapidly than larger molecules. The medium-sized molecules, such as lipids, relax faster as their frequency of rotation is closer to the Larmor frequency than that associated with pure water or larger molecules such as proteins. Thus, T1 relaxation times depend on magnetic field strength because the latter affects the Larmor frequency. Thus water has a long T1.

Transverse magnetisation occurs because the magnetic field generated by the surrounding electrons exposes the precessing nuclei to different field strengths. Loss of transverse magnetisation (phase coherence) occurs as the magnetic moments get out of phase as a result of their mutual interaction. Anything that changes the magnetic field strength also changes the precessional frequency and causes a loss of phase coherence (dephasing) and shrinking of the transverse magnetisation. This is called T2 relaxation or spin-spin relaxation (Fig. 15). It denotes the loss of phase coherence caused by interactions between neighbouring magnetic moments. T2 is the time required to reduce the transverse magnetisation to 37% of its original value.

In biological tissues, the main contribution to T2 relaxation is from the relatively static magnetic field from neighbouring protons. Large molecules, which tend to reorient more slowly than small molecules, promote T2 relaxation and have shorter T2 times. Free water has a longer T2 than water associated with macromolecules. The T2 is relatively independent of the field strength.

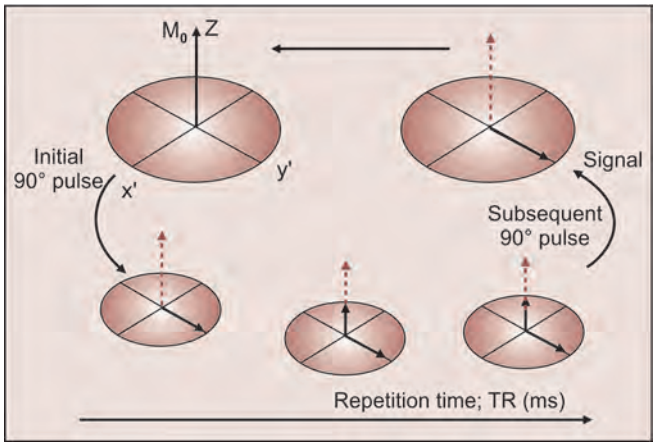


Fig. 14: Spin-lattice relaxation time

Repetition Time

The time between two RF excitation pulses is called the repetition time (TR). The TR can be chosen from a certain minimum value, depending on the imaging technique and the MR system, to very long times.

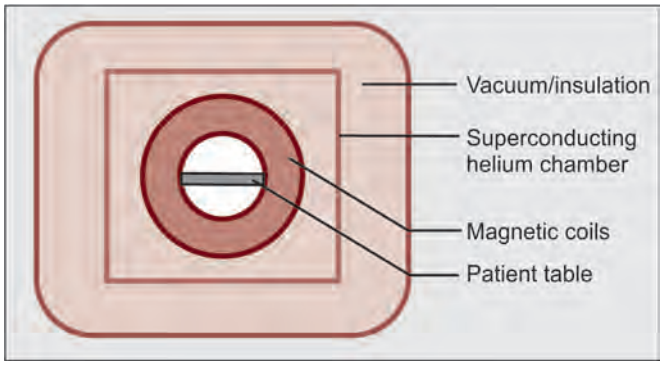


Fig. 16: Showing schematic representation of the superconducting MR systems. The bore is surrounded by the coils of the wire through which electric current is passed and cooled by liquid helium to achieve magnetisation and desired field strength

Longer values of TR allow more T1 relaxation to occur, and this property can be exploited to manipulate the contrast between tissues with different T1s or the signal-to-noise ratio in an image.

Echo Time

The time from the centre of the RF excitation pulse to the centre of the echo is the echo time (TE). The amplitude of the transverse magnetisation at the echo peak depends on TE and T2 of the tissue. As TE is prolonged, the transverse magnetisation becomes weaker. Adjusting TE influences the contrast between tissues that have different T2s.

Slice Orientation

The orientation of a slice, i.e. axial, coronal or sagittal, depends on which of the three magnetic field gradients is activated during the RF pulse. An RF pulse in the presence of the z gradient creates a transverse slice. The x and y gradients select slices in the sagittal and coronal orientations, respectively. Oblique slices are created by activating two or more gradients during an RF pulse.

Slice Position

Slices are located where the Larmor frequency matches the frequency of the RF pulse. The slice-selection gradient lowers the Larmor frequency on one side of the centre of the magnet and raises it on the other side. Slice position is controlled by changing the frequency of the RF pulse because changing the amplitude of the slice-selection gradient would inadvertently alter the thickness of the slice.

INSTRUMENTATION

The key components of an MR system are the magnet, the gradient, the RF subsystem and the computer.

The Magnet

The magnet is the main component of the MR system. There are three types of magnets in common use for

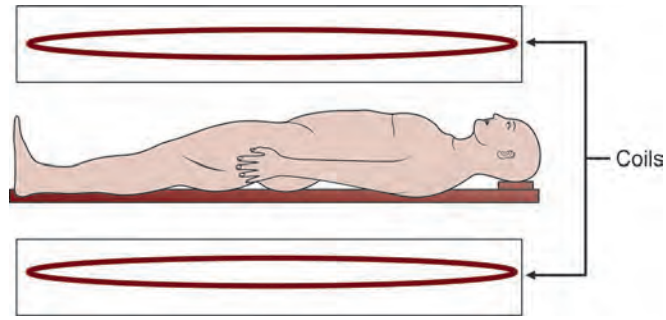


Fig. 17: Schematic diagram of a permanent MR system showing the generation of the magnetic field in a vertical direction by magnetised ceramic blocks

MRI—permanent magnets, resistive electromagnets and superconducting electromagnets. The higher the field strength the better is the signal-to-noise ratio. The strength of the magnetic field is measured in Gauss (G) or Tesla (T) units (10,000 G = 1 T). Diagnostic MR systems usually employ magnets with operating field strengths ranging from 0.02 to 3 T. Research systems operate above 3T up to 9T.

Superconducting Magnets

These are the most commonly used magnets and operate at field strength above 0.5 T. Some metals (e.g. Hg) and alloys (e.g. niobium/titanium, Nb/Ti; niobium/tin, Nb3Sn; and vanadium/gallium, V3Ga) lose their electrical resistance at very low temperatures and become superconductors. The superconductor most widely used in the construction of clinical magnets is Nb/Ti. This alloy becomes superconducting at 10° Kelvin (K) in the absence of an external magnetic field. This temperature is provided by a bath of liquid helium (4° K) (Fig. 16).

Resistive Magnets

A resistive magnet is an electromagnet in which the magnetic field is generated by the passage of electrical current through a wire. The disadvantage is their high-power consumption, limiting field strength.

Permanent Magnets

It uses a horse-shoe magnet. An advantage of these low field permanent magnet systems is that their C-shaped design is patient friendly and therefore useful in claustrophobic patients. Their field strength is limited to 0.5 T (Fig. 17).

Magnetic Field Gradients

Magnetic field gradients are activated as pulses for a short duration at timed intervals. It is a magnetic field that increases in strength along a particular direction, e.g. x, y and z gradients, according to the direction of change of the magnetic field strength. The strength of a gradient refers to the rate at which its magnetic field changes with distance.

Radiofrequency System

The excitation of the nuclei is done with a short duration RF pulse close to or at the Larmor frequency of the nuclei. The desired frequency is produced by a frequency synthesizer. The receiver detects signals in the high and very high frequency (HF and VHF) range. The magnetic resonance signals are typically a few μV in amplitude.

Transmitter and Receiver Coils

The body part to be examined is placed inside a coil. Separate coils can be used for transmitting and receiving or a single coil can be used for both excitation and detection (transceiver coil). A coil is a winding of low-resistance wire, usually made of copper. Volume coils are used for large body parts. Surface coils are used to study small regions such as the eye. The advantage of surface coils is that their signal-to-noise ratio is better as the part is close to the coil. Surface coils can receive a good signal from the tissues within the depth of half its diameter.

COMMONLY USED PULSE SEQUENCES

Spin-Echo Pulse Sequence

In a spin-echo pulse sequence two RF pulses, i.e. 90° and 180°, are applied spaced by a time interval of TE/2. After the nuclei are excited by a 90° pulse, the spins dephase in the x′-y′ plane and this is followed by a refocusing 180° pulse. The faster spins lie behind the slower ones, but at time TE/2 they make up, thus producing an echo.

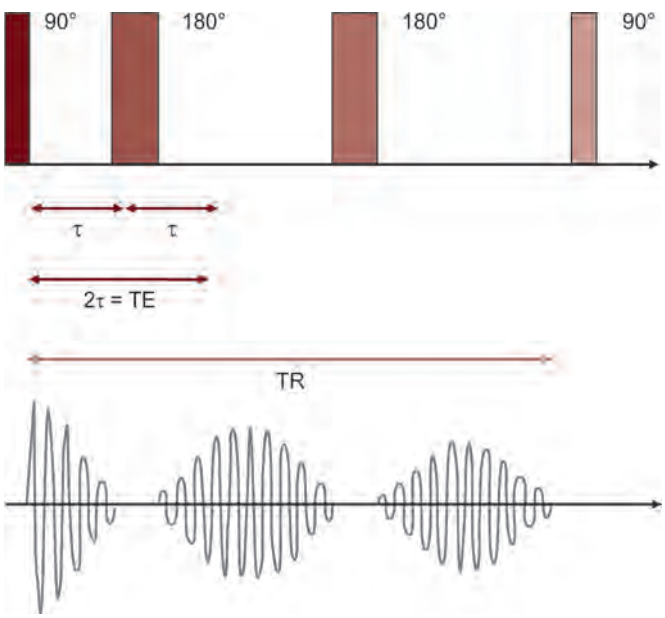


Fig. 18: Diagram of a spin-echo pulse sequence. The spin system is excited by a 90° pulse. After a time delay, one or several 180° pulses follow. This leads to the formation of an echo. The time between the 90° pulse and the peak of the echo is called echo time (TE). TR is the repetition time between two complete pulse sequences

The 180° pulse results in reversal of the phase of each spin. The position of the spins has not changed, so they will continue to rotate in the same direction. However, the 180° pulse causes the spins to return towards their starting point, rather than rotating further away from it. This 90°–180° pulse sequence is called spin-echo sequence (Fig. 18). By altering the echo delay time, and the sequence TR, the spin-echo sequence can be used to obtain T1, T2 or proton density images. The spin-echo sequence has been largely replaced by faster sequences such as fast spin echo and fast gradient recalled echo (GRE).

Gradient Echo Imaging

Gradient echo imaging is an imaging technique by which images can be acquired in much shorter times than conventional pulse sequences. The basic difference between spin-echo and gradient echo imaging is that gradient echo uses gradient reversals to get an echo, and spin echo uses 180° rephrasing pulse and gradient echo uses flip angle less than 90° (Fig. 19).

Inversion Recovery Imaging

The inversion recovery sequence uses a 180° inverting pulse, a 90° pulse and a rephrasing 180° pulse. The inversion time (TI) is determined by the TR and T1 of the tissue needed to be suppressed (Fig. 20). Commonly used inversion recovery pulse sequence are:

1. Fluid attenuated inversion recovery (FLAIR) whereby the cerebrospinal fluid (CSF) bright signal is suppressed. It is now a routinely used sequence in

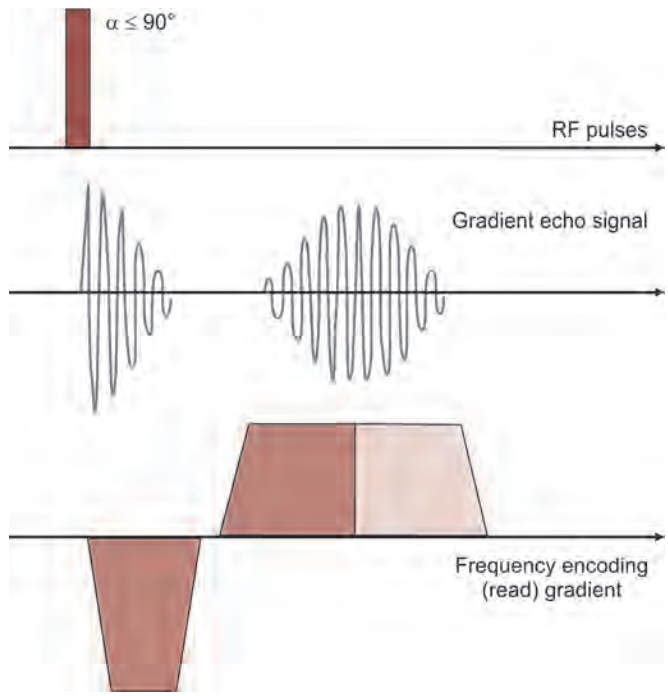


Fig. 19: Formation of a gradient echo. Instead of the 180° pulse, a gradient pulse (-G) is used followed by a second gradient pulse of opposite polarity (+G). In gradient echo sequence, the signal decay is determined by T2*, which is always less than T2

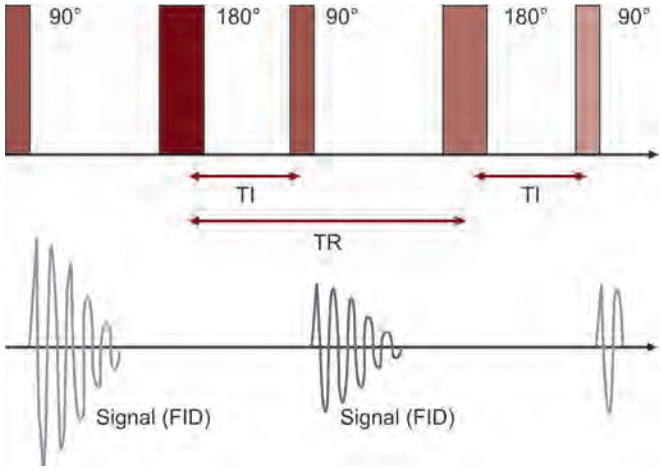


Fig. 20: Pulse sequence diagram of an inversion recovery pulse sequence. The 180° inverting pulse is followed by a 90° pulse and 180° rephasing pulse

brain imaging and especially to image periventricular plaques in multiple sclerosis.

2. Short tau inversion recovery (STIR) sequence is mainly used in imaging the optic nerves. It suppresses the orbital fat and highlights the lesions within the optic nerve, mainly in optic neuritis.

MAGNETIC RESONANCE CONTRAST

Most of the contrast agents in clinical use enhance tissue relaxation. Gadolinium is a rare earth element and toxic by itself, hence it is chelated with multi-dentate ligands for safety such as diethylenetriamine pentetate (DTPA) and tetraazacyclododecane tetraacetic acid (DOTA). It is a paramagnetic substance that shortens the T1 relaxation and hence makes the tissues with contrast appear bright.

Safety

- These contrast agents are considered safe with a rate of adverse reaction such as nausea and vomiting (1–2%) and hives (1%). Severe anaphylactoid reactions have been reported with an estimated rate of 1 in 200,000 and 1 in 400,000.
- These contrast agents can be safely used in children above 2 years.
- They should not be used in patients with compromised renal function. There have been cases reported of nephrogenic systemic fibrosis in patients with compromised renal function.
- Should not be used in pregnancy as its bioeffect on the foetus has not been established.

MAGNETIC RESONANCE ANGIOGRAPHY

Advantages of magnetic resonance angiography (MRA) versus catheter angiogram are:

- Non-invasive or minimally invasive
- Three-dimensional information can be obtained

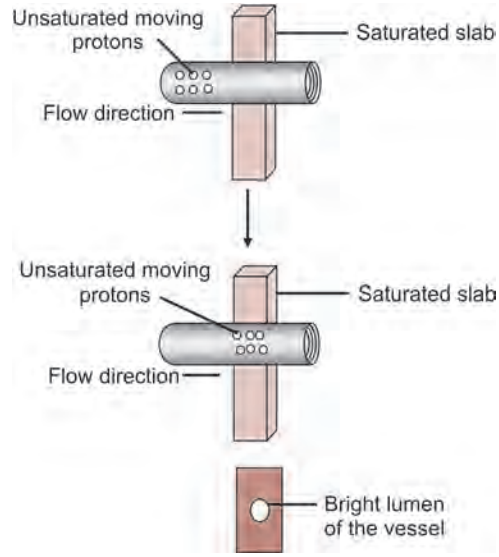


Fig. 21: Schematic representation of time-of-flight angiogram

- Can give surrounding soft tissue details

Disadvantages include:

- Flow dynamic information is lacking

Techniques of Magnetic Resonance Angiography

The commonly used techniques in clinical practice are:

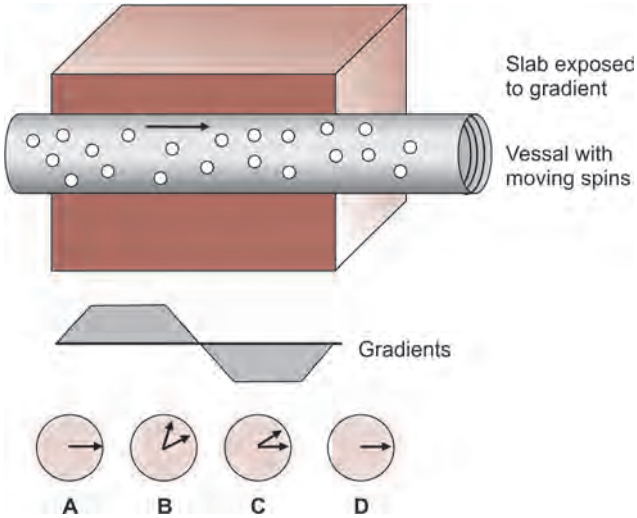
- Time-of-flight (TOF) MR angiogram
- Phase contrast (PC) MR angiogram
- Contrast-enhanced (CE) MR angiogram

Time-of-Flight Magnetic Resonance Angiogram

This is the most widely used MR angiography technique for imaging the intracranial circulation. It gives reliable vascular information without the need for intravenous contrast.

The basic principle involves suppression of the static background tissue and retaining the signal from the flowing blood. The saturation of the stationary tissue is done by using very short TR so that the stationary spins do not have enough time to regain their longitudinal magnetisation. The flowing (unsaturated) spins which enter the slice are unaffected by the slice selective RF pulse and will be fully magnetised producing a bright signal (Fig. 21). The signal produced is directly proportional to the velocity of the flowing blood. Flow saturation will occur when the spins in the imaging volume are not entirely replenished after each pulse.

The TOF angiogram can be obtained using 2-D or 3-D sequences. In a 2-D sequence, sequential thin sections are obtained whereas in 3-D a slab of tissue is excited. Each of them has their advantages and disadvantages. Two-dimensional angiograms are used to evaluate slow flowing blood, but are susceptible to turbulent flow. There is less spatial resolution. Three-dimensional angiograms have high spatial resolutions and are less susceptible to turbulent flow.



Figs 22A to D: Schematic diagram of a phase contrast MR angiogram. (A) Spins in the stationary tissue at time 0. (B) Spins dephasing after exposed to gradients. (C) Spins rephasing after switching off gradient. (D) Stationary spins rephased while moving spins are out of phase

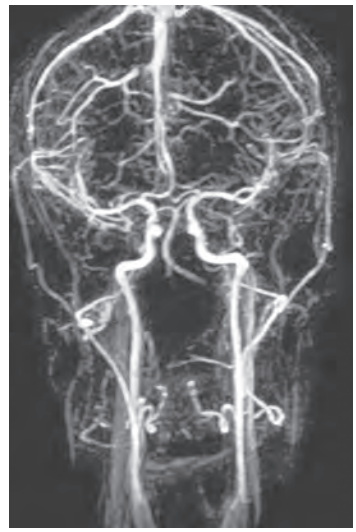


Fig. 23: Contrast- enhanced time-resolved imaging of contrast kinetics angiogram image of the brain

Phase Contrast Magnetic Resonance Angiogram

Moving spins undergo a phase shift in the presence of paired opposing gradients. This phenomenon is utilised in phase contrast magnetic resonance angiogram (PC MRA) The amount of phase shift increases with increasing flow velocity. When the flowing blood (moving spins) moves along the direction of the gradient field, it precesses faster as the field increases and undergoes a phase change. Thus, the motion is phase encoded giving it both direction and magnitude (Figs 22A to D).

The amount of phase shift is directly proportional to the flow velocity, gradient strength and time interval between the gradient applications. By choosing an appropriate velocity encoding value (VENC), fast or slow flowing blood can be imaged. Phase contrast MRA can be acquired as both 2-D and 3-D sequences.

Advantages of phase contrast magnetic resonance angiogram: It gives:

- Flow quantification
- Flow direction
- Excellent background suppression
- Can be used for imaging areas of slow flow

Disadvantages of phase contrast magnetic resonance angiogram: The disadvantage is as follows:

- Long scan time.

Contrast-Enhanced Magnetic Resonance Angiography

The limitations of TOF and PC angiograms, such as flow saturation, flow-related artifacts, breathing and pulsation artifacts, made depiction of blood vessels in the body, especially the abdomen, difficult. By using intravenous contrast and rapid gradient imaging, it is now possible to obtain MRA images almost at par with conventional angiogram. The technique involves capturing of high magnetisation strength during the first pass of the vascular contrast, i.e. gadolinium, by appropriate timing using 3-D acquisition (Fig. 23).

Advantages: The advantages are as follows:

- Insensitive to saturation effects of the RF pulse as against TOF angiogram and therefore can cover vessels over a larger FOV.
- Useful in large aneurysms where flow is complex.

NEWER ADVANCED MAGNETIC RESONANCE IMAGING TECHNIQUES

Diffusion-Weighted Imaging

It is based on the principle of Brownian motion, which is dispersion or random translation of a molecule in a liquid due to thermal agitation.

Motion of molecules in biological tissues is complex. Neuronal tissue consists of tightly and coherently packed axons surrounded by glial cells. The movement of water molecules is hindered in a direction perpendicular to the orientation of the axonal fibres. Thus motion of molecules in biological tissues is anisotropic. The cell membranes are thought to be responsible for anisotropic diffusion rather than myelin. The restricted diffusion appears as a bright signal on diffusion-weighted images (Fig. 24).

Applications

- Stroke
- Multiple sclerosis
- Tumours
- Trauma
- Abscess

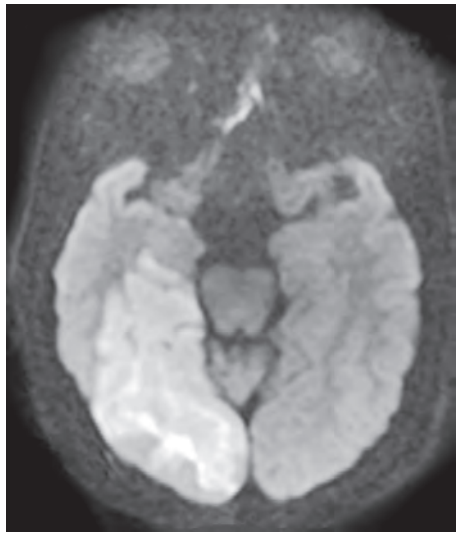


Fig. 24: Axial diffusion-weighted image showing restricted diffusion in the right occipital lobe suggestive of acute right posterior cerebral artery infarct

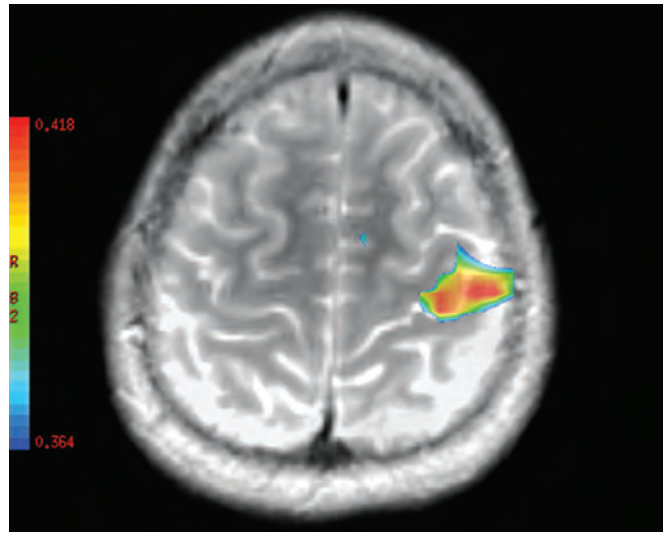


Fig. 25: MRI showing activation of the left motor cortex after right finger tapping

Lesions Bright on Diffusion Images

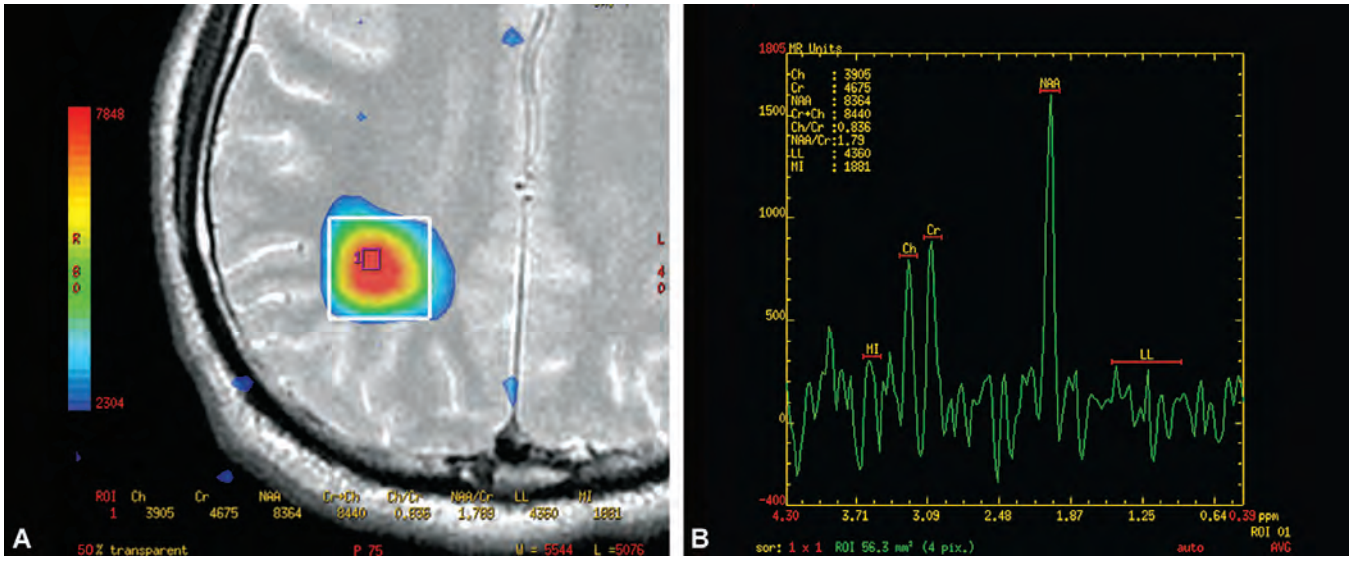
- Acute infarct
- Bacterial abscess
- Acute demyelination
- Epidermoid cyst
- Tissues with high cellularity
- Subacute haemorrhage

Functional Imaging

It is the demonstration of brain activation to a specific stimulus based on the functional anatomy of the brain, e.g. the primary visual cortex is activated using a flicker display or alternating checkerboard pattern as a visual stimulus. Once the brain is activated using a stimulus, there is change in the blood flow to the particular region due to the increased demand for oxygen and glucose. This increase in oxygen, i.e. deoxyhaemoglobin concentration causes local susceptibility effects which are used to receive the signals using appropriate pulse sequences. This is termed as blood oxygen level-dependent (BOLD) contrast imaging (Fig. 25).

Magnetic Resonance Spectroscopy

Magnetic resonance spectroscopy utilises the differences in the resonance frequency of nuclei due to their different chemical bond. This is also termed as chemical shift imaging. The frequency difference varies with the magnetic field and is directly proportional to the external magnetic field. It is expressed in parts per million (ppm). The advantages of higher field strength, while performing spectroscopy, are that it provides better signal-to-noise ratio and better separation of metabolite peaks.



Figs 26A and B: Multi-voxel MR spectroscopy TE=1044 ms (A) Showing the voxel placed in the normal parietal white matter with NAA colour map. (B) Showing normal spectrum

1H (proton) spectroscopy is used for brain imaging as it is easy to perform and gives a better signal-to-noise ratio as compared to 23Na and 31P. Of all the atomic nuclei, 1H has the strongest response and is found in all biochemicals. MR spectroscopy thus provides details of the brain chemistry (Figs 26A and B). The spectrum is read from right to left and the metabolites detected on brain spectroscopy are:

- Lipid 0.9–1.4 ppm
- Lactate 1.3 ppm
- N-acetyl aspartate (NAA) at 2 ppm
- Creatine (Cr) 3.0 ppm
- Choline (Cho) 3.2 ppm
- Myo-inositol 3.5 ppm

The TE affects the metabolites detected, thus short TE ~30 ms shows metabolites with short and long T2 relaxation times and with long TE ~ 270 ms only metabolites with long T2 relaxation times are detected, therefore the spectrum primarily consists of NAA, Cr and Cho. Another advantage of long TE ~ 144 ms is that the lactate peak at 1.3 ppm gets inverted. Rather than absolute concentrations, one should rely on the various ratios to give a clinical diagnosis.

Ratio	Normal	Abnormal
NAA/Cr	2.0	< 1.6
NAA/Cho	1.6	< 1.2
Cho/Cr	1.2	> 1.5

Indications

- Tumours
- Radiation necrosis versus recurrence
- Infections
- Neurodegenerative disorders
- Metabolic brain disorders
- Stroke

Magnetic resonance spectroscopy should be carefully interpreted and correlated with MR images to make a final diagnosis.

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11 Radiology: Intracranial Tumours

Kesavdas

IMAGING MODALITIES

In the management of patients with suspected or confirmed intracranial tumours, imaging of the brain is often indicated at different stages and usually has a significant role in each of them. The role of imaging includes localisation and assessment of the extent of abnormality, characterisation of the abnormality, distinction of neoplasms from non-neoplastic processes, assessment of the nature of tumour, planning for surgery or other types of therapy, intra-operative control of resection progress and finally monitoring of response to therapy.

Computerised tomography (CT) is a good screening method for the demonstration of supratentorial abnormalities, because it is accurate and the imaging method, most often available. It takes a much shorter time and is less costly. It is superior in depicting the presence of calcification and bone abnormalities such as destruction, erosion, penetration and hyperostosis. However, imaging of posterior fossa lesions is limited due to bone artifacts. The definition of the extent of oedema is poor and the neuroanatomical depiction is poor in comparison to magnetic resonance imaging (MRI).

MRI has a higher sensitivity in the demonstration of oedema and is better for earlier detection of tumours. It gives a more accurate definition of the extent of surrounding oedema and mass effect. Brainstem structures are better identified. It gives a better characterisation of brain tumours and hence is extensively discussed in this section. Along with the advanced techniques (discussed below), MRI has become the most useful pre-operative imaging tool.

Intra-operative ultrasonography is useful in real-time update for the detection of brain and/or tumour shift during surgery. It is inexpensive compared to intra-operative magnetic resonance (MR) imaging. Both these techniques are being used by neurosurgeons for image-guided surgical procedures and have led to improved surgical results. Positron emission tomography imaging of brain tumours with F-18-fluorodeoxyglucose is helpful in prognostic stratification of patients and detection of early tumour recurrence following surgery and radiation/chemotherapy.

APPROACH TO BRAIN TUMOURS

Intracranial tumours must be analysed considering the patient's age and in recognising the most frequent histologies that occur in various age groups. Approximately 15–20% of all intracranial tumours, mostly primary lesions, occur in children below 15 years of age. A higher proportion of paediatric intracranial tumours occur in the posterior fossa. A tumour in the cerebellum in the elderly is usually a metastasis. The histologic spectrum and location of intracranial tumours vary considerably between children and adults. The specific location of the mass becomes equally important in imaging analysis because certain types of intracranial tumours tend to occur with a higher frequency in specific locations. Accurate compartmentalisation of the mass will limit the differential diagnosis to a few relevant possibilities.

The radiologist must first determine whether the mass arises from within the brain parenchyma (intra-axial) or from outside the brain parenchyma (extra-axial, in which case symptoms are usually due to compression of subjacent brain). Intra-axial tumours are twice as common as extra-axial tumours. Radiologic clues that a tumour is extra-axial include:

- Widening of the ipsilateral subarachnoid space
- Cerebrospinal fluid (CSF) cleft between the mass and the brain parenchyma
- Deviation of pial vessels between the mass and the brain tissue
- Buckling of the grey matter (GM)/white matter (WM) junction
- Broad base along the dural or calvarial surface
- Adjacent bony changes such as hyperostosis in meningioma or erosion in acoustic neurinoma.

The prognosis and treatment of intracranial tumours are highly dependent on tumour histology. The signal characteristics of the tumour may provide clues about its histology. Tissue characterisation is better possible with MRI than CT. However, the latter is definitely better in showing calcification within the tumour. Histologic features, such as calcium and fat, are readily identified on cross-sectional imaging. T1 hyperintensity

in MRI may represent haemorrhage (methaemoglobin), melanin (in metastatic melanomas), fat, calcification or slow vascular flow. Haemorrhage within a tumour is usually seen in glioblastoma multiforme (GBM), anaplastic oligodendroglioma, ependymoma, etc. Metastases from renal cell carcinoma, choriocarcinoma, breast carcinoma, melanoma, lung carcinoma and thyroid carcinoma may have associated haemorrhage. T2 hypointensity may represent haemorrhage (haemosiderin), calcification, proteinaceous material or flow. Cell composition and relative water content are suggested by imaging. Tumours that show CT hyperdensity and T2 hypointensity often have high nucleus-to-cytoplasm ratios with decreased relative water content. This is suggestive of densely cellular tumours such as lymphoma, primitive neuroectodermal tumour (PNET)/medulloblastoma, pinealoblastoma, metastases from adenocarcinoma/prostate and, sometimes, meningioma. Tumours, such as GBM and higher grades of glioma, metastases and lymphoma in an immunocompromised patient may show necrotic areas within the tumour. Hypervascular tumours, such as GBM, haemangioblastoma and metastases from renal cell carcinoma, may show flow voids within the lesion.

Compressive effects on adjacent brain tissue, extent of vasogenic oedema, accompanying the mass and obstructive hydrocephalus are easily and non-invasively assessed. Intravenous contrast agents augment lesion conspicuity and reveal enhancement characteristics that can help improve specificity. Enhancement reflects the breakdown of the blood-brain barrier (BBB), which is normally absent in structures such as the pituitary gland, pineal gland, choroid plexus and meninges. Several criteria are important for the differential diagnosis of brain tumours: signal contrast with normal brain, tumour structure, the presence or absence of tumour margins, extent of perifocal oedema, indirect tumour signs, relation of tumour to blood vessels, richness of tumour blood supply and degree of contrast enhancement.

ADVANCED NEUROIMAGING OF BRAIN TUMOURS

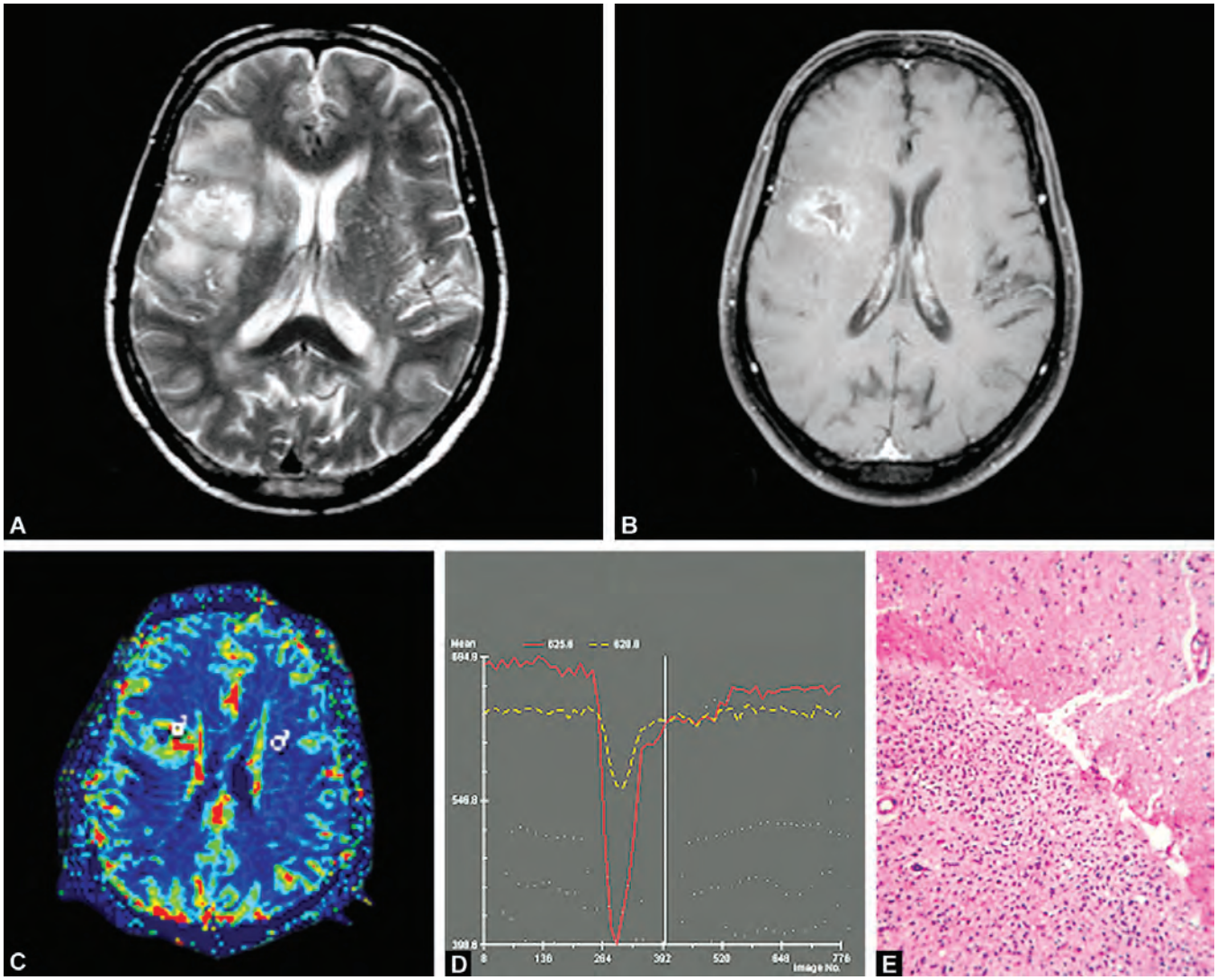
The imaging of brain tumours has significantly improved with the use of advanced MR techniques such as perfusion, spectroscopy, functional imaging, diffusion tensor and conventional MR imaging (MRI) provides mainly anatomical or structural information about the brain. Unlike conventional imaging, advanced MR techniques also provide physiological information concerning metabolism and haemodynamics.

Perfusion Imaging

Brain tumours can induce angiogenesis or the formation of new blood vessels. Hypoxia occurs as the tumour, which outgrows its blood supply, can produce angiogenic cytokines; these cytokines are responsible for angiogenesis.[21] Tumour vessels that are produced in this manner are histologically abnormal and more permeable than normal. They are also disorganised and tortuous. These vascular abnormalities and altered flow dynamics lead to changes in blood volume and flow, which are seen in MR perfusion images. The most frequently used measure of perfusion is the cerebral blood volume (CBV). The CBV (or the volume of blood passing through a portion of the brain) is measured in millilitres of blood per 100 grams of brain tissue (ml/100 g).

The most common perfusion technique is T2 dynamic susceptibility imaging.[4] The T2 effects of gadolinium result in decreased signal intensity during the passage of gadolinium. The change in signal intensity is plotted against time to form a signal intensity time curve. The CBV is estimated from the area encompassed by the curve, which is inverted in this case, since there is signal loss. Repetitive imaging is performed shortly before, during and after the passage of gadolinium. Generally, 0.2 mmol/Kg of gadolinium is injected at a high rate using a power injector. The CBV is normalised to uninvolved portions of the brain. The cases in which an arterial input function is not determined, only a relative CBV (rCBV) can be calculated. Dynamic susceptibility perfusion imaging is based on the premise that contrast material remains within the intravascular compartment. High permeability or leaks in regions of marked breakdown of the BBB results in intravascular gadolinium extravasating into the interstitial space. Extravasation can significantly affect calculations and alter CBV values. Using T1-weighted dynamic perfusion imaging, one can eliminate the problem with the breakdown of the BBB and permeability.[3,17,18] In this technique, tumour enhancement or transendothelial permeability is measured using the *Ktrans* parameter.

In general, high-grade brain tumours have greater rCBV than low-grade lesions (Figs 1A to E).[14] MR perfusion can help identify and localise higher grade components of a tumour for guiding stereotactic biopsy and can also provide a non-invasive estimate of tumour grade. Since the enhancing or even the T2 borders of gliomas do not represent the true margins of the tumour, MR perfusion can be more sensitive in defining the true extent of a glioma than anatomic MR imaging. Better delineation of tumour borders can help in radiation and surgical planning. In the future, MR perfusion imaging will probably play a role in better defining tumour margins for radiation and surgical planning. Differentiating tumour recurrence from radiation necrosis is a problem that clinicians and radiologists face frequently. The advantage of MR perfusion CBV data is its high positive predictive value for the presence of high-grade malignancy. In other words, if the CBV maps reveal elevated perfusion, it indicates the presence of a tumour. The specificity of the diagnostic task can be increased when perfusion imaging is combined with MR spectroscopy.



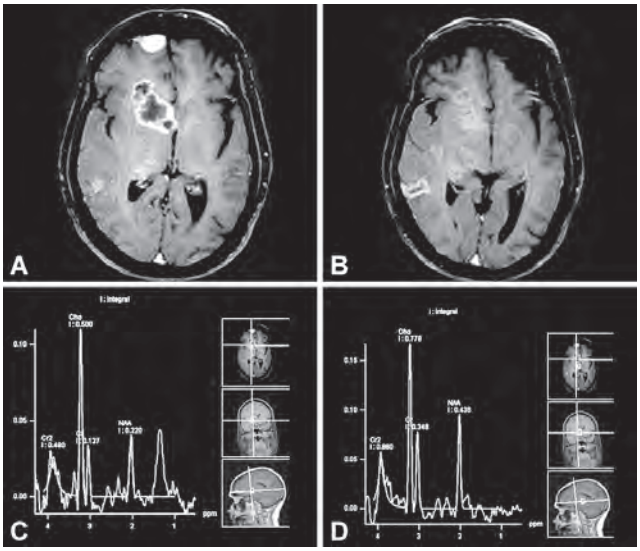
Figs 1A to E: (A) Axial T2-weighted image shows a hyperintense mass with surrounding oedema in the right frontal lobe. (B) Post-contrast axial T1-weighted image shows enhancement of the lesion except in the central area. (C and D) rCBV map and time intensity curve of the T2* dynamic susceptibility weighted perfusion imaging shows increased CBV within the lesion. (E) Haemotoxyline and Eosin staining of the resected mass lesion was suggestive of glioblastoma multiforme

Spectroscopy

Clinical applications of proton magnetic resonance spectroscopy (1H-MRS) are increasing as the techniques and hardware have become more robust and user-friendly. Proton MRS provides biochemical and metabolic information about tumours and normal brain. Spectroscopy can be done in single or multi-voxel (MRS imaging) forms. The two most commonly used methods for volume selection/excitation are stimulated echo acquisition mode and point-resolved spectroscopy sequence.

The advantage of single-voxel 1H-MRS is its short acquisition time (approximately 5 minutes). The downside is that it lacks spatial resolution and cannot be used to better define the true extent of a glioma. Histologically, gliomas are heterogeneous and, therefore, single-voxel spectroscopy cannot be used to map regional metabolic variation. In the spectroscopy literature, the most commonly used echo times are 144 msec and 270 msec. At these long echo times, the spectrum is dominated by five different metabolite peaks: choline (Cho)-containing compounds; creatine (Cr); N-acetylaspartate (NAA); lactate and lipid. The choline peak reflects cell membrane turnover. Creatine is a good surrogate for energy synthesis, and NAA is a marker that is exclusive to neuronal cells. Lactate results from anaerobic metabolism and is detected in necrotic tumours and infarcted tissue. Cellular and myelin breakdown products result in prominent lipid peaks. In tumours, choline-containing compounds are increased, and NAA is decreased relative to uninvolved or normal brain tissue. This pattern of metabolic change is the spectroscopic hallmark of brain tumours.

Combined with MRI, MRS can aid in the evaluation of tumour type and grade.[11] The higher-grade gliomas tend to exhibit higher Cho/Cr and Cho/NAA ratios (Figs 2A to D). The high-grade gliomas also tend to have lipid and lactate as the result of necrosis. MR spectroscopy can help differentiate enhancing tumour



Figs 2A to D: (A and B) Axial post-contrast images show a peripheral enhancing mass lesion close to the right frontal horn with central area of necrosis. Enhancing lesions are also noted in the right thalamus and surrounding parenchyma. (C and D) Multi-voxel spectroscopy (TE: 135) reveals elevated choline in the mass and the surrounding parenchyma suggesting spread of the lesion in the surrounding parenchyma. Pathological diagnosis was GBM

from other causes of enhancement (mainly necrosis) and is more specific in differentiating non-enhancing tumour from oedema and other causes of T2 prolongation. These qualities have been exploited in order to better define the true extent and morphology of gliomas. MR spectroscopy is utilised more and more by different groups in assessing response to therapy in patients with primary brain tumours or metastases. MR spectroscopy can non-invasively enable the distinction between a solitary metastasis and high-grade gliomas, particularly when combined with perfusion MR imaging.

Functional Magnetic Resonance Imaging

Functional MRI (fMRI) provides activation maps that reflect haemodynamic variations related to neuronal activity and identify the eloquent cortex. Blood oxygen level-dependent (BOLD) imaging examines changes in local tissue oxygenation to exploit the magnetic property changes of haemoglobin as an intrinsic contrast agent. An increase in brain activity causes an increase in oxygen consumption and an over-compensatory increase in regional cerebral blood flow (CBF), with a net effect of increased diamagnetic oxyhaemoglobin and decreased paramagnetic deoxyhaemoglobin. Paradigms may be tailored for language, speech, comprehension, memory and motor testing. Pre-operative fMRI may be used to better determine the relationship between tumour margins and the eloquent cortex, interrogate the supplemental cortex or test bilateral haemispheres (Fig. 3).[12] Another technique that is coming up for mapping the eloquent cortex is magnetic source imaging

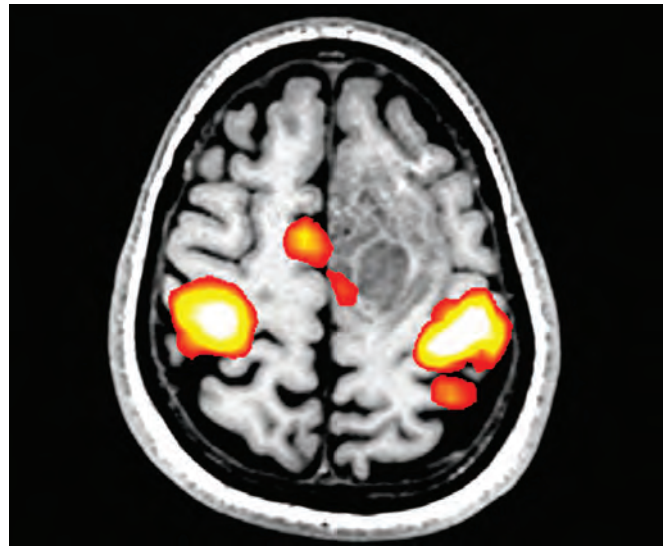


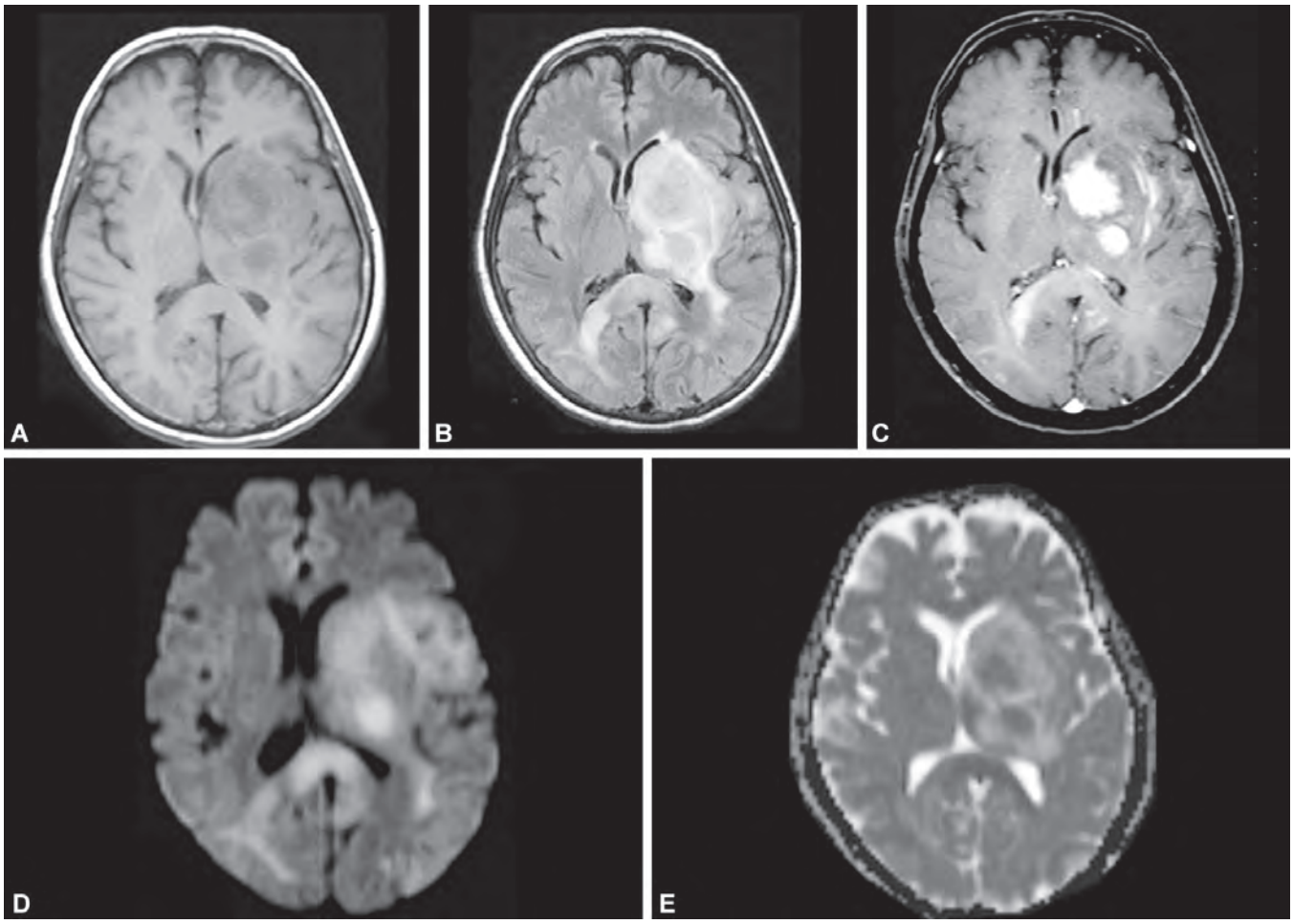
Fig. 3: Real-time blood oxygen level-dependent functional MRI done during bilateral hand movement shows the relation of the tumour with the primary motor hand area. Note the supplementary area is placed very close to the lesion

where the information from magnetoencephalography is combined with MRI.

Diffusion Weighted Imaging and Diffusion Tensor Imaging

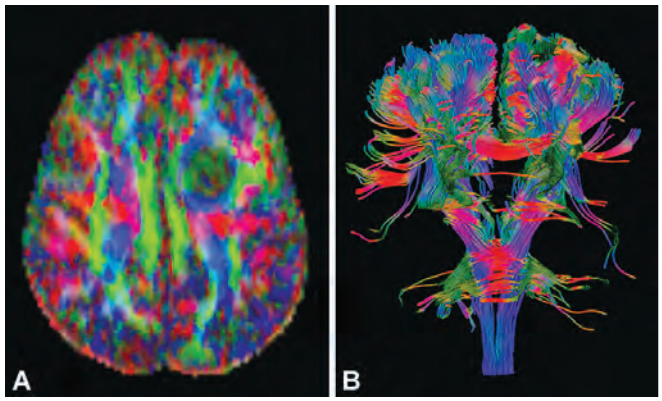
Diffusion weighted and diffusion tensor imaging is an MRI technique that is sensitive to directional movements of water molecules and that allows the identification of functional WM tracts *in vivo*. Diffusion weighted imaging can give information about the cellularity of the tumour (Figs 4A to E) and can also differentiate infective brain abscess and a necrotic tumour which may both look alike in the conventional MRI.[2] Diffusion tensor imaging has the potential to establish spatial relationships between eloquent WM and tumour borders and provide clinically valuable information to assess the progression and regression of WM tracts as a result of tumour growth or resection (Figs 5A and B). There are two main reasons why pre-operative identification of WM tracts is important. First, accurate localisation of important WM tracts can affect the decision of whether or not to operate. Secondly, pre-operative localisation of important WM tracts is essential in surgical planning.

In GM, it is usually sufficient to characterise the diffusion characteristics with a single apparent diffusion co-efficient (ADC), because measured water diffusivity is largely independent on the orientation of the tissue. However, in an anisotropic area, such as white matter, where the measured diffusivity is known to depend upon the orientation of the tissue, a single ADC is not able to describe the orientation-dependent water mobility in the tissue. Diffusion tensor imaging, which is based on the orientation-dependent water diffusion, can be obtained using a single-shot diffusion-weighted (DW) spin-echo



Figs 4A to E: (A to C) Axial T1-weighted, axial FLAIR and post-contrast T1-weighted images show a T1 isointense, FLAIR hypointense and intensely enhancing mass lesion in the left basal ganglia and thalamus. (D and E) Diffusion weighted image and ADC map show restricted diffusion within the lesion suggesting high cellularity. The lesion was proved to be a primary CNS lymphoma

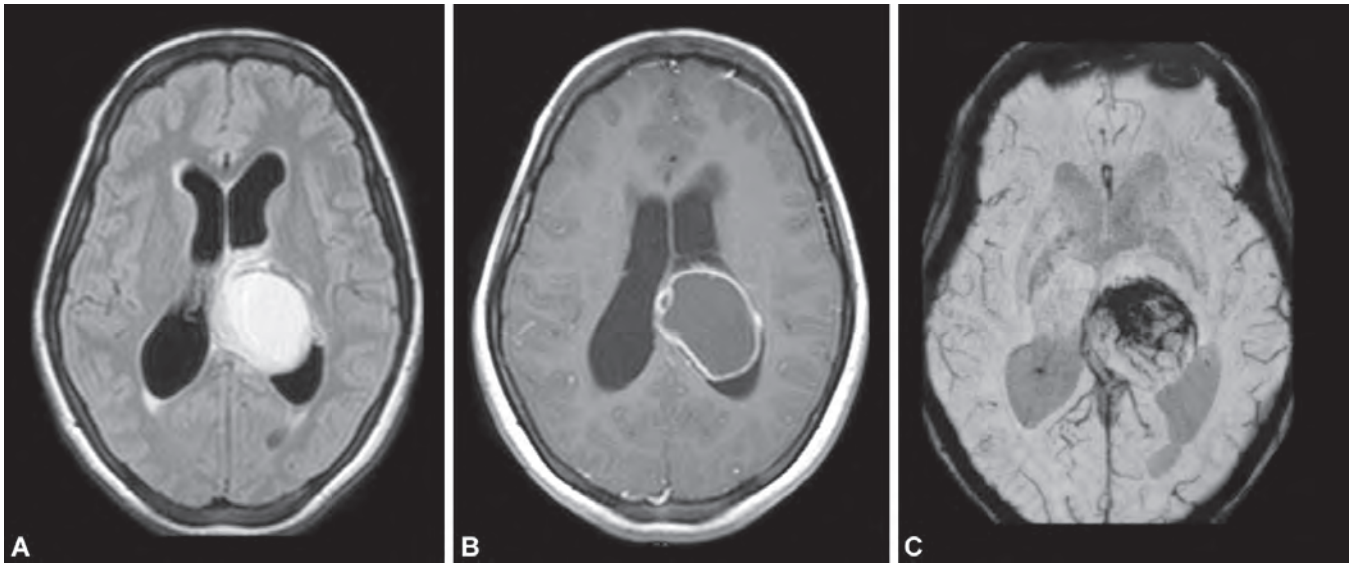
echo-planar imaging (EPI) pulse sequence, in which two symmetric trapezoidal gradient pulses are added around a 180° re-focusing pulse in the required gradient channel. Sets of DW-EPI images are collected with diffusion gradients applied sequentially along three directions for diffusion weighted imaging (DWI) and at least six predetermined directions for DTI. In DTI, the elements of the tensor obtained are used to yield a mean diffusivity map (D) and the fractional anisotropy (FA). Previous studies have shown that neoplasms and surrounding oedematous brain have an increase of free water fraction (high D value) and loss of structural organisation (reduced FA value).[16] A number of recent developments have led to a new application of DWI termed diffusion tractography. This application uses diffusion tensor data to identify specific white matter tracts as opposed to white matter tracts in general.



Figs 5A and B: (A) Fractional anisotropy map. (B) Fibre tracking in a patient with glioma demonstrate displacement of white matter tracts

Susceptibility Weighted Imaging

Susceptibility weighted imaging (SWI) is a sequence that is sensitive to T2 effects. It uses magnitude or phase images, the combination of the two image sets, obtained with a three-dimensional, fully velocity-compensated, gradient echo sequence. SWI has exquisite sensitivity to the venous vasculature, blood products and changes in iron and calcium content. In tumour imaging, it has a role in picking up micro-haemorrhages and the venous vasculature within the tumour (Figs 6A to C).[20]



Figs 6A to C: (A) Axial FLAIR image shows a hyperintense mass lesion. The mass is in the left thalamic region and is seen extending to the level of the left lateral ventricle. (B) Post-contrast T1-axial image shows enhancement of the periphery. (C) Susceptibility weighted image shows bleeds within the mass lesion. Pathological diagnosis was high grade glioma

SPECIFIC TUMOURS

Glioma

Astrocytomas are the most common primary intra-axial masses in adults. According to the World Health Organisation (WHO) three-tier classification scheme, grade I tumours are either pilocytic or fibrillary. These are diffusely infiltrative tumours that may show CT hypodensity and very mild T1 hypointensity with T2 hyperintensity in MRI and usually no enhancement. Grade II tumours are anaplastic with evidence of vascular hyperplasia and mitotic figures. They have an aggressive appearance with prominent enhancement and mass effect. Grade III tumours are GBM with areas of necrosis and haemorrhage, and are highly aggressive tumours that have outgrown their own blood supply. De-differentiation from lower to higher grade tumours is usually associated with contrast enhancement.

Pilocytic astrocytomas are histopathologically distinct from the more infiltrative low-grade astrocytomas. Patients usually present at less than 1 year of age (80% at less than 20 years). Nearly two thirds of these tumours arise from the cerebellar hemisphere with a dominant cyst and avidly enhancing mural nodule. Most of the remaining tumours occur in the hypothalamic-optic region. On MRI, the solid component shows T1 isointensity to hypointensity and T2 hyperintensity, while the cystic component shows T1 hyperintensity relative to CSF. Elevated protein in the cyst fluid may cause slight T1 hyperintensity to CSF.

Brainstem gliomas account for 1% of tumours in adults and 10–20% of tumours in children. MR shows T2 hyperintensity with mass effect and variable enhancement, which does not correlate with prognosis. Diffuse brainstem gliomas are the most common, at 58–75%. These are usually fibrillary astrocytomas that are centred at the pons and show ill-defined margins, T2 hyperintensity and mass effect. Focal tumours of the mid-brain, medulla and cervicomedullary junction have distinct margins, may be solid and/or cystic, and usually do well after aggressive resection, which is easier to perform for dorsal or lateral exophytic tumours.

Oligodendrogliomas

These tumors originate from the oligodendroglia. CT demonstrates calcification in more than 80% of cases. The tumours tend to be subcortical in location with T1 hypointensity and T2 hyperintensity. Similar to the more common astrocytomas, oligodendrogliomas vary from low grade to high grade.

Glioma Tumour Evaluation to Differentiate Low and High Grade Tumours

In terms of predicting a high grade glioma (HGG), conventional imaging has 73% sensitivity, 65% specificity and 44% negative predictive value (NPV) as compared to perfusion MRI, which achieves 95% sensitivity, 57% specificity and 79% NPV.[14] MR spectroscopy using Cho/Cr and Cho/NAA can also help predict HGG, although their addition may not improve the utility of perfusion MRI. Given the inherently heterogeneous nature of these tumours, one can use CBV maps to guide stereotactic biopsy of the area of maximal angiogenesis to target the highest-grade portion rather than rely on contrast enhancement, which only reflects BBB breakdown. During chemotherapy and radiotherapy, rCBV values have been shown to correlate better with a patient's clinical course than conventional images, and perfusion MRI has shown similar success in patients treated with anti-angiogenic agents.[1] Perfusion MRI may be able

to better predict outcome in patients with low grade tumours (LGGs).

Evaluating Peri-tumoural Region to Differentiate Metastases from Primary Tumour

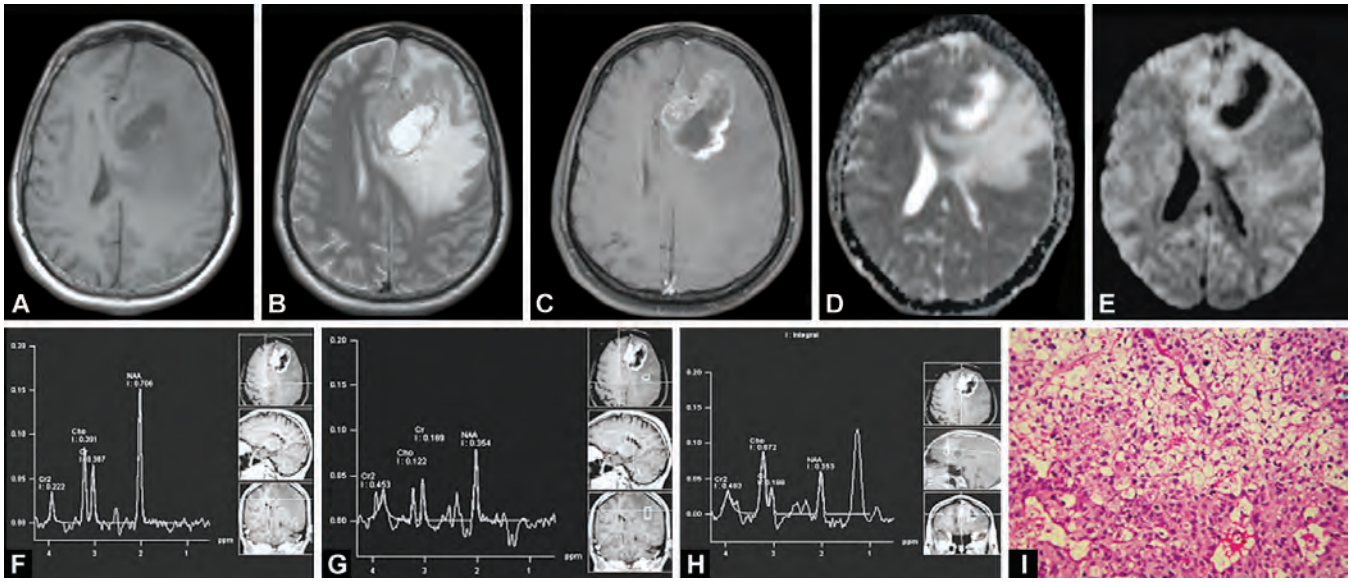
The peri-tumoural region of metastases represents vasogenic oedema caused by increased interstitial water (Figs 7A to I), in contrast to the peri-tumoural region of gliomas, which consists of tumoural infiltration into the brain parenchyma and accompanying neovascularity beyond the contrast-enhancing margins of the tumour (Figs 1 and 2). Due to the presence of these infiltrating tumour cells, peri-tumoural perfusion MRI and MR spectroscopy of gliomas as compared to metastases show increased rCBV and increased Cho. Peri-tumoural MD (mean diffusivity) of metastases is greater than that of HGGs, probably because of the contribution of infiltrating tumour cells to the glioma peri-tumoural signal abnormality. Primary brain tumours are infiltrative by nature, and perfusion MRI/MRS of normal-appearing brain tissue beyond the peri-tumoural region of T2 hyperintensity may also show hyperperfusion and abnormal metabolites related to tumour cells.[5,15]

Gangliogliomas

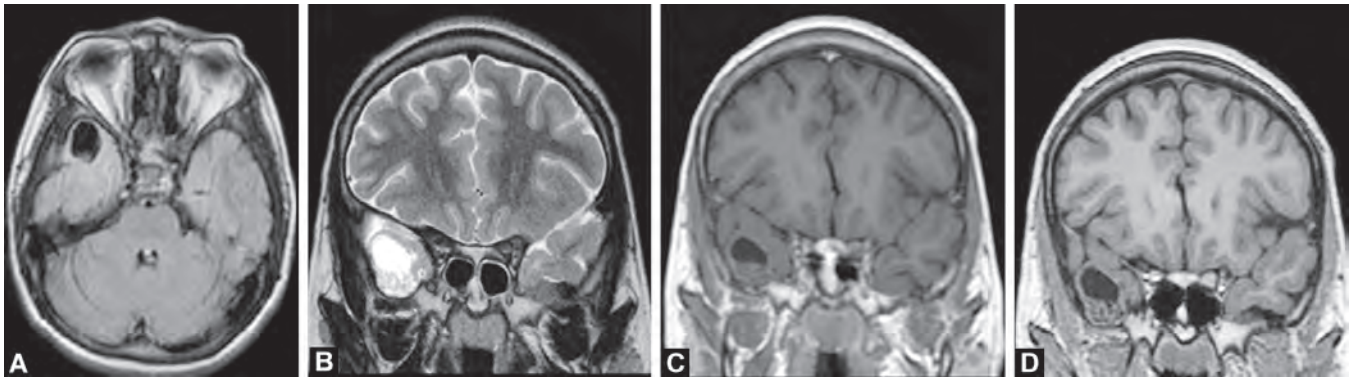
Gangliogliomas are mixed tumours whose cells originate from both glial and neuronal lines. They tend to be of low grade and have a good prognosis, although some may have more aggressive features and de-differentiation into higher-grade lesions. The lesion is usually cortical, especially in the temporal lobes. These are slow-growing tumours with a longstanding course, which may result in thinning of the overlying bony calvarium (Figs 8A to D). Tumours may also present in the brainstem. They are commonly cystic well-delineated lesions which may also have a solid component. They appear homogeneously hyperintense on T2-weighted images. CT in these tumours is of value in picking up calcification alone.

Meningioma

Meningioma is the most common extra-axial neoplasm of adults, representing 20% of all primary intracranial tumours. These are twice as common in females and occur most often in middle-aged patients. Meningiomas originate from neoplastic meningothelial (arachnoid cap) cells, and their distribution parallels that of the cap cells, which are most abundant in arachnoid granulations. Predispositions to meningioma development include neurofibromatosis type 2, familial susceptibility, hormonal factors and previous ionising radiation. Common sites are the parasagittal and convexity dura, sphenoid ridge, and parasellar and cerebellopontine angles. Parasagittal meningiomas have a propensity to invade the dural venous sinuses and cavernous sinus meningiomas cause encasement and narrowing of the internal carotid arteries. The varying histologic types and composition lead to some variability in imaging features. The majority of histopathological subtypes are benign (80–90%); atypical (5–15%) and anaplastic/malignant (1–3%) grades are uncommon.[13] Recurrence is likely after incomplete surgical resection and with atypical or anaplastic pathology. Calcification can be detected by CT in roughly 20% of cases. There may be a bony reaction in the adjacent skull, usually hyperostosis due to stimulation of a bony reaction

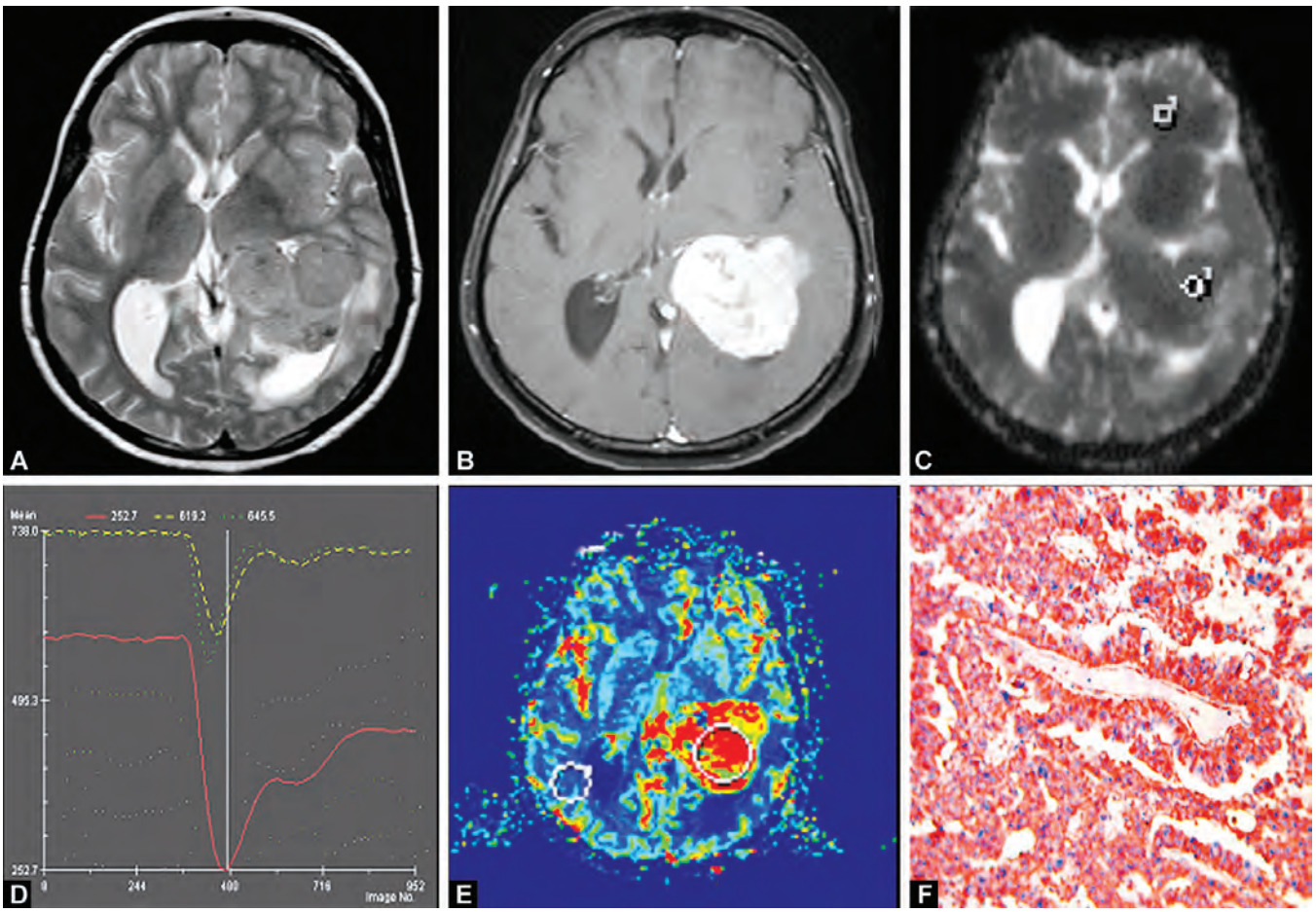


Figs 7A to I: (A) Axial T1-weighted image shows a hypointense mass lesion with central necrotic area. (B) Axial T2-weighted image shows hypointense peripheral area which in post-contrast image. (C) Shows enhancement. (D and E) ADC map and diffusion images show that the necrotic area has facilitated diffusion while the surrounding area has restricted diffusion. (F) Multivoxel spectroscopy (TE: 135) from a normal area in the opposite hemisphere shows normal spectrum. (G) Spectrum from the surrounding oedema does not reveal raised choline. A small inverted lactate is seen. (H) Solid area of the tumour shows raised choline and lipid. (I) H and E staining of the resected mass shows the lesion to be a metastasis from squamous cell carcinoma



Figs 8A to D: Patient with longstanding intractable epilepsy. (A) Axial FLAIR image shows a well defined cystic lesion in the right temporal lobe. (B) Coronal T2-weighted image shows the solid areas within the tumour. A bony scalloping of the temporal bone is also noted. (C and D) Coronal post-contrast images do not reveal enhancement within the lesion. The lesion was a ganglioglioma

through growth into the Haversian canals, and less frequently to bone destruction. They show T1 and T2 isointensity relative to the cortex. Enhancement is usually relatively homogeneous with occasional cystic components, areas of necrosis or calcification. Oedema in the brain adjacent to a meningioma is variable and more frequent in larger lesions. Demonstration of indistinct tumour margins with adjacent brain parenchyma should suggest more aggressive tumours. Perfusion MRI shows hypervascular tumours (Figs 9A to F) with greater elevations of the endothelial permeability constant *Ktrans* in atypical and anaplastic meningiomas as compared to typical meningiomas.[23]



Figs 9A to F: (A and B) Axial T2-weighted image and post-contrast image show a T2-hypointense mass lesion enhancing intensely after contrast administration. (C) Restricted diffusion is noted within the mass. (D and E). Time intensity curve and rCBV map shows marked increase in rCBV. (F) The pathological diagnosis was papillary meningioma

Choroid Plexus Papillomas

Choroid plexus papillomas and carcinomas may be present at birth, and the former is twice as common as the latter. In children, these tumours are typically located in the trigone of the lateral ventricles, usually on the left side. In adults, they are more common in the fourth ventricle. The tumours have fine, lobulated or papillary margins. They are homogeneous with mild T2 hyperintensity, although they may contain focal hypointensities from calcifications or enlarged flow voids from branches of the anterior and posterior choroidal arteries. Although hydrocephalus may occur due to tumour overproduction of CSF, it more commonly occurs due to mass effect and mechanical obstruction, similar to other intraventricular tumours.

Central Neurocytomas

These are heterogeneous masses with cystic areas, calcifications and haemorrhage. These tumours show neuronal differentiation and tend to occur in young patients at the age of 20–30 years. These tumours were previously mistaken for intraventricular oligodendrogliomas, and are characteristically attached to the septum pellucidum and located in the body of the lateral ventricle (Fig. 10). They have a well-circumscribed smooth or lobulated margin with solid and cystic components and heterogeneous enhancement.

Chordomas

Chordomas arise from remnants of the primitive notochord. These tumours are most common in the sacrum (50%), with intracranial tumours occurring almost exclusively in the clivus (35%). They are benign, but locally aggressive tumours that destroy bone and may grow into the nasopharynx, parasellar region, or pre-pontine cistern.

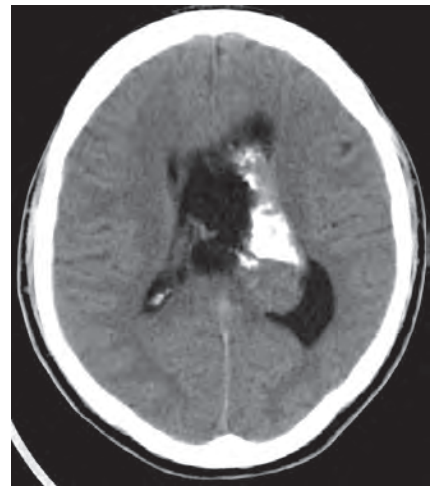
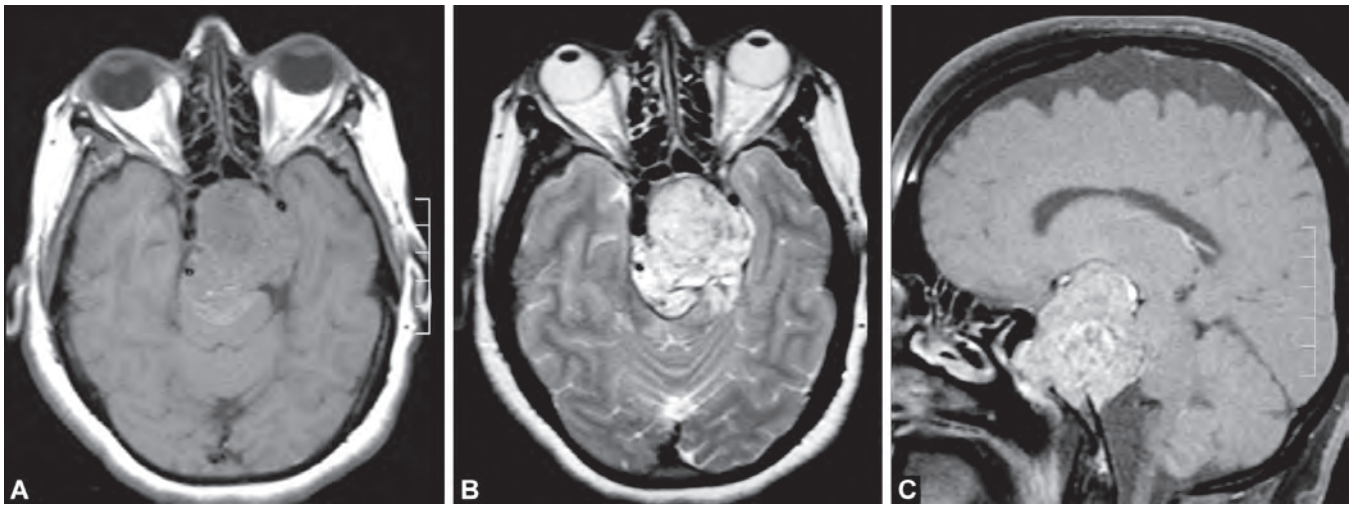


Fig. 10: Contrast CT shows a mass lesion within the left lateral ventricle extending below to the level of foramen of Monroe (not shown). The lesion shows calcification and cystic areas and minimal peripheral enhancement. The lesion proved to be a central neurocytoma

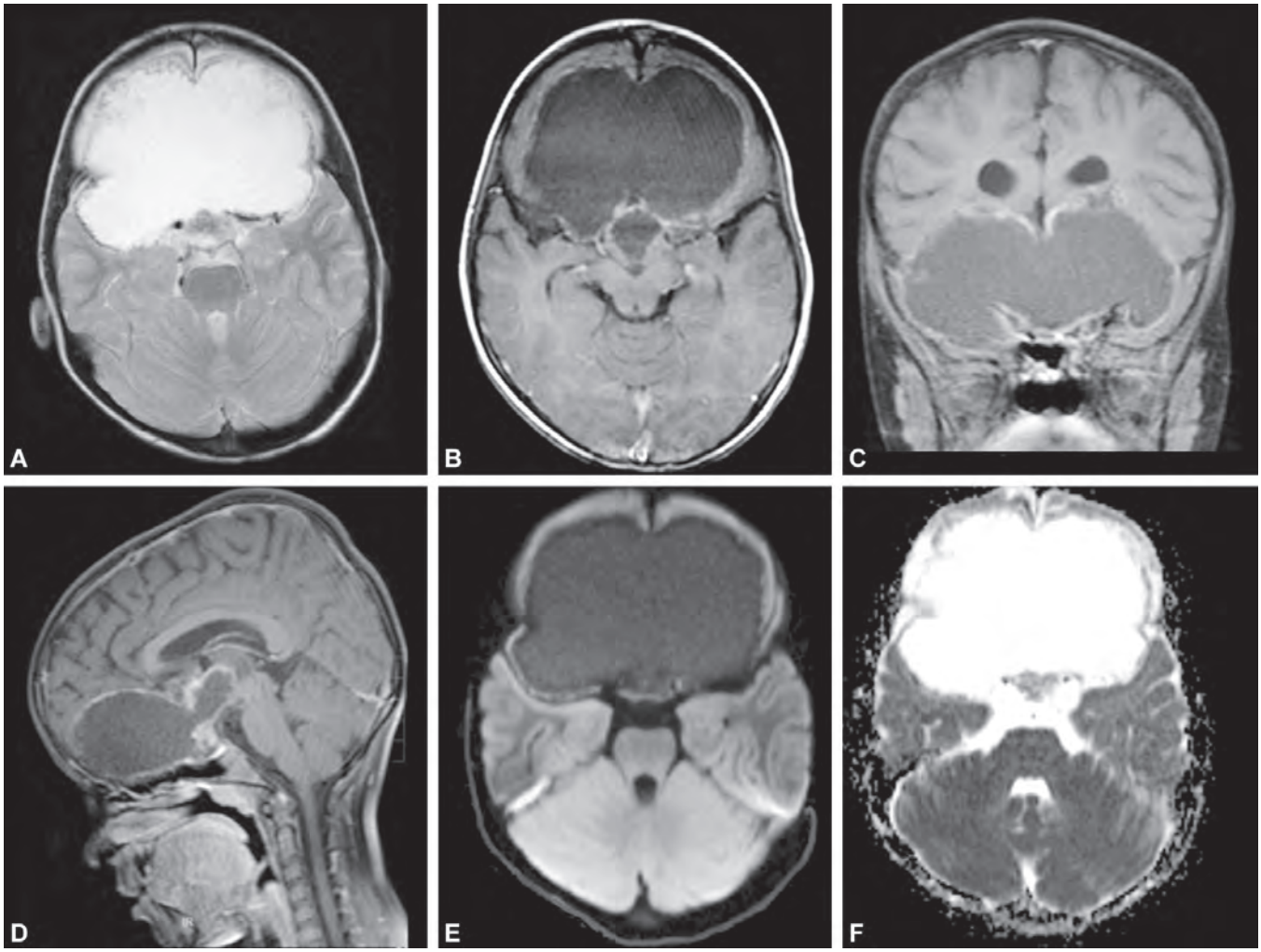
Imaging shows a lobulated enhancing soft-tissue mass centred on the clivus exhibiting bone destruction and areas of calcification, which are better seen on CT. MRI shows marked T2 hyperintensity that reflects the high water content of these tumours, and may exhibit internal reticulations or septations (Figs 11A to C).

Craniopharyngiomas

Craniopharyngiomas arise from metaplasia of squamous epithelial remnants of Rathke's pouch, from which the anterior pituitary develops. These tumours are usually centred in the suprasellar cistern and may extend into the sella, retroclival region and third ventricle; 5% may be purely intrasellar and rarely may be located in the third ventricle. They have a bimodal distribution, with a



Figs 11A to C: (A) Axial T1-weighted image shows an isointense mass lesion in the sella, suprasellar region extending to the left cavernous sinus. (B) Axial T2-weighted image shows the lesion to be predominantly hyperintense with minimal inhomogeneties. (C) Sagittal post-contrast image shows the lesion extension in the clivus and sphenoid sinus. Lesion shows enhancement after contrast. The lesion was a chordoma

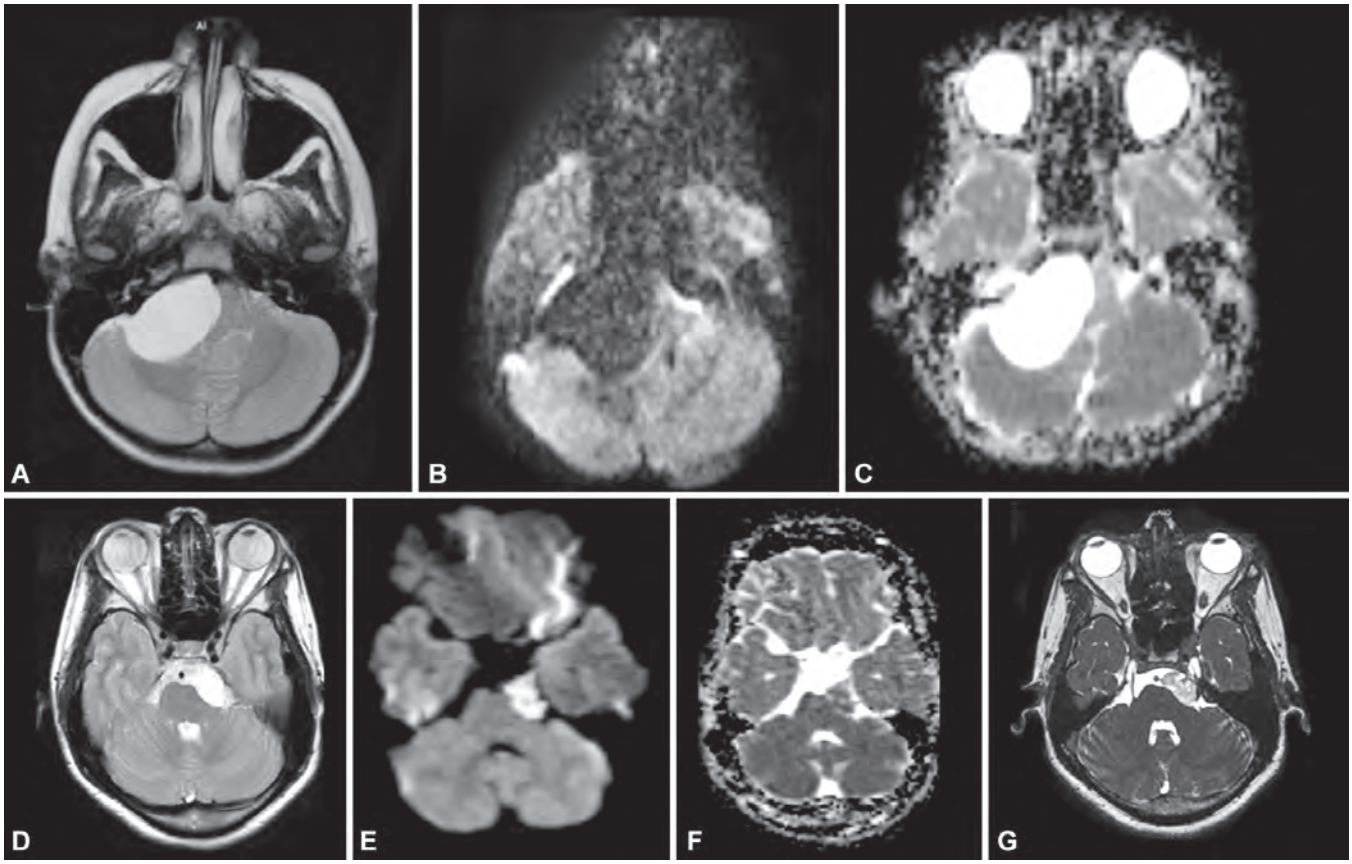


Figs 12A to F: Thirteen-year-old boy. (A) Axial T2-weighted image shows a hyperintense mass lesion in the suprasellar region extending to the anterior cranial fossa. The hyperintense mass is bordered by linear hypointensity. (B to D) axial, coronal and sagittal post-contrast images show enhancement of the periphery of the cystic lesion. (E and F) DWI and ADC maps show that the lesion is cystic and shows facilitated diffusion. The lesion was diagnosed as craniopharyngioma. Cystic areas of craniopharyngioma usually show facilitated diffusion

larger peak at 5–15 years than at 50–60 years. They may be cystic, solid or mixed cystic and solid. Nearly half of paediatric suprasellar tumours are craniopharyngiomas. These tumours are of the adamantinous variety, with lobulated contours, predominantly cystic or mixed cystic and solid with calcification, intensely enhancing solid components, and encasement of the circle of Willis vessels (Figs 12A to F).[10] The squamous papillary craniopharyngiomas tend to occur in older adults and present with predominantly solid tumours. Calcifications and recurrence are both less common in adults. MR often shows heterogeneous signal intensity with T1 isointensity to hyperintensity, fluid-attenuated inversion recovery (FLAIR) and T2 hyperintensity.

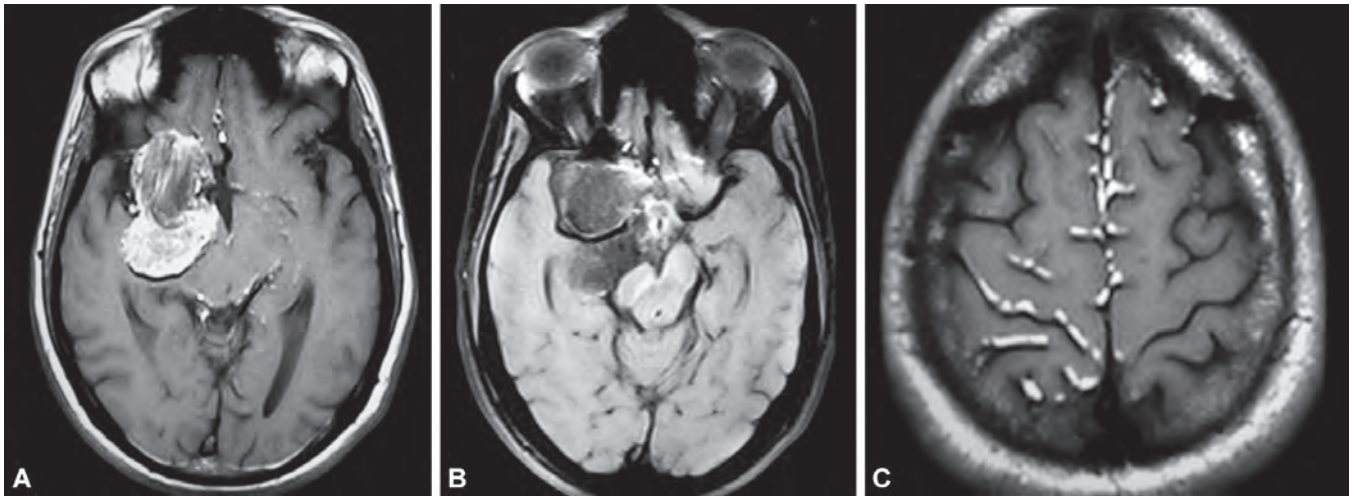
Dermoids and Epidermoids

These tumors represent non-neoplastic inclusion cysts that presumably arise from ectodermal cell rests during embryogenesis. Epidermoids are composed of desquamated cyst wall contents from an ectoderm-derived epithelial lining. They are most frequently found off the midline with insinuation into cisternal spaces and fissures, most often in the cerebellopontine angle (CPA), and less frequently around the sella. Their hyperintensity on FLAIR and DWI allows them to be readily distinguished from arachnoid cysts (Figs 13A to G).[26] Dermoids are similar to inclusion cysts, but their lining may also contain ectodermal-derived appendages (e.g. hair, teeth and sweat glands). They are more typically found near the midline and may be associated with a dermal sinus. The contents are oily with lipid metabolites that give rise to imaging features similar to those of fat, while ectodermal appendages contribute to heterogeneity. Fat characteristically results in chemical shift artifact, with spatial misregistration shown as bright and dark bands along the frequency-encoding direction. Ruptured dermoids may simulate acute subarachnoid haemorrhage as the oily contents are released into the subarachnoid space (Figs 14A to C).

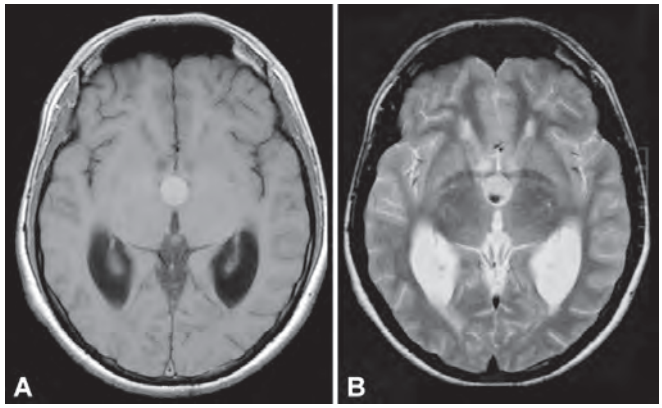


Figs 13A to G: (A) Axial T2-weighted image shows a well defined hyperintense mass lesion in the right cerebellopontine (CP) angle cistern. (B and C) Diffusion weighted image and ADC map show the lesion to have increased diffusion like that seen in the CSF. The lesion was diagnosed as arachnoid cyst. (D) Another patient in whom the MRI reveals a left CP angle mass, hyperintense in T2-weighted image. (E and F) Diffusion weighted image with ADC map shows the lesion to have mild restriction of diffusion. (G) 3D CISS sequence showing the mass is well localised in the right CP angle. This sequence is useful in defining the boundaries of intraventricular and intracisternal mass lesions

Other non-neoplastic extra-axial lesions include arachnoid cyst (a CSF-filled cavity within the arachnoid membrane that follows CSF intensity on all sequences), colloid cyst (anterior third ventricle at the foramen of Monro) (Figs 15A and B), neuroepithelial cyst (most likely intraventricular with choroidal origin), ependymal cyst and neurenteric cyst (cyst wall composed of gut/respiratory epithelium, remnant of the neurenteric canal during embryogenesis). A tall peak at 2 ppm in MR spectroscopy will help diagnosing cysts lined with ciliated columnar epithelium.[17]



Figs 14A to C: (A) Axial T1-weighted image shows a hyperintense mass lesion on the right side of the suprasellar cistern extending to the right Sylvian fissure. (B) The hyperintense signal is getting suppressed in fat saturation sequence. (C) The hyperintense fat is seen in the sulci and cisterns suggesting the possibility of a ruptured dermoid



Figs 15A and B: (A) Axial T1-weighted image shows a well defined hyperintense mass lesion in the anterior third ventricle suggestive of colloid cyst. (B) Axial T2-weighted image shows the lesion to be hyperintense with a hypointense area within. A colloid cyst shows varying intensity depending on the protein content of the fluid within the cyst

Ependymomas

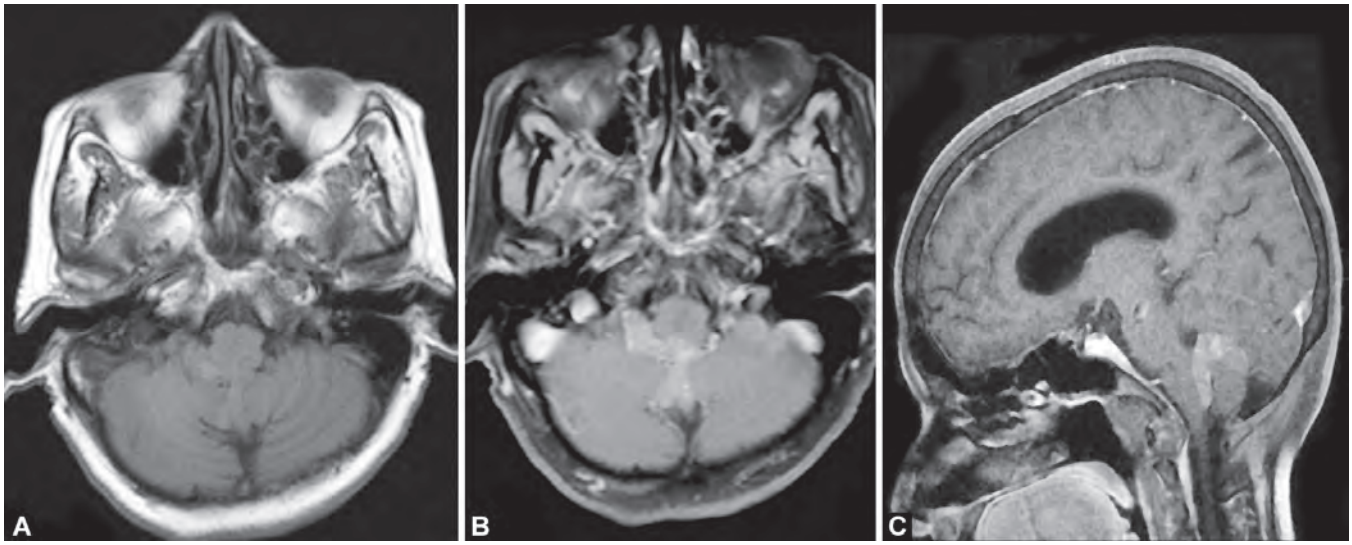
Ependymomas are glial tumours derived from differentiated ependymal cells along the ventricular system. In 60–70% of cases, these tumours occur in the infratentorial compartment and are intraventricular as they arise from the floor of the fourth ventricle. Most occur in children below 10 years old, and characteristically exit through the foramina of Lushka or Magendie (Figs 16A to C). The supratentorial tumours occur in patients 30–50 years old and may be transependymal, intraventricular or more commonly intraparenchymal. Extraventricular tumours are thought to arise from ependymal cell rests, which are predominantly located at the angled margins of the ventricles. The signal characteristics are nonspecific, with T1 hypointensity and T2 isointensity to hyperintensity, cystic changes in 74%, and haemorrhage in 13–21%.[6,7] Calcifications occur in half of these tumours, as opposed to the PNET/medulloblastomas, in which calcification is uncommon. The tumours show intense but heterogeneous enhancement with little or no peritumoural oedema.

Germ Cell Tumours

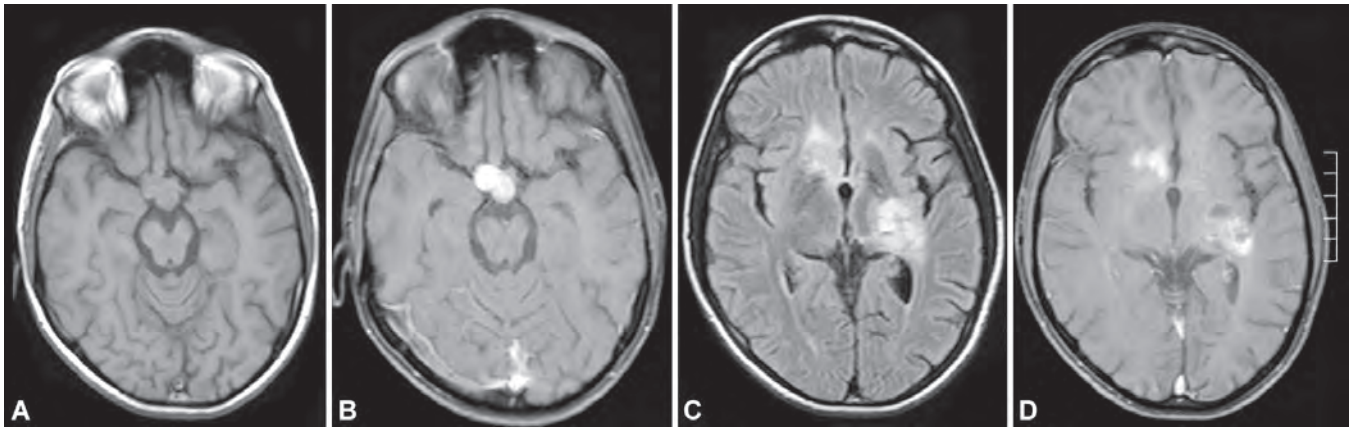
Germinomas are the most common intracranial germ cell tumours (GCTs), accounting for 60% of pineal GCTs and 40% of pineal masses. Around 90% of patients with GCTs are below 20 years of age. Clinically, suprasellar germinomas often present with diabetes insipidus. Germinomas are twice as common in the pineal region as in the suprasellar region, although 5–10% involve both areas simultaneously. Other possible midline locations include the thalamus, and fourth ventricle. Suprasellar germinomas are more common in females, while pineal germinomas have a marked male predominance (9:1). CT demonstrates a hyperdense, vividly enhancing mass that can be described as engulfing the pineal gland calcification. MR shows T1 isointensity and slight T2 hypointensity similar to that of GM because of the high nucleus-to-cytoplasm ratio. There is strong enhancement (Figs 17A to D). Metastases may occur due to dissemination via the CSF or ependymal surfaces. MRI is highly sensitive for diagnosing pineal or suprasellar mass lesions, but has limited specificity for distinguishing GCTs from other tumours. In these situations, evaluation of the CSF for specific protein markers can help establish the diagnosis and discriminate germinoma from nongerminoma lines (i.e. teratoma, choriocarcinoma, mixed germ cell, endodermal sinus and embryonal carcinoma).

Hemangioblastomas

Hemangioblastomas are the most common primary intraparenchymal infratentorial tumours in adults. These benign tumours represent 10% of all posterior fossa



Figs 16A to C: Axial T1 weighted, post-contrast axial and sagittal image show a T1-isointense mass lesion extending from the fourth ventricle to the foramen of Luscka and Magendie, which shows enhancement after contrast administration. The lesion is suggestive of ependymoma



Figs 17A to D: Young male patient showing. (A) A suprasellar isointense mass lesion in the T1-weighted image. (B) The mass enhances intensely after contrast administration. (C) Another FLAIR hyperintense mass is seen in the left basal ganglia. (D) This lesion also shows contrast enhancement. The lesion was proved to be germinoma

masses, with 83% occurring in the cerebellar hemispheres and characteristically contacting the pial surface. They present as a cystic mass with a highly vascular, solid mural nodule in 60% of patients. Enlarged, serpentine flow voids representing feeding vessels may be seen with MRI. The tumours are well defined and may induce a minimal surrounding parenchymal reaction. The cyst wall does not enhance, is not neoplastic, and does not have to be resected at surgery. Excision of the solid mural nodule is usually curative. Hemangioblastomas usually occur in young males. The principal differentiating feature between these tumours and similar-appearing juvenile pilocytic astrocytomas is age, [since the latter tend to occur in children (5–15 years old)] and their vascularity. Up to 25% of hemangioblastomas are associated with von Hippel-Lindau syndrome, in which case the tumours present at a younger age and are multiple, occurring in the cerebellum, brainstem and spinal cord (Fig. 18).

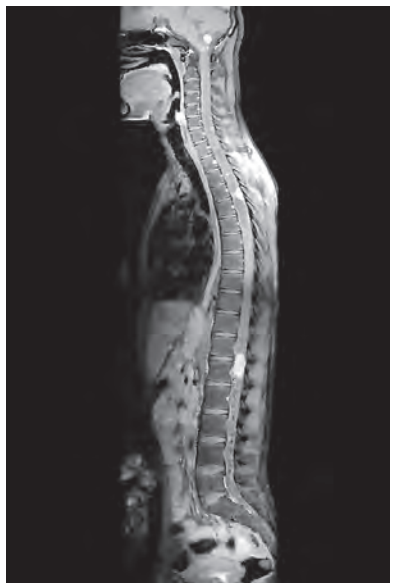


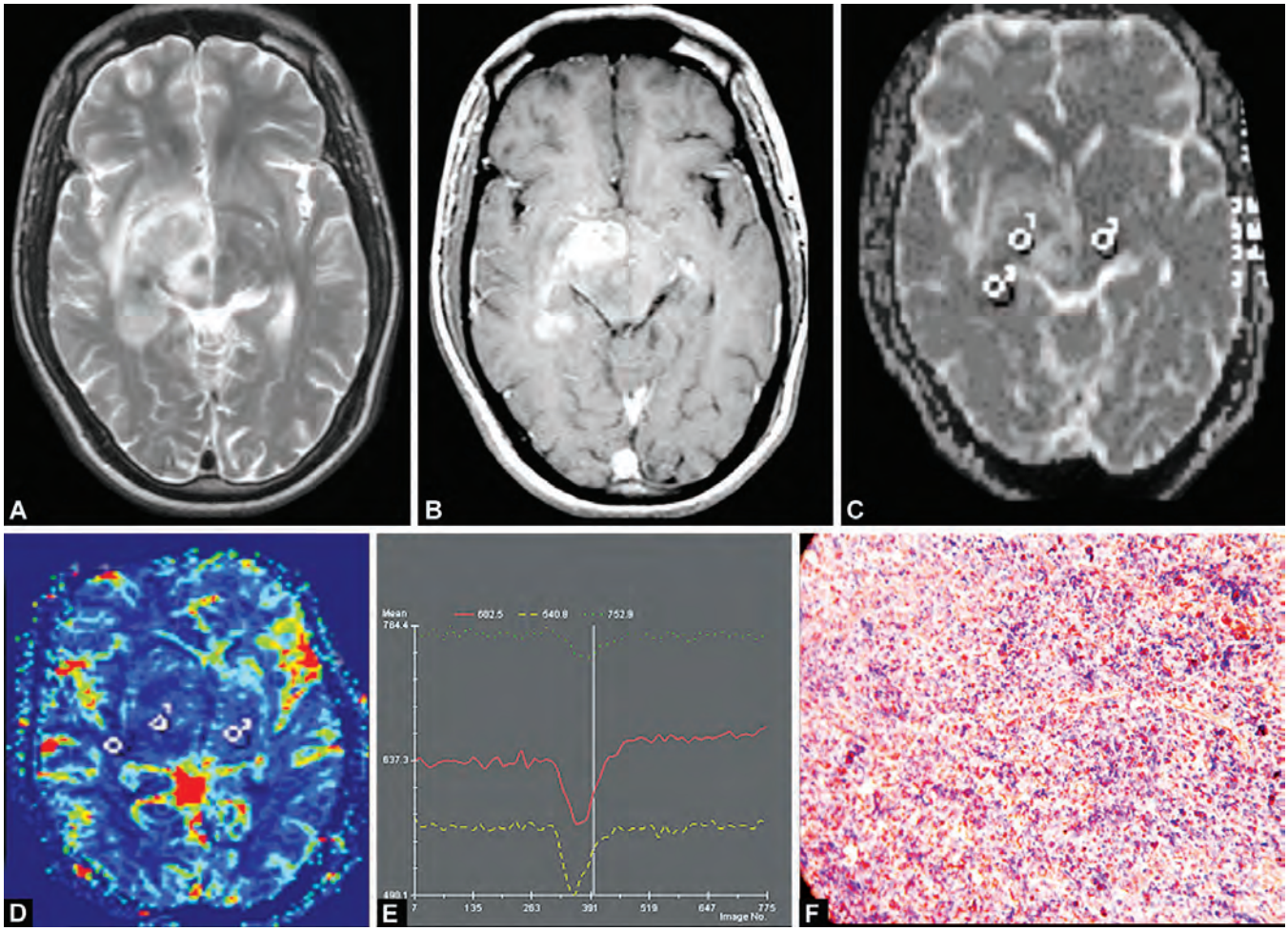
Fig. 18: Patient with Von Hippel-Lindau syndrome. Post-contrast sagittal T1-weighted image shows an enhancing mass lesion in the cerebellum. Note multiple enhancing lesions in the spine with syrinx and serpiginous flow voids. Findings are suggestive of multiple hemangioblastoma.

Lymphoma

Lymphoma has increased in incidence over the past two decades, largely due to an increased incidence in patients with acquired immunodeficiency syndrome (AIDS). However, the incidence of lymphoma has also risen in immunocompetent patients with no identifiable environmental or behavioural causes. A pre-operative diagnosis of primary cerebral lymphoma is of paramount importance to the neurosurgeon. These tumours are exquisitely sensitive to chemotherapy and radiation therapy. Conventional images often show multiple enhancing masses that often involve the deep GM, periventricular white matter, subependymal region, corpus callosum or are located adjacent to CSF spaces. They show T1 hypointensity to isointensity and are hypointense on T2WI with isointensity to mild hyperintensity because their dense cellularity leaves little interstitial room for water accumulation. Diffusion restriction with diffusion hyperintensity and ADC hypointensity may occasionally mimic an infarct. Homogeneous enhancement is absent in AIDS patients, whose tumours are more likely to have central necrosis. Despite conventional imaging features that may suggest a highly malignant neoplasm, perfusion MRI will often show only modest increases in perfusion that are much less than expected for high grade glioma.[4] This is because neovascularity is not a prominent feature of lymphomas, since the tumour cells instead grow around blood vessels in an angiocentric pattern (Figs 19A to F).

Paragangliomas

Paragangliomas may arise at the jugular foramen (glomus jugulare) or in the middle ear cavity (glomus tympanicum). These tumours arise from glomus bodies (neural crest derivatives) and often present with pulsatile tinnitus. Glomus jugulare tumours originate in the adventitia of the jugular foramen and may occlude the jugular vein with growth. At the time of diagnosis, there is usually infiltration of the tumour into the bony margins of the jugular foramen with a pattern of



Figs 19A to F: (A and B) Axial T2 weighted and post-contrast T1-weighted images show a hypointense lesion in T2 W1 image with intense post-contrast enhancement. (C) ADC map shows a low ADC in this lesion. (D and E) rCBV map and time intensity curve show that rCBV is not increased. (F) H and E staining of the resected mass was suggestive of lymphoma

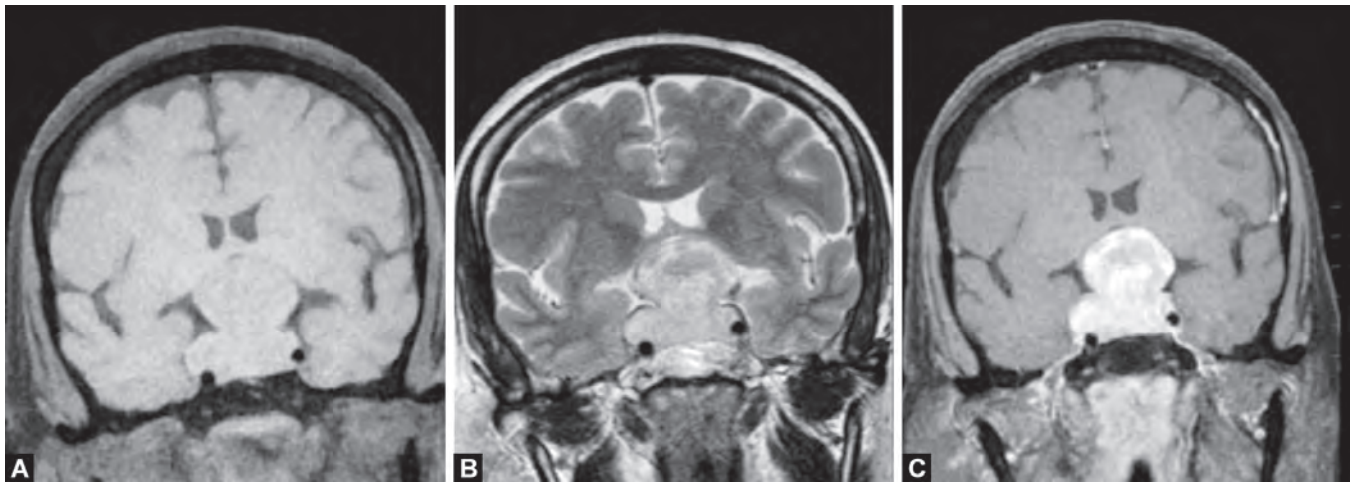
permeative bone destruction that is best seen with CT scan. MRI shows an enhancing soft-tissue mass centred on the jugular foramen (jugulare) or inferior portion of the middle ear cavity (tympanicum), or spanning both (jugulo-tympanicum). A soft-tissue component may grow intracranially towards the cerebellopontine angle. These highly vascular tumours are characterised by direct visualisation of prominent vessels within a mass evidenced by MRI "flow voids" or a "salt and pepper" appearance.

Metastases

Metastases are the most common supratentorial and infratentorial neoplasms in adults, accounting for more than 40% of all tumours. About half of these lesions are reported to be solitary; however, with the use of higher doses of gadolinium (as well as higher field strengths), the number of lesions detected is increasing. In decreasing order of numbers, metastases tend to arise from the lung (50%), breast (15%, in women), melanoma (11%), kidney and gastrointestinal primaries, although rarely metastases from primary CNS tumours may also occur. They are often located at the GM/WM junction, reflecting the normally high perfusion of the cerebral cortex. Lesions often have a fair amount of vasogenic oedema (recognised by the sparing of the arcuate fibres along with its frond-like appearance). Foci of T1 hyperintensity (seen in 3–14%) may represent blood products (from melanoma, thyroid, renal, breast and lung primaries) or melanin (in melanomas). These may be distinguished from benign haemorrhagic lesions by their relatively delayed haemoglobin evolution and incomplete haemosiderin periphery. Mucinous metastases tend to show T2 hypointensity, especially in metastatic colon adenocarcinomas. Calcification typically occurs in lung or breast metastases. Cystic lesions are associated with metastatic squamous cell carcinoma. Leptomeningeal metastases are more commonly due to adenocarcinomas and melanoma than haematological malignancies. These are best evaluated by both contrast T1-weighted images (T1WI) and contrast FLAIR images,[25] which show curvilinear or nodular pial enhancement (35%), hydrocephalus (13%) and cranial nerve deposits (11%).[8]

Pituitary Adenomas

Pituitary adenomas represent 33–50% of all sellar and parasellar masses (Figs 20A to C). In 66–75% cases, the



Figs 20A to C: (A) Coronal fat suppressed T1-weighted sequence shows an isointense sellar, suprasellar mass lesion. (B) Coronal; T2-weighted image shows the lesion to be isointense to hypointense. (C) Post-contrast image shows enhancement within the lesion. The pituitary gland is not seen separately. The right cavernous sinus and carotid artery is encased, the optic chiasm could not be visualised separately. Suggestive of pituitary macroadenoma

tumours are hormonally active and likely to present earlier with endocrine dysfunction. The hormones include growth hormone, adrenocorticotropin, prolactin and thyrotropin. Hormonally-inactive tumours present with larger sizes due to mass effect on adjacent structures. Adenomas usually demonstrate T1 hypointensity; however, variable signal intensities may occur due to intratumoural haemorrhage, which is more common after medical treatment with bromocriptine. Complicated macroadenomas may present with cystic changes and haemorrhage, including fluid-fluid levels. Coronal DCE-MRI is the most sensitive method for detecting pituitary adenomas, particularly microadenomas. There is avid, immediate enhancement of the normal anterior pituitary tissue, infundibulum and cavernous sinuses due to the pituitary's lack of a BBB and the adjacent hypothalamo-hypophyseal venous plexus. The adenoma shows delayed enhancement, with the differential most apparent in the first minute after injection. Secondary signs of a small, usually laterally located mass include increased gland height, eccentric superior convexity, contralateral deviation of the infundibulum and focal erosion of the sellar floor.

Medulloblastomas/Primitive Neuroectodermal Tumours

Medulloblastomas/PNET are the most common posterior fossa neoplasms in children (more than 33%), although they may also occur in the supratentorial compartment and have a second incidence peak in adults. PNETs classically originate in the midline cerebellar vermis in children and are more common in males, with a 2:1 ratio. They represent a spectrum of disease with a varied degree of aggressiveness, the most aggressive being the atypical teratoid/rhabdoid tumour. Desmoplastic medulloblastomas in adolescents and adults are often eccentrically located, and arise from the cerebellar hemisphere rather than the vermis. CT shows homogeneously hyperdense vermian masses. MRI reveals well-circumscribed T1 hypointense and T2 intermediate/isointense tumours that distort the fourth ventricle, which is usually displaced in an anterior-inferior direction. The site of origin may be obscured by large tumours. For distinction from fourth ventricle ependymomas, MRS of medulloblastoma shows high choline, low NAA and no lactate peak. Contrast MRI of the entire neuraxis must be performed because subarachnoid drop metastases occur in 15–50% of cases. Supratentorial PNETs are also aggressive malignancies with areas of cystic change, calcification, haemorrhage, heterogeneous enhancement and relatively little surrounding oedema. They have a similar propensity for leptomeningeal and CSF dissemination, and a poor outcome.

Rathke's Cleft Cysts

These originate from persistent remnants of Rathke's pouch. They are composed of a fibrous wall lined by a single layer of ciliated cuboidal or columnar epithelium. CT shows a hypodense cyst. Depending on the fluid composition and concentrations of protein, cholesterol and triglyceride, MR demonstrates variable T1 and T2 signal intensity. Forty percent of these cysts are intrasellar and intra-pituitary, and larger cysts extend into the suprasellar cistern. The cyst wall should show no calcification and no enhancement; however, an enhancing rim of compressed normal pituitary tissue or reactive granulation tissue may be observed.

Schwannoma

Schwannoma is the most common type of neurogenic tumour, and neurofibroma is much less common. Schwannomas originate from Schwann cells whose myelin processes surround axons of cranial nerves. They are most frequently found at the transition zone

between oligodendroglial and Schwann cell coverings of the axons. The peak incidence occurs in patients 50–60 years old, and they are slightly more common in females than in males. They originate much more frequently from sensory than motor nerves, and thus, identification of a nerve root signature can help improve diagnostic certainty. Since these tumours are well delineated and encapsulated, they affect the cranial nerve of origin and adjacent brain by compression rather than invasion. The vestibular division of the eighth cranial nerve (i.e. in the internal auditory canal and CPA) is the most frequently affected, followed by the fifth and seventh cranial nerves. MR usually demonstrates a T1 isointense to hypointense and T2 hyperintense extra-axial mass. Even very small intra-canalicular vestibular schwannomas can easily be seen with high-resolution (512 matrix) T2WI or 3D constructive interference in the Steady State (CISS) images. The presence of microbleeds within the tumour in the T2 gradient sequence or susceptibility weighted image helps in diagnosing schwannomas (Figs 21A to C), especially when placed at unusual locations.[19] Schwannomas show intense enhancement that is usually homogeneous in smaller tumours and more heterogeneous in larger tumours due to necrosis or cyst formation.

TUMOUR-MIMICKING LESIONS

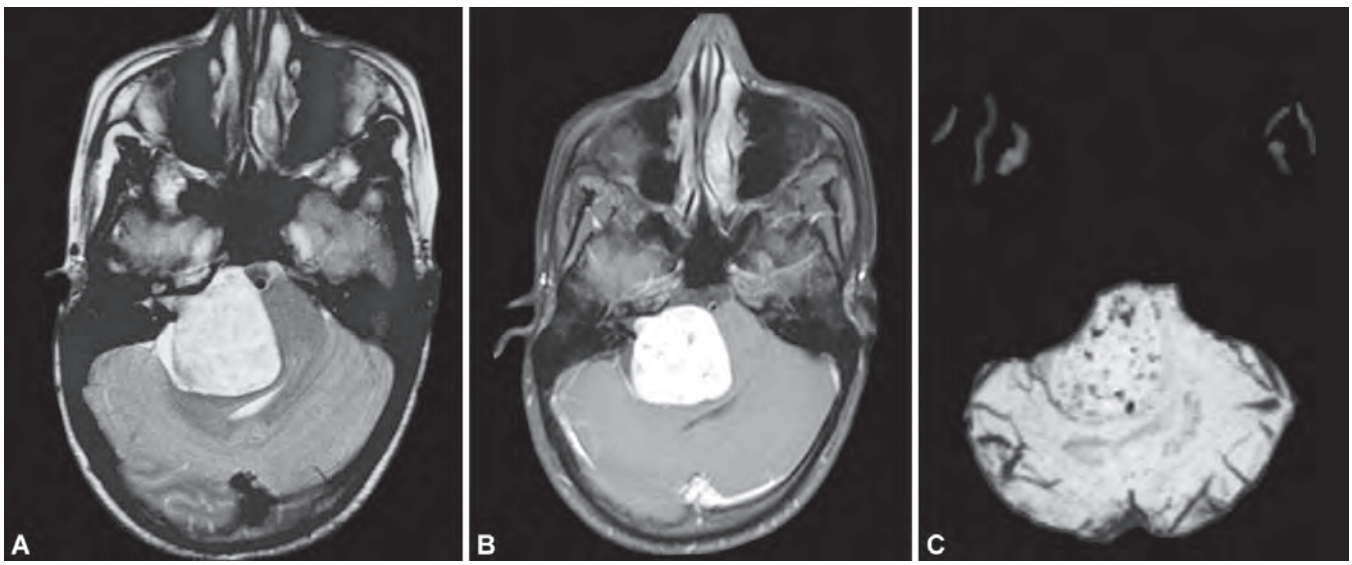
Some non-neoplastic entities may mimic malignancy due to overlapping signal abnormalities, enhancement patterns and mass effect with conventional imaging. Advanced MRI, particularly perfusion MRI and MR spectroscopy, may be very helpful in these situations. Lack of angiogenesis should suggest a tumour-mimicking lesion. A peripherally enhancing mass lesion that shows diffusion restriction and surrounding T2 hyperintensity may represent a brain abscess or metastasis. The abscess often shows a thin peripheral T2 hypointense rim, which is thought to represent free radicals caused by the inflammatory process, but this is not always readily apparent. Perfusion MRI of the capsular portion of these lesions will show significantly decreased perfusion for the abscess compared to the neoplasm.[9]

Tumefactive demyelinating lesions (Figs 22A to E) may present with enhancement, central necrotic change, mass effect and surrounding T2 hyperintensity similar to brain tumour findings based on conventional images. Perfusion MRI of these lesions may show mild hyperperfusion, although a conspicuous absence of hyperperfusion is more typical. Blood vessels in the areas of demyelination are intrinsically normal in comparison to the tumoural neovascularity. An examination of the source T2 images often reveals the presence of small venules streaming through the lesions without mass effect, which is a highly specific sign.[5]

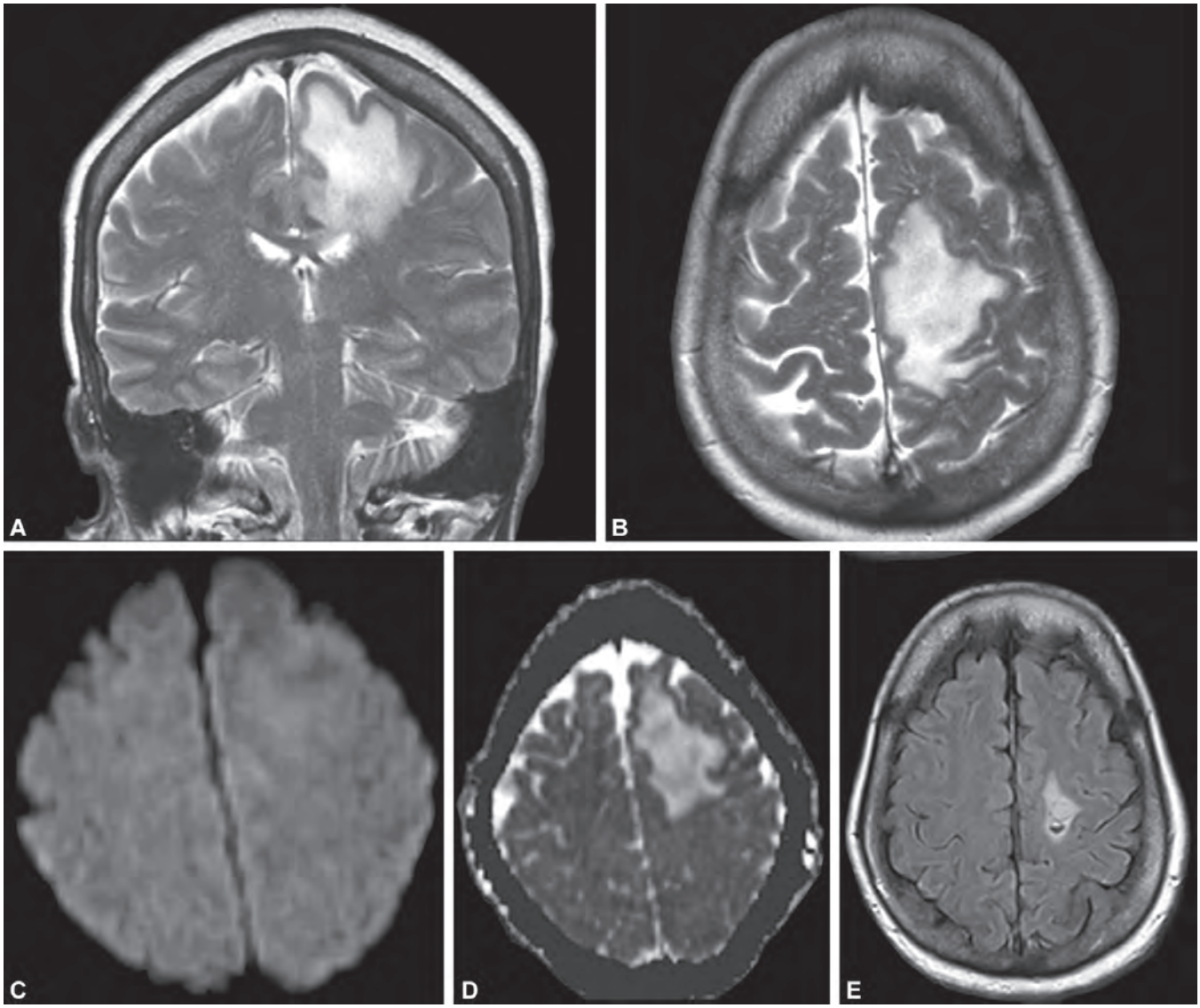
Acute to subacute infarcts may occasionally present with an atypical location or history and mimic a tumour, especially if there are DWI/ADC discrepancies. Ischaemia should decrease to absent perfusion with decreased CBV and CBF; however, the CBV may also be increased if there are adequate collaterals or luxury perfusion.

POST-SURGICAL IMAGING

Imaging is performed after surgical resection to evaluate for residual tumour and assess potential complications. MRI is the preferred modality though most of the centres still perform CT.[24] The initial post-operative scan is obtained within 24 hours using conventional sequences. In this time frame, post-operative changes affecting the BBB are not manifest, and any enhancement is thought to represent residual enhancing tumour rather than post-operative changes in the tissue. Non-contrast T1WI is essential because a fair amount of hyperintense



Figs 21A to C: (A) Axial T2-weighted image shows a hyperintense mass lesion in the right CP angle extending into the internal auditory meatus. (B) Mass shows intense enhancement after contrast administration. (C) Susceptibility weighted image shows micro-haemorrhages within the tumour

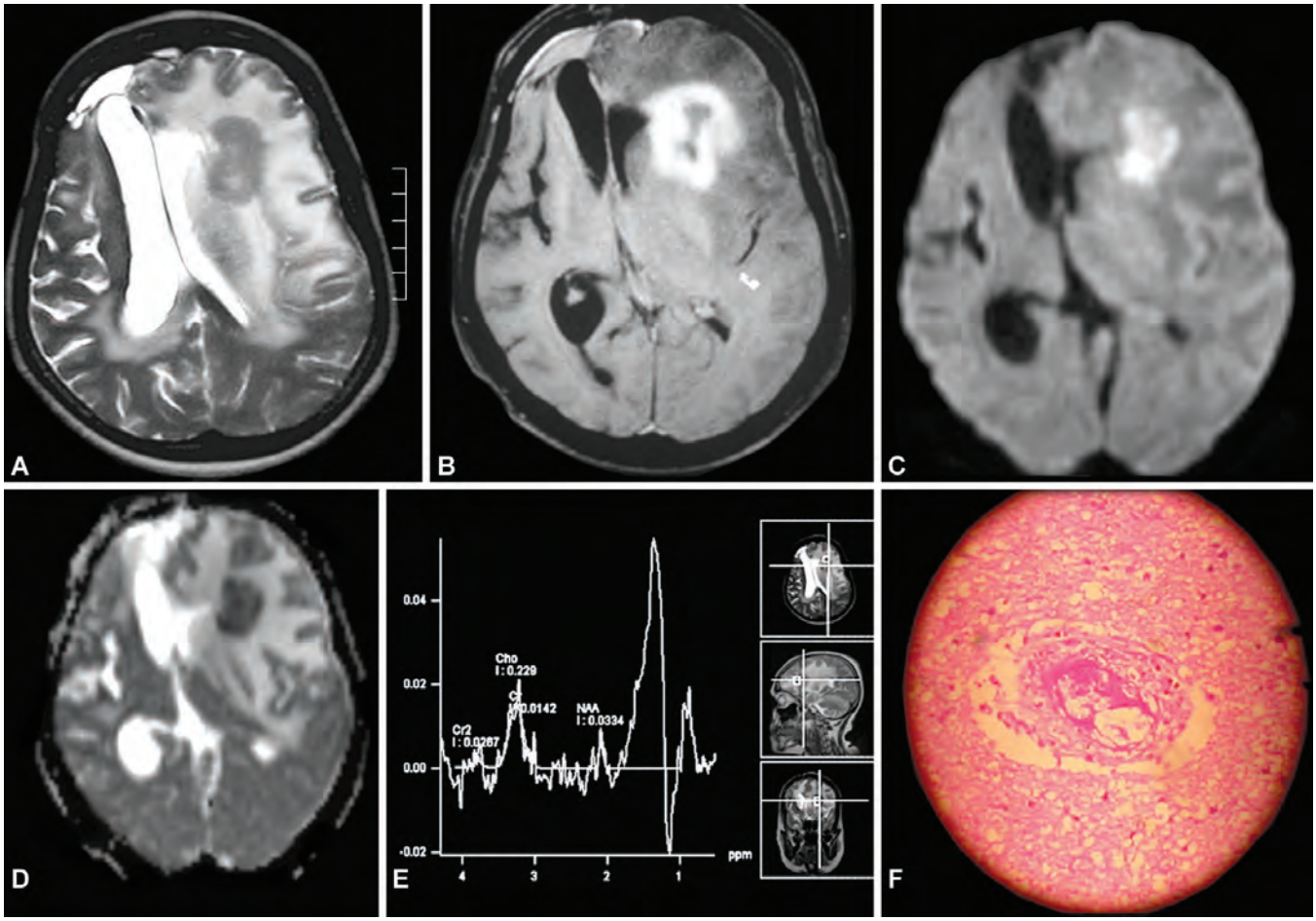


Figs 22A to E: (A and B) Coronal and axial T2-weighted images show a lesion with white matter oedema with mass effect on the left frontal horn. (C and D) Diffusion weighted image and ADC map do not slow diffusion restriction. A biopsy revealed the lesion to be demyelination. Patient was put on steroids. (E) Axial FLAIR image taken after therapy shows lesion resolution

blood product may be present. DWI is useful in the post-operative period for patients complicated by acute neurologic deficits, since the cytotoxic oedema of acute infarction is characterised by restricted diffusion (DWI hyperintensity and ADC hypointensity), in contrast to vasogenic oedema of tumour, which has elevated diffusion due to increased extracellular water (DWI hypointensity to slight hyperintensity and ADC hyperintensity). The first follow-up examination occurs 6 weeks after surgery. Scanning earlier than this can be fraught with difficulty due to exuberant post-operative contrast enhancement. If the tumour did not enhance pre-operatively, however, it will not enhance in the month following surgery. Further follow-up will be dictated by the clinical therapeutic protocol. Tumours after gross total resection tend to be followed at 3 months, 6 months and then annually. In patients undergoing medical therapy, examinations are typically performed at 4–6 weeks, with courses of chemotherapy in-between. Follow-up in patients receiving chemotherapy and/or radiation therapy should include at least one advanced imaging method (perfusion or spectroscopy) in order to differentiate between therapeutic effects and disease progression. When patients are no longer actively receiving aggressive treatment, follow-up occurs at 3-month intervals. The presence of any imaging changes with mass effect should prompt further investigation with advanced methods.

RADIATION NECROSIS VERSUS TUMOUR RECURRENCE

Therapeutic necrosis (secondary to radiation therapy or chemotherapy) cannot be distinguished from residual or recurrent tumour by conventional imaging methods, which show enhancing mass lesion(s) in the radiation bed due to disruption of the BBB with surrounding



Figs 23A to F: Known case of high grade glioma, the patient had undergone surgery and irradiation. (A) Axial T2-weighted image shows hypointense mass lesion with surrounding oedema and mass effect. (B) Except for a small central area, the lesion shows enhancement. (C and D) Restricted diffusion is noted in the diffusion weighted image. (E) Multi-voxel spectroscopy (TE: 135 ms) shows decreased choline and NAA. A large lipid peak is seen. Possibility of radiation necrosis was considered. (F) H and E Staining of the specimen revealed radiation necrosis

oedema and mass effect. The contrast enhancement simply reflects a breakdown of the BBB, which may occur in both tumoural disease and therapeutic necrosis. For this common clinical scenario, advanced imaging can be very helpful.

Perfusion MRI will show significantly reduced or even absent capillary volume in areas of therapeutic necrosis, which manifests as a "cold" region on an rCBV map. MR spectroscopy will reveal decreased metabolites manifested by reduced Cho/Cr and NAA/Cr ratios (Figs 23A to F), and mild NAA increases are often seen with successful therapy.[22] These techniques may be misleading, however, if inflammatory cells in the areas of radiation necrosis are hypermetabolic, leading to false-positive studies, and comparison with normal-appearing brain may be difficult due to radiotherapy and/or chemotherapy-induced metabolic depression.

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12 Radiology: Intracranial Infections

Bejoy Thomas

INTRODUCTION

In spite of the eradication of many infective diseases due mostly to better immunisation strategies, general improvement in health and hygiene and development of effective antimicrobial therapy, the incidence of central nervous system (CNS) infections, especially opportunistic infections appears to be on the rise worldwide. This has many reasons, including the occurrence of widespread epidemics of acquired immunodeficiency syndrome, use of immunosuppressant medications and emergence of new and variant strains of the micro-organisms causing intracranial infections. With the advent of newer diagnostic methods, especially advanced applications of MRI, imaging plays a crucial role in the early diagnosis of many infective lesions of the brain and the spine.

CNS infection can result from bacteriae, viruses, fungi and parasites. It can manifest as cerebritis, cerebral abscesses, meningitis, encephalitis, subdural empyema and effusions, and ventriculitis. The pathogen can reach the brain via the haematogenous route and rarely by direct spread from an adjacent infective focus, e.g. infection in middle ear or paranasal sinuses.

Various imaging modalities can be used to diagnose the manifestations, as well as sequelae of infective lesions of the CNS. However, MRI is the most advanced method for diagnosing and characterising infective lesions.

Computerised tomography (CT) scan appears to be a less sensitive alternative in detecting early lesions. Intravenous administration of gadolinium based contrast agents improves the sensitivity of detecting them, especially meningitis and cerebral abscesses. Diffusion weighted imaging (DWI), diffusion tensor imaging (DTI), proton magnetic resonance spectroscopy (MRS), magnetisation transfer imaging and perfusion imaging may help in early detection and finer sub-classification of CNS infections.

In this chapter, we will discuss various infective conditions of the brain and their imaging characteristics.

PYOGENIC INFECTIONS

It can manifest as cerebritis, cerebral abscesses, meningitis, encephalitis, empyema and ventriculitis.

Cerebritis

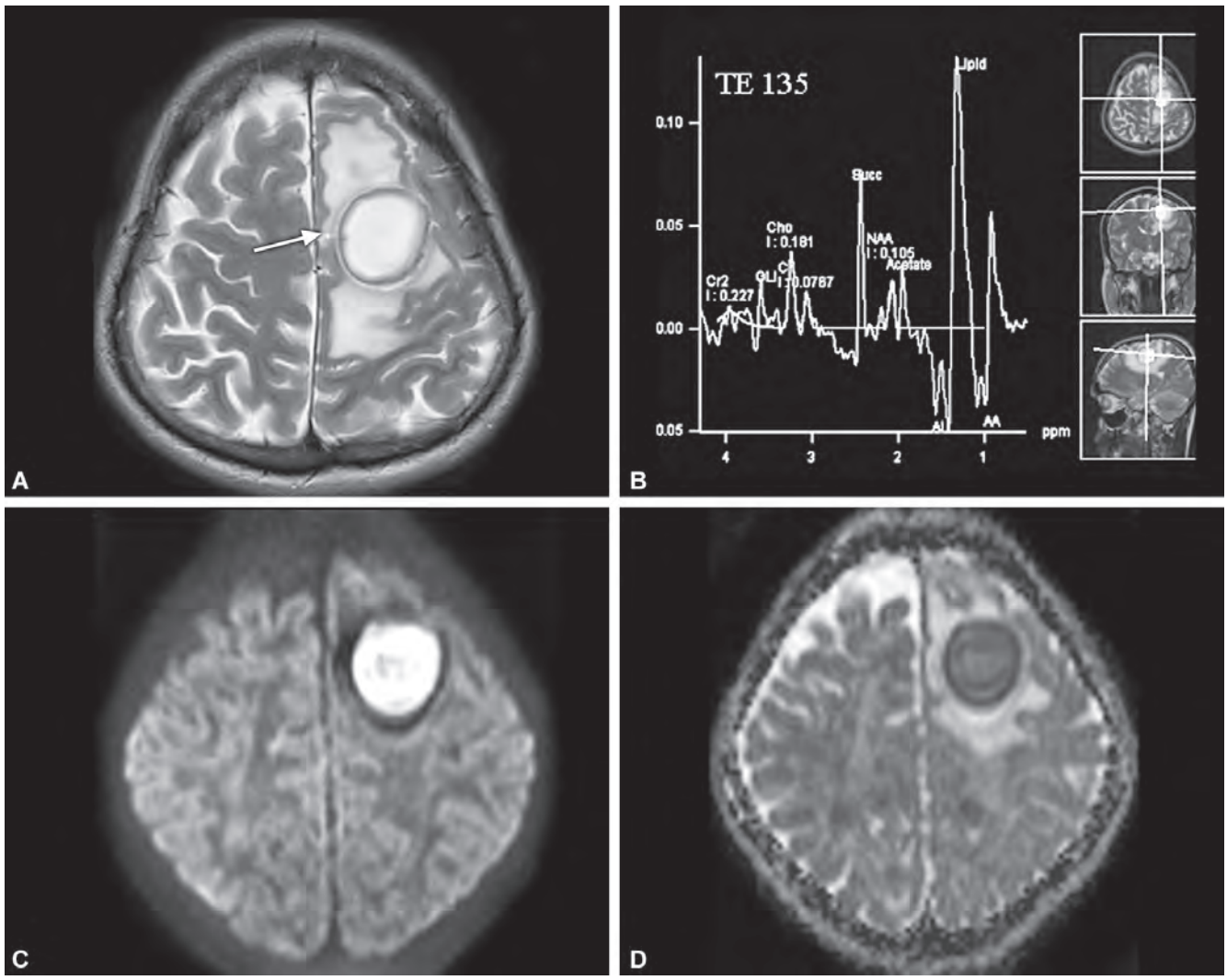
It is the earliest manifestation of a cerebral infection that may progress to the formation of a brain abscess. Usually it occurs 2–3 days following pathogen inoculation. Pathologically, localised yet poorly demarcated areas of parenchymal softening with scattered coagulative necrosis, oedema, congestion, petechial haemorrhages and perivascular inflammatory infiltrates can be noted at this stage. It results from direct spread of infection (head and neck infections/meningitis) or from haematogenous spread.

Magnetic resonance (MR) is more sensitive than CT in detecting cerebritis.[16] MR imaging shows an ill-defined area of isointensity or hypointensity with subtle mass effect (sulcal effacement or ventricular compression) on T1WI and contrast enhancement is absent or minimal. On fluid-attenuated inversion recovery (FLAIR) and T2WI, the infected tissue is hyperintense. In the absence of purulent fluid, DWI may show restricted diffusion in early cerebritis. It might be attributed to hypercellularity, brain ischaemia or cytotoxic oedema. Spectroscopy also may show abnormality, especially the presence of lactate, but the changes could be non-specific.

Cerebral Abscesses

Evolution of an abscess is characterised by four stages: early cerebritis; late cerebritis; early capsule formation and late capsule formation. In the final stages, the surrounding area of cerebritis extends only minimally beyond the capsule and the capsule is well formed on its cortical side than on its ventricular side. The length of time required for formation of a mature abscess varies from a few weeks to several months. In haematogenous spread, lesions are usually seen in the grey-white matter junction of ACA and MCA territories. Cerebellar abscesses constitute 2–14% of all cases.

The central liquefied portion is slightly hyperintense to cerebrospinal fluid (CSF) on T1WI and would be isointense to CSF on T2WI. The peripheral rim is hypointense to CSF on T2WI and hyperintense on T1WI and shows peripheral contrast enhancement on contrast enhanced T1 weighted sequences. This property of the rim has been attributed to collagen, haemorrhage and paramagnetic free radicals, within the macrophages which are peripherally distributed. This hypointense rim usually resolves with successful surgical and/or medical treatment. So, the rim may be a better indicator of response to treatment than the residual enhancement. The differential diagnosis for ring



Figs 1A to D: Pyogenic abscess involving the left frontal lobe. (A) T2 weighted axial FSE shows a cystic mass lesion with a hypointense rim (arrow) and surrounding oedema. (B) Proton MR spectroscopy at TE 135 ms shows the characteristic peaks. (C) Diffusion weighted image. (D) ADC map show restricted diffusion within the lesion

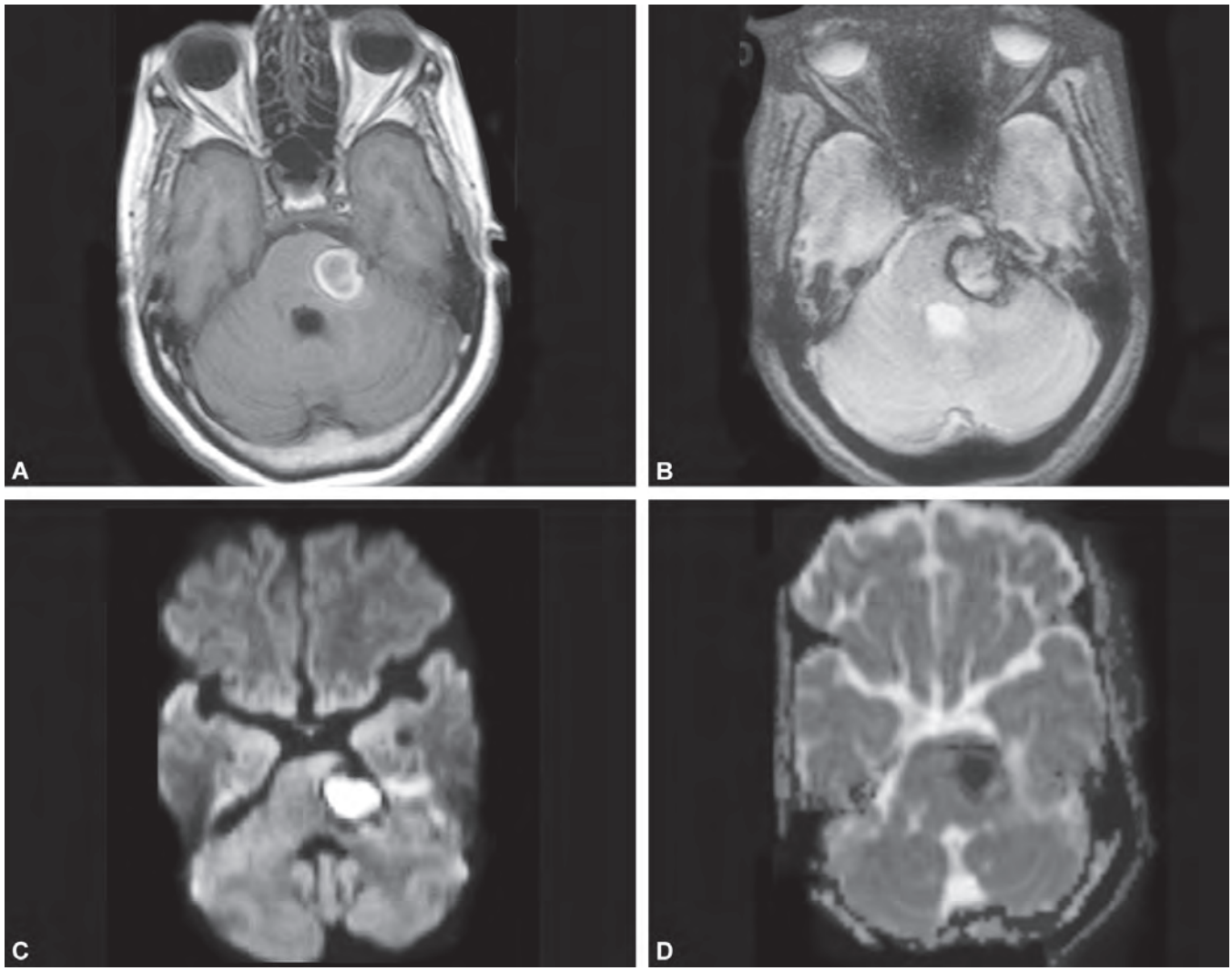
enhancing lesions includes primary brain tumours (e.g. necrotic glioblastoma), metastases, resolving haematoma, infarction and demyelinating diseases. DWI and MRS may help in the differentiation[21] (Figs 1A to D).

Ring enhancement of an abscess is usually thin and smooth, thinner along the medial margin. Sometimes, nodular or solid enhancement, incomplete thin rings or thick and irregular rings may be seen. Contrast enhancement may be reduced in patients receiving steroid or antibiotic treatment. Daughter abscesses appear as small adjacent rings, often along the medial margin of the parent abscess. Oedema surrounding the abscess may be greater in volume than the abscess itself. If the abscess ruptures into the ventricles, it results in ventriculitis or ependymitis, which carries a bad prognosis.[24]

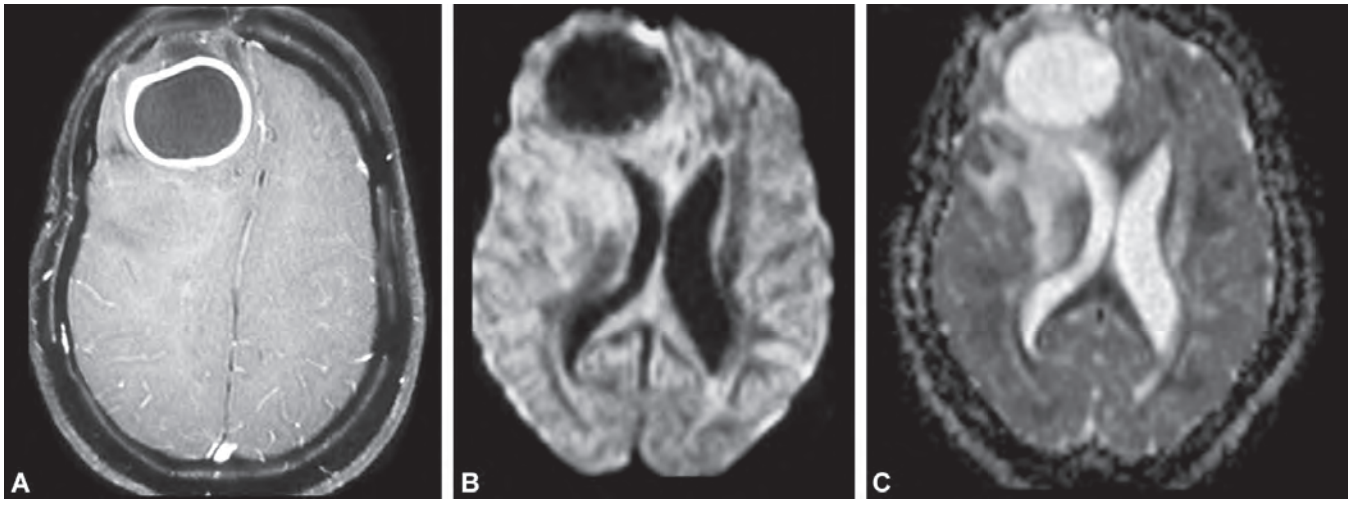
DWI shows restricted diffusion in the abscesses with calculated apparent diffusion coefficient (ADC) values in the range of 0.21–0.31. The structure of pus with its high cellularity and viscosity is responsible for the restricted diffusion. The presence of large molecules, like fibrinogen, also may play a key role in restricting the diffusion of pus. The closest differential diagnosis will be an acute infarct, which could be differentiated with other clinical and imaging features. However, hyperacute haematoma also may show diffusion restriction and should not be mistaken for an abscess (Figs 2A to D). It should also be noted that some of the abscesses may not show diffusion restriction (Figs 3A to C) and necrotic tumours very rarely show diffusion restriction.[18]

Diffusion tensor imaging, shows in addition to low diffusivity, a high fractional anisotropy (FA) in some parts of the abscess cavity.[14] FA value as high as that of the normal white matter is seen in the abscess with "orientations", apparently caused by organised inflammatory cells in the cavity. Recently, it has been shown that the 'pseudo-fibres' constituted by these cells produce high planar anisotropy (CP) on calculating the "diffusion metrics" in these abscesses.[20]

Magnetic resonance spectroscopy appears to be very useful in differentiating and characterising cerebral



Figs 2A to D: Pontine cavernoma with recent bleed. (A) Axial T1. (B) T2 GRE images show haematoma with blood in oxy Hb stage (hyper acute) in the central portion. (C) Diffusion weighted image. (D) ADC map show restricted diffusion within the lesion



Figs 3A to C: Right frontal cystic lesion. (A) Axial contrast enhanced fat saturated T1 weighted image shows a ring enhancing cystic mass lesion. (B) Diffusion weighted image. (C) ADC map show facilitated diffusion within the lesion. It proved to be a chronic sterile abscess

abscesses. MRS shows acetate (1.92 ppm), lactate (1.3 ppm), alanine (1.5 ppm), succinate (2.4 ppm) and complex peak at 0.9 ppm indicating cytosolic amino-acids like valine, leucine, isoleucine. With the characteristic imaging features, acetate and succinate are fairly specific for cerebral abscesses. In addition, necrotic or cystic tumours do not show peaks at 0.9 which usually inverts at TE 135. However, they can show lactate/lipid peaks. Acetate and pyruvate/succinate peaks were found to disappear within 1 week after instituting therapy for an abscess. Amino-acid peaks were found to disappear within days with persistence of only lactate. MRS also helps in differentiating aerobic and anaerobic abscesses.[10] DWI and MRS also may help in differentiating pyogenic abscesses from tubercular and fungal abscesses.[23]

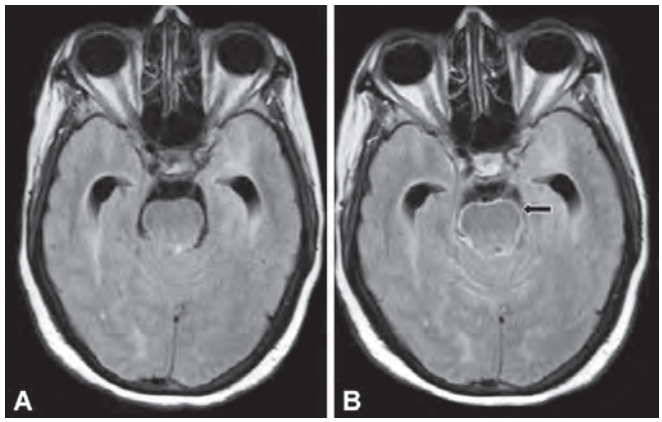
With treatment, an abscess may resolve with decrease in oedema, mass effect and degree of enhancement. However, enhancement might persist even after a full course of antibiotics, yet the lesion usually resolves within the succeeding 3–4 months. Focal gliosis or calcification may remain.

Septic Embolism and Mycotic Abscesses

This can occur in patients with history of intravenous drug abuse, bacterial endocarditis or children with congenital cyanotic heart disease. It can result in major arterial branch infarction, as also multiple small abscesses located at the grey-white matter junction. Mycotic aneurysms involve intermediate to small branch arteries and are usually located in more peripheral arterial branches. They are usually small and are difficult to be detected with cross-sectional imaging and often require digital subtraction angiography for detection.

Meningitis

Meningitis is acute or chronic inflammation of the leptomeninges. It occurs either secondary to haematogenous spread, direct spread from the adjacent focus of infection or from penetrating injury to the brain. Pathologically, the affected region shows congestion and hyperaemia of the pia-arachnoid and distension of the subarachnoid space by exudates.



Figs 4A and B: (A) Pre-contrast. (B) post-contrast FLAIR images show pial enhancement along the brain-stem with dilatation of the temporal horns suggestive of meningitis

Magnetic resonance imaging forms the most sensitive method for detecting meningeal inflammation. Unenhanced scans may be unremarkable in the acute stage. Post-gadolinium images show leptomeningeal enhancement. Pre-magnetisation and post-magnetisation transfer Gd increases the sensitivity of displaying leptomeningeal enhancement (Figs 4A and B). Magnetisation transfer ratios (MTRs) from the affected meninges may give clues to the aetiological nature of meningeal inflammation.[15] Recently, it has been shown that contrast enhanced FLAIR imaging helps in detecting subtle meningeal enhancement and many medicines, including ibuprofen can produce aseptic inflammation of the meninges which can mimic infective meningitis.[29,30]

Complications

Meningitis can result in several complications and include arterial and venous infarcts, abscess and cerebritis, subdural collection and empyema. Hydrocephalus and rarely ventriculitis may also follow meningitis. Venous infarcts are seen as hyperintense areas in the subpial cortex and underlying white matter, usually near the vertex due to superior sagittal sinus thrombosis. MRI with MR venography may help in detecting such complications (Figs 5A to C).

Subdural Collections

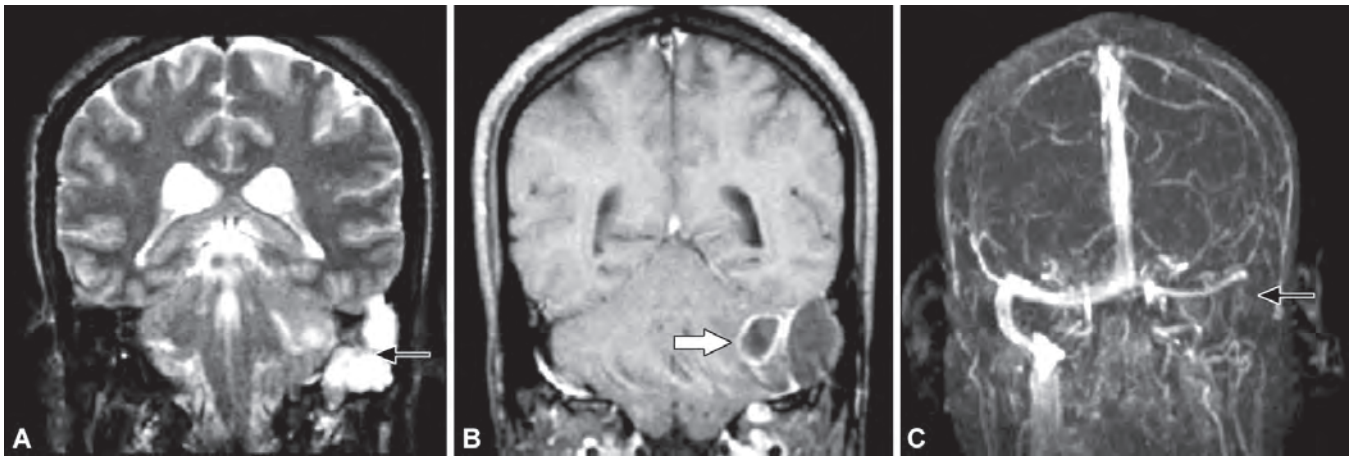
These could be subdural effusion or subdural empyema. Subdural effusion secondary to *H. influenzae* is usually bilateral and is seen as crescentic collections along the frontal and parietal cortices. They are isointense to CSF in all sequences. The underlying cerebral cortex does not show signal changes. Post-Gd images usually do not show enhancement. Calcification of the margins of the effusion may be a sequel. Subdural empyema usually shows enhancement of the periphery with restricted diffusion within it on DWI.[32]

Hydrocephalus

Hydrocephalus can be communicating or non-communicating, more frequently seen in children than in adults. It occurs due to adhesions or loculations secondary to meningitis. Ventricular dilatation with transependymal periventricular CSF seepage (T2 hyperintensity) is seen especially on FLAIR sequences. Basilar and supratentorial enhancement of the subarachnoid spaces could be seen in association with communicating ventricular enlargement.

Empyema

They represent purulent collections in the subdural and/or epidural space. In 65–70% of cases, it is secondary to otorhinologic infections with a very rapid clinical course. In the remainder it is due to previous head trauma, neurosurgical procedure or secondary to bacteraemia or meningitis. There can be either epidural or subdural empyema.



Figs 5A to C: Left mastoiditis complicated with cerebellar abscess and venous sinus thrombosis. (A) Coronal T2 FSE shows the collection in the left mastoid cavity (thin arrow). (B) Coronal contrast enhanced fat saturated T1 weighted image shows ring enhancement along the cerebellar abscess (thick white arrow). (C) MR venogram shows occlusion of the left distal transverse and sigmoid sinuses (thick arrow) with no flow in the left proximal internal jugular vein

Epidural Empyema

It shows lentiform collections, continuous across the midline with a hypointense margin on both the T1WI and T2WI (medially displaced dura).

Subdural Empyema

These are crescentric or lentiform in shape, located on cerebral convexities and are frequently bilateral. On T1WI they appear hyperintense to CSF which becomes iso to hyperintense on T2WI and PD (high protein content). Abnormal signals in the underlying brain parenchyma can be noted. Sulcal effacement and dural venous thrombosis may be associated. Prominent enhancement of the margins of the empyema may be noted.

Pyogenic Ventriculitis

Gram-negative bacteria, in particular, resistant to standard antibiotics are the most common cause of infective ventriculitis. Ventricular debris was the most characteristic finding which is irregular in contour because of the high protein content and possibly, necrotic material. Elevated protein content in CSF might be related to a decrease in CSF production. Tufts of glial tissue projecting through areas of denuded ependyma into the ventricular exudate also might contribute to the intraventricular debris. Hydrocephalus has been documented in many cases. Periventricular signal abnormality, detected in 78% of cases with MR imaging, likely reflects the periventricular inflammatory change. Periventricular signal abnormality includes swollen subependymal astrocytes and perivascular infiltration with lymphocytes and plasma cells. Chronic infection might result in subependymal astrocytic and microglial proliferation.

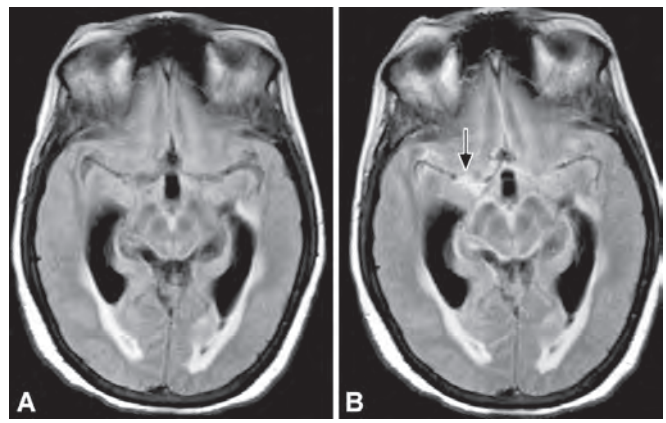
MYCOBACTERIUM TUBERCULOSIS INFECTION

Adult tuberculosis often results from post-primary infection and most cases of childhood TB are due to primary infection. Intracranial TB can present as meningitis, abscess, focal cerebritis and tuberculomas.

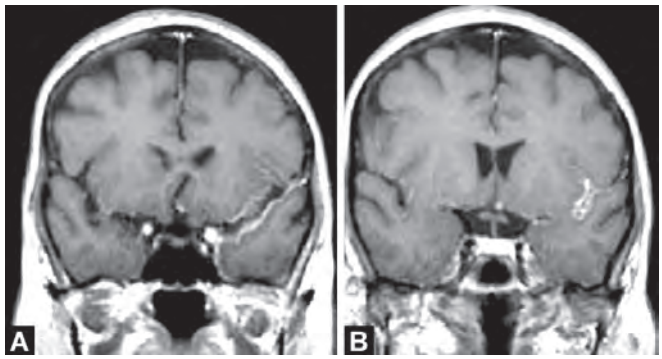
Tuberculous Meningitis

Tuberculous meningitis (TBM) usually shows enhancement of basal cisterns, meningeal enhancement, hydrocephalus and parenchymal infarctions usually of the perforator territory (e.g. basal ganglia) both on CT[4,5] and MRI.

The basal meninges are involved early in the course of the disease with thick gelatinous exudates. Circle of Willis vessels may be involved resulting in arteritis, thrombosis and infarction. Hydrocephalus, usually communicating, occurs in most cases. Hydrocephalus can be occasionally obstructive due to mass effect. MR imaging, especially Gd enhanced scans help in demonstrating the extent of exudates (Figs 6A and B, 7A and B). MTR from the meninges may help in differentiating TBM from pyogenic meningitis. The MT ratio of TB meningitis could be in the range of 19.49 +/- 1.22, in contrast



Figs 6A and B: (A) Pre-contrast. (B) post-contrast FLAIR images show thick exudates with enhancement along the basal cisterns, especially the right MCA cistern (arrow) with dilatation of the ventricles suggestive of the possibility of tuberculous meningitis



Figs 7A and B: Coronal contrast enhanced T1 weighted images show enhancement along the left MCA cistern and the Sylvian fissure in tuberculous meningitis

to viral meningitis with MTR of 8.2 +/- 0.8; pyogenic meningitis of 30 +/- 0.17; and cryptococcal meningitis of 27.2 +/- 1.7.[15]

Chronic sequelae include mental retardation, paralysis, cranial nerve palsy, seizures, and speech or visual deficits.

Tuberculomas

They may develop secondary to haematogenous spread or extension into the adjacent parenchyma, via cortical veins or small penetrating arteries. They can show various stages and are composed of central solid/liquid caseation, surrounded by a capsule of collagenous tissue, epithelioid cells, giant cells and phagocytes. They usually occur in the grey-white junction, periventricular regions, subarachnoid, subdural and epidural spaces. On CT, the immature forms appear as small discs and rings with massive oedema, while the mature forms appear as large rings or lobulated masses. The large rings enclose a mass, whereas the lobulated masses represent coalesced small discs and rings forming a large tuberculoma.[6] Target sign may be seen on CT scan. MR imaging shows variable findings, depending on the stage of the tuberculoma.[13] On T1WI it is usually isointense to grey matter with a slightly hyperintense rim. T2WI shows signals iso to hypointense to brain parenchyma, due to paramagnetic free radicals or high cellular density (Figs 8A to C). If hyperintense on T2, it is due to liquefactive necrosis of the centre. Perilesional oedema is less compared to pyogenic abscess which can be intense in the early stages. Post-Gd images show intense nodular or ring like enhancement. Healed tuberculomas may show calcification. Healing time depends on the size of the initial lesion. Tuberculomas may have distinctive MRS and MTR findings. Prominent lipid peaks (0.9, 1.3, 2.0 ppm) and phosphoserine peaks (3.7 ppm) have been noted on proton MRS. The MT ratio of tuberculomas could be in the range of 19.49 +/- 1.22. Neurocysticercosis (NCC) in contrast can show a MTR of 32 +/- 1.8.[15]

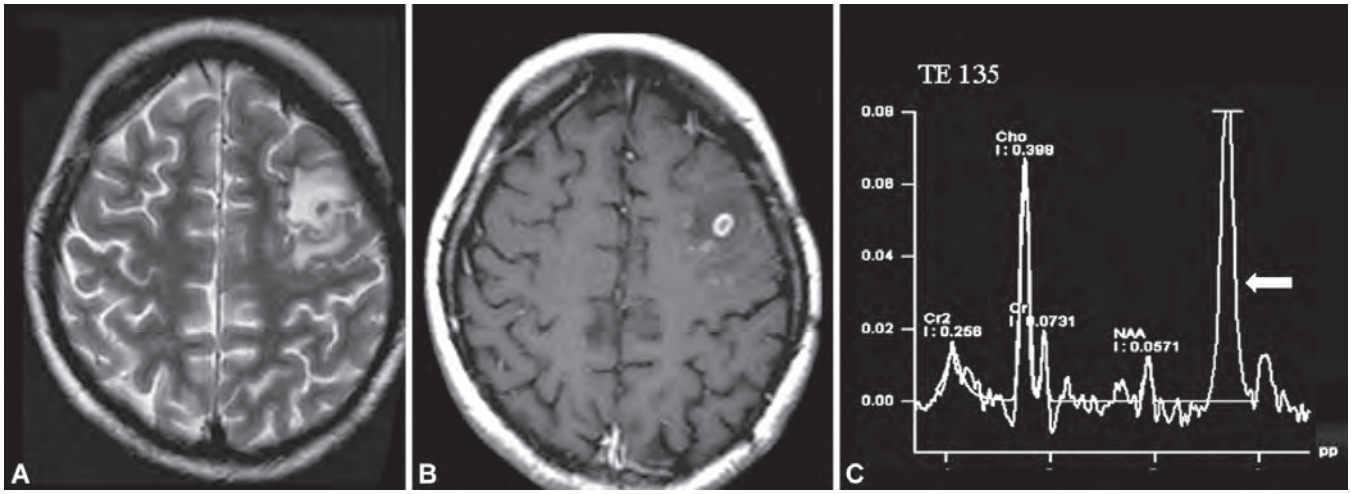
Tuberculous Abscess

Tuberculous abscess may develop due to liquefactive breakdown of caseated tuberculomas. They are usually larger than a tuberculoma. On CT they appear hypodense, with surrounding oedema and mass effect and ring enhancement.

MRI shows central hyperintensity on T2WI with post-Gd ring enhancement. DWI shows restricted diffusion with MRS showing a strong lipid lactate peak and sometimes a phosphoserine peak.

NEUROCYSTICERCOSIS

Neurocysticercosis is a common parasitic infection of the CNS. This disease is prevalent in developing countries and particularly affects the socially and economically deprived classes of society, where hygiene is often poor. Man gets afflicted by the parasite when he consumes infected pork or vegetables contaminated with parasitic eggs. NCC is caused by the larvae of *Taenia solium*, *Cysticercosis cellulosae* and less frequently by *Cysticercosis racemosae*. *C. cellulosae* is characterised by a small cyst of



Figs 8A to C: Left frontal tuberculomas in the solid caseation stage. (A) Axial T2 weighted FSE shows hypointense lesions with surrounding oedema. (B) Axial contrast enhanced T1 weighted image shows ring enhancement of the lesions. (C) Proton MR spectroscopy shows a prominent lipid peak (arrow)

5–15 mm, the cyst wall is thin and transparent and the cyst contains clear fluid with a pearly white invaginated scolex. *C. racemosae* are often large, measure 4–12 cm and are devoid of a scolex. Occasionally, a solitary cyst, especially one in the fourth ventricle can acquire a large size.[25,33] Based on the location of the cysts, five forms are recognised: parenchymal; spinal; arachnoid; ventricular and mixed.[13]

The cysts can remain viable in the CNS for several years depending on the immune status of the individual. Morphologically, four stages of disease are identified, namely vesicular, colloidal, granular nodular and calcific stages. In the vesicular stage, the cyst is well defined, contains a scolex and is viable. The colloidal stage is characterised by death and disintegration of the cyst, the cyst fluid becomes turbid and there is an associated inflammatory process. In the granular nodular stage, the cyst wall retracts with thickening of the capsule. Chronic inflammatory infiltrates are seen around the cyst with moderate to intense fibrillary astrocytosis. In the calcific stage, the lesion retracts to a fraction of its initial size, fibrosis gradually replaces the lesion and often it gets calcified.[9,13]

Neurocysticercosis can present clinically with a wide spectrum of symptoms. Epilepsy is the most common and often, the only symptom of parasitic infestation. Other manifestations include headache, arachnoiditis, focal neurological deficits, hydrocephalus, raised intracranial pressure and rarely encephalitis.[9]

MRI is the investigation of choice for evaluation of NCC. Contrast MR and advanced imaging like spectroscopy helps in further delineation and can aid in the diagnosis when there is a diagnostic dilemma. One disadvantage of MR is that small calcific nodules may be too subtle and are often missed in conventional MR and, sometimes, even in gradient echo sequences. Detection of these calcifications is important, as it can act as epileptogenic foci and can present with intractable seizures. However, the novel susceptibility weighted imaging sequences can detect these calcifications easily,[30] as is also the case with CT.

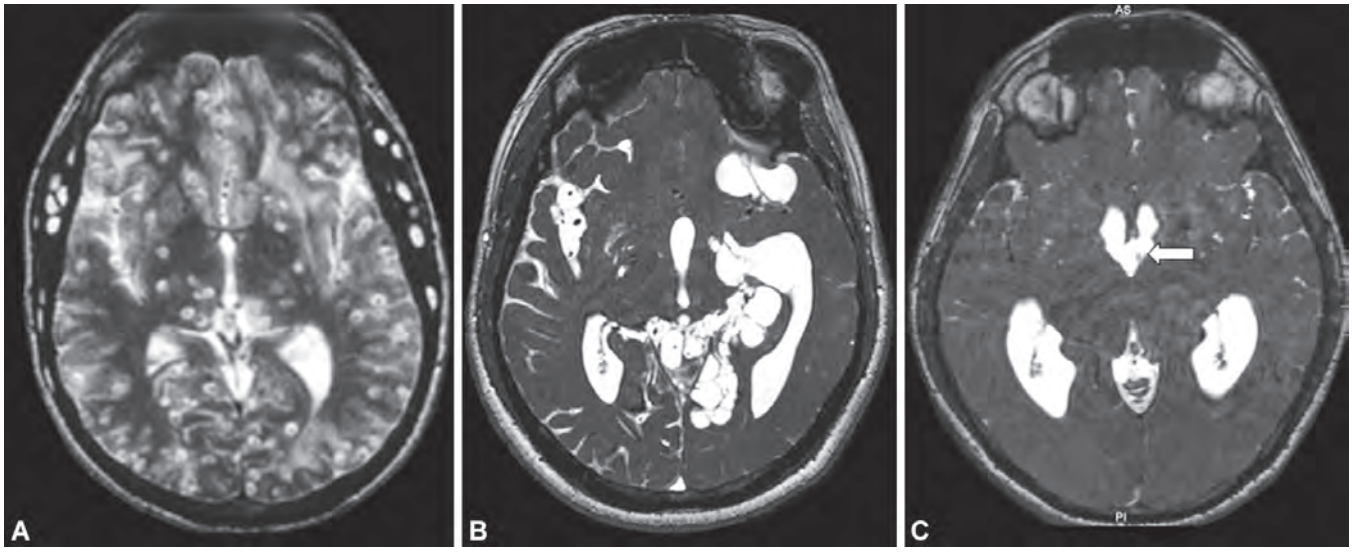
MRI can identify various stages of NCC and this reflects evolution of the parasite through different pathological changes.[13] In the acute phase of invasion, MR may show a focal non-enhancing hyperintensity or small contrast enhancement, due to mild inflammatory reaction. In the vesicular stage, a typical 1–2 cm cyst is demonstrated, which appears as a well defined hyperintense lesion on T2W and hypointense on T1W sequences similar to CSF (Fig. 9A). The larval scolex may be identified which is seen as a 1–2 mm mural nodule which appears hyperintense on T1 and hypointense on T2W. The demonstration of a scolex is pathognomonic of cysticercosis. There is no oedema, mass effect or enhancement at this stage.[9,13]

The colloidal stage is characterised by the death of the parasite which invokes a surrounding inflammatory reaction. The cyst contents become turbid due to increased protein content, which is seen as hyperintense on T1W and T2W. There is adjacent moderate to marked oedema and there is solid or ring enhancement. The cyst capsule is thickened and appears hypointense on T2W images. In the granular nodular stage, the cyst shows uniform ring enhancement and there is reduction in the oedema and mass effect. In the final stage, the cyst becomes calcified and may not be detected with conventional MR. Gradient and susceptibility weighted sequences are sensitive to calcified lesions.[9,13] These lesions do not show contrast enhancement or mass effect, although there are reports describing enhancement in calcified NCC.[28]

The cisternal form of NCC involves the subarachnoid spaces and basal meninges. They are commonly located in the cisterna magna, cerebellopontine angle cistern or sellar cisterns. Cysts are usually large and may attain giant proportions. These are racemose cysts and lack a scolex. Usually, these are single cysts, but imaging may show these cysts to be multi-loculated, which may be due to the infolding of the cyst wall or agglomeration of multiple cysts presenting as a nodular mass (Fig. 9B). Sometimes, this may be seen as asymmetrical CSF spaces and a high index of suspicion is needed to identify this. FLAIR imaging with 100% supplemental oxygen improves the conspicuity of cisternal cysts,[7] so also with the use of thin heavily T2 weighted sequences like CISS or FIESTA. These cysts can provoke inflammatory reaction, resulting in severe basal arachnoiditis, communicating hydrocephalus, vasculitis and basal ganglia infarcts.[3,9,13]

Intraventricular NCC occurs in 20% of the cases.[9] This is most commonly detected in the fourth ventricle due to dependant gravitation of the cysts. Other less common sites include the aqueduct of Sylvius and the third and lateral ventricles (Fig. 9C). Early diagnosis is important as the mobile cysts can cause acute obstruction to the ventricular outflow, resulting in sudden death. The cyst is often similar to CSF in all sequences; however, the identification of the cyst wall or scolex, if present, helps in the correct diagnosis. These cysts often conform to the ventricular wall and may be mistaken for a dilated ventricle.[25,33] Sometimes, the cyst can cause ependymal inflammation which may be seen as a high intensity rim in FLAIR images or as thin contrast enhancement of the ependymal wall. O_2 supplementation does not improve the conspicuity of these cysts. 3D CISS has been shown to be more sensitive and specific than conventional MR to detect the cyst wall and scolex of intraventricular cysts.[12] Intrathecal iodinated contrast administration and imaging with CT may identify these cysts as filling defects. Intrathecal gadolinium administration has also been tried.

Spinal cord involvement is reported in 2–5% of NCC.[9,31] Extramedullary cysts are more common than intramedullary forms and usually these patients have the manifestations of this parasite elsewhere in the body, which helps in the diagnosis. The cysts can be solitary or conglomerated, commonly located in the thoracic



Figs 9A to C: Neurocysticercosis. (A) Axial T2 weighted FSE showing the brain parenchyma and the temporalis muscles studded with cysticercal cysts in the vesicular stage. (B) Axial T2 weighted 3D-CISS demonstrating racemose cysticercosis in another patient. (C) Axial T2 weighted 3D-CISS showing cyst within the third ventricle in a third patient (arrow)

cord and may show non-specific imaging findings. Co-existant CNS infection or CSF analysis may resolve the issue.

MR spectroscopy of NCC may show lactate (1.3 ppm), acetate (1.98 ppm), cytosolic amino acids (0.9 ppm), alanine (1.47 ppm) and succinate (2.4 ppm). The presence of strong succinate with a smaller acetate peak may help in differentiating NCC from pyogenic brain abscess.[1] Choline, n-acetyl aspartate (NAA) or creatine peaks are not observed within the cysts. DWI of NCC show high ADC consistent with the cystic lesion.[1,26]

In developing countries, apart from NCC, several other prevalent neurological diseases, for example, tuberculosis, can present with a similar clinical and radiological picture. In order to improve the specificity, diagnostic criteria have been put forth based on clinical, radiological and epidemiological parameters proposed by del Brutto et al. which is given in Table 1. Modifications have been suggested for Indian patients.[8,11]

Table 1: Diagnostic criteria and degree of certainty for human neurocysticercosis

Absolute criteria	1. Histological demonstration of parasite
	2. Direct visualisation of parasite by fundoscopy
	3. Visualisation of scolex on CT/MR
Major criteria	1. Lesions suggestive of neurocysticercosis (NCC) on CT/MR
	2. Positive immunological studies
	3. Plain X-ray shows calcifications in muscles
Minor criteria	1. Subcutaneous nodules
	2. Soft tissue or intracranial calcifications
	3. Clinical history suggestive of NCC
	4. Disappearance of NCC with anti-helminthics
Epidemiologic	1. Living or hails from endemic regions
	2. Frequent travel to endemic areas
	Household contact with *Taenia solium*

- *Definitive*: (1) one absolute criterion; (2) two major criteria; (3) one major + two minor + one epidemiologic.
- *Probale*: (1) one major + two minor; (2) one major + one minor + one epidemiologic; (3) three minor + one epidemiologic.
- *Possible*: (1) one major; (2) two minor + one epidemiologic.

Differential diagnosis includes tuberculosis, brain abscess, cystic tumours and hydatid cysts. Tuberculosis is an important differential diagnosis which needs to be excluded as both are widely prevalent in developing countries and the therapeutic options are entirely different for both the conditions. Clinical and CT criteria have been suggested to differentiate both the diseases, however they are not reliable. NCCs are usually small, less than 2 cm, round and uniformly enhance with contrast and there is absence of severe mass effect. Newer techniques like magnetisation transfer, DWI and MR spectroscopy can settle the issue to a greater extent.

Electro-immuno transfer blot assay for the detection of *T. solium* antibodies has sensitivity of more than 90% and specificity of 100%. But, this test can be frequently false negative in single cysticercal lesions and its sensitivity and specificity decreases with calcified lesions.[11]

NEUROBRUCELLOSIS

It is a rare zoonotic disease with the primary hosts being camels, sheep and goats and humans act as the secondary host. This disease is usually transmitted through consumption of uncooked meat or unpasteurised dairy products. Neurobrucellosis occurs in 5–10% of cases of brucellosis and affects both the central and

the peripheral nervous systems. It preferentially affects the auditory system with occurrence of sensorineural hearing loss. Three types of imaging abnormalities can be seen[2]: inflammation, white matter changes and vascular insults. Inflammation may result from granulomas or enhancement of the meninges (basal meningitis), perivascular space or lumbar nerve roots. White matter changes manifest as hyperintense lesions on T2WI in the form of diffuse involvement of the arcuate fibres or periventricular regions (corpus callosum) or as focal demyelination. Vascular insult is likely to be due to one of two mechanisms: (a) inflammatory process (vasculitis) of the small vessels or venous system causing lacunar infarcts, small haemorrhages, or venous thromboses; (b) a haemorrhagic stroke caused by rupture of a mycotic aneurysm, a likely sequel of embolic stroke from brucellar endocarditis.

ANTHRAX MENINGOENCEPHALITIS

Infection with the *Bacillus anthracis*, a large gram-positive, spore-forming bacillus is transmitted to humans by contact with infected animals or contaminated animal products. CT and MRI show multiple haemorrhagic lesions at the grey-white matter junction of the cerebrum and diffuse meningeal enhancement. Haemorrhage in the deep grey matter, ventricle, supra and infratentorial subarachnoid spaces and diffuse meningeal enhancement can also be seen. However, no parenchymal enhancement has been reported.

VIRAL INFECTIONS OF THE BRAIN

Viral infections of the brain result usually in aseptic meningitis or viral encephalitis.

Pathological features include neuronal degeneration and inflammation. It can range from diffuse brain congestion and oedema to haemorrhage and necrosis. MRI shows scattered or confluent areas of hyperintensity on T2WI and iso to hypointense on T1WI. Haemorrhage may be present. Localised or generalised atrophic changes may be seen.

Herpes Simplex 1 Encephalitis

Herpes simplex 1 (HSV-1) encephalitis initially involves the cerebral cortex, causing neuronal destruction and cytotoxic oedema. A characteristic pattern of distribution is exhibited by the pathogen, with the anterior and medial aspects of the temporal lobes and the inferior portion of the frontal lobes initially being affected. The process may then extend to include the insular cortex. The lentiform nucleus is typically spared. Bilateral mesial temporal involvement is almost pathognomonic for HSV encephalitis, particularly when asymmetric.

CT is usually normal during the early stages of infection and abnormal parenchymal or meningeal enhancement is rarely detected before the 2nd week of clinical symptoms. MR imaging, especially DWI is more sensitive during the initial course of the disease. The involved areas appear hypointense on T1WI and hyperintense on T2WI. DWI can show restricted diffusion in the early course of the disease. Focal areas of haemorrhage may be detected on gradient images in areas of herpetic involvement, but is a rare finding. The leptomeningeal and gyral enhancement associated with HSV encephalitis typically occur along the temporal lobes, insular cortex, subfrontal area and cingulate gyrus (Figs 10A and B). These lesions are more conspicuous if magnetisation contrast pulse is turned.

If the patient has HIV infection, the white matter is predominantly affected, especially in the occipital lobe and exceptionally in the cerebellum. The hippocampi, frontobasal, insular and temporal cortices are spared.[27]

MRS shows reduced NAA between 7 weeks and 14 weeks after onset, whereas choline can be elevated, with the presence of lactate. Glial proliferation in HIV-related herpes simplex encephalitis can be associated with progressive myoinositol increase.

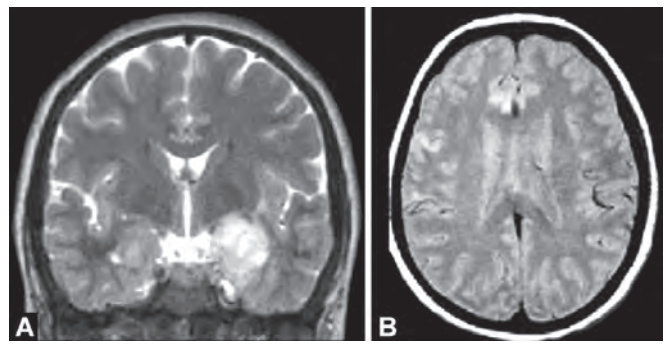
Japanese Encephalitis

The natural transmission cycle of the Japanese encephalitis (JE) group involves infection of a mosquito vector alternating with viral amplification in a variety of vertebrate hosts. Human disease is incidental to this cycle. It presents after a brief, non-specific prodromal febrile illness. Seizures are a prominent manifestation in children.

Adults usually present with more obviously encephalitic symptoms. Cranial nerve palsies, particularly of the VII nerve, occur in 50% of cases. Movement disorders are a major feature in 40% of patients and include choreiform movements, Parkinsonism and other tremors.

Thalamic lesions are most frequently hypointense on T1-weighted images and hyperintense on T2-weighted images, but high signal intensity on T1-weighted images, consistent with subacute haemorrhage, has also been described.

The basal ganglia and midbrain are frequently involved by JE. These lesions are more likely to be



Figs 10A and B: Herpes simplex encephalitis. (A) Axial. (B) Coronal T2 weighted FSE showing mesial temporal and cingulate hyperintensity

asymmetric than are those within the thalami. Co-infection with NCC is also known in endemic areas.[17]

Rabies Encephalitis

It is an acute infection involving the CNS in humans and other mammals caused by an RNA virus of the rhabdovirus family. Human rabies presents in two forms: encephalitic and paralytic. The passage of the virus to the CNS occurs axonally through retrograde axoplasmic flow of approximately 12–24 mm per day, until the virus reaches the next neuronal cell body.

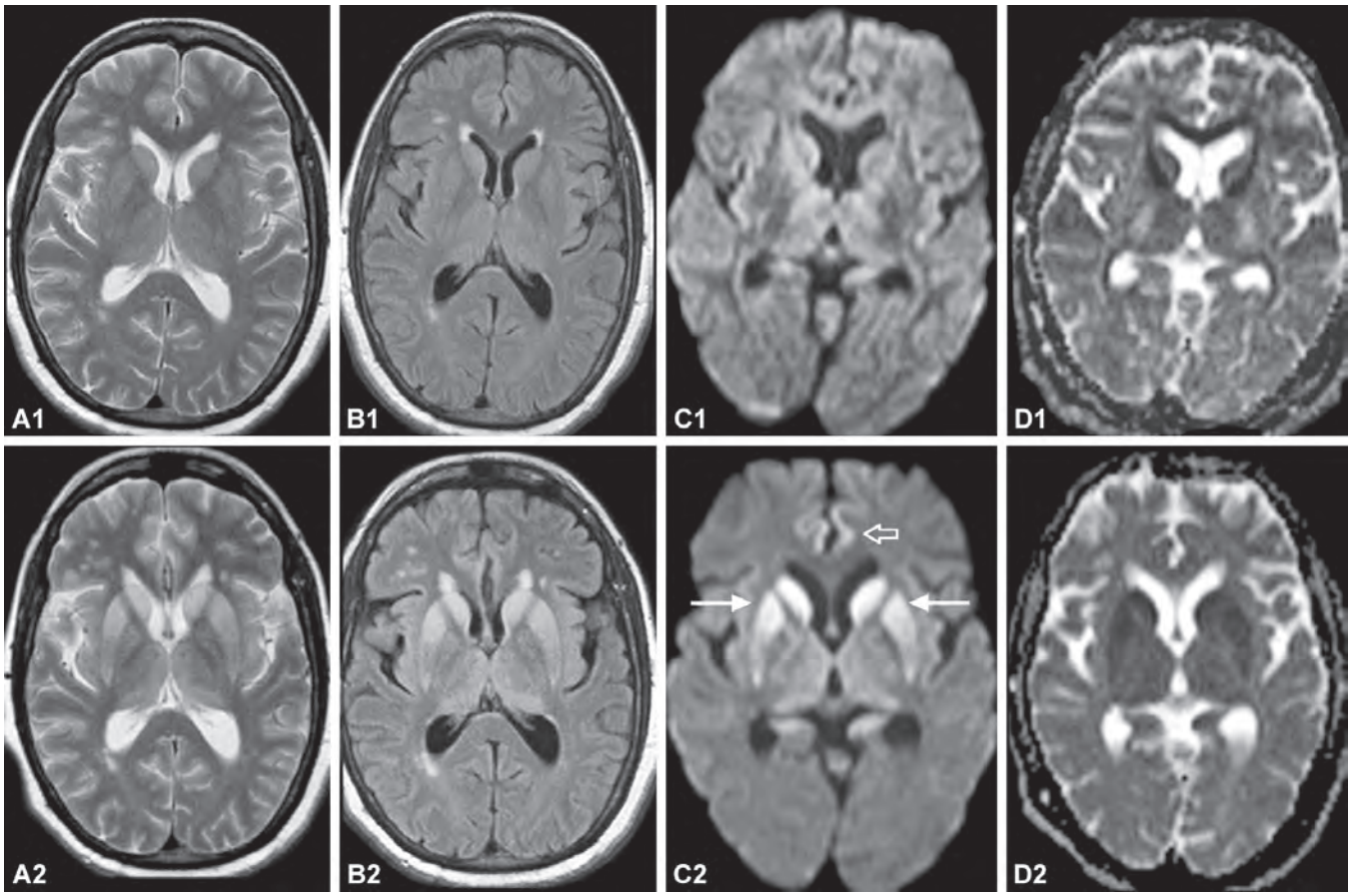
In paralytic rabies, the medulla and the spinal cord are mainly involved by extensive neuronal damage and inflammation, whereas in the encephalitic form, it is the brainstem and the cerebrum, particularly the limbic system. Involvement of the basal ganglia and the thalamus are usually seen late in the disease. CT scan shows focal or diffuse areas of decreased attenuation and, as areas of hyperintensity on T1- and T2-weighted MR images in the basal ganglia, periventricular white matter, hippocampus and brain stem.[22] Diffuse cerebral oedema may be seen in advanced stages.

Creutzfeldt-Jakob-Disease

Creutzfeldt-Jakob-Disease (CJD), a fatal neuro-degenerative disorder, is diagnosed by the detection of an accumulation of an abnormal form of the human prion protein (PrPSc) in the brain. Brain biopsy or autopsy is required for a definitive diagnosis. In sporadic CJD, diagnostic MR examinations are performed frequently and reveal typical findings. Hyperintense signal-intensity abnormalities, initially reported on T2-weighted and proton attenuation (PD)-weighted images, are also detectable on FLAIR and diffusion-weighted images (DWI) involving the head of the caudate nucleus and in the putamen (Figs 11A to D). In addition, the cortical ribbon can also show hyperintensity. DWI shows a decrease of the ADC in the affected areas, most probably because of the characteristic neuropathologic spongiform neuropil changes.[19] The disease has a fatal course.

Acute Disseminated Encephalomyelitis

It is a monophasic post-infectious (varicella, measles and rubella) or post-vaccinial inflammatory disorder that is pathologically characterised by an acute perivenous lymphocytic inflammation with confluent demyelination. It presents with seizures, focal neurologic signs and



Figs 11A to D: Creutzfeldt-Jakob-Disease (CJD). (A) Axial T2 weighted FSE. (B) FLAIR. (C) DWI. (D) ADC 3 months apart (1 and 2, upper and lower rows, respectively) showing the involvement of the head of the caudate nucleus and the putamen with diffusion restriction more evident on the second row (thin arrows). Note also the cortical ribbon sign (thick arrow)

alteration of consciousness that develop days to weeks after the onset of presumed viral infection. CSF analysis reveals mild pleocytosis.

MR imaging usually shows T1 and T2 prolongations, typically bilateral and asymmetric, in the deep and subcortical white matter of the cerebrum, cerebellum and brainstem with no mass effect. The corpus callosum may be involved in acute disseminated encephalomyelitis (ADEM) and these patients nearly always have asymmetric callosal lesions and their white matter has lesions as well. After contrast material infusion, the lesions in ADEM will show various patterns of enhancement, depending on their acuity. Improvement of white matter lesions may take a long time and part of the white matter damage may be permanent.

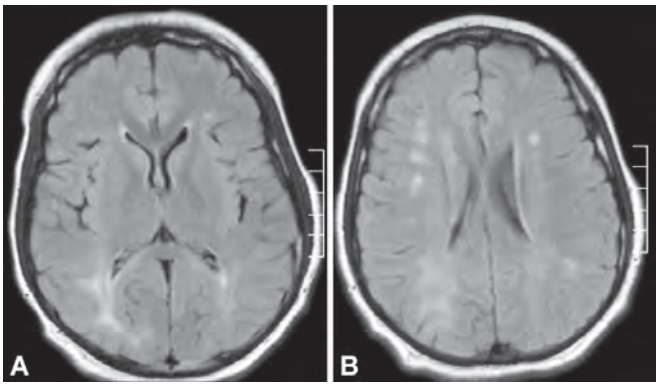
Subacute Sclerosing Panencephalitis

This is attributed to slow progressive infection by measles virus. Children between the ages of 5 years and 12 years who had clinical measles 3 years before are affected. Clinically, four stages are recognised from initial mental or behaviour abnormalities to loss of cerebral cortical function. Death usually occurs within 2–6 years. White matter abnormality seen in the centrum semiovale is either patchy or diffuse and there is minimal inflammation. Gliosis can occur in the grey matter, basal ganglia, pons and thalamus. MR shows bilateral periventricular white matter hyperintensities on T2WI (Figs 12A and B). No mass effect is seen. Frontal and/or occipital involvement can be more extensive.

FUNGAL INFECTIONS

They are divided into those that predominantly infect the immuno-compromised (Aspergillus, Candida, Mucormycosis) and those that infect immuno-competent individuals.

Cryptococcus and Histoplasma spread haematogenously, reach the microvasculature of the meninges, penetrate the vessel walls and result in an acute or chronic leptomeningitis.



Figs 12A and B: Subacute sclerosing panencephalitis. (A and B) Axial FLAIR images showing the characteristic parieto-occipital involvement

Cryptococcus Neoformans

It is the most common fungus to affect the CNS and to cause meningoencephalitis and is usually associated with HIV infection or AIDS and rarely seen in immuno-competent healthy persons.

It reaches the CNS through the haematogenous route from a peripheral focus in the lung. It extends into the parenchyma, either through the choroid plexus or through the Virchow-Robin spaces. Expansion of these spaces forms the pseudocystic lesions, characteristic of this disease.

It evokes minimal inflammatory response and does not release any exotoxin and thus causes little tissue necrosis. Therefore, secondary changes such as fibrosis, calcification, infarction or haemorrhage are rare and symptoms are caused by compression of the surrounding structures, as the infective focus enlarges. The avascular pseudocysts are seen as well circumscribed, round to oval hypointensities on T1WI and hyperintensities on T2WI, which fail to enhance after administration of contrast medium.

Granulomatous lesions enhance with contrast medium administration and are hyperintense on T2WI. They are located preferentially on the ependyma of the choroid plexus. Meningeal involvement often is inferred from the progressive ventriculomegaly on sequential images, but neither meningeal enhancement nor ventricular dilatation is specific for cryptococcosis. Periventricular oedema appears to result from altered CSF dynamics and seeping of the CSF into the interstitial space across the subependymal gliotic layer.

Candidiasis

On T2WI candida abscess appears as an area of a well demarcated hypointense signal surrounded by a larger area of high signal intensity. Meningitis, meningoencephalitis and granuloma may also result.

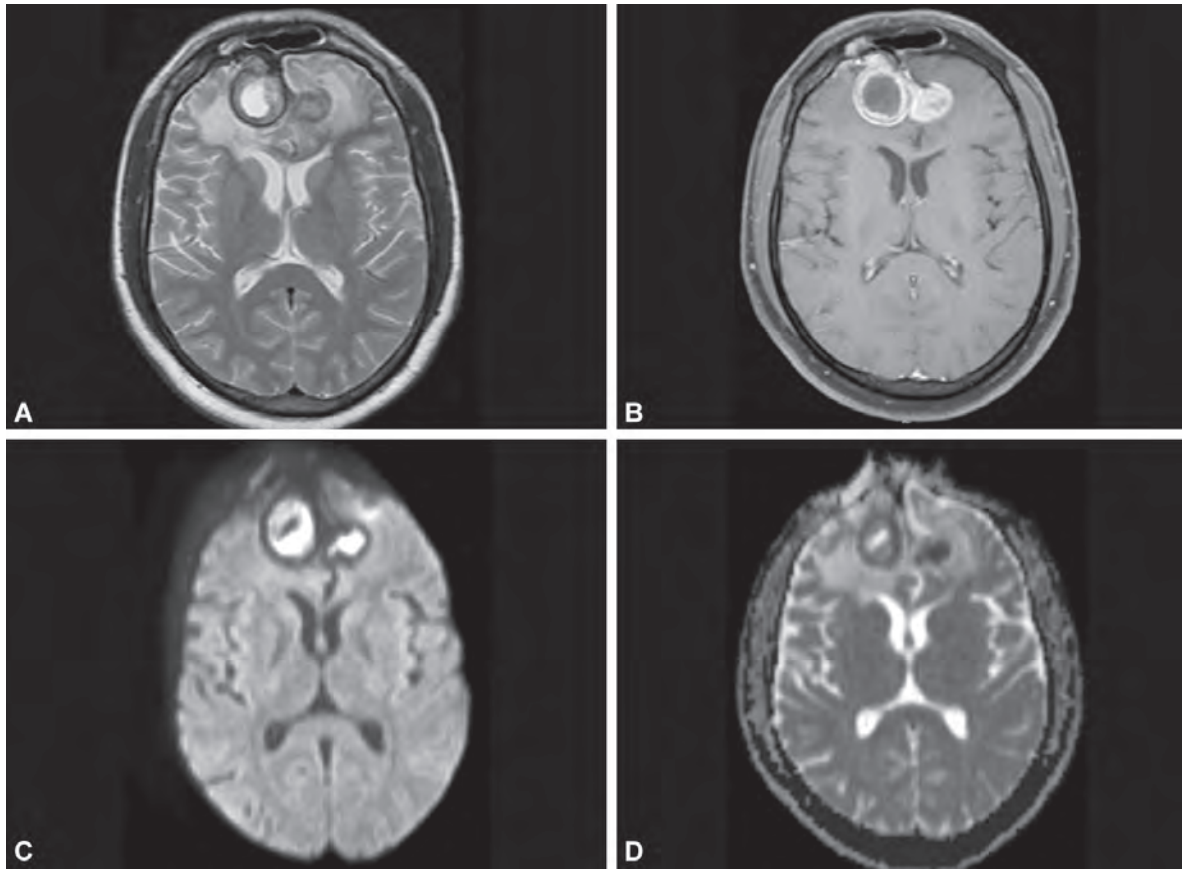
Aspergillus Infection

Aspergillus infection occurs by direct extension from the nasal cavity or paranasal sinuses or by the haematogenous route.

With direct spread, vascular invasion is often observed resulting in angiitis, thrombosis and infarction. Meningitis can result with extension into the subarachnoid spaces. With haematogenous spread, the vessels get occluded, producing infarction, septic infarction, cerebritis and cerebral abscess.

The presence of haemorrhage gives a clue to the diagnosis of aspergillosis. Fungal organisms were detected in the encapsulated lesion, but they were not commonly found in vessels or in the parenchyma outside the abscess.

Usually abscesses are hypointense on T1WI and hyperintense on T2WI with or without mass effect.



Figs 13A to D: Right frontal fungal abscess extending to left side. (A) Axial T2 weighted FSE showing the lesion with hypointense rim. (B) Axial contrast enhanced fat saturated T1 image shows ring enhancing cystic mass lesions. (C) Diffusion weighted image. (D) ADC map show the characteristic restricted diffusion

Hypointensity on T2WI also can be seen (Figs 13A to D). DWI show centrally restricted diffusion. The changes in diffusion are a likely reflection of proteinaceous fluid and cellular infiltration in the lesions.

Mucormycosis

Mucormycosis occurs in uncontrolled diabetic or immunocompromised patients. It spreads from the PNS along perivascular and perineural channels, through the cribriform plate into the frontal lobe or through the orbital apex into the cavernous sinus. It causes either infarction or fungal abscess and involves the base of the brain and cerebellum after invasion of the infratemporal fossa or orbit. It appears hypo or hyperintense on T2WI and hyperintense on T1WI and may demonstrate peripheral post-Gd enhancement.

CONCLUSION

Infections of the brain can be best imaged with MRI and advanced MR applications help in management decisions.

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SECTION

3

Congenital

NK Venkatramana

13 Embryology: Skull and Vertebral Column

Muthukumar N

DEVELOPMENT OF THE VERTEBRAL COLUMN

The vertebral column consists of 33 vertebrae, which include 7 cervical, 12 thoracic, 5 lumbar, 5 sacral and 4 coccygeal. There are regional differences in the anatomy of the vertebrae. However, despite these regional differences, the development of the vertebral column conforms to a general plan with some regional variations.[4,9,12–15]

Each vertebra passes successively through three different stages of development, which are as follows:[2,4,17]

1. Blastemal or membranous
2. Cartilaginous
3. Bony

As the notochord forms, the mesoderm condenses on either side of the notochord as two parallel longitudinal columns known as the paraxial mesoderm (Fig. 1). Initially, this mesoderm exists as a pair of unsegmented, longitudinal strips along the rostro-caudal axis. Later, the paraxial mesoderm begins to undergo segmentation resulting in the formation of the somites. The *somite* formation occurs first in the rostral end and then progresses sequentially caudally. The rate of formation of the somites has been estimated to be one pair every three hours. Initially, a cavity known as the *somitocele* (Fig. 2) is present within the somite which later disappears as the somites mature.

Each somite differentiates into a ventro-medial part known as the *sclerotome* and a dorso-lateral part known as the *dermo-myotome* (Fig. 3).[2,16,17] The dermo-myotome then forms the dermatome (forms dermis) and the myotome (forms muscle). The myotome differentiates to form two components, dorsally the epimere and ventrally the *hypomere*. The epimere gives rise to the epaxial muscles (dorsal skeletal muscles) and the hypomere gives rise to the hypaxial muscles (ventral skeletal muscles and the limb muscles) as shown in Figure 4.

During the 4th week the polymorphous cells of the sclerotome migrate ventro-medially around the notochord and form the rudiment of the centrum of the blastemal vertebra. Thereafter, the cells extend dorsally around the developing neural tube. These bilateral dorsal extensions meet in the midline dorsally to form the neural arch. The mesenchyme that intervenes between adjacent somites is related on either side to an intersegmental artery. Subsequently, each sclerotome is divided by a horizontal fissure known as the *sclerotomic fissure* (also known as von Ebner's fissure) into a less dense cranial half and a more dense caudal half (Fig. 5). The caudal half of one sclerotomic segment fuses with the cranial half of the subsequent sclerotomic segment to form the definitive centrum of the vertebra. The sclerotomic fissure and the mesenchymal condensation around it form the *perichordal disc* which persists into adult life as the *intervertebral disc* (Fig. 6). The nucleus pulposus of the intervetebral disc is notochordal in origin whereas the annulus fibrosus is mesenchymal in origin. The neural arches are related to that part of the centrum, which is derived from the cephalic part of the sclerotome. Thus, the vertebral body is derived from two adjacent sclerotomes. Close to the neural arch, each centrum gives rise to a costal element that extends laterally through the segmental myotomes.

The boundary of the head and neck corresponds to the boundary between the 5th and 6th somites. The first true somite disappears and somites 2–5 (known as occipital somites 1–4) fuse to form the basioccipital bone. The vertebrae are formed from the 6th somite onwards caudally. C1 (atlas) is formed by the fusion of the caudal half of the occipital somite 4 with the cranial half of the cervical somite 1. The shift of the somite number accounts for the production of seven cervical vertebrae from eight cervical somites.[17] The 1st to 28th pair of

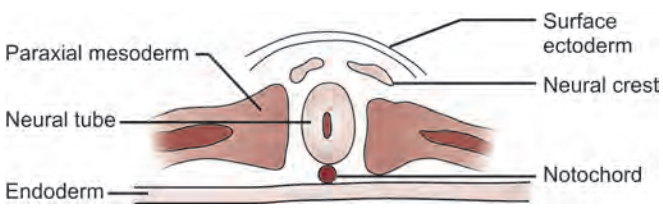

Fig. 1: Schematic representation of the development of the paraxial mesoderm and its relationship to the notochord and the developing neural tube

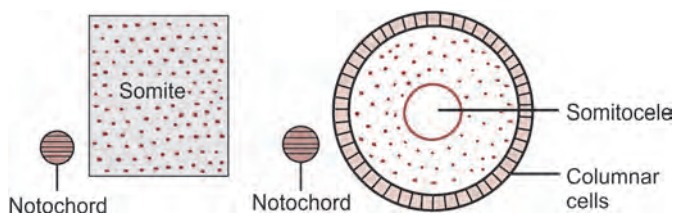

Fig. 2: Schematic representation of the development of the somite and its relationship to the notochord

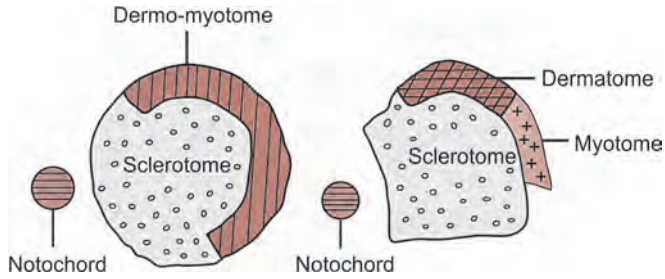

Fig. 3: Schematic representation of the differentiation of the somite into the ventromedial part, sclerotome, and the dorsomedial part (dermo-myotome) and further differentiation of the dermo-myotome into dermatome and myotome

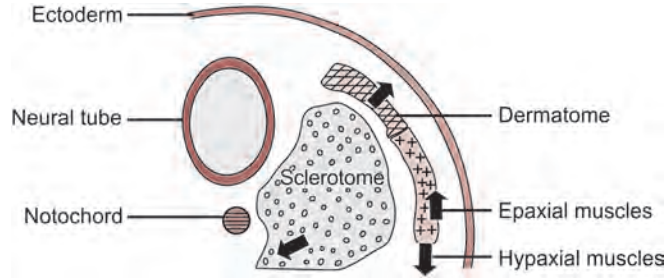

Fig. 4: Schematic representation of the migration of the different components of the somite to form the vertebra and its associated musculature. The sclerotomal cells migrate to surround the notochord and the neural tube to form the vertebra. The myotome differentiates into the epimere, which gives rise to the epaxial muscles and the hypomere, which gives rise to the hypaxial muscles

somites is formed from the primitive streak by a process known as *primary gastrulation*. All the other caudal somites are formed from the tail bud by a process known as *secondary gastrulation*. It is believed that in humans, the boundary between primary and secondary gastrulation lies at the level of the 5th lumbar vertebra.

During the 6th week, chondrification starts in the membranous vertebra. Two cartilaginous centres appear in the centrum and fuse to form a single mass. Each neural arch is chondrified from one centre and fuses later with the centrum. Ossification begins in the 7th week. The vertebra is ossified from three primary centres and five secondary ossification centres. There is one primary centre for the centrum and one centre each for the neural arch. At puberty, five secondary ossification centres appear; one for the spinous process, one each for the transverse processes, two ring-like epiphyseal centres for the upper and lower surfaces of the centrum.

Regional Variations in the Development of the Vertebral Column

Cervical

The costal elements of the upper three cervical vertebrae are connected to each other in front of the corresponding centrum by bands of mesenchymal condensation. Later, this mesenchymal condensation persists only in the first cervical vertebra and forms the *hypochordal bow*, which

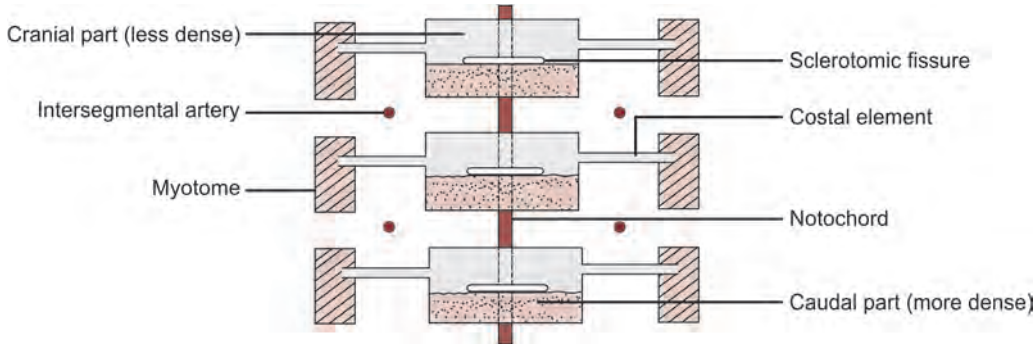

Fig. 5: Schematic representation of the division of the sclerotome, into cranial and caudal halves, by the sclerotomic fissure and the relationship of the sclerotome to the intersegmental artery and the developing myotome

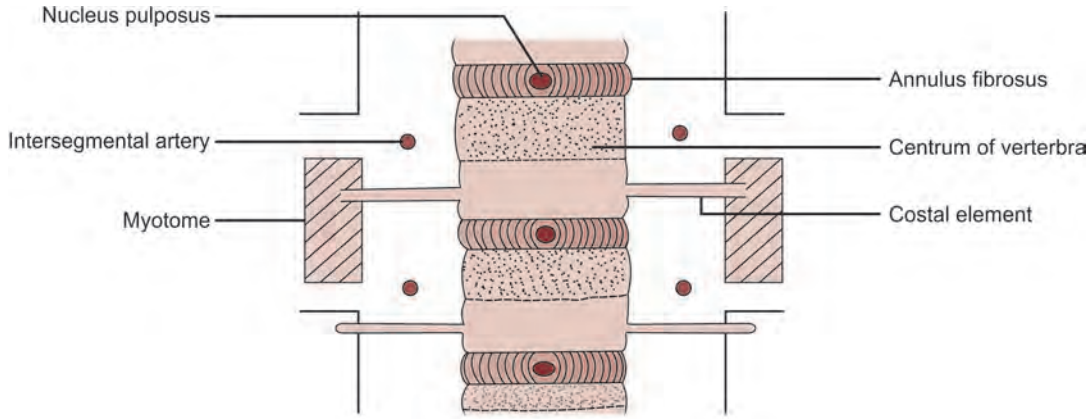

Fig. 6: Schematic representation of the development of the vertebra and the intervertebral disc

later gives rise to the anterior arch of atlas.[4] The centrum of the atlas is detached from the anterior arch and fuses with the centrum of the axis and forms the odontoid process or dens. In the cervical region, the costal element and the transverse elements of the developing vertebra are fused around the foramen transversarium. The costal element is represented by the anterior root, anterior tubercle and costo-transverse bar. The transverse element is represented by the posterior root and the posterior tubercle. In the cervical vertebrae, the distal portions of the costal elements do not develop. However, occasionally, when the distal portion of the costal process develops in the seventh cervical vertebra, it results in the formation of a cervical rib.

Thoracic

In the thoracic region, the costal elements form the ribs. As the ribs grow outwards through the segmental myotomes, they form the costal arches. The ventral end of the upper seven or eight arches unites to form the sternal plates. Finally, the sternal plates fuse in the midline to form the sternum.

Lumbar

The transverse processes of the lumbar vertebrae are formed from the costal elements and the true transverse elements are represented by the mamillary and accessory tubercles.

Sacrum

In the upper sacral vertebrae, the costal and transverse elements are fused to form the lateral mass of the sacrum. The anterior two-thirds of the lateral mass are derived from the costal elements and the posterior one-third from the transverse elements. The lateral surface of the lateral mass of the sacrum bears an articular surface through which it articulates with the ileum.

Molecular Basis of Vertebral Column Development

The authors of recent molecular studies have elucidated the genetic specification of the mammalian body plan, including, the axial skeleton. They have identified a number of developmental control genes and their role in segmentation. It is imperative for a contemporary clinician to be aware of the molecular and genetic perspectives of development so that he/she can integrate the modern molecular knowledge with problems of clinical dysmorphology as future developments in molecular biology may lead to genetic/molecular manipulations to treat many neurological illnesses.

It has been shown experimentally that the somites, and even the unsegmented paraxial mesoderm, are already skeletogenically predetermined with respect to morphological features characteristic of their axial level. For example, it has been shown experimentally that thoracic somites that are heterotopically grafted to the cervical region give rise to ribs in the host embryos. Consequently, the developmental fate of the sclerotomal cells must be specified long before the identity of the individual vertebral segment is morphologically apparent. This morphogenetic specification of the vertebral phenotype is controlled by a number of genes. These genes involved in embryogenesis encode a set of instructions or rules of assembly. Implementation of these one-dimensional rules via gene expression and protein interaction produces the three-dimensional structure, viz. the vertebral column.

Hox Genes

These are also known as *homeobox genes*. These genes were originally identified in the fruit fly, *Drosophila melanogaster*. Hox genes encode transcription factors which act as regulators of downstream gene activity and are characterised by a highly conserved 180-base pair sequence called the *homeobox*. The homeobox encodes a 60-amino acid helix-loop-helix DNA motif within the encoded transcription factors. The Hox genes play a fundamental role in the establishment of the body plan, including specification of the axial skeleton.[5,6,16,17] All vertebrates, including human beings, contain 39 Hox genes that are distributed on four linkage groups or clusters designated as Hox A, B, C, and D on chromosomes 6, 11, 15 and 2 respectively (Fig. 7). One of the interesting features of these genes is that the linear order of each gene, from the 3′ end to the 5′ end, is the same as its expression, along the cephalocaudal axis of the embryo, a feature referred to as *collinearity*. Those at the 3′ end have a more rostral expression and those at the 5′ end have a more caudal expression. In addition, those at the 3′ end are expressed earlier than those at the 5′ end. Thus, there is both a spatial and temporal pattern of expression of the Hox genes. The Hox genes are numbered sequentially from 1 onwards, with 1 corresponding to a cephalic gene and 13 a more caudally located gene. Hox A-6, Hox B-6, Hox C-6, and Hox D-6 are located at the same relative positions in their respective clusters and are referred to as a paralogous group.[17]

Hox Codes

Hox genes are expressed in developing ectodermal structures, such as the rhombomeres and neural crest, and in a wide variety of mesodermally derived organs, such as the somites, heart, kidney, testis, etc., but not in any endodermally derived structures.[5,16,17] The striking feature of Hox genes is that they have overlapping expression domains, but with clear cut cephalic boundaries. Thus, at any point along the cephalocaudal axis of the embryo, cells of the central nervous system (CNS) and paraxial mesenchyme (which later form the somites) have a characteristic complement of gene expression. This complement of Hox gene is believed to form the Hox code that specifies the position along the cephalocaudal axis.

Hox genes are necessary to establish the correct positional specification within the craniocaudal sequence of

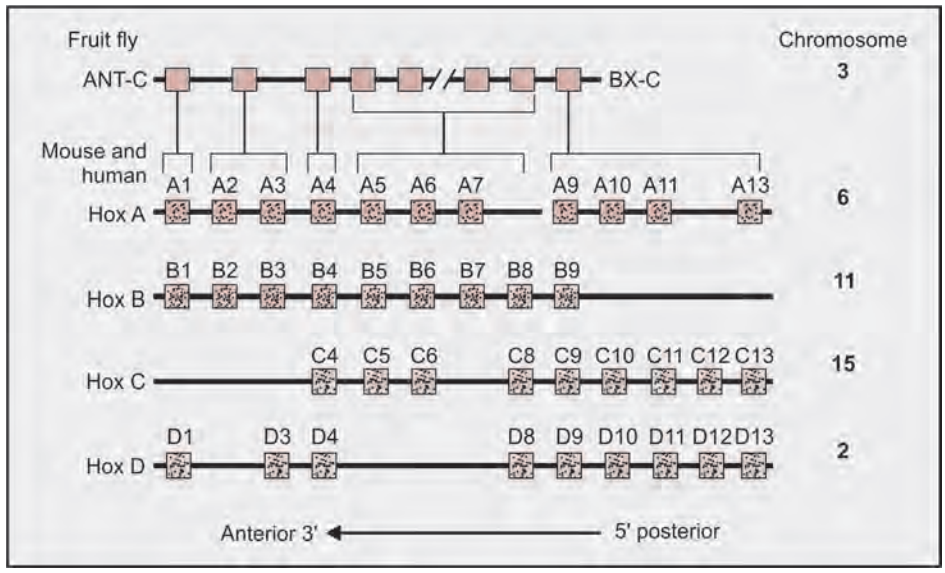

Fig. 7: Diagram representing the chromosomal organisation of Hox genes in the mouse and human and their derivation from the ancestral complex equivalent to that found in the fruit fly: 1. There are four clusters (A,B,C,D) on different chromosomes; 2. There are four paralogous groups defined vertically across the clusters and consisting of up to four genes, each on a different chromosome; 3. The expression of the genes along the craniocaudal axis of the embryo maps in a 1:1 fashion, those in the 3′ end are expressed cranially and earlier than those in the 5′ end which are expressed more caudally and later, thus the expression of these genes has a spatial and temporal pattern (Adapted from Neurosurgical Focus. 1999;6(6):Article 1.)

somites. The axial expression of Hox genes follows a general principle: the more 3′ the position of a gene in the chromosomal cluster, the more anterior is its boundary of expression in the neural tube and prevertebrae. Mutations in the Hox genes, and teratogen-induced disturbance of Hox gene expression, can both cause alterations of the number and identity of the vertebrae that form at or near the anterior limit of their expression domain. For example, in experimental studies, it has been shown that inactivation of homeobox-containing gene HoxD3 results in mutant mice in which the atlas assimilates into the basiocciput. Thus, by losing the function of a Hox gene, the first cervical vertebra is transformed into a more rostral identity, which is termed as "*anterior homeotic transformation*".[5] Conversely, extension of an expression domain rostrally can transform structures into a more caudal identity, a phenomenon known as "*posterior homeotic transformation*". The common form of craniovertebral junction anomaly, assimilation of atlas, is believed to be a form of anterior homeotic transformation.

Pax Genes

These are also known as "*paired-box*" genes.[5] These genes possess a phylogenetically well-conserved DNA sequence called the paired-box. The Pax genes also encode DNA-binding domains, which is a typical feature of a regulatory protein. This family of Pax genes contains nine genes divided into four classes that are widely dispersed around the genome and are not clustered (unlike the Hox genes). Mutations in Pax genes are believed to be responsible for some major birth defects in humans. Two genes, Pax-1 and Pax-9, control segmentation of the somites and sclerotomes to establish intervertebral boundaries. In particular, the Pax-1 gene has been found to be pivotal in the reorganisation of the sclerotome.

Initially, the Pax-1 involved in the primary segmentation of the paraxial mesoderm into somites. Subsequently, a peptide signal encoded by *Sonic hedgehog gene* (Shh gene), emanating from the notochord and the ventral floor plate of the neural tube, acts on the somites to induce sclerotomal differentiation (Fig. 8). The sclerotome itself then differentially expresses Pax-1, with expression ventrally reflecting the dorsoventral specification of each vertebra.[5,16] Within this ventral expression domain of the sclerotomes, much more intense expression is demonstrated at those axial levels at which the intervertebral discs will form, and this appears to function in the resegmentation of the vertebrae. Thus, the Pax-1 gene acts like a "*resegmentation gene*".[5] Impaired or reduced expression of Pax-1 gene will result in local or widespread fusion between the sclerotomal primordia. The perturbations in the expression of Pax-1 gene may be due to mutations or may be due to non-genetic causes like teratogens. Irrespective of the cause, impaired expression of the Pax-1 gene results in vertebral fusions, the localisation and extent of the congential anomaly along the craniocaudal axis reflecting the timing and duration of the teratogenic insult.[5]

Sonic Hedgehog Gene

The Sonic hedgehog gene acts as a signalling switch that is used in differentiating subpopulations of cells throughout the embryo.[5,16] Its actions will vary depending upon where the signal is being secreted, how far away the responsive cell population is and how Shh is proteolytically cleaved. Shh acts by binding to the

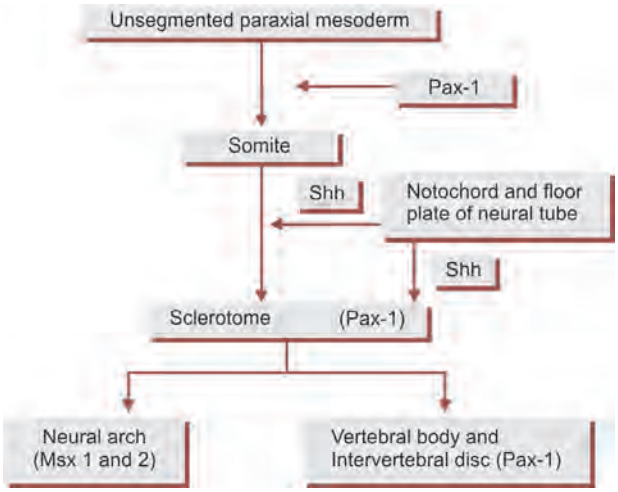

Fig. 8: Schematic representation of the cell-signalling events necessary to build a vertebral body. Initially, expression of a regulatory gene, Pax-1, is involved in primary segmentation of the paraxial mesoderm. Subsequently, a peptide signal encoded by the Sonic hedgehog gene (Shh), emanating from the notochord and the ventral floor plate of the neural tube, acts on the somite to induce sclerotomal differentiation. The sclerotome itself then differentially expresses Pax-1, with expression ventrally reflecting the dorsoventral specification of each vertebra. The formation of the neural arch is under the influence of Msx1 and Msx2 genes which are expressed under the influence of BMP-4 signals emanating from the surface ectoderm and the roof plate of the neural tube (Adapted and modified from Neurosurgical Focus. 1999;6:(6):Article 1.)

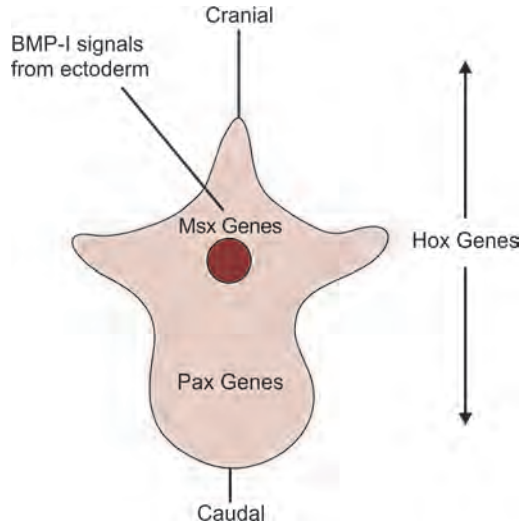

Fig. 9: Schematic representation of the genetic events controlling the development of the vertebral column. The rostrocaudal differentiation of the vertebral column is under the influence of Hox genes. The dorsoventral differentiation of each vertebra is under the influence of Pax and Msx genes (Refer text for further details)

membrane receptor patched (ptc). As mentioned in the preceding paragraphs, Shh signals emanating from the notochord and floor plate of the nerual tube act on the somites to induce sclerotomal differentiation. The Shh gene is strongly expressed in the primitive node, suggesting that this gene plays a key role in gastrulation. Additionally, the Shh gene is expressed in a left-right asymmetric pattern during gastrulation, which makes it a candidate agent that normally establishes left-right differences. Thus, during gastrulation, Shh is at first uniformly expressed in the primitive node and the primitive streak. Later, another gene known as "*Activin receptor IIa*" is expressed in the right half of the primitive node and this restricts Shh expression.[16] Activin receptor IIa gene activates other downstream genes which become localised to the mesoderm on the right side of the primitive node and streak. The Shh, which is now restricted to only the left side of the node acts on the other genes also, which are known as *nodal* and *lefty* which become lateralised to the mesoderm on the left side.[16] Faulty signalling by the Shh across the embryonic midline may be responsible for the split vertebral bodies or hemivertebrae that are often encountered in clinical practice.[5]

Msx1 and Msx2

These genes are expressed by the sclerotomal cells that migrate dorsally around the neural tube to form the neural arch. The expression of these genes is controlled by the roof plate of the neural tube and the surface ectoderm via *BMP4 signals* [Bone Morphogenic Protein (BMP)].[5,16] In experimental studies, it has been shown that interruption of the function of these genes results in spina bifida.

The development of the vertebral column is a consequence of a balance between proliferation, apoptosis and differentiation of cells. Sclerotomal differentiation is positively regulated by signals from the notochord, the neural tube and the myotome. Chondrogenic differentiation of the ventral mesoderm also requires inductive signals from the notochord. The function of different gene families is controlled by signals from adjacent structures. The very complex network regulating diverse events of vertebral column development is not fully understood. However, a brief summary of the genetic control of vertebral column development is diagrammatically represented in Figure 9. Clinical classification of vertebral anomalies and scoliosis is shown in Figure 10. Table 1 summarises the genes involved in congenital vertebral disorders.

Development of the Skull

The skull has two distinct portions: the one which surrounds the brain and organs of special senses, viz. the *neurocranium* and that which forms the lower face and jaws, viz. the *viscerocranium*. The neurocranium consists of vault of the skull and the base of the skull. The vault of the skull is *membranous* in origin and the base is *cartilaginous* in origin.[3,4,17]

Vault of the Skull

The membranous neurocranium which goes to form the cranial vault is mesenchymal in origin. This mesenchyme is derived from the neural crest.[7] All the sutures

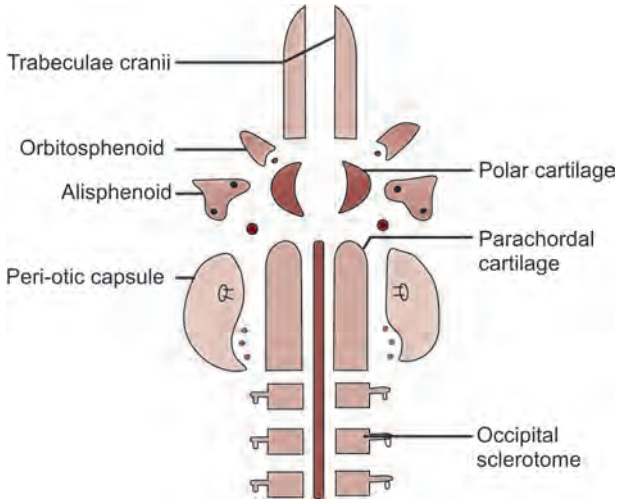

Fig. 10: Clinical classification of vertebral anomalies and scoliosis proposed by International Consortium for Vertebral Anomalies and Scoliosis (ICVAS)[17]

of the calvarial bones are also derived from the neural crest.[7,11] The bones that go to form the cranial vault are sometimes referred to as dermal bones. These include the frontal bones, the parietals, the squamous parts of the temporal bones and the upper (interparietal) part of the occipital squama. These bones first appear at about the 30th day of gestation when they begin to form curved plates of mesenchyme at the sides of the developing brain and gradually extend cranially to blend with each other. They also extend towards and reach the base of the skull. The bones of the cranial vault are formed by a wave of osteodifferentiation moving radially from ossification centres within the desmocranial mesenchyme.[17] When the adjacent bones meet, proliferation of the osteogenic front ceases and sutures are induced to form. Once sutures are formed and the fibrous desmocranium is replaced by mineralized bone, a second phase of development occurs in which growth of the cranial bones occurs at the sutural margins. Growth of the calvarial bones is closely related to the development of the dura mater. It has been shown in experimental studies, that when the sutures are transplanted with intact dura, it results in a continuous fibrous suture between developing vault bones, whereas in transplants in which dura mater is removed bony fusion occurs.

Base of the Skull

With the exception of the orbital plate of the frontal bone and the lateral parts of the greater wings of the sphenoid which are membranous in origin, the rest of the base of the skull is preformed in cartilage. Thus, the bones of the base of the skull that are preformed in cartilage include: the occipital (except the interparietal part), the petromastoid part of the temporal, the body, lesser wings and the roots of the greater wings of sphenoid, and the ethmoid.

The formation of the cartilaginous base of the skull occurs in three main regions, viz. caudally, in relation to the notochord known as the *parachordal cartilage*, intermediately, in relation to the hypophysis known as the hypophyseal cartilage and rostrally, between the orbits and nasal cavities and known as the *interorbitonasal cartilage*.

The parachordal cartilage (Fig. 11) is developed from the paraxial mesenchyme related to the cranial end of the notochord and the first five (occipital) somites. The cephalic part of the notochord extends up to the future dorsum sellae of the sphenoid bone. The parachordal

Table 1: Congenital vertebral disorders and the genes involved as per Giampietal et al.[6]

Disorder	*Predominant vertebral disorders*	*Genes*
Spondylocostal dysostosis	• Loss of normal vertebral morphology throughout the entire spine	• Delta-like 1 (DLL3)
	• Non-progressive scoliosis	• Mesoderm posterior 2 (MESP2)
	• Symmetric thoracic cage	• Lunatic fringe (LFNG)
Spondylothoracic dysostosis	• Fusion of all ribs at the costovertebral junctions bilaterally	• MESP2
	• Vertebral segmentation and formation defects	• E103X
Alagille syndrome	• Butterfly vertebral anomalies (errors in somitogenesis)	• JAG1 • NOTCH2
Congenital scoliosis	• Fused vertebrae	• DLL3
	• Vertebral body formation defects like hemivertebrae and mixed defects	• CHD7
Split cord malformations	• Spina bifida	• MTHFR gene • VANGL1 gene
Klippel-Feil syndrome	• KF1-C1 fusion is the most rostral	• KF1: Autosomal recessive
	• KF2-C2-C3 fusion is dominant and most rostral	• KF2: Autosomal dominant
	• KF3-C3 (C2-3 or C3-4) most rostral fusion. Isolated fusions	• KF3: Autosomal recessive and autosomal dominant
	• KF4-Wildervanck syndrome	• KF4: X-linked dominant

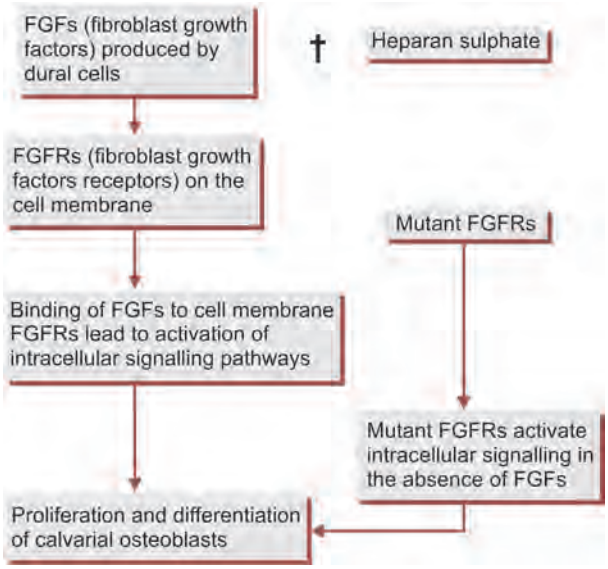

Fig. 11: Schematic representation of the development of the base of the skull

cartilages are paired structures that subsequently unite to form the *basal plate*. The basal plate is continuous behind with the four occipital sclerotomes. The centres of the sclerotomes fuse to form the *basiocciput*; the rudimentary transverse processes unite to form the ex-occiput which persists as the jugular processes; the laminae of the sclerotomes meet behind forming the foramen magnum and continue further upwards as the supra-occiput which forms the lower part of the occipital squama. The hypoglossal nerve, the nerve of the occipital myotomes, passes through the occipital bone; this canal is sometimes divided by a bony spicule and represents the fused intervertebral foramina of the occipital sclerotomes. On each side of the basal plate a cartilaginous *periotic capsule* envelops the membranous otocyst. Each capsule is perforated medially by the facial and the vestibulocochlear nerves. The otic capsule is separated from the cranial-most occipital sclerotome by a space which forms the *jugular foramen* for the transmission of the glossopharyngeal, vagus and accessory nerves. The periotic capsule is later ossified to form the petromastoid part of the temporal bone. It is notable that the region of fusion between the rostral part of the occipital bones and the portion of the parachordal plate that is of somitomeric origin corresponds to the spheno-occipital synchondrosis that is the site of growth until 20 years of age.

The *hypophyseal cartilage* ossifies to form the postsphenoid part of the sphenoid bone. It is derived from the paraxial mesenchyme and the neural crest. The paraxial mesenchyme contributes to the caudal part of the sella turcica, whereas the neural crest forms the more rostral portion of the sella turcica. A pair of *polar cartilages* appears by the side of the developing hypophysis cerebri, and encircle the developing pituitary gland in front of and behind the stalk. The fused mass thus forms the posterior part of the body of the sphenoid bone. The polar cartilages are continuous behind with the parachordal cartilages at the basiocciput. A pair of cartilaginous elements, known as, *alisphenoids* develop on either side of the polar cartilages. The alisphenoids form the greater wing of the sphenoid bone, and is perforated by the maxillary and the mandibular divisions of the trigeminal nerve.

The *interorbitonasal cartilage* (also known as the trabecular cartilage) is a bilateral structure with two separate centres of chondrification. It is of neural crest origin. At the rostral end of the developing base of the skull, a cartilaginous plate known as the *trabeculae cranii*, appears in the median plane and gives rise to the cribriform plate of the ethmoid bone. The trabecula is continuous behind with the fused polar cartilages. A *nasal capsule* is formed by the chondrification around the olfactory placode. The nasal capsules give rise to the labyrinth of the ethmoid bone and most of the nasal septum. Lateral to the trabeculae cranii, a cartilaginous element known as the *orbitosphenoid* develops on each side. The orbitosphenoid grows medially around the optic nerves and fuses with the polar cartilage to form the lesser wing of the sphenoid bone, and is separated from the alisphenoid (from which the greater wings of sphenoid bone develop) by the superior orbital fissure.

The development of the base of the skull (chondrocranium) is summarised in Table 2. The ossification of the chondrocranium starts during foetal life continues after birth and is completed after puberty.

Molecular Biology of Skull Development

Rapid advances in molecular biology in the last decade have uncovered some of the clues to the complex molecular mechanisms underlying normal and abnormal formation of the cranial bones and sutures. An understanding of these molecular mechanisms may eventually lead to manipulations of the molecular milieu by modifying specific gene activities or signalling pathways thereby altering the growth of the craniofacial skeleton. This also has important implications for understanding the various craniosynostosis syndromes and their treatment.

Table 2: Development of the base of the skull (chondrocranium)

Embryonic primordium	*Post-natal structure*
Trabeculae cranii	Cribriform plate of ethmoid
Orbitosphenoid	Lesser wing of sphenoid
Fused polar cartilage	Body of sphenoid
Alisphenoid	Greater wing of sphenoid
Basal plate (fused parachordal cartilages) and fused centra of the occipital sclerotomes	Clivus
Peri-otic capsule	Petromastoid part of temporal bone
Fused laminae of the occipital sclerotomes	Lower part of the occipital squama

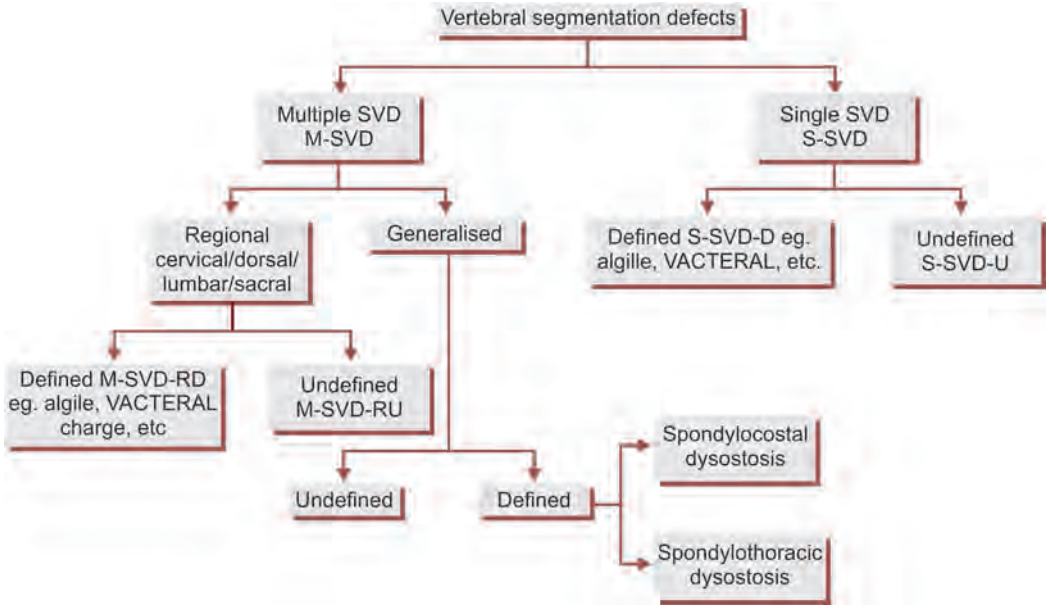

Fig. 12: Schematic representation of the mode of action of fibroblast growth factor (FGF) signalling mediated by normal and mutant fibroblast growth factor receptors (FGFRs) in calvarial osteoblasts. FGFRs consist of extracellular ligand-binding, transmembrane, and intracellular kinase domains. Upon binding to the FGF and heparin sulphate complex, normal FGFRs activate intracellular kinase domains and the resultant intracellular signalling leads to proliferation and differentiation of calvarial osteoblasts. However, mutant FGFRs activate the intracellular kinase domains even in the absence of FGFs thereby activating the intracellular signalling pathways and resulting in the proliferation and differentiation of calvarial osteoblasts

Fibroblast Growth Factor Receptors

Fibroblast Growth Factor Receptors (FGFRs) are cell surface receptors for fibroblast growth factors (FGFs), which elicit a variety of cellular functions in different cell types, including cell proliferation, differentiation, migration, and pattern formation. FGFRs belong to a family of proteins known as transmembrane tyrosine kinases.[1,8] So far, four FGFRs (FGFR 1-4) have been identified. They all have an extracellular ligand-binding domain, a transmembrane domain, and an intracellular kinase domain (Fig. 12). These receptors differ in their ligand specificity and tissue distribution. For example, in calvarial bone, FGFR1 is mainly expressed in differentiated osteoblasts, while FGFR2 is expressed in preosteoblasts. On the other hand, FGFR3 is mostly found in cartilaginous tissues, and FGFR4 expression has not been identified thus far in craniofacial bones. The principle function of FGFRs is to transduce extracellular FGF signals to the intracellular compartment, where a cascade of specific biochemical events lead to activation or repression of target genes and proteins. Ultimately, cellular behaviour, such as proliferation and differentiation, is modified. It is now believed that signals generated by FGFs that are synthesised by dural cells regulate suture development via the FGFRs present in the advancing osteogenic front (Fig. 12).

The importance of FGFR function in normal suture development is amply demonstrated in molecular genetic studies of craniosynostosis syndromes associated with FGFR mutations. Mutations of FGFR genes lead to activation of FGFRs in the absence of FGF thus initiating an intracellular signalling pathway (Fig. 12). For example, it has been shown that in Apert's syndrome, mutations of the FGFR2 have an effect on the phenotype of the calvarial bone cell. In patients with Apert's syndrome, there is accelerated ossification and increased thickness of subperiosteal bone compared to normal calvarial bone. Thus, it can be concluded that FGFR2 mutation is the reason for increased osteogenic activity in the cells at the calvarial bony margins that leads to premature suture closure.[10]

Msx Genes

The Msx genes belong to a family of homeobox containing genes. The exact role of Msx genes in skull bone and suture development has not been fully elucidated. Similar to other homeobox containing genes, it plays an important role in pattern formation in the developing embryo. It is also involved in other important developmental events, such as programmed cell death (apoptosis) and tissue interaction. Therefore, it is believed that Msx2 gene product might influence suture development by altering the apoptotic rate in suture cells or by interaction between sutures and adjacent tissues or both. The homeobox domain of the Msx2 is believed to bind to specific DNA sequences of specific target genes and determine if and when they should be expressed, e.g. in Boston-type craniosynostosis, the mutation of Msx2 gene leads to the mutant Msx2 to stay bound to the target genes for a prolonged period, resulting in enhanced Msx2 activity in cells. Therefore, gain of function of Msx2 could be the underlying molecular basis of Boston-type craniosynostosis. Members of the Msx gene family (Msx1 and Msx2) are normally strongly

expressed in the neural crest derived mesenchyme of the developing facial prominences, and there is now strong evidence for a role of these genes in the specification of the skull and face. In experimental studies, targeted disruption of Msx1 gene function produces a number of defects in facial structures and mutations of Msx2 produce defects in skull ossification with persistence of calvarial foramina.

TWIST Gene

The protein product of the TWIST gene is a transcription factor.[1] The TWIST gene regulates the expression of a number of genes by binding to regulatory regions of the target genes. It is expressed in a wide variety of embryonic tissues and in the neonatal calvarial osteoblasts. Mutations in the TWIST gene are responsible for the Saethre-Chotzen syndrome (SCS), a form of autosomal dominant craniosynostosis. TWIST genes are also believed to act as upstream regulators of FGFRs.

Transforming Growth Factors (TGFs)

Transforming growth factor-beta (TGF-β), 1 to 3 belong to a family of related heparin-binding peptides.[1] They are involved in diverse biological activities in normal growth and development of various organs, including regulation of osteoblast and chondrocyte differentiation, proliferation and matrix gene expression. These activities are mediated by high affinity receptors that are associated with intracellular signalling. Experimental studies have shown the importance of TGF-β in suture formation. Expression of TGF-β1 and β2 is shown in association with obliterating sutures, while increased expression of TGF-β3 is found in non-fusing sutures. All the three isoforms of TGF-β are expressed in the dura mater. Recent studies have shown that the different isoforms of TGF-β might determine calvarial bone growth at the sutures as well as their patency.

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14 Embryology: Brain and Spinal Cord

Muthukumar N

INTRODUCTION

Neurosurgeons are often confronted by embryological development gone awry in the form of various congenital malformations of the nervous system. A working knowledge of the normal embryogenesis is essential to understand the complexities of various congenital malformations. This chapter reviews the normal processes occurring in the development of the central nervous system and the developments in this field, especially, the developments in molecular biology as applied to embryology.

For the purposes of clarity, the development of structures during normal embryogenesis of the nervous system is described in series; in reality, the formation of these structures is concurrent.

DEVELOPMENT OF THE CENTRAL NERVOUS SYSTEM

The Embryonic Disc

The union of the sperm and the egg creates the single-celled zygote and subsequent repeated divisions form the 12-cell morula to 16-cell morula, which enters the uterus. A cavitation within the morula creates two cellular groups, the outer trophoblast, which contributes to the formation of the placenta and a group of centrally located cells, the internal cell mass, which gives rise to the embryo. At 7–12 days of development, this structure, now called the blastocyst implants into the uterine wall. With further development, the internal cell mass separates from the overlying trophoblast to create a slit-like amniotic cavity, which progressively enlarges and ultimately contains the embryo. Simultaneously, the internal cell mass becomes the flattened and circular embryonic disc with two layers, the bilaminar embryo (Fig. 1). The outer layer adjacent to the amniotic cavity is called the epiblast, which gives rise to all or nearly all the cells of the embryo. The inner layer adjacent to the yolk sac is called the hypoblast and does not contribute to embryonic development.

At 13–15 days of development, the hypoblastic cells near the future rostral end of the embryo form a thickened circular area called the prochordal plate (future site of the mouth) and in the caudal end, the cloacal membrane (future site of anus). In both these regions, the outer and inner layers of the embryo are fused. The prochordal plate is important because it is an organiser of the head region. At these two areas where the bilaminar disc is fused, the interposition of the mesoderm, which takes place during the next stage, is limited.

Gastrulation and the Trilaminar Embryonic Disc

Gastrulation is the process by which the bilaminar embryonic disc is converted into a trilaminar embryonic disc by the interposition of a mesoblastic layer between the epiblast and hypoblast. At about 15 days of development, a linear thickening called the primitive streak appears in the caudal midline of the embryo. The primitive streak is limited caudally by the cloacal membrane. Progressively, the primitive streak increases in length and a thickening forms at the rostral end of the primitive streak known as the primitive knot or Hensen's node (Fig. 2). A longitudinal groove then appears in the primitive streak and deepens at the level of the Hensen's node to form the primitive pit. Cells from the epiblast migrate into the primitive streak and groove, separate from the epiblast and migrate rostrally between the epiblast and hypoblast to form the mesoblast, thus creating the earliest stage of the trilaminar embryo. The epiblast (ectoderm) is destined to form the CNS (neurectoderm) and the epidermis (cutaneous ectoderm); the mesoblast

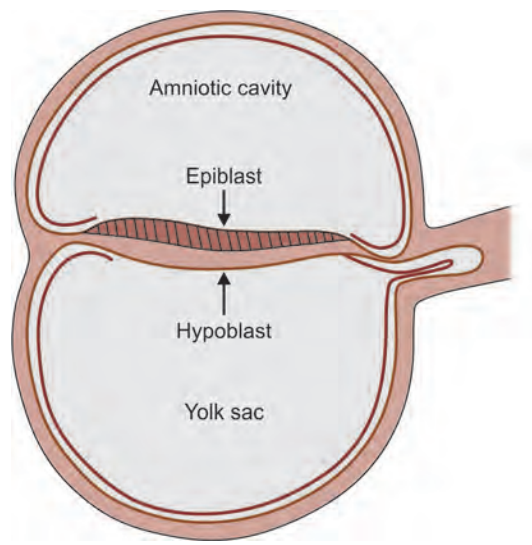


Fig. 1: Schematic representation of the bilaminar embryonic disc with the epiblast related to the amniotic cavity and the hypoblast related to the yolk sac

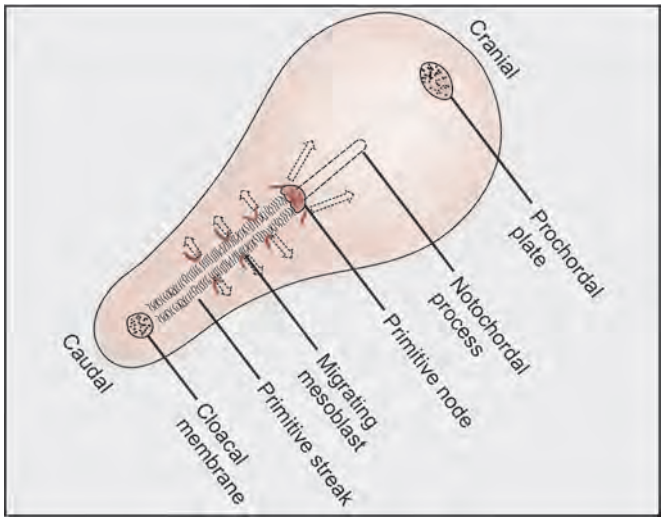
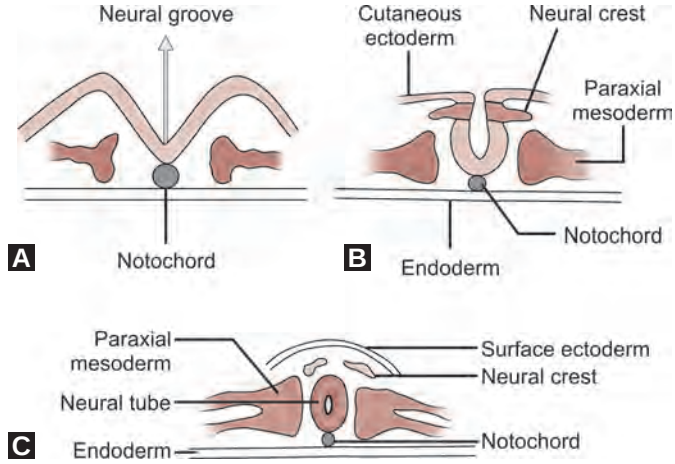


Fig. 2: Schematic representation of the embryonic disc at the commencement of gastrulation. Cells from the epiblast migrate into the primitive streak and pass between the epiblast and hypoblast. Formation of the notochord is also seen

(mesoderm) forms the skeleton, striated and smooth muscles, connective tissues, blood vessels, blood cells and bone marrow and the reproductive and excretory organs. The hypoblast (endoderm) is the source of the epithelial linings of the respiratory and digestive tracts and glandular cells of the liver and pancreas. The primitive streak is the source of the intraembryonic mesoderm until approximately the 4th week of development, and then it rapidly regresses in size and disappears. During its functional lifetime, the embryo increases in length 5-fold, by the complex development of the embryo rostral to the primitive streak.

Development of the Notochord

At about 16–17 days of development, some of the mesoblastic cells migrate in the midline rostral to the Hensen's node between the ectoderm and the endoderm, all the way to the prochordal plate to form a solid rod-like structure known as the notochord. The notochord is represented during life by the nucleus pulposus of the intervertebral disc. However, the notochord is the structure around which the skull and the vertebral column will eventually form and, moreover, during development, the notochord plays an important role as an embryonic inducer, which is important for the formation of the neural plate from which the neural tube develops. Changes in the notochord (to be described below) take place almost concurrently with the changes in the neural tube (also to be discussed later). As the notochord extends cranially towards the prochordal plate, the intraembryonic mesoderm originating from the primitive streak forms two parallel streaks on either side of the developing notochord, to form the paraxial mesoderm (Figs 3A to C). Initially, the notochord remains as a solid cord of cells known as the notochordal process. Subsequently, the primitive pit extends into the notochord and converts



Figs 3A to C: Formation of the neural groove: (A) Notochord. (B) Paraxial mesoderm. (C) Neural crest

the notochord into a tubular structure known as the notochordal canal (Fig. 4). Later, the notochordal canal becomes incorporated with the underlying endoderm by a process known as the intercalation of the notochord (Fig. 5A). During this process, the amniotic cavity is transiently in communication with the yolk sac through the neurenteric canal (Fig. 5B). This neurenteric canal is a transient structure. Subsequently, the notochordal plate, which had become fused with the underlying endoderm once again, forms an infolding to form the notochordal process. This is known as the excalation of the notochord (Fig. 5C). This process of intercalation and excalation of the notochord is the period during which three different types of occult spinal dysraphism are known to develop, viz. neurenteric cyst, split cord malformation, and combined anterior and posterior spina bifida.

Formation of the Neural Tube

The neural tube is the primordium of the brain and the spinal cord. The process by which the neural tube is formed is known as neurulation. Primary neurulation is the process by which the brain and the spinal cord up to L1 level are formed. The portion of the spinal cord

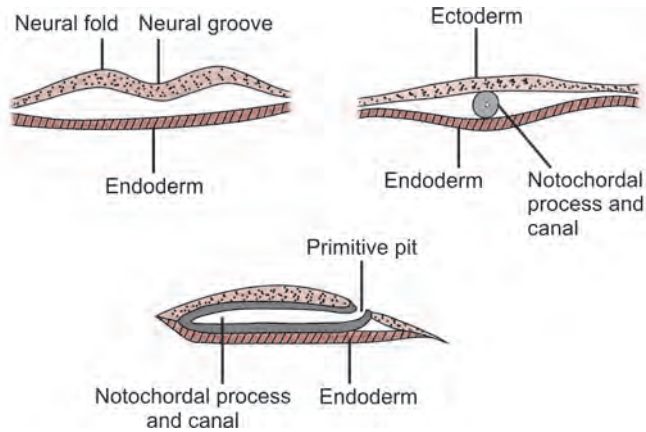
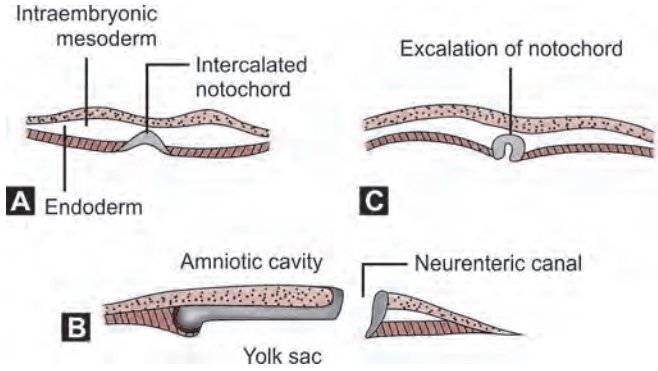


Fig. 4: Schematic representation of the formation of the notochordal process and canal and its relationship to the ectoderm and endoderm



Figs 5A to C: Schematic representation of the (A) Intercalation of notochord. (B) Formation of the neurenteric canal which forms a transient communication between the yolk sac and amniotic cavity. (C) Excalation of the notochord

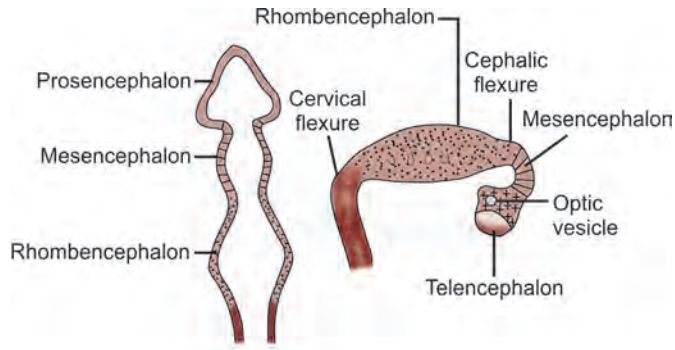


Fig. 6: Schematic representation of the development of the three primary brain vesicles and the formation of the cervical and cephalic flexures

distal to L1 is formed by a process known as secondary neurulation, which involves two stages, viz. canalisation and regression. Disorders of primary neurulation are responsible for the various forms of open dysraphism and disorders of secondary neurulation are responsible for the various forms of closed spinal dysraphism.

Neurulation

As mentioned previously, the notochord is an important embryonic inducer. In response to the notochord, the overlying ectoderm begins to thicken and forms the neural plate. A longitudinal depression develops in the neural plate to form the neural groove, the sides of which are elevated to form the neural folds. The neural folds then fuse in the midline to form the neural tube. With the formation of the neural tube, the cutaneous ectoderm once again becomes continuous in the midline and the neural tube subsequently detaches from the cutaneous ectoderm and comes to lie dorsal to the notochord (Fig. 3). The fully formed neural tube has two openings, the anterior and posterior neuropores, which remain temporarily open at the cephalic and caudal ends of the embryo. Through these openings, the neural tube communicates with the amniotic cavity. The amniotic fluid circulates through the neural tube and provides nourishment to the neural tube. The anterior neuropore closes by the middle of the 4th week at about the 20-somite stage and the posterior neuropore closes by the end of the 4th week at about the 25-somite stage. The position of the anterior neuropore is represented in the adult by the lamina terminalis. The posterior neuropore closes at the level of the spinal cord segments L1 or L2 with a range of error of two segments above or below (T11 or L4).

Development of the Brain

At the time of closure of the anterior neuropore, the rostral end of the neural tube shows three dilatations known as brain vesicles. The three early subdivisions are known as the "prosencephalon" or forebrain, "mesencephalon" or midbrain, and the "rhombencephalon" or hindbrain (Fig. 6). These three vesicles are demarcated by two constrictions between them. The constricted region between the mesencephalon and the rhombencephalon is known as the isthmus. The prosencephalon subsequently is subdivided into two parts: the telencephalon or the cerebral hemispheres and the diencephalon or thalamus. The mesencephalon or the midbrain shows less change during development than the other divisions. The hindbrain vesicle is subdivided into two parts: the "metencephalon" from which develop the pons and the cerebellum; and the "myelencephalon" from which develops the medulla oblongata (Fig. 7). The primitive cavities of the brain vesicles are the forerunners of the ventricular system. The cavities of the telencephalon become the lateral ventricles and the cavity of the diencephalon persists as the third ventricle. The cavity of the mesencephalon becomes progressively narrowed to form the aqueduct of Sylvius and the cavity of the hindbrain becomes the fourth ventricle.

Flexures of the Brain

Two prominent flexures occur in the rostral portion of the neural tube at an early stage. The "cervical flexure" develops at the junction of the rhombencephalon and

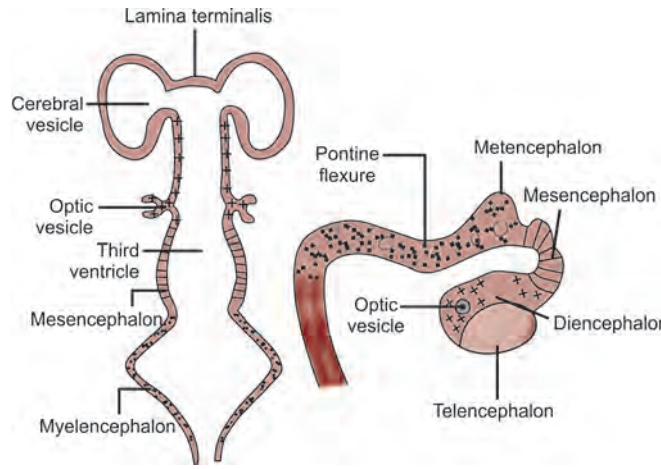


Fig. 7: Schematic representation of the development of the brain vesicles and the formation of the pontine flexure

the spinal cord, with its concavity directed ventrally and the "cephalic flexure" occurs at the junction of the mesencephalon and rhombencephalon (Fig. 6). At about the 6th week of development, a third flexure, known as the "pontine flexure", develops in the rhombencephalon with its concavity directed dorsally and divides the rhombencephalon into two segments, viz. the metencephalon and the myelencephalon (Fig. 7). It is believed that these flexures develop as a result of differences in the rates of cell proliferation and cell movement. At this stage, the developing brain has five different subdivisions: (1) the telencephalon; (2) the diencephalon; (3) the mesencephalon; (4) the metencephalon and (5) the myelencephalon. Each of these five subdivisions undergoes distinct developmental changes. In the following discussion, these developmental changes are considered separately for the purposes of clarity. However, it should be noted that these changes take place simultaneously.

The developing neural tube is divided into a dorsal "alar lamina" and a ventral "basal lamina". The alar lamina is sensory in function and the basal lamina is motor in function, the two being separated by the "sulcus limitans".

The Hindbrain

The development of the pontine flexure with a ventral convexity during the 6th week stretches the roof plate of the hindbrain to form a diamond-shaped outline, as a result of which the alar lamina comes to lie almost in the same plane as the basal lamina, resulting in the rhomboid shape of the fourth ventricle. As a result of these changes, the alar and basal laminae come to occupy the ventral wall of the hindbrain, the former being dorsolateral and the latter ventro-median in position. The portion of the hindbrain in the caudal slope of the pontine flexure is known as the myelencephalon and that in the cranial slope of the flexure is known as the metencephalon.

The basal lamina of both the myelencephalon and metencephalon gives rise to the motor neurons, which are arranged in three elongated but interrupted columns (Fig. 8). They are from medial to lateral:

- the "somatic efferent column" which supplies the striated muscles which are myotomic in origin
- the "branchial or special visceral efferent column" which supplies the muscles derived from the branchial arch
- the general visceral efferent column which provides pre-ganglionic fibres to the parasympathetic ganglia, supply the secreto-motor fibres to various glands and innervate the unstriped muscles of the alimentary and respiratory systems and the heart.

The alar lamina of the hindbrain differentiates into the sensory neurons, which form the following longitudinal, but interrupted columns from lateral to medial:

- the "general visceral afferent column" receives sensations from the viscera

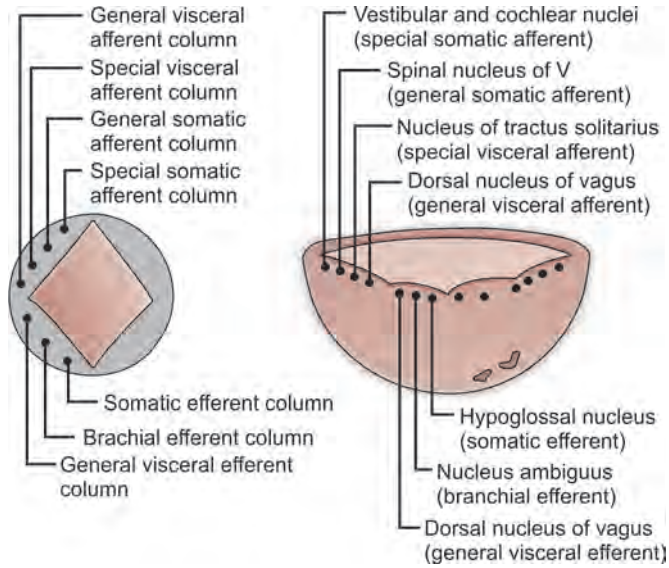


Fig. 8: Schematic representation of the development of the basal and alar laminae of the metencephalon and myelencephalon

- the "special visceral afferent column" receives taste sensations from the tongue, palate, etc.
- the "general somatic afferent column" receives exteroceptive sensations from the face, scalp and external ear
- the "special somatic afferent column" concerned with the sense of hearing and equilibrium.

Myelencephalon

The myelencephalon develops into the medulla oblongata. It extends from the first spinal nerve root of the cervical cord to the beginning of the pontine flexure. It consists of a lower closed part and an open upper part, which forms the caudal part of the floor of the fourth ventricle. Because of the development of the pontine flexure, the roof plate expands and as a result the alar lamina is displaced laterally and comes to lie almost in the same plane as the basal lamina. The sulcus limitans continues to mark the boundary between the alar and basal lamina. Derivatives of the basal lamina form the motor nuclei of the cranial nerves and come to occupy positions in the floor of the fourth ventricle medial to the sulcus limitans. The most medial cell column gives rise to the general somatic efferent fibres that form the hypoglossal nerve. Lateral to this are located the special visceral efferent and general visceral efferent fibres. The special visceral efferent column gives rise to the nucleus ambiguous which contributes fibres to the glossopharyngeal, vagus and accessory nerves to supply the muscles derived from the third, fourth and sixth branchial arches, respectively. The general visceral efferent column, which is also located medial to the sulcus limitans is represented by the dorsal motor nucleus of the vagus and the inferior salivatory nucleus. These supply pre-ganglionic parasympathetic fibres that are widely distributed.

Derivatives of the alar plate form the sensory relay nuclei lateral to the sulcus limitans. The most lateral of these nuclei are the special somatic afferent represented

by the auditory and vestibular nuclei and the general somatic afferent represented by the trigeminal complex. Medial to this group lie the solitary nuclei representing the general and special visceral afferent cell columns. Some cells derived from the alar lamina migrate ventrally to form the inferior olivary complex, which is the largest cerebellar relay nucleus of the medulla. Cortically derived fibres of the medulla come to occupy the ventromedial regions near the midline and form the medullary pyramids.

In the upper portions of the developing myelencephalon, in the region of the fourth ventricle, the roof plate consists of a single layer of ependymal cells covered by a thin layer of piamater. These two layers form the tela choroidea and prolongations of these into the ventricle form the choroid plexus. Openings in the roof plate (foramina Magendie and Luschka) appear by the 4th to the 5th months and, thereby, establish communication between the ventricular system and the subarachnoid space.

Metencephalon

The metencephalon gives rise to the pons and the cerebellum. The pons consists of two parts, viz. a dorsal portion lying in the floor of the fourth ventricle known as the pontine tegmentum and a ventral portion in which some cortical efferent fibres terminate, while others continue to more caudal regions. The pontine tegmentum is derived from the basal plate. The general somatic efferent column is represented by the medially placed nucleus of the abducens nerve. The special visceral efferent column is represented by the motor nuclei of the trigeminal and facial nerves, which supply the muscles of the first and second branchial arches. The general visceral efferent column is represented by the superior salivatory nucleus, which supplies secretomotor fibres to the submandibular, sublingual and the lacrimal glands. In addition, cells of the basal plate also contribute to the pontine reticular formation. Ventromedial portions of the alar plate form cell groups similar to that of the medulla. These cell groups include the special somatic afferent (vestibulocochlear), general somatic afferent (trigeminal) and the special and general visceral afferent (solitary nucleus). The pontine nuclei, which are located in the ventral portions of the pons, are derived from the alar plate.

Development of the Cerebellum

The dorsolateral portions of the alar lamina of the metencephalon form the rhombic lips from which the cerebellum is derived. At first the rhombic lips are widely separated from each other. Later, as the transverse rhombencephalic sulcus deepens at the pontine flexure, the cerebellar rudiments of both sides fuse in the midline caudal to the roof of the mesencephalon to form the transverse cerebellar plate. At 3 months of age, the cerebellar primordia have a dumb-bell shaped appearance. The unpaired central part of the cerebellar primordia represents the vermis and the paired lateral knobs represent the developing cerebellar hemispheres.

As the development progresses, numerous fissures appear on the surface of the cerebellar primordia and divide into lobes. The earliest of these fissures is the posterolateral sulcus, which separates the nodule from the vermis in the midline and the flocculus from the cerebellar hemispheres (Fig. 9). Thus, the flocculonodular lobe is formed. The flocculonodular lobe is otherwise known as the archicerebellum, which establishes connections with the vestibular system and plays an important role in the regulation of equilibrium and posture. As the cerebellar rudiment grows in a dorso-caudal direction, the flocculonodular lobe comes to occupy the anterior part of its inferior surface. During the 3rd month, three fissures develop; the primary fissure that develops on the cephalic slope of the cerebellum separates the anterior lobe from the rest of the cerebellum; the secondary fissure and the post-pyramidal fissure develop on the caudal slope of the cerebellum and demarcate the uvula and pyramid. The uvula and the pyramid, along with the anterior lobe, form the paleocerebellum. The paleocerebellum is also known as the spinocerebellum because it regulates the tone and posture of the limbs and is phylogenetically later in appearance than the archicerebellum. That portion of the cerebellum between the primary and posterolateral fissures represents the neocerebellum, which is phylogenetically the latest and helps in co-ordination of voluntary movements.

Histogenesis of the cerebellar cortex: The cerebellar primordia initially consist of a germinal zone at the surface of the fourth ventricle. This germinal zone gives rise to the Purkinje and Golgi-II cells that migrate outward to form the Purkinje cell layer. The germinal zone of the fourth ventricle also produces neuroblasts that migrate outward to the pial surface and form a second germinal zone called the external granular layer. The neuroblasts of the external granular layer produce three distinct types of cells (interneurons), viz. the basket and stellate cells of the molecular layer and the granule cells of the granular layer. The newly formed granule cells migrate

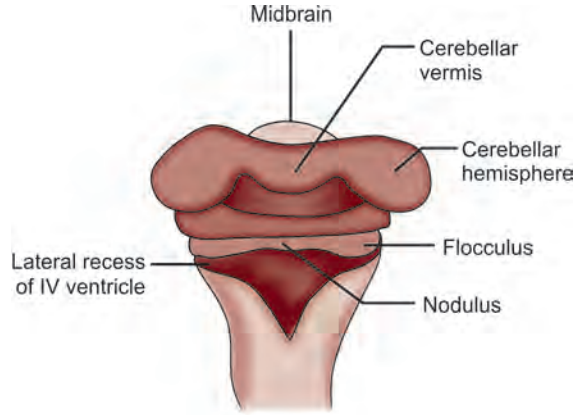


Fig. 9: Schematic representation of the development of the cerebellum

across the molecular and Purkinje cell layers to reach the granular layer. This migration of granule cells is guided by the radial glial fibres of the Bergman astrocytes. The neuroblasts of the mantle zone form the deep cerebellar nuclei.

Mesencephalon

The mesencephalon is the smallest brain vesicle which ultimately forms the midbrain, the shortest division of the brainstem. At the time of formation of the pontine flexure, the midbrain forms a conspicuous projection on the dorsal side of the flexure. However, the prominence of the midbrain is subsequently overtaken by the growth of the cerebral hemispheres. The cavity of the midbrain vesicle is markedly reduced during development and ultimately forms the cerebral aqueduct. The portion of the midbrain dorsal to the aqueduct forms the midbrain tectum and the portion ventral to the aqueduct has two subdivisions: a dorsal midbrain tegmentum and a ventral crus cerebri.

In the midbrain too, the alar and basal laminae are separated by a well-defined sulcus limitans. The motor neurons derived from the basal lamina give rise to the general somatic efferent column and ultimately form the nuclei of the oculomotor and trochlear nerves, which innervate the extraocular muscles derived from the preotic somites. Motor neurons that go to form the general visceral efferent column migrate dorsally and form the visceral component of the third nerve complex, supplying pre-ganglionic parasympathetic fibres to the pupil. The general somatic afferent column is represented by the mesencephalic nucleus of the trigeminal nerve, which invades the alar lamina of the midbrain from the isthmus rhombencephali and this nucleus receives proprioceptive impulses from the muscles of mastication, facial muscles and probably, the ocular muscles. The cells of the special somatic afferent column are represented by the superior and inferior colliculi, which act as relay centres concerned with vision and audition, respectively. These are formed from the alar plates. The inferior colliculus is formed by proliferation of neuroblasts to produce a small central homogeneous cell mass surrounded by a narrow cortical rim. The superior colliculus is a stratified structure formed by waves of migrating neuroblasts. Here, the cell migrations follow an "inside-out" sequence in that the cells forming the deeper layers are formed first followed by the cells forming the more superficial layer. As a result, cells destined for the superficial layers have to migrate through the deeper layers. The exact origin of the red nucleus, substantia nigra and midbrain reticular formation is not clearly understood at present.

Diencephalon

That portion of the prosencephalon caudal to the interventricular foramen constitutes the diencephalon. During early embryonic development, the prosencephalic vesicle gives rise to the optic vesicles. The optic vesicles are attached to the prosencephalic vesicle at the region of the developing diencephalon. The diencephalon consists of two lateral walls, and thin roof and floor plates.

Each lateral wall presents a hypothalamic sulcus, which extends from the region of the aqueduct of Sylvius to the interventricular foramen. Most of the structures of the diencephalon are derived from the alar lamina. The basal lamina is not represented in the diencephalon. The hypothalamic sulcus divides the lateral wall into the dorsal and ventral areas. The anterior part of the dorsal area develops into the thalamus and the posterior part gives rise to the metathalamus, viz. the medial and lateral geniculate bodies, which are important relay centres concerned with audition and vision. Because of the exuberant growth of the thalamus, the cavity of the diencephalon becomes obliterated to form the third ventricle. In 80% of humans, the two thalami are connected by the interthalamic adhesion or the massa intermedia. Early in development, the thalamus is separated laterally by an extra-neural cleft. Later, this cleft becomes obliterated by the projection fibres of the internal capsule. The ventral area below the hypothalamic sulcus differentiates into groups of hypothalamic nuclei. The floor plate of the diencephalon forms the following structures. Posteriorly, the cells of the floor plate proliferate to form the mamillary bodies. Anterior to the mamillary bodies, another cell proliferation results in the formation of the tuber cinereum. The floor of the diencephalic vesicle forms a tubular extension, which grows towards and fuses with Rathke's pouch. The diencephalic component of this fused structure forms the posterior lobe of the pituitary and the Rathke's pouch component forms the anterior lobe of the pituitary. The lamina terminalis, which forms the anterior wall of the third ventricle, represents the site of closure of the anterior neuropore. The lamina terminalis, however, is believed to be a telencephalic derivative. Its ventral part gives rise to a matrix from which the optic chiasm develops.

The roof plate of the diencephalon becomes thinned out and its rostral parts invaginate to form the choroid plexus of the third ventricle. The caudal portion of the roof plate thickens and evaginates posteriorly to form the pineal body. Rostral to the pineal body are situated the following: the posterior commissure, the habenular commissure and the habenular nuclei. These three structures, along with the pineal body, constitute the epithalamus.

Telencephalon

The telencephalon is composed of a median part and two lateral diverticula known as the cerebral vesicles. The anterior part of the median portion forms the lamina terminalis, which represents the site of closure of the anterior neuropore and thus the cephalic end of the primitive neural tube. The cerebral vesicles represent the rudiments of the cerebral hemispheres and develop as bilateral evaginations from the lateral wall of the forebrain during the 5th week of development. The cavity of the cerebral vesicles forms the lateral ventricles,

which communicate with the third ventricle through the foramen of Monro. The cerebral vesicles expand at first forwards, then upwards and finally backwards. As the vesicles grow backwards, they successively overlap the diencephalon and the mesencephalon. The lower part of the medial wall of the cerebral hemisphere remains thin and consists of a single layer of ependymal cells covered with the overlying vascular mesenchyme. It is continuous medially with the upper margin of the foramen of Monro. From the tela choroidea of the third ventricle, the choroid plexus projects laterally through the medial wall of the lateral ventricle through a cleft known as the choroidal fissure. The choroid fissure follows the downward and forward growth of the temporal lobe and thus assumes a C-shape.

The pallial tissue of the developing hemisphere consists initially of ependymal, mantle and marginal zones from inside out. The cells of the ependymal zone migrate outwards to become neuronal and glial cells upon maturation. The mantle zone becomes the white matter of the cerebral hemisphere. The marginal zone forms the cortical plate. Migration takes place first in the phylogenetically older areas, viz. the archipallium constituted by the hippocampal formation, followed by the paleopallium constituted by the piriform area and finally in the neopallium. The cortical layers develop in an "inside-out" fashion. The cells destined for the deeper layers are formed first followed by those destined for the superficial layers. Thus, the newly formed cells must migrate past the older cells to reach their destination and they are guided in their migration by the radial glial fibres. In the human foetus, this migration of cortical cells takes place between 7 and 16 weeks of gestation. In the early weeks of gestation, the surfaces of the cerebral hemispheres are smooth. During the 6th and 7th months of gestation, the surfaces of the cerebral hemisphere grow rapidly and develop convolutions (gyri) separated by deep furrows (sulci). The development of the sulci also takes place in an orderly fashion, viz. the phylogenetically older sulci appear first followed by the more recently acquired sulci. As a result of the formation of sulci and gyri, two-thirds of the cerebral cortex becomes buried in the walls and floor of the sulci when the brain attains its adult size.

Histogenesis of the Neural Tube

Histogenesis of the nervous system conforms to a general plan with regional variations in some parts of the nervous system. The lumen of the neural tube forms the ventricular system of the brain and the central canal of the spinal cord. Initially, the neural tube is lined by a single layer of undifferentiated neuroepithelial cells or stem cells. The continued proliferation of these neuroepithelial cells makes the single-layered neural tube into a multilayered neural tube with three distinct zones. The innermost zone is called the germinal or ependymal zone, the intermediate zone is called the mantle zone and the outer zone is the marginal zone. In the single-layered neural tube, the cells are limited by an external limiting membrane and an internal limiting membrane. The neuroepithelial cells are wedge-shaped and possess cytoplasmic processes, which reach the internal limiting membrane. Nuclei of these cells undergo characteristic oscillatory movements. First, the nucleus of an actively dividing cell migrates towards the external limiting membrane and then moves back towards the internal limiting membrane. DNA replication occurs only when the nucleus is near the external limiting membrane. Once the DNA replication is complete, the nucleus moves towards the lumen of the neural tube. Mitotic division occurs only when the nucleus reaches close to the internal limiting membrane. The divided daughter cells move from the germinal or ependymal zone into the matrix zone for further differentiation. These migrating cells are either immature neurons (neuroblasts) or glial cell precursors (spongioblasts). Some cells remain in the ependymal zone and eventually become the ependymal cells that line the ventricles of the brain and the central canal of the spinal cord. In the mantle zone, further differentiation into spongioblasts and neuroblasts occurs. The spongioblasts differentiate into astrocytes and oligodendrocytes. The microglia, however, are mesodermal in origin and appear in the mantle zone and marginal zone from the blood histiocytes when the vascular system grows around the neural tube.

The differentiation of the neuroblasts into neurons takes place in the following sequence: the neuroblasts migrating from the ependymal zone lose their cytoplasmic processes and become apolar neuroblasts. Subsequently, these cells develop two cytoplasmic processes and become bipolar neuroblasts. One of these cytoplasmic processes elongates and becomes the axon while multiple other cytoplasmic extensions increase in number and form the multipolar neuroblast. During the earlier stages of histogenesis of the neural tube, there is an overproduction of neurons. Eventually, the neurons that do not reach their appropriate locations in the CNS or those that do not reach their intended targets die, so that the total number of neurons is reduced to the normal population size. Movements of neurons to their intended locations and targets are guided by the proteins known as cell adhesion molecules and substrate adhesion molecules.

Neural Crest and its Differentiation

The neural crest cells are derived from the neuroectoderm. Initially, the crest cells border the tips of the neural folds and are continuous at the periphery with the cells of the surface ectoderm. When the two neural folds fuse dorsally to form the neural tube, the neural crest cells intervene in a wedge-shaped area between the surface ectoderm and the neural tube (Fig. 3). Neural crest cells extend from the region of the mesencephalon to the caudal somites. Neural crest cells are a highly pluripotent

Table 1: Derivatives of the cranial neural crest

	Derivatives
Nervous system	Sensory ganglia
	Sympathetic ganglia (V, VII, IX, X)
	Parasympathetic ganglia of the neck
	Neuroglial cells
	Schwann cells
Skeletal system	Maxilla
	Mandible
	Palatine
	Facial complex
	Cranial vault
Connective tissues	Cranial musculature
	Adenohypophysis
	Lingual glands
	Thymus
	Thyroid and parathyroids
	Corneal endothelium and stroma
	Vascular and dermal smooth muscles
	Melanocytes and melanophores

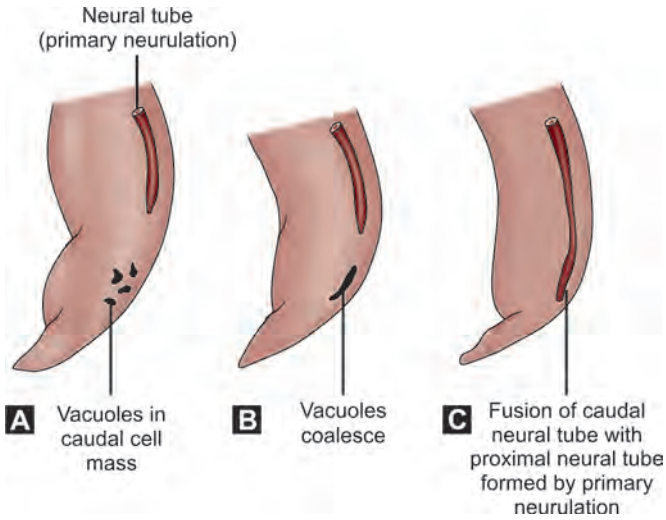
cell population that plays a significant role in the development of various structures. Neural crest cells migrate extensively throughout the embryo in four overlapping domains (cephalic, trunk, sacral and cardiac). The structures that are derived from the cranial neural crest are summarised in Table 1.

Development of the Spinal Cord

As can be understood from the preceding discussion on neurulation, the portion of the spinal cord up to the lumbar segments is formed by a process known as primary neurulation (discussed earlier). The distal portion of the spinal cord is formed by a process known as secondary neurulation. This process of secondary neurulation consists of two stages (Figs 10A to C): (1) canalisation of the tail bud and (2) regression or retrogressive differentiation.

Canalisation of the Tail Bud

Canalisation of the tail bud takes place during embryonic stages 13 through 20 (days 28 to 48). Caudal to the posterior neuropore, the tail bud contains an undifferentiated mass of cells known as the caudal cell mass, derived from the primitive streak. Under an intact covering of the cutaneous ectoderm, the caudal cell mass develops vacuoles around which cells assume a neural appearance. Subsequently, the vacuoles coalesce to form the neural tube, which then fuses with the more proximally placed neural tube formed by primary neurulation. The ventriculus terminalis, which marks the level of the future conus medullaris, becomes identifiable during days 43 to 48. Certain forms of occult spinal dysraphism, such as lumbosacral lipoma and lipomyelomeningocoele, are believed to have their origin during this period.



Figs 10A to C: Schematic representation of the development of the caudal spinal cord by secondary neurulation

Regression

The process by which the filum terminale and cauda equina are formed from that portion of the neural tube formed by canalisation and by which the conus medullaris eventually comes to lie at its adult level is termed as regression or retrogressive differentiation. This process begins as early as 43–48 days of gestation and continues throughout the foetal period and into the early postnatal period. The ventriculus terminalis is a localised dilatation of the central canal in the conus medullaris and can be identified to lie opposite the second coccygeal vertebral level early in development. At this stage of development, the spinal cord and the vertebral body levels corresponds segment for segment. During the process of regression, the ventriculus terminalis "ascends" both by regression of the caudal neural tube, as well as by the disproportionate growth of the vertebral column, resulting in the formation of the filum terminale. At birth, the conus lies opposite the third lumbar vertebral body and eventually reaches its adult position at the L1-L2 interspace by the 3rd month of life. As a result of these changes, the lumbar and sacral nerve roots which, early in their development, exit directly opposite their segmental spinal cord levels of origin become elongated as the conus "ascends", thus forming the cauda equina. Abnormalities during this stage of development result in "tight filum terminale", one of the most common causes of tethered cord syndrome.

Like other parts of the central nervous system, the developing spinal cord also has three layers: the germinal or ependymal layer, the mantle layer and the marginal layer. Cell proliferations in the mantle layer produce anterior and posterior thickenings known as the basal lamina and the alar lamina (Fig. 11). The basal lamina gives rise to the anterior horn of the spinal cord and the alar lamina gives rise to the posterior horn of the spinal cord. Neuroblasts of the basal lamina become the efferent peripheral neurons. Their axons penetrate the marginal layer and emerge from the spinal cord as the

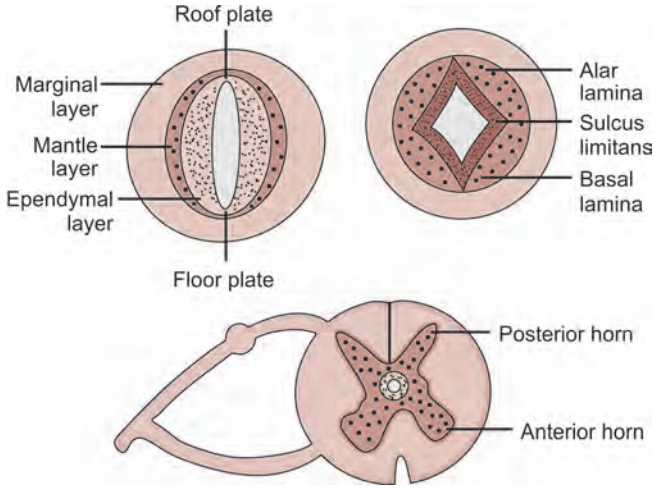


Fig. 11: Schematic representation of the development of the basal and alar lamina of the spinal cord

ventral root fibres to innervate the skeletal muscles or the autonomic ganglia. Some of the neuroblasts of the basal plates also give rise to the neurons which contribute to the local neuronal circuits forming the association cells and commissural cells, the axons of the former remaining on the same side of the spinal cord and the axons of the latter crossing over to the opposite side. Both cells contribute to ascending and descending pathways in the spinal cord. Cells of the alar lamina have axons that remain within the nervous system. Parts of these axons arch anteriorly, cross through the basal lamina to the opposite side, and reach the marginal layer, where they ascend or descend for variable distances. The expansion of the alar plates in a medial direction brings these plates into close opposition resulting in the formation of the posterior median septum. However, in the region of the basal plates, an invagination forms resulting in the formation of the anterior median fissure.

As development proceeds, the proliferation of the germinal cells of the ependymal zone gradually decreases and ultimately stops altogether. As more and more stem cells are transformed into neuroblasts, the germinal zone progressively diminishes in size and ultimately is reduced to a single layer of columnar epithelial cells lining the central canal of the spinal cord. The mantle layer progressively increases in size and becomes the grey matter of the spinal cord, which is surrounded by the marginal layer, which contains the descending and ascending axons and ultimately becomes the white matter of the spinal cord.

Development of the Meninges

The meningeal layers in the spine and in the cranium up to the midbrain are derived from the paraxial mesenchyme. The meninges overlying the cerebral hemispheres are derived from the neural crest. The dura mater constitutes the pachymeninges, and the pia and arachnoid, together, constitute the leptomeninges. All the three meningeal layers are derived from a loose mesenchyme known as the meninx primitiva or primary meninx that surrounds the primitive neural tube. Once the cerebrospinal fluid starts egressing from the ventricles it passes through the meninx primitiva and separates the meninx primitiva into the pia mater and arachnoid.

Molecular Basis of Brain Development

During the latter part of the last century, the study of embryology has led to significant advances in our understanding of the many processes that are involved in the formation and development of an embryo. Recently, the underlying mechanisms involved at a molecular level are beginning to be elucidated. Recent advances in molecular biology have allowed biologists to uncover, characterise and ultimately manipulate the genes that make up the genome of the fertilised egg. These advances have helped us in understanding the fundamental principles of development; how genes control cell behaviour and, thus, how they determine the pattern and form of an embryo. These advances are helping clinicians to understand the multitude of malformations encountered. Therefore, it is imperative that neurosurgeons, because of the wide variety of congenital malformations of the nervous system encountered by them, keep abreast of these developments. Only by understanding the processes involved during normal development we can begin to unravel the mechanisms that are responsible when things go wrong. These developments in basic sciences should be utilised for clinical benefit, principally to aid with pre-natal diagnosis and, ultimately, to enable therapeutic intervention.

Molecular Regulation of Neural Induction

Induction of neural plate formation is controlled by several factors. In the developing embryo, bone morphogenetic protein-4 (BMP-4) is elaborated by the developing ectoderm and mesoderm. Under the influence of BMP-4, the ectoderm becomes epidermis and the mesoderm differentiates into intermediate and lateral plate mesoderm. However, in the region of the ectoderm destined to become the future neural plate, the activity of BMP-4 is blocked by three molecules, viz. noggin, chordin and follistatin. These molecules are secreted by the primitive node, notochord and the paraxial mesoderm. However, these neural inducers form only the neural plate that goes to form the forebrain and midbrain regions. Induction of the neural plate regions that go to form the hindbrain and spinal cord depends upon two proteins, Wnt-3a and fibroblast growth factor (FGF). In addition, retinoic acid and homeobox genes play an important role in organising the craniocaudal axis of the developing nervous system.

Homeobox Genes (Hox Genes)

The Hox genes were originally identified in the fruit fly *Drosophila melanogaster*. These genes are a family of regulatory genes (with a phylogenetically highly conserved

domain called the "homeobox"), which appears to play a fundamental role in the establishment of the body plan. All vertebrates, including humans, contain 39 Hox genes that are distributed on four linkage groups or clusters designated Hox A, B, C and D on chromosomes 6, 11, 15, and 2, respectively (For a detailed discussion on homeobox genes refer the chapter on Embryology of the Skull and Vertebral Column).

During early development, the hindbrain is transiently partitioned into eight transverse neuroepithelial segments called rhombomeres (r1-r8), each of which adopts a distinct set of molecular and cellular properties and ordered domains of Hox gene expression (Fig. 12). These rhombomeres give rise to well-defined regions of the adult brain and their segmental organisation is critical for the establishment of cranial ganglia, branchiomotor nerves and pathways of neural crest migration. For example, the motor nerves of the first three branchial arches (trigeminal, facial-acoustic and glossopharyngeal) are respectively derived from nuclei confined to rhombomeres 2, 4 and 6. In addition to patterning the cranial nerves, the rhombomeric organisation of the hindbrain is also linked to the patterns of cranial neural crest cell migration. Hindbrain derived neural crest cells migrate ventrolaterally as three segmental streams adjacent to r2, r4 and r6, which enter the first, second and third branchial arches, respectively. Substantially fewer neural crest cells delaminate from r3 and r5 compared to the even-numbered rhombomeres. Thus, hindbrain segmentation is a conserved strategy used by vertebrates for organising diverse craniofacial features such as cranial ganglia, branchiomotor nerves and neural crest. The Hox genes play an important role in hindbrain segmentation as well as in the neural crest cells derived from the hindbrain region. The neural crest cells derived from various rhombomeric segments also exhibit the same Hox gene expression as their corresponding rhombomeric segments. This patterned Hox gene expression is carried to the branchial arches populated by the neural crest cells. In summary, the positional information that controls pharyngeal arch patterning is first contained in the rhombencephalon and then transmitted to the pharyngeal area via the neural crest cells. Thus, Hox genes are important for conferring anteroposterior identity of rhombomeres and for the normal development of the branchial arch structures.

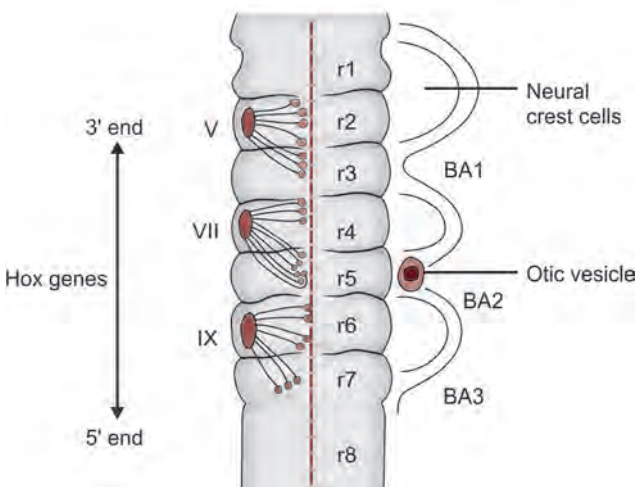


Fig. 12: Schematic representation of the division of the hindbrain into eight rhombomeres and the derivation of the pharyngeal arches from the hindbrain related neural crest cells. This patterning of the hindbrain and the pharyngeal arches is determined by the Hox genes. The Hox code is carried from the hindbrain segments into the pharyngeal arches through the migrating neural crest cells

Sonic Hedgehog Gene

Sonic hedgehog (SHH) gene is a signalling switch used in differentiating subpopulations of cells throughout the embryo. SHH function is determined by where the signal is being secreted, how far away the responsive cell population is and how SHH is proteolytically cleaved. SHH acts by binding to the membrane receptor patched (ptc). Abnormal expression of SHH is thought to lead to holoprosencephaly. SHH induced patterning of the embryo is found in the ventral neural tube, parts of the developing brain and developing limb buds.

Otx, Emx, LIM 1 and EN Genes

Otx genes (orthodenticle genes), Otx 1 and Otx 2, empty spiracle genes (Emx-1 and Emx-2) and LIM 1 genes are involved in the specification, regionalisation and terminal differentiation of the rostral central nervous system, especially, the forebrain. It is believed that modification of their regulatory control may have influenced the morphogenesis and evolution of the brain. The Engrailed 1 and 2 (EN1 and EN2) are two homeobox containing genes and are expressed at the junction of the developing hindbrain and midbrain. EN1 regulates the development of the dorsal midbrain (tectum) and cerebellum, whereas EN2 is involved only in cerebellar development. Other genes that are involved in brain development are WNT1 and NKX2.1.

Molecular Regulation of Cortical Development

Cerebral cortical development consists of three major processes: cell proliferation and apoptosis (programmed cell death), neuronal migration and cortical organisation. Cell proliferation is the process that takes place in the germinal zones of the developing prosencephalon. Before neurogenesis, the pool of progenitor cells is expanded through a series of cell divisions in which both the daughter cells re-enter the cell cycle as progenitors. Eventually, under the influence of signals that are not yet known, the fraction of post-mitotic cells that exit the cell cycle to become neurons or glia gradually increases until the proliferative potential of the germinal zone is exhausted. Certain proteins that have a role in this differentiation have been identified.

Neuronal migration requires the migrating young neuron to attach to radial glial cells that span the developing hemisphere from the germinal zone to the pia, to

Table 2: Genes and site of action

Genes	*Site of Action*
Hox genes	Segmentation of the hindbrain; hox codes are also carried into the pharyngeal arches through the migrating neural crest cells
EN1 and EN2	EN1 regulates the development of the midbrain, tectum and the cerebellum; EN2 regulates the development of the cerebellum
Otx 1 and 2, Emx 1 and 2	Specify the identity of various forebrain and midbrain regions
LIM1	Specifies the identity of forebrain and midbrain areas by supporting Otx2
Fibroblast growth factor–8 (FGF-8)	Induces the expression of Brain factor-1 (BF1), which regulates the development of the cerebral hemispheres, especially, the basal telencephalon and retina
SHH	Plays an important role in the ventral patterning of the entire central nervous system
NKX2.1	Regulates the development of the hypothalamus
WNTI	Assists in the development of the cerebellum
Filamin-1, LIS1 and doublecortin	Neuronal migration from the germinal zone of the neural tube to their final positions in the cortex
Reelin and mDab1	Termination of neuronal migration

migrate along the radial glial cells and to detach when they reach the proper layer of the cerebral cortex. Some proteins have been identified that play important roles in these steps. The filamin-1, LIS1 and doublecortin genes encode proteins that play an important role in the migration of neurons along the radial glial cells. Mutations of these genes are known to result in various types of neuronal migration disorders. Two other proteins, neureglin and astrotactin, have been identified regulating the interactions between the migrating neurons and radial glial cells. Termination of neuronal migration is brought about by an extra-cellular protein known as reelin and the cytoplasmic protein known as mDab 1. The molecular mechanisms that are involved in cortical organisation are gradually being elucidated.

A brief summary of the molecular control of brain development is given in Table 2.

Molecular Regulation of Spinal Cord Development

At the neural plate stage in the spinal cord region, the entire plate expresses genes that encode transcription factors, viz. PAX3, PAX7, MSX1 and MSX2. This expression pattern is altered by the sonic hedgehog gene (SHH) and bone morphogenetic proteins 4 and 7 (BMP 4 and 7). Expression of SHH by the notochord results in the ventralisation of the neural tube and formation of the floor plate, which also subsequently expresses SHH. The latter represses the expression of PAX3, PAX7 and MSX1 and MSX2. This results in the formation of the floor plate and basal lamina from which the motor neurons of the spinal cord originate. At the same time, BMP-4 and BMP-7 expressed from the surface ectoderm close to the neural plate up-regulate the expression of PAX3 and PAX7, resulting in the formation of the roof plate and the alar lamina, which are sensory in function. PAX3 and PAX7 are also necessary for the formation of neural crest cells.

Post-natal Growth of the Brain

At birth the volume of the brain is approximately 25% of the volume in adult life. The greater part of the increase occurs in the 1st year at the end of which the volume of the brain increases to 75% of the adult volume. This growth can be accounted for by an increase in the size of the nerve cell somata, the proliferation and increase in the dimensions of their dendritic processes, axons and their collaterals and by the growth of the neuroglial cells and cerebral blood vessels and by the acquisition of myelin sheaths by the axons. The great sensory pathways (visual, auditory and somatic) myelinate first, and the motor fibres later. During the second and subsequent years, growth progresses more slowly, reaching the adult size by the 17th or 18th year largely due to continued myelination of the various fibres.

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15 Congenital Malformations of Cerebrum

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The development of the central nervous system (CNS) is very complex. Neurogenesis, apoptosis, neurulation, neural crest separation, cell migration, axonal path finding, dendritic sprouting, synaptogenesis, neurotransmitter biosynthesis and myelinisation are the various steps involved.[34,64] Each of these processes should be proper for normal development. Brain malformations are congenital deviations in form and/or structure of the developing CNS.[63] Congenital malformations of the brain are common clinical conditions which are one of the leading causes of infant morbidity, mortality and foetal loss.[29] Even in the general population they are the leading causes of clinical presentations like epilepsy and cerebral palsy.[32,34]

So far, only descriptive terms have been used for most CNS malformations with their clinical and radiological features. However, detailed neuropathology studies have paved the way for precise diagnosis and cause analysis. Prenatal brain imaging has aroused the interest in foetal neuropathology and significantly transformed the concepts of brain malformations.[13,31,32,35,51] Primary malformations are due to genetic or chromosomal mutations and secondary malformations to exogenous causes.[32] By definition, inherited factors can only cause primary malformations and secondary malformations cannot be inherited, but inherited factors can predispose to secondary malformations. Genetic screening plays a significant role in distinguishing the two classes of malformations. Recent neuropathological studies have made it clear that brain malformations are phenotypically unique and causally heterogeneous. Understanding the molecular cascades of the signalling pathways and developmental neuroscience have shed light on the diversity, heterogeneity and the role of mutations involving different genes. In addition, these signalling pathways could be the target of toxic agents which can produce similar malformations.[32]

DEVELOPMENT AND PATHOGENESIS

The morphological abnormalities are directly derived from alterations of the morphogenic processes. Identification of these features will help in the diagnosis of lesions which are due to the distortion of the normal embryogenic process. During the 1st week after fecundation, the egg divides and migrates from the fallopian tube and gets implanted in the uterine mucosa. During the 2nd week, the amniotic cavity develops and the inner cell mass has a two-layer organisation—epiblastic and endoblastic layers. During the 3rd week, the invagination of the epiblastic cells between the epiblast and the endoblast produces the mesoblast. During the 4th week, the neural plate will form and fold itself along its long axis to form the neural tube which closes. During this process the surface ectoderm gets separated allowing the interposition of mesenchyme. If the process of closure of the neural tube fails, the resulting malformations belong to the group of open dysraphisms. Failure of closure of the calvarium and anterior cerebrum results in cranial encephalomeningocoele. Exencephaly is an extreme form and if the herniated brain is destroyed by necrosis, it will lead to anencephaly.[18] The minor equivalent of this disorder is the atretic parietal encephalocoele.

During the 5th week, a defect in the anterior end of the neural plate can lead to a group of malformations affecting the brain, the placode derived organs and the face. The anterior neural crest develops into most of the facial skeleton, the telencephalic meninges, calvarium and superficial covering.[19] Adjacent portions of the neural plate give rise to the hypothalamus, neurohypophysis and optic chiasm in the midline and the cerebral hemisphere laterally. When the neural tube closes, its cephalic end develops flexures and dilatations resulting in three primary cephalic vesicles namely: prosencephalon; mesencephalon and rhombencephalon. They further differentiate into five vesicles: the telencephalon forming the lateral hemispheres and laminae terminalis; the diencephalon forming the forebrain; the mesencephalon forming the midbrain; and the metencephalon and myelencephalon forming the hindbrain.[60,69] At the forebrain level, lack of differentiation can result in a single prosencephalic vesicle leading to various forms of holoprosencephaly.[5–8] Septo-optic dysplasia is a variant which presents with no continuity between the hemispheres, with normal commissures and a single ventricular cavity without a septum.[22] During the 6–8th weeks, the rhombencephalon develops a significant evagination resulting in the development of the cerebellum and opening of the fourth ventricle,[10] synchronising with the transformation of solid meninx primitiva into rigid dural layers and the fluid-filled subarachnoid space.[49,60,67,68,70–73] During this process cystic cavities can develop in the posterior

fossa and if only the posterior membranous area of the rhombencephalic roof is involved, malformations such as enlarged "Blake's pouch" with abnormal location of the tentorium can occur.[2,79] When the anterior membranous area is defective, it will lead to the entire spectrum of Dandy-Walker malformations.

- Embryonic period—First 8 weeks, post-fertilisation
  - o Gastrulation and notochord formation — 2–3 weeks
  - o Dorsal induction — 3–4 weeks
    - – Primary neurulation
    - – Secondary neurulation
  - o Ventral induction — 5–6 weeks
- Foetal period—8 to 38 post-fertilisation weeks
  - o Neuronal proliferation, differentiation and histogenesis — 2–4 months
  - o Migration — 3–5 months
  - o Myelination and organisation — 3rd trimester–post-natal

Commissural Agenesis

There are three telencephalic interhemispheric commissures namely: paleocortical anterior commissure; archicortical hippocampal commissure and the large neocortical corpus callosum connecting most of the neocortex. The agenesis could be complete or partial with cysts including lipoma of the corpus callosum or isolated agenesis of a single commissure.[58,59]

Malformation of Cortical Development

Malformation of cortical development includes all varieties of cortical malformations previously described as cortical dysplasias or neuronal migration disorders. They can be classified based on the pattern of cortical formation as defects of:

a. Cellular multiplication
b. Cellular differentiation
c. Cellular migration
d. Cellular organisation.[7,55,56]

Cellular Multiplication

It starts as soon as the neural tube is completed in the periventricular layer. The primitive germinal cells divide symmetrically and produce pairs of daughter cells. The faulty multiplication can result in an abnormal size of the brain.[16]

Cellular Differentiation

As the cells are dividing, one cell will remain the germinal matrix and other cells get differentiated and become neuronal or glial cells and migrate towards their final position in the cortex. When there is a defect in this process due to any mechanism, the cells will have the characteristics of both neurons and glia, and they fail to migrate and segregate properly. They look abnormal, as giant dismorphic neurons or huge balloon cells. If this defect is localised, it leads to focal cortical dysplasias and if it is large, it can lead to hemimegalencephaly.

Cellular Migration

The neuronal cells migrate towards the cortex in a radial pattern established by the radial glia, which act as a guideline from the ventricle to the pial surface. Defects in this process will lead to neurons in abnormal locations forming masses called "grey matter heterotopias", which could be nodular or laminar, and depending on the location could be periventricular or subcortical. Subcortical laminar heterotopia is a band of grey matter located in the white matter just below the normal looking cortex and described as double cortex. It has a genetic horizon with a defect on chromosome X and also chromosome 17. Excessive migrations into superficial molecular layers may occur, leading to the Walker-Warburg syndrome, where the neurons pass the brain surface to invade the meningeal space.

Cellular Organisation

Intrinsic organisation of the cortical layers occurs with the development of the intracortical connections and then the extracortical connections mediated by the transitory subplate during the 20th and 25th weeks of gestation. Disorders at this stage will result in abnormal folding of the cortex and lead to microgyria, polymicrogyria, etc.

Cysts in the extracerebral spaces may be related to cerebral malformation or may be purely intrameningeal. They are classified according to the histology of the membrane as arachnoid cyst, neuroglial cyst and glioependymal cyst. They are usually located in the suprasellar cistern, middle cranial fossa or posterior fossa.

Schizencephaly

It is characterised by the presence of unilateral or bilateral, symmetrical or asymmetrical transcerebral clefts. The lips may be opposed or largely open with the presence of a cyst. The walls of these clefts are lined with cortex, usually dysplastic, with its pial covering. This extends all the way to the ventricular ependyma which is the hallmark of the malformation. The exact process of this malformation is not clear.[81,82]

Most CNS malformations isolated or associated with other malformations are usually identified by the descriptive terms such as microcephaly, lissencephaly, polymicrogyria and hydrocephaly. However, this description does not help us to understand the mechanism. They are classified as:

a. Abnormal brain size (microcephaly/megalencephaly).
b. External form (holoprosencephaly/lissencephaly).
c. Internal configuration (hydrocephaly/agenesis of corpus callosum).

CONCEPTS, CAUSES AND CLASSIFICATION

There are many causes of congenital malformations (Table 1) which include, chromosomal abnormalities, gene defects, foetal infection, exposure of the foetus to harmful chemicals, radiation, foetal hypoxia and often more than one of these factors may play a role and, therefore, the resultant malformation may not follow a specific pattern.[40,41] Further, the malformations are closely linked to the development stage at which time one of these aetiological factors may induce the malformation. Since many of the structures of the brain form at the same time, the resultant malformation may lead to defects in multiple structures of the brain. Due to these factors, classification and grouping are often difficult and less rewarding. In spite of this, a classification system is required for better understanding, prognostication, counselling and management of these conditions.

Table 1: Different causes of congenital malformations

Anomalies of dorsal induction	*Anomalies of ventral induction*
• Primary neurulation (neural tube defects)	
o Encephalocoeles	• Holoprosencephaly
o Craniorachischisis totalis	• Septo-optic dysplasia
o Anencephaly/exencephaly	• Agenesis of septum
o Chiari malformation[52]	• Diencephalic cyst
Anomalies of neuronal proliferation and differentiation	*Anomalies of neuronal migration*
• Micro/megalencephaly	• Lissencephaly
• Phakomatoses	• Pachygyria
• Colpo/porencephaly	• Schizencephaly
• Hydranencephaly	• Polymicrogyria
• Cong tumours/vascular malformations	• Heterotopias
	• Dysgenesis of corpus callosum[1]

Morphogenic Classification

- Defects in neural tube closure
- Forebrain growth failure
- Midbrain malformations
- Hindbrain malformations
- Abnormal cortical development
- Miscellaneous.

Classification Based on Developmental Stages

- Weeks 1–3 – Early stages of layer formation
- Weeks 4 – Neurulation
- Weeks 5 – Disorders of the anterior neural plate, abnormal diverticulation
- Weeks 6–8 – Dandy-Walker spectrum, cystic malformation of posterior fossa

Classification Based on Structural Process

- Commissural agenesis
- Malformations of cortical development
- Cellular multiplication symmetrical divisions
- Cellular differentiation
- Cellular migration
- Cellular organisation
- Extracerebral cysts
- Vascular malformations
- Uncertain process—schizencephaly.

Molecular Genetics

Each single process of CNS development is under genetic control, most often including various genes with different modes of transmission. The distinction between dominant, recessive and X-linked disorders is extremely useful for clinical diagnosis, linkage analysis and for genetic counselling. Dominant diseases manifest in the heterozygous state, that is, when only one abnormal gene is present and the corresponding allele on the homologous chromosome is normal. By definition, the responsible gene must be located on one of the 22 autosomes. So, there is a one in two chance that half of the offspring will inherit the disease. The recessive diseases require inheritance of a mutant allele of the same genetic locus from each parent. X-linked disorders and X inactivation is the third pattern of inheritance. During embryonic development, one of the two X chromosomes in each somatic cell of a female is irreversibly inactivated. The inactivated X chromosome is made permanently non-functional. If a mutation occurs on one of the X chromosomes, one half of the cells will be normal and the other half will express the mutant genotype. The actuarial risk for brain malformations evaluated by frequency may vary from a 50% recurrence risk for autosomal dominant, 25% for autosomal recessive and under 1% for a new mutation. Molecular genetics has brought new insights into the aetiology and pathogenesis of nervous system malformations and, in addition, provided tools for accurate genetic diagnosis and prenatal detection. Many malformations previously thought to be single mutant disorders are now commonly recognised to result from many independent genetic mutations. Gradients of genetic expression along the axis of the neural tube established at the time of gastrulation may explain many varieties and clinical expressions of cerebral malformations.[34]

Prenatal screening also involves ultrasound examination and foetal MRI to achieve accurate morphological diagnosis.[32,36]

STRUCTURAL IMAGING

Congenital cerebral malformations commonly manifest as epilepsy and neurodevelopmental deficits. Numerous studies have shown that MRI scan is superior to CT scanning in detecting the abnormality and associated

structural defects. Gross abnormalities, such as lissencephaly or schizencephaly, may be identified on CT scan, but are more clearly seen using MRI and also in greater detail. Multiple techniques, like fat-suppression sequences and magnetic resonance venography, give additional information required for diagnosis and surgical planning.

Normal magnetic resonance studies do not exclude neuronal migration disorders, especially focal cortical dysplasia.[23] In a recent series of malformations of cortical developments (MCDs), 68 out of 100 individuals had normal CT scan and 19 out of 36 patients had normal previous conventional MRI.[74] The presence of cortical dysplasia is best established by application of the following sequences:

1. Multiple sequences, including T1-weighted, T2-weighted, fast FLAIR and proton density, help to confirm the nature of ectopic tissue, allow good discrimination of grey and white matter and identification of foci of T2 prolongation (seen typically with polymicrogyria and focal cortical dysplasia).
2. Volumetric acquisition with thin (≤ 1.5 mm) partition enables complete coverage and reformatting in any plane, for detailed visualisation of data and 3-dimensional constructions.
3. The use of surface coils improves discrimination by increasing the signal-to-noise ratio. Magnification techniques and phase-array coils enable detection of subtle abnormalities.

FUNCTIONAL IMAGING

Functional imaging techniques include single photon emission computed tomography (SPECT), positron emission tomography (PET) and functional MRI (fMRI) techniques. These techniques are becoming increasingly important in the evaluation of patients with congenital malformations. They provide information regarding the epileptic focus, functional status, ictal activity, blood flow changes, metabolism and neuroreceptors, and also delineates the function of abnormal ectopic grey matter which is important in surgical planning.

CLINICO-RADIOLOGICAL FEATURES

Microencephaly

It is a descriptive term for a small brain (weight and size less than three standard deviations for age) which may or may not be associated with microcephaly. It is usually a silent familial trait or may be associated with mental retardation in several syndromes with autosomal recessive inheritance. It is relatively a common finding in chromosomal and metabolic diseases. Abnormal brain growth, faulty neurogenesis, brain atrophy and abnormal programmed cell death are the usual proposed causes. Pathologically, there may be gyral retraction ranging from pachygyria to agyria. Histology shows a four-layered cortex with chaotic polymicrogyria, inverted cortical layering, heterotopias, neuroglial ectopia and lack of maturation.[21,43]

Megalencephaly

It is a large brain (by size and weight) which is above two standard deviations for age. It may affect a single hemisphere (hemimegalencephaly or may be associated with ventriculomegaly), could be isolated or in association with other developmental disorders like Soto's syndrome or osteochrondral dysplasia. It could be silent or manifest with seizures and psychomotor impairment. In hemimegalencephaly (Fig. 1) the large hemisphere usually shows an abnormal gyral pattern with abnormal cortical plate organisation. In addition, abnormal angiogenesis may be seen in Klippel-Trenaunay syndrome.

Hydrocephaly

It is ventricular enlargement caused by excessive production of CSF, insufficient absorption or disturbance in the circulation. Depending on the pathology, it could be monoventricular, biventricular, triventricular or tetraventricular enlargement. Aqueductal stenosis due to Bickers-Adams syndrome or atresia (forking) is well known.

Lissencephaly

It describes the morphologically smooth brain (Fig. 2). The term is also used for agyria/pachygyria due to abnormal corticogenesis. Total absence of convolutions leads to agyria (smooth brain). Pachygyria is an intermediary form with less frequent broad gyri and shallow sulci. These two can coexist in the same brain. More than 25 syndromes, associated with this anomaly in association with mental retardation, and epilepsy have been described.[76]

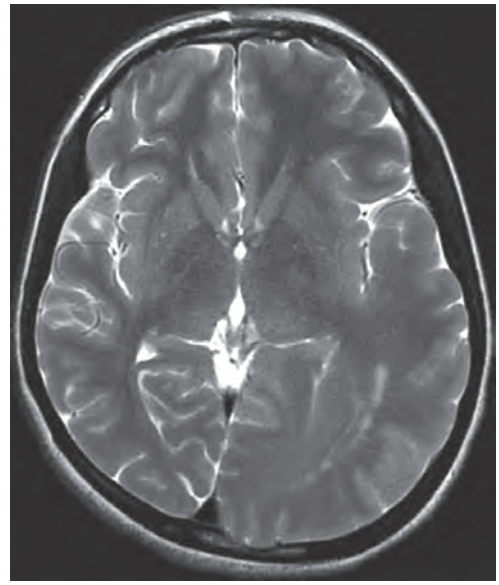


Fig. 1: Hemimegalencephaly involving only left parietal lobe

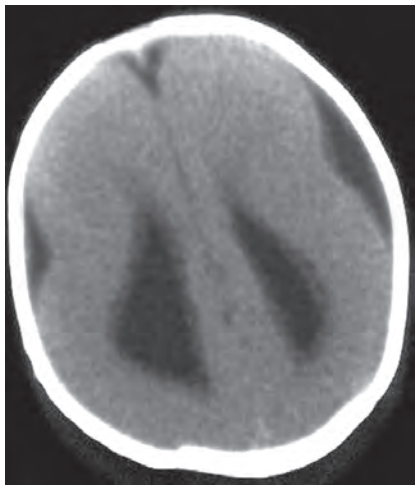


Fig. 2: Lissencephaly

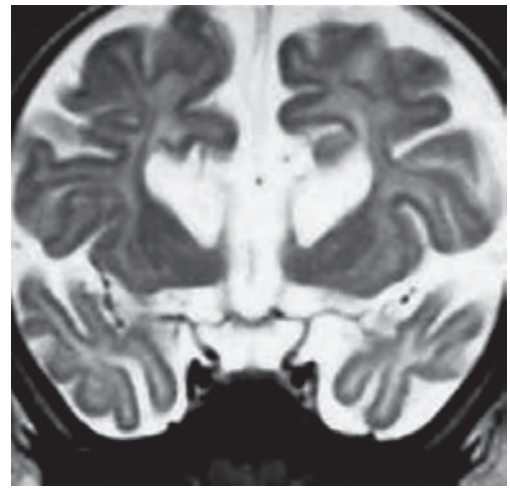


Fig. 3: Corpus callosum agenesis

Classical Lissencephaly or Type 1

It is due to abnormality in two genes, namely LIS 1 gene mapping on chromosome 17p 13.3 and DCX gene mapping on abnormal XQ 22.3. Radiologically, there could be reversal of grey-white matter ratio. Histologically, there is a four-layered cortical organisation made up of the following:

1. Superficial hypocellular layer
2. Cellular zone of hypertrophic large pyramidal cells
3. Underlying pachycellular layer
4. Large rim of ectopic neurons.

Cobblestone Lissencephaly or Type 2

It is a distinct cytoarchitectural disorder occurring in a group of autosomal recessive disorders like Walker-Warburg syndrome, Fukuyama muscular dystrophy and muscle-eye-brain disease usually associated with early hydrocephalus and agyric nodular brain surface.

"Cobblestoned" disorder is usually associated with cerebellar dysplasia, brain stem disorganisation, microophthalmia and retinal dysplasia. In addition, encephalocoeles and genital malformation in males have also been reported.

Walnut Type Lissencephaly or Type 3

It is described in relation to Neu-Laxova syndrome. Severe microcephaly, joint deformities and skin abnormalities are the usual features.[12,24–28,30]

Holoprosencephaly

It morphologically refers to a spectrum of forebrain malformations characterised by failure of the prosencephalon to form two lateral telencephalic vesicles.

It is usually associated with a spectrum of craniofacial abnormalities. Single calculi, atresia of the aqueduct, single medially fused cerebellar hemispheres and spina bifida have also been described.[15] Based on the severity, it has been divided into three groups: (a) lobar; (b) semilobar and (c) lobar with numerous transitional forms. The histopathology is usually diagnostic. Chromosomal aneuploidy accounts for 24–45% cases involving chromosomes 13 and 18. Septo-optic dysplasia (de Morsier syndrome) is also a midline developmental field defect. CNS malformations are characterised by an abnormal septum pellucidum, dysplasia of the optic chiasm or optic nerves and pituitary abnormalities. This anomaly is usually sporadic and is commoner in females.[17,37,53,58]

Agenesis of Corpus Callosum

It may be total or partial due to failure of the corticocortical tracts to cross the midline. In total agenesis, the medial surface of the hemisphere shows the characteristic absence of the cingulate gyrus and radial arrangement of the convolutions with an abnormal callosal artery. The callosal fibres that have failed to cross remain on either side of the lamina terminalis and form anteroposterior bundles called "Probst bundles" in association with the fornix. In partial agenesis, the body and splenium will be missing. Anterior agenesis is extremely rare. In severe hydrocephalus, the roof of the third ventricle may bulge into the interhemispheric region resembling the wall of a cyst. Corpus callosum agenesis[54] (Fig. 3) may be isolated or associated with an incredible number of syndromes like golden hour syndrome, Aicardi syndrome, Apert syndrome, etc. The isolated ones are usually clinically asymptomatic. The chromosomes 18 and 8 are the most commonly involved in this condition, in addition to many metabolic diseases.[20,32]

Schizencephaly

Schizencephaly is a developmental disorder of cortical migration that was first described in 1946 by Yakovlev and Wadsworth.[78,79] Schizencephaly is a cerebrospinal fluid-filled cleft extending from the ependymal surface of the brain to the pia (Fig. 4). The clefts are lined with thickened four-layered grey matter oriented parallel to the major sulcus. Other cortical areas may also show disordered migration with pachygyria, polymicrogyria and heterotopias.

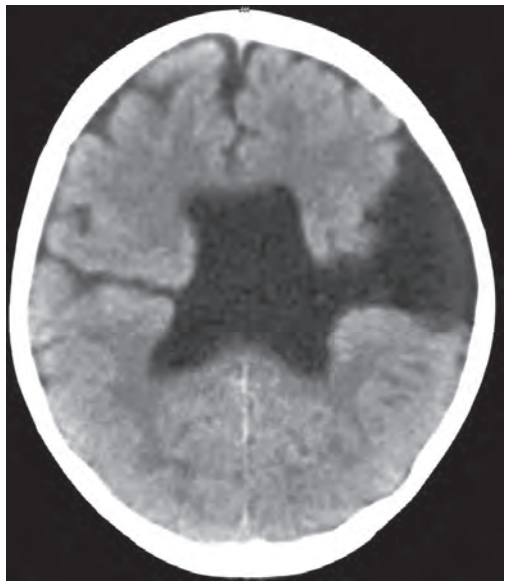


Fig. 4: Schizencephaly

There are two types of schizencephaly:

(1) *Closed-lip (type I) schizencephaly*: These are grey matter lined clefts which are in apposition to each other. Usually the ventricular margin shows an outpouching at the site of closed-lip schizencephaly, acting as an important clue.

(2) *Open-lip (type II) schizencephaly*: These are larger, grey matter lined clefts which are separated with an obvious defect in ventricular margin.

Schizencephaly can be unilateral or bilateral. Associated findings may include heterotopias, absence of septum pellucidum, hippocampal abnormality, pituitary hypoplasia and callosal dysgenesis.

It usually develops before the end of the 2nd month of gestation. The description of a few familial cases of schizencephaly raised the possibility that genetic factors could play an important role in the pathogenesis of this malformation. This possibility has strongly been supported by the presence in some schizencephaly patients of germ line mutations of the homeobox gene EMX 2.[38]

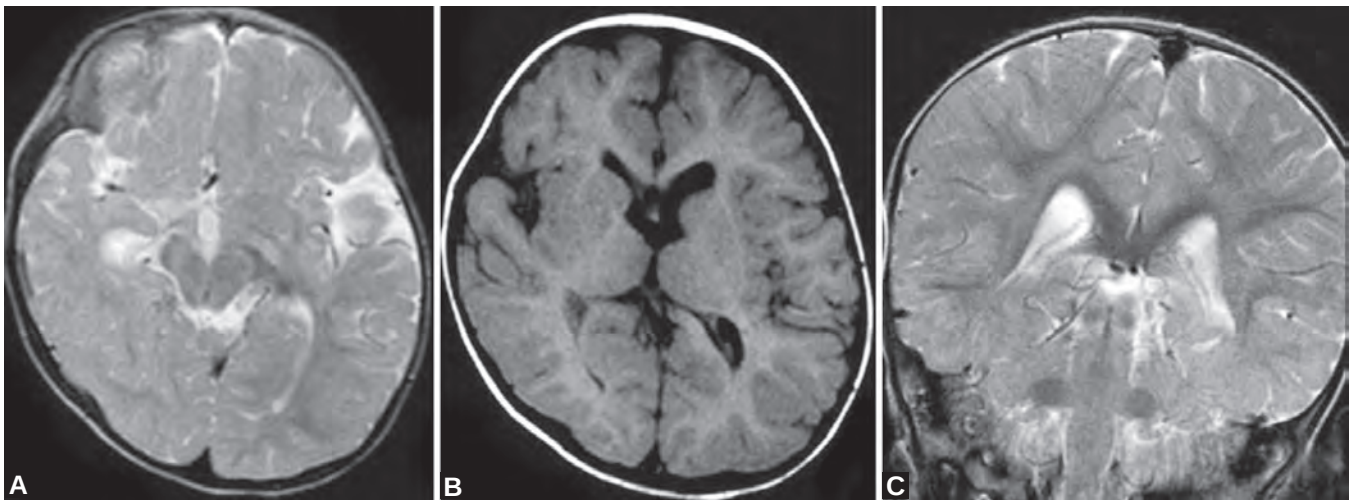
Patients with schizencephaly may present with features resembling those of polymicrogyria. Patients can be divided into those with bilateral and unilateral schizencephaly. Bilateral are less common than unilateral. Approximately 30–40% of patients have bilateral schizencephaly. Bilateral lesions are often asymmetric, with type I schizencephalic lesions in one hemisphere and type II lesions in the opposite hemisphere. The localisation of these lesions follows the vascular supply territory, with the majority of clefts localised in the fronto-temporal regions. Occasionally, these lesions are also localised to the occipital or precentral frontal regions.[48]

Clinical observations have identified that patients with bilateral schizencephaly often have moderate to severe motor dysfunction, characterised as spastic quadriparesis, marked developmental delay, mental retardation and language disorders. The seizure disorder in the unilateral group of patients is focal motor, but often sensory, as well as complex partial seizures.

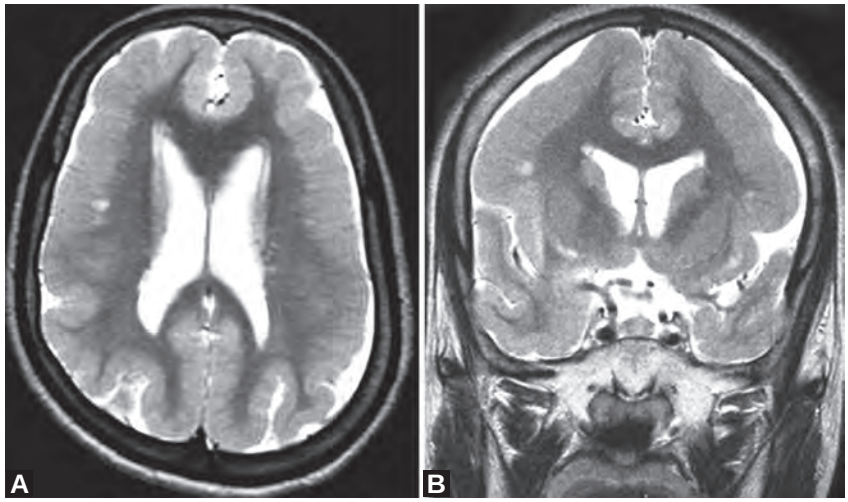
Pachygyria

Pachygyria (Figs 5A to C) is a milder variant of lissencephaly characterised by broad gyri and a thick cortex with an abnormal cytoarchitecture, although histologically the pachygyric cortex may have a more organised cortical structure than in lissencephaly. It is also clear that in many cases lissencephaly and pachygyria coexist in the same patient. Pachygyria is seen in metabolic CNS disorders, such as the Zellweger syndrome (ZS), neonatal adrenoleukodystrophy (NALD) and glutaric aciduria IIA.

On MRI, the cortex appears thicker and the typical figure 8-shaped image seen in lissencephaly is not present in pachygyria. The clinical presentation includes developmental delay and seizures, and half of the patients have microcephaly.



Figs 5A to C: Pachygyria with polymicrogyria



Figs 6A and B: Agyria pachygyria. T2-weighted image showing shallow sulci with thickened cortex and irregular grey-white junction

Polymicrogyria

The term "polymicrogyria" (Figs 5A to C) refers to an abnormal macroscopic appearance of the brain gyration that is characterised by too many small, abnormal gyri. In some cases, the gyri are shallow, small and are separated by shallow sulci, whereas in other cases the gyri are wider.

Histologically, the cortex consists of the molecular and wide neuronal layer (in some cases, there are three poorly defined neuronal layers). These layers are irregularly over-folded and fused, eliminating the sulci and there is evidence of midcortical ischemic laminar necrosis in layer 5. Superficial to this cortical band, the cortex consists of normal layers 4, 3 and 2.

Polymicrogyria can be diffuse or focal, bilateral or unilateral, symmetric or asymmetric. It is diverse in its aetiology and pathogenesis. Although most of the experimental and human foetal pathology data suggest that polymicrogyria may be the result of a post-migratory ischaemic mechanism, others have postulated a premigratory mechanism for some cases of polymicrogyria. Some forms of polymicrogyria are associated with mutations of PAX6, TBR2 and other genes. Bilateral peri-Sylvian polymicrogyria due to mutations of SRPX2, a form of bilateral frontoparietal polymicrogyria, resembles cobblestone lissencephaly. Other forms of polymicrogyria are acquired and are caused by disruptions. Polymicrogyria often occurs with foetal cytomegalovirus infection and prenatal hypoxic-ischemic encephalopathy, including vascular problems related to twinning.

Clinically, patients with polymicrogyria have an extremely variable presentation, depending on the location, extent and whether there is involvement of the contralateral hemisphere. Diffuse polymicrogyria may present with severe developmental delay, microcephaly and hypotonia. Polymicrogyria can be localised to one hemisphere and may also be one of the histologic changes in patients with hemimegalencephaly. MRI findings demonstrate a thick cortex that can be interpreted as pachygyria. However, cortical thickness is less than that observed in pachygyria. The sulci are shallow and the underlying white matter may show an abnormal T2 signal (Figs 6A and B).

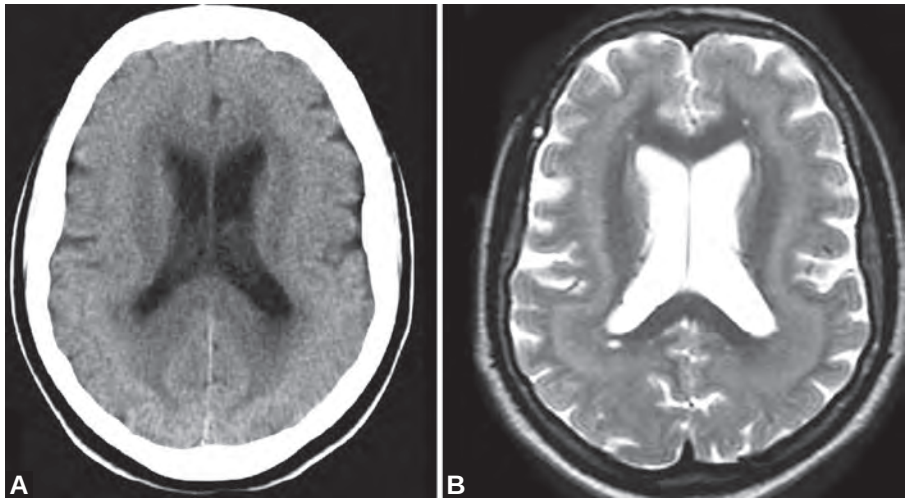
HETEROTOPIAS

Heterotopias are a collection of nerve cells in abnormal locations due to an arrest in the migration process. It can be an isolated disorder or may occur in association with other structural anomalies. Hetrotopias can be of the following types:

(a) Band heterotopia
(b) Subependymal heterotopia
(c) Focal heterotopia.

Band Heterotopia or Double Cortex Syndrome

This syndrome is prevalent in females. Patients have mild to moderate developmental delay, pyramidal signs and, in some cases, there may be associated dysarthria. Full scale IQs ranging from severely low to normal have been reported. EEG investigations usually demonstrate generalised spike-and-wave discharges or multifocal EEG abnormalities. Classic MRI findings demonstrate a band of subcortical grey matter heterotopia underlying the cortical mantle and separated from it by a thin rim of white matter (Figs 7A and B). This is usually more obvious over the fronto-central-parietal region.[61,62] Pathologic specimens have demonstrated normal lamination in cortical layers 1 through 4. Layers 5 and 6 cannot be seen, and layer 6 is merged with the U-fibres of the white matter. Functional MRI studies in double cortex have shown that these regions may play a role in normal brain functioning.[65] Periventricular heterotopias may be seen in tuberous sclerosis, but there the lesions are usually calcified and have a heterogeneous intensity on MRI scanning.[44]



Figs 7A and B: Band heterotopia

Subependymal Heterotopias

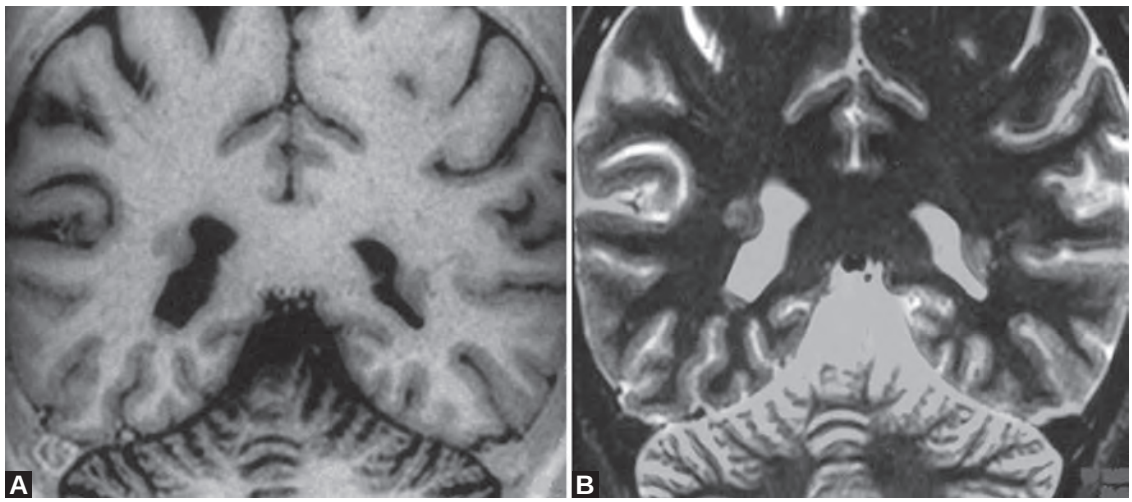
Heterotopias are defined as nodular grey matter masses that can be diffuse, bilateral or unilateral. Subependymal heterotopias comprise one of the most common forms of developmental disorders. These can range from a few nodular clusters of neurons to diffuse lining of the ependymal regions. Clinically, patients with subependymal heterotopias have normal neurologic development, unlike most other neuronal migration disorders.[14]

Most patients with periventricular nodular heterotopia (Figs 8A and B) present with epilepsy (80%). Seizures may be generalised or may appear localisation related, suggesting mesial temporal, neocortical temporal or parieto-occipital origin.[47] Interestingly, those who developed seizures did so in the second decade of life, relatively later than in other MCDs. Onset of epilepsy in the second decade of life, normal developmental milestones and intelligence, and overwhelming female preponderance differentiates subependymal heterotopia from other cortical dysgeneses.[75] The typical MRI features consist of multiple smooth nodules of cortical grey matter in all sequences, protruding slightly into the ventricular lumen, resulting in an irregular ventricular outline and no enhancement on contrast. Subependymal nodules seen in patients with tuberous sclerosis may be mistaken for that seen in heterotopia.

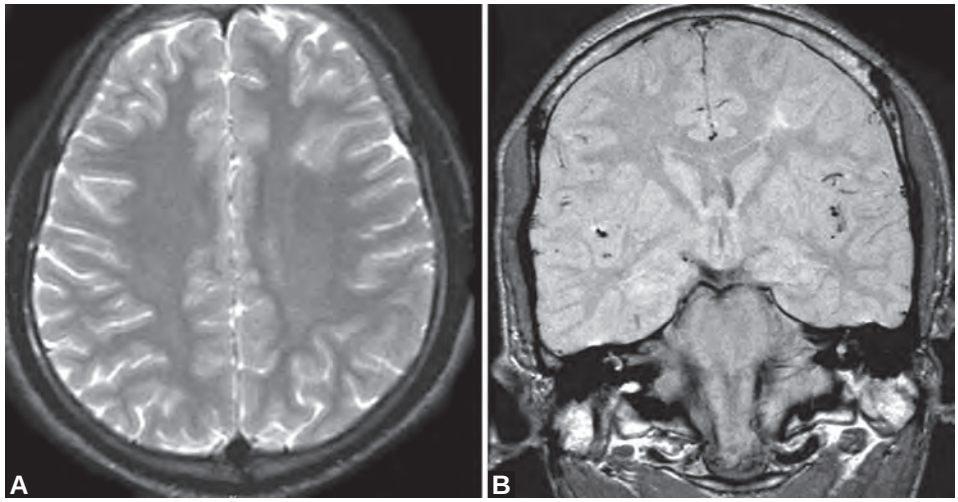
Several syndromes occur in conjunction with heterotopia. The best defined syndrome is bilateral diffuse heterotopia or periventricular nodular ectopia secondary to the mutation of chromosome Xq28.[80] Filamin 1 is the gene defect. Since this disorder is X-linked, it is observed primarily in women, but Dobyns and his colleagues[25] have reported three unrelated boys with bilateral periventricular nodular heterotopias, cerebellar hypoplasia, severe mental retardation, epilepsy and syndactyly. Other reported congenital abnormalities are short gut syndrome, congenital nephrosis and frontal dysplasia.[39]

Focal Cortical Dysplasia

Focal cortical dysplasia (FCD) (Figs 9A and B) is probably the most common form of focal developmental disorder diagnosed in patients referred for intractable epilepsy. Pathologic characteristics are disruption of



Figs 8A and B: Periventricular nodular heterotopia. T1 and T2 coronal images showing periventricular lesions with signal intensity of grey matter suggestive of periventricular nodular heterotopia



Figs 9A and B: Focal cortical dysplasia

cortical lamination with giant neurons and large astrocytes. These changes range from mild cortical disruption without apparent giant neurons to the most severe forms in which cortical dyslamination, large bizarre cells and astrocytosis are present. The most prominent histologic feature is the presence of a large number of abnormal cells with total loss of histologic architecture. Since the original description by Taylor in 1971, FCD has now been recognised to encompass a spectrum of changes, which range from mild cortical disruption without apparent giant neurons to the most severe forms, in which cortical dyslamination, large bizarre cells and astrocytosis are present.[42]

FCD can be classified into two types based on the presence of balloon cells. Type I is without balloon cells and type II is with balloon cells. Type II is more severe and is characterised by the presence of increased cellularity, giant cells and cortical chaos. In a study by Mackay et al.,[50] it was found that pathological findings in FCD and tuberous sclerosis were characterised by the presence of balloon cells.

The clinical manifestations of those with cortical dysplasia are variable. Seizures begin in the first decade of life, usually after the age of 2 or 3 years, but sometimes shortly after birth. In some patients, seizures present in the second decade. The seizures may be partial motor, partial complex or secondary generalised. The location of the lesion corresponds to the clinical presentation. The majority of patients tend to have extratemporal cortical dysplasias. The frontal lobes and, in particular, the precentral and post-central gyri appear to be more involved than other regions in the brain. In a study, correlating pathology and MRI findings in children with intractable partial seizures, cortical dysplastic lesions were present in 23% of patients.[46] Among those with these lesions, the central cortex was involved in almost half. The reasons for this involvement stem from the propensity of the precentral and postcentral gyri to ischaemic injury, as observed in other developmental disorders such as polymicrogyria and schizencephaly.

The presence of FCD in temporal lobes of patients undergoing resection ranges from 6 to 20% in different studies. Porter et al.[66] found cortical dysplasia in 21 out of 33 (64%) paediatric patients with refractory temporal lobe epilepsy. Temporal lobe developmental malformations with cortical dysplasia and balloon cells may coexist with mesial temporal sclerosis (dual pathology).

There is a correlation between the degree of histologic changes and the MRI findings, indicating that only in the most severe cases the abnormality could be detected by MRI. It is likely that high resolution MRI may increase the sensitivity for the detection of these lesions. The most obvious MRI finding of FCD is abnormal signal intensity in the white matter, resulting in a poor grey-white differentiation. The presence of a radiated abnormal signal extending from the ependymal surface of the ventricle to the overlying cortex, termed "transcortical malformation" of cortical development, helps to distinguish FCD from neoplasms.[11] However, this feature is not only recognised in patients with FCD but also in those with tuberous sclerosis. Immunocytochemical staining for tuberin, which is defective in tuberous sclerosis, is effective for differentiation of the two conditions.[57]

Though FCD is a major cause of medically intractable epilepsy, the cellular mechanisms underlying the epileptogenicity of FCD remain largely unknown. Recent work supports the role of developmental alterations of the balance between excitation and inhibition in the pathogenesis of epileptic focal discharges in paediatric patients. Aronica et al.[4] found that there is high expression of metabotropic glutamate receptors (mGluRs), especially mGluR1α and mGluR5, in the dysplastic neurons, suggesting a possible contribution of these glutamate receptors in the intrinsic and high epileptogenicity of dysplastic cortical regions.

MANAGEMENT

The management of patients with congenital malformations includes establishing the cause of the malformation with genetic studies and establishing the foci of epilepsy.

Once such information is gathered, the management includes physical rehabilitation, pharmacotherapy to control seizures and spasticity, genetic counselling, and appropriate surgical treatment.

Best results are obtained when complete or major excision of both the MRI-visible lesion and the cortical areas displaying ictal electrographic activity can be performed. This is more likely when the degree of histological abnormality is mild to moderate or when the lesion is in the temporal lobe. In the case series, reported by Fish et al.[33] from the Montreal Neurological Institute, the results of resection of cortical dysplasia were disappointing. More severe histopathologic abnormalities and central insular or multilobar lesions usually lead to less favourable results; either the major excision of the visualised lesion is impractical or the lesion is microscopically more extensive than shown by the MRI. Rougier et al.[77] reported the results of 100 cortical resections for medically refractory epilepsy and found surgery to be an effective treatment for more than 50% of long-lasting medically intractable seizures. Silbergeld et al.[78,79] reported the benefit of resective surgery in four patients with medically refractory epilepsy due to schizencephaly after proper and extensive pre-surgical evaluation.

Multilobar resection or hemispherectomy for patients with infantile spasms associated with cortical dysplastic lesions and for patients with hemimegalencephaly are often associated with dramatic improvement in seizure control. Callosotomy can be performed in selected patients with diffuse cortical dysplasia who have intractable drop attacks. Bernasconi et al.[9] analysed the results of surgical treatment of intractable epilepsy in patients with subcortical band heterotopia or double cortex syndrome. Their results did not support focal surgical removal of epileptogenic tissue in patients with double cortex syndrome, even in the presence of a relatively localised epileptogenic area.

PROGNOSIS

The prognosis of patients with malformations of cortical development and epilepsy depends on a number of factors. Kobayashi et al.[45] reported that patients with cortical malformations and age of onset less than 3 months (early-onset) had a poorer prognosis when compared to patients with age of onset more than 3 months (late-onset). Patients with early-onset seizures often had FCD while those with late-onset had polymicrogyria. In all seizure free patients epilepsy began after 3 months of age. Patients with mental retardation, bilateral cortical involvement and diffuse EEG abnormalities are thought to have a poor prognosis.[61,62] In most of the studies, patients with MCDs were found to have intractable epilepsy and progressive mental and motor decline and this may be due to selection bias. Ambrosetto[3] reported a small case series of patients with unilateral opercular neuronal migration disorder. All patients had normal intellectual function, normal EEG (except one) and good seizure outcome. Patients with heterotopias and schizencephaly, especially focal and unilateral ones, are found to have a good outcome. Those with lissencephaly and hemimegalencephaly often have intractable epilepsy and are associated with mental retardation. Patients with FCDs tend to have a worse outcome as compared to those with other types of focal lesions.[56] Lesions outside the temporal and frontal lobes were correlated with poor surgical outcome, as were generalised interictal EEG abnormalities, which may reflect extensive or multiple lesions.

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16 Encephalocoeles

Ashok Kumar Mahapatra

DEFINITION AND HISTORICAL ASPECTS ON ENCEPHALOCOELES

Encephalocoeles are a group of conditions in which there is protrusion of the brain or both meninges out of the cranial cavity through a skull defect. Depending on the content or herniation, it may be a cranial meningocoele or meningoencephalocoele. When herniated brain contains part of the ventricle, the condition is named as hydroencephaly. Thus, encephalocoele is a general term used for all the above abnormalities.

According to Emery and Kalhan,[28] the first medical report on encephalocoele appeared in 16th century. However, deformities like encephalocoeles were first illustrated in Medieval art and archaic sculpture. In 1813, Ritcher et al. first described a case of nasal encephalocoele (Fenger[31]). Heinecke, in 1882, classified encephalocoeles (Fenger[31]) depending on the hernial tract. Stadfeldt, in 1903, first coined the term fronto-ethmoid encephalocoele (Bumenfeld and Skolnik[12]). Browder and de Veer,[10] in 1934, termed nasal encephalocoeles as "Rhinoencephalocoeles".[9] Tandon,[98] in 1970, reported a comprehensive classification of all encephalocoeles and provided the first large series of these lesions from India. Suwanwela and Suwanwela,[95] in 1972, proposed a morphological classification of sincipital encephalocoeles. Tessier,[100] in 1976, described different facial clefts and correlated them with the congenital deformities.

INCIDENCE OF ENCEPHALOCOELES

Encephalocoeles occur less commonly than spinal dysraphism. The incidence of encephalocoeles is reported to be 1 per 3,000–10,000 live births.[15,41,52,59,90] Overall, occipital encephalocoeles are more frequent than anterior encephalocoeles (75% vs 15%). In general, encephalocoeles are occipital in 75%, frontoethmoidal in 13–15% and parietal in 1–12% cases. Basal encephalocoeles, such as transethmoid and trans-sphenoid encephalocoeles are rare.[40,55,58,60,67,89] The author has encountered eight cases of intranasal encephalocoeles in a series of 102 cases.[67] Trans-sphenoidal encephalocoeles are rare and less than 50 cases have been reported in the literature. In the Western Hemisphere, occipital encephalocoeles constitute 80–90% of all encephalocoeles.[71,79,90] A higher incidence of anterior encephalocoele is reported from Thailand, Indonesia, India, Papua New Guinea and Africa.[7,25,50,63,64,79,93,95,107] The incidence of anterior encephalocoele reported from the West is 1 per 35,000–40,000 live births.[23,93,103]

EMBRYOLOGY

There is no clear-cut explanation for maldevelopment of the neural tube at the cephalic end, leading to encephalocoele. Normally, in embryogenesis, the neural tube closes between the 27th day and 28th day of gestation. However, the anterior and posterior ends of the neural tube close at different times. The anterior neuropore, which lies at the level of the foramen caecum, closes around the 24th day. The development of various neural tube defects has been attributed to either primary failure of closure of the neural tube, or rupture of the neural tube due to some unknown reasons after it has closed around the 27–28th day of gestation.[9] Severe forms, like anencephalus and cranioschisis, may point to an earlier defect, may be in the early neurulation stage. The unfused cephalic end of the neural fold or defective closure of the anterior neuropore may communicate with the amniotic cavity, when skin, cranium and dura fail to cover neural tissue. However, the above hypothesis does not explain the occurrence of occipital or sincipital encephalocoeles with healthy skin cover and the absence of cranial dysraphism.[27,28] Gardner's[35] hydrodynamic theory does not quite explain the pathogenesis. However, rupture of a well-formed neural tube at a later date could explain the well-formed skin cover and lack of cranial dysraphism, as is usually the case with encephalocoeles. The neuroschisis theory proposes the formation of a bleb over the neural tube, which, on healing, gets adherent to cutaneous ectoderm and that can explain the formation of an encephalocoele.

Despite the generally unsatisfactory explanations of defective embryogenesis, there are several aetiological factors which may be responsible for the formation of encephalocoeles.[16,47,48,53,70,75,82,103] Williamson et al.[103] postulated that a viral antigen due to viral infection during early pregnancy may lead to neural tube defects. Hyperthermia, irradiation, hypervitaminosis, hypoxia and salicylates have been reported to cause encephalocoeles both in experimental animals as well as in human beings.[16,55,71] Moerman[75] et al. in 1992, postulated that

an amniotic band and adhesions result in the formation of encephalocoeles. Leong and Saw[58] described displacement of the hindbrain in patients with occipital encephalocoele, which corresponds to the area of the anterior neuropore.

Anterior encephalocoeles are due to failure of the anterior neuropore, which lies in front of the foramen caecum in the floor of the anterior cranial fossa just ahead of the crista galli, which marks the junction of the frontal bone with the ethmoid bone. Failure of the anterior neuropore in early embryonic life leads to herniation of neuroectodermal tissue, interposed between the mesodermal elements, which later are supposed to form the frontal and ethmoid bones. The exact aetiology of anterior encephalocoeles is not known. Geoffery and Hilliance (quoted by Gisselson[37]) suggested the adhesive theory. Wiese et al.[104] suggested the theory of primary mesodermal failure leading to defective bone formation.

CLASSIFICATION OF ENCEPHALOCOELES

A large number of classifications of encephalocoeles (Table 1) are available depending on several aspects, such as site of cranial defect, whether or not the encephalocoele is seen from outside and the size of the encephalocoele.[4,5,22,42,65,66,91] Encephalocoeles are classified as occipital, parietal, frontal, nasal and nasopharyngeal type.[88,107] Suwanwela and Suwanwela[95] have put forward the morphological classification of sincipital encephalocoeles.

A large number of authors have classified anterior encephalocoeles (Table 2). Heinecke, in 1882, classified them as: (a) spheno-pharyngeal, (b) spheno-orbital and spheno-maxillary types (quoted by Fenger[31]), depending on the hernial tract. Mesterton, in 1885, classified anterior encephalocoeles as: (a) naso-frontal; (b) naso-ethmoidal and (c) naso-orbital types. Bumenfeld and Skolink,[12] in 1965, named these encephalocoeles as: (a) trans-ethmoidal; (b) trans-sphenoidal; (c) spheno-ethmoidal and (d) spheno-maxillary. Suwanwela and Suwanwela[95] proposed the classification of sincipital encephalocoeles on a morphological basis. The inner and outer defects in the skull are enumerated in Table 3.

ASSOCIATED PATHOLOGY

A large number of systemic abnormalities have been reported along with encephalocoeles (Table 4).[2,8,35,41,69,75,87,91,102] The musculoskeletal system is widely involved. Rarely, the retina and vitreous can be abnormal.[29,76,87] Morika et al.[76] had described progressive hormonal and visual disturbance, which has been described as "morning glory syndrome". Knobloch and Layer described Knobloch syndrome in 1971,[87] which included a skin defect and visual problems. Associated anomalies can include many genetic syndromes, such as Meckel-Gruber, Von Voss, Chemke, Roberts and Knobloch syndrome.[7,92] Other non-genetic anomalies may include cryptophthalmos, amniotic band, spina bifida, agenesis of corpus callosum

Table 1: Classification of encephalocoeles

A. Congenital:
   Acquired—post-traumatic, post-operative, post-irradiation
B. According to the locations:
   1. Anterior encephalocoeles (frontoethmoidal or sincipital)
   2. Occipital or sub-occipital encephalocoele
   3. Basal:
      - Trans-sphenoidal
      - Transethmoidal
      - Intranasal
      - Spheno-oribital
      - Transtemporal
   4. Cranial vault:
      - Frontal
      - Parietal
      - Temporal
      - Through anterior or posterior fontanel
C. According to the size:
   - Small encephalocoele
   - Giant encephalocoele
D. According to the content:
   - Cephalocoele
   - Encephalocoele
   - Meningoencephalocoele
   - Cranial meningocoele
   - Hydroencephalomeningocoele
E. Encephalocoele as a part of complex syndrome such as:
   - Chiari III—Malformation
   - Knobloch syndrome
   - Morning glory syndrome
   - Walker-Warburg-Syndrome (WWS)
F. Overt:
   Occult
   - Intranasal
   - Intraorbital
   - Intratemporal
   - Intradiploic

Table 2: Various classification of anterior encephalocoeles

Authors	*Year*	*Types*
Heinecke	1882	• Spheno-pharyngeal • Spheno-orbital • Spheno-maxillary
Mesterton	1885	• Naso-frontal • Noso-ethmoidal • Naso-orbital
Bumenfeld and Skolnik	1965	• Trans-ethmoidal • Trans-sphenoidal • Spheno-ethmoidal • Spheno-maxillary
Suwanwela and Suwanwela	1972	1. Fronto-ethmoidal: • Naso-frontal • Naso-ethmoidal • Naso-orbital

Contd...

Contd...

Authors	*Year*	*Types*
		2. Interfrontal 3. Sphenomaxillary
Tandon[107]	1973	1. Frontal 2. Frontonasal 3. Frontoethmoidal 4. Naso-orbital
Tessier	1976	1–14 clefts
Mahapatra et al.	1995	1. Frontoethmoidal • Nasofrontal • Nosoethmoidal • Naso-orbital 2. Interfrontal 3. Transethmoidal 4. Sphenoethmoidal 5. Trans-sphenoidal 6. Orbital encephalocoeles

Table 3: Site of bony defects in anterior encephalocoeles

Type of encephalocoele	*At skull base*	*In the face*
A. Nasofrontal (Glabellar)	Between frontal and ethmoid bone in front of crista Galli	At the junction of frontal and nasal bone
B. Nasoethmoidal (Anterior Nasal)	do	At the junction of nasal bone and nasal cartilage
C. Naso-orbital (Nasolacrimal)	do	Between frontal process of maxilla and lacrimal bone
D. Transethmoidal (Naso-pharyngeal)	do	No outer defect, encephalocoele in nasopharynx or in nasal cavity
E. Trans-sphenoidal (Intrasphenoidal)	Through the body of sphenoid or sphenoid sinus	No outer defect
F. Interfrontal	—	Through metopic suture or anterior fontanel

Table 4: Systemic abnormalities associated with encephalocoeles

– Cleft lip cleft palate	– Visual disturbances
– Micrognathia	– Vitreoretinal degeneration
– Microcephaly	– Retinal detachment, myopia
– Scalp defects	– Dextrocardia
– Hair Collar sign	– Septal defects
– Klipple–Feil deformities	– Patent ductus arteriosus
– Vertebral abnormalities	– Pulmonary hypoplasia
– Polydactyly	– Renal hypoplasia
– Spina–Bifida	– Renal agenesis
– Diastematomyelia	

and Dandy-Walker syndrome. The most common chromosomal abnormality is Trisomy.[18]

CLINICAL PRESENTATION

Classically, patients with encephalocoeles are born with a swelling at birth. The size and content of the encephalocoeles are variable. In occipital encephalocoele, a globular swelling is noticed over the occipital bone in the midline. Encephalocoeles could be pedunculated or sessile.[53,60] The size of the encephalocoele is hardly ever indicative of its content. Most encephalocoeles are brilliantly transilluminant on examination. However, when a large amount of gliosed brain is present inside the sac, there may be variability in the degree of transillumination.

Usually the head size is small.[32,74] The larger the brain herniation, the smaller is the head size. Sometimes the encephalocoeles may be very large and are called giant encephalocoeles.[2,74,86] The head may be smaller than the size of the encephalocoele. Over the years, the author has encountered four patients with giant encephalocoeles, three in the occipital (Figs 1A to D) and one in the frontal area. The diameter of the head in the patient with a frontal encephalocoele was 11 cm as compared to the diameter of the encephalocoele which was 14 cm. In one patient with a lobulated occipital encephalocoele, the lobules were 14 × 18 × 17 cm in diameter, respectively as compared to the diameter of the head which was only 12 cm. These giant encephalocoeles do contain a large amount of brain and pose a considerable problem during closure. The author has operated upon 22 giant encephalocoeles of which 16 were occipital[2,86] (Table 5).

The site of the encephalocoeles is frequently occipital or suboccipital.[15,52,53,59,79] Around 10% of the encephalocoeles could be anteriorly located.[32,79,95] Rarely, encephalocoeles could be temporal[13,19,53,55,78,102] or parietal[71] in location. They could also be rarely intranasal[6,26,61,84] transethmoidal[40,55,58,73,89,107] or orbital[18,57] in location (Table 6). Very rarely the encephalocoele can be located at the anterior or posterior fontanel.[68] The author has operated on two each of these types.

Patients with frontoethmoid encephalocoele (Fig. 2) present with a swelling over the root or the bridge of the nose at birth[51,63,65,93,95,107] (Fig. 3). Patients with nasopharyngeal, sphenoethmoidal and trans-sphenoidal encephalocoeles do not have an obvious external swelling and may present with nasal obstruction or CSF rhinorrhoea.[3,64,65,67,89] These patients may also present with recurrent attacks of meningitis.[21,54,63,65] Frequently, patients with intranasal encephalocoele may present

Table 5: Experience of giant encephalocoele at AIIMS

	No.
Occipital	16
Frontoethmoidal	4
Anterofrontal	2
Total:	22

Table 6: Locations of anterior encephalocoeles at AIIMS in 118 patients (1971–2006)

		No.
A.	Frontoethmoidal group	92
	(a) Nasofrontal	8
	(b) Nasoethmoidal	76
	(c) Naso-orbital	8
B.	Transethmoidal nasopharyngeal	10
C.	Orbital	10
D.	Trans-sellar trans-sphenoidal	3
E.	Anterior fontanel	2
F.	Interior fontanel	1
	Total	118

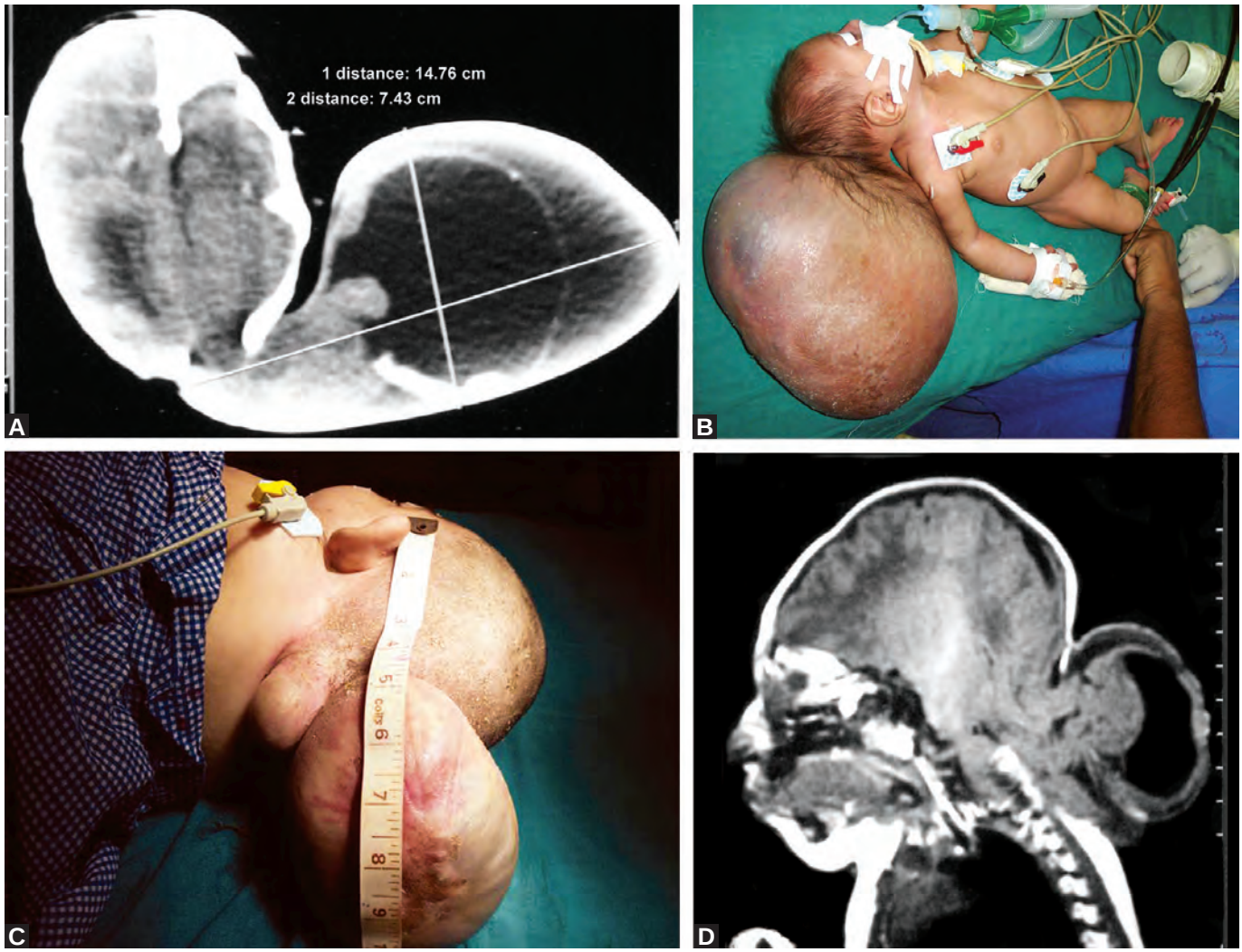
to the otolaryngologist and be diagnosed as having a polyp. It is only after biopsy or following surgery, when a patient develops CSF rhinorrhoea, an encephalocoele may be suspected[3,20,48,63,65] Rarely, encephalocoeles may present in the mouth through a cleft palate[58] (trans-sphenoidal transpalatal encephalocoele).[59,83,89,102]

Orbital encephalocoeles usually present with proptosis. It could be a part of a naso-orbital type of encephalocoele[18,23,30,44,63,93,94] where there is proptosis along with hypertelorism (Fig. 4). However, orbital encephalocoeles can present with proptosis without hypertelorism.[18] Orbital encelphalocoeles could also be a part of neurofibromatosis, when there is congenital absence of the wing of the sphenoid bone.[30] The proptosis disappears on assuming the supine position.

ANTERIOR ENCEPHALOCOELES

Nasofrontal Type

This type is also called frontonasal or glabellar encephalocoele. The internal bone defect is round or oval shaped and present in front of the crista galli.[38] The crista galli projects into the defect and forms the posterior margin. The anterior cranial fossa is deep. The facial bone defect is at the junction between the frontal and the nasal bones. Hypertelorism may or may not be present. However, the maxilla, nasal bone and nasal process of the maxilla are normal (Fig. 3). This type is relatively rare.[64,67,93,95]



Figs 1A to D: Clinical photographs of two neonates with giant occipital encephalocoele, with respective CT scans

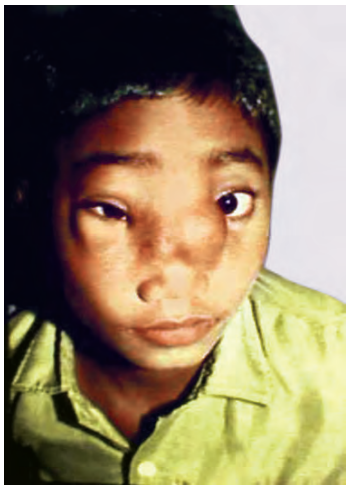


Fig. 2: Clinical photograph of a child showing frontal ethmoidal encephalocoele

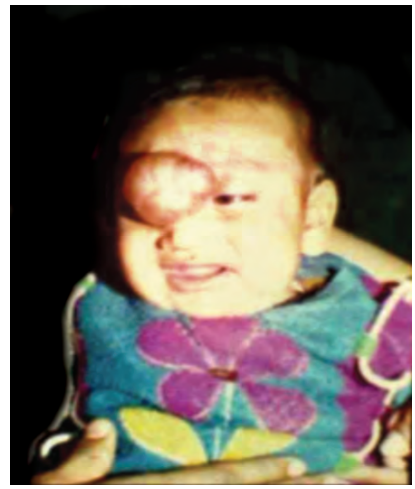


Fig. 3: Clinical photograph of an 8-month-old child with a frontonasal encephalocoele without hypertelorism

Nasoethmoid Type

This is the commonest type of sincipital encephalocoele and constitutes 85% of anterior encephalocoeles[23,25,51,64,67,81,90,97] (Fig. 2). This type is called long nose encephalocoele. The cranial defect lies in front of the crista galli in the floor of the anterior cranial fossa. The outer or facial defect lies at the junction of the nasal bone and nasal cartilage.[7,95,107] The neck of the encephalocoele is very long. The nasal bone and frontal process of the maxilla form the antero-superior part of the sac. The nasal cartilage and nasal septum form the postero-inferior wall. The lateral part of the sac extends into the orbit and presents at the inner canthi. Thus, the encephalocoele pushes the orbit and the eyeball laterally and downwards, and produces a marked degree of hypertelorism (Fig. 5). The swelling widens the bridge of the nose and pushes the tip of the nose downwards, thus elongating the nose considerably.[7,25,65,67]

Naso-orbital Type

This is a rare form of fronto-ethmoidal encephalocoele.[64,65,93,95,99] Among 118 cases of anterior encephalocoeles, the author found 8 such cases (Table 6). The inner skull defect lies in front of the crista galli and the outer defect is present between the frontal process of the maxilla and the lacrimal bone. The frontal process of the maxilla forms the anteromedial boundary, whereas the lacrimal bone forms the posterior-lateral part of the sac. The outer swelling appears at the inner canthus of the eye and may be unilateral or bilateral. The eyeball and the inner canthus are pushed laterally and downwards (Fig. 6). Thus, in all these patients, some degree of hypertelorism is invariably present (Fig. 7). The nose and nasal bones are normal.

Trans-sphenoid Encephalocoeles

This is the rarest form of encephalocoele reported in the literature.[1,56,59,74,104] Pollack et al.[83] reviewed 8 cases of trans-sphenoid and transethmoid encephalocoeles. Abiko et al.[18] in 1988, reported a single case. The bony defect is present over the roof of the sphenoid sinus. Thus, the encephalocoele may come through the sella or through the planum sphenoidale and enter into the sphenoid sinus and nasopharynx. The patient may have a history of CSF rhinorrhoea. A history of endocrine disturbances is also reported in these patients.[1,45,81,102] Rarely, they may have visual problems.

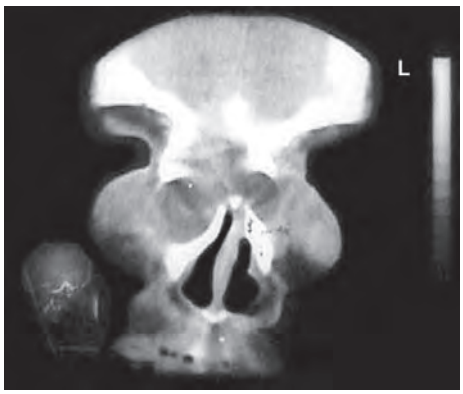


Fig. 4: CT scan of head of an 8-year-old child which shows bilateral naso-orbital encephalocoele

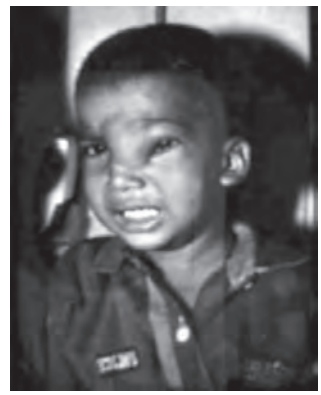


Fig. 5: Clinical photograph of a 5-year-old child with left sided naso-orbital type encephalocoele pushing the eyeball laterally. There is mild hypertelorism

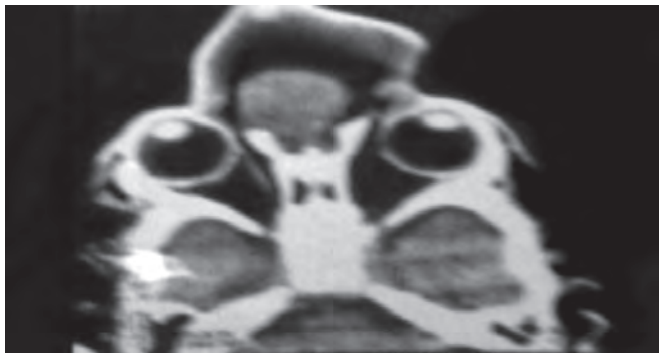


Fig. 6: CT scan axial cut of a child with nasoethmoid encephalocoele with gross hypertelorism

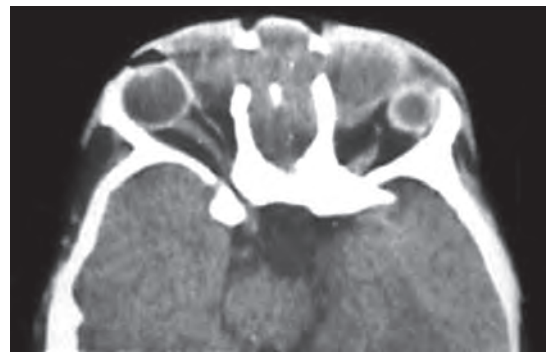


Fig. 7: CT scan of a child with bilateral naso-orbital encephalocoele showing hypertelorism

RARE CLINICAL FEATURES

Hypertelorism is a common finding in anterior encephalocoeles (Table 7).[22,44,52,65,93,94,100,105]

Mahapatra et al.[65] and Mahapatra[66] had reported a much higher incidence of hypertelorism. Rarely, maxillary and zygomatic bone abnormalities are also seen. Neurofibromatosis and 13-15 trisomy[21] syndrome have been reported in patients with encephalocoeles.

Mental retardation is reported depending upon the degree of brain damage. Suwanwela[95] and Suwanwela et al.[93] reported a much higher incidence of mental retardation in patients with anterior encephalocoele. However, the series presented by us reported a lower incidence of mental retardation.[64,66] Children with occipital encephalocoeles with cerebellum and brainstem herniating into the sac may present with poor cry and suckling.[53,82] Increased tone in the limbs and defective temperature regulation indicate a poor prognosis.

The problems of smell and vision are rarely discussed. It is logical to think that smell abnormalities will occur in patients with fronto-ethmoidal or sphenoethmoidal encephalocoeles. In unilateral naso-orbital encephalocoeles with a paramedian anterior fossa defect, smell is likely to be preserved on one side.[66] Visual abnormalities are due to a variety of reasons and may be due to herniation of the occipital lobes into an occipital encephalocoele, chiasmal abnormality in trans-sphenoid encephalocoele or due to orbital encephalocoele[18,29] pressing on the optic nerve. Visual deterioration can also be due to associated hydrocephalus.[48] Rarely, visual deterioration may be due to associated vitreoretinal degeneration.[87]

Few rare syndromes are associated with encephalocoeles. "Knobloch syndrome"[87] was described by Knobloch and Layer in 1971. This syndrome is transmitted by an autosomal recessive gene and characterised by vitreoretinal degeneration with retinal detachment, high myopia and encephalocoele. "Morning glory syndrome"[76] is a condition characterised by nasal encephalocoeles associated with progressive hormonal and visual problems. The basal encephalocoeles are either the trans-sphenoidal or sphenoethmoidal type. Due to pituitary involvement, patients present with dwarfism, polyurea and polydipsia. There is deficiency of growth hormone and ADH.

"Von Voss-Cherstvoy syndrome"[62] is another clinical entity first described by Von Voss et al. in 1979. The syndrome is characterised by an occipital encephalocoele along with phocomelia and cerebellar anomalies and is transmitted by an autosomal recessive gene.[33] The limb abnormality is more often due to a defect in the radius. The other anomalies associated involve the face, heart, lungs, urogenital system, gastrointestinal system and thrombocytopenia. Lubinnsky et al.,[62] in 1994, reported four cases and reviewed the literature on the subject. Walker-Warburg syndrome (WWS) is a lethal, complex syndrome involving the CNS and the eyes, and is genetically transmitted by an autosomal recessive gene. Martinez et al.[69] reported nine children with WWS out of whom eight had occipital encephalocoeles.

Prenatal diagnosis is possible by ultrasound scanning.[11,19] The earliest reported diagnosis is by 13 weeks of gestation. The ultrasound appearance of an encephalocoele is variable in the 1st trimester. Once an encephalocoele is diagnosed, a search for an associated anomaly can be made. Chromosomal abnormalities have been recorded in 15–40% and, therefore, karyotyping should be done in the mother.[17] Maternal serum alpha-fetoprotein levels are elevated in only 3% in the mother, because most encephalocoeles are

Table 7: Clinical presentation in patients with anterior encephalocoeles at AIIMS in 118 patients

Finding	*Number of patients*
Swelling over the nose and at inner canthus	92
Hypertelorism	92
Proptosis	15
CSF rhinorrhoea	16
Leaking encephalocoele	5
Meningitis	6
Nasal obstruction	10
Mental retardation	10
Neurofibromatosis Type I	8
Cleft palate	6

covered with skin. In the 2nd trimester, ultrasound scanning is the mainstay of foetal imaging. Although, ultrasound scanning is traditionally used as the mainstay in foetal imaging, the resolution and details of findings in the brain are limited by the mother's body characteristics and the surrounding amniotic fluid. Hence, foetal MRI is the investigation of choice. MRI is also far better in resolving posterior fossa anatomy. The fluid and CSF filled cavities are best demonstrated in MRI scan. The contents of the encephalocoele are well-depicted on MR scan. MRI scanning helps in visualising associated intracranial anomalies such as chiari malformation, Dandy-Walker Syndrome, agenesis of corpus callosum and porencephalic cyst (Fig. 8). More experience will enhance the role of foetal MRI in prenatal evaluation of the brain.

Investigations

Diagnosis of encephalocoele is not difficult. However, a large number of factors influence the treatment and ultimate outcome.[23,32,60,62,72,76,80,107] These include the presence of hydrocephalus, associated CNS anomalies, facial deformity and associated systemic abnormalities. Assessment of all the above factors needs proper investigation which may include the radiological, genetic and hormonal assessment.

The radiological investigations have changed over the years due to advances in imaging modalities. Plain X-ray shows a soft tissue mass and a circular smooth bone defect in the sub-occipital area, the skull vault or at the skull base depending on the site of the encephalocoele. It may show a nasopharyngeal soft tissue mass or displacement of the nasopharyngeal air shadow in sphenoidal or nasopharyngeal encephalocoele.[56,59,74] In sincipital encephalocoeles, X-ray skull will show a deformity of the orbits and increased interorbital distance in cases of hypertelorism.[15,19,45,55] Plain X-ray skull will show an enlarged orbit in case of intraorbital encephalocoeles.[18,30,45,57] Plain X-ray may show hypoplasia of the anterior or middle fossa,[53] skull deformity, craniostenosis, etc.

Carotid angiograms and pneumoencephalograms have been used as investigations in the past.[32,36,96] Suwanwela et al., in 1973,[96] reported the value of ventriculography in patients with anterior encephalocoeles, which helped in assessing the communication between CSF pathways and the encephalocoele sac. Cerebral angiography delineates the intracranial vasculature including the sagittal and transverse sinus. In a large number of cases, there may be abnormality of dural venous sinuses.[14] Though angiography remains the criteria for depicting vascular anomalies, it is rarely used in evaluation of encephalocoeles. MRA and MRV also help in assessment of vascular anomalies, including venous anatomy.

Recently, CT and MRI scans are commonly used modalities in the diagnosis of craniocerebral anomalies including encephalocoeles[1,39,44,47,52,64,65] There are only a few reports on MRI findings.[14,39] CT scan helps in evaluation of the ventricular system. The contents of the encephalocoele can be made out and the bony defect in the skull base can be delineated with bone window settings.[7,14,34,39,66,83] Hydrocephalus is commonly associated with posterior encephalocoeles. However, in anterior encephalocoeles, associated hydrocephalus is reported in 10–15% of cases.[23,32,44,52,64] CT scan can also detect associated anomalies like agenesis of the corpus callosum,[1,47,102] porencephalic cyst (Fig. 8), Dandy-Walker malformation, etc. In transethmoidal or trans-sphenoidal encephalocoeles, CT shows the soft tissue density in the sinuses and the bone defect in the skull base[47,59,61,88,93,105] (Fig. 9). In orbital encephalocoele, its relationship to the eyeball and optic nerve can be evaluated by high resolution CT. The bone cut may show a sphenoid wing defect

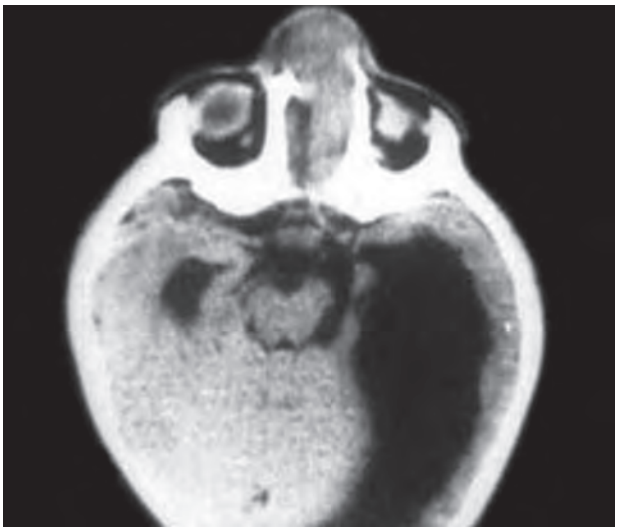


Fig. 8: CT scan head of a child with nasoethmoid encephalocoele which also reveals a porencephalic cyst

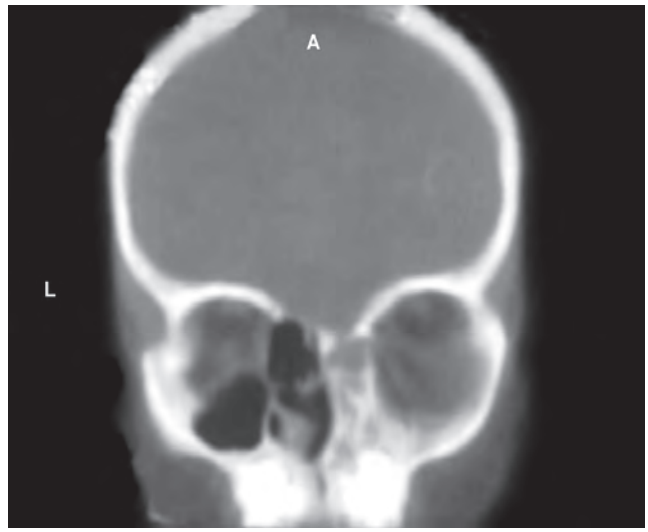


Fig. 9: Coronal CT scan of child with transethmoid nasopharyngeal encephalocoele showing soft tissue opacity in nasopharynx and nose

(as shown in Fig. 4). Metrizamide CT cisternography is useful in cases of occult encephalocoele.[20] Three dimensional CT scans are also used for the evaluation of basal defects.[39] MRI helps in soft tissue delineation. It also helps in diagnosis of Chiari malformation, syringomyelia and associated cortical dysplasia.[14,39]

Isotope studies are sometimes useful in the diagnosis of encephalocoele.[3,96,106] Yoshimoto et al[106] reported a transethmoid encephalocoele in a 2-year-old child who had bacterial meningitis. Isotope cisternography confirmed the presence of CSF rhinorrhoea. Anand et al[3] suggested pre-operative and intra-operative isotope imaging which may help in selection of the appropriate surgical approach.

Recently, visual evoked potentials have been used to assess occipital lobe and anterior visual pathway function.[29] Surprisingly, not much literature is available on visual evoked potentials. When VEPs are recordable from the sac, it indicates the presence of occipital cortex within the sac. Absence of visual evoked potentials may suggest a defect in the visual cortex or dysplasia of optic pathways.[15,53] The limitation of VEP must be emphasised in neonates or infants, in whom the delay could be physiological. The author had performed VEP in three patients with occipital encephalocoeles which showed grossly abnormal waves in two and absent response in one patient.

MANAGEMENT

The principle behind the management of encephalocoeles is to excise the encephalocoele and to repair the dural defect after putting back the herniated brain inside the cranial cavity, if possible. Sometimes, it may not be possible to push the brain into the cranial cavity. Then, the choice is to either excise a part of the brain or to give support to the brain in an extracranial space. Except for the situation with CSF leak, probably there is no indication for emergency surgery.[64,65,67,86] Sometimes, in a patient with a leaking encephalocoele associated with hydrocephalus, shunt surgery may stop the CSF leak and allow the skin to heal. A large number of children with occipital encephalocoele require CSF shunting.[32,42,67,69] According to Tandon (1970),[98] nearly 50% of occipital encephalocoeles have associated hydrocephalus and some may develop after repair.

Fortunately, most of the encephalocoeles have a good skin cover hence, emergency surgery is not required. The surgery can be delayed for weeks and months depending on the condition of the neonate. Surgery is simple when an encephalocoele is small, has a narrow neck, a small cranial defect and very little or no brain inside the sac. An occipital encephalocoele without brain herniation can be operated easily.[43] However, when the sac contains cerebrum, cerebellum and brainstem, surgery may be harmful and it is better to avoid an operation.[29,36,41,55,60,67] Many authors have reported a poor outcome in patients with microcephaly with a large volume of neural tissue within the sac.[41,44] Some authors have treated occipital encephalocoeles in special ways.[34,42,49] Gallo[34] discusses the management of a giant occipital encephalocoele. The technique he described comprised of an extracranial compartment created by utilising a fine tantalum mesh to enclose the herniated brain for protection.

Generally, patients with occipital encephalocoeles are operated upon in the prone position, with controlled ventilation and closed temperature monitoring. Aspiration of CSF prior to incision in patients with a large encephalocoele helps in dissecting out the sac (Figs 10A and B). For a circular encephalocoele with a small occipital bone defect, a transverse incision is ideal. The sac is separated from the skin flap (Figs 10C to E). Patients in whom the encephalocoele extends above and below the posterior fossa, a vertical incision is preferable. Sometimes the brainstem and occipital lobe are present in the sac. Care must be taken to identify the contents of the sac. Rarely, the sagittal sinus, torcula and transverse sinus are in the vicinity of the sac (Fig. 1B). It is always preferable to preserve the neural tissue. The dural defect can be repaired by using pericranium as a graft. In neonates and infants, no attempt should be made to cover the bone defect by a bone graft.[46,53,68,86] In older children with a large cranial defect, autogenous bone graft or acrylic plate may be used for closure of the defect.

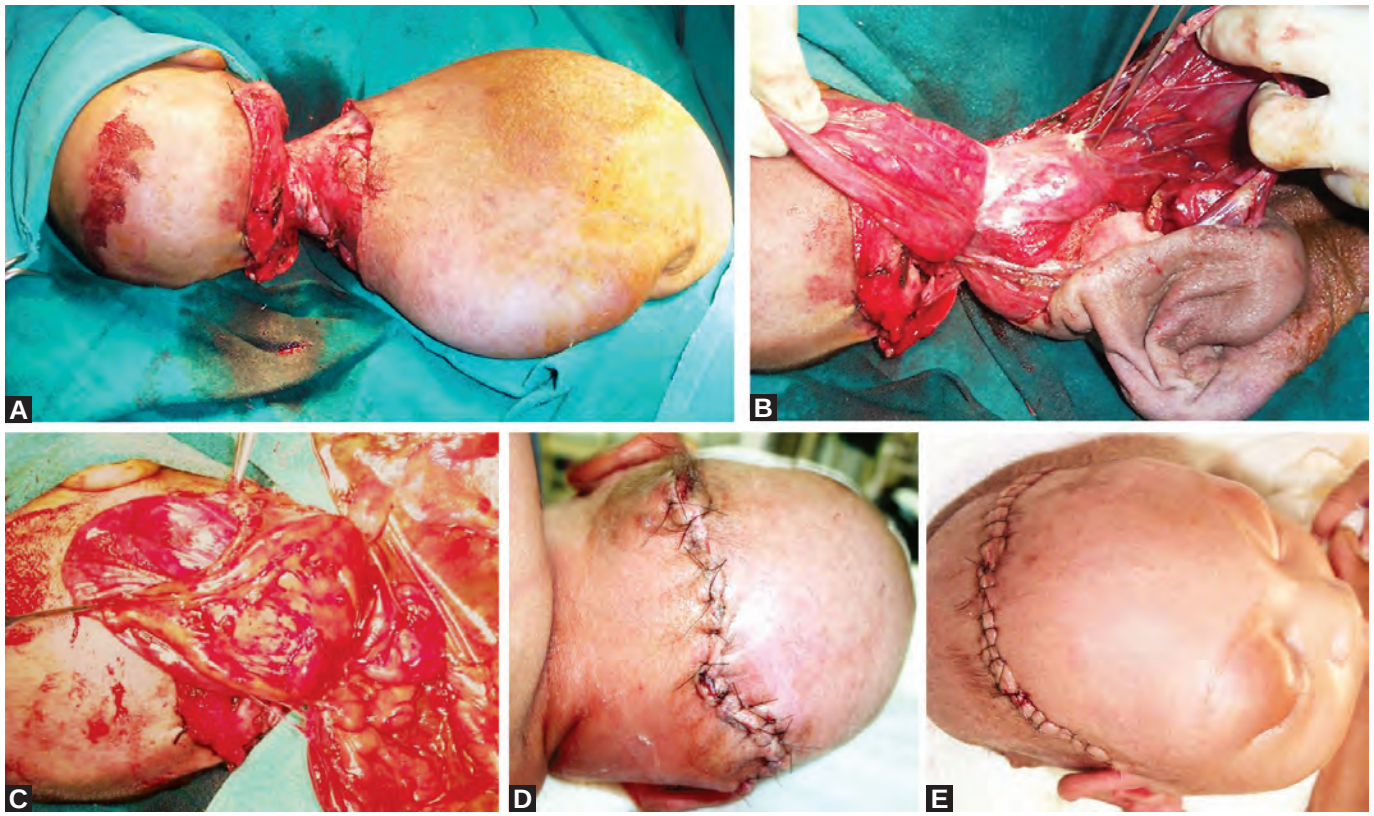
Post-operatively, there may be a CSF leak or acute hydrocephalus may develop. Patients in whom shunt is not performed prior to encephalocoele repair may need ventriculoperitoneal shunt subsequently. Patients may present initially with CSF leak and meningitis.[53] External ventricular drainage is the only alternative in patients with meningitis. Once the meningitis is adequately controlled, a VP shunt can be performed.

Prognosis in Patients with Occipital Encephalocoeles

A large number of factors influence the outcome in patients with occipital encephalocoele. These include site, size of the encephalocoele, amount of brain herniated into the sac, the presence of brainstem, occipital lobe with or without dural sinuses and the presence of hydrocephalus.[15,21,34,48] One of the most important prognostic factors is the presence of associated brain and systemic anomalies.[34,48,58,62,72,82,91] Overall, the outcome in occipital encephalocoele is not very good. In giant encephalocoeles, the mortality and morbidity rates are high. Amongst 14 children with occipital encephalocoele in our series, two died of hypothermia and the third succumbed to meningititis.

Encephalocoeles through the Cranial Vault

Encephalocoeles through the cranial vault are rare. It may be through the frontal, parietal or temporal bones. Encephalocoeles can occur through the anterior or posterior fontanel. Parietal or interparietal encephalocoeles are probably the most common encephalocoeles of the



Figs 10A to E: Intra-operative photograph of a child with occipital encephalocoele showing surgical steps

cranial vault.[71,72] Interparietal encephalocoeles are difficult to treat and do have a poor prognosis.[32,35] Only 15% of these patients have normal mental development, while the rest have mental and physical abnormalities.[71,72] Treatment in patients with small parietal encephalocoeles is not difficult. Patients with large skull defects need cranioplasty. On several occasions, when there is a large cranial defect, the author has used split autogenous outer table grafts.

Temporal and Parietal Encephalocoeles

These are uncommon encephalocoeles.[32,78] They constitute 1% of all cases of encephalocoeles. Rarely, a temporal encephalocoele may develop following radiation[55] and present with CSF otorrhoea. Clyde and Stechison[19] reported a case of temporal encephalocoele presenting with CSF rhinorrhoea. The surgical procedure is similar to that of occipital encephalocoeles.

TREATMENT

Treatment of Trans-sphenoid Encephalocoele

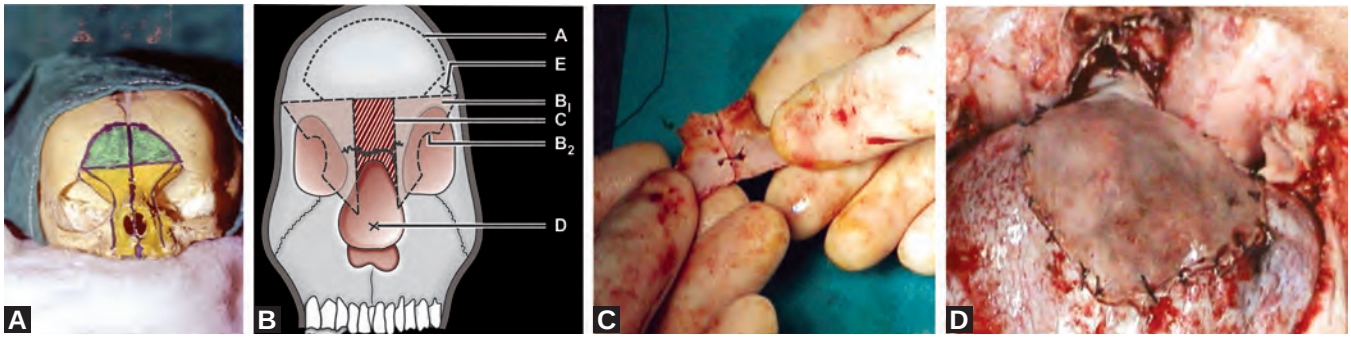
It is rare and only less than 50 cases are reported in the world literature.[40,45,56,59,83,89] Small children with a cleft palate may present with respiratory obstruction or recurrent chest infection. Management is difficult and they need early surgery. The surgical approach can be transpalatal or transcranial.[31,59,83] Some authors have preferred the transcranial approach to the transpalatal one. They repair the temporosphenoidal encephalocoele with a vascularised split calvarial graft. In the author's experience transpalatal surgery is easier and less traumatic. Among our three patients, two had transpalatal repair, however, the third patient had transcranial surgery.

Treatment of Anterior Encephalocoeles

The principle behind the management of anterior encephalocoeles is to repair the dural defect and to correct the bony deformities. Unfortunately, a large number of patients have facial abnormality due to associated hypertelorism,[23,25,51] and an elongated nose. Sometimes, the malformations are complex. Hence, the facial deformity plays an important role in corrective surgery. The cosmetic outcome depends upon the experience of the surgeon, age of the patient, degree of deformity and the teamwork between the neurosurgeon and the plastic or craniofacial surgeon (Figs 11A to D).

One stage repair of encephalocoeles along with the correction of the facio-orbital deformity is a long procedure and requires on an average 6–8 hours of surgery (Fig. 12).[23,25,65,99,104] Hence, the timing must be such that the child is able to withstand a long procedure. In our centre, we prefer to do the surgery when the child is older than 8–10 months.[25,64,65] Early surgical repair is ideal, as the bones are thin and moulding of the bones is easy. Early surgery also prevents CSF leak and the risk of meningitis.

A ventriculoperitoneal shunt prior to corrective surgery prevents post-operative CSF leak in patients with hydrocephalus. One stage correction of the craniofacial



Figs 11A to D: Diagrams showing the bone prior to and after the correction, with bone cuts and amount of bone need to be excised, it also shows dural repair

deformity is ideal.[23–25,44,52,65,77,84,93,100] The factors which influence the surgery are the type of encephalocoele, degree of hypertelorism, degree of nasal deformity and associated CSF leak or meningitis. It was Tessier who popularised the concept of one stage repair.[100] Sometimes, in a small child leaking CSF, a two-stage procedure may have to be carried out.[64,65] Recently, a large number of authors have reported good results with one stage craniofacial correction.[22,23,25,51,65,85] One-stage correction involves bifrontal craniotomy, fronto-orbital osteotomies and medial advancement of the orbit, after excising the extra-bone in the midline to correct the hypertelorism (Figs 11B and C). The initial part of the surgery deals with delineation of the neck of the encephalocoele, followed by excision of the herniated gliosed brain. The dural defect is closed by a dural graft (Fig. 11D). The type of correction of hypertelorism depends upon the degree of hypertelorism (Figs 4, 6, 13A and B). In case of mild hypertelorism, excision of soft tissue in the medial canthus and fixing the medial canthi to the nasal bone may suffice[64,65] (Fig. 5). Sometimes, nibbling of bone at the medial canthi followed by reconstitution of the medial canthus by canthal stitch corrects the hypertelorism.[25,64] Overcorrection of hypertelorism is important, as a significant amount of soft tissue may still be left in the medial canthus at the end of the operation. The aim is to achieve an inner canthal distance of 25 mm. Sometimes, a classical Tessier's operation may not be necessary. Recently, Mahapatra[64-67] had reported advancement of the medial half of the orbit medially and placing a supraorbital bone graft on either side (Fig. 12). By using the above procedure, operating time can be reduced on an average by 90–100 minutes.

Reconstruction of the nose is an important step in correction of anterior encephalocoeles.[23,25,42,85,100] The nasal deformity is maximal in patients with a nasoethmoid type of anterior encephalocoele. Extra skin over the encephalocoele has to be excised. The bridge of the nose is reconstructed by using either a rib or split calvarial graft.[25,65,85,99] Overall cosmetic correction is satisfactory in my experience (Figs 14A and B). Sometimes, to achieve a cosmetically excellent result, several small plastic surgical procedures may be necessary depending on the need of an individual patient, to correct nasal deformity or to excise extra skin or soft tissue at the medial canthi. This is basically because cosmetic acceptance depends upon the socio-economic status and age of the patient. In girls, the need for a better cosmetic result is more. An important post-operative problem following anterior encephalocoele repair is CSF leak leading to meningitis (Table 8). A large number of children do develop transient CSF rhinorrhoea which stops within few days. A small number of patients need lumboperitoneal shunt when CSF leak persists. In our series of 103 patients, there were three post-operative mortalities.[64] One patient died of aspiration pneumonitis, and two due to fulminant meningitis.

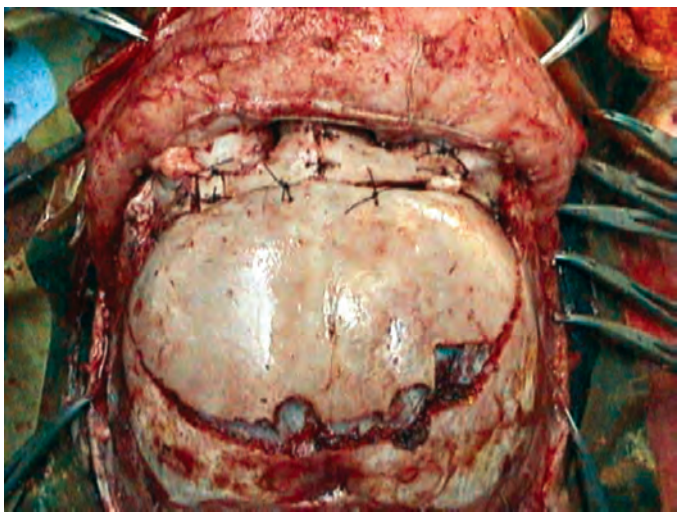
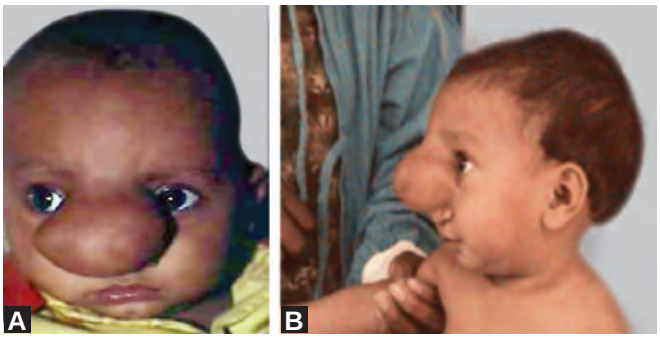


Fig. 12: Diagram showing medial half orbit advanced medially with supraorbital gap covered on either sides by bone grafts

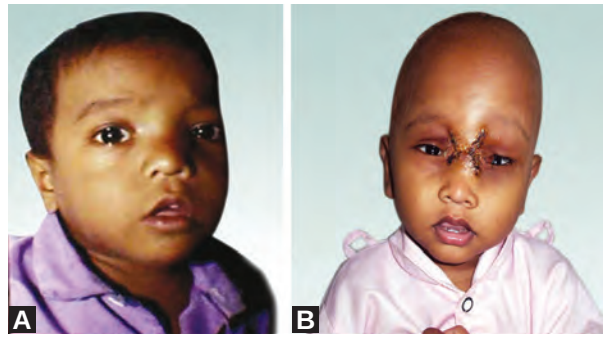
Table 8: Post-operative complications in 118 cases of anterior encephalocoele treated at AIIMS (1972–2006)

	No.
Wound infection	5
CSF rhinorrhoea	15
Meningitis	4
Infection of bone graft	2
Mortality	4*

*(two cases of hypothermia)



Figs 13A and B: Pre-operative clinical photograph of a patient of nasoethmoid type of encephalocoele with gross hypertelorism



Figs 14A and B: Pre-operative and post-operative clinical photograph taken on 6th post-operative day showing intercanthal stitch *in situ*

Prognosis in Patients with Anterior Encephalocoeles

Generally, the prognosis in children with anterior encephalocoele is better than occipital encephalocoele.[67,72,79,85,101] On the contrary, occipital encephalocoele with hydrocephalus carries a much poorer prognosis.[67] In the author's experience the intellectual function is good in patients with anterior encephalocoele.[64,67] Except for cosmetic problems, which can be corrected with appropriate craniofacial surgery, patients are normal. In the absence of hydrocephalus or meningitis, a large number of children are likely to have normal intellectual development.[22,65,67,72,79] Thus, the overall outcome in children with anterior encephalocoeles is more favourable[64,67] as compared to occipital encephalocoeles.

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17 Intracranial Arachnoid Cysts

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INTRODUCTION

Bright is given the credit of first describing arachnoid cysts (ACs).[8,83] He described these as, "serous cysts forming in connection with the arachnoid and apparently lying between its layers". The brain is completely impressed by them so that when the fluid is let out, a permanent cavity remains, and even the bone of the skull is moulded to their form". Describing another case, he says, "On sawing through the skull cap, a sudden gush of limpid fluid attracted attention and this had been contained in a cyst formed by splitting of the arachnoid membrane...".[83] His description, more than one and one half centuries old, is accurate even today and has practically encompassed all the relevant clinical aspects.

ACs are "intra-arachnoidal" collections of cerebrospinal fluid (CSF). These cysts are found within the arachnoid as isolated collections of CSF. AC may be found anywhere along the CSF axis; the intracranial cysts are all intradural while those located in the spinal canal may be extradural or intradural.[43] Over the years, a variety of names have been given to these lesions, for example, meningitis serosa circumscripta, cerebral pseudotumour, brain cyst, chronic arachnoiditis, chronic cystic arachnoiditis, leptomeningeal cyst, pseudo-porencephalies or closed porencephalies, temporal lobe agenesis syndrome, extracerebral cysts of middle cranial fossa, AC of middle fossa and, of course, AC.[17,40,83,98,100]

Most of the ACs are discovered in the first two decades of life, 60–80% being discovered by 16 years of age. Their occurrence in adults has also been well documented. Some may be discovered when investigations are performed for an unrelated malady and yet others only at autopsy. It has also been documented in foetuses and non-human population.[10,15,45,46,89] Improved diagnostic methods have resulted in more of these cysts being discovered.

"Congenital ACs" which are true or "primary ACs" are not the same as "secondary ACs" which are merely trapped collections of CSF. Thus, the latter variety cannot be included in the category of "True AC" but should be included under the category of leptomeningeal cysts. Although most of these cysts are usually congenital, they may follow trauma or infection of the central nervous system (CNS). The congenital variety accounts for 1% of all intracranial space occupying lesions.

These cysts may be associated with other developmental anomalies of the brain and, by indenting and exerting pressure on the subjacent brain, they may cause secondary local atrophy and gliosis.

Of the many theories proposed to explain their origin, abnormal splitting of the arachnoid during embryogenesis is widely accepted. Their association with the CSF cisterns lends support to this theory. Their clinical features, radiologic features and pathology have been well elucidated, but their management is still shrouded in controversy. "The surgical treatment is as variable as the location of the cyst."[40] In addition, their natural history too has not been well defined since they are well known to be small or large at the time of presentation, and may increase in size or resolve over time.[66,81,82,106]

Currently, there is a resurgence of interest in the origin, pathogenesis and structure of ACs. A better understanding of these factors will directly influence the clinical management of patients with these cysts, since there is a persistent debate as to the choice of the type of surgical treatment.

EMBRYOLOGY AND ANATOMY

A loose and sparsely cellular area lies between the developing neural tube and the notochord at 35–38 days of gestation. This mesodermal derivative is the meninx primitiva. At 48–53 days, this region cavitates. The loose mesenchymal tissue surrounding the developing neural tube forms a compact outer layer and a loose inner layer. This outer part corresponds to the dura; the loose layer which lies deeper gives rise to the pia and the arachnoid. A cavity forms between the outer compact layer and the portion of the inner layer which forms the arachnoid. This cavitation results in the formation of the subarachnoid space.[74,112] This cavity is not a uniform space, but resembles a "meshwork". When the rhombic roof ruptures, the CSF secreted by the choroid plexus finds its way into this "primitive" subarachnoid space and flows through this mesh-like space, the outer wall of the space being formed by the arachnoid and the inner wall by the pia. The CSF is propelled through by this meshwork of tissues by the "pump-like action of the choroid plexuses of the cerebral ventricles".[54] This meshwork probably persists since numerous trabeculae within the subarachnoid space have been observed during microneurosurgery. In addition, "the arachnoid

partitions the subarachnoid space into relatively discrete chambers".[112]

Two theories have been proposed to explain the formation of AC. One holds that sequestration of the CSF resulting from an aberration of the flow of the CSF results in the formation of AC.[86] The other postulates that an abnormal splitting of the primordial arachnoid and the subsequent aberration in the formation of the CSF spaces leads to the formation of the AC.[8,38,100] In the initial stages when the cysts are very small, they probably are completely enveloped by CSF. But as the cyst increases in size, its walls fuse with the arachnoid, thereby trapping the vessels which traverse this space.[100]

If the rhombic roof does not perforate fully, the CSF may find its way into the rhombic roof forming an AC within the cisterna magna.[74]

Suprasellar AC is considered to be an outpouching of the membrane of Liliequist.[74] If this membrane remains imperforated, it prevents the flow of CSF from the infratentorial to the supratentorial compartment. This results in the formation of a diverticulum and, over a period of time, the continued dilatation results in the formation of a suprasellar AC.[36]

ACs are thus congenital malformations, which are wholly intra-arachnoidal, lying between the layers of the arachnoid,[100] the outer and inner layers being formed by the barrier cell layer and basal cell layer, respectively.[8] These are "not simply a dilation of the subarachnoid space walled off by adhesions".[100] ACs are thus isolated from the rest of the subarachnoid space, although CSF can gain entrance into the cyst. The veins which lie in the vicinity of these cysts—during cyst formation—can become "incorporated" into these cysts. These are seen lying within the cysts, unsupported.

The causative factors of these cysts are quite varied. By and large, the most common variety is the congenital form. The other causes include trauma and inflammation. Some experts do not consider the cysts which follow trauma and inflammation as the true AC.[86] This is so because the cysts which follow trauma and infection are not true AC, but merely localised collections of CSF surrounded by scarred arachnoid.[48] Nevertheless, these collections of CSF continue to be called ACs. In addition, not all cysts which are initially diagnosed as congenital AC (based on clinical, imaging or operative findings) are true AC. Some of them may be glioependymal cysts, ependymal cysts or simple cysts lined by atrophic brain.[8]

Some of these cysts may be small and be discovered only at autopsy while others may manifest even in the neonatal period; and yet others have been seen to increase in size over a period of time or be discovered only at autopsy. The exact mechanisms or the factors which lead to the expansion of the cyst are unknown. A variety of factors may come into play in the expansion of these lesions.

Agenesis of the temporal lobe was proposed as a causative factor for middle cranial fossa AC by Robinson in 1964.[8] However, subsequent work has proven that this is not the case. Macroscopic and microscopic observations have shown that the temporal lobe in these patients is normal. Robinson subsequently corrected his earlier conjecture of temporal lobe agenesis.[8,94] An autopsy study has shown that there is "no significant difference in the weight or volume of the cerebral hemispheres to suggest any evidence of agenesis or hypoplasia involving the affected hemispheres".[94] Other studies have also shown that there is no "agenesis" of the temporal lobe, and the surrounding brain is structurally normal. The re-expansion of the temporal lobe following treatment also proves that the temporal lobe is not dysgenetic.[17,44,94]

True AC may be the result of an inflammation occurring in the 6–8th week of embryonic life.[38] Several examples have been attributed to a previous episode of leptomeningitis, most often in early life or even in utero and, occasionally, a previous event of this nature has been clinically documented. Other examples include traumatic injuries, including birth trauma.

Okumora et al. have suggested that ACs are secondary to primary cerebral hemispheric maldevelopment and, therefore, they constitute a form of external hydrocephalus.[77] In any event, congenital ACs must be differentiated from those that follow structural destructive lesions, like porencephaly, that form part of a pre-natal or post-natal encephalopathy.

A minor subarachnoid bleed may result in the formation of a small cyst which subsequently increases in size.[20,40] ACs which follow inflammation, unlike true AC, have inflammatory cells and haemosiderin deposits in the wall.[74,84] These, in addition, may increase in size over a period of time.[88] ACs have also been reported to following craniotomy.[63,105] True ACs are in no way related to porencephalic cysts.

True ACs are congenital and the evidence to support this is strong and may be summarised as follows:

- They occur predominantly in the paediatric age group—as much as 60–80% being discovered by the 16th year of life.[8]
- Most required treatment in the paediatric age group.
- Associated expansion or bulging of the calvarium at the site of the cyst.
- An acquired cause cannot explain the gross and microscopic pathology.
- The subarachnoid cisterns and spaces are not one continuous sea of CSF. Careful dissection and observation during microsurgery clearly reveals the presence of numerous trabeculations and strands in the subarachnoid spaces. In addition, the cisterns are divided into discrete compartments which communicate with one another. These indicate that these cysts result from an abnormal splitting and loculation of CSF as a consequence of an embryologic error.
- The walls of the AC are continuous with the arachnoid; the cyst thus is an "island" in an "ocean" of CSF.
- All cysts are related to a subarachnoid cistern.
- Presence of other congenital brain anomalies.

- Normal structure of the brain as seen during surgery and the re-expansion following surgery.[104]

PATHOGENESIS OF CYST EXPANSION

The expansion of the cysts over time has been attributed to a variety of causes. These include flow of CSF into the cyst by a ball-valve action, secretion of CSF by the cyst wall, secretion by a choroid-like structure in the wall or osmotic gradient.[39] The exact cause has not been determined yet. Direct observational evidence exists only for accumulation of CSF by ball-valve action. A slit valve mechanism was observed in a child with a suprasellar AC during endoscopic surgery. The valve, formed by an arachnoid membrane, was seen to open and close with pulsations.[92] The slit valve mechanism has not only been observed intra-operatively but also pre-operatively using cine mode MRI.[90] Vascular pulsation is the force which propels the CSF into the cyst. The fluid may gain entrance into the cyst during the various phases of the cardiac cycle.[18,75,91] Intra-operative observations during endoscopic surgery have elegantly demonstrated the ingress of CSF during the various phases of the cardiac cycle. The wall of the cyst was seen to pulsate corresponding to the cardiac activity. The wall of the cyst "detaches from the solid surfaces, brain parenchyma, skull base or a major intracranial artery".[91] Inspection of the arachnoid at this time has revealed minute perforations in the wall and the pulsations of the brain are transmitted to the CSF spaces which in turn forces CSF into the cyst. These minute perforations in the cyst wall are not apparent all the time, but only during certain phases of the cardiac cycle. As mentioned earlier, a slit valve mechanism has also been observed.[91,92] Some of these fenestrations have been shown by using the microscope.[39] Communication with the surrounding CSF has also been shown during pneumoencephalography and also cisternography using water-soluble contrast media.

Secretion of CSF by the cyst wall has been postulated to be a mechanism by which these cysts expand. Go et al. in their study have shown microvilli which have features that are observed in fluid-secreting or fluid-absorbing tissues. Also, the ultracytochemical evidence of Na^+–K^+–ATPase and alkaline phosphatase in the plasma membranes of the lining cells suggest a capacity for fluid secretion.[39] Although these indicate possible secretory activity, no direct evidence for secretion exists. Until this is observed directly or definite proof for this is available, this has to be accepted only as a hypothesis.

The protein content of the CSF in the cyst, ventricles and lumbar subarachnoid spaces are not the same.[74] As a result of a haemorrhage from the veins traversing the cyst, the protein content in the cyst can increase, thus setting up an osmotic gradient.[17,29] But, since the fluid within these cysts is almost identical to CSF, the reason for expansion of the cyst by flow of fluid due to an osmotic gradient is difficult to accept as a general rule.

Secretion from choroid-like structures present in the cyst wall has also been postulated to be a cause for the increase in the size of the cyst.

PATHOLOGY

Macroscopic Appearances

Rengachary and Watanabe have compared the structure of normal arachnoid with that of the wall of an AC and have noted similarities and differences.[84] This has provided an insight into the pathogenesis of this lesion. The most striking histological finding in the AC is the splitting of the arachnoid membrane to enclose the cyst, while the pia-mater remains as a separate intact membrane. The normal arachnoid membrane seems to blend with the outer layer of the cyst wall at the margin of the cyst. The cyst is, therefore, intra-arachnoid with an inner and outer wall formed by the arachnoid membrane. Grossly, the cyst consists of a thin transparent wall. Its outer part is distinct from the inner layer of the dura. On its inner aspect, it shows a plane of cleavage from the underlying pia-mater. The cyst is usually filled with clear, colourless fluid. The watery content of an AC is readily seen through its delicate translucent wall. When the wall is punctured, the contents spill to expose the flattened gyri of the adjacent brain. Thereafter, the delicate membrane may be hard to find, its thin substance being almost inapparent. Occasionally, the cyst fluid may be xanthochromic and rich in protein and can be mistaken for a subdural hygroma.[67] Urich et al. have observed that subdural hygroma may also be a secondary complication in children with ACs.[103]

Vessels lie unsupported in the cyst and may rupture easily leading to intracystic haemorrhage (Fig. 1).

ACs of the cerebellopontine angle and parietal lobe have been respectively shown in Figures 2 and 3.

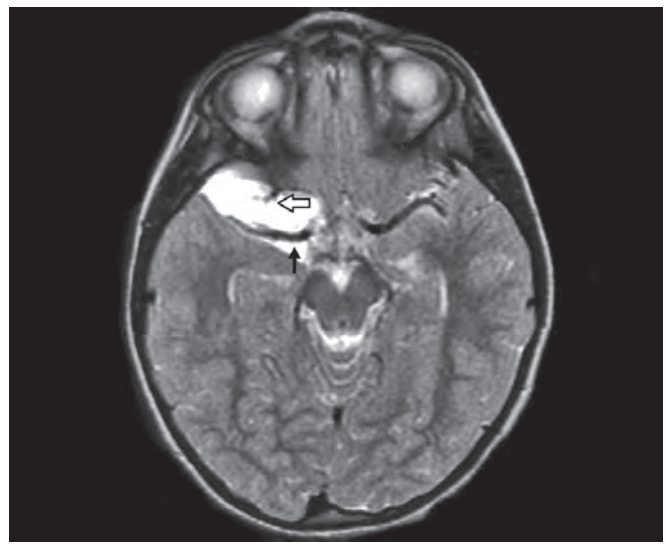


Fig. 1: MR showing unsupported vessels in a Sylvian arachnoid cyst. (Vertical solid arrow: middle cerebral artery. Horizontal open arrow: unsupported vein)

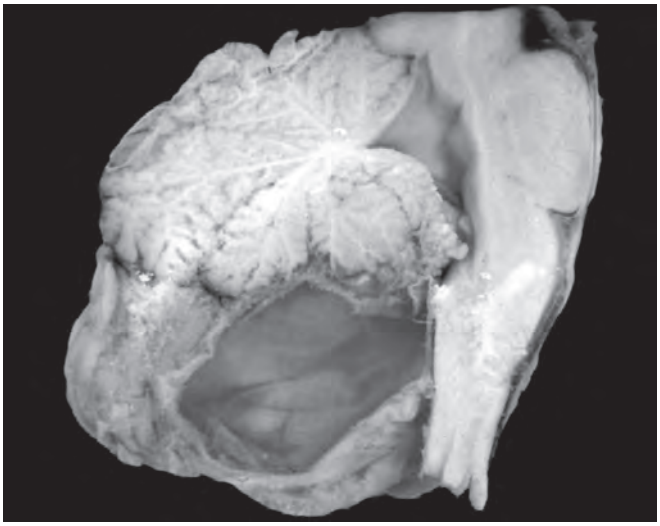


Fig. 2: Cerebellopontine angle arachnoid cyst

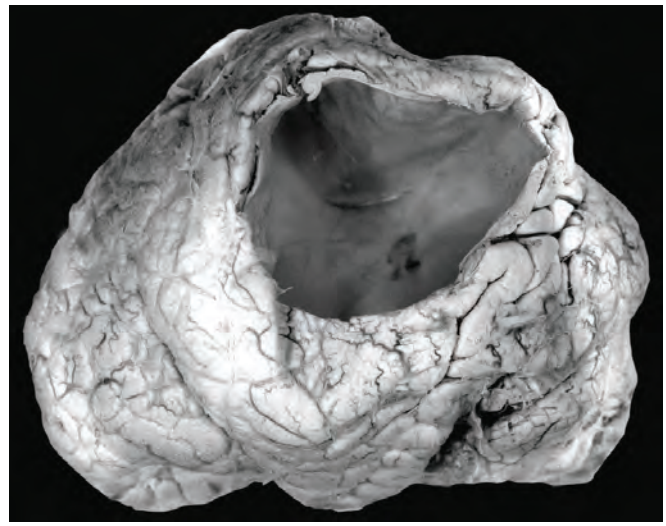


Fig. 3: Parietal lobe arachnoid cyst

Microscopic Appearances

The light microscopic and ultrastructural features of ACs are comparable to the normal arachnoid mater with a few differences.

Normal Arachnoid Mater

Light Microscopic Features

The arachnoid mater consists of a subdural cell layer, a trabecular connective tissue layer and an inner surface cell layer. The arachnoid cells in the subdural layer are flat, having elongated nuclei and dark tapering cytoplasm. The cells are stacked at random. The thickness of this layer varies in the different parts of the CNS. In the very thick area, the cells are plump and clumped irregularly as meningothelial nests.[84] Here, cytoplasmic whorls, psammoma bodies and calcified small vessels are seen. The second layer or trabecular connective tissue layer is a well developed distinct layer in adults. From this layer, traversing trabeculae arise which are attached to the pia mater. There are few cells within this connective tissue. Occasionally, sparse plump arachnoid cells are present. The inner surface cell layer covers the subarachnoid space. The cells in this layer do not tier. Small blood vessels are encountered in this layer, which are also surrounded by a single layer of arachnoid cells. Occasional macrophages are often found in the subarachnoid space.[84]

Transmission Electron Microscopic Features

The subdural arachnoid cells are flat, electron dense and stacked either in a few or several layers in the thin and thick zones of the membrane, respectively. They are connected by frequent gap junctions and desmosomes. They often form onion and skein like concentric whorls made of branching, fine cytoplasmic processes of arachnoid cells. The nuclei of these cells are usually located at the periphery of whorls. An incomplete basal lamina is noted between the arachnoid cell of the innermost tier and the trabecular connective tissue. This tissue separates the subdural arachnoid cells from the subarachnoid space. The trabecular connective tissue contains only a few cells. The thin inner surface arachnoid cells that line the subarachnoid space are similar in structure to the subdural arachnoid cells.

Arachnoid Cyst

Light Microscopic Features

The majority of cases exhibit features suggestive of splitting of the arachnoid membrane. The cyst wall consists of a vascular collagenous membrane. The collagen bundles in the adjacent normal arachnoid membrane and in the superficial layers of the dome of the cyst are compact, while the collagen fibres in the deeper layers of the dome and in the inner wall of the cyst are more loosely arranged. The inner wall of the cyst and pia mater are in direct contact with each other. Here, the subarachnoid space is obliterated.

The dense collagenous tissue in the dome of the cyst is covered by thick layers of subdural arachnoid cells. Two types of cells are seen. The outer tiers are composed of dark cells which are similar to normal arachnoid mater. The inner tiers are composed of lighter cells with large, round nuclei and abundant cytoplasm. The light arachnoid cells are frequently seen lining the subarachnoid space and these cells are also sparsely scattered in the connective tissue. In addition, there are also a few haematogenous cells within the trabecular connective tissue. Blood vessels are scarce in the cyst wall. There are no traversing trabeculae in the cyst lumen.

Transmission Electron Microscopic Features

The superficial dark arachnoid cells which form the outer tiers within the dome of the cyst have condensed nuclei and cytoplasm. The cytoplasm contains abundant filaments and a fair number of rough endoplasmic reticulum, free ribosomes, mitochondria and Golgi complexes.

The inner surface of the AC wall is lined by clear arachnoid cells. These are hyperplastic, larger and appear as evenly hydrated cells, and resemble foetal arachnoid cells. The cells in both layers are closely stacked and connected by frequent desmosomes and gap junctions. The clear arachnoid cells of the inner layer are bordered by incomplete basal lamina. Such cells are also found in the trabecular connective tissue. In contrast to the normal, arachnoid mater where trabecular clear arachnoid cells are widely separated by connective tissue, the clear arachnoid cells in the cyst wall are frequently clustered, with closely opposing plasmalemmas connected by gap junctions and desmosomes.

Immunohistochemical Findings of Arachnoid Cysts

The epithelial nature of the lining cells can be established by immunoreactivity for epithelial membrane antigen. As expected, the cysts are negative for markers found in other intracranial and intraspinal cysts such as GFAP, carcinoembryonic antigen and transthyretin.[65]

NATURAL HISTORY

The natural history and behaviour of these cysts are quite variable and uncertain. Little is known about the natural history of these lesions.[2] Some make their presence felt very early in life, while others are discovered only at autopsy. Even large cysts have been noted at autopsy.[52,94] These cysts are well known to expand over a period of time and manifest as space-occupying lesions or haematomas often following a trivial trauma, with features of increased intracranial pressure.[19] They are also known to disappear after a head injury or undergo spontaneous rupture.[71,82] As discussed above, in addition to disappearing they are also known to grow or fluctuate in size.[7,11]

INTRACRANIAL CYSTS

Clinical Features

Incidence and Distribution

These congenital lesions account for about 1% of all intracranial mass lesions and in 0.5% of autopsies they are seen as incidental findings. Most of the cysts are in the Sylvian fissure region. Males are affected more than females and the cysts occur more often on the left side.[74] While left sided cysts in the Sylvian fissure region are more common in males, the distribution of cysts in other locations is equal in both the sexes.[108,109] About 60–90% of patients are in the paediatric age group and the majority manifest within the first 6 months of life.[44] In 25% of the cases, it is diagnosed at birth. Associated brain malformations may be seen in a significant number of these patients. The cyst is single in 87.5% of patients.

While nearly 50% of the cysts are in the region of the Sylvian fissure, the next common site is the posterior fossa—which accounts for about 20% cases; 10% are in the supracollicular area while 9% are found in the sellar and suprasellar areas. The distribution in the other areas is as follows: interhemispheric fissure 5%; cerebral convexity 4% and clival area 3%. Bilateral, multiple, intraventricular, interpeduncular, intradiploic, craniovertebral junction and clival area cysts are very rare.[4,38,51,73,80,84,102] Rarely, a cyst may extend to more than one compartment.[5]

ACs occurring in siblings, at different sites in the same patient and symmetrically are also rare as are familial cysts.[74,79]

Manifestations—General

Although the cysts in the various locations have specific clinical features, some of the manifestations which have overlapping features can be considered first. Some features are fairly specific for certain cysts that a diagnosis can be made easily. These depend on the location of the cyst, i.e. Sylvian fissure cysts usually cause fits, haemiplegia and headache; suprasellar cysts result in hydrocephalus, endocrine problems and bobble-head doll syndrome; posterior fossa cysts lead to ataxia, hydrocephalus and features of posterior fossa neoplasm. Symptoms can fluctuate in intensity leading to an error in the diagnosis. It has to be emphasised here that these cysts may remain asymptomatic even when large and may be discovered only at the time of autopsy. The aetiology of the symptoms can be classified into "fluid related symptoms", "epilepsy" and "deficiency syndromes".[38]

Headache is a fairly common feature, both in children and adults. The headaches are just a manifestation of the raised intracranial pressure. Up to 70% of patients experience chronic headaches.[74] Enlargement of head size, tense or full anterior fontanelle and wide open sutures are often seen in children.[5]

In children, a diagnosis of congenital hydrocephalus may be made since their proximity to the CSF cisterns causes hydrocephalus by obstruction to the flow of CSF.[29] The incidence of hydrocephalus varies from 30–100% depending on the location of the cyst. Hydrocephalus is common in posterior cranial fossa cysts, but it is seen in almost all midline cysts.[38]

Seizures are common and form an important clinical feature in as many as half the number of patients.[74] These are so, especially in Sylvian fissure cysts. The seizure focus is adjacent to the AC in about a quarter of the patients only. This has led to questioning the validity of postulating the AC as the primary cause of seizures.[6]

Middle cranial fossa or Sylvian fissure cysts may cause "global impairment of brain function by interfering with the blood supply." This has been demonstrated by single photon emission computed tomography studies.[93] Left temporal ACs have also been shown to cause problems in cognition. These improve after surgery.[110] Although endocrine symptoms are commonest in suprasellar cysts, they are not unknown in other cysts.[69]

Peripherally located cysts, usually, are diagnosed later than centrally located cysts since the latter, by causing hydrocephalus, make their presence felt earlier.[38]

In older patients, cysts, when discovered, are usually asymptomatic and occur as incidental findings.[38]

Following rupture, these may present as subdural hygromas or haematomas.[28,33]

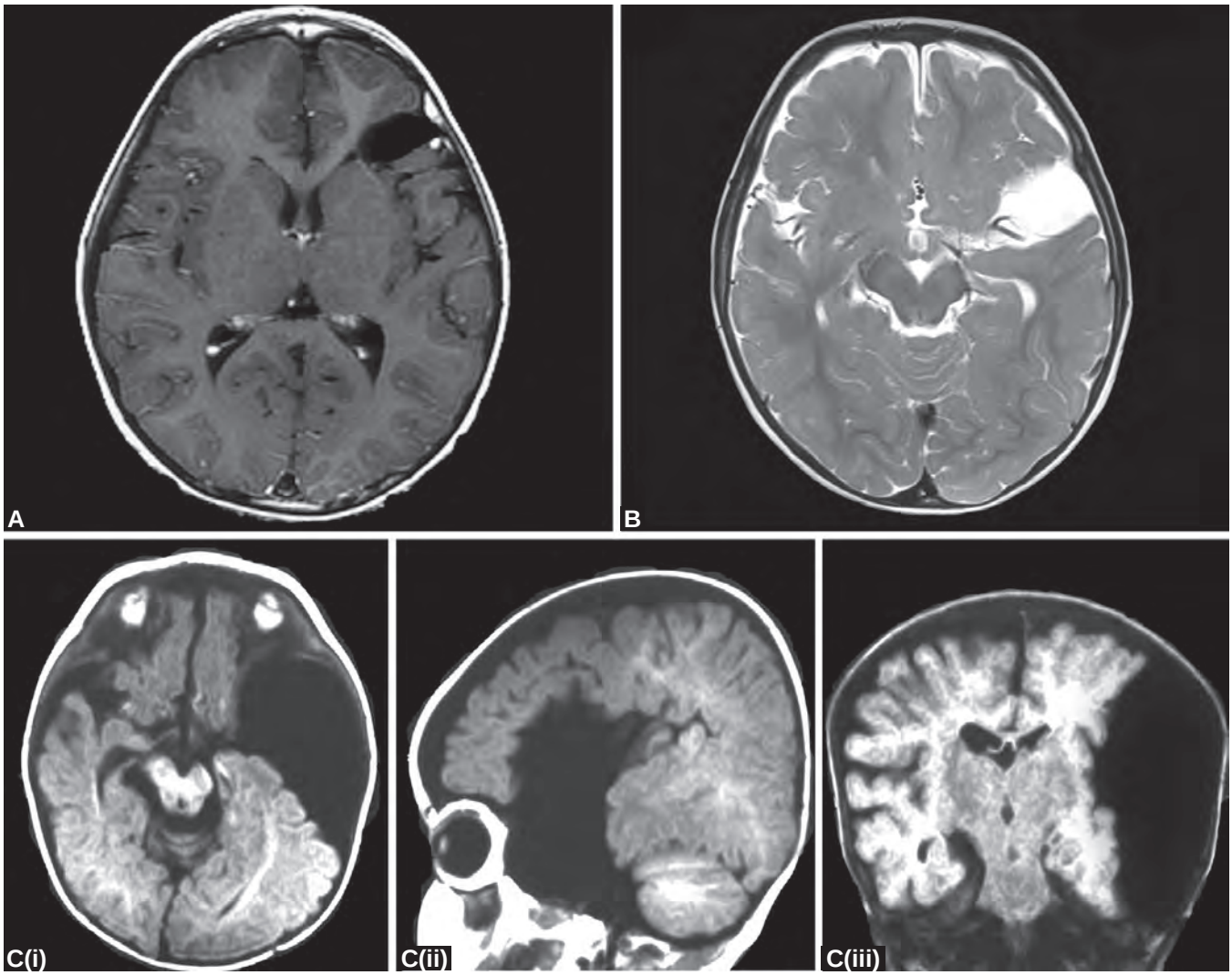
Manifestations—Specific

Sylvian Fissure Cysts

Included in this group are temporal cysts and cysts in the middle cranial fossa. This is the commonest site of occurrence of AC (Figs 4A to C). The incidence ranges from 49% to as much as 68% in some series.[38,84] Headache and seizures are the commonest presentation of AC in this location. Headache reflects the raised intracranial pressure and may not point to the pathology or have localising value. In infants and children, the calvarium may exhibit a bulge and this can be observed clinically and on imaging studies. If the cyst is longstanding or large, there may even be an asymmetrical enlargement of the head. In addition, these may cause changes in the sphenoid wing. The cranial deformity and the midline shift, which are often present, result from the mass effect of the cyst. Since these are located primarily within the Sylvian fissure or are closely related to it, the Sylvian fissure is spread out resulting in a "foreshortening" of the temporal lobe.[5] The Sylvian vessels are pushed posteromedially and lie deep to the cyst. In addition, anomalies of the venous system may be present.[74] These cysts are highly susceptible to trauma and bleeding.[104] Among all groups of cysts, these are most often associated with intracystic haemorrhage.[74] The haemorrhage may not be associated with any definite history of trauma or, if a history of trauma is present, the injury may be trivial. The veins snap easily because they do not have any support and are just bathed by CSF. Such a haemorrhage inside the cyst may present as a subdural haematoma, and be diagnosed as such.[19,33,104] Their presentation as subdural hygromas is also known.[28]

These cysts have been classified into three types based on their size, appearance and CT cisternographic findings by Galassi et al. as follows:

Type I: These are small biconvex cysts which are located in the anterior part of the Sylvian fissure. They do not exert any mass effect or cause cranial deformity.



Figs 4A to C: (A) Type I Sylvian fissure arachnoid cyst. (B) Sylvian fissure arachnoid cyst (Type II cyst). (C) MR images of Sylvian fissure arachnoid cyst: (i) axial; (ii) sagittal and (iii) coronal views. This is a Type III cyst

CT cisternography discloses free communication with the subarachnoid space.

Type II: The cysts are medium sized and quadrangular or triangular in shape. They occupy the anterior and the middle part of the Sylvian fissure. The insula (which corresponds to the medial straight border of the cyst) is exposed and the temporal lobe is "shortened". The frontal lobe may be displaced anteriorly. Bony changes, if any, are minimal. Early pooling of the contrast and partial communication with the subarachnoid space are found on cisternography.

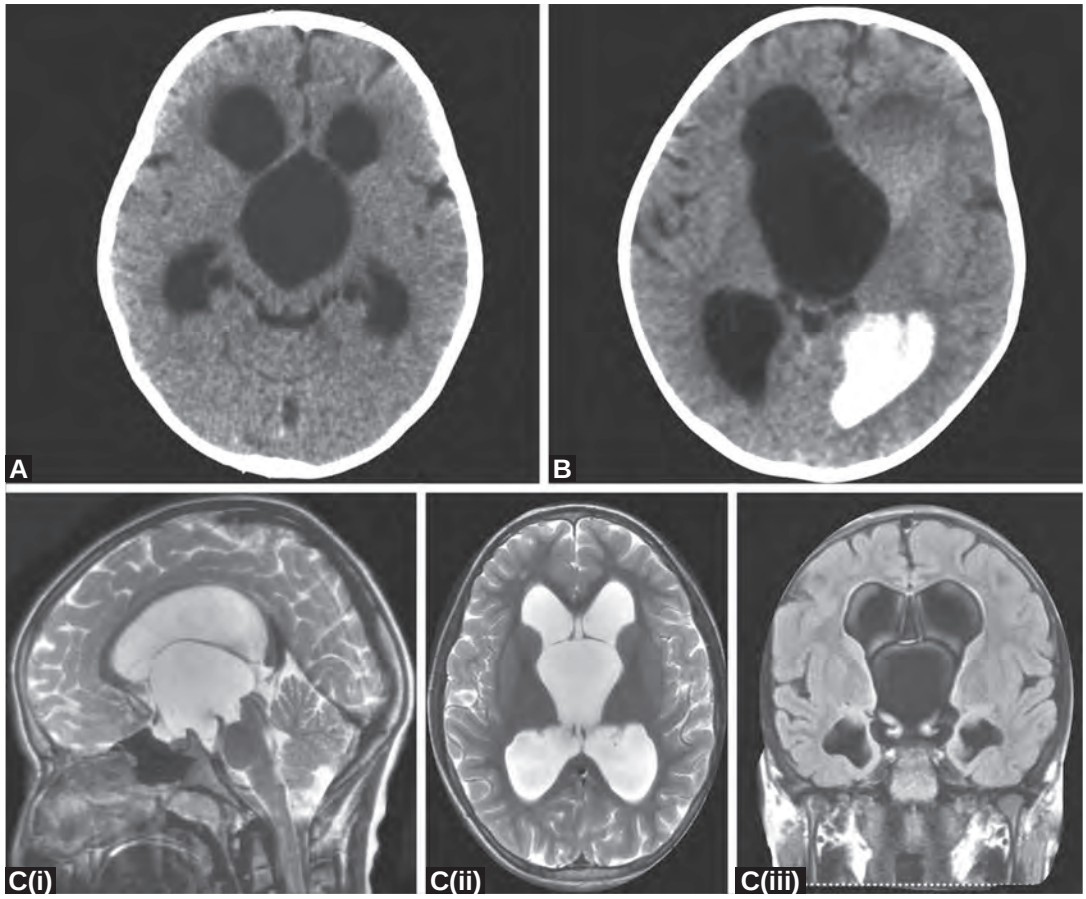
Type III: These cysts are large and oval or round in shape and involve the whole of the Sylvian fissure. They exert considerable mass effect on the brain with severe compression of the brain and midline shift. Deformity of the cranium is marked. Communication with the subarachnoid spaces is not apparent on cisternographic studies, but some contrast may pool around the cyst.[34,86]

The evolution of Type III cysts is unclear (at the present time) as to whether they evolve from Type I or II cysts or they arise *de novo*. If Type I or II cysts progress onto Type III cysts, they need treatment as soon as the diagnosis is made. This is a subject for future studies. Following treatment, re-expansion of the brain is seen in Type I and Type II cysts unlike in Type III cysts where the re-expansion is not full. A Type I cyst is usually discovered incidentally and often needs no treatment unlike Type III cysts, which always are symptomatic. The management of Type II cyst depends on the overall case scenario.

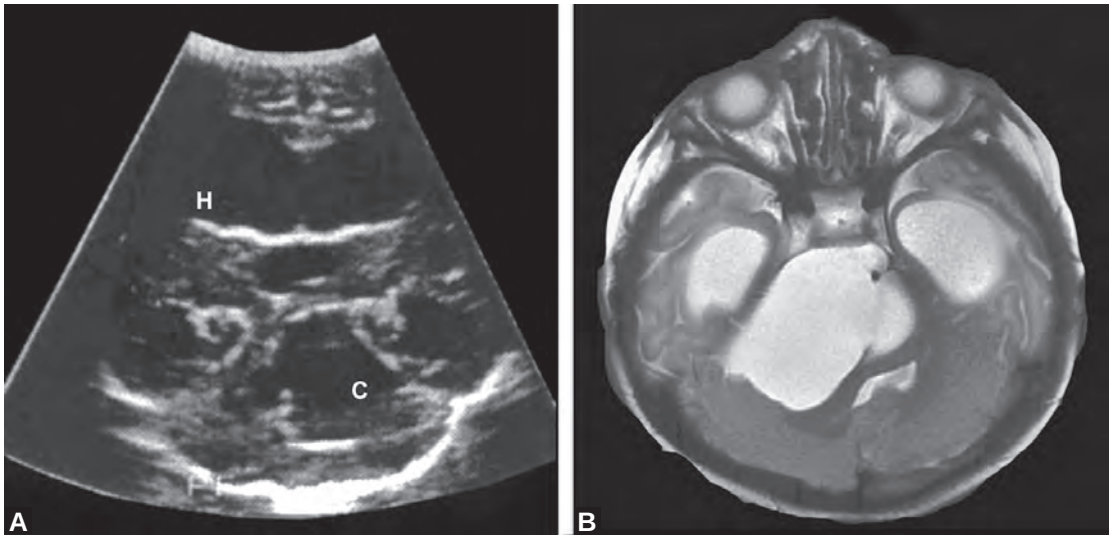
Suprasellar Cysts

These cysts (Figs 5A to C) account for 9–15% of all intracranial ACs depending on the nature of the series and the study.[36] As mentioned earlier, these are considered to be an outpouching of the membrane of Liliequist. Two varieties of suprasellar AC have been described the communicating and the non-communicating variety.[37] Communicating cysts communicate with the pontine cistern and non-communicating cysts are pinched off during development and are thus true cysts.[36] As they grow, these tend to invaginate the third ventricle and in addition exert pressure on the pituitary stalk. They may also bulge out through the Foramen of Monro.[74]

Many of these cysts may have only minimal symptoms and a few signs of localising value but, at times, they have features which are virtually diagnostic. A common presenting feature is hydrocephalus and the resulting features of raised intracranial pressure like headache and vomiting may also be present. Hydrocephalus is actually a very common presenting feature. These cysts may then be mistaken for congenital hydrocephalus, particularly if the attendant features of raised intracranial



Figs 5A to C: Suprasellar AC. (A) Axial CT: note the resemblance to bunny's head. (B) Ventriculography with water-soluble contrast shows the cyst to a non-communicating type of cyst. (C) MR: (i) sagittal; (ii) axial and (iii) coronal



Figs 6A and B: (A) Ultrasound image of large cerebellopontine angle cyst causing hydrocephalus. (B) MR of same patient showing cerebellopontine AC causing hydrocephalus. Note the displaced basilar artery

pressure are present.[38] "Bobble-head doll syndrome" is considered diagnostic of suprasellar AC. This syndrome is characterised by a rhythmic 2–3 per second antero-posterior oscillation of the head and trunk. The clinical features are due to the hydrocephalus or compression of the adjacent structures. Suprasellar AC can be mistaken for a dilated third ventricle but it can be differentiated from the latter by its shape, configuration of the frontal horns of the lateral ventricles and also the adjacent structures. In addition, enhancement of the adjacent brain may be seen in AC.[38] These cysts may invaginate into the sella turcica and cause a bitemporal field defect in addition to behaving as an intrasellar mass. They can lead to a variety of endocrine dysfunctions like deficiency of growth hormone and thyrotropin or, by stimulating the hypothalamo-pituitary-gonadal axis, lead to a tall statured and overweight individual.[1] Precocious puberty, panhypopituitarism and diabetes insipidus have also been reported.[42,70] The list of differential diagnoses include craniopharyngioma, Rathke's cleft cyst, colloid cyst of III ventricle, epidermoid cyst, lipoma, ependymal cyst, parasitic cyst and dilated III ventricle in hydrocephalus.[36] AC do not show calcification on CT and present with fewer endocrine symptoms in comparison to craniopharyngioma or Rathke's cleft cyst.[97]

Posterior Cranial Fossa Cysts

The common presenting features are those of a posterior cranial fossa mass lesion namely headache, vomiting and cerebellar signs. Infants may be referred for evaluation of an enlarged head which results from the mass in the posterior cranial fossa. Some of the clinical features apart from hydrocephalus and features of raised intracranial pressure may be very subtle. These cysts can be in the midline or laterally placed as in the cerebellopontine angle (Figs 6A and B). In the latter instance, all the features of a mass in the cerebellopontine angle may be present, viz. sensorineural hearing loss, facial weakness, corneal anaesthesia, etc. Variations of this theme may also be present.

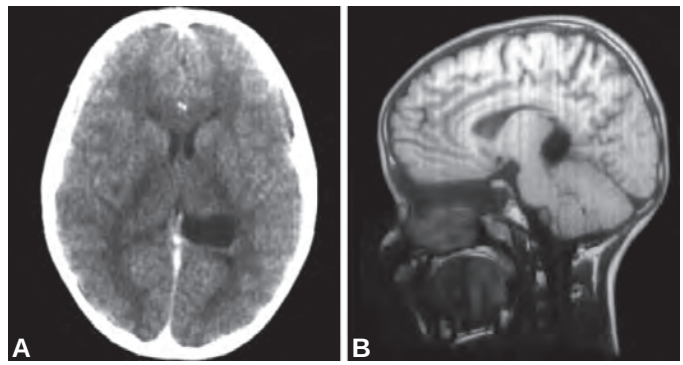
Parasagittal and Interhemispheric Cysts

These two types of cysts are seen more or less in the same region and one may be mistaken for the other, but there are important differences between the two. Parasagittal cysts are seen off the midline while interhemispheric cysts straddle the midline. An important differentiating feature is that the latter are associated with agenesis of the corpus callosum. In addition, parasagittal cysts are unilateral and hence may cause the midline to be shifted to the contralateral side. Being unilateral, parasagittal cysts cause hemicranial enlargement.[85] Parasagittal cysts are elongated while interhemispheric cysts take on a butterfly shape. Compression of the adjacent cerebral tissue is often a feature of parasagittal cysts.[5,85]

Pineal and Quadrigeminal Cistern Region Cysts

AC in relation to the pineal gland and its environs are not common, but are not unknown (Figs 7A and B). The commonest presenting symptom is hydrocephalus. AC here mimics pineal tumours but unlike pineal tumours, Parinaud's syndrome may not be seen.[40,86]

Incisural region cysts also invariably cause hydrocephalus and cortical enhancement may be seen around the cyst.[38]



Figs 7A and B: AC in the region of the incisura. (A) Axial CT. (B) Parasagittal MR

Convexity Cysts

Convexity cysts, even when large, may not manifest many localising signs apart from a local bulge. In infants, these may be mistaken for a subdural hygroma, but ACs do not have an enhancing membrane.[86]

Intraventricular and Intradiploic Cysts

ACs are very rare in these locations. Intraventricular cysts may arise within the ventricles or they may be manifestations of extraventricular cysts which have invaginated into the ventricles. Intradiploic cysts present as erosions of the skull commonly seen in middle-aged patients.[86]

Radiology

ACs present with certain characteristic features on imaging studies. Although a radiologic diagnosis can be made with certainty on many occasions, at times the differentiation from other lesions (for example, suprasellar AC versus suprasellar epidermoid/craniopharyngioma) can pose difficulties.

Plain Skiagrams

Plain skiagrams are no longer in vogue for the diagnosis of AC since other imaging modalities have proven to be more effective. But, nevertheless, at times that may be the first investigation done in the workup of a patient with AC or in a trauma victim who has an undiagnosed AC.

The radiographic features are a reflection of the location of the cyst. Only certain cysts present characteristic features, like those in the Sylvian fissure. Sylvian fissure cysts cause an asymmetry of the vault, as parasagittal and convexity cysts. In addition, Sylvian fissure cysts may elevate the sphenoid and cause the floor of the middle fossa to be bowed downwards. If there is significant mass effect, the groove for the sagittal sinus may also be displaced.[5] In cysts of the Sylvian fissure region, the lesser wing of sphenoid may be displaced forwards. Convexity and parasagittal cysts cause a localised bulge in the calvarium or, if large, an asymmetry of the vault.

Sonography

Sonography is usually done as a screening procedure when a neonate or infant presents with a bulging fontanelle or increasing head size. Sonography reveals ACs to be anechoic fluid-filled mass lesions with sharp margins. Mass effect may also be seen as well as other brain anomalies.[30,76] The findings on sonography must be correlated with other imaging studies.[13]

Computerised Tomography Scan

CT scan features of AC are fairly characteristic and the diagnosis is straightforward in almost all the cases. The basic appearance of these lesions is a hypodense cystic lesion without any calcification, but with well defined non-enhancing, smooth and round borders. Unless there has been a haemorrhage in the cyst, the contents have the attenuation value of CSF. If the cyst is adjacent to the calvarium, a bulge or asymmetry of the cranium may be seen. The cyst itself may have straight biconvex or biconcave borders. A straight medial border is often a characteristic finding in AC of the Sylvian region. The cyst may be biconvex or round in shape. Sharp margins and a cystic appearance are the bases for diagnosis.[107] The inner margin is straight, where it is attached to the leptomeninges.[64] Although the foregoing are the fundamental characteristics of AC, variations of the theme may be encountered every now and then.

Convexity cysts are biconvex or semicircular and may have a straight inner margin which represents their attachment to the rest of the arachnoid.[9] Cortical enhancement may be seen around the cyst.[38] Intracystic haemorrhage will change the attenuation value of the CSF within the cyst.

Although differentiation from other cystic lesions, like cystic gliomas, Dandy-Walker malformation, porencephaly, dilated third ventricle, craniopharyngiomas, Rathke's cleft cysts, lipomas and epidermoids, may be difficult on CT, it is possible in most instances.[44] Neoplasms exhibit enhancing borders and the presence of a mural nodule is a give-away sign for these. The cerebellar vermis is absent or attenuated in Dandy-Walker malformation unlike in AC of the posterior fossa.

The problems of differentiating suprasellar AC from other lesions in this area can be obviated by a study of the CT anatomy of the suprasellar area. The normal suprasellar region resembles a six-pointed star, which is referred to as the "suprasellar star". The anterior limb of the star is formed by the interhemispheric fissure, the two anterolateral limbs are formed by the Sylvian fissure, the two posterolateral limbs are formed by the peri-mesencephalic cisterns while the interpeduncular cisterns go to form the posterior limb. The shape of the suprasellar cistern is altered by pathologies located here. In addition, the normal slit-like shape of the third ventricle should also be taken into account when the CT images are interpreted. Like the shape of the suprasellar cistern, the change in the shape of the third ventricle helps in diagnosing the nature of the lesions present here. The commonest difficulty encountered is differentiating suprasellar AC from the dilated third ventricle seen in hydrocephalus. The five-pointed or six-pointed star configuration of the suprasellar cistern becomes oval or rounded in suprasellar cysts. The change in shape is "primarily the result of notching and lateral displacement of the mesial temporal lobe and flattening and posterior displacement of the brainstem".[36] The dilatation of the basal cisterns helps in differentiating suprasellar cysts from a dilated third ventricle and ependymal cysts of the third ventricle. The suprapineal recess of the third ventricle is more dilated in hydrocephalus than in AC.[36] Calcification is characteristic of epidermoids and craniopharyngiomas. In addition, the borders may

be irregular and enhancement may be seen. A negative attenuation value is seen in lipomas. Suprasellar AC may pose difficulties in the diagnosis. Suprasellar cysts are well demarcated round cystic masses which do not enhance with intravenous contrast. No areas of calcification or fat are present. These allow differentiation from neoplasms, dermoids/epidermoids and lipomas.[36] On axial imaging studies, the suprasellar cyst has been described as resembling a bunny's head.[86] Suprasellar cysts are seen as low density cystic areas in front of the cerebral peduncles and may go laterally up to the Sylvian fissure. Cortical enhancement may be seen around the cyst.[38] The definitive way to differentiate a dilated third ventricle from suprasellar AC is to do contrast cisternography. The contrast does not pool in the AC when it reaches the intracranial compartment unlike in the third ventricle. Communication between the cyst and the subarachnoid space can be demonstrated by air, metrizamide and isotope studies.[43,84,85] Water-soluble contrast studies have disclosed the following three kinds of cysts:

1. Those that communicate freely with the CSF space.
2. Those that communicate slowly.
3. Those that do not communicate.

The smaller cysts communicate freely with the subarachnoid spaces while the larger are of the non-communicating variety.[74] This has a practical significance in that it may be possible to manage the rapidly communicating cysts without surgery,[74] but eventually the contrast enters all the cysts albeit at varying rates. This has led some to question the division into communicating and non-communicating varieties.[24] The preferred term should be slowly communicating and rapidly communicating cysts. The slowly communicating cysts (which are often the large ones) cause neurologic problems and have features of expansile lesions.[24] During cisternography immediately after injection of the contrast, it does not enter the cyst, but the contrast is seen only in the subarachnoid space and this helps in delineating the cyst wall.[87] The contrast enters the cyst in about 6 hours and by 24–48 hours, all cysts are free of contrast even though the contrast clearance occurs at the normal rate from the subarachnoid spaces.[24] The rapidly communicating cysts may just be an arachnoid diverticulum, while the slowly communicating ones may represent a true cyst.[112]

Magnetic Resonance Imaging

MRI adds information to our study and understanding of these lesions. Information which may not always be available on CT may be obtained through MR imaging, even though the diagnosis may be apparent on CT. The basic appearance of these lesions on MR is the same as CT, namely well demarcated non-enhancing CSF containing cystic lesions without any calcification, but MR shows additional features which cannot be seen on CT.

MR shows indirect evidence of bony changes, namely a bulge in the bone and erosion of bone if present. Since cortical bone does not give any appreciable signal on MR, it is seen as a dark curvilinear shadow adjacent to the brain or the lesion.[107] The marrow, however, is seen as an area of increased signal adjacent to the shadow of the inner table. Changes in the calvarium will be seen as an alteration in the normal configuration of the inner table and the marrow. Bone erosion is seen as "decreased thickness" of the marrow signal, or "an interruption in the continuity of the marrow signal".[57] The latter finding has to be interpreted with caution since the marrow signal may not be continuous in all the areas.[107] The excellent soft tissue contrast afforded by the MRI reveals the anatomy in exquisite detail. Like the CT, in the MR images, the cyst is seen as a sharply demarcated hypodense (on T1 study) non-enhancing lesion. The "low signal of cyst fluid on T1 images gives good contrast with adjacent brain and is useful for initial diagnosis and definition".[107] MR, to sum up, is invaluable in evaluating the soft tissue abnormalities, haemorrhages and in delineating the anatomy of the adjacent brain.

Care has to be exercised in interpreting the images if the cyst contents do not appear identical to CSF. There may be several reasons for this. A difference in signal value may be seen between the intraventricular and the extraventricular CSF because of a difference in protein value. Ventricular CSF protein is 15 mg% and it increases to 30 mg% in the basal cisterns. Signal intensity from the ACs is the same as extraventricular CSF.[15] These differences in signal may be subtle and may be overlooked unless a special effort is taken to assess the signal changes. Signal from the cyst on spin echo is higher than ventricular CSF and similar to cisternal CSF.[74] The signal variations may represent minor haemorrhages or may represent some other complication.

The multiplanar imaging capabilities result in advantages which cannot be conferred by CT. The mass effect is best seen in coronal views.[107]

The CT appearance, in the presence of intracystic haemorrhage, varies depending on the "age" of the blood in the cyst. Even if the CT does not reveal haemorrhage and the cyst contents appear isodense on CT, MR may show the haemorrhage.[50] However, the increased signal from the cyst has to be interpreted with caution and correlated with the clinical picture and other investigations since the cyst may contain an increased amount of protein due to other reasons or the pathology may be something else, for instance a neoplasm.

Since the signal from the cyst is the same as CSF, signals from the cyst contents, which are not the same as CSF, should be interpreted with caution since these may be due to a neoplasm. If the signal intensity is the same as CSF in T1 and T2 weighted images, then it is almost pathognomonic of AC. Even if the features are the same as CSF, the presence of enhancement of the cyst walls or mural nodule favours neoplasm.[107]

In an uncomplicated AC, the surrounding brain is normal.[107] Hence, if no abnormal signals are seen from the surrounding brain, differentiation from post-operative, post-traumatic or post-infective/inflammatory cysts

is easy. In all these latter instances, the surrounding brain is abnormal.

MR is also very useful in differentiating AC from other lesions. Steady-state precession (PSIF) MR sequence with cine gating helps in differentiating cysts from enlarged CSF spaces and increases the certainty of establishing cyst communication with CSF spaces.[49] The other lesions which cause interpretive difficulties on CT can be diagnosed with greater certainty on MR using different imaging protocols, since the signal characteristics are different for different lesions. In diffusion weighted images, abscesses, epidermoids and cholesteatoma are hyperintense while ACs are hypointense.[12,61]

Management

Of all the controversies concerning AC, the management of these lesions alone has not been laid to rest. The best operative intervention for children with ACs remains the subject of controversy.[53] The surgical treatment is as variable as the location of the cyst.[40] There are proponents and opponents for every method of managing these lesions. Extremes of views have been presented. On the one hand, the mere presence of these cysts has been considered an indication for surgery since they may rupture or may lead to intracranial haemorrhage.[2] The "middle of the road" policy of not treating asymptomatic or accidentally discovered cysts has also been advocated. At the other end is the proposal to follow a "wait and watch" policy even for large cysts until a causal relationship with the symptoms is proven.[99]
The management of these lesions can be divided into the following groups:

- Conservative approach for all cysts
- Surgery for all lesions (even for asymptomatic lesions)
- Craniotomy and fenestration
- Shunt procedures
- Endoscopic surgery
- Other methods of management

Surgery is indicated in large cysts, which exert a mass effect, or when there is hydrocephalus, fits, features of raised intracranial pressure, a neurologic deficit caused by the cyst or the presence of other symptoms like endocrine, visual/ophthalmic deficits (as may be seen in suprasellar cysts).

Craniotomy and Fenestration

Craniotomy and fenestration of the cyst into the ventricle or adjacent subarachnoid cistern has been proposed as the definitive or curative treatment for these lesions. Recent reports stress that craniotomy for cyst fenestration is associated with a low incidence of morbidity and mortality and may leave the child shunt-independent.[53] The most important step in the operation is the fenestration of the cyst into the adjacent subarachnoid cistern or ventricle. Mere excision of the outer wall may result in a failure. The successful outcome of the surgery hinges on the principle of restoring normalcy to CSF circulation. This can be accomplished only by establishing a communication with the adjacent subarachnoid cistern. Primary treatment is, therefore, resection of the cyst wall and opening of the cyst into adjacent cisterns.[79]

Although the surgical steps vary a bit for cysts in the various locations, the fundamental steps and techniques are the same for all. Suitably placed scalp and bone flaps are reflected. Care has to be exercised during the elevation of the bone flap since the bone may be thinned out or eroded by the cyst. The dura is often times thinned and stretched over the cyst and appears bluish over the cyst region because of the underlying lake of CSF. The dura has to be opened carefully. Usually, the dura separates well from cyst, but adherence at one or two places is not uncommon. In the areas where the dura is adherent, dissection has to be done carefully for two reasons: (1) to prevent inadvertent rupture of the cyst and (2) to prevent rupture of the vessels which are either draped over the dome of the cyst or those which course inside the cyst. After the dura is opened, the cyst is seen. The cyst wall is usually transparent, but may be translucent in a few places. A few vessels may be seen coursing over the cyst wall. These vessels may be coagulated and divided. The outer wall of the cyst is then opened widely. Inside the cyst, veins are seen coursing towards the surface. These veins are coagulated and divided. Care has to be exercised in opening the cyst since these unsupported veins may rupture leading to troublesome bleeding. The brain surrounding the cyst appears normal with a normal sulcal and gyral pattern. However, the brain is compressed and, depending on the location of the cyst, the displacement varies. Once the cyst has been opened, the CSF has to be drained very slowly. Rapid suctioning of the CSF will lead to serious brain shift and cause a haemorrhage away from the site of surgery. This may not be apparent until there is a post-operative problem or post-operative imaging is done. Since the CSF is clear, even a few drops of blood can make progress difficult for the field will become "clouded" by the blood tinged CSF. In this instance, CSF is aspirated slowly with the suction set at low power or through a cotton ball or pattie. The bleeder is identified and coagulated. Unless there has been haemorrhage resulting in adhesions, the cyst is unilocular. "Arachnoidoplasty" has been recommended as an alternative to wide excision of the outer wall of the cyst. Here, instead of wide excision of the outer wall, a linear incision is made in the outer wall of the cyst. After the fenestration of the inner wall, the incision in the outer wall is closed. This technique reduces the chances of the post-operative CSF leak.[95]

After opening the cyst, fenestrating the inner wall may be more physiologic and may obviate the need for a shunt.[95] Mere excision of the outer wall leads to failure because this just creates a communication with the subdural space and not the subarachnoid space.[29] This procedure may lead to the formation of a subdural collection with mass effect.

The findings after opening the cyst depend on the location of the cyst. In Sylvian region cysts, the middle cerebral and internal carotid arteries and their branches are seen without any difficulty. When the microscope is angled to look slightly deeper and posteriorly, the third cranial nerve and the tentorial edge come into view. In addition, the optic nerve is also seen. On opening the arachnoid along the medial surface, the basilar artery and the other structures in the region of the basal cisterns are readily apparent. The medial wall of the cyst is opened widely into the chiasmatic and basal cisterns.

Suprasellar cysts can be approached through a transcallosal, transventricular or subfrontal approach. If the transcallosal route is chosen, once the corpus callosum is incised and the third ventricle opened, the cyst wall is seen. The cyst is then opened widely into the ventricle. The approach involves opening the cisterns in relation to the corpus callosum. Hence, communication with the CSF cistern is established. But to create a wide fenestration, an extensive splitting of the corpus callosum may be needed and this may not be advisable. In suprasellar cysts, effective decompression is not obtained if the cyst is drained only into the subarachnoid cistern. Hence, the cyst should also be drained into the ventricle. For suprasellar cysts, resection leads to good results and even the endocrine symptoms improve.[52]

Upon opening a midline posterior cranial fossa cyst, the floor of the fourth ventricle is seen in addition to the cervicomedullary junction. In laterally placed cysts (i.e. at the cerebellopontine angle), all the structures located there are clearly visible without any retraction. The posterior fossa cysts are widely fenestrated into the adjacent CSF cisterns; in the case of midline cysts into the fourth ventricle and cisterna magna and in the case of the cerebellopontine angle cysts into the CP angle cistern and, if possible, into the cisterna magna.

Once the cyst is widely fenestrated, the dead space may be filled with irrigating fluid to prevent pneumocephalus and also to allow a gradual re-expansion of the brain. Post-operative haemorrhage may result because of the sudden re-expansion of the brain. The dura is closed watertight and the bone flap is anchored and wound closed in the usual manner.

The complications specific to this procedure include haemorrhage in the operated site because of the dead space or snapping of the unsupported veins, failure of the brain to re-expand, aseptic meningitis, subdural collections and a neurologic deficit resulting from brain shift due to rapid decompression.

The success rate, i.e. relief of symptoms and radiologic improvement is 60–96%.[8,86] The reasons for failure of the procedure are due to reformation of cyst walls, incomplete or inadequate fenestration, closure of fenestration, deficiency of flow from the cyst into the ventricle or cistern. Failure to treat the attendant hydrocephalus might also militate against a successful result. For posterior fossa cysts, craniotomy gives better results than shunts.[31]

Shunting

Shunting has been advocated as a treatment modality for intracranial AC. The fundamental idea is to divert the CSF to the peritoneum—as one would in hydrocephalus—where it will get absorbed.

The standard techniques used to perform a ventriculoperitoneal shunt are used. The proximal end of the shunt is placed in the cyst cavity while the distal end is in the peritoneum. There are no hard and fast rules regarding the choice of shunt opening pressure. This is based only on the surgeon's experience and judgement. The proximal end is placed in the cyst cavity through a suitably placed burr hole. The burr hole has to be placed in such a way that it will not be a problem should a craniotomy become necessary as an emergency or as a planned surgical procedure. The proximal end is connected to the reservoir and the distal catheter.

A straightforward ventriculoperitoneal shunt has been proposed as a first line of treatment if contrast cisternography shows good communication of the cyst with the CSF pathways. If the communication is not good, cysto-peritoneal shunt may be needed.[112] The results of shunting are best for middle cranial fossa cysts.[23]

The complications of shunting as a treatment modality for AC are the same as shunting for hydrocephalus. The common problems are shunt failure and infection. In addition, "Slit cyst syndrome" which is similar to the slit ventricle syndrome has also been described.[86] Here, the patient manifests with features of raised intracranial pressure even though the imaging studies show a slit-like cyst. The shunt does not always result in a cure, since the shunts do malfunction at a rate higher than shunts for hydrocephalus.

Endoscopic Surgery

Endoscopic surgery may, in the future, become the standard way to treat intracranial AC. The technique may appear to be simple to the unwary. The investment in technology and instrumentation is high and the learning curve is "steep and long", but this confers the advantage of being minimally invasive. The basic principle here is the same as in craniotomy, viz. establishing a communication between the cyst and the normal CSF pathways.[21]

The endoscope is introduced into the cyst through a suitably placed burr hole. The possible need for converting the procedure into a craniotomy as an emergency or elective procedure at a later date has to be borne in mind when planning this procedure. Once the scope is introduced into the cyst, the anatomy has to be thoroughly studied and the cyst contents inspected. Care has to be taken to avoid the veins which course unsupported through the cyst. The inner wall of the cyst is approached and it is fenestrated. The instruments used to fenestrate depend on the surgeon's choice and experience. The grasping forceps, diathermy (unipolar/bipolar) or laser may be employed. Several holes are made

and these are enlarged with a balloon catheter such as Fogarty catheter. Performing the procedure under constant irrigation keeps the field clear and also clears the tissue debris. Meticulous haemostasis is mandatory. If the cyst is in close relation to the ventricle, in addition to cysto-cisternostomy, cysto-ventriculostomy can also be performed for added benefit. In other words, ventriculo-cysto-cisternostomy is better than ventriculo-cystostomy.[27] This may particularly be useful in suprasellar cysts where the failure rate of surgery is high for any surgical procedure. Endoscopic marsupialisation of the roof of a suprasellar cyst alone has given good results.[16] Endoscopy may be the treatment of choice in the future for AC, especially for deep seated cysts.[22,26,47,56] Further, endoscopy is a good alternative for failed craniotomy or shunt.

Several adjuncts have made endoscopic management easier and more precise. Frameless stereotaxis has proved useful for endoscopic surgery of deep seated cysts but it may not be needed for large lesions,[3,41] or the surgery can be started with the endoscope and then can be converted to a microsurgical technique with endoscope assistance.[35] Endoscopic surgery for AC has been divided into various groups as "endoscopic neurosurgery (EN), endoscope-assisted microneurosurgery (EAM) and endoscope-controlled microneurosurgery (ECM)".[49] These techniques have resulted in an overall success rate of 70%. The best success rates were achieved in patients with intraventricular cysts (89%) and posterior fossa AC (78%). Symptomatic improvement was best achieved in patients with hydrocephalus or focal neurological deficits (81%).[49] It appears that endoscopic management has the advantages of craniotomy combined with the less invasive nature of shunts. Intraventricular cysts and suprasellar AC are easily approached using EN, whereas posterior fossa and Sylvian AC may be more effectively treated using a combined technique (EAM or ECM).[49]

Other methods have also been described to manage AC. It has to be emphasised here that they have not withstood the test of time. Some are only anecdotal and only a limited number of patients have been treated using that modality.

For intrasellar AC, trans-sphenoidal approach and excision has been reported to give good results. This can be done for small intrasellar AC but larger ones or those with suprasellar extension will need a craniotomy for effective management.[68]

Stereotactic intracavitary irradiation, using colloidal Phosphorus-32, has been administered leading to good results.[58,101] Cyst aspiration as a treatment for AC has also been advocated,[29] but simple aspiration through a burr hole and cyst drainage leads to recurrence of the cyst. Cysto-subdural shunt has also been reported to give good results.[108] Cysto-ventriculostomy using stereotactic guidance has been done and the reported results have been good.[25]

SPINAL CYSTS

Introduction

Many congenital and developmental cysts are seen in the spinal canal, namely, ACs, neurenteric cysts, epithelial cysts and inclusion cysts. Spinal ACs are not as common as their intracranial cousins. A variety of names have been used to describe these lesions: "subdural ACs, arachnoid diverticula, leptomeningeal cysts and meningeal hydrops".[77] Unlike their intracranial counterparts, these may be intradural or extradural, with the intradural variety being the commonest.[77]

Embryology

The embryology of these lesions (unlike the intracranial cysts) has not fully been elucidated. The origin of these is more often than not congenital, although these "cysts" may follow inflammation, haemorrhage, myelography or trauma, just like they do intracranially[32,60,62] (refer to the discussion in intracranial AC). Extradural cysts originate as small arachnoid diverticula through defects in the dura.[14] Intradural cysts are thought to arise from the septum posticum which lies on the dorsal aspect of the cord.[14] An alternate theory suggests that the variations in intraspinal CSF pressure leads to the dilatation of the low resistance areas, resulting in the formation of the cyst.[77] An alternate hypothesis envisages that all these "arachnoid diverticula result from hypertrophy, proliferation and dilatation of arachnoid granulations".[77]

Clinical Features

These are the commonest among cystic lesions occurring in the spinal canal.[77,78] The commonest location of these lesions is the mid-thoracic level on the dorsal aspect. Their occurrence on the ventral aspect of the spinal cord is rare,[55,62] Although these occur in other regions too, the incidence is lower.

The common presenting feature is slowly evolving paraparesis. On clinical grounds, it is impossible to attribute the cause of compression to AC. The motor deficit is worse than the sensory or autonomic deficits.[111] In addition, the patients may have root pains and kyphosis. The cause of the latter is unclear.[14] An important differential diagnosis is multiple sclerosis since the symptoms may fluctuate.[14,77] In addition, the symptoms in communicating AC may vary with posture. Spinal meningeal cysts have been classified into three types:[72]

Type I: Extradural meningeal cysts without involvement of spinal nerve root fibres.

Type IA: Extradural meningeal cyst ("extradural arachnoid cyst").

Type IB: Sacral meningocoele ("occult sacral meningocoele").

Type II: Extradural meningeal cysts with involvement of spinal nerve root fibres

(Tarlov's perineural cyst, spinal nerve root diverticulum).

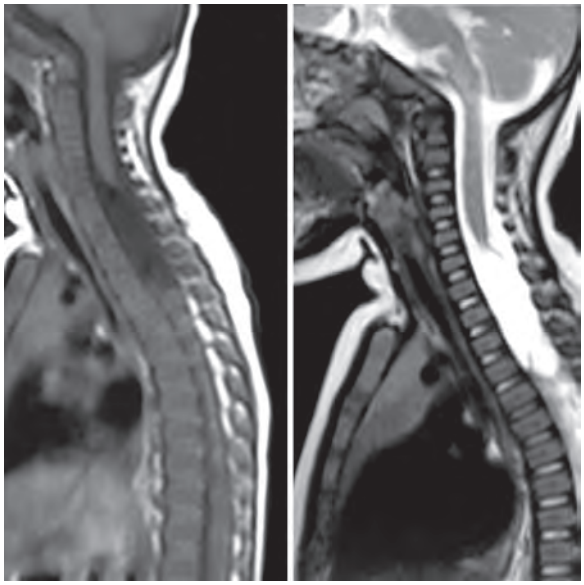


Fig. 8: Spinal arachnoid cyst in the thoracic region (Sagittal MR images)

Type III: Spinal intradural meningeal cysts ("intradural arachnoid cyst").

Radiology

Plain films show erosion of the pedicles at the level of the lesion. Myelography shows, in addition to a filling defect, pooling of the contrast medium inside the cyst if it is of the communicating variety. MRI, however, is the investigation of choice (Fig. 8). This shows a non-enhancing cystic lesion with signals similar to CSF.[77] Cine MRI can demonstrate abnormal fluid flow and spinal cord compression caused by a spinal intradural AC."[96]

Treatment

Like the intracranial cousins, these lesions have to be managed surgically. The outer wall is widely excised. If by doing this, a communication with the CSF space cannot be established a fenestration has to be done. The results of surgery are often very good,[55,62] particularly if surgery is done early.[59,62,77] Shunting may be useful in recurrent lesions.

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18 Craniofacial Deformities (Craniostenosis)

Uday Andar, Nitin Mokal

HISTORY/INTRODUCTION

Surgery for craniofacial deformities has evolved over the years just as all other branches of surgery, the most significant factor being the better understanding of the growth of the craniofacial skeleton, and the various driving forces that promote and demote its growth. Though the problem was identified very early in the history of medicine, evident because of the deformed face and the abnormal dentition, its significant contribution in retarding intelligence, increasing intracranial pressure and causing severe airway and visual disturbance has been understood only recently.

Many would consider Prof. Paul Tessier as the father of modern craniofacial surgery. His single minded dedication to this specialty and imaginative surgical procedures has brought a great change in the way craniofacial surgery is looked upon today. The involvement of more than ten specialists in the care and management of these children, only emphasises the modern day understanding of this complex problem and the need to have a dedicated specialty department. Historically, the first operation in India for craniofacial deformity secondary to frontonasal encephalocele—a modified Tessier operation was carried out at AIIMS.[3,4] This was later applied to other craniofacial anomalies.

NORMAL CALVARIAL GROWTH

Craniofacial growth is influenced immensely by the rate of growth of the structures that it protects. Hence, at birth, the cranium is larger than the face because the brain is more developed than the relatively smaller facial skeleton including the teeth. Later on, the cranial growth slows down, and the facial skeleton comparatively grows faster.

The processes involved in normal growth of the craniofacial skeleton are as follows:[1]

Endochondral Ossification

Its growth mainly occurs in long bone endochondral cartilage and, therefore, may contribute very little in the cranium. It occurs mainly at the synchondroses at the skull base.

Intramembranous Ossification and Sutural Growth

Most of the skull bones are membranous bones and their growth is spurred on by the osteoblastic activity in the surrounding periosteum externally and the outer dura internally. This active bone formation may be maximum at the sutural interfaces. These sutural interfaces are under stress due to the growing brain, growing facial musculature and the orbits and the teeth. This continuous stress stimulates bone deposition at these junctions and craniosynostosis interferes with this process and prevents growth.

Remodelling

It is the process by which deposition and resorption of bone occurs in different areas of the skull vault and it is most simply demonstrated by the changes in curvature that occur in the calvarial bone as the skull vault enlarges in the early years of life.

Displacement

It occurs when the bone gets deposited over the suture lines and the enlarging brain displaces the calvarial bones outwards and away to remodel. This type of growth is seen in the mandible where anterior displacement of the body occurs by growth of the condylar neck.

INCIDENCE, AETIOLOGY AND PATHOGENESIS OF PREMATURE CRANIOSYNOSTOSIS

Craniosynostosis occurs due to the premature fusion of a single suture or multiple sutures. The overall prevalence of craniosynostosis is around 1 in 2,500 live births, with ranges of 1 in 709 to 1 in 3,225 of births.[2] The wide variation seen is due to differences in the various criteria under which one labels craniosynostosis.

The last decade of intensive research has linked many of the multiple suture "syndromic synostosis" to a series of mutations in the fibroblast growth factor receptor (FGFR) genes 1–3. Human FGFR mutations follow non-random themes. Specific FGFR3 mutations generate craniofacial dysostosis, some without skeletal abnormalities.[9,13,14]

Common syndromic craniosynostosis, like Apert and Crouzon, have a prevalence of about 1 in 65,000, each, forming about 4–6% of all craniosynostosis. There is evidence of FGFR2 mutation in Apert syndrome, FGFR3 in Crouzon syndrome and FGFR1 in Pfeiffer syndrome. Almost all Apert's and about 50% of Crouzon's arises de novo and there is a correlation with increase in paternal age. The prevalence of Pfeiffer syndrome is lower than others, but there is no definite percentage data.

Apart from this, there are rarer types of single gene syndromes associated with other malformations, metabolic storage disorders and learning disabilities. There are chromosomal aberrations of which craniosynostosis may be a feature. There are teratogenic causes associated with anticonvulsants (valproate, hydantoin), cytotoxic agents (methotrexate, cyclophosphamide, cytarabine), abortifacients and other drugs (chlorpheniramine, nitrofurantoin, chlordiazepoxide and fluconazole).

Isolated craniosynostosis is far more common than multiple syndromic synostosis. Sagittal synostosis seems to be the commonest, followed by coronal and metopic synostosis. True lambdoid synostosis is rare and is difficult to distinguish from deformational posterior asymmetry, which is considered to be positional moulding of the cranium.

Sagittal synostosis accounts for almost 55% of all craniosynostosis.[8,15] It is sporadic, commoner in twins and, though there may be a family history, the inheritance pattern is low. It is three times more common in males than the females.

Coronal suture involvement accounts for about 20% of all craniosynostosis.[11,17] It is almost twice as common in females, and the unicoronal type is twice as common as the bicoronal type. This type is associated with family history, increased paternal age and FGFR3 mutation, especially when it is bicoronal.

Isolated metopic craniosynostosis has a wide reported range varying from 14% by Lajeunie et al.[12] and 3% by Singer,[17] (1999) to 50% by Shuper et al.[16] It is twice as common in males. It can be associated with learning disability, without evidence of high intracranial pressure (ICP). There can be associated chromosomal aberrations. foetal valproate exposure is increasingly recognised as a cause of metopic synostosis with or without learning disability, behavioural disturbances, limb and nail defects and neural tube defects.

Isolated lambdoid craniosynostosis is in the majority of cases deformational. Contributing factors include intrauterine constraint, prematurity, complicated delivery and laying the baby excessively on one side while sleeping. This type is mostly managed conservatively.

CLASSIFICATION AND TERMINOLOGY

Over the years, the nomenclature for various craniofacial deformities has remained constant, but with the entry of molecular genetics, there have been additional terms given to the complex multisutural synostosis. However, in simple terms, these deformities can be classified into three different varieties:

1. Secondary
2. Simple
3. Complex

1. Secondary craniosynostosis can occur as a result of twinning, amniotic bands or uterine abnormalities, and is seen in preterm babies. It can also occur in newborns with hyperthyroidism or maternal hyperthyroidism during pregnancy.[5,7] Pan sutural synostosis is seen in children with microcephaly, where the brain is small and underdeveloped.
2. Simple anomalies include single suture or two suture involvement and are named as:
   - *Sagittal Synostosis or Scaphocephaly or Dolichocephaly*: it is so called when the sagittal suture is singularly prematurely fused and the head attains a long antero-posterior length with or without frontal bossing.[10]
   - *Unicoronal synostosis*: it is also called plagiocephaly, when there is flattening of one side of the forehead and a mild facial scoliosis, due to premature fusion of one coronal suture.
   - *Metopic synostosis or Trigonocephaly*: this occurs when there is premature fusion of the metopic suture, and the forehead assumes a triangular shape like the keel of a boat.
   - *Lambdoid synostosis*: it is also called posterior plagiocephaly when a single lambdoid suture fuses to produce asymmetric occipital flattening.
   - *Bicoronal synostosis or Brachycephaly*: this is a condition where both coronal sutures fuse prematurely and the skull assumes a spherical shape.
   - *Acrocephaly or Turricephaly or Oxycephaly*: a condition where both coronals and anterior sagittal sutures fuse and the skull assumes a pointed tower like shape.
3. Complex craniofacial deformities are mainly associated with syndromes and FGFR mutations and they are named as follows:
   - Crouzon syndrome: this syndrome was described by Crouzon in 1912. Apart from craniosynostosis, this condition manifests maxillary hypoplasia, exorbitism with hyperteleorism and type III malocclusion. There are no obvious skeletal anomalies. There may be associated FGFR3 mutation and phenotypic variability between generations is a common observation.
   - Apert syndrome: this was described by Apert in 1906. It is characterised by bicoronal and anterior sagittal synostosis, midface retrusion and hypertelorism with orbital proptosis and complex syndactyly of hands and feet. They can also have sporadic visceral malformations and skin abnormalities.

- Saethre-Chotzen syndrome: this syndrome is so named after the two people who described their findings in different families around 1931–32. The features here include bicoronal synostosis with variable involvement of the metopic, sagittal and lambdoid sutures. There is associated proptosis, low set frontal hairline, parrot beaked nose, strabismus and brachydactyly.
- Pfeiffer syndrome: this syndrome has features of bicoronal synostosis to pan sutural synostosis and clover leaf deformity of the skull. It was described by Pfeiffer in 1964, and it includes limb anomalies like thick broad thumb and toe, fusion between thumb phalanges and soft tissue syndactyly of thumbs and fingers.
- Clover leaf or Kleeblattschadel deformity: this is an uncommon and severe form of craniosynostosis resulting from the fusion of both coronal and a combination of metopic, lambdoid and sagittal sutures. The midface is retruded with ocular ectopia and dental malposition. The posterior fossa is small and there is cerebellar tonsillar herniation. There may be severe airway obstruction and the clinical prognosis is often poor, unless improved by some very aggressive surgical management.
- Carpenter syndrome: this is a rare syndrome where the cranial deformity mainly involves the sagittal and lambdoid sutures asymmetrically and severely. The affected person is usually short, obese and neurodevelopmentally slow.
- Antley-Bixler syndrome: this is also a rare type of synostosis where there is involvement of coronal and lambdoid sutures, with dysplastic ears, radiohumeral synostosis, long tapering fingers and upper airway abnormalities.
- Jackson Weiss syndrome: this syndrome was reported in the Amish population in 1976. There is craniosynostosis with midfacial hypoplasia and foot abnormalities.
- Muenke syndrome: this syndrome is so described due to its molecular abnormality, which was described in 1977 by Muenke. Here too, there is a coronal synostosis associated with FGFR3 mutation.

RADIOLOGY

Any unusual shape of the head at birth usually sets off a series of investigations which include CT scan of the head, MRI and X-rays of the skull, hands, feet and the cervical spine.

Plain X-ray of the skull is the most commonly used modality and is a good investigation to assess the primary condition and to confirm that there is no other contributory factor like dysplasia or just positional change in shape.

Skull X-ray AP and AP Towne's with lateral view is capable of showing sutural absence, parasutural sclerosis, sutural narrowing and heaping or enostosis and also to confirm whether the entire suture or only part of it is involved.

Computed tomography scan of the head and brain, with 3-D reconstruction, gives an even better picture of the skull bones and sutural fusion, along with the deformity of the sphenoid plate and base of skull asymmetry.

MRI scan is helpful in children with syndromic anomalies to define the airways, cranio-vertebral junction anomalies, hydrocephalus, venous sinus anatomy and any other cerebral or cerebellar anomalies as also the upper laryngo-pharyngeal airway.

Hydrocephalus may occasionally be associated with syndromic synostosis, like Apert, Crouzon or Clover-leaf syndrome, and can be picked up during the course of investigations. If decompression is carried out early, then hydrocephalus may regress, and if not, may require shunt surgery. The mechanism of hydrocephalus may be aqueductal stenosis or venous drainage obstruction in a crowded posterior fossa.

Many experienced units around the world have given up routine X-rays and repeated CT scans of the head in obvious cases of scaphocephalies, and unicoronal synostosis, proceeding for surgical reconstruction.

TREATMENT OF CRANIOSYNOSTOSIS

The treatment of children with this deformity is a challenging surgical task. As mentioned earlier, it requires close co-ordination with specialists in neurosurgery, plastic surgery, maxillofacial surgery, orthodontics, ophthalmologists, ENT specialists and, of course, medical specialists including psychologists, speech therapists, geneticist and trained nursing and paramedical staff. The outcome of recent research has further helped to device various ways for managing some of the more complicated of these anomalies, which are dynamic and continue to worsen with growth.

It is, therefore, prudent to identify the correct timing of surgery in order to achieve an optimum cosmetic effect. The earliest times that surgery can be considered in the various regions of the craniofacial skeleton are when that region completes its full growth potential and this is approximately as follows:

Cranium:	1 year (6 months for sagittal)
Orbits:	5 years and above
Upper maxilla:	9–12 years
Lower maxilla:	17 years and above
Mandible:	17 years and above.

The reasoning behind this careful timing is to minimise relapse of the deformity and repeat surgeries in many cases. It means that the final stage of facial correction can effectively be undertaken at the age of 17–18 years, whereas the unisutural purely cranial deformities can be done between 6 months and 24 months of life.

Apart from this, other factors which need to be considered and influence the timing of reconstructive surgery are: raised intracranial pressure, airway obstruction,

feeding difficulties, ophthalmic problems, cognitive and behavioural problems, disorders of dental occlusion and psychological problems.

In day to day practice, however, the majority of Apert's, Crouzon's, Pfieffer's and other pan sutural synostosis will require some kind of early intervention to release high ICP or respiratory obstruction or exorbitism and the risk of loosing vision.[6] Following this, they will require a definitive cosmetic reconstructive surgery later in life as a final touch.

SURGICAL INCISIONS AND PROCEDURES

The site and size of incisions is mainly dependant on the amount of exposure of the surgical area required. In almost all cranial exposures, a bicoronal incision extending from three fingers above the mastoid and behind the ear, going all the way across to a similar location via the vertex, is by far the best and gives the best exposure anteriorly, posteriorly and in both temporal regions and the best post-operative healed scar with minimally visible hair loss. For facial and midfacial exposures, there are subconjunctival, infraorbital and subciliary incisions as per the preference of the maxillofacial/plastic surgeon.

In sagittal synostosis, where the shape of head is long with a bit of frontal bossing and temporal hollowing, the attempt is to give it a rounded shape as far as possible. This surgery is ideally carried out in the first 6 months of life for the best results. Any corrective surgery for scaphocephaly after the age of one year becomes extensive and potentially more risky. The craniectomy performed is as shown in the Figures 1A to D.

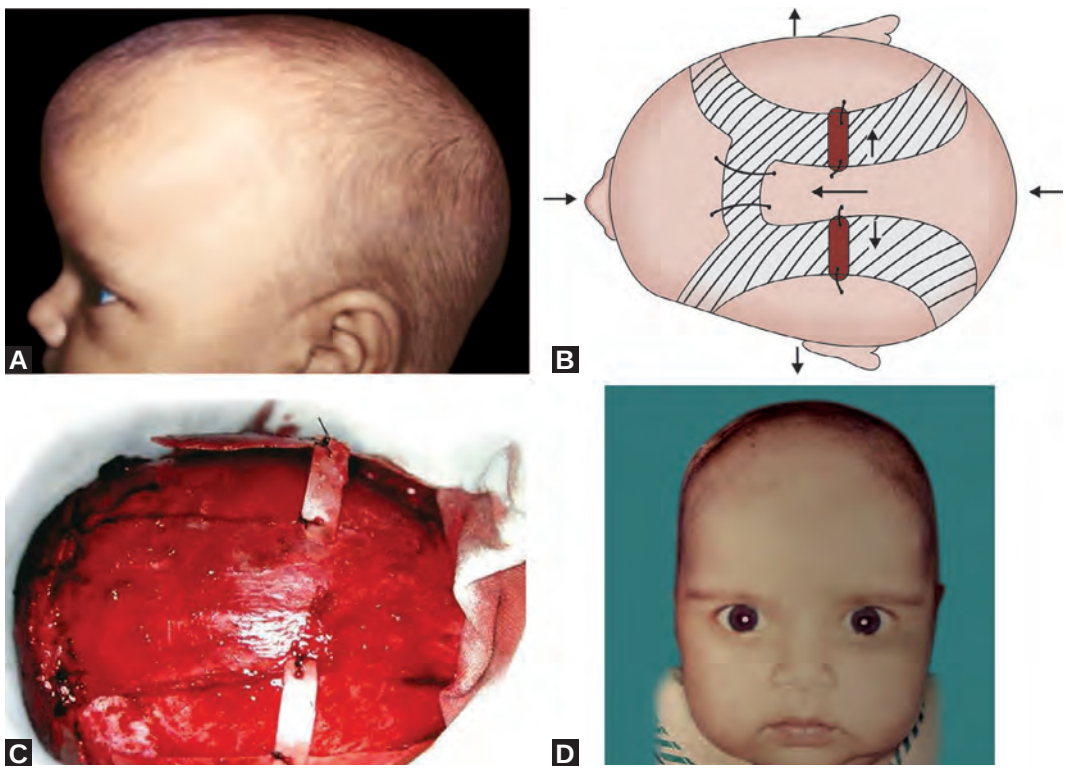
In anterior unilateral plagiocephaly, a plan for surgical repair can either be a standard bifrontal craniofacial advancement or many do believe in repairing the affected side only. The aim is to achieve an overcorrection to make up for any future regression or relapse as far as possible. This is illustrated in Figures 2A to C.

In trigonocephaly, brachycephaly and anterior plagiocephaly, the aim is to remodel the fronto-orbital region by flattening the forehead and at the same time pulling it in front. Thus, a bifrontal bone flap is raised in one block and the supraorbital bar is taken separately, which includes the root of the nose, part of the orbital roof and some part of the lateral orbital wall. We have found it useful to artificially create a long root for the nose, to give a better post-operative result (Fig. 3).

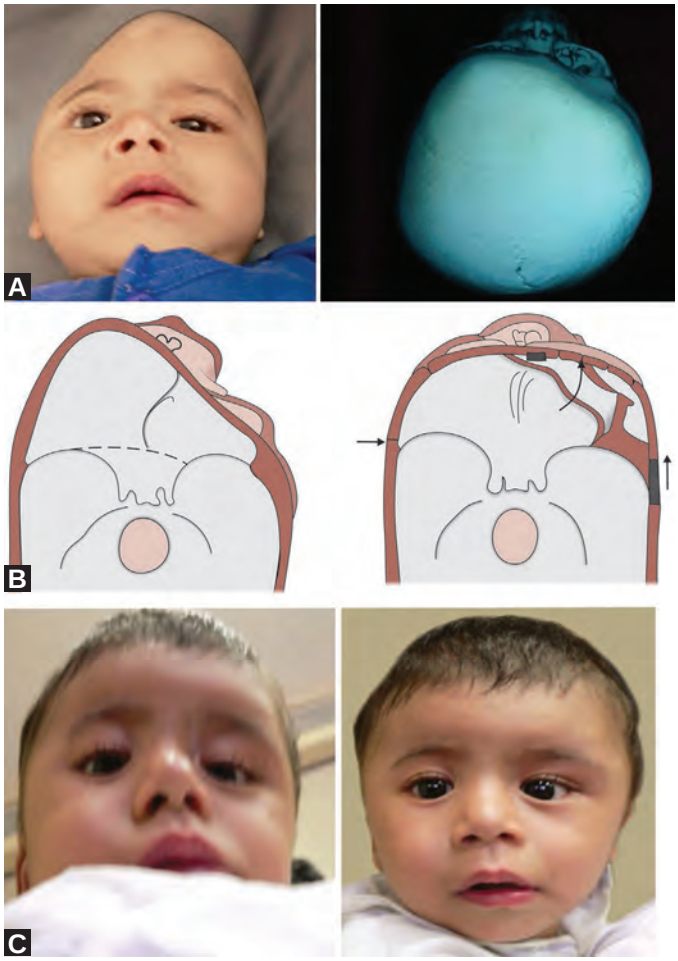
In some pan sutural synostosis, where the ICP is very high, with evidence of papilloedema, but it is too early for frontal remodelling, a posterior vault decompression may be performed. This provides expansion of the cranium and adequate release of ICP. It also gives time for the surgeon to wait for further facial growth before any definitive craniofacial remodelling (Fig. 4).

In the syndromic varieties, where there is need for repositioning of the maxilla, a Le Fort III or Le Fort I corrective osteotomy is necessary.

The monobloc frontofacial osteotomy combines a transcranial frontal advance and extracranial Le Fort III midfacial advance into a single procedure, making use of external distraction frames. This procedure addresses raised ICP, exorbitism, respiratory passage compromise, maxillary hypoplasia and dental malocclusion, all



Figs 1A to D: (A) Pre-operative picture. (B) Operative plan. (C) Intra-operative picture. (D) Post-operative 3 months later



Figs 2A to C: (A) Pre-operative picture with CT scan. (B) Operative plan for unilateral correction. (C) Few months after surgery

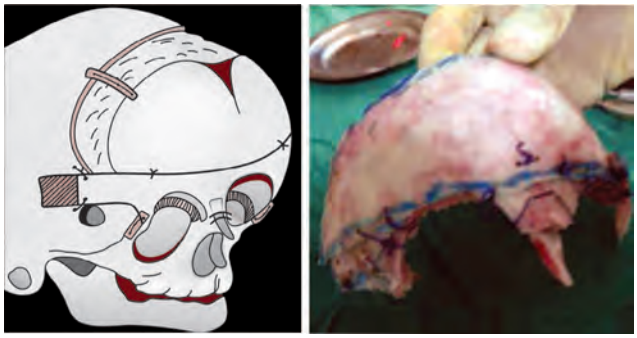


Fig. 3: Frontal remodelling with extra-long root of the nose

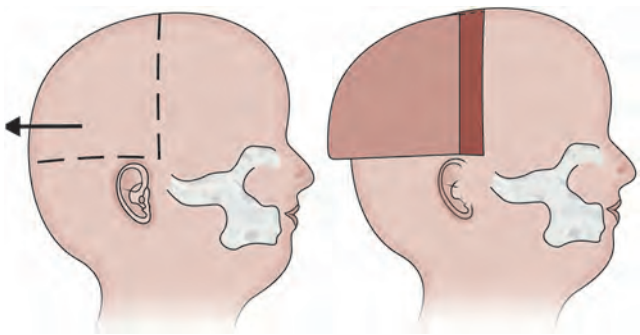


Fig. 4: Posterior vault expansion

together. This cannot be undertaken at very young ages, though there are reports of 3- and 4-year-old who have undergone this procedure, with considerable risk and morbidity (Fig. 5).

COMPLICATIONS OF SURGICAL TREATMENT

The complications of surgical treatment are divided into intra-operative, early post-operative and late post-operative stages.

Intra-Operative Stage

- Injury to the venous sinuses, severe bleeding and haemorrhagic shock
- Injury to the cerebral cortex
- Injury to the eyeball
- Acute brain swelling due to venous drainage compromise, either due to the position or discontinuation of a major emissary vein.

Early Post-Operative Stage

- Airway compromise due to local oedema
- Extra- and intra-parenchymal haematomas
- Fluid and electrolyte imbalance
- Visual compromise or ocular palsies
- CSF leak from the wound or rhinorrhoea, ottorrhoea
- Infection
- Failure of bony fixation.

Late Post-Operative Stage

- Exposure of miniplates and screws used for fixation
- Damage to roots of the teeth and devascularisation
- Soft tissue absorption and hollowing of temporalis muscle area
- Relapse of the bony fusion.

Discussing each of these complications is beyond the scope of this Chapter; it is recommended to refer to the textbook on craniosynostosis mentioned in the references. The dictum is to be extra careful in the pre-operative evaluation and anticipate intra-operative problems, so that, one is prepared for it already (Figs 6A to D).

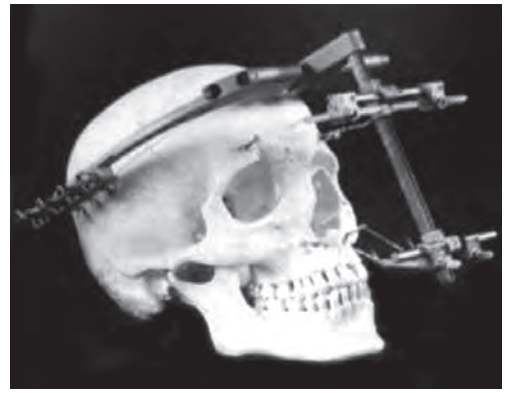
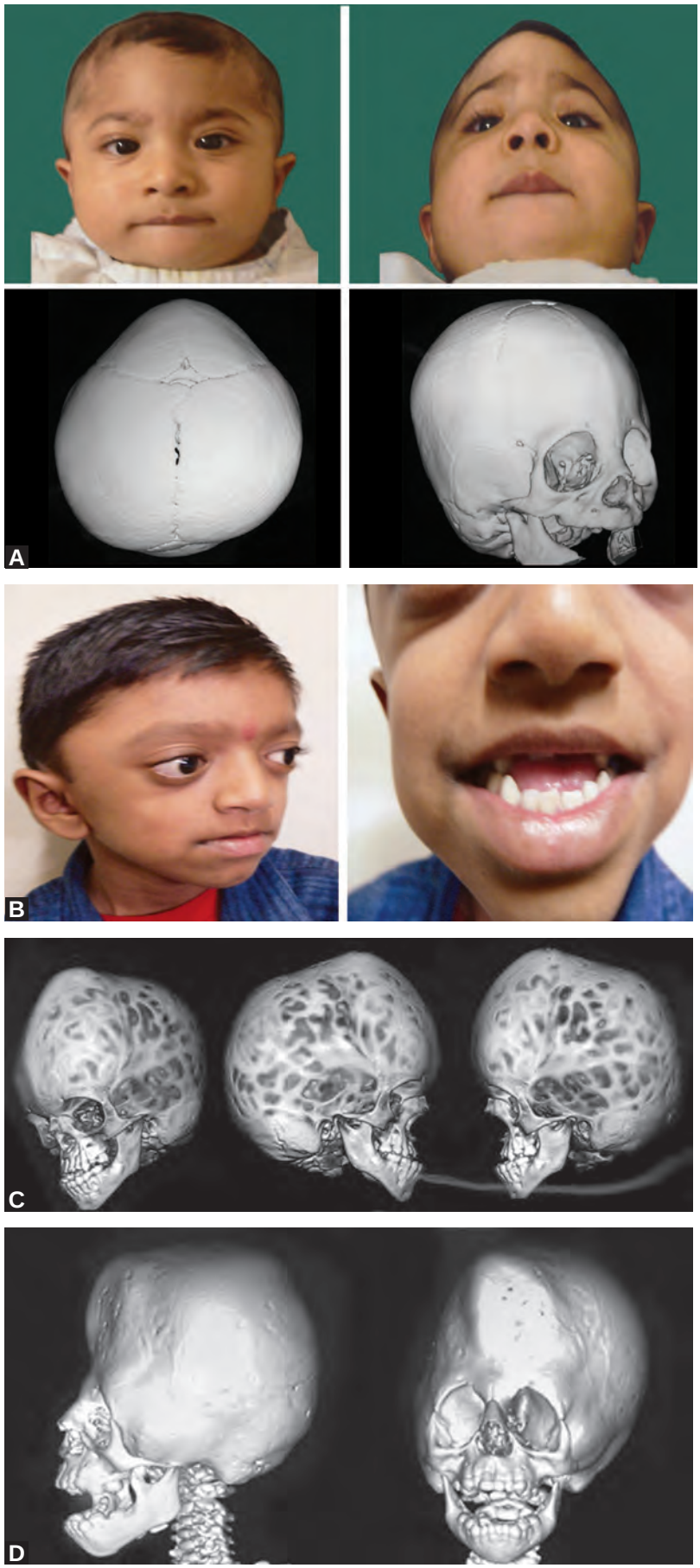


Fig. 5: Frontofacial monobloc using distraction externally



Figs 6A to D: (A) Metopic synostosis. (B) Older Crouzon syndrome. (C) CT scan showing effects of raised ICP. (D) CT scan of pan synostosis

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19 Spinal Dysraphic States

Venkatramana NK

INTRODUCTION

Spina bifida literally means "spine in two parts" or "open spine".[46] Spinal dysraphism involves a spectrum of congenital anomalies resulting in a defective neural arch through which meninges and/or neural elements herniate leading to a variety of clinical manifestations.[31,46] They are divided into aperta (visible lesion) and occulta (with no external lesion).[31,46] Meningocele, myelomeningocele (Fig. 1), lipomeningomyelocele, myeloschisis and rachischisis are the usual names associated depending on the pathological findings. Meningocele (Fig. 2) by definition involves only the meninges with no neural involvement. The other lesions will have a variable extent of neurological involvement. Spina bifida aperta is usually associated with a skin defect with an impending risk of cerebrospinal fluid (CSF) leak constituting "open defects", whereas the occult forms will have full skin cover thickness. Both forms demand different approaches in their management.

PREVALENCE

The estimated incidence of spinal dysraphism is about 1–3/1,000 live births.[31,33] The prevalence of spinal dysraphism has been on the decline world over in the last few decades due to better nutrition for women, folic acid supplementation, improved antenatal care and high resolution ultrasound for prenatal screening and biochemical markers.

EMBRYOLOGY

The embryogenesis of the first 2 months of gestation can be divided into 23 stages. The neural plate is formed at stage 8 around the 18th day followed by neural folds and its fusion. The expansion of the neural tube and subsequent closure will be completed by 28th day. Open defects occur when the caudal neuropore fails to close. The secondary neurulation sets up the spinal cord formation. Defects at this stage will result in occult dysraphism, connecting the epidermis and the mesenchymal tissues leading to a variety of anomalies and tethered cord.[10,31,78,79]

Failure of primary neurulation leads to open dysraphism posing the risks of CSF leakage and exposure of the neural placode. The extent and severity of neurological deficit depends on the degree of malformation of the neural placode and also the level of the defect. The higher the level usually the worse is the prognosis. A spectrum of neurological abnormalities, like hydrocephalus, Chiari malformation, syrinx, gyral malformations,

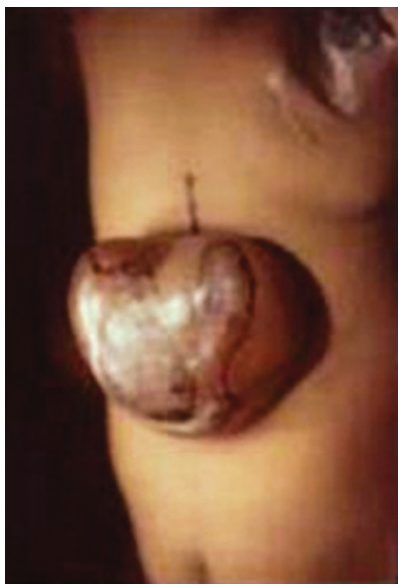


Fig. 1: Myelomeningocele

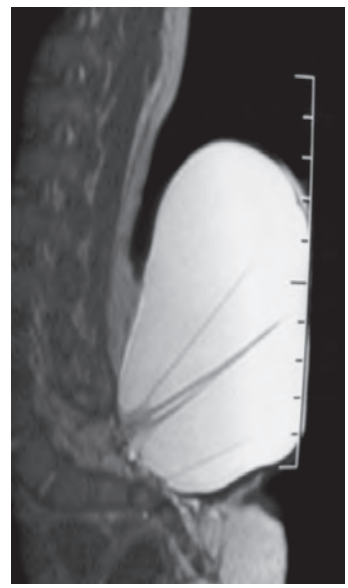


Fig. 2: Meningocele

skeletal malformations and urovesical defects, can be associated. In occult dysraphism, the overlying skin is intact but the spinal cord will be anchored to various tissues starting either from skin, subcutaneous tissue, adipose tissues or cartilage.

AETIOLOGY

The cause of spina bifida is multifactorial with both genetic and environmental factors playing a part. Recent information has stressed on the importance of maternal nutrition and folic acid supplementation, which have contributed to a major reduction in incidence.[79,87]

SYMPTOMATOLOGY

Open dysraphism presents with a swelling over the back which is noticed at birth. Symptoms are primarily referred to CSF leak or the exposed spinal cord. Since the skin over the swelling is poorly developed, it usually gives way during labour resulting in CSF leak, contamination and meningitis. Defects predominantly involve the thoracolumbar, lumbosacral, lumbar, thoracic, sacral and cervical in the order of occurrence. Incidence of high-cervical lesions is about 3.9%.[110] Neurological deficits include motor, sensory and sphincter dysfunction depending upon the severity and level of defect. In severe cases, hypotonic are flexic limbs, sphincter atonia with rectal prolapse may be seen. Chiari malformation presents with lower brainstem and lower cranial nerve dysfunction. The presence of a large head usually indicates hydrocephalus. The associated skeletal abnormalities are kyphosis, scoliosis and deformities of the long bones and feet, hemivertebrae, defective ribs, etc.

ASSESSMENT

The initial assessment of the newborn is extremely important preferably done by both a paediatrician and a neurosurgeon. Examination of the head and neck involves the assessment of head size, shape, skull bones and openness of fontanellae, lacunar skull defects and the size of the posterior fossa. Examination of the back needs assessment of the neural placode, level of the lesion, condition of the skin, extent of skin defect and associated deformities. Examination of the lower limbs for detection of the deformities of the foot and abnormalities of long bones is important. A detailed neurological examination is necessary to assess the level of motor weakness, sensory level and sphincter dysfunction.

PRENATAL DIAGNOSIS

Prenatal screening for neurological abnormalities is based on ultrasound performed routinely or oriented by maternal alpha fetoprotein (AFP) screening. It should be performed around 12, 22 and 32 weeks. Maternal serum screen can detect up to 80% of spina bifida and 90% of anencephaly.[11,17] Sonography may identify up to 90% of myelomeningoceles. Over the last few decades, the diffusion of routine ultrasound has changed the spectrum of the neonatal neurological malformations. Gross lethal abnormalities nearly always result in termination of pregnancy depending on the regional legal system. A growing number of more subtle abnormalities including midline or posterior fossa abnormalities are being discovered. But their postnatal outcome cannot always be predicted accurately, despite the use of foetal magnetic resonance imaging (MRI). Maternal serum screening for chromosomal abnormalities is also increasingly being used. Only in selected situations amniocentesis is contributory.[4,12,21,27,72,95,117]

RADIOLOGICAL ASSESSMENT

Radiological assessment should be done at the earliest depending on the clinical condition. Plain X-rays will reveal skull defects, spine deformities and bony anomalies. MRI is the investigation of choice to study the neural tissue abnormalities and also to assess the severity of hydrocephalus and Chiari malformation (Figs 3A to D). However, ultrasonography can be used to obtain quick information regarding hydrocephalus.[16,42,45]

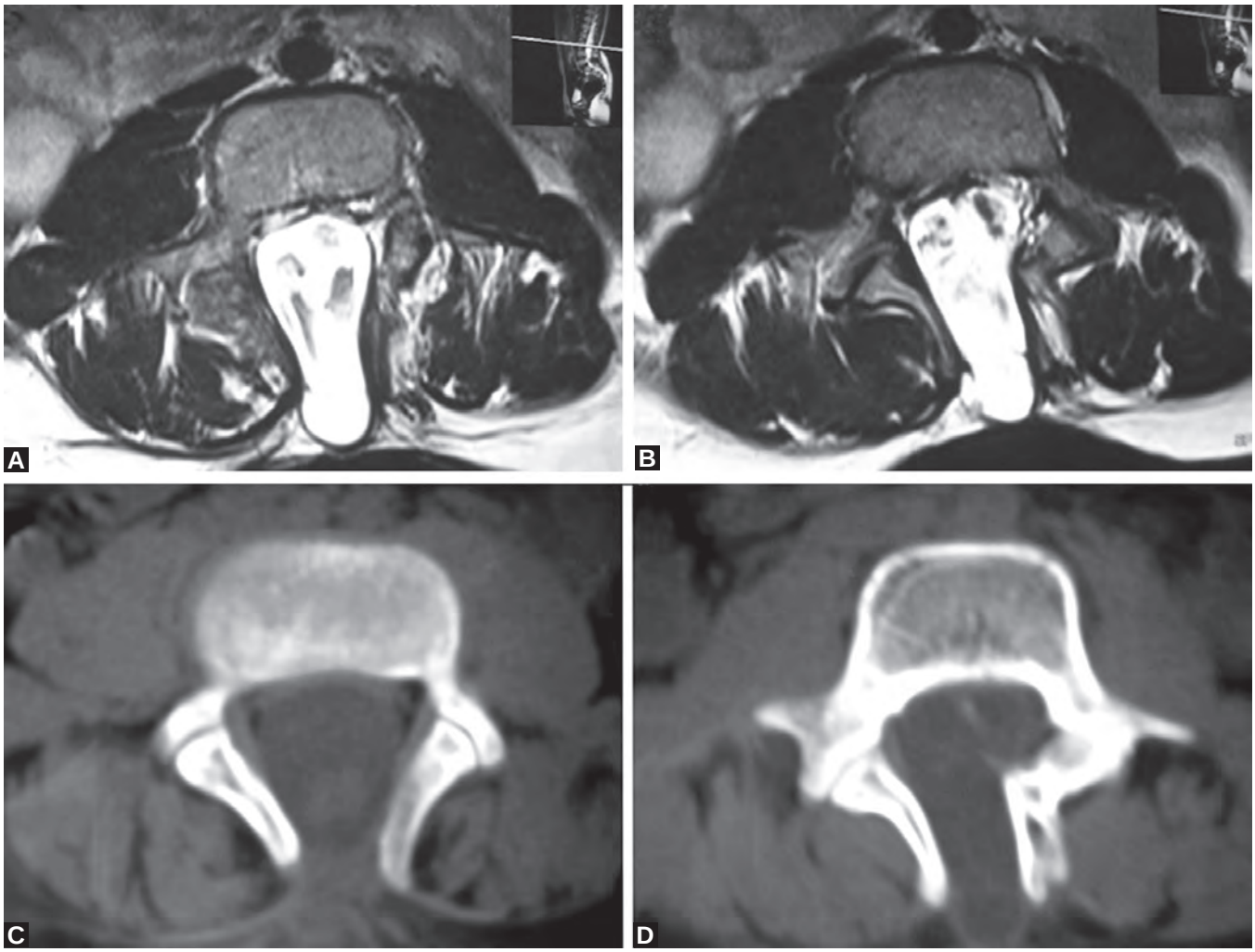
MANAGEMENT

Management of these children needs multidisciplinary approaches. Complete clinical evaluation and appropriate investigations are necessary. Parents need to be counselled and informed regarding the immediate as well as long-term management strategy.[24,25]

The management of a pure meningocele involves a simple repair, while that of a myelomeningocele or myelocele is prolonged, complicated and costly. The treatment does not begin or end with the surgical correction of the local defect, but begins from the moment of birth and continues till such time as maximum possible rehabilitation has been achieved. The total care of such a child requires collaboration between the neurosurgeon, orthopaedic surgeon, plastic surgeon and the urologist. The help of a team of physiotherapists and rehabilitation experts will also be necessary to give the child the best chance for self-sufficiency. Special educational facilities will be required as the child grows up.

SURGICAL TREATMENT

The aim of surgery is to free the placode from the surrounding abnormal skin and to reposition it into the spinal canal with reconstruction of the dura and coverings to prevent CSF leak and infection. The surgical technique depends on the size and the level of the lesion. The help of paediatric, orthopaedic and plastic surgeons may be necessary. Several attempts for maternal foetal surgeries to improve their outcomes were made. The role of foetal surgery for myelomeningocele is yet to be proved.[52,53]



Figs 3A to D: Spina bifida

PATIENT SELECTION

There is considerable controversy regarding selection of patients with myelomeningocele for surgery, i.e. who should be offered surgery and who should not. In the 1960s with the advent of aseptic techniques and antibiotics there was an initial period of enthusiasm when all patients were recommended emergency surgery within 48 hours.[108] Disillusionment followed with Lorber[70] and Ramamurthi[99] suggesting that patients with extensive paralysis, severe hydrocephalus, kyphosis and major associated congenital anomalies in other systems be left unoperated.

But as mortality figures reduced,[14,77] the mood has again changed with more and more surgeons in favour of early surgery.[101] Matson,[73] recognising the variable expression of this malformation, emphasised the importance of considering every child individually. His approach was to identify those who could live rather than identifying children who should be left to die. Though there is no definite method of prognosticating outcome, certain guidelines do exist. Major associated congenital defects of other systems, megalencephaly at birth, severe orthopaedic problems with gibbus at the site of dysraphism, dislocated hips[69] and poor general condition of the child are associated with a poor outcome. Total paralysis with incontinence does not appear to improve with time. It is worth remembering that severe cord lesions higher than the tenth dorsal level are not suitable for orthopaedic rehabilitation.[44] In some patients, one may operate to make nursing care easier or to lessen the social stigma.[2]

Socioeconomic circumstances play an important part in the decision regarding treatment, especially in the developing countries. These patients need repeated hospitalisation for treatment under various specialities. It may be kinder to the child and the family who cannot afford it, to deny operative correction of the myelocele in the first place.[99]

Timing of intervention primarily depends on the clinical condition of the child, and the impending risks. Surgery need not be done as a compelling emergency but should be undertaken as soon as it is practical.[94] In case of suspected meningitis, CSF infection or colonisation of the wound, prophylactic antibiotics and anticonvulsants will form the initial treatment. The child is nursed in an incubator and routine blood counts and serum electrolytes have to be monitored. Blood

grouping and cross matching is done for possible transfusion. Careful assessment of body weight is essential for intra-operative management. The newborn child with myelomeningocele should have saline dressings.[49] It is essential not to use corrosive agents, spirit or antiseptics indiscriminately over the open defects to avoid damage to the underlying exposed neurological tissue.

SURGICAL TECHNIQUE

To obtain successful repair, it is essential to study the surface anatomy and its relationships to the surrounding structures. At the apex of the myelomeningocele usually the flat neural placode is located and from its edge the remnants of the arachnoid membrane gets attached at the nerve root entry zone. From this junction the nerve roots emerge and exit through neural foramina located ventrally. They are seen through the transparent arachnoid membrane which is fused with the skin at the lateral edges of the lesion. The dura mater which is defective posteriorly is loosely adherent to the underlying soft tissue of the back and densely adherent to the bony structures underneath. Rostrally, the dura forms a tube and the neural placode continues into it, which leads to functional spinal cord.

The child is operated upon under general anaesthesia with endotracheal intubation in the prone position with the head and neck placed comfortably. The first step is to isolate the neural placode, while salvaging the nerve roots as much as possible irrespective of their functional status. It is essential that no skin element becomes buried in the repair to prevent the possibility of an implantation dermoid. A vertical midline incision is preferable. In a circumferential fashion, the arachnoid is lifted and the nerve roots are identified. This technique is continued all-round till the neural placode is completely free. The neural placode can then be inverted and sutured. The dura is dissected from the underlying soft tissue. The dural closure needs to be made watertight with a graft, if necessary. The overlying skin is dissected from the underlying fascia and musculature, mobilised and approximated. If necessary, relaxing incisions or flaps may be used to close larger defects. Kyphotic deformity or gibbus can pose special problems. Reigel[100] and Sharrad[107] et al.[109] had advocated resection of the kyphus with primary spinal fusion at the time of surgical repair.[100,109] When the dysplastic skin (Fig. 4) is large causing larger skin defects, balloon tissue expanders can be used to enlarge the normal skin area and reflected subsequently to cover the defect (for detailed operative technique, please check Textbook of Operative Neurosurgery).

Post-operative care is equally important. The child is nursed in the prone position, and the wound is protected from faecal and urinary contamination. Symptomatic hydrocephalus or ACM needs to be treated simultaneously. Supportive nutrition and antibiotics are required. Adequate urological treatment can prevent future complications of the upper urinary tract.[1,8,9] Early management maintaining a low intravesical pressure and intermittent catheterisation with or without pharmacotherapy is beneficial, but urological management should ideally be based on and modified by the urodynamic studies.[1,8,9,18,40,41,56,71,80]

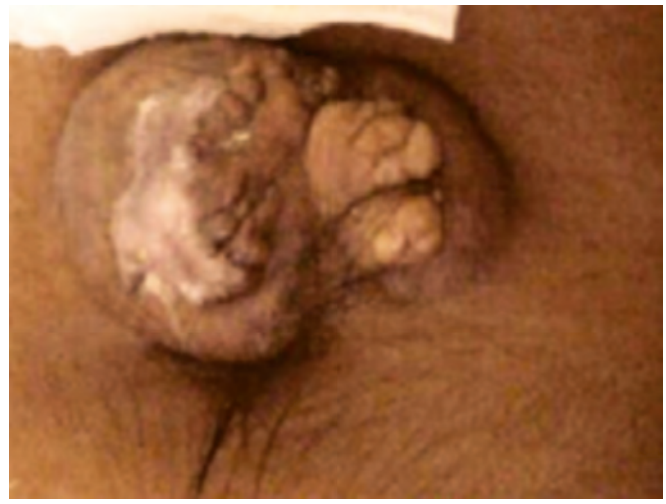


Fig. 4: Dysplastic skin

TETHERED CORD SYNDROME

Tethered cord syndrome has been defined as progressive neurological deficits from the restraint of spinal cord movement and traction due to either anatomical or physiological reasons. The advent of MRI and the present understanding of embryogenesis have led to the recognition of this syndrome more often in paediatric neurosurgical practice. The neurological deficits are insidious and progressive and may be motor, sensory, urorectal, pain and/or scoliosis.[11,29,53,118,121]

Embryogenesis

A diagnosis of tethered cord is made when the tip of the conus is below the level of the lower border of the L1 vertebral body. The ascent of the cord, which occurs throughout the embryonic, foetal and postnatal period requires a well-formed cord and a smooth meningeal covering. During neurulation, the ectoderm on either side of the neural plate comes close together as the neural tube closes. When neural tube fusion is complete, the ectoderm detaches on either side in an event called dysjunction and fuses. If, however, the dysfunction occurs before the neural tube closure is complete, or if the closure is faulty, mesenchymal cells gain access to the central canal of the neural tube. The mesenchymal cells then differentiate into fatty tissue to form a lipomyelomeningocele[90] which is essentially a mass of fat extending from the conus medullaris to the subcutaneous plane underlying an intact skin. All the manifestations of lipomyelomeningocele can be explained by this mechanism of embryogenesis.

The solitary thickened filum terminale, however, needs another explanation. If one recollects the complex embryogenesis of the filum terminale, with the very high possibility of a developmental error occurring, it is not difficult to explain the non-resilient, thickened filum terminale. An error in the canalisation of the caudal cell mass may be another explanation for the origin of a lipomyelomeningocele.

According to Marin-Padilla,[93] dural schisis is the basic defect resulting in the various forms of tethering, with a short thick filum terminale occurring as a secondary event. This is not supported by the occasional intra-operative observation of the cut ends of the filum terminale springing back on being divided, as well as the clinical improvement which occurs when the filum terminale alone is divided. Occult spinal dysraphism with tethered cord may be associated with anorectal malformations.[14,30]

Pathogenesis

It is the cord which is tethered, with the nerve roots lying lax and even loosely on either side. The effects of the tethering is maximum close to the site of tethering and when the tethering lesion extends over a distance the maximum effect is on the cord adjacent to the caudal end of the lesion, where the maximum stress lies. Here, it is physically elongated and functionally the most affected.

Tethered cord can result from a variety of conditions. This can broadly be classified into the following points:

- *Anatomical*: In anatomical condition, the conus is placed at a lower level than normal.
- *Physiological*: This is due to tight or thick filum. In this variety, the conus may be at the normal level but the movement of spinal cord is restrained resulting in neurological deficits and vesicle dysfunction called "non-neurogenic bladder".
- *Developmental*: This could be secondary to a variety of conditions like congenital anomalies, terminal lipoma, intra-spinal lipoma,[65,67] lipomyelomeningocele,[32] split cord malformations, sacral agenesis and other occult dysraphic states.
- *Post-operative*: Post-operative tethering that occurs after surgery for myelomeningocele or dermoid or recurrent adhesions from previous surgery often termed retethering.[119,120]

Clinical Features

The name tethered cord implies that the spinal cord is attached tightly to a congenitally abnormal structure in the lumbosacral area, as well as at the cranio-vertebral junction. With growth, the spinal cord is stretched between these two points, resulting in insidious and progressive neurological deterioration. The popular belief that the deterioration occurs mostly during the phases of rapid growth is not confirmed. During embryonic life, the spinal cord lies way down at the sacral segments and gradually the conus ascends and reaches the adult level to L1, as confirmed by ultrasonographic studies. In this pathological situation, the spinal cord is tethered to anatomical structures lower down, preventing the ascent of the conus in parallel to the vertebral growth. On the other hand, there is disproportionate growth between the spine and the spinal cord resulting in progressive traction. Normally, when a child bends forwards, there is an ascent of the spinal cord by one to two segments. The filum can be short and thick with a variable quantity of fibrous tissue making it tight and preventing such movement.

Several theories have been proposed to explain the neurological deterioration in tethered cord syndrome. With the ongoing stretching central fibres are subjected to traction injury, resulting in structural damage. Yamada et al. have shown that the mechanical stretching of the cord during physical activity leads to changes in intracellular respiration, reduction in cytochrome oxidase and shift in redox curves.[121] A third possible mechanism is by ischaemic injury. Traction and elongation of the spinal cord can compress the radial perforating vessels resulting in ischaemic damage. Once the neurological deficit occurs it is rarely reversible, therefore, it is important to treat them prophylactically.[88–90,92,104,121]

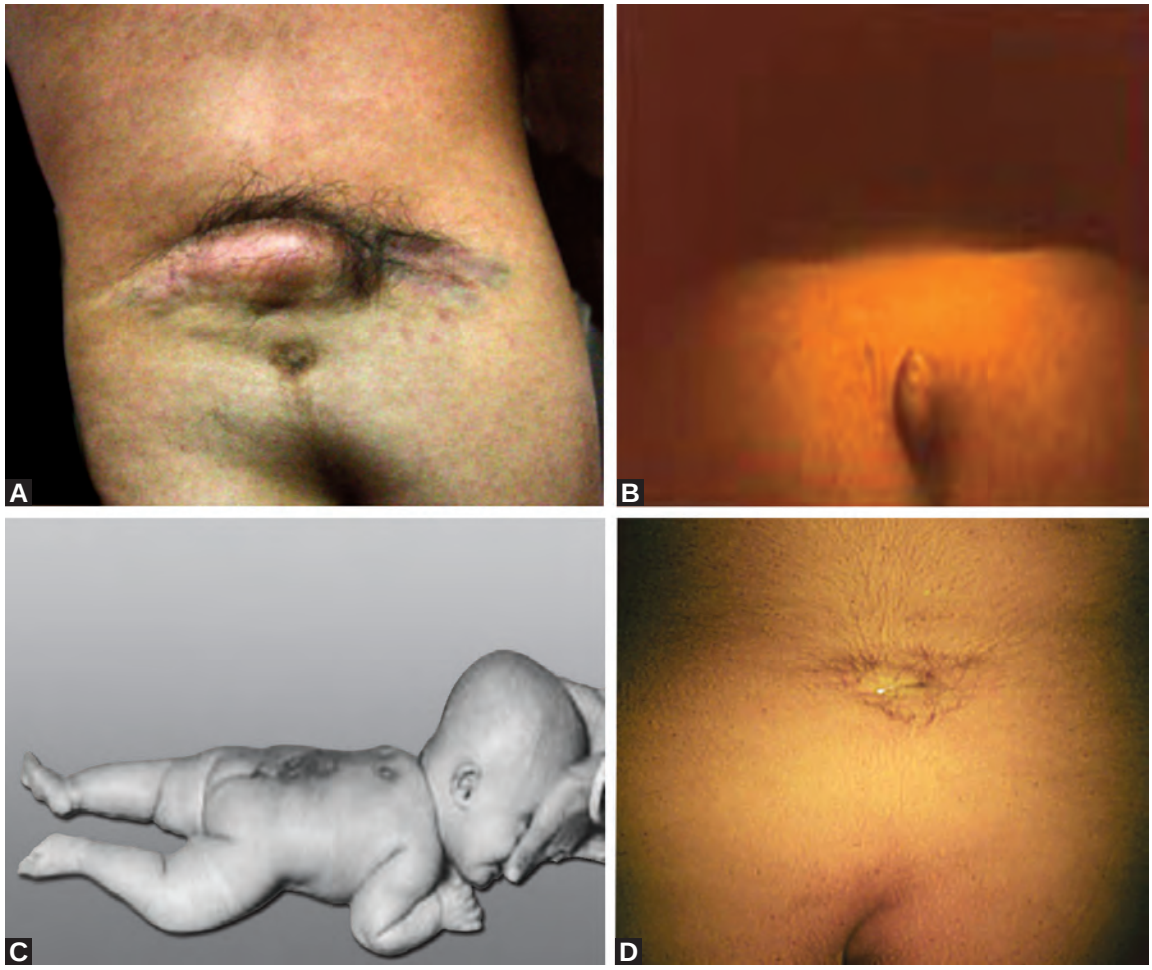
Symptoms

The predominant symptoms can be motor in the form of insidiously progressive distal weakness and spasticity, and sensory ones like sensory loss, paraesthesias and trophic ulcers. Neurovesical dysfunction is one of the commonest presentations, ranging from a minor bladder disturbance to frank urinary incontinence, occasionally associated with bowel movement dysfunction. At times, pain can be the major symptom. It may be radicular or funicular, low back or calf muscle pain. The scoliosis due to tethering is a much debated issue, but there is enough evidence to suggest that it is due to the tethering.

Neurological Examination

A detailed neurological assessment is mandatory. Neurocutaneous markers, like tuft of hair, nevus, dysplastic skin, angiomatous patches, lipoma, dermal sinus, presence of human tail and absence of gluteal folds are strong indicators.[18,20] Neurovesical dysfunction, leg pain, scoliosis, motor or sensory deficits, should prompt the clinician to look for possible tethering even in the absence of cutaneous markers (Figs 5A to D).

Tethering being a congenital phenomenon, these children often present to their paediatricians, with vague leg pains; to orthopaedicians with gait disturbance and deformities; to urologists with bladder symptoms, frequent or persistent bed wetting and finally to neurosurgeons when the neurological deficits become overt. Hence, awareness about this syndrome among the medical fraternity is necessary.



Figs 5A to D: (A) Lipoma with tuft of hair. (B) Tail. (C) Tuft of hair. (D) Dysplastic skin

The diagnosis should be based on a high index of clinical suspicion, a detailed neurological examination and investigation for confirmation. MRI is the choice of investigation to identify the anatomical location of the conus and associated abnormalities (Fig. 6). The classical dorsal displacement of the conus with a large, ventral CSF space is often suggestive. Early appearance of lumbar potentials in SSEP has been found valuable, though often difficult to record in children.[13,55]

Indication for Treatment

Any child with progressive neurological deterioration of motor, sensory or urinary function should be treated.

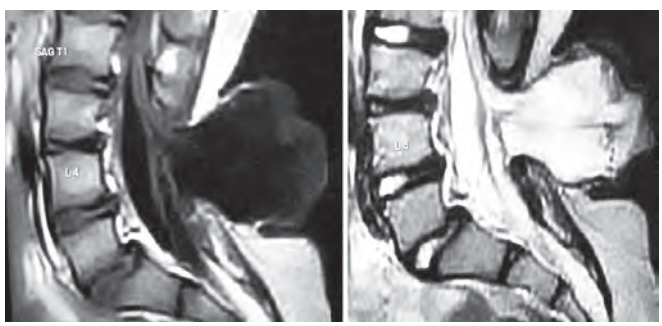


Fig. 6: Imaging of tethering

Pain, spasticity, gait abnormality, persistent or progressive scoliosis are the other indications. Knowing the mechanisms of neurological deterioration prophylactic surgery is logical. If the neurological deficit has already occurred, surgery should be done as soon as the diagnosis is established.

The Principles of Surgery

- Complete untethering of the spinal cord.
- Proper dural reconstruction with adequate CSF space around the spinal cord to prevent retethering.

Retethering

A theoretical risk of retethering exists after the treatment of any tethered cord (Fig. 7) or some of these complex anomalies. Every known precaution should be adopted to prevent such a possibility. This includes complete untethering of all the contributory structures, proper concealing of rough and possible adhesive surfaces by pial sutures, laminectomy to accommodate the thickened cord and to facilitate upwards movement, duraplasty to create a reservoir of CSF around the repaired structures and epidural fat grafts to prevent fibrosis. Some studies reported the advantage of nursing the child in the prone position post-operatively. Subtle neurological worsening

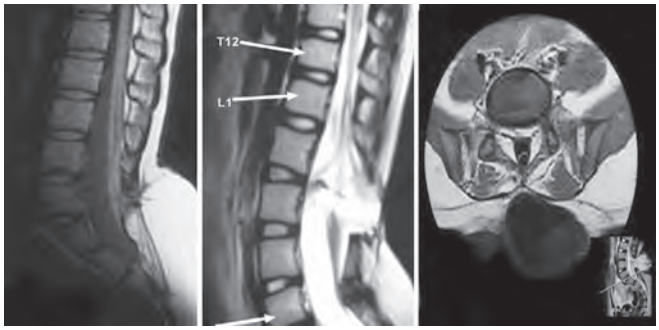


Fig. 7: MRI of tethered cord

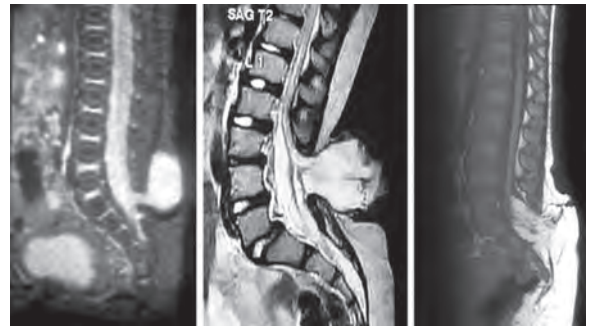


Fig. 9: Lipomyelomeningoceles

or progression of deformities should be looked for during follow-up. MRI should be repeated at the earliest suspicion. At present, there is no foolproof investigation to demonstrate retethering. MRI in the prone position to demonstrate CSF dorsal to the conus has been suggested. Serial electrophysiological and urodynamic studies seem to be indicative. Till such time, clinical diagnosis remains the gold standard. All symptomatic children suspected to have retethering (Fig. 8) should be re-operated to prevent further deterioration. But surgery on purely radiological suspicion for retethering is controversial.

Lipomyelomeningocele

Lumbosacral lipomyelomeningocele (Fig. 9) is a subcutaneous fibro-fatty mass that traverses the lumbodorsal fascia causing a spinal laminar defect, penetrating the dura and tethering the spinal cord. Lipomas are one of the important causes of spinal cord tethering almost all of them have a low lying conus. The term lipomyelomeningocele is used despite the overlying skin being normal. They arise from a disorder of embryogenesis. They usually consist of a single cell type but may have fibrous tissue, muscle cells, neural tissue and a variety of other cell types that arise from all the embryonic layers. The incidence is approximately one in 4,000 births in the USA with a slight female preponderance. True incidence of terminal lipomas is not known. MR studies have shown that 13–26% of lesions account for tethering.[5,15] Symptoms and signs are mainly related to the traction on the lower spinal cord, leading to motor deficits, sensory disturbances, spasticity, urodynamic, urorectal dysfunctions and skeletal deformities.[36] The pathogenesis and natural history of these complex anomalies are not clearly understood. But it is certain that almost all deteriorate in their neurological status over course of time. Proper treatment at the appropriate time will prevent neurological deterioration. Surgical treatment is complex as they pose several challenges and there is a risk of neurological deterioration. A variety of factors can influence the outcome. Anatomical features like size of the lipoma, location (midline or paramedian), wide bony defect, defective muscles and fascia and poor cleavage at the neurolipomatus junction. Physiological factors like degree of traction and the ability to withstand the effects of traction. Pathological factors like vascularity of the fibrolipomatous structures and associated anomalies.[64,66,115]

Lumbosacral lipomyelomeningoceles have been classified by Chapman[23] as dorsal, transitional and terminal types and by Aris as of five types: dorsal, caudal, combined, filar and lipomeningomyelocele.[6]

In Dorsal variety, the lipoma (Fig. 10) enters into the segment of spinal cord dorsally through a fibrofatty pedicle below which normal cord and dura exists. Transitional variety is essentially a dorsal type which covers the entire conus and extends up to the filum. Distally no normal cord exists, whereas in the terminal variety (Fig. 11), normal looking conus ends in the lipoma through a dural defect and all the sacral roots will be cranial to the lipoma.

Diagnosis in 90% of children is made by the presence of a visible lipomatous mass in the midline on the

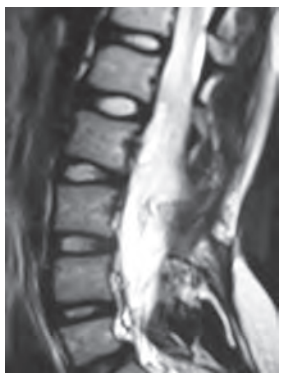


Fig. 8: Retethering

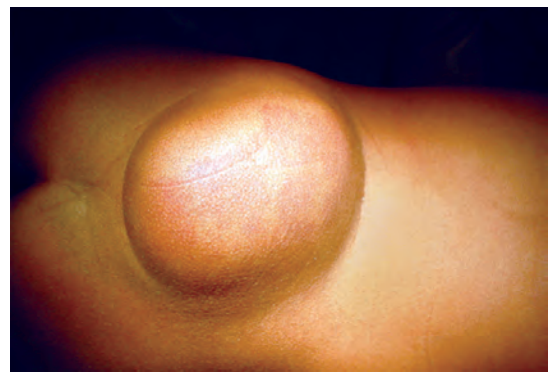


Fig. 10: Lipoma

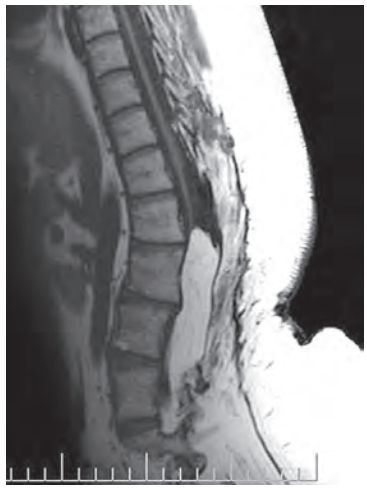


Fig. 11: Terminal lipoma

back or a cutaneous marker. Associated hydrocephalus or cranial anomalies are extremely low though the other spinal anomalies can be associated. MRI (craniospinal screening) is the choice of investigation for a comprehensive assessment. The surgical treatment is aimed at complete untethering and prevention of retethering of the cord. Based on the progressive irreversible worsening, prophylactic surgery has been recommended by many authors.[28] There is no controversy regarding lipomas of the filum terminale. Reports from Paris group with 18.7% delayed deterioration on 10 year follow-up of asymptomatic conus lipomas and from the Osaka group stating 88% of their children operated upon prophylactically deteriorated with time, has created further debate on this issue.[5,28,62,74,96,113]

Surgical Technique

Broad principles include vertical skin incision, dissection of subcutaneous lipoma up to the fascia, excision of extraspinal component of lipoma, identification of upper and lower intact laminae and performing laminectomy, identification of normal dura above and below and separation of dural tube from the thoracolumbar fascia all round. Then dural opening (circumferential) around the fibro-fatty stalk, removal of intradural lipoma, gentle dissection of the fibro-fatty pedicle up to the neural structures over the dorsal surface of cord and removal of fibrous tissue up to the neurofibrolipomatous junction, removal of other fibrous bands and finally detachment of the filum. The spinal cord should eventually be made free from five structures: skin, subcutaneous tissue, thoracolumbar fascia, dura and filum terminale to achieve complete untethering.

All known precautions to prevent retethering, like pial, closure to cover the raw dorsal surface of the cord and duraplasty to enlarge the subarachnoid spaces and to facilitate free CSF circulation around the repaired surface of the cord are to be adopted. Replacement of free fat over the dura will fill the dead space, protect the soft tissue, prevent CSF leak and prevent skin edge necrosis.

Surgery for terminal lipomas is relatively easy. One needs to separate the dura from the lipoma and disconnect the neural tissue at the neurolipomatous junction which is often clearly evident.[47,63,76,85,86,93,111,115,116]

Myelocystocele

It is an occult form of spinal dysraphism with a localised, cystic dilatation of the central canal of the spinal cord herniated through a posterior spina bifida. Terminal myelocystocele truly is an anomaly of the caudal cell mass associated with anomalies of the anorectal system, lower genito-urinary system and vertebrae such as anal atresia, cloacal extrophy, lordosis, scoliosis and variable degree of sacral agenesis. They constitute 4–8% of occult dysraphism and rarely occur in the lower thoracic region. The lesion consists of skin covered lumbosacral spina bifida, arachnoid lined meningocele directly continuous with the subarachnoid space and a low lying hydromyelic spinal cord that traverses the meningocele and forms a distal sac which does not communicate with the subarachnoid space. The MR appearance is distinctive and is characterised by trumpet like flaring of the distal cord central canal into an ependyma lined terminal cyst. Surgical correction cannot only release tethering but also prevent the complications.[31,75,94]

SPLIT CORD MALFORMATIONS

Split cord malformations (SCMs) (Fig. 12) are increasingly being recognised as one of the causes of tethered cord syndrome. They are defined as a form of occult spinal dysraphism, in which any part or entire spinal cord, cauda equina and filum terminale are divided into two lateral parts by a dorsal/ventral spur.[3] Renaming them as SCMs have reduced the conflict in terminology, though the pathogenesis of these complex anomalies still remains controversial. The diagnosis has become easy and certain with the advent of MRI. It is necessary to screen the entire spine in order to recognise all the associated anomalies and to plan the management strategies.

Split cord malformations are rare and complex conditions. In the recent years, MRI has renewed the interest in diagnosis, basic understanding and management of these anomalies.[3] Several terminologies were in vogue in literature like "diastematomyelia" (Olivier) and "diplomyelia" (Bruce) with a poor distinction. Pang et al. have proposed a unified theory and named them "Split cord malformations".[22,88,90] The most widely accepted theory about embryogenesis of this complex malformation was originally proposed by Bremer[14] and subsequently modified by Pang et al.[14,88] as "Unified theory of embryogenesis". The basic error appears to be development and persistence of accessory neurenteric canal (ANC). In the early weeks of gestation, the primitive neurenteric canal temporarily connects the yolk sac (endoderm) with the amniotic cavity (ectoderm). Simultaneously, an ANC appears and its persistence will result in a variety of malformations.[14,88] The persistence of the anterior end of

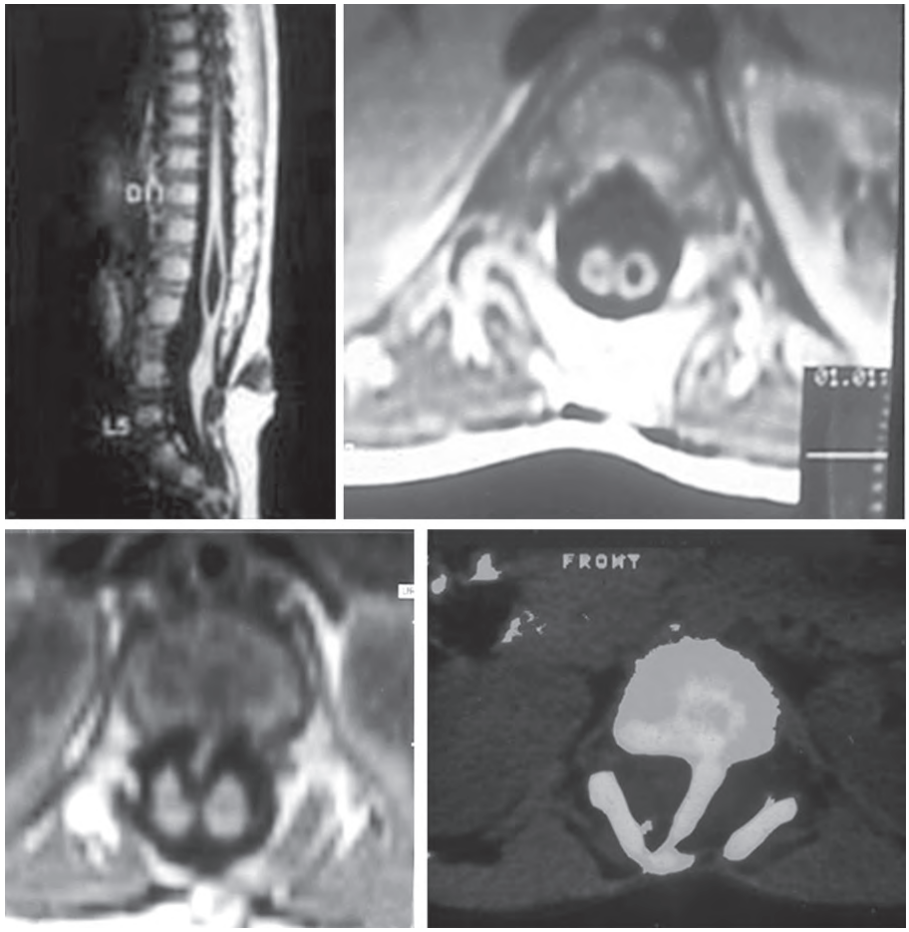


Fig. 12: Split cord malformations

this canal will result in intestinal malformations and of the posterior end in cutaneous malformations like angiomas, hypertrichosis, dermal sinus or dermoid, whereas the persistence of the intermediate part causes a split in the notocord and the neural placode. The division of the notocord then leads to formation of hemiverterbrae, bifid, hypertrophic, hyperplastic vertebrae or fusion of vertebral bodies or posterior elements. The division of the placode later on leads to the formation of two hemicords. If the mesenchyme surrounding the ANC contains precursor meningeal cells, it will result in the formation of dural and bony spurs within, leading to SCM type I. If meningeal cells are not incorporated then it is not involved in the formation of the dural sac and once the ANC disappears it will be transformed into an intradural fibrous band situated between the two hemicords, thus leading to SCM type II. The persistence of the ANC could occasionally interfere with the neurulation process leading to the formation of a meningocele or meningomyelocele, compounding these malformations further.[14]

The original description diastematomyelia denotes splitting of the cord with a bony spur extradurally. Spinal roots arise from the lateral aspect of the hemicords with no medial roots. Diplomyelia is supposed to represent true hemicords and, therefore, harboured in a single dural tube, with medial roots from each hemicord. While others believe that diplomyelia is an extremely rare condition, associated with split of the ventral and dorsal horns. Pang introduced the term "*split cord malformation*". SCM type I constitutes 40–50% of SCM.[88,90,91] Widening of interpedicular distances and hyperplastic laminae are usually associated.[38] The dural sac is always double with division of the spinal canal and cords by an extradural bony or cartilaginous spur. The spur can be anteroposterior, usually attached to the posterior surface of the vertebral body. Rarely, it can have a dorsal attachment to the spine. The spur can divide the canal into two symmetrical halves or can be slanting in the axial plane dividing the canal asymmetrically. In such situations, one of the hemicords can be hypoplastic. Harwood-Nash et al.[46] have reported such asymmetry in 50%. In the majority, the spur is located in the lumbar region and less frequent in lower thoracic, cervical and upper thoracic regions, respectively. Double level spurs have also been reported occasionally. The separation of the cords can extend over several segments before they reunite caudally and the spur is located in the crouch. SCM type II accounts for 50–60% of SCMs. In this anomaly, the dural sac is single with one spinal canal and two almost equal and symmetrical hemicords between which an anteroposterior fibrous band tethering the cords to the dura. Recently, the importance of these fibrous bands as the cause of symptomatic tethering has been highlighted by several authors.[3,35,37,89]

Surgical Technique

The child is positioned prone with underlying supports. A midline skin incision is made extending above and below the level of the lesion. Subcutaneous tissue and the paraspinal muscles are carefully separated. Usually, the widened interpedicular distance or thick posterior elements will assist as a landmark to locate the spinal segments involved. It is preferable to expose the normal laminae one level above and below. The laminae can be hyperplastic or fused. Laminectomy is started at the normal level and continued on both sides close to the pedicles in an encircling fashion, protecting the dura and preserving the facet joints. The central bony spur with its attachment to the lamina is isolated. The two dural tubes are identified and protected. The bony spur is gradually nibbled till its attachment after careful and adequate separation from dura. The dura is then opened in the midline at the normal level extending down elliptically on either side of the sleeve of the spur joining in the midline caudally. The arachnoid is also opened. The dural sleeve over the spur is then completely excised. The cords are inspected anteriorly and posteriorly and all the surrounding arachnoidal and fibrous bands are removed. After securing haemostasis, the dura is closed posteriorly in the midline converting it into a single dural tube. The anterior defect of dura need not be closed. In type II malformations, posterior bony elements almost look normal and hence a marker will be necessary. After laminectomy or laminotomy of the required levels, the dura is opened in the midline. The hemicords are inspected under magnification for the fibrous bands. The fibrous band is usually located ventrally between the hemicords. The band is released from its dural attachment. Other fibrous bands, if present, should be released. The filum is untethered and the dura is closed in the midline. In complex malformations, the other associated anomalies are also dealt with appropriately.[3,98,102,103,109,112]

COMPOUND OR COMPOSITE SPLIT CORD MALFORMATION

Usually these are associated with open dysraphic states. Various forms of split cord can frequently coexist in children with dysraphism, the so-called composite lesions. It could be type I or II or may be a combination at the same or at different levels. Occasionally, the division of the cord is not so clear but there may be a double central canal and duplicated dorsal or ventral horns. Diffuse structural disorganisation and dysgenesis is also known. Occasionally, the two hemicords are partially bridged known as Horse-shoe cord. Composite lesions are associated with other forms of occult dysraphism such as lipoma, dermoid or epidermoid, sinus tract or a teratoma.[48,50] The overall outcome is good in isolated SCMs in comparison to complex varieties. One should carefully evaluate these children to exclude polymalformation syndrome. Several bony and visceral anomalies are known to coexist.[51] Although the majority are diagnosed in infancy, symptoms can manifest at any age and become symptomatic by the second decade. The neurological symptoms can vary from pain, bowel and bladder dysfunction, motor or sensory deficits. Spinal deformity, asymmetry of the limbs, gait disturbance and trophic ulcers are the other associates. In older children pain (lumbago or lumbosciatic) and paraesthesias are more common.[58,68,82] One should search for an anomaly of spinal alignment, midline cutaneous anomaly, enlargement of the spinal canal and an echoic mass in the spinal canal (spur) in prenatal ultrasound examination.[83] Plain X-ray, CT scan, CT myelography and MRI are the imaging modalities used. The radiological abnormalities have vividly been explained by Neuhauser et al.[84] Although some can be recognised on plain X-ray, high-resolution CT scan is sometimes necessary in identifying the spur. MRI is the procedure of choice to demonstrate the spinal cord, the dural sac, the spur, the location of the filum terminale and other associated abnormalities. The filum terminale may be short and thick in 40%. The spinal cord at times is completely split into two separate filums. Hydrosyringomyelia, dermal sinus, dermoid, epidermoid or lipoma can be associated. The CT and MRI can be complementary in increasing the diagnostic accuracy. Urodynamics also forms an important aspect of evaluation to assess the bladder function.[3,7,8,46,58]

DERMAL SINUS

Congenital dermal sinuses (Fig. 13) are a unique form of occult dysraphism presenting with meningitis, tethering or neurological compression with an incidence of one in 1,500 births. The dermal sinus tracts are lined by squamous epithelium and may present anywhere in the midline from the lumbosacral region to the occiput or nasion. Despite an innocuous external appearance the tract may extend over several spinal levels before entering the dura and getting attached to the filum or the spinal cord. Dermoid and epidermoid nodules are frequently associated with these tracts. The small sinus osteum is

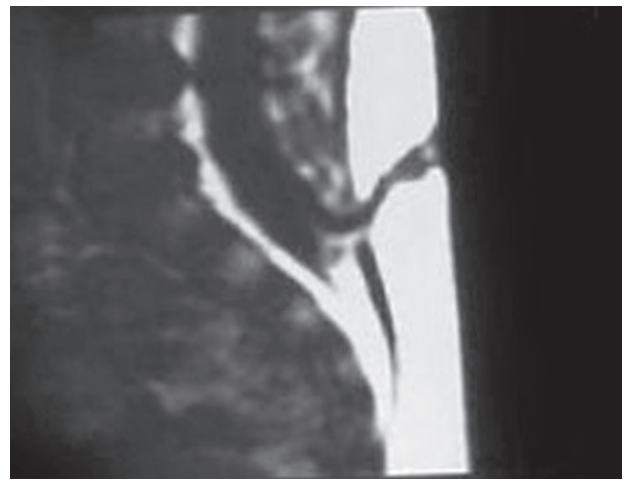


Fig. 13: Dermal sinus

quite often overlooked unless a discharge is noted by the parents. The neurological examination is nearly always intact. The MRI is diagnostic. Embryologically, the formation of the dermal sinuses may reflect incomplete dysjunction. Focal, incomplete separation of the cutaneous ectoderm from the neural ectoderm during the 4th week of foetal development retains the adherence of these layers. Altered dysjunction can lead to dermal sinus terminating in the subcutaneous tissues or may extend to an intramedullary location. The most common location is the lumbosacral area. Thoracic and cervical dermal sinuses are present in 10%. These are usually in the midline providing a portal for infection leading to meningitis or intraspinal abscesses. The most common organisms are *Staphylococcus aureus* and *Escherichia coli* followed by *Proteus* species and anaerobes. Multiple organisms may be cultured. Recurrent meningitis is one of the classical presentations. Neurological examination is normal except in situations where the dermoid or epidermoids leading to cord compression. The treatment includes antibiotics and complete surgical excision of the sinus tract and the associated lesions. Incomplete removal is the usual cause for recurrences.[26,39,54,66,81,97,114]

SYNDROMES OF THE TETHERED CORD

Tethered cord syndrome may occur with the conus in normal position with or without associated neurocutaneous markers. These children usually present with hyper-reflexic neurogenic bladder which was earlier referred to as non-neurogenic bladder. Urodynamic studies often reveal detrusor hyper-reflexia. There is growing evidence that sectioning of the filum improves the bladder function in 96% of patients.[59,60]

TETHERED CORD SYNDROME IN ADULTS

Though unusual, but has a well established entity. The later onset of presentation may be related to the cumulative effects of repeated microtrauma. Distinct precipitating events preceding the symptoms like heavy weight lifting, trauma and lithotomy position have been described in 60%. In many respects it is similar to the paediatric population except that the incidence of low back pain and leg pain is significantly high in adults. MRI is diagnostic though indications for surgery are still controversial and not clear. The majority improve with proper surgical sectioning of the filum.[19,43,59,71,89]

NEUROGENIC BLADDER WITH CONUS AT NORMAL POSITION

These children usually present to the urologists with urinary incontinence and/or associated complications. Tethered cord syndrome has been postulated as a cause of neurogenic hyper-reflexic bladder even in the presence of a conus medullaris at a normal position. These conditions were earlier coined by different names like non-neurogenic–neurogenic bladder. It usually presents in children less than 10 years. They do not have associated regional, neurological or vertebral anomalies. Urodynamics are highly suggestive. Release of filum terminale has shown significant improvement in their bladder control and also the urodynamic abnormalities. Selcuki et al. described 96% improved bladder function.[34,57,61,105,106]

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20 Hydrocephalus

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INTRODUCTION

Hydrocephalus is a condition wherein excess of cerebral spinal fluid (CSF) accumulates within the ventricular system of the brain, leading to increased intracranial pressure (ICP). This condition apparently can result from various conditions that can affect a foetus, infant, child and adult.[50] Numerous definitions of hydrocephalus have been proposed, the summary of which indicates an underlying imbalance between the production of CSF and its absorption.[60] Although over production of CSF as a cause of hydrocephalus is well recognised in association with choroid plexus papillomas, these are rare tumours in clinical practice.

HISTORY[14,59]

Hydrocephalus has been recognised for centuries. Accumulation of fluid in various intracranial compartments was recognised by Hippocrates (BC460–377) and Claudius Galen (130–200AD).[24] The cerebral ventricles have interested and fascinated physicians for a long time. They were thought to be the seat of the human spirit "pnuema animolis". The large head was attributable to "water on the brain". The first description of internal or ventricular hydrocephalus was made by Rhazes (850–923 AD). However, the first morphological description of hydrocephalus with anatomical enlargement of the ventricles leading to damage of the brain parenchyma was by Andreas Vesalius (1514–64). Jean Louis Petit (1664–1750) gave more complete descriptions and Giovanni Morgani (1680–1771) described the clinical features of a bulging fontanelle and sutural widening in paediatric hydrocephalus. The studies of Thomas Willis (1621–75) facilitated the understanding of the ventricular system and CSF pathways. For the first time he proposed the choroid plexus as the site of CSF production and also introduced the concept of absorption into the venous system via the meningeal "glandules" presumed to be the arachnoid granulations. Franciscus Sylvius (1614–72), Alexander Monroe (1733–1817) and Francois Magendie (1783–1855) have made important anatomical contributions. Finally, Key and Redzaus (1876) established the modern concept of CSF circulation. At this stage, the diagnosis and management was not clear leading to high mortality. Dandy and Blackfan (1913) further contributed by developing experimental models of hydrocephalus and created a means of classification, differentiating between the non-communicating (obstructive) and communicating forms with distinct possible treatment strategies. The treatment options were extirpation of the choroid plexus, removing obstructive pathologies or creation of conduits to drain CSF from the intracranial compartment. The history of the treatment of hydrocephalus has been dealt with in detail by John Scarff in 1963. Dandy in 1922 proposed third ventriculostomy for obstructive hydrocephalus. CSF diversion included planting the ureter into the spinal theca following nephrectomy, thus draining CSF to the bladder. Other surgical procedures include Torkildsen's procedure of draining the lateral ventricle into the cisterna magna and ventriculocisternostomy in aqueductal obstruction. A flood of operative techniques for the diversion of CSF came into use since 1939. In the 1950s, synthetic, biologically tolerated polymers, particularly silicone elastomer became available and thus heralded the shunt era of treatment of hydrocephalus. Meanwhile, advancement in optics and endoscopes popularised endoscopic third ventriculostomy, as originally described by Mixter.

EMBRYOLOGY

The ventricular system develops from the corresponding vesicles of the developing neural tube. The cavity of each telencephalic vesicle becomes the lateral ventricle and that of the diencephalic becomes the third ventricle. The cavity of the rhombencephalon forms the fourth ventricle. Its continuation into the spinal cord is the central canal. During development, each lateral ventricle is a spherical space within the telencephalic vesicle and with the forward and backward growth the ventricle gets elongated antero-posteriorly. The posterior end of the telencephalic vesicle now grows downwards and forwards to form the temporal lobes, making the ventricles "C" shaped. Finally, the occipital horns grow backwards. The approximation of the two growing telencephalic vesicles makes the medial walls of the lateral ventricles appose each other. The floor of this group becomes the roof of the third ventricle and its lateral invagination forms the choroidal fissure. A fold of pia mater extends into this fissure, forming the telachoroidea. A bunch of capillaries develop within this fold leading to the formation of the choroid plexus.[27,29,50]

CEREBROSPINAL FLUID PRODUCTION AND ABSORPTION

The majority of CSF production is by the choroid plexus, contributing 70–80% of the daily volume. A small proportion of CSF may be produced from the ependyma and brain parenchyma. CSF production occurs by a combination of filtration across the endothelium and active secretion of sodium by the choroidal epithelia. Although the cerebral perfusion pressure and ICP do appear to have some effect on CSF production, it is largely independent of these pressures under physiological conditions. CSF which is largely formed in the lateral ventricles passes through the foramen of Monroe into the third ventricle and reaches the fourth ventricle through the aqueduct of Sylvius and then presumably exits through median foramen of Magendi and the lateral foramina of Luschka. According to Weed[68] the formation of CSF creates dissection of the intercellular space of the meninx primitiva to form the subarachnoid space. From the subarachnoid space CSF reaches the parasagittal arachnoid granulations and part of it goes down the spinal subarachnoid space.[68]

Cerebrospinal fluid is produced at the rate of 0.33 ml/min, approximately 500 ml/day. The total volume of CSF varies with age and in adults is 100–150 ml of which 15–25 ml is contained within the ventricles. The mechanism of absorption of CSF has been extensively investigated. Direct absorption from the brain parenchyma, choroid plexus and by the lymphatic channels in the region of the cribriform plate has been postulated. The arachnoidal villi and granulations contribute to the maximum absorption. They are the herniations of arachnoidal tissue into the dural venous sinuses. Two mechanisms have been proposed. The "closed" mechanism, where the villi are blindly diverticulated and absorption occurred by a process of seepage across the endothelial covering. The open mechanism indicates the presence of channels across the villi, opening and closing in a valve like manner permitting unidirectional flow of CSF. Tripathi and Tripathi have proposed a transmembrane transport mechanism, consisting of vacuoles carrying CSF across the endothelial layer. Recently, the role of CNS microcirculation in the absorption of CSF is contributing to the understanding of the pathogenesis of hydrocephalus. As these mechanisms are not still clear, we are forced to follow our understanding and classification based on traditional concepts of CSF circulation.[50,62]

AETIOLOGY AND PATHOPHYSIOLOGY OF HYDROCEPHALUS

The incidence of congenital hydrocephalus is about 0.2–0.5/1,000 live births. A higher incidence has been reported in elderly primiparus mothers. It can be associated with variety of physiological and pathological conditions.[11,12,60] An obstruction at any point in the CSF pathway may result in hydrocephalus. Traditionally, obstruction within the ventricular system is called noncommunicating hydrocephalus and when the impairment is in the circulation through the subarachnoid space or absorption to the venous system, it is called communicating hydrocephalus. Wherever the aetiology is known, it is further divided into congenital and acquired forms. The aetiology of congenital hydrocephalus remains obscure. An inheritable form of aqueductal stenosis has been described in males (X-linked hydrocephalus). The other mechanism of hydrocephalus is over production, seen in papilloma of the choroid plexus.

Rekate has classified hydrocephalus based on CSF flow obstruction. Impaired absorption is another mechanism where venous sinus occlusions, vein of Galen malformations and developmental anomalies like craniostenosis with malformations of the skull base can lead to the development of hydrocephalus. Absence or disease of the arachnoidal villi, resulting in disturbance of absorption can also result in hydrocephalus.[67]

CLASSIFICATION

Based on the results of their neutral phenosulphonaphthalein tests, Dandy and Blackfan subdivided hydrocephalus into two groups.[10] If the chemical injected into the lateral ventricle was recovered within 20 minutes from the spinal subarachnoid space, the hydrocephalus was termed "communicating", implying a patent communication between the ventricles and the subarachnoid space. If there was no recovery, the hydrocephalus was termed "non-communicating" or obstructive. With present day radiological, computerised tomography (CT) and magnetic resonance imaging (MRI) techniques, it is possible to localise with accuracy the exact site of blockage to the flow of CSF. Hence, a more helpful classification is as follows:

1. The hydrocephalus may be due to:
   A. Over production of CSF (a rare entity)
   B. Obstructive: wherein there is obstruction to the flow of CSF in the
      - Lateral ventricles
      - Foramen of Monroe
      - Third ventricle
      - Aqueduct of Sylvius
      - Fourth ventricle
      - Subarachnoid spaces
   C. Absorption defect
2. Based on the site of blockage to the CSF flow the hydrocephalus may be:
   A. Monoventricular or unilateral
   B. Biventricular (both lateral ventricles)
   C. Triventricular (third and both lateral ventricles)
   D. Panventricular (fourth, third and both lateral ventricles)

Depending on the exact aetiology, a secondary classification could be added under the following headings:[35]

1. Congenital
2. Traumatic
3. Inflammatory
4. Neoplastic
5. Degenerative

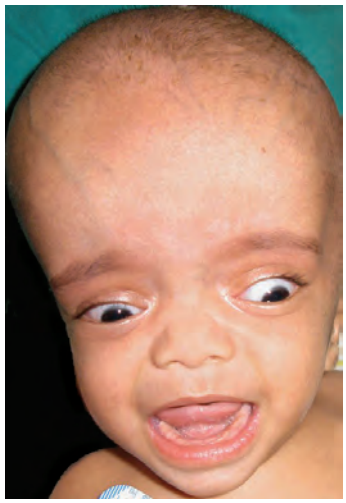

Fig. 1: Setting sun sign

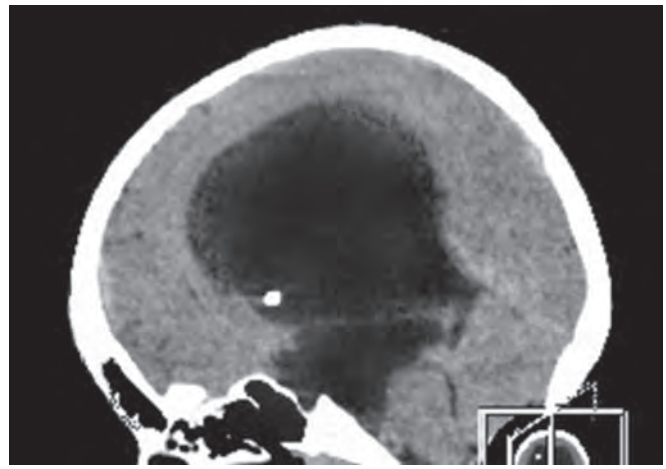

Fig. 2: Sagittal reconstruction CT scan of the brain in a patient with aqueductal stenosis

CLINICAL FEATURES

The presentation of hydrocephalus differs in the case of the neonate and infant compared to the older child or adult. Prior to closure of the cranial sutures and obliteration of the fontanelle, hydrocephalus results in disproportionate head growth. Thus, over the first 2–3 years of life, measurement of the occipito-frontal circumference and plotting this on a centile chart provides a simple and sensitive test. Wherever possible, sequential measurements (corrected for gestational age) should be obtained in order that the trend of head growth in relation to the centile lines can be demonstrated. Clinical symptoms are often subtle and include general irritability, poor feeding and slow attainment of milestones. In addition to head size, clinical signs include bulging of the fontanelle, separation of the cranial sutures, prominent scalp veins and sun-setting appearance of the eyes (Fig. 1). This latter clinical sign is attributed to pressure on the mid-brain tectum by CSF in the supra-pineal recess. Papilloedema can be difficult to diagnose in the infant and indeed is not uncommonly absent in infantile hydrocephalus and so is an unreliable sign in this context.

In older children and adults, the classical symptom complex of raised ICP, headache, vomiting and drowsiness is more likely to herald an underlying diagnosis of hydrocephalus. Where hydrocephalus has developed insidiously, cognitive impairment, poor concentration and behavioural changes occur. Visual obscurations and papilloedema are more common than in the younger age group. In both groups of patients, the presence of bradycardia, hypertension and irregularities in breathing pattern imply critical elevation of ICP and should be treated promptly.

INVESTIGATIONS

In the neonate, the supratentorial ventricular system can be reliably evaluated using ultrasound. This is the imaging modality of choice in the investigation and monitoring of the infant with an open fontanelle. Hematomas or other ventricular masses responsible for hydrocephalus can also be identified. Ultrasound provides a non-invasive and readily available tool for both diagnostic purposes and, by means of sequential studies, a way of charting changes in ventricular size.

Plain X-rays of skull may give an indication. A large skull with different shapes of the vault, sutural separation, cranio lacunae, flat anterior cranial fossa and thinning of vault bones may be seen. Sellar changes and beaten silver appearance may be seen as a sign of raised ICP. A small posterior fossa is often associated with aqueductal stenosis and a large one might suggest Dandy Walker cyst. Multiple calcifications may be an indication of infectious aetiology. Ventriculography was the gold standard during yester years and can demonstrate the size of the ventricles and also the site of the obstruction. It is still valuable in evaluating CSF dynamics. Cerebral angiography is not a usual investigation except in vein of Galen malformations and major venous anomalies. However, hyperplasia, occlusion and elongation of cerebral arteries are usually seen. The venous angle seen in the venous phase is an indicator of the degree of hydrocephalus.[3,48]

Computerised Tomography and Magnetic Resonance Imaging

In order to more fully evaluate the entire ventricular system and investigate the underlying aetiology of hydrocephalus, CT or MRI scanning is required (Figs 2 to 11). Clearly, there is a range of normal ventricular size and, indeed, ventricular size changes with age, rendering absolute measurements of ventricular dimensions of little use. No single radiological parameter can be relied upon to distinguish hydrocephalus from the other causes of ventricular enlargement mentioned above. Some features, however, are strongly suggestive, particularly when occurring in combination. Enlargement of the temporal horns of the lateral ventricles and enlargement of the third ventricle, commensurate with the enlargement

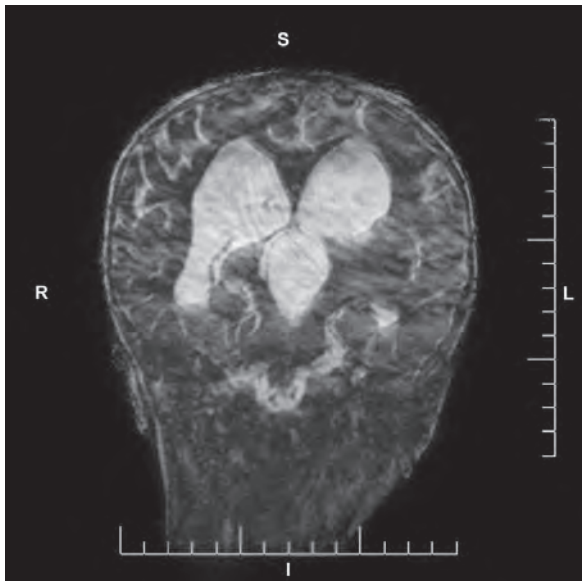

Fig. 3: MRI of the brain, coronal T2W image in a patient with aqueductal stenosis

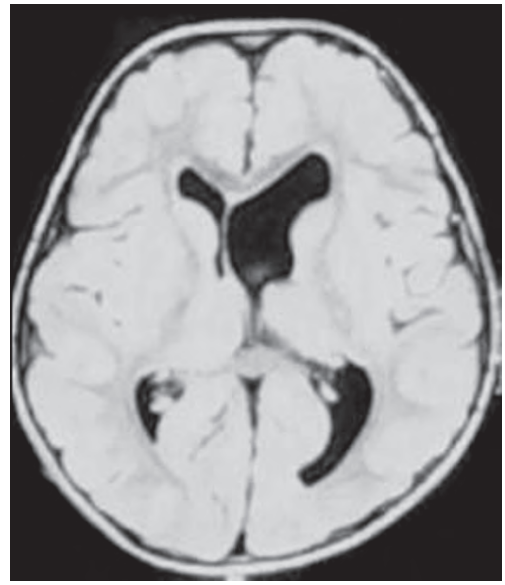

Fig. 4: MRI of the brain, axial T1W image showing asymmetrical ventricles

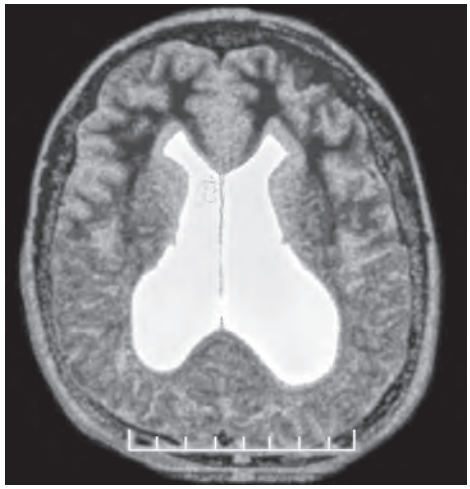

Fig. 5: Colpocephaly

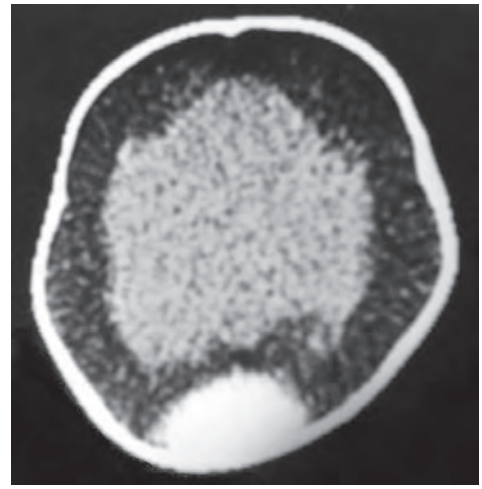

Fig. 6: CT ventriculogram in a patient with hydrocephalus

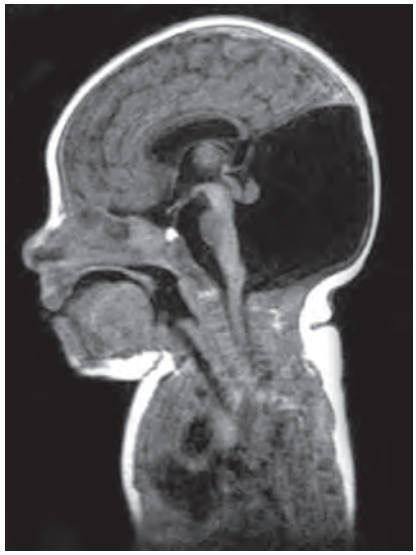

Fig. 7: MRI of the brain T1W sagittal image showing Dandy Walker malformation

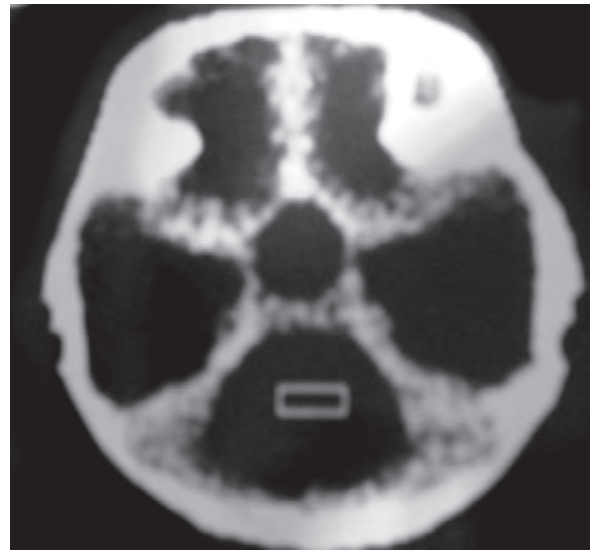

Fig. 8: CT scan of the brain showing Dandy Walker malformation

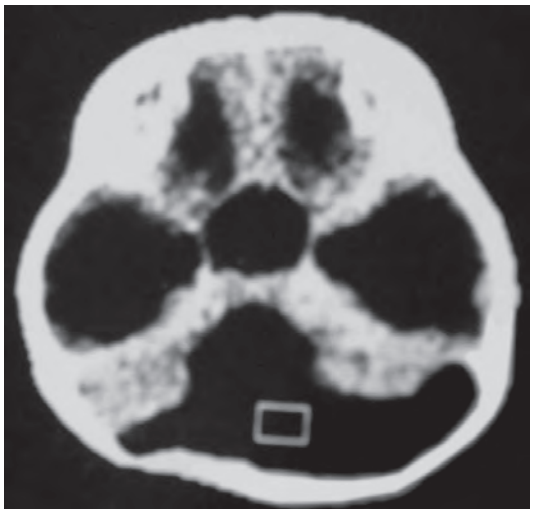

Fig. 9: CT scan of the brain showing Dandy Walker malformation variant

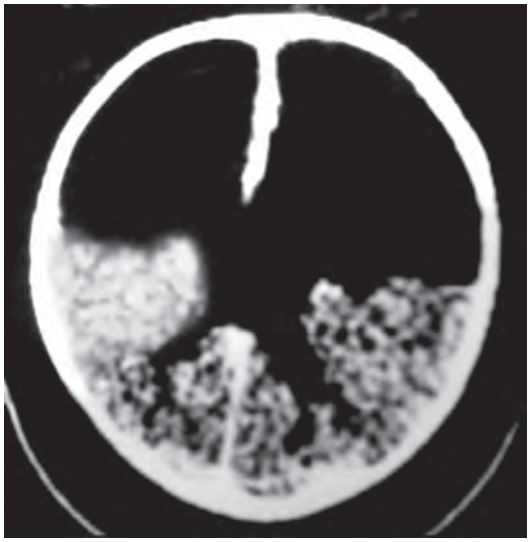

Fig. 10: CT scan of the brain showing grossly dilated frontal horns

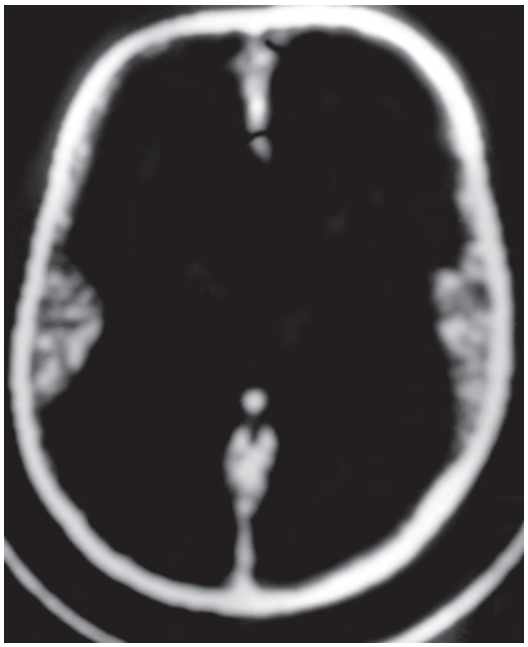

Fig. 11: CT scan of the brain showing gross hydrocephalus

of the rest of the ventricular system, are findings in favour of hydrocephalus. Obliteration of the basal cisterns and effacement of the cortical sulci further support a diagnosis of hydrocephalus. When the ventricles are under pressure, there may be transependymal flux of CSF into the periventricular parenchyma, particularly at the tips of the frontal, occipital and temporal horns. This appears as a low density on CT scan or a rim of high signal intensity on the T2-weighted MRI scans.

Volumetric Measurements

Several methods have been used to calculate ventricular volumes right from the days of pneumoencephalography. Linear measurements, planimetric methods, direct calculation of volume and CT planimetry were used in the past.[6,43,44,53,56] These are not of much clinical use.

Electrophysiology

Electroencephalography (EEG) and evoked potentials, although not of diagnostic value, have been studied usefully in evaluating clinical outcomes in hydrocephalus. The electrical activity has been correlated to the functional integrity of the cortical mantle. The EEG abnormalities could be focal or diffuse and are useful in detecting seizure discharges. The incidence of seizures in hydrocephalus can vary from 18.2-65% (Inees and Markendy). The other abnormalities include focal slowing, focal attenuation, multifocal paroxysmal discharges and generalised discharges.[9,52] Because of the close anatomical relationship of the posterior visual pathway, enlarged ventricles might contribute to visually evoked potential (VEP) abnormalities.[64] Similar abnormalities were reported in brainstem evoked potentials (Figs 12 and 13). These could be due to increased ICP, decreased cerebral blood flow, herniation of the upper brainstem or congenital anomalies, affecting the auditory or visual system and technically due to alteration of the medium, through which the electrical signals are conducted.[65,66] Brainstem auditory evoked potentials, when serially performed, help in identifying the structural abnormalities of the brainstem and can also be an early indicator of shunt malfunction.[13,45,63,65]

Natural History

Laurence suggested that the outlook hydrocephalus was not without hope and survival into adult life was between 20% and 30%. Among the survivors 73% were educable.[7,19]

TREATMENT

Treatment of hydrocephalus is indicated wherever the hydrocephalus is progressive and is associated with increased ICP.[41] A variety of treatments have been tried for hydrocephalus.

Medical Management

Medical measures may be appropriate under certain circumstances. Osmotic diuretics and acetazolamide

Patient no.	Age (years)/sex	Side	Individual wave latencies							Interwave latencies		
			I	II	III	IV	V	VI	VII	I - III	III - V	I - V
1.	18/F	R	1.25	2.40	3.80	4.40	5.6	7.7	8.40	2.55	1.80	4.35
		L	1.45	2.8	3.8	5.25	5.9	7.2	8.0	2.3	2.10	4.4
2.	2/F	R	1.2	2.2	3.3	4.4	5.3	6.2	6.4	2.1	2.0	4.1
		L	1.2	2.0	3.2	4.3	5.2	6.0	7.2	2.0	2.0	4.0
3.	2.5/M	R	1.5	2.9	4.3	6.2	7.5	8.8	9.4	2.8	3.2	6.0
		L	1.5	2.8	4.0	5.0	6.2	7.7	8.4	2.5	2.2	4.7
4.	2.5/M	R	1.3	2.0	3.0	–	–	–	–	1.7	–	–
		L	1.4	2.5	3.3	4.4	5.2	5.8	7.3	1.9	1.9	3.8
5.	3/F	R	1.3	2.0	3.8	5.6	6.6	8.1	9.8	2.5	2.8	5.3
		L	1.3	2.1	3.4	5.1	6.2	7.8	9.1	2.1	2.8	4.9

Fig. 12: Pre-operative brainstem auditory evoked response in congenital hydrocephalus

(inhibitor of carbonic anhydrase) may be useful, Carbonic anhydrase is present in the choroid plexus and is necessary for the formation of CSF. However, the effects are not sustained and, hence, it is useful only in benign intracranial hypertension or as a temporary measure in post-haemorrhagic hydrocephalus. Historically, compression bandage of the head has been advocated in neonatal hydrocephalus.[24,25] However, it has no place in the modern era.

Bypassing the site of obstruction to CSF flow by diverting the CSF, from the ventricular cavity to a site where it is readily absorbed, is the basic principle underlying the treatment of hydrocephalus. Based on this, shunt procedures have become the mainstay of surgical treatment even in severe hydrocephalus. Shunts can alter the process dramatically in infantile hydrocephalus. Neuroendoscopic third ventriculostomy is an important alternative in select situations. Numerous shunt systems have been devised and marketed.[16,17]

The list of procedures are mentioned here for the sake of historical importance (John E. Scarff)[10]

Therapy based on physiological principles
- a. Choroid plexectomy—Dandy 1918
- b. Third ventriculostomy—Dandy 1922.

Intracranial shunts using tubes
- a. Ventriculocisternostomy—Torkildsen 1939
- b. Ventriculo-transcallosal shunt anterior—Lazorthes
- c. Ventriculo-transcallosal posterior—Kleizer and Geuma
- d. III to IV ventricular shunt—Leksel 1949
- e. Ventriculo-ambiens shunts—Kluzer
- f. Ventriculo-chiasmatic—Feld
- g. Ventriculo-subdural—Forrest
- h. Ventriculo-mastoid—Nosik

Extracranial shunts
- a. Ventriculoatrial—Nusen, Spitz 1952
- b. Ventriculoperitoneal—Scot, Wyan 1958
- c. Ventriculopleural—Heile

Shunts into epithelialised ducts
- a. Ventriculocholecystostomy—Snuth et al.
- b. Ventriculosalpingostomy—Harsh
- c. Ventriculoileostomy—Narmann
- d. Ventricle to thoracic duct
- e. Ventricle to Stensen's duct—Parkinson
- f. Ventriculoureteral shunt—Matson

Lumbar SA to lumbar epidural—Hakim et al.
Theco-peritoneal shunt—Jackson, Snodgrass 1955
Miscellaneous
- To vertebral body—Radvon Teimn
- To Retroperitoneal space—Aboylker.

The shunt assembly comprises a proximal catheter located in the cerebral ventricle and a distal catheter draining into the selected site of CSF absorption, connected by a valve and reservoir incorporated into the shunt system. Numerous shunt systems are available in the market, although all of them have their shortcomings and are prone to similar complications. The proximal catheter has a blind ended tube with multiple side holes to facilitate CSF drainage. A number of devices are available like stylet, endoscope and navigation assistance to facilitate the placement of the catheter into the ventricle. The valve designs are based on differential pressures, fixed and programmable or flow control types. Four types of differential pressure valves are commonly

Patient no	Age (years)/sex	Side	Individual wave latencies							Interwave latencies		
			I	II	III	IV	V	VI	VII	I - III	III - V	I - V
1.	18/F	R	1.4	2.2	3.4	4.7	6.1	7.1	8.4	2.0	2.7	4.7
		L	1.2	2.1	3.4	4.8	6.0	7.4	8.7	2.2	2.6	4.8
2.	2/F	R	1.2	1.8	3.0	4.0	4.7	5.8	6.8	1.8	1.7	3.7
		L	1.2	2.2	3.1	3.7	4.7	5.8	7.1	1.8	1.8	3.6
3.	2.5/M	R	1.6	2.6	3.4	4.7	5.6	6.8	8.5	1.8	2.2	4.0
		L	1.7	3.4	4.0	4.8	5.6	7.6	9.0	2.3	1.6	3.9
4.	2.5/M	R	1.3	2.4	3.2	4.2	5.2	6.5	7.8	1.8	2.0	3.95
		L	1.4	2.2	3.1	4.4	5.3	6.9	8.0	1.7	2.3	4.0
5.	3/F	R	1.2	2.5	3.3	5.1	5.9	7.8	8.9	2.1	2.6	4.7
		L	1.4	2.2	3.5	5.3	6.2	7.7	9.3	2.1	2.7	4.8

Fig. 13: Post-operative brainstem auditory evoked response after shunt

available: slit valves; midtre valves; ball and spring and diaphragm walls. The fixed valves have low, medium or high pressure alternatives. The setting defines the opening or, more commonly, the closing pressure of the valve. In order to overcome the limitations of the fixed-resistance valves, programmable valves have been developed whose operating pressure can be varied. An externally applied magnetic field is used to alter the position of an internal rotor and thus vary the pressure setting. The pressure gradient across the valve is the difference between the intraventricular pressure and the intra-abdominal pressure in the supine position. In addition, posture, gravity and the added hydrostatic pressure can alter the differential pressures. Anti-siphon device is a siphon controlled device and can be incorporated with the valves. This device houses a mobile membrane which moves in response to the pressure change. When the intrashunt pressure falls, the membrane will occlude the shunt lumen, thereby preventing over drainage. The peritoneal cavity is the most common site of placement of the distal catheter.[23] The alternate sites are the right atrium, pleural cavity and the gall bladder.

Indian Shunt Systems

The cost of most internationally available shunt systems are relatively high for people in most developing countries. To make matters worse, periodic revisions of shunt systems and associate infections adds to the cost. To overcome this problem, many innovative shunt systems have been designed in India. These include: Upadhyaya shunt system; Chhabra shunt system and Sri Chitra shunt system. Chhabra shunt systems include "Slit N Spring", "Z" Flow, Low Pressure, Medium Pressure and High Pressure. These valves were evaluated and compared with the Western systems and found to be equally effective. Low cost of these shunts is of major advantage.

Endoscopic Treatment

With the improvement in the optics and advent of modern neuroendoscopes, variety of treatments are now possible through endoscopic techniques. Popular among them is the endoscopic third ventriculostomy for aqueductal stenosis. In addition, septostomy, extirpation of choroid plexus, removal of paracytic cysts, removal of migrated shunts and arachnoid cysts can be treated effectively through neuroendoscopy (Figs 14 and 15).

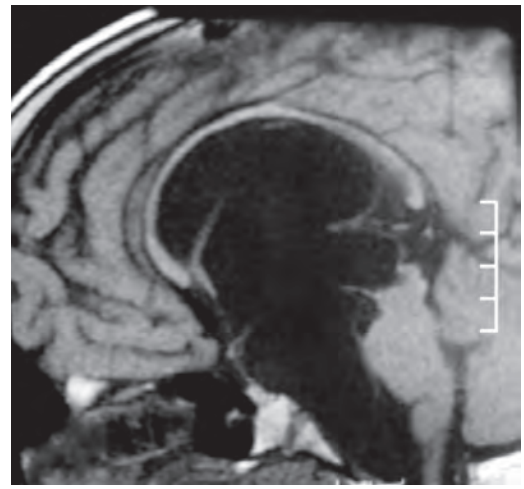

Fig. 15: MRI of the brain sagittal T1W image following endoscopic ventriculo cysto cisternostomy

Complications of Shunts

An extensive range of complications ascribable to shunt surgery have been reported in the literature. They could be classified as mechanical like shunt blockage, disconnection, migration and shortening of length. The flow related complications are CSF over drainage leading to subdural haematoma (Fig. 16), subdural collections, extradural haemorrhage (Fig. 17), low pressure headaches, secondary craniostenosis and cranial deformity and asymmetrical drainage can lead to trapping or isolation of a part of a ventricular system. The slit ventricular syndrome can also occur (Fig. 18). Complications related to absorption are intra-abdominal fluid collections, loculations and hydrocoele and perforation of the stomach,

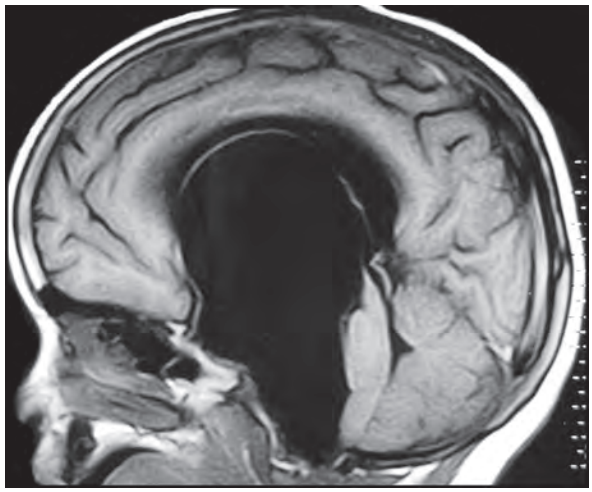

Fig. 14: MRI of the brain sagittal T1W image showing arachnoid cyst with hydrocephalus

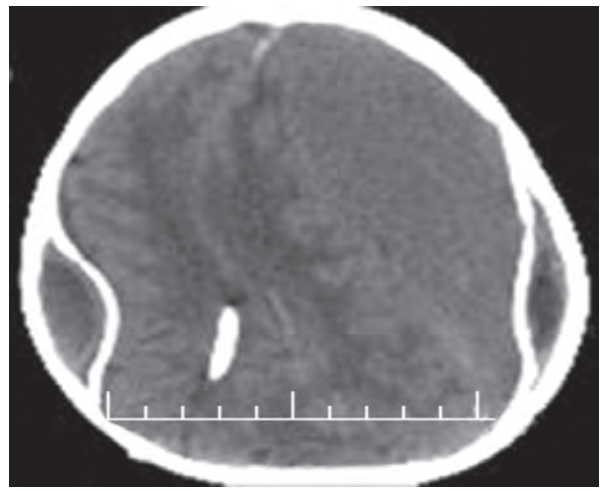

Fig. 16: CT scan of the brain showing bilateral subdural haematoma following ventriculoperitoneal shunt

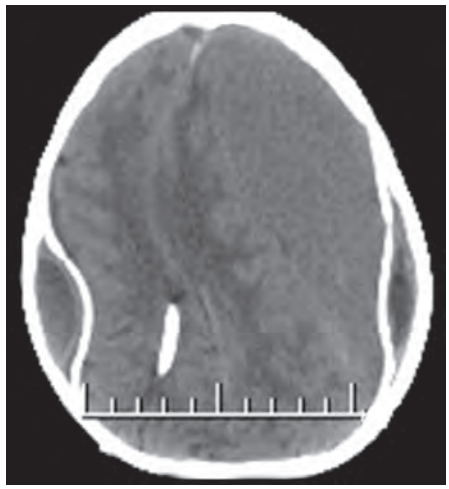

Fig. 17: CT scan of the brain showing bilateral extradural haemorrhage and contralateral subdural haematoma following ventriculoperitoneal shunt

large and small bowel, gall bladder and vagina have been described.[18,28,57]

Shunt infection is one of the most common causes accounting for significant morbidity and mortality. The reported series show the incidence to range from 5-15%. Some centres have reported an incidence as low as 1%. Although many factors appear to contribute to shunt infection, primarily it is assumed to be due to contamination of the shunt system at the time of surgery. Approximately 70% of shunt infections will present within 2 months and the remaining by 6 months of the surgical procedure and rarely beyond 6 months.[5,8] A high index of suspicion is maintained for symptoms like pyrexia, meningismus, irritability and lack of well being. CSF examination is needed to confirm the diagnosis and it may be obtained by the aspiration of the reservoir or from the ventricle. Appropriate antimicrobial therapy and management of the shunt system is necessary for a good outcome. The most common source

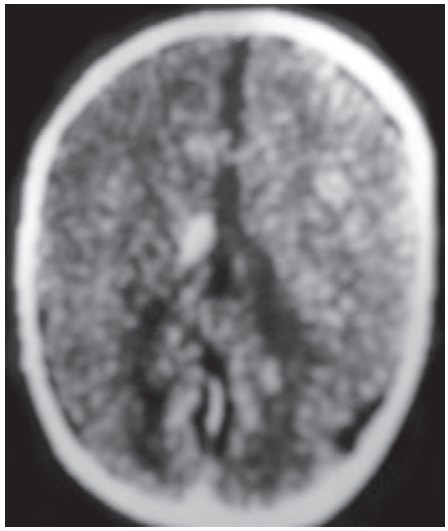

Fig. 18: CT scan showing slit ventricles following ventriculoperitoneal shunt

of infection is coagulase negative *Staphylococci* particularly *S. epidermidis*. *S. aureus* is also well recognised. *Enterococci micrococci* and *coryneforms* account for a significant proportion.[2] Controversy exists as to the need for immediate removal of the shunt system. The most common strategy is to remove the shunt and insert an external ventricular drain for the duration of antibiotic coverage and a fresh shunt inserted once the CSF is sterile. There are several reports indicating that antibiotics given at the time of surgery would reduce the incidence of infection. The role of prophylactic antibiotics, its type, duration and route of administration is still controversial. The more recent technique of antibiotic delivery has been to incorporate antibiotics into the silicon tubing which gradually leaks out and provides protection in the early post-operative period. Antibiotic impregnated shunts are now available; however, the long-term results need to be evaluated.[1,21,26,30,36,46]

Miscellaneous complications: seizures, metastasis, haemorrhage related to catheters and silicone allergy.[4,31,32]

INTELLECTUAL OUTCOME[15,22,37,40,49,51,54,55,58,61,64]

The determinants of intelligence levels and the pattern of intelligence in hydrocephalic children are not fully understood. Many studies have been published concerning the intelligence in both treated and untreated groups, but the criteria for the diagnostic studies, time of intervention and IQ assessment methodologies were different. Hagberg and Sgogrin defined an IQ of 90 as normal. But Lorber and Zachary used IQ greater than 70 as normal.[37] Foltz and Shurtlef described children as "functional", in whom the IQ is more than 75. The age, at which the shunt is placed, the type of hydrocephalus, status of shunt function, associated anomalies and consequent complications, have been incriminated as the responsible factors for a poor IQ. In addition, genetic, social, educational and economic backgrounds also seem to influence the intellectual outcome. However, reviews suggest that there is a decline in mortality and 50–70% incidence of normal IQ with an effective functional shunt. Nulscen and Rekate have correlated IQ with the width of the frontal cortical mantle and concluded that patients with a mantle of less than 2 cm are educable and the IQ was found to be normal in patients with a cortical mantle of more than 3 cm.[51,54,55] The type of hydrocephalus, degree of ventricular dilatation and number of revisions does not seem to affect IQ, as suggested by Dennis and Raimondi. Children with myelomeningocoele have additional problems due to the added physical disability. Untreated children have a mortality of over 80%. Gilllian, Soare and Raimondi reported an IQ of above 80 in 63% of their children with meningomyelocoele and hydrocephalus. IQ seems to have an inverse relationship between the location of the sac and sensory level, as reported by Lorber. The perceptual motor deficit in children with myelomeningocoele could be part of the

Table 1: Measurements of cortical mantle

Group	*Frontal in mm*				*Parietal in mm*			
	Right		Left		Right		Left	
	Pre-op	Post-op	Pre-op	Post-op	Pre-op	Post-op	Pre-op	Post-op
Mean	6.71	19.73	6.51	18.51	15.29	28.99	14.71	28.18
SD	9.27	11.84	8.30	10.21	10.86	12.04	11.13	12.72

disease entity or related to decreased stimulation due to disability or due to a combination.[58,61] Upadhyaya, in his Indian series, did not find any correlation between age at operation or nature of hydrocephalus, but the severity of hydrocephalus seems to correlate with the decline in the IQ. The prognostic factors reported are:

- Clinical—aetiology, degree of motor and sensory deficits, level of meningocoele, severity of hydrocephalus, seizures, ventriculitis and sex of the child
- Radiological—nature of the hydrocephalus, degree of ventricular dilatation and topography of the cerebral vasculature
- Peri-operative—age at the time of surgery, continuing shunt function and complications

Gessel's developmental schedules or Baley scales of infant development are the usual scales used for intellectual assessment in these children. Venkataramana et al.[64] conducted a prospective study on neuropsychological development in 40 children with hydrocephalus. Fifteen of them had associated myelomeningocoele. Only six of them had age appropriate neuropsychological development before surgery. Following shunt surgery, improvement in neuropsychological function was observed in all children. However, the extent of improvement in relation to mental age was significantly higher when CSF diversion was done prior to 6 months of age. Recovery of neuropsychological function seems to have a particular pattern and suggests some form of hemispheric functional lateralisation. It was observed that social and adoptive functions improvement correlated with increase in the right frontal cortical mantle and language development was related to increase in the left frontal and parietal cortical mantle. The motor development was related to both cortical mantles. Reconstitution of cortical mantle results from diminution of white matter oedema and due to reactive astrocytosis. Improvement in the functional status and neurological recovery is reversible only up to a stage. Children with head circumference of more than 50 cm and shunt intervention done beyond the age of 18 months have a higher incidence of subdural haematomas and their intellectual outcomes were uniformly poor , suggesting that beyond a stage the cortical mantle loses its ability to reconstitute, thereby leading to poorer outcomes.[15,22,40,49,64]

Table 1 demonstrates the increase in the cortical mantle thickness following shunt in the frontal as well as parietal cortices on both sides. This clearly demonstrates early shunt treatment reduces the ventricular volume with a corresponding reconstitution of cortical mantle.

Table 2 shows commonly used indices and its correlation with the psychological development assessed in the form of motor, language, adoptive and social functions. Of them post-operative improvement in the cella media index seems to be consistently correlating the motor improvement and to certain extent language and adoptive functions. On the contrary, the improvement in the anterior horn index has a high correlation with the improvement in adoptive functions, whereas the absolute third ventricular diameter seems to be correlating with language and social development.

The mean values of cortical mantle thickness in the frontal and parietal areas on both sides were correlated with the psychological development (Table 3). The results shows that the improvement in social and adoptive functions correlates with the increase in the right frontal cortex, language with the left frontal cortical thickness and the motor development with bilateral increase in the frontal cortices.

SPECIAL TYPES OF HYDROCEPHALUS

Post-Haemorrhagic

During embryonic development, the germinal matrix is the site of intense cellular proliferation. The germinal matrix is a large structure. It begins to involute by the end of 2nd trimester which is completed by 34 weeks. The blood vessels of the germinal matrix have immature connective tissue and lack auto-regulatory capacity. Due to these factors, premature infants born before 34 weeks have a high incidence of intracranial haemorrhage.

Table 2: Correlative values of ventricular indices with psychological development

	Psychological Development			
Index	Motor	Languages	Adaptive	Social
Cella Media Index	0.047	0.216	0.04	0.097
Ant. Horn index	0.139	0.182	0.211	0.512
Absolute III Ventricular diameter	0.096	0.143	0.201	0.4522

Table 3: Correlative values of cortical mantle thickness with psychological development

Cortical Mantle Thickness		*Psychological Development*			
		Motor	Languages	Adaptive	Social
Frontal	Right	0.483	0.277	0.451	0.468
	Left	0.454	0.403	0.019	0.295
Parietal	Right	0.257	0.180	0.261	0.422
	Left	0.355	0.352	0.317	0.337

Haemorrhage is reported in 40–45% of immature infants whose birth weight is less than 500 g and 20% of infants who suffer intraventricular haemorrhage will develop hydrocephalus requiring a shunt. The majority occurs within the first few days of birth and the clinical symptoms can be misleading due to prematurity. Serial ultrasound examinations are helpful, especially when the head circumference is increasing. A ventricular catheter with a subcutaneous reservoir is much safer in avoiding repeated cerebral punctures. Intraventricular fibrinolytic therapy instituted soon after the haemorrhage is detected may prevent chemical arachnoiditis and reduce shunt dependency.[33,34,38,42,69]

Meningomyelocoele

Hydrocephalus complicates open spina bifida in 85–90% of patients. It may manifest after closure of the meningomyelocoele, as the sac acts as a CSF sump. This is usually associated with Chiari malformation; it is preferable to treat hydrocephalus simultaneously to facilitate wound healing after myelomeningocoele repair.[39]

Aqueduct Stenosis

The growth of the tectum and tegmentum makes the lumen of the neural tube narrow in the region of the mesencephalon, leading to narrowing of the aqueduct of Sylvius. Aqueductal stenosis occurs in approximately 10% of children. Several theories exist regarding primary versus secondary forms of aqueductal stenosis. Communicating hydrocephalus with external pressure on the mesencephalon has been proposed as a cause for obliteration of the aqueduct secondarily. Scaring, and gliosis following infection or haemorrhage can cause acquired stenosis. Tumours from the surrounding structures may block the aqueduct. Imaging is confirmatory in such situations.[70]

Dandy Walker Syndrome

This syndrome comprises of agenesis of the cerebellar vermis with cystic dilation of the fourth ventricle, enlargement of the posterior fossa and hydrocephalus. The hydrocephalus manifests in the post-natal period. Additional brain malformations leading to neural developmental delay is reported in 70% of cases. Treatment with placement of a proximal catheter in the lateral ventricle, fourth ventricle and both the ventricles with a wide connecter, have been described. The ideal is to treat the fourth ventricular hydrocephalus and subsequently the supratentorial hydrocephalus, by shunt or endoscopic method.

Post-Meningitic

Hydrocephalus can occur following a range of infectious or inflammatory diseases. Organisation of the inflammatory exudate with scaring or gliosis can produce obstruction to CSF flow, both in the ventricular system and in the basal cisterns, cortical subarachnoid space and may also lead to occlusion of the arachnoidal villi, leading to either obstructive or communicating hydrocephalus (Figs 19 and 20). Bacterial, parasitic and granulomatous infections like tuberculosis and fungal infections can lead to hydrocephalus. It is far more frequently observed in association with the last two conditions. Hydatidosis and toxocara and viral infections are rare causes (Fig. 21). Hydrocephalus in the presence of infection poses several management challenges. Hydrocephalus can be

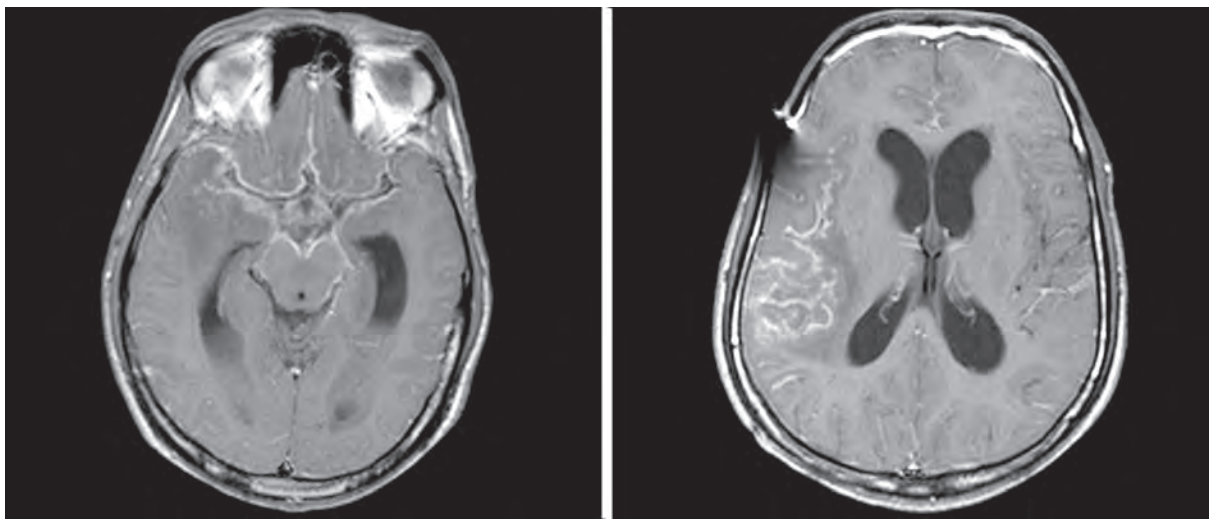

Fig. 19: MRI of the brain showing meningitis with hydrocephalus

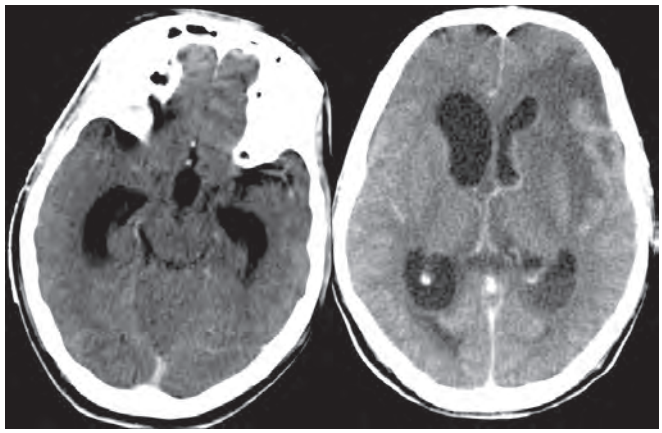

Fig. 20: CT scan of the brain showing meningitis with ventriculitis

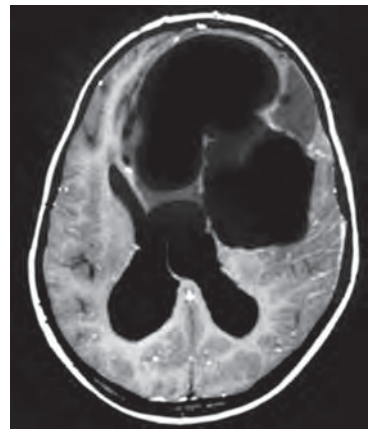

Fig. 21: MRI of the brain showing hydatid cyst with hydrocephalus

acute, causing severe rise in the ICP and rapid deterioration of the clinical condition. The goals of treatment are early diagnosis, effective relief of raised ICP, CSF diversion and treatment of the primary infection. Clinical evaluation, radiological imaging (Tables 4 and 5) and CSF examination including cultures are essential for establishing the diagnosis. In granulomatous infections, at times, it is very difficult to differentiate the type of infection warranting tissue diagnosis or stereotactic biopsy. The outcome depends on effective management of infection, hydrocephalus and the associated complications. External ventricular drainage may be used as a temporary measure till the infection is resolved, before implanting a shunt or doing third ventriculostomy. The incidence of shunt infection or malfunction is very high. Endoscopic third ventriculostomy is gaining popularity with 50–60% success rates in select cases.

Subarachnoid Haemorrhage

Hydrocephalus can occur in 10–15% of patients with subarachnoid haemorrhage. The incidence increases with intraventricular haemorrhage. The mechanism in impaired absorption due to blockage at multiple sites.

Normal Pressure Hydrocephalus

Usually seen in adulthood, it is characterised by gait deterioration, dementia and urinary incontinence. Imaging usually shows enlarged ventricles. In some cases, it may be secondary to infection or haemorrhage in the past. The ICP related symptoms may not be evident. A number of investigations have been advocated in selection of patients for shunt therapy, like isotope cisternography, infusion tests to detect increased CSF resistance in flow, ICP monitoring and therapeutic lumbar drainage. CSF diversion, in carefully selected patients, leads to favourable clinical outcomes.[20]

Hydrocephalus and Venous Hypertension

The role of raised venous pressure as a cause of hydrocephalus has been described long ago as otitic-hydrocephalus. Similar clinical situations have also been described in anchondroplasia and syndromic craniostenosis. The deformed skull base resulting in narrowing of the jugular foramen leading to impaired intracranial venous drainage has been attributed. The raised pressure within the cranial venous sinuses reduces the pressure gradient across the arachnoid villi, leading to impaired absorption. Hydrocephalus also accompanies vein of Galen aneurysms.[47,48]

Arrested Hydrocephalus

Hydrocephalus may evolve into a chronic state in which persistent ventricular enlargement with normal CSF pressures exists. Although it is a controversial entity, it appears to be a compensated hydrocephalus. Treatment strategies should be weighed between the benefit versus complications in individual situations. The exact criteria on which arrested hydrocephalus is based is not clear. However, they need to be monitored for clinical and intellectual development. Disproportionate head

Table 4: Imaging characteristics in infections

	Plain CT	*Contrast CT*	*T1*	*T2*	*FLAIR*	*Enhancement*
Tuberculoma	Isodense	Disc/ring enhancement also nodular lesions	Iso to hyper intense	Hypointense	Hypointense	Thin irregular wall
Cysticercosis	Hypodense	Ring enhancement	Hypodense	Hyperdense	Hypointense	Thin smooth ring enhancement
Abscess	Hypodense	Ring enhancement	Hypodense	Hyperdense	Isodense	Thin smooth ring enhancement

Table 5: Special sequences in infections

	Diffusion	*Perfusion*	*T2 relaxation*	*MT imaging*	*Spectroscopy*
Tuberculoma	Free	Hypoperfused	Decreased	Decreased	Large lipid lactate
Cysticercosis	Free	?	Increased	Decreased	Pyruvate
Abscess	Restricted	Hypoperfused centre Hyperperfused wall	Increased	Decreased only in the wall	Serine and other amino acids

growth, progression of ventricular size and intellectual decline are indications for intervention.

Multiloculated Hydrocephalus

Multiloculated hydrocephalus is still a challenge to treat. It usually occurs after an initial episode of neonatal meningitis or a germinal matrix haemorrhage. CT scan or MRI is usually diagnostic. CT ventriculography has been advocated to delineate the communication between the cysts. This condition needs to be differentiated from cysts associated with hydrocephalus, including dorsal cyst malformations. Among the various treatment options available, placement of multiple shunts, single shunt with multiple fenestrations of all the loculations, craniotomy with lysis of intraventricular septations, stereotactic cyst aspiration or endoscopic cysts fenestration with shunt insertion have been described. The endoscopic option appears the most ideal and can be performed through a single burr hole with the aid of a steerable endoscope. Large fenestrations are usually recommended to prevent recurrent cyst formation. Identifying the loculated cysts is usually a problem, as most often the differentiation between normal parenchyma and the septum is difficult, as well as it is easier to get disoriented during the endoscopy. Intra-operative ultrasound or navigational systems can be of considerable help. After the perforations are made, the multiple cavities are communicated with each other and a single shunt can be placed into one of the major cavities. Repeat procedures are also advised in case the initial one fails to relieve the symptoms. However, the intellectual outcome in these children's has been poor. Only 20% of them can reach normal expected levels of IQ with the best possible treatment. The number, extent of loculations, degree of parenchymal damage, aetiology and effectiveness of treatment seems to influence the ultimate outcome. If the loculations are unilateral, they can be communicated to the opposite ventricle through a septum pellucidotomy.

Hydrocephalus Ex-vacuo

This condition generally indicates enlargement of the ventricles secondary to cerebral parenchymal damage. The ex-vacuo of cerebral atrophy can be associated with ageing, head trauma, severe infection, hypoxia or ischaemic insults. Following radiotherapy and chemotherapy, ventricular enlargement can occur. They are usually associated with white matter loss and concomitant enlargement of the cortical sub-arachnoid spaces and basal cisterns. Peri-ventricular lucency is absent. A number of structural abnormalities of the brain, such as calpocephaly, holoprosencephaly and agenesis of the corpus callosum may also be associated with ventricular enlargement and do not necessarily require any intervention.

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21 Endoscopic Management of Hydrocephalus

Aaron Mohanty

INTRODUCTION

With the rapid technical advancement in the recent past, there has been an upsurge in the number and variety of endoscopic procedures performed in various surgical disciplines. Similarly, with the advent of better quality endoscopes and improvement in diagnostic modalities, neuroendoscopic procedures for obstructive hydrocephalus have gained wide acceptance. Endoscopic approaches for obstructive hydrocephalus and certain intraventricular lesions with gross hydrocephalus are being routinely performed as the dilated ventricles provide easy access for endoscopic navigation. However, with the advent of thinner endoscopes and frameless guidance devices, endoscopic approaches to lesions with mild or moderately dilated ventricles are becoming feasible.

NORMAL ENDOSCOPIC ANATOMY

It is important that the neurosurgeon be well versed with the endoscopic ventricular anatomy as the limited field of vision obtained during a neuroendoscopic procedure can cause considerable difficulty in orientation. Important neural and vascular structures adjacent to the neuroendoscope, but outside the field of vision, are at risk of being injured during the endoscopic procedure. The loss of stereoscopic vision and absence of depth perception are also certainly disadvantageous and warrant a clear knowledge of the ventricular anatomy.

APPROACH

The majority of the neuroendoscopic procedures are performed in the lateral and the third ventricles. The standard approach is a precoronal burr hole at Kocher's point (3 cm from the midline, just anterior to the coronal suture on the right side). This point is ideal for reaching the foramen of Monro and the third ventricle. However, in certain circumstances where a more posterior visualisation is required, a parietal burr hole may be placed. For approaching a lesion in the temporal horn, a burr hole in the temporal region may be considered. Alternatively, the temporal horn can be approached through the dilated atrium of the ipsilateral ventricle.

After the burr hole is made, the dura is coagulated and incised. The trocar with the cannula is subsequently introduced into the ventricle. In patients with small ventricles, stereotactic guidance may be used for cannulating the ventricles. The trocar is removed and the endoscope is introduced into the ventricles through the cannula. Orientation to the ventricular structures is achieved initially by adjusting the camera to make necessary alterations so that the operative view matches the position of the patient.

Lateral Ventricles

Often the initial and most important landmark is the foramen of Monro. In cases with developmental anomalies, the location of the foramen of Monro can be identified by locating the choroid plexus and the formation of the internal cerebral veins. The choroid plexus is located at the floor of the lateral ventricles traversing from the lateral to the medial side and enters the foramen of Monro (Fig. 1). Also seen are the thalamostriate and the septal veins which traverse from the lateral and medial sides, respectively and join at the foramen of Monro to form the internal cerebral vein. The medial and anterior border of the foramen of Monro is formed by the fornices. In cases, where the septum is absent, the fornices can be seen as two distinct bundles. The central part of the lateral ventricle up to the ventricular trigone can often be visualised by angling the endoscope posteriorly. Visualisation of the temporal horn requires a flexible scope.

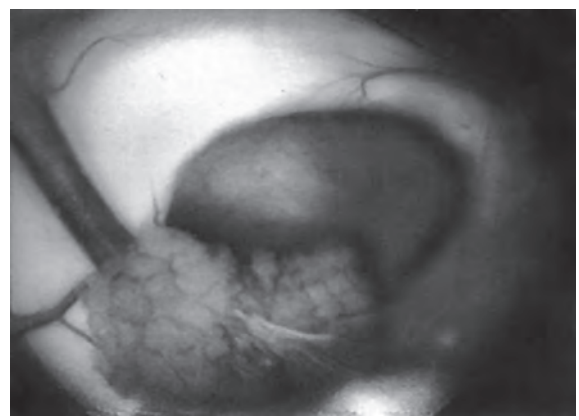

Fig. 1: Endoscopic view of the foramen of Monro: Note the dilated foramen of Monro. The choroid plexus is entering into the foramen at 7 o'clock position. The septal vein is seen just above that. The third ventricular cavity can be seen through the dilated foramen

Third Ventricle

Through the foramen of Monro, the floor of the third ventricle can be visualised (Fig. 2). Subsequently, the endoscope may be navigated through the foramen of Monro. It is pertinent to note that in cases where the foramen is not dilated a smaller diameter endoscope should be used. In the floor of the third ventricle, the paired mammillary bodies can be visualised. The thin membrane anterior to it is called the tuber cinereum, which is often thinned out and translucent in chronic hydrocephalus. The basilar artery pulsations can often be seen through the thinned out membrane. Anterior to it is the infundibular recess (Fig. 2) and the optic chiasma.

The aqueductal inlet is located posterior to the mammillary bodies and often requires a 30° angled scope. The posterior commissures and the pineal recess can be identified just superior to it. Visualisation of the aqueduct for procedures, like aqueductoplasty, often requires a fibreoptic endoscope. Often interthalamic adhesions of various degrees are visualised and large adhesions may hinder the navigation of the instrument.

Aqueduct and Fourth Ventricle

The fibreoptic endoscope can be navigated into the aqueduct in cases where an adequate aqueductal opening permits cannulation. In obstructive hydrocephalus, the aqueduct may be obstructed by a thin septum or a gliosis or may be thinned out. The fourth ventricle and the choroid plexus are identified and the structures in the fourth ventricle can be visualised. The fibreoptic scope can be navigated through the outlet foramina, and the basal cisterns, foramen magnum region and upper cervical region can be inspected.

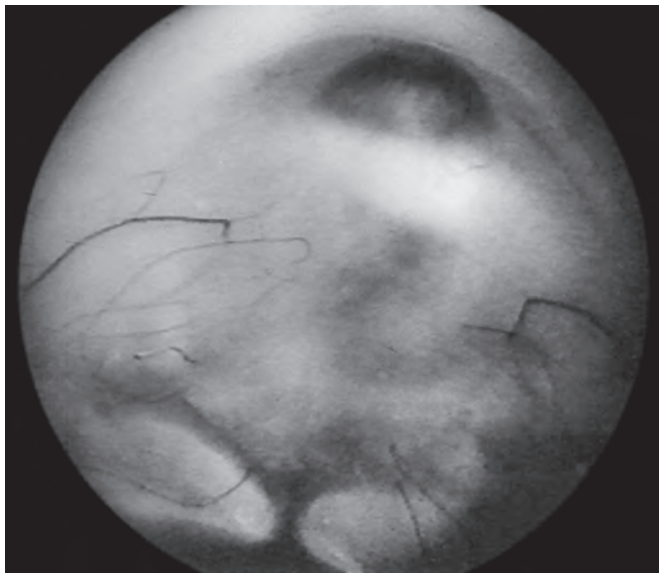

Fig. 2: Third ventricular floor: the mammillary bodies can be identified at 6 o'clock position. The thinned out floor (Tuber cinereum) is visualised anterior to it. The white band seen in the anterior part of the floor is the dorsum sella which is prominent due to the thinned out floor. The dark area at 12 o'clock position is the infundibular recess (the red spot—as it appears pinkish red during the normal endoscopic procedure due to presence of large number of blood vessels)

INSTRUMENTATION

Three prototypes of neuroendoscopes are currently in use: the rigid Hopkins Lens scope; flexible fibreoptic scope and the rigid fiberscope.

Rigid Endoscope

Conventional rigid endoscopes have solid rod lenses and fibreoptic illumination. The recent endoscopes have an outer diameter ranging from 2.6 mm to 6 mm. The larger diameter endoscopes allow for larger working channels and hence a variety of accessory instruments can be used. Rigid endoscopes can have a viewing angle from 0° to 120°. The 0° telescope is the most useful in routine practice; however, the rest are required to inspect the inaccessible areas or to "look around the corner". Rigid endoscopes have the advantage of better vision, better surgical orientation and are easy to use. There are more operating channels available for a rigid endoscope than a fibreoptic endoscope. They are also sturdier and have a longer life than fibreoptic scopes.

Fibreoptic Endoscopes

Significant technical advancements have resulted in the availability of thinner fibreoptic scopes with diameters as small as 0.7 mm. However, the quality of viewing of these thinner endoscopes is poor. Fibreoptic endoscopes are advantageous in their flexibility and ability to explore the areas where a conventional rigid endoscope cannot be navigated. Thin instruments can be passed through the endoscope for obtaining a biopsy. A poor picture quality, difficult orientation and a high maintenance cost are the disadvantages of a fibreoptic endoscope.

Rigid Fibrescope

In this third prototype, fibreoptic bundles are compactly arranged in a rigid frame structure. This architecture adds the advantage of easier orientation and smooth passage of reasonably sized instruments while maintaining the thinner diameter of the flexible scope.

Though several arguments continue regarding the advantages of the rigid and flexible systems, they are considered to be complimentary to each other and for an ideal situation the availability of both during a neuroendoscopic procedure is desirable. The flexible endoscopes can be used through the working channel of the rigid endoscope thus, limiting the problems in orientation (mother-daughter approach).

STABILISATION AND GUIDING DEVICES

The endoscopes with camera attachments are heavy and hence devices are essential to provide the necessary stabilisation during the operative procedure which

frees the endoscopist from holding the instrument. The Gaab's rigid endoscope can be attached to the conventional Leyla retractor by fixators or special holding devices may be used.

Stereotactic Guidance

Stereotactic guidance has been considered to be helpful in patients with small ventricles with difficult cannulation with a plan to reach deep seated targets which may be difficult to identify under normal circumstances. The endoscope can be attached to the stereotactic guiding device. Neuronavigation has especially been useful in planning the trajectory, maintaining the trajectory during the procedure and avoiding injury to adjacent structures. Image guidance is helpful in patients with anomalies of the ventricular system and in patients with multiloculated hydrocephalus. Other adjuncts which often have been used include ultrasound[47] and robotic assisted endoscopic third ventriculostomy (ETV).[51,53]

Additional/Supplementary Instrument

A variety of micro-instruments which are currently available for use along with the neuroendoscope are: grasping forceps for the biopsy; balloon catheters for ventriculostomy; aspiration needles; micro-scissors; bipolar or monopolar RF (saline torch); Nd YAG laser and KTP laser. Intraluminal ultrasound has also been used.

An ultra-light microchip camera transmits the images to a video unit for the purposes of display and recording. A sterile operative field is thus maintained as the surgeon performs the procedure while observing the monitor. However, eye-hand coordination is often difficult and the loss of image quality during the transmission has to be accepted.

The complexity of the operative procedure demands a highly specialised neuroendoscopic team which includes a neurosurgeon, neuroendoscopic anaesthetist, instrument nurse and an assistant.

ENDOSCOPIC PROCEDURES FOR OBSTRUCTIVE HYDROCEPHALUS

The various procedures currently performed for obstructive hydrocephalus are summarised in Table 1.

Third Ventriculostomy

Endoscopic third ventriculostomy has been considered as an acceptable alternative in the treatment of obstructive hydrocephalus in adults and children. Though it was performed as early as 1923 by Mixter, the procedure did not gain widespread acceptance due to inadequate instrumentation. However, availability of better endoscopes with illumination and a growing dissatisfaction with the existing shunt systems lead to renewed interest in endoscopic ventriculostomy.

Table 1: Endoscopic procedures for obstructive hydrocephalus

Pathological condition	*Endoscopic procedures performed*
Aqueductal stenosis	• Third ventriculostomy • Aqueductoplasty (Aqueductal reconstruction) • Aqueductal stenting
Posterior fossa tumour with hydrocephalus	• Third ventriculostomy
Fourth ventricular outlet obstruction	• Third ventriculostomy
Unilateral hydrocephalus	• Septostomy • Foraminoplasty
Multiloculated hydrocephalus	• Membrane fenestrations with endoscopic ventriculoperitoneal shunt insertion
Trapped fourth ventricle	• Endoscopic third ventriculostomy with aqueductal stenting
Miscellaneous	• Endoscopic shunt placement • Removal of adherent ventricular catheter • Removal of migrated ventricular catheter • Choroid plexus coagulation

Patient Selection

As will be discussed later, patients with acquired aqueductal stenosis are considered to be the ideal candidates for third ventriculostomy.[5,12] Aqueductal obstruction due to posterior fossa tumours are also benefited by a third ventriculostomy.[38] The role of third ventriculostomy in hydrocephalic children with myelomeningocoele has been controversial, though a few studies have found it useful.[14,48] Patients with communicating hydrocephalus theoretically would not benefit from the procedure although evidence in this regard has been lacking.

The technical feasibility for performing a third ventriculostomy requires an adequate sized third ventricle so that the endoscope can be navigated with ease without damaging the adjacent hypothalamus and thalamus. The floor of the third ventricle should be examined regarding its thickness by pre-operative magnetic resonance imaging (MRI) as a thin third ventricular floor is easier to perforate than a thicker one. An ectatic basilar artery, if identified pre-operatively, may contraindicate a third ventriculostomy due to risk of injury to the vessel (Fig. 3).

Operative Procedure

A precoronal burr hole is placed just anterior to the coronal suture 2–3 cm away from the midline. The placement of the burr hole is important, as a direct view to the foramen of Monro can be obtained from a properly placed burr hole thus, enabling the usage of only a rigid endoscope. The trocar and cannula are reintroduced into

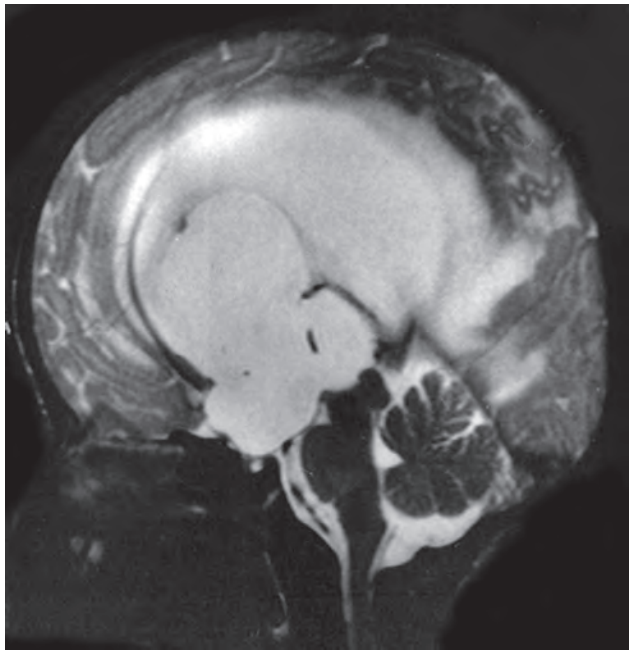

Fig. 3: Sagittal T2-weighted MRI scan of a child with obstructive hydrocephalus showing a long segment aqueductal stenosis. Note the bifurcation of the basilar artery which is placed anteriorly considerably diminishing the space for an endoscopic third ventriculostomy to be performed

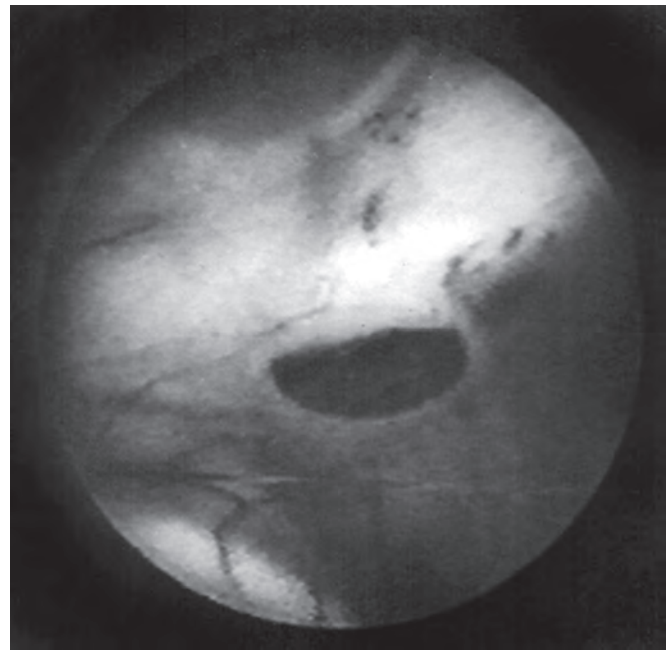

Fig. 4: Initial fenestration performed between the basilar artery and the dorsum sella

the ventricular system after a preliminary ventricular tap is done to assess the exact depth before the insertion. The trocar is then removed and the 0° endoscope is introduced into the lateral ventricle. The foramen of Monro is identified using the standard landmarks as described earlier and the endoscope is navigated into the third ventricle. The mammillary bodies are identified and the thinned out floor of the third ventricle just anterior to it is visualised (Fig. 2). The basilar artery pulsations are often seen through the thinned out floor and the perforators sometimes can be identified. Using a fibreoptic scope or a 30° angled scope the inlet of the stenosed aqueduct can be visualised. A site is chosen in the midline between the basilar artery and the clivus (Fig. 4). Sometimes, the space is very narrow (due to an ectatic basilar artery) and a perforation may be made as close to the clivus as possible. The perforation is made either with the scope itself, with a specially devised forceps,[6] by monopolar or bipolar coagulation or assisted by laser.[50] This is the most critical step of the surgery and a properly performed fenestration is essential in avoiding injury to the basilar artery, which is the most dangerous complication of the procedure. Though all the above techniques have been used, the author prefers fenestration with a 4F Fogarty's catheter with the stylet in place. Presence of the stylet inside the catheter renders adequate firmness to the tip to fenestrate the floor in a single attempt, thus, preventing multiple attempts which can injure the hypothalamic nuclei. Though the ideal fenestration is considered to be in the midline, it is not uncommon to see that the fenestration wavers slightly to the side opposite the burr hole (i.e. to the left side in the right burr hole approach) due to the trajectory. Visualisation and identifying the basilar bifurcation and its branches is highly essential and is the key to prevent an intra-operative catastrophe of injuring the vessels. In patients with thickened or deformed floor (e.g. patients with previous ependymitis, myelomeningocoele), it is difficult to identify the vessels and the proper site for fenestration. Several adjuncts have been used: stereotactic guidance, ultrasound guidance[33] and pulse waved microvascular Doppler probe.[39] After the initial fenestration is made, it is dilated to an adequate size. Several techniques have been proposed by various authors. The most common technique is dilatation with a 4F Fogarty's catheter (Fig. 5). The author usually dilates the balloon to its maximum to achieve the maximum size fenestration. Alternatively, passage of the endoscope itself has been used to achieve the required dilation. Electrocoagulation and cutting probes have also been used for enlargement which, however, potentially can damage the adjacent hypothalamic nuclei by thermal injury.

There is often another thin membrane below the floor which is described as the "second membrane" or the "Liliequist's membrane". Perforation of the membrane is essential for a functioning third ventriculostomy. The scope is then gently advanced to visualise the basilar artery. Continuous irrigation of the ventricular cavity is carried out with Ringer's lactate solution at body temperature to clear the minor bleeding, which might occur during the procedure.

Complications

A transient arrhythmia often occurs during the perforation, which usually settles by itself. In case the

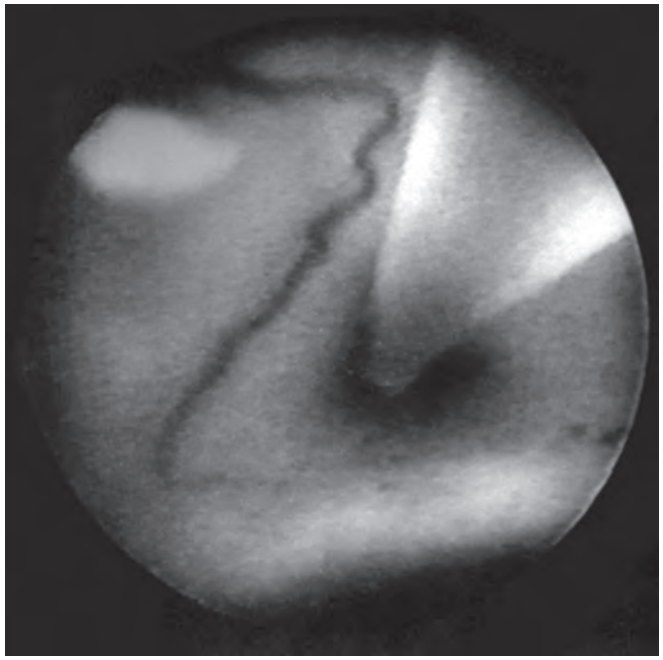

Fig. 5: Aqueductoplasty being performed with the help of a 4F Fogarty's catheter

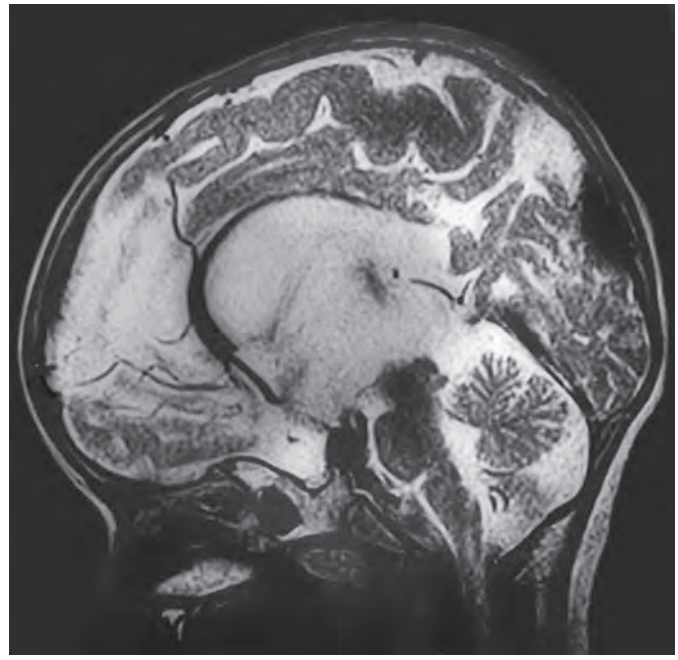

Fig. 6: T2 sagittal MRI scan of a patient with aqueductal stenosis demonstrating a good flow void (represented by the dark area in front of the basilar artery) in the region of the third ventricular floor

perforation is performed away from the midline hypothalamic damage may result leading to water and electrolyte imbalance which, however, usually is transient. Transient pareses of the III and VI cranial nerves have also been observed.[50] Bleeding from the edges of the perforation is usually self-limiting. However, damage to the basilar artery may occur and may be fatal during the procedure or lead to formation of a pseudoaneurysm.[22] Hence, every attempt should be made to identify the basilar artery through the thinned out floor and avoiding the site of perforation too close to it. Subdural effusions and subdural haematoma can occur due to sudden release of cerebrospinal fluid (CSF).[25]

In a series of 193 endoscopic third ventriculostomies, a mortality of 1%, permanent morbidity of 1.6% and a transient morbidity of 7.8% was reported.[41] The authors, while noting a steep learning curve, ascertained that ETV performed correctly is a safe, simple and effective treatment option for various forms of non-communicating hydrocephalus.

Assessment of Effectiveness

After a functioning third ventriculostomy, the ventricle size often remains large for a prolonged period, though a significant decrease in size is sometimes noted. In a previous study, an average of 35% decrease in third ventricular size and 33% reduction in lateral ventricular volume was noted in patients following a successful third ventriculostomy.[44] Improvement in the pre-operative downwards bulging of the third ventricular floor has also been noticed in the post-operative MRI scans. Additionally, the periventricular lucencies resolve, symptoms resolve and the head size enlargement arrests. The CSF cisterns become prominent suggesting a patent third ventriculostomy.

Radiological studies can demonstrate patency of the fenestration. Though contrast ventriculograms were initially performed with the advent of MRI, flow void through the floor can often be visualised (Fig. 6). T2-weighted fast spin echo images or 2D phase contrast images have been used to assess the flow through the third ventricular floor and have been found to be equally effective in assessing the patency.[9] However, routine assessment of the patency of the third ventriculostomy site is probably not warranted and should be reserved only for cases of clinical failure.[2]

Success Rates

Unfortunately, till now, there has been no reliable predictor for a successful outcome in third ventriculostomy for obstructive hydrocephalus. In a series of 100 consecutive patients, an overall success rate of 76% was reported.[15] The success rates of the procedure depend on the primary aetiology for the hydrocephalus, age of the patient and other associated conditions.

Age and Outcome

Age has been found to be the single most predictive factor in assessing the prognosis of ETV. In large series, success rates of 70–81% in patients older than 2 years and between 45% and 50% in children below 2 years of age is reported.[15,16,48] In a recent multicentre study of 368 patients, age was the most significant determining factor in both the univariate and the multivariate

analysis. A progressive increase in the success rate with increasing age was demonstrated.[8] The 5-year-success rate in patients younger than 1 month was 28% while it was 68% in children older than 10 years. Others have reported similar results.[3,17] Though the reason for the lower success rates in young infants is unclear, inadequate absorption of the CSF by the neonatal and infantile brain has been considered to be the possible cause.

Aetiology and Outcome

The aetiology of hydrocephalus has also been found to be a significant factor in determining the success rates. Reduction in the absorption mechanism of the CSF at the arachnoid granulations as in post-infectious and post-haemorrhagic hydrocephalus has been associated with a lower success rate in this population. Additionally, inflammation at the third ventricular floor can obscure the landmarks and be associated with technical failures. The success rate has varied from 23% to 65% with the lower rates associated with coexistence of haemorrhage and infection.[27,46] The degree of scarring in the basal cisterns has been found to be directly related to the overall outcome in several recent studies.[4,27] ETV has also been found to be successful in the management of hydrocephalus associated with the chronic stages of tubercular meningitis.[4]

Myelomeningocoele with Hydrocephalus

ETV is often considered difficult in patients with spina bifida due to associated anomalies in the third ventricular floor and in the region of the upper brainstem. The success rate of ETV in patients with myelomeningocoele depends on the age of onset of hydrocephalus and any previous shunt insertions. The success rate has varied from 27% in patients who had ETV as their initial procedure to 77% in patients where a previous shunt has been inserted, and the ETV was performed as a subsequent procedure.[14] An overall success rate of 72% was reported in a series of 69 patients who had ETV performed for hydrocephalus associated with myelomeningocoele, though the success rate improved to 80% in patients who were either over 6 months of age or had a previous shunt inserted.[49] Poor absorptive capacity in the initial neonatal period was considered to be the deciding factor for the lower success rate in the early infantile period.

Chiari Malformation and Hydrocephalus

Several reports have demonstrated the efficacy of ETV in managing the hydrocephalus associated with Chiari malformation. In patients with Chiari malformation, the obstruction to the CSF flow occurs in the region of the foramen magnum and the outlet of the fourth ventricle and the success of the ETV relates to diverting the fluid away from the obstruction site into the basal cisterns. Shrinkage of the associated syrinx has also been well demonstrated.[7,29]

Fourth Ventricular Outlet Obstruction

Obstruction to the fourth ventricular outlet results in obstructive hydrocephalus. Commonly due to an inflammatory process, this can be due to either infectious or post-haemorrhagic aetiology. ETV has been found useful in 65% of patients who had outlet obstruction resulting in obstructive hydrocephalus.[27]

Obstructive Hydrocephalus Due to Tumours

Endoscopic procedures have been found to be useful in three areas in patients with intraventricular or paraventricular tumours with hydrocephalus. Associated obstructive hydrocephalus caused by tumours located at or distal to the posterior third ventricle can be treated with ETV. Third ventriculostomy has been found to be effective in posterior third ventricular and tectal plate tumours as an alternative to ventriculoperitoneal (VP) shunt placement.[35] It has also been used as a CSF diversion procedure in fourth ventricular tumours. Secondly, it can be used to biopsy the lesions during the same sitting while performing the third ventriculostomy. This allows obtaining a histological diagnosis prior to attempting definitive tumour removal. In patients with highly radiosensitive tumours (germinoma), a subsequent second procedure can thus be avoided. Thirdly, in selected intraventricular tumours complete tumour excision can be performed endoscopically.[34]

The efficacy of ETV in tumour-related hydrocephalus has been demonstrated in several series. Sainte-Rose et al.[38] in a study of 206 patients found that ETV performed prior to the posterior fossa surgery significantly reduced the incidence of post-operative hydrocephalus and requirement for a VP shunt.[38] In another study, an initial success rate of 95% of ETV in pre-operative hydrocephalus in posterior fossa tumours was noticed though 16% of patients developed a post-operative hydrocephalus requiring a VP shunt.[36] In pineal region tumours, a success rate as high as 91% has been demonstrated.[35] Tectal plate tumours have similarly been managed with ETV and biopsy.[31]

Dandy-Walker Malformation

Endoscopic third ventriculostomy has been extended to the treatment of obstructive hydrocephalus associated with Dandy-Walker malformation. In patients with Dandy-Walker malformation with an open aqueduct, a third ventriculostomy should suffice in diverting the CSF from the site of obstruction. As in other patients with obstructive hydrocephalus, the success rate depends on the age of the patient. An overall success rate of 76% has recently been reported.[26] In the uncommon association of Dandy-Walker malformation with aqueductal obstruction, third ventriculostomy has often to be combined with an aqueductal stent placement.[23]

Considering the above, it is apparent that adult patients with obstructive triventricular hydrocephalus, due to aqueductal stenosis, tectal plate tumours and posterior

Table 2: Classification of aqueductal stenosis

• Long segment aqueductal stenosis (stenosis > 5 mm)
• Short segment aqueductal stenosis (stenosis < 5 mm)
• Aqueductal web

fossa tumours, are excellent candidates for the procedure. Though the success rate of ETV in premature infants drops down to 32%,[3] the comparatively lower success rate in children should not deter the surgeon from performing a third ventriculostomy as a 50% chance of shunt independency often can be achieved. Even in patients with implanted ventricular shunts, third ventriculostomy may be effective and should be considered upon shunt failure.[52]

Aqueductal Reconstruction

Aqueductoplasty and aqueductal stenting have emerged as exciting options for a selected group of patients with obstructive hydrocephalus. The increased usage of MRI in cases of obstructive hydrocephalus has identified a subgroup of patients who could benefit from an aqueductal reconstruction procedure. Aqueductal stenosis, from a neurosurgeon's perspective, is classified as long segment stenosis, short segment stenosis and aqueductal web (Table 2). A long segment aqueductal stenosis with the length of the stenosis exceeding 5 mm (Fig. 7) is not suitable for an aqueductal reconstruction procedure as attempting a reconstruction would lead to periaqueductal region damage. On the other hand, fenestrating the thin web that often blocks the aqueduct (aqueductal web, Fig. 8) or dilating or stenting a segment of stenosis less than 5 mm in length (short segment stenosis,

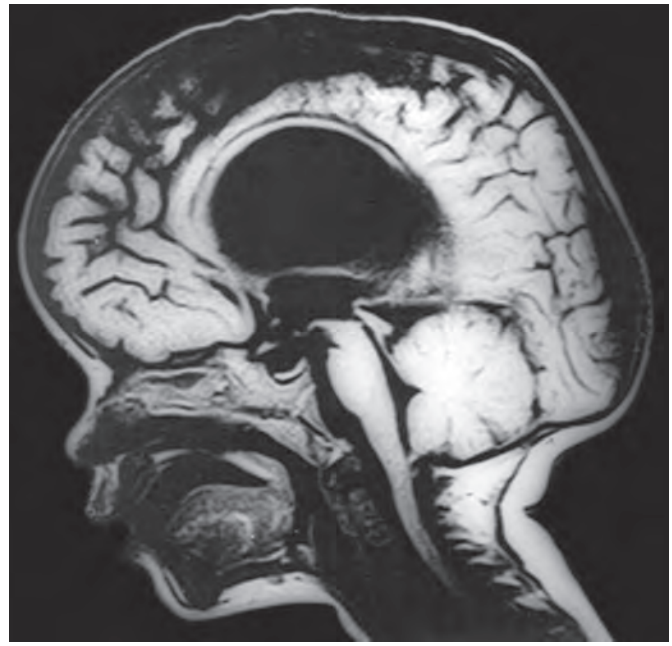

Fig. 8: Aqueductal web: Note the aqueductal web in the proximal aqueduct causing an obstructive hydrocephalus

Fig. 9) is often not difficult. Such cases are ideal candidates for aqueductoplasty or aqueductal stenting. Aqueductal stenting in conjunction with ETV or VP shunt has also been considered for the management of an isolated fourth ventricle.[24,37,43,45]

Technique

A pre-operative MRI study is essential before considering an aqueductal reconstruction procedure. The length of stenosis, angulation of the aqueduct and the size

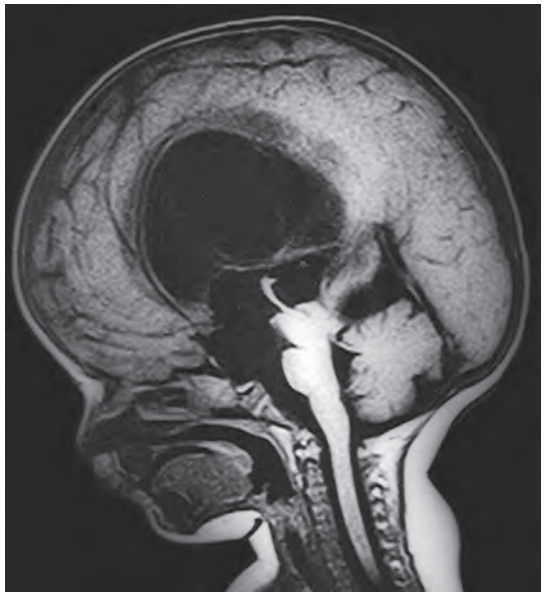

Fig. 7: Long segment aqueductal stenosis: T1 sagittal image MRI of a child with obstructive hydrocephalus demonstrating a long segment aqueductal stenosis. Aqueductal reconstruction procedures are contraindicated in such a situation as it can lead to injury to the mesencephalon and the periaqueductal grey

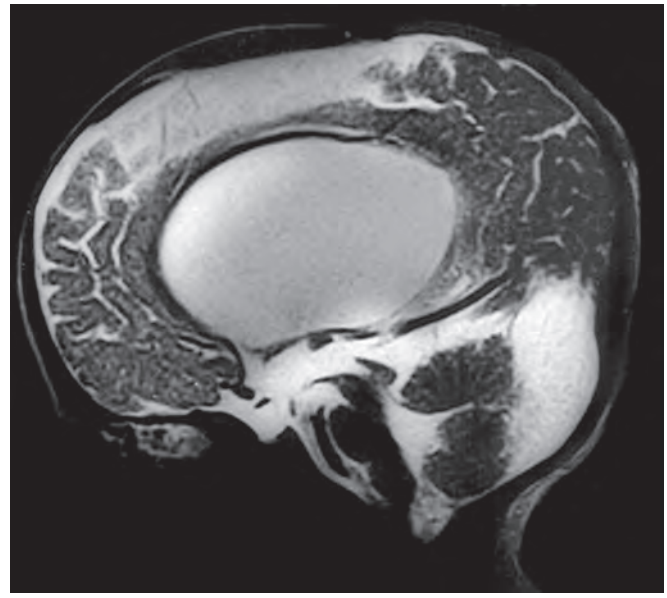

Fig. 9: Short segment aqueductal stenosis: There is short segment aqueductal stenosis causing obstructive hydrocephalus. Aqueductal web (Fig. 8) and short segment aqueductal stenosis is amenable for aqueductal reconstruction

of the fourth ventricle are all important observations, which guide the neurosurgeon and reduce the risk of operative damage to the aqueduct. As mentioned earlier, observation of a long segment aqueductal stenosis is a contraindication for an aqueductal reconstruction procedure. The pre-operative sagittal MRI also guides the neurosurgeon regarding the optimal trajectory of placement of the burr hole, which should be more anterior than the conventional burr hole used for ETV.

After placement of the burr hole, the rigid endoscope is introduced into the lateral ventricle and subsequently is navigated into the third ventricle. After entry into the third ventricle, the endoscope is gently angled posteriorly, care being taken not to injure the rim of the foramen of Monro. The stenosed aqueduct can be identified behind the mammillary bodies (Fig. 10). Subsequently, a soft tipped 3F Fogarty's catheter is used to fenestrate the obstructing element and gently dilate the stenosed aqueduct. The author uses one of the following two as the stent: (a) modified 4 cm ventricular sleeved catheter (aqueductal stent) (Fig. 11) or (b) a long ventricular catheter with an attached reservoir at the burr hole site. In the first option, the free standing stent is prevented from migrating downwards by the sleeve which rests in the aqueductal inlet. To avoid a distal migration, an enthusiastic dilatation of the stenosed aqueduct is not performed. In the second option, the stent is fixed into position by its attachment with the reservoir at the burr hole site. These stents traverse from the frontal region to the fourth ventricle through the foramen of Monro, third ventricle and aqueductal inlet and have a reduced incidence of migration. However, these stents often can fall short with growth and development of the child.

Complications

Aqueductal reconstruction procedures are relatively safe if adequate care is taken not to injure the adjacent periaqueductal region. It is important that the procedure is performed under direct vision and the surgeon should be prepared to abandon the procedure for favour of third ventriculostomy or a VP shunt, if required. Injury to the cranial nerve nuclei in the region of the upper brainstem can cause dysconjugate eye movements and upwards gaze paresis.[10,42] Transient loss of consciousness has also been reported due to injury to the periaqueductal grey.

Success Rates

The success rate of a technically successful aqueductoplasty and aqueductal reconstruction procedure is almost equivalent to the ETV procedures.[10,11,40] In a well documented series, aqueductoplasty was reported to be successful in 82% of cases with short segment aqueductal stenosis and aqueductal web.[42] However, a 25% reclosure rate was noted during extended follow-up requiring resurgery. Placement of an aqueductal stent, though obviates the reclosure seen with aqueductoplasty, has been associated with stent migration.

Choroid Plexus Coagulation

Initially attempted by L'Espinase and Dandy, endoscopic choroid plexus coagulation was subsequently practiced by Griffith.[13,32] An occipital approach appears suitable for ablation of the majority of the choroid plexus of the lateral ventricles. Using bipolar or monopolar coagulation or Nd YaG laser, the plexus can be coagulated. It is often advised to maintain a CSF drain for the first few days. A 52% success rate with no mortality in children with communicating hydrocephalus has been reported.[13]

Multiloculated Hydrocephalus

Multiloculated hydrocephalus usually occurs after an initial episode of neonatal meningitis or a germinal matrix haemorrhage. Requiring drainage of all the cavities by a CSF drainage procedure, the management of this unfortunate event is one of the challenges for any paediatric neurosurgeon. Among the various treatment options available are placement of multiple shunts, single shunt with multiple perforations traversing all the loculations

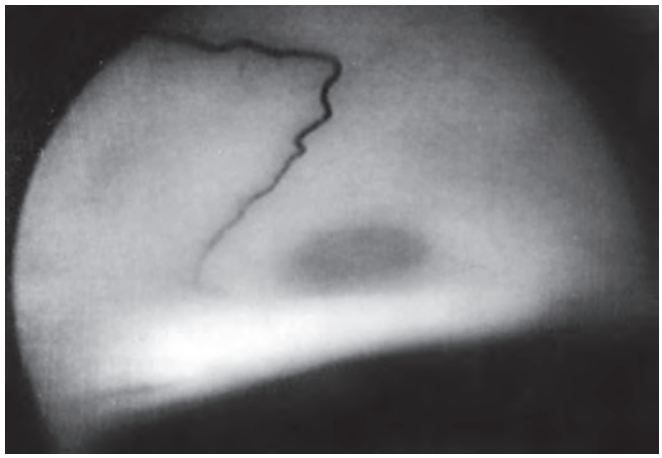

Fig. 10: Endoscopic view of the stenosed aqueduct

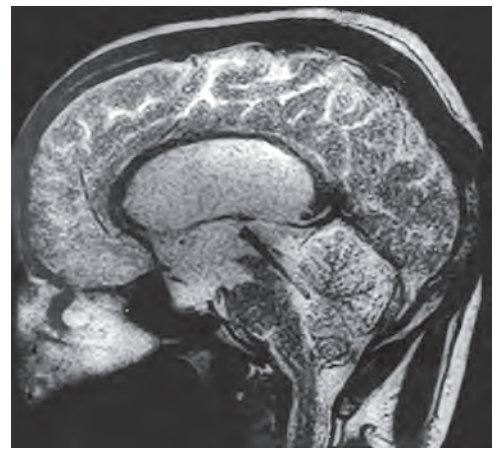

Fig. 11: T2-weighted sagittal image of a patient with placement of aqueductal stent. Note: The wider shoulder of the stent preventing distal migration of the stent

or craniotomy with lysis of intraventricular septations.[30] Stereotactic cyst aspiration or endoscopic cyst fenestrations with shunt insertion have been described. The endoscopic option appears the most ideal and can be performed through a single burr hole with the aid of a steerable endoscope. A large fenestration is usually performed to prevent recurrent cyst formation.[20] Identifying the loculated cysts is usually a problem as most often the difference between the normal parenchyma and the septum cannot be made. Intra-operative ultrasound or navigational systems can be of considerable help in identifying the loculations. After the perforations are made, the multiple cavities are communicated with each other and a single shunt can be placed into one of the major cavities with endoscopic guidance. Alternatively, third ventriculostomy can be performed. However, identifying the normal landmarks poses considerable difficulty due to adhesions and scarring. Repeat procedures are also advised in case the initial one fails to relieve the symptoms. In a series of 34 cases of loculated hydrocephalus, a considerable reduction in the shunt revision rate was achieved during a mean follow-up of 26 months.[20]

Septum Pellucidotomy

In unilateral hydrocephalus due to tumours or adhesions at the foramen of Monro, the septum pellucidum[18] can be perforated endoscopically. Also in cases of triventricular hydrocephalus due to cysts and tumours at the foramen of Monro the septum can be perforated and a lateral ventricular shunt may be avoided.[1] Successful endoscopic fenestration of congenitally occluded foramen of Monro has been described.[28]

Intraventricular Shunt Catheter Placement and Removal of Dislocated Shunt

In cases of multiple shunt malfunctions due to repeated blockage of the ventricular catheter by choroid plexus the proximal ventricular catheter can be placed properly ahead of the choroid plexus in the frontal horn. Though a previous study had demonstrated the decrease in shunt revision rate from 67-49% within 1 year,[21] a recent prospective, randomised, multicentre trial did not find any reduction in revision rates between endoscopically placed shunts and non-endoscopic groups.[19] Endoscopes have also been used for the removal of dislocated and migrated shunt tubes.

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22 Normal Pressure Hydrocephalus

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INTRODUCTION

Normal pressure hydrocephalus (NPH) is a clinical syndrome characterised by a triad of altered mentation, gait difficulties and sphincter disturbances, together with ventriculomegaly and normal cerebrospinal fluid (CSF) pressure.

The term "*normal pressure hydrocephalus*" was introduced by Hakim in his thesis paper in 1964.[44] In the English literature, the concept of NPH was introduced by Adams et al. (in which Hakim was a co-author). It was published in the New England Journal of Medicine in 1965.[1] Before 1965, several papers had shown the apparent paradox of progressive hydrocephalus without overt signs of intracranial hypertension, but the disease was not established as a separate entity.[127] In 1936, Riddoch had described the syndrome closely resembling the one described by Adams and Hakim.[93] This syndrome had also been described by McHugh[78] and by Messsert and Baker.[80] In the latter paper, there had been relief of symptoms after CSF shunting. Penfield[86] had also described some exceptional cases where CSF spaces were closed and the ventricles progressively enlarged without the measured ventricular pressure rising above 150–200 mm H_2O.

NPH has been classified into two groups. The first group is secondary NPH with a known cause, which includes patients with a past medical history of meningeal irritation (e.g. trauma, meningitis, subarachnoid haemorrhage and subdural haematoma).[104] The second group is idiopathic normal pressure hydrocephalus (iNPH), which includes patients in whom no apparent cause is detectable.

Thousands of elderly people with the classical features of gait difficulty, incontinence and dementia may have the potentially treatable iNPH. The entity may either be confused with other diseases that bear a close resemblance to NPH like dementia associated with Alzheimer's disease or the movement disorders associated with Parkinson's disease, or NPH may co-exist with these diseases. Furthermore, this elderly population may have several comorbid conditions compounding their management problems. With increased health care and improved longevity of life, the number of patients with this entity is likely to increase. In the developed countries, this entity has a very high prevalence with a study quoting that about 5% of the total population of the USA may be suffering from NPH.[73] The ataxia, dementia and incontinence associated with the more advanced stages of iNPH become less responsive to treatment as the duration of the disease increases. Thus, patients with symptoms of less than 2 years duration are more responsive to drainage procedures than those in whom these symptoms have persisted for a longer time. Hence, early detection and management of this disease is extremely vital.

INCIDENCE

Clarfield[20] analysed 32 studies with 2889 patients who presented with the symptom of dementia. The iNPH was diagnosed in 1.6% of these patients. Dauch et al.[24] reported its maximum incidence in the seventh decade, but 25% of the patients in their series were below 50 years of age. In adults, NPH may occur at any age. Some authors have reported the presence of NPH in children, but whether this disease actually exists in children is still controversial. The children may manifest poor scholastic performance, walking retardation in infants or repeated falling spells in older children and delayed bladder control. The sex distribution reported in the literature has a male predominance in nearly every series with the male-female ratio being approximately 2:1.

AETIOLOGY

The aetiopathogenetic factors responsible for iNPH are still not known and various theories have been proposed to account for the progressive ventricular dilatation associated with near-normal CSF pressures as well as the regional cerebrovascular changes.[43,82,119] These include:

Increased Venous Resistance

According to one theory in iNPH, decreased CSF resorption occurs at the level of the arachnoidal villi and granulations (probably due to leptomeningeal fibrosis) as well as the brain parenchyma (i.e. transcapillary and transvenular increased vascular resistance). Decreased CSF absorption increases the transmantle pressure (i.e. the pressure difference between the ventricles and the subarachnoid space) causing ventricular enlargement.[18,21] Thus, often, the ventricles may be dilated out of proportion to any sulcal enlargement, which distinguishes it from cortical atrophy.[52]

Bateman[4,5] has suggested that increased transvenular resistance in the territory of the superior sagittal sinus leads to ventricular enlargement and decreased blood supply in the same territory. He proposed a test for diagnosing NPH based on the quantitative measurement of inflowing carotid or basilar arteries and the outflowing superior sagittal or straight sinus. The net systolic pulse volume and the temporal difference in the arterial and venous peaks may diagnose NPH.

Tissue Distortion

Distortion and stretching of the periventricular tissues including blood vessels increase cerebrovascular resistance and cause ischaemia. In the early stages, the mechanical strain of the brain parenchyma and the interstitial pressure are more pronounced in the periventricular region. Later, the periventricular tissue yields the brain parenchyma shrinks, and CSF pressure returns to normal creating the NPH state.[61,82] Once this state is reached, the gradient of stress distribution is more pronounced at the periphery of the brain causing cerebral blood flow (CBF) to be reduced at the periphery of the cerebral mantle or evenly throughout the cerebral mantle and its white matter.[21,61,82]

Interstitial Fluid Pressure Increase

Suffusion of CSF into the periventricular tissues and the reversal of interstitial fluid flow compress local vessels. The interstitial tissue pressure is too low to actually compress the capillaries. However, the failure of autoregulation and accumulation of toxic/vasoactive substances causes border-zone ischaemia and tissue damage of white matter even with modest systemic hypotension or rises of intracranial pressure (ICP), e.g. even during the rapid eye movement phase of sleep.[18]

Watershed Ischaemia

Watershed ischaemia within the corona radiata may occur in the boundary zone between the middle cerebral artery perforators and the medullary branches from the pial arteries. This may be compounded by a disturbance of cerebrovascular autoregulation within the white matter.[22] This is because the corona radiata is vulnerable to reductions in the cerebral perfusion pressure even within the conventionally defined autoregulatory range when accompanied by impairment of CBF pressure autoregulation. There is also reduced cerebrovascular responsiveness to acetazolamide or CO_2 compared with normal controls.[56]

Vasoactive Metabolites

In iNPH, CSF suffuses from the ventricles into the parenchyma and the flow of interstitial fluid is reduced. This causes interstitial/extracellular oedema predominantly in the periventricular tissue and leads to accumulation of inappropriate vasoactive metabolites in this oedema. These metabolites may interfere with intrinsic mechanisms (e.g. nitric oxide) subserving cerebrovascular reactivity. The accumulation of amyloid protein may also damage tissues including vessels. These lead to failure of autoregulation in iNPH.

Vascular Disease

Bradley[14-17] has proposed that the venous resistance may increase in elderly patients due to deep white matter ischaemia. In NPH patients, there is a high incidence of periventricular white matter hyperintensities representative of small vessel ischaemic changes. In some iNPH cases, cerebral small vessel disease perhaps occurs due to hypertension and may cause multiple, small, deep cerebral infarctions in the periventricular white matter and basal ganglia. These multiple areas of infarction reduce the elasticity of the periventricular tissue leading to enlargement of the ventricles provoked by intraventricular CSF pressure pulsations, which are also increased in the case of systemic hypertension. This causes maximum dilatation of arteries, resulting in the loss of autoregulation and lack of response to acetazolamide. When arterioles occlude, the draining venules also close. The CSF normally drained by these veins becomes obstructed causing transient elevations of intraventricular pressure and ICP, resulting in ventricular enlargement.

CRITERIA FOR DIAGNOSIS

The guidelines for the diagnosis and management of iNPH published in the supplement of "*Neurosurgery*" in 2005 have suggested that "*PROBABLE iNPH*" may be diagnosed based on the following criteria:[92] The onset should be insidious, usually in a patient above the age of 40 years, with a minimum duration of at least 3–6 months and be slowly progressive over time. There should not be evidence of an antecedent event, like head trauma, intracerebral haemorrhage, meningitis or any known causes of secondary hydrocephalus, nor any other neurological, psychiatric or general medical conditions that may explain the syndrome. The clinical features must be in the form of gait/balance disturbance with at least one other area of impairment in cognition, urinary symptoms or both.[55,73]

With respect to gait/balance, at least two of the following should be present that are not entirely attributable to other conditions. These include decreased step, height and length; decreased speed and increased trunk swaying during walking; widened standing base with toes turned outwards during walking; spontaneous or provoked retropulsion; en bloc turning or impaired walking balance.

Cognition impairment may be in the form of increased response latency, decreased fine motor speed and accuracy, difficulty in maintaining attention, and impaired recent recall, impaired insight, abstraction, multi-step procedures, working memory and behavioural or personality changes.

Urinary incontinence in the absence of any primary urological disorders may be episodic or persistent urinary urgency (frequent perception of a pressing need to void), frequency (>6 voiding episodes in an average 12 hours period despite normal intake) and/or nocturia (need to urinate >2 times in an average night).

The computed tomography (CT)/MRI must show ventricular enlargement that is not entirely due to cerebral atrophy or congenital enlargement (Evan's index >0.3); no macroscopic obstruction to CSF flow; a callosal angle of > 40 degrees on coronal magnetic resonance imaging (MRI); a decrease in the diameter of the corpus callosum on sagittal MRI as the dorsal surface of the ventricle domes upwards and evidence of periventricular lucency (that is not due to ischaemia or demyelination as distinguished by fluid attenuated inversion recovery sequences).[41] An MRI may also show an aqueductal or fourth ventricular flow void arising from a signal artifact created by hyperdynamic CSF flow through the cerebral aqueduct. Supportive evidence may be in the form of serial brain imaging showing progressive enlargement; a radionuclide cisternogram showing delayed clearance of radiotracer over the cerebral convexity over 48–72 hours; a cine MRI study showing increased ventricular flow rate and a single photon emission computed tomography (SPECT)-acetazolamide challenge showing decreased periventricular perfusion that is not altered by acetazolamide.

On lumbar puncture (LP), the CSF opening pressure should be in the range of 5–18 mmHg (or 70–245 mm H_2O).

If patients do not meet all of the above criteria, but are still suspected of having iNPH, certain exceptions are permissible for a designation of "POSSIBLE". The clinical presentation and history may include any of the following six exceptions:

1. Symptoms have a subacute or indeterminant mode of onset.
2. Symptoms begin at any age following childhood.
3. Symptoms have less than a 3 months or indeterminant duration.
4. Symptoms remotely follow events, such as mild head trauma, intracerebral haemorrhage, childhood and adolescent meningitis or other conditions, that the clinician judges unlikely to be immediately causally related.
5. Symptoms coexist with other neurologic, psychiatric or general medical disorders that the clinician judges not to be entirely attributable to these conditions.
6. Symptoms are non-progressive or not clearly progressive; if either incontinence and/or cognitive impairment is present in the absence of gait or balance disturbance or if gait disturbance or dementia occur alone.

On brain imaging, the ventricular enlargement is associated with cerebral atrophy that may explain the ventricular size or there are structural lesions that may influence the ventricular size. The opening pressure measurement outside the range required for iNPH which also places the patient in this category.[79]

The condition is unlikely to be iNPH, if there is no evidence of ventriculomegaly. There are signs of increased ICP, e.g. papilloedema; no symptom in the clinical triad of NPH is present and/or the symptoms may be explained by other causes.

CLINICAL FEATURES OF IDIOPATHIC NORMAL PRESSURE HYDROCEPHALUS

Idiopathic normal pressure hydrocephalus occurs due to insufficient CSF absorption. It may lead to symptoms due to vascular ischaemic effects, elevated transmantal pressure, axonal stretching of the periventricular white matter and deformation of the brain parenchyma. It has been suggested that ventricular enlargement leads to vascular stretching, decreased compliance and high pulse pressure leading to local barotrauma or tangential shear stress.[12,42]

Gait Abnormality

Gait impairment is the commonest and, often, the first symptom in patients with NPH.[29] The spectrum of gait disturbance ranges from a non-specific imbalance to complete inability to walk and a magnetic retropulsive stance. Initially, there may be slowing with difficulty in turning and a mild instability, which may not be distinguishable from the senile gait or very early Parkinsonism gait.[29,102,120] On progression of the disease, stride length shortens and gait speed slows and there is decreased floor clearance and difficulty in turning. In late phases of the disease, the gait becomes a "*magnetic gait*", and the patients appear to have forgotten how to take a step or even to stand.[10,105]

An analysis of gait of iNPH patients shows decreased cadence, decreased step height, diminished stride length and reduced counter rotation of the shoulders relative to the pelvis during walking.

The posture in these patients is known as "*hydrocephalic astasia-abasia*" and is forwards leaning with a wider sway and imbalance accentuated by eye closure.

Other movement disorders commonly seen are limb and trunk apraxias, inability to climb into one's own bed, difficulty in turning and shifting position and various akinetic, tremulous, hypertonic and hyperkinetic movements.

The features that distinguish iNPH from Parkinson's disease are the absence of significant resting tremor or drooling, and failure to improve when levodopa is administered.[102,106] In the former condition, cogwheel rigidity, if present, is mild compared to the degree of gait difficulty. In cerebellar diseases, ataxia, dysarthria, gaze-evoked nystagmus and appendicular dysmetria may be present, while these are not a feature of chronic hydrocephalus.

When gait disturbance is the predominant symptom of NPH, it implies an improved chance of responsiveness

to CSF shunting; the absence of gait ataxia, on the other hand, predicts poor responsiveness to shunting.[103] It is also true that after CSF diversion, gait abnormality is the most likely component of the symptom triad to improve.[58,103,120] The ventricular size on radiology may not reliably predict the degree of gait abnormality or its improvement after surgical intervention.

In iNPH, gait disturbances may arise due to compression of upper motor neuron fibres passing through the medial portion of the corona radiata as a consequence of ventricular dilatation. Electromyography suggests contraction of the antagonistic muscle groups and increased activity in the antigravity muscles acting on the hip and knee joints. This disorder of phased activation of muscle groups points towards subcortical motor control indicative of premotor pathway involvement. With progression of the disease, and extensive subcortical white matter changes, the pyramidal tracts also become involved manifesting with extensor plantar response. Subcortical dopaminergic nigrostriatal pathway impairment may also contribute to gait and movement disturbances by leading to a disturbance in motor planning. Impaired input from the sensorimotor cortex, the superior frontal cortex, and the anterior cingulate gyrus to the reticular formation in the tegmentum of the brainstem may also contribute to the gait and stance disorder.[103,120]

Cognitive Deficits

NPH is the cause of less than 1% of all dementias. Initially, there is slowing of mental processing, reduced organisational and problem-solving skills and a reduction in prior interests. Patients may become more taciturn, less spontaneous in conversations, withdrawn and apathetic. This abulia reflects bifrontal lobe dysfunction and leads to changes in personality, memory loss and a reduced ability to perform mechanical activities or to think three-dimensionally.[121] As the dementia progresses, patients may have difficulty in finding words. Aphasia, however, is not prominent in the dementia of NPH. By the time significant memory deficits appear, motor slowing and some degree of gait apraxia are typically evident. When the dementia is moderate to advanced, it may overlap clinically with Alzheimer's dementia, Lewy-body dementia or subcortical dementias. A distinction can be made by the presence of a wide-based "*magnetic*" gait in NPH, which is not a feature of Alzheimer's dementia.[122] Vascular dementia can be distinguished by magnetic resonance (MR) imaging of the brain that may show scattered or extensive ischaemic changes in the latter disease. Cognitive impairment is the least likely component of the clinical triad to recover. If the dementia is severe, CSF shunting may result in little or no improvement.[36,89,111,114,120] Various psychometric tests have documented that NPH does not fit the criteria of degenerative (Alzheimer type) or atherosclerotic dementia.[122] Patients with NPH exhibit subcortical type of mental deficits including forgetfulness, decreased attention, inertia and mental slowness with a pattern of memory impairment that differs from the cortical dementias as seen in Alzheimer's disease. NPH is also not associated with "*aphasia-apraxia-agnosia syndrome*", which characteristically occurs in cortical dementias.[106] When significant intellectual loss occurs in the clinical presentation, other diagnosis should be considered and shunt surgery should be avoided even in the presence of ventricular dilatation. Significant hippocampal atrophy on MRI studies is an important neuroimaging criterion for the diagnosis of Alzheimer's disease.[47]

Various psychiatric disorders in association with iNPH are depression, mania, aggression, obsessive compulsive disorder, psychosis and disturbance of impulse control.

Urinary Incontinence

Disturbances of bladder control range from urinary frequency to incontinence. Urinary incontinence may be present in about half of the patients diagnosed with NPH. Incontinence typically signifies a late stage of NPH, although some degree of urgency is often present even in the early stages.[121] Bladder symptoms may not improve or resolve with CSF diversion.[2] Patients with more advanced iNPH may show indifference to the episodes of incontinence due to an associated frontal lobe syndrome. The gait disturbance, apraxia and bradykinaesia may also physically prevent the patient from performing successful toileting. The problems in urinary function may initially be due to the involvement of sacral fibres of the corticospinal tract and later may be a feature of dementia.[120]

Urinary frequency, urgency and incontinence may also result from a variety of common disorders, including benign prostatic hyperplasia, cystitis and other causes of a flaccid or spastic neurogenic bladder. The evidence of hyperactivity of urinary bladder with strong contractions elicited by infusions of small volumes of fluid into the bladder may help in distinguishing iNPH from other conditions. Incontinence is not specific for NPH and appears to be a poor independent predictor of the response to treatment.

Other reported symptoms of NPH are syncopal episodes, changes of sleep pattern, oculomotor abnormalities and endocrinal disturbances. The clinical features that are not expected with iNPH are papilloedema, seizures and headaches.

On the basis of the clinical presentation alone, Black[9] reported that the most favourable response to shunting was in patients with the complete triad who achieved a 61.2% rate of improvement and a 35.4% complication rate.

Differential Diagnosis of Normal Pressure Hydrocephalus

This includes a number of conditions that are common in the elderly age group and have been elucidated by Azeddine et al.[6,66] and by the iNPH guidelines. These

include neurodegenerative disorders, like Alzheimer's disease, Parkinson's disease, Huntington's disease, frontotemporal dementia, progressive supranuclear palsy, amyotropic lateral sclerosis and multisystem atrophy; vascular dementias including cerebrovascular disease, stroke, multi-infarct state, Binswanger's disease, leukoencephalopathy and vertebrobasilar insufficiency; hydrocephalic disorders, like aqueductal stenosis, arrested hydrocephalus, long-standing overt ventriculomegaly syndrome and non-communicating hydrocephalus; infectious diseases, like Lyme, HIV and syphilis and urological disorders, like urinary tract infections, bladder or prostate cancer and benign prostatic enlargement. Many miscellaneous disorders may simulate features of NPH in the elderly age group. These include B_{12} deficiency, collagen vascular disorders, epilepsy, depression, traumatic brain injury, spinal stenosis, Chiari I malformation, post-subarachnoid haemorrhage hydrocephalus, spinal cord tumours and carcinomatous meningitis among several other causes.

Diagnosis

Since first described by Adams, Fisher and Hakim in 1965, NPH has mainly been diagnosed clinically.[1,7] Due to the clinical features of NPH overlapping with other types of dementia, imaging has been used to strengthen the diagnosis in uncertain cases. Different imaging modalities have also been used to help in providing any potentially useful prognostic information.[119]

There is no consensus about which tests work and how reliable they are. The various modalities used for diagnosing iNPH and for prognosticating the outcome of treatment are discussed here. Imaging evaluations, such as pneumoencephalography and angiography, are not discussed because they are no longer in use.[54]

Computed Tomography

The CT scan shows the presence and extent of hydrocephalus as well as the degree of existing cortical atrophy. The CT diagnosis of NPH (Fig. 1) relies on enlargement of the lateral and third ventricles, enlargement of the temporal horns, prominent basilar cisterns, enlarged suprasellar cistern, non-visualisation of the high cerebral convexity sulci, and possible enlargement of the fourth ventricle.[40] The temporal horn dilatation is thought to be more specific for the diagnosis of NPH and correlates with positive findings on radionuclide cisternography.

The Evans index (or frontal horn ratio) is the most commonly used parameter for the evaluation of ventricular dilatation. It is the ratio of the maximum width of the frontal horns to the maximum width of the inner table of the cranium. Ratios greater than 0.32 are consistent with the diagnosis of NPH. However, it cannot differentiate NPH from cortical atrophy or obstructive hydrocephalus as the ratio may increase in all three entities. Furthermore, higher pre-operative Evans ratio (Fig. 2) (e.g. > 0.40) does not correlate with clinical improvement.[121]

Primary cortical atrophy may cause ex-vacuo ventricular dilatation. On CT scan, the cortical sulci and basal cisterns may become prominent. However, 50–60% of patients with cortical atrophy and classical signs of iNPH may still respond to shunting.[90,95,109] The presence of periventricular lucencies around the ventricular system may correlate with clinical improvement. However, they may also be found in non-NPH dementia.[100]

Nuclear or Computed Tomography Cisternography

Cisternography, originally described with radionuclides, has also been performed with iodinated contrast agents.[46,85] In both techniques, the CSF kinetics are similar. Radionuclide cisternography is performed by injecting an isotope iodine[131] labelled serum albumin or indium[111] via a LP. A two-dimensional gamma imaging is done intermittently over 24–48 hours. In hydrocephalic patients, both the ventricular reflux and delayed ascent and prolonged activity of the tracer over the cerebral convexity are evaluated. Nuclear or CT cisternography may show ventricular reflux with a slow cortical uptake. There is also persistence of ventricular reflux for more than 24 hours, a feature that helps in discriminating NPH from cerebral atrophy and in determining the shunt responsive patients.[50]

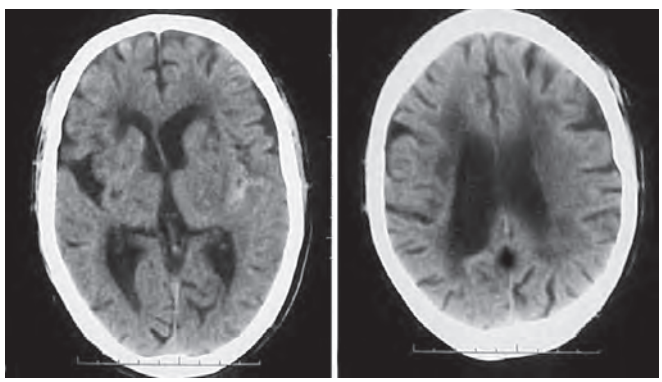

Fig. 1: CT diagnosis of a case of normal pressure hydrocephalus

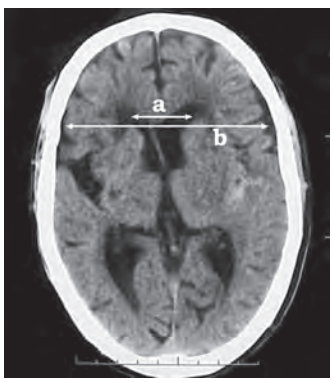

Fig. 2: Calculation of Evans ratio

The advantages of the CT technique include direct visualisation of intrathecal injection under fluoroscopy and improved spatial resolution, possibly for quantitative analysis. However, this poorly evaluates flow at the cerebral convexities, which is more easily seen with the radionuclide technique. CT is also more susceptible to motion artifact, which is common with demented patients. Overall, there is no greater advantage of CT cisternography over the radionuclide technique. The recent recommendation is that cisternography is not very helpful in identifying patients with iNPH and should not be included as an option. It may reveal disordered CSF absorption at the level of the arachnoidal villi, but is insensitive to resistance at the level of the veins. In patients who have an associated cortical atrophy, it cannot predict the response to shunting.[116]

A xenon-CT performed simultaneously with an intrathecal infusion test under pressure-volume stress may show disturbances in CBF autoregulation. A reduction of the regional CBF is usually associated with cortical atrophy.[65,69,71,108]

Magnetic Resonance Imaging

The assessment of NPH using MR imaging includes a study of the same parameters assessed on CT scans. In addition, a detailed study of the periventricular white matter is also possible because of its improved visualisation.[32,62] The presence of these changes is considered as a negative prognostic indicator. However, patients with even severe white matter changes on MR imaging may be benefited from surgical shunting and may have excellent clinical outcomes. The periventricular white matter has been studied in patients having NPH using an MR imaging technique called magnetisation transfer (MT). This technique measures the interaction between the pool of unbound water protons in tissues and the pool of water protons bound to macromolecules such as proteins and membranes. White matter changes with a high rate of MT are considered abnormal. These are detected much earlier on MT sequences than on routine T2 weighted imaging.[28,51,114]

Using three-dimensional (3D) MR imaging, Tsunoda et al.[112,113] compared the total intracranial and ventricular CSF volumes in patients with NPH with those of normal, age-matched controls and patients with cerebrovascular disease, and found increased total intracranial CSF volumes in the former. Thus, patients with NPH had ventricular volume to total intracranial volume ratio higher than those of both comparison groups. In fact, ratio values greater than 30% are seen only in patients with NPH indicating a very high specificity.[125]

According to Holodny et al.,[47] patients with Alzheimer's disease have significantly decreased hippocampal volumes along with increased size of perihippocampal fissures compared with both NPH patients and normal age-matched controls.

MR has also been used to study the pathophysiology of NPH by evaluating the presence of decreased vascular compliance in the superior sagittal sinus and straight sinus in NPH patients.[53] Bateman[5] demonstrated that the vascular compliance in NPH patients was decreased compared to control patients with or without cerebral atrophy. Interestingly, vascular compliance in NPH patients studied after removal of CSF approximated values seen in the control groups.

Magnetic Resonance Cerebrospinal Fluid Flow Studies

The use of MR imaging to evaluate the dynamics of CSF flow includes both qualitative as well as quantitative evaluation. Quantitative measurements include assessment of flow velocity and the flow volume through the cerebral aqueduct.[14–17,34,35,75,76,113]

On MR imaging, a signal void (Jet sign) is seen in the region of the cerebral aqueduct. This is because the velocity of fluid motion increases when larger volumes move through passages with decreasing cross-sectional areas.[48] The velocity of moving CSF is also related to viscosity, cerebral compliance, heart rate, cardiac output, blood pressure and cerebral autoregulation.[3] Patients with iNPH have a pathological cerebral compliance and a majority of them suffer from hypertension. Some of them also have impaired CBF autoregulation. These patients may have a hyperdynamic CSF motion that appears as CSF flow void[34,35,59] This is recognised as a signal loss within the ventricular system on T2 weighted MR scans and may be due to dephasing of protons that move along a gradient that is perpendicular to the imaging plane.[25] Although aqueductal flow void may be seen in normal persons, its extension to the adjacent third and fourth ventricles is more marked in the iNPH group than in normal persons. The signal void observed in patients with hydrocephalus is often more pronounced than in patients with normal ventricles. This is due to the presence of higher volume, turbulent CSF flow in these patients. This finding has been used to triage patients to CSF shunting based on the appearance and extent of the flow void.[87,118] In 1991, Bradley et al.[15] suggested that patients with an increased flow void on MR imaging were more likely to have a good or excellent response to shunting. In 1993, Mascalchi et al.[28,76] prospectively demonstrated the possible utility of this finding in predicting shunt-responsiveness using a qualitative, gradient-echo cine technique. However, other papers including a study by Krauss et al.[59] in 1997 disputed this finding. In the latter study, the degree and extension of the CSF flow void were not found to have significant predictive value in determining the outcome of shunting. The volume of CSF pulsating back and forth through the aqueduct during systole or diastole (the aqueductal CSF stroke volume) as well as its velocity have also been measured using phase contrast MR

imaging.[53,68,84] However, the cut-off point of CSF flow volume at which a diagnosis of iNPH may be made and the response to shunting determined with certainity have still not been decided.

Cerebral Perfusion

Cerebral perfusion studies showed decreased CBF in iNPH. However, as CBF is also decreased in patients with cerebral atrophy, it may be difficult to distinguish between the two conditions using this technique.[63,123] Alzheimer-type dementia may be differentiated as a regional decrease in CBF of the temporoparietal area may be present. Normalisation or near normalisation of CBF after LP in patients having iNPH has prognostic importance as this subset of patients may improve after shunting.[64] The acetazolamide challenge test (i.e. a vasomotor response to carbonic anhydrase inhibitors) or inhaled CO_2, which normally increases CBF, often fails to do so in iNPH patients, particularly in the periventricular white matter.[81] This is possibly due to the existence of already maximally dilated arterioles as a result of local ischaemia. The acetazolamide challenge test may also be used to select patients for shunting, since the patients with a good response to ventriculoperitoneal (VP) shunting usually have a pre-operative CBF above 20 ml/100 g/min.[3] In support of this, a haemodynamic test conducted by Mori[83] in a multi-institutional study in Japan on patients with iNPH consisted of (apart from the other tests) identification of arterial hypertension as a risk factor and of determining whether or not CBF was greater than 20 ml/100 g/min with impaired vascular response to acetazolamide in the periventricular area.

Cerebral Metabolism

^{18}F-fluoro-deoxy-glucose positron emission tomographic (PET) scans of the brain have demonstrated globally decreased brain metabolism and CBF in patients with iNPH when compared with controls.[49] Momjian et al.[82] found a more pronounced CBF reduction adjacent to the ventricles on PET scans and a logarithmic normalisation with distance from the ventricles. Thus, there is an enlargement of the area of the region of subcortical periventricular low CBF.[82] This area also shows a greater restoration of CBF after shunting than the cortex, which correlates with clinical improvement. However, individual patients have heterogeneous CBF defects and no characteristic and consistent pattern has been found in most of the studies.

Enlargement of the subcortical low cerebral flow region taken from slices through the midbrain or basal ganglia as demonstrated on SPECT using either ^{99}mTc hexamethylpropyleneamine or ^{123}I-isopropylamphetamine may also be useful in identifying candidates for shunt surgery.[107]

Transcranial Doppler Ultrasonography

Transcranial Doppler (TCD) ultrasonography has been used to study the pre-operative and post-operative cerebral haemodynamics in iNPH.[27,97] One study conducted pre-operatively claimed that patients who showed normal or near normal CO_2 reactivity of the brain before surgery, showed the greatest clinical improvement after treatment. Other studies comparing the pre-operative and post-operative imaging showed that patients who responded positively to shunting had a statistically significant increase in CO_2 reactivity in the anterior cerebral arteries, middle cerebral arteries, or both after surgery.[67] Measurement of the pre-operative end diastolic velocities also has prognostic significance. When CBF velocity is maximum at the diastolic phase of the cardiac cycle, it indicates that the patient may be benefited by CSF shunting. TCD has not been used to diagnose or plan treatment of patients with iNPH routinely and is currently only being performed in a few institutions for research of CBF patterns in iNPH.[31]

Tap Test

The tap test is one of the commonly used tests to determine the clinical response to installation of a shunt in iNPH. It is easy to perform and is inexpensive. It has been documented that if after CSF (40–50 cc) drainage through an LP the patient improves clinically, it indicates that he/she may be shunt responsive.[94,103] The sensitivity and specificity of the test increases when more fluid is tapped. A positive predictive value of more than 70% has been reported. If, however, the patients are selected for a shunt procedure based only on a positive tap test, a considerable number of shunt-responsive NPH patients would be missed. Thus, NPH patients should not be excluded for shunt surgery based on a negative spinal tap test since a CSF tap test has a good positive predicitive value but a low specificity.[23,118,128] When combined with SPECT measurements of CBF before and after the tap test, higher predictive rates of shunt responsiveness are obtained. An increase of more than 80% in CBF after CSF removal was predictive of response to shunt surgery with an accuracy of 77%.[38,45,128]

Measurement of Cerebrospinal Fluid Opening Pressure

Manometric measurement of CSF opening pressure on LP is also used for determining shunt responsiveness in patients with iNPH. LP is performed in the left lateral decubitus position with the zero point of the manometer being positioned at approximately the height of the atrium of the heart. Before a pressure reading is made, the patient should fully be relaxed, preferably with legs extended, for a period of 5 minutes after the LP needle is introduced. CSF pulsations should synchronise with cardiac pulsations. This ensures that the tip of the needle is adequately in the subarachnoid space when the

measurement is made. In normal volunteers, the CSF opening pressure averages 122 ± 34 mm H_2O (8.8 ± 0.9 mmHg). In patients with iNPH, the CSF opening pressure averages 11 ± 3.3 mmHg (150 ± 45 mm H_2O) but may fall between 4.4 mmHg and 17.6 mmHg (60–240 mm H_2O). Thus, in iNPH, the mean CSF opening pressure is slightly higher than normal but is still within the normal range. In iNPH, there may be transient high pressure waves (B waves) during prolonged intraventricular pressure monitoring, but these waves are not sustained. CSF opening pressures in the range of 105–190 mm H_2O may indicate probable iNPH. At the extremes of the expected range (60–104 mm H_2O or 191–240 mm H_2O), iNPH may be possible. Pressures outside this range would make the diagnosis of iNPH unlikely. Thus, iNPH may be distinguished from secondary forms of hydrocephalus where the CSF pressure is usually high (usually above 18 mmHg; 245 mm H_2O) and the increased CSF pressures are sustained.[51,83,109]

Continuous Intracranial Pressure Monitoring

Continuous ICP recording over 24 hours has been correlated with the outcome following installation of a shunt. A normal or slightly elevated ICP (> 15 mmHg) and an increased frequency of B waves (occupying more than 50% of the monitoring period) may be indicative of a lower compliance. However, there is a lack of normal age-matched control data in the literature.[57] It has been proposed that the amplitude and duration rather than the frequency of B or A waves are important. However, both A and B waves often poorly predict which patients will respond to shunt surgery.[98,118]

Controlled Continuous Lumbar Drainage

Controlled continuous lumbar drainage consists of draining 10 cc of CSF per hour for a period of 72 hours. In Haan's[41] study, all patients with a positive test improved after shunting. However, the potential risks and disadvantages (hospitalisation and costs) prevent this test from being routinely used in clinical practise.[124] Reported complication rates with ELD are 5–20% and may be in the form of severe nerve root irritation and infections.[19]

Impedence of Flow Offered by Cerebrospinal Fluid Absorption Pathways

This resistance offered by CSF absorption pathways may be measured by several methods. In the Katzman[99] test, a pump introduces artificial CSF or saline into the lumbar subarachnoid space at a known constant rate. The resistance is the difference in the final steady-state pressure reached and the initial pressure divided by the infused flow rate. In the bolus method, about 4 ml is injected into the lumbar subarachnoid space at the rate of 1 ml/sec. This method measures both the resistance offered by the CSF absorption pathways as well as the brain compliance (defined by the pressure-volume index). A third method calculates the resistance and compliance during ascending pressure curves in response to a known infusion rate.[96] Thus, it is not essential to reach the steady state using this method. A constant pressure and ventriculocisternal method has also been described. In a study conducted by Kahlon et al.[51] the lumbar infusion test was performed with two needles inserted in the lower lumbar subarachnoid space, one of which was connected to a pressure recording device. The initial steady state CSF pressure was recorded before starting a constant rate infusion of Ringer solution through the needle. The CSF pressure was continuously recorded for at least 45 minutes through the other needle via the pressure monitoring device attached to the needle to establish a steady state pressure plateau representing the pressure level at which absorption balanced infusion. The steady state plateau pressure exceeding 22 mmHg was used as a criterion for shunt surgery.[79]

A problem with measuring impedence of CSF flow is that it increases with age even in normal individuals. Headache and meningismus may occur following fluid infusion. This test may help in increasing the accuracy for identifying iNPH when tap test results are negative.

The predictors of good surgical candidates for shunting in iNPH are summarised in Table 1.

SURGICAL MANAGEMENT OF IDIOPATHIC NORMAL PRESSURE HYDROCEPHALUS

Patient Selection

The pathophysiology of iNPH is not well established and it is not possible to ascertain when the point of "*irreversibility*" of brain injury is reached.[8] Patients with severe cerebrovascular disease do not respond as well

Table 1: Predictors of good surgical candidates for shunting in iNPH

Evaluation parameters	*Positive predictor*
Clinical examination	Presence of classic triad, especially gait disturbance as the primary symptom
Lumbar puncture	Opening pressure > 100 mm water
Cisternogram	Typical NPH pattern, especially persistent ventricular activity at 48 hours
Continuous CSF monitoring	CSF recording pressure >180 mm water; frequent beta waves
Cranial CT scan	Enlarged ventricles; periventricular hypodensities; flattened cortical sulci; small or absent perihippocampal fissures
MRI	All of the above, specially small or absent perihippocampal fissures
Transcranial Doppler studies with carbon dioxide reactivity	Reactivity above 25% with pathologic readings on pressure recordings

to shunting but may still derive some benefit from the procedure.[39,119] The neurological decline in spite of shunt placement in iNPH may be related to the progression of comorbid conditions rather than as sequelae of iNPH. Malm et al.[70] reported that the number of patients with improvement following shunt surgery declined from 64% at 3 months to 26% at 3 years. These findings suggest that shunt may not always arrest the progression of iNPH or its associated comorbid conditions.[37] However, even a temporary improvement ranging 1–3 years in such patients in an advanced age makes a substantial difference to their quality of life. The CSF shunt improves the symptomatology of patients with iNPH due to its dual action, i.e. the diversion of a greater proportion of CSF as well as the provision of additional capacitance. The latter is because, with modulation of pulse pressure, the interstitial oedema and pressure also decrease, improving perfusion and decreasing ischaemia This may be the reason why third ventriculostomy is also effective in some patients of iNPH.[32] As small vessel atherosclerosis is a slowly progressive disease, at some point, CSF diversion is not enough to improve perfusion.[123] Thus, patients with severe white matter disease or those with very low CBF may not respond to shunting, since irreversible atrophy has already taken place in these individuals.[56,60,107] The damage may be more diffuse than that seen on the T2 weighted MR image. This is because the MT ratio is often decreased (indicating loss of myelin protein) and the apparent diffusion coefficient is often increased (indicating increased interstitial oedema) in these patients who seem to be having normal appearing white matter on T2 weighted images.

Surgical diversion of CSF is recommended for iNPH patients in whom there is a favourable risk-to-benefit ratio.[117,120] Factors, such as coagulation status, immune incompetence, comorbidity, functional status and advanced age, should be taken into account while considering surgical intervention.[8] In general, patients exhibiting negligible symptoms may not be suitable candidates for surgical management, given the known risks and complications associated with shunting in iNPH.

The medical treatment of NPH consists of acetazolamide and repeated LPs, which have occasionally yielded prolonged clinical improvement.[81]

Current Recommendations of the iNPH Guidelines for iNPH Diagnosis and Use of Supplemental Prognostic iNPH Tests for Identifying Shunt Responsive Patients

On the basis of clinical examination and neuroimaging (CT/MR), the patient may be categorised as "*probable*", "*possible*" or "unlikely".

Improvement following shunt placement for "*possible*" or "*probable*" iNPH ranges from approximately 61% to slightly less than 50%. Thus, if the classical triad is present and no other illness accounts for the clinical presentation, then one may proceed directly to CSF diversion without supplemental tests.[55,72,112] In the unlikely NPH category, a shunt placement is usually deferred.[98]

Supplemental testing may be in the form of CSF tap test, resistance to flow of CSF determination and/or external lumbar drainage. This may be done in order to increase the certainty of positive shunt response beyond 50 to 61%.[23]

A favourable clinical response to a 40–50 ml CSF tap test indicates that the patient is likely to be benefited from CSF diversion surgery.[19,23,45,94,128] This may be performed for three consecutive days and clinical assessment made. If the tap test does not elicit a favourable clinical response, however, it cannot be used as an exclusionary test due to its low sensitivity (26–61%). Thus, if a negative tap test is obtained, supplemental tests should be performed. If the opening pressure during tap test exceeds 18 mmHg, a diagnostic work up for secondary causes of hydrocephalus should be initiated.[94]

Determination of resistance to CSF flow may be performed on an outpatient basis, like the tap test, and carries a higher sensitivity (57–100%) than the tap test.

Prolonged external lumbar drainage in excess of 300 ml has a high sensitivity (50–100%) and is the most effective supplemental test for identifying surgery responsive iNPH.[74] However, it requires hospital admission and may be associated with complications like severe headache, subdural hygroma/haematoma and meningismus.

Type of Shunt

Various shunt diversion procedures have been described for the treatment of iNPH that have included the VP and ventriculoatrial (VA) shunts, the lumboperitoneal shunt and the ventriculopleural shunt.[7,8] The most commonly used CSF diversion procedures in iNPH are the VP and lumboperitoneal shunts. However, patients who have a history of peritonitis or multiple abdominal operations may not have adequate CSF drainage due to decreased absorptive capacity of the peritoneal cavity. In these patients, a VA shunt may be preferred.

Endoscopic third vetriculostomy has also been advocated as a therapeutic option in selected patients. ETV reduces the intraventricular pressure (with a consequent increase of the CBF and also restores the normal CSF dynamics. Thus, ETV showed a 72% response rate in NPH in the series by Gangemi et al.[33] which is comparable to the improvement seen in various shunting procedures.

Valve Selection

The shunt valve selection may have a bearing on the outcome of iNPH since it maintains a balance between an efficient CSF drainage and prevention of overdrainage related complications.[13,126,129] The valve designs may be of different types:

- Differential pressure valves (e.g. Chhabra shunt): A spring loaded ball check valve or the opposed leaves

of a slit valve will open, if the pressure differential across the valve mechanism exceeds a set value. They may be categorised into low pressure (approximately 20–40 mm H_2O); medium pressure (approximately 50–90 mm H_2O) and high pressure (approximately 100–140 mm H_2O). One of the problems with these valves is that, in an upright position of the patient, the increased hydrostatic column of CSF builds up a high pressure differential across the valve. This may permit a propensity to over drainage (siphoning) of CSF. To counteract this gravity dependent drainage, antisiphon devices may be added in series immediately distal to a differential pressure valve.[26] However, in patients with iNPH in whom the CSF pressure is truly normal (including lack of frequent B waves), placing an antisiphon device may be ineffective.

- Flow limiting valves: These may either (i) have a differential pressure valve that in conditions of normal CSF flow limits CSF flow rate by narrowing the aperture of the valve mechanism and in conditions of high ICP, switches to a high flow rate (e.g. NMT Orbis-Sigma and Phoenix shunts); or (ii) incorporate a high flow resistance tube without a differential pressure mechanism in series to an adjustable differential pressure valve that prevents gravity dependent overdrainage by selectively reducing high CSF flow rates when the patient is in an upright position (e.g. Codman FloGuard valve); or (iii) incorporate a dual stage differential pressure valve (containing tantalum spheres that move within the valves in response to gravity) which has a low pressure in the supine position and a high pressure in the upright position (e.g. Miethke dual switch valve).[126]
- Programmable valves (e.g. Sophy and Codman-Medos valves): These permit the opening pressures of the differential pressure valve mechanisms to be changed non-invasively.[52] The valve adjustments may be made depending upon whether or not overdrainage, underdrainage or a subdural fluid accumulation is occurring.[9,88,129]

The use of an adjustable valve may be beneficial in the management of iNPH due to the increased capability of non-invasively managing both overdrainage and underdrainage. In the study of McConnell et al.[77] a careful volumetric analysis has revealed that changes in ventricular volume correlated with adjustments in valve pressure settings for those patients who improved clinically after shunting. Various retrospective series comparing the non-programmable with programmable shunt systems, however, have so far not yielded any statistically significant benefit in using any specific valve type or configuration.

Clinical Scales for Assessing Outcome

The various scales used for assessing clinical outcome at follow-up after shunt placement have included the Stein and Langfitt scale, the Black scale, the modified Rankins' scale and Boon's Dutch NPH scale.[11] Assessment of cognitive functions may objectively be done using the Mini-mental state examination (Table 2).

Management of Patients Who Fail to Improve or Those Who Deteriorate Clinically Following Shunt Placement

Subdural Fluid Collection Following Cerebrospinal Fluid Diversion

In case a subdural haematoma/hygroma with significant symptoms and mass effect develops, it should surgically be evacuated. In case it is small or asymptomatic then it may be followed using repeated CT scans. In case there is recurrence, persistence or increase in the size

Table 2: Clinical scales for objective assessment of iNPH patients

A. Stein and Langfitt scale[101]	
0:	No neurological deficit, able to work
I:	Minimal deficit, able to function independently at home
II:	Some supervision required at home
III:	Custodial care required despite considerable independent function
IV:	No practical capacity for independent function

Source: Stein SC, Langfitt TW. Normal pressure hydrocephalus: predicting the results of cerebrospinal fluid shunting. J Neurosurg. 1974;41:463–70.

B. Black scale[9]	
Excellent:	Resumed pre-illness activity without deficit
Good:	Resumed pre-illness activity with deficit, improved in two or more categories
Fair:	Improved but did not return to previous work, improved in one category
Transient:	Temporary major improvement
Poor:	No change or worsening
Dead:	Died within 6 weeks of surgery or as a result of surgery

Source: Black PM. Idiopathic normal pressure hydrocephalus: results of shunting in 62 patients. J Neurosurg. 1980;52:371–7.

Contd...

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C. Grading scale for NPH established by the reseach committee on intractable hydrocephalus, Ministry of Health and Family Welfare of Japan, 1996

Grade	Definition
Gait disturbance	
0	Normal
1	Unstable but independent gait
2	Walking with one cane
3	Walking with two canes or a walker frame
4	Walking not possible
Dementia	
0	Within normal range
1	No apparent dementia but apathetic
2	Socially dependent but independent at home
3	Partially dependent at home
4	Totally dependent
Urinary incontinence	
0	Absent
1	Absent but with polyuria or urinary urgency
2	Sometimes only at night
3	Sometimes even during the day
4	Frequent
Total grade:	0 to 12

Source: Mori K. Management of idiopathic normal pressure hydrocephalus: a multi-institutional study conducted in Japan. J Neurosurg. 2001;95:970–3.

D. Modified Rankin scale[91,115]

Grade	Description
0	No symptoms
1	No significant disability despite symptoms: able to carry out all usual duties and activities
2	Slight disability: unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability: requiring some help, but able to walk without assistance
4	Moderately severe disability: unable to walk without assistance, and unable to attend own bodily needs without assistance
5	Severe disability: bedridden, incontinent and requiring constant nursing care and attention

Source:

1. Van Swieten JC, Koudstaal PJ, Visser MC, et al. Interobserver agreement for the assessment of handicap in stroke patients. Stroke. 1988;19:604–7.
2. Rankin J. Cerebral vascular accidents in patients over the age of 60. II. Prognosis. Scott Med J. 1957;2:200–15.

E. Folstein mini-mental status examination[30]

Score	Task instructions
5	Date orientation: 1 point each for year, month, day of week, season and date.
5	Place orientation: 1 point each for state, country, town, building and floor or room.
3	Register objects: Name three objects slowly and clearly. Ask patient to repeat them. 1 point each for each item correctly repeated
5	Serial sevens: Ask patient to count backwards from 100 by 7. Stop after five answers. 1 point for each correct answer
3	Recall objects: Ask patient to recall the objects mentioned above. 1 point for each item correctly remembered
2	Naming: Ask patient to name watch and pencil. 1 point each for each correct answer
1	Repetition: Ask patient to repeat the phrase: "No ifs, ands or buts". 1 point for correct answer
3	Comprehension: Ask patient to: (1) Take paper in left hand. (2) Fold it in half. (3) Put it on the floor. 1 point for each correct movement

Contd...

Contd...

1	Reading: Ask the patient to read the statement "Close your eyes" and follow instructions. 1 point if the patient's eyes close
1	Writing: Ask the patient to write a sentence. 1 point, if the sentence has a subject, a verb and makes sense
1	Drawing: Ask patient to copy a pair of intersecting pentagons onto a piece of paper. 1 point if the Figure has 10 corners and 2 intersecting lines

A score of ≥ 24 is considered normal.

Source: Folstein MF, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12(3):189–98.

F. Dutch NPH scale[10]

Scale

1. Gait scale: It evaluates 10 features of gait and measures number of steps and seconds required for a 10 m walk. Range: 2–40.

$$\text{Outcome measure: } \frac{\text{preop score} - \text{last or mean F/U score}}{\text{preop score}} \times 100$$

2. Dementia scale: This scale composed of the 10 words, digit span forwards and backwards, trial making, and finger tapping tests. Range: 4–40.

$$\text{Outcome measure: } \frac{\text{preop score} - \text{last or mean F/U score}}{\text{preop score}} \times 100$$

3. NPH scale: It composed of the sum of gait scale and dementia sale. Range: 6–80.

$$\text{Outcome measure: } \frac{\text{preop score} - \text{last or mean F/U score}}{\text{preop score}} \times 100$$

4. Modified Rankin scale: This disability score was extended to a 7 point scale by including a grade 4 (defined as moderate disability, partially independent, and needing assistance for less than 50% of the day. Range: 0–6.
   Outcome measure: preop grade—last or mean follow-up grade
5. Modified mini-mental state examination:[110] This evaluates disturbance of cognition. Range: 0–100.
   Outcome measure: preop score—6 or 12 months score

Level of improvement: Improvement in NPH scale score

	Improvement in modified (%)	Rankin score
None	<15	< 1 grade
Moderate	15–29	1 grade
Marked	30–44	2 grades
Excellent	≥ 45	≥ 3 grades

Source:

1. NPH Scale: Boon AJ, Tans JT, Delwel EJ, et al. Dutch normal pressure hydrocephalus study: prediction of outcome after shunting by resistance to outflow of cerebrospinal fluid. J Neurosurg. 1997;87:687–93.
2. Gait and Dementia Scale: Boon AJ, Tans JT, Delwel EJ, et al. Dutch normal pressure hydrocephalus study: baseline characteristics with emphasis on clinical findings. Eur J Neurol. 1997;4:39–47.
3. Modified Rankins Score: van Swieten JC, Koudstaal PJ, Visser MC, et al. Interobserver agreement for the assessment of handicap in stroke patients. Stroke. 1988;19:604–7.
   Rankin J. Cerebral vascular accidents in patients over the age of 60. II. Prognosis. Scott Med J. 1957;2:200–15.
4. Modified Mini-Mental State Examination: Teng EL, Chui HC. The modified mini-mental state (3MS) examination. J Clin Psychiatry. 1987;48:314–8.

of the haematoma/hygroma then consideration for valve adjustment may be done.[18] The settings of the adjustable valves should be increased. In case of fixed valves, replacement with an adjustable valve, the addition of an antisiphon device or revision with a higher pressure valve may be carried out.

Unchanged or Increased Ventricular Size

In case of adjustable valves, the valve settings may be lowered. If the patient does not improve even at the lowest settings and the CT still shows no change in the ventricular size, then shunt patency should be

evaluated using X-ray or radionuclide evaluation or by an LP, ventricular tap or shunt chamber tap. If initially a fixed valve had been placed, then one directly proceeds for evaluation of shunt patency. If the shunt is working, a lower pressure valve is placed, the antisiphon device is removed or the distal slit valves may be removed. In case the shunt is not working, it is replaced.

Whenever there is lack of improvement, other comorbid conditions (like ischaemic cerebrovascular diseases and extensive white matter diseases) and social influences must also be evaluated.

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23 Bony Anomalies of the Craniovertebral Junction

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INTRODUCTION

The term craniovertebral junction (CVJ) refers to the occipital bone that encircles the foramen magnum, the atlas and the axis cervical vertebrae. The medulla oblongata, cervicomedullay junction and upper cervical spinal cord pass through the bony canal formed by these structures. The CVJ has a predilection for a variety of congenital anomalies due to its complex embryological development. Any bony abnormalities that affect this complex can result in neural compression along the entire circumference, vascular compromise and abnormal cerebrospinal fluid (CSF) dynamics.[25] In order to treat the patients with CVJ anomalies, a detailed knowledge of the embryology, anatomy as well as CVJ biomechanics is essential.

EMBRYOLOGICAL ANATOMY OF CRANIOVERTEBRAL JUNCTION

The bony cranial base is formed by the process of endochondral ossification in which a cartilaginous framework first develops, followed by bony osteogenesis; remodeled by distorting forces of brain and eye morphogenesis. During the 4th week of gestation,[42] somites are formed, of which four occipital somites and the upper two cervical somites are involved in the development of CVJ.[28] The first two occipital sclerotomes ultimately form the basiocciput. The third sclerotome is responsible for the exoccipital centre and forms the jugular tubercle. The fourth occipital sclerotome is called the proatlas and has three divisions: (1) hypocentrum that forms the anterior tubercle of the clivus; (2) centrum that forms the apical ligament and the apex of the dens and (3) third division, which is the neural arch of the proatlas that has further two subdivisions, the ventral rostral part and the dorsal caudal part. The ventral rostral part forms the occipital condyles, the anterior portion of the foramen magnum and the alar and cruciate ligaments, whereas the dorsal caudal portion forms the posterior arch of atlas and its lateral masses. The hypocentrum of the first cervical (C1) sclerotome forms the anterior arch of atlas, the centrum forms the dens and the neural arch of C1 forms the posterior-inferior arch of atlas. The 2nd cervical spinal segment has three similar divisions: (1) hypocentrum, which disappears; (2) centrum, which forms the body of the axis and (3) neural arch, which forms the facets and posterior arch of axis. The odontoid process fuses with the base of the axis by the age of 8 years. On the other hand, the tip of the dens is not ossified at birth and is represented as a separate ossification centre that usually appears at age 3 and fuses with the remainder of the dens by the age of 12.[50]

Wide varieties of congenital anomalies are possible because of this complex developmental sequence. More often, multiple abnormalities are present in a single individual, which may involve both osseous and neural structures. This maldevelopment usually occurs between the fourth and the seventh months of intrauterine life. CVJ anomalies can be classified into the following types:

- Failure of segmentation
- Failure of fusion of different bony components
- Hypoplasia
- Ankylosis

Various genetic associations have been found with CVJ anomalies. A study shows a high association of methylenetetrahydrofolate reductase (MTHFR) gene 677C to T polymorphism and higher T allele frequency (which encodes enzymes of the folate pathway implicated in the causation of neural tube defects) with atlantoaxial dislocations, especially the irreducible variety.[35] Homeotic transformation due to mutation or disturbed expression of the *Hox* gene has been postulated as a possible mechanism responsible for assimilation of the atlas into the occiput. The *PAX* regulatory genes control segmentation of the somites and sclerotomes to establish vertebral boundaries. During chondrification of the vertebrae, the *PAX* gene is strongly expressed in the developing vertebrae and, therefore, its expression may underlie vertebral fusion and may be responsible for the Klippel-Feil anomaly (bony fusion of adjacent vertebrae). There is increased incidence of occipitocervical instability and CVJ abnormalities associated with Down's syndrome.[36,47]

CLASSIFICATION

The congenital CVJ anomalies may be divided into the following:

1. Malformations of occipital bone
   a. Manifestations of occipital vertebrae, i.e. clivus segmentations, remnants around foramen magnum, proatlas remnants
   b. Basilar invagination
   c. Condylar hypoplasia
   d. Assimilation of atlas

2. Malformations of atlas
   a. Atlas assimilation
   b. Atlantoaxial fusion
   c. Hypoplasia of atlas arches
3. Malformations of axis
   a. Segmentation defects of C1-C2 or C2-C3 vertebrae
   b. Dens dysplasia
      i. Hypoplasia of the dens
      ii. Ossiculum terminale
      iii. Os odontoideum
   c. Irregular odontoid segmentation
4. Syndromic atlantoaxial instability
   a. Inborn errors of metabolism (Morquio syndrome)
   b. Down's syndrome
   c. Grisel's syndrome

Malformations of the Occipital Bone

As mentioned earlier, the four occipital somites and upper two cervical somites are involved in the development of CVJ. The malformations of the occipital somites may take many forms often with varied symmetry. There may be clivus segmentation, remnants around foramen magnum or proatlas remnants. Sometimes, a condylar canal may traverse through the clivus representing the primitive neural canal. These anomalous developments are collectively termed as "manifestations of occipital vertebrae". Some of the minor anomalies may go undetected throughout life. Some may cause various neural compressive myelopathies. There may be neck pain with assorted rotatory neck deformities like "cocked robin" appearance due to asymmetric maldevelopment around the foramen magnum.[33]

Basilar Invagination and Platybasia

Basilar invagination (BI) is a congenital form of occipital hypoplasia, which manifests by prolapse of the spinal column into the skull base (Fig. 1).[25,26,50] Platybasia is often used synchronously with BI; it is an anthropological term used to describe an abnormal excessive obtuse angulation of the basal angle between the anterior skull base and the clivus. This angle is normally 132 degrees, but when platybasia is present it exceeds 142 degrees. Basilar impression refers to cranial base flattening, platybasia or BI developing as a result of some bone softening due to acquired conditions like osteogenesis imperfecta, Paget's disease or hyperparathyroidism.[15,41,48] Two types of BI have been described: (1) anterior or vertebral invagination which is characterised by shortening of the occipital base and the clivus with concomitant platybasia and shallow posterior fossa and (2) paramedian invagination resulting from hypoplasia of the occipital bones. In this case, the clivus develops normally, but is displaced posteriorly. In this type of BI, condylar hypoplasia is also frequently found. Apart from these two extreme types of BI, some overlapping varieties of BI may also occur.[1,4] Other anomalies associated with platybasia are Klippel-Feil syndrome and occipitalisation of the atlas. BI has also been associated with Down's syndrome and skeletal dysplasia.[20,25,50]

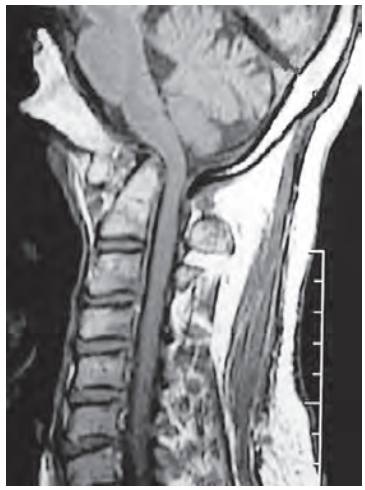


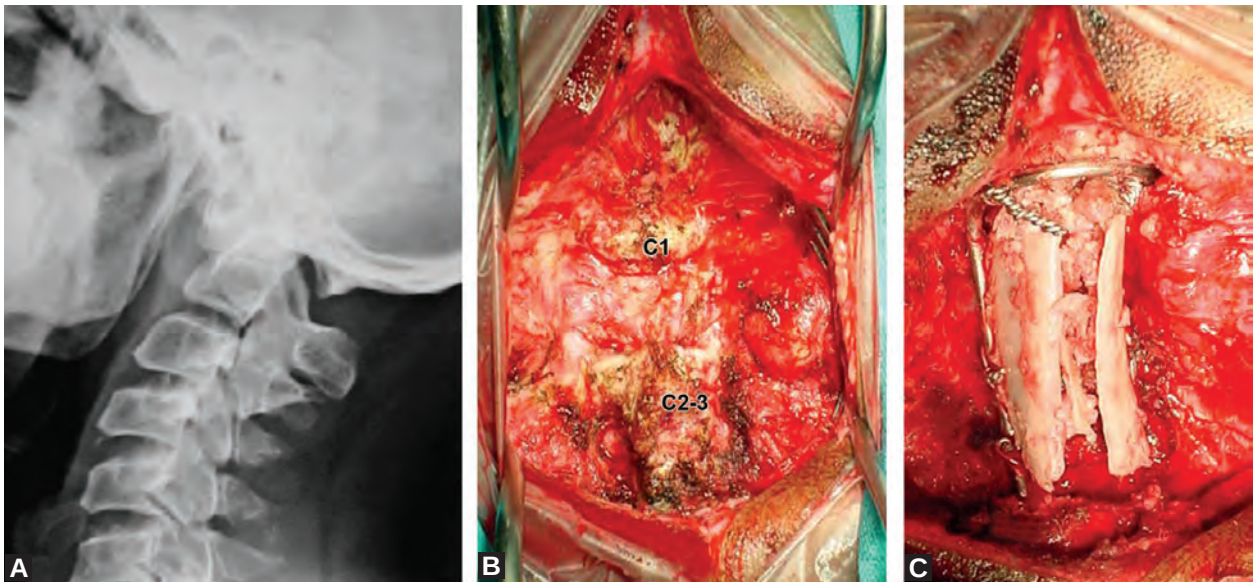
Fig. 1: Sagittal T2-weighted MR image showing BI with central dislocation of the odontoid into the foramen magnum causing cervicomedullary compression

Symptoms of BI are related to compression of the cervicomedullary junction, which develop when the midsagittal diameter of the foramen magnum is less than 19 mm. The most common presenting symptom in BI is neck pain. This symptom is present in 80–85% of patients and frequently originates in the suboccipital area and radiates to the vertex.[13,50] The most frequent neurological sign elicited relates to myelopathy. BI is also often associated with atlantoaxial dislocations and Chiari I malformations. The treatment of BI should start with skull traction to attempt reduction of the ventral compression and to change the curvature of the posteriorly directed odontoid to a more vertical one. Reduction in general is better in children than in adults. The treatment following traction is relatively straight forward. In the reducible variety of atlantoaxial dislocation associated with BI, an occipitocervical fusion is required with or without posterior fossa or upper canal decompression. On the other hand, in patients with the irreducible variety of atlantoaxial dislocation, or a pure BI that is causing neural deficits and canal compromise, a transoral decompression is required to remove ventral compression. This extensive osteoligamentous removal is frequently followed by instability requiring dorsal occipitocervical fusion with or without posterior decompression.

Malformations of Atlas

Atlas Assimilation

Atlas assimilation, also called occipitalisation of atlas, is one of the most common anomalies of the CVJ affecting 0.14–2.7% of individuals.[21] To qualify as atlas assimilation, there must be bony continuity between the atlas and skull base, not merely radiological evidence of lack of movements (Figs 2A to C).[27] Assimilation of atlas may involve the anterior arches, the lateral masses or the posterior arch.[30] When the condyles are fused to the lateral masses, the deformity is usually asymmetric. The most common cause of symptoms related to atlas assimilation



Figs 2A to C: (A) A lateral radiograph of the cervical spine showing atlantoaxial dislocation with occipitalisation of the atlas with C2-C3 fusion. (B and C) An intra-operative photograph of the same patient where occipitalisation of the posterior arch of atlas and C2-C3 fusion is seen. A contoured rod fusion was performed for the coexisting C1-C2 instability

is its association with atlantoaxial dislocation.[5,27] The other associations with atlas assimilation are Klippel-Feil syndrome (fusion of cervical vertebrae), BI and Chiari malformation.[5,16,28] The neurological deficits may range from neck pain to subtle myelopathy to severe quadriparesis. Symptoms of intracranial hypertension may be found secondary to obstruction of CSF outflow owing to the crowded posterior fossa and associated Chiari malformation.[27] Sometimes, an asymptomatic person may develop weakness secondary to trauma or sudden neck flexion and extension.[25] Asymptomatic atlas assimilation does not require treatment. However, surgical decompression with or without stabilisation may be needed in those patients with symptoms due to foramen magnum stenosis, associated irreducible or reducible atlantoaxial dislocation, BI or Chiari malformation. Due to the non-availability of a well developed posterior arch of atlas, an occipitocervical rather than a C1-C2 fusion is required for posterior stabilisation.

Occipitalisation of atlas is often associated with Klippel-Feil syndrome with the classical triad of low hairline, a short neck and a webbed neck with restriction of neck movements. Deafness, cleft face, high arched palate, facial palsies; cardiovascular disorders such as mitral valve disease, ventricular septal defect, coarctation of aorta and patent ductus arteriosus; genitourinary tact disorders such as unilateral, horse-shoe or ectopic kidney; bicornuate uterus; or thoracic dysplasias, ectopic lung, or rib fusions may be associated.

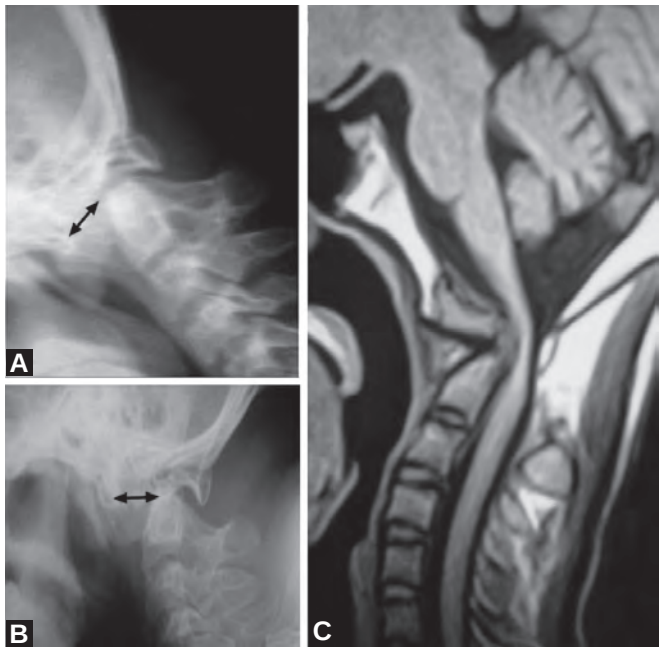
Aplasia and Hypoplasia of the Anterior and Posterior Arches of Atlas

Congenital anomalies of the atlas are frequently manifested as aplasia or hypoplasia of the atlas arches.[25,26] The lateral masses and part of the posterior arch of C1 develop from the proatlas. Anomalies of the ring of C1 can take many shapes, with clefts within the ring of the atlas being more common than complete aplasia.[52] Defects in the anterior arch ring are quite rare, being observed in less than 0.1% of adult spines; however, defects within the post ring are much more common, occurring in anywhere from 0.5 to 5% of anatomical specimens.[31] Ninety-seven per cent of posterior clefts cases are noted in the midline, with only 3% of posterior clefts located in a lateral position near the sulcus of the vertebral arteries.[43] Defects within the ring of C1 are frequently associated with Klippel-Feil syndrome and spina-bifida of the axis.[18] In addition, a prominent tubercle of the neural arch of C2 has also been observed in several cases. It has been proposed that it represents a posterior tubercle of the atlas which has become fused to the axis. An assimilated posterior arch is often associated with asymmetrical lateral occipito-C1-C2 joint synostosis.

Radiographic evaluation with plain films can be misleading, with clefts frequently simulating Jefferson fractures.[9,43] Congenital anomalies of the C1 arches may also produce lateral defects on AP open mouth views.[9,19] This finding may be responsible for causing confusion between the diagnosis of arch hypoplasia and the Jefferson fractures in cases of cervical trauma. The overriding in congenital anomalies is only of a 1–2 mm magnitude, whereas Jefferson fractures usually produce an offset of 7.3 mm.[19]

Congenital Anomalies of Atlantoaxial Joint

The most complex articulation in the cervical spine is between the atlas and the axis. Three joints link the atlas and the axis, the two facet joints on the lateral aspect and the third one which is the most important between the odontoid and the anterior arch of atlas. The



Figs 3A to C: (A) A lateral radiograph in flexion showing an atlantoaxial dislocation. (B) The dislocation is irreducible in extension. (C) T2-weighted sagittal MRI showing the atlantoaxial dislocation causing significant thecal compression

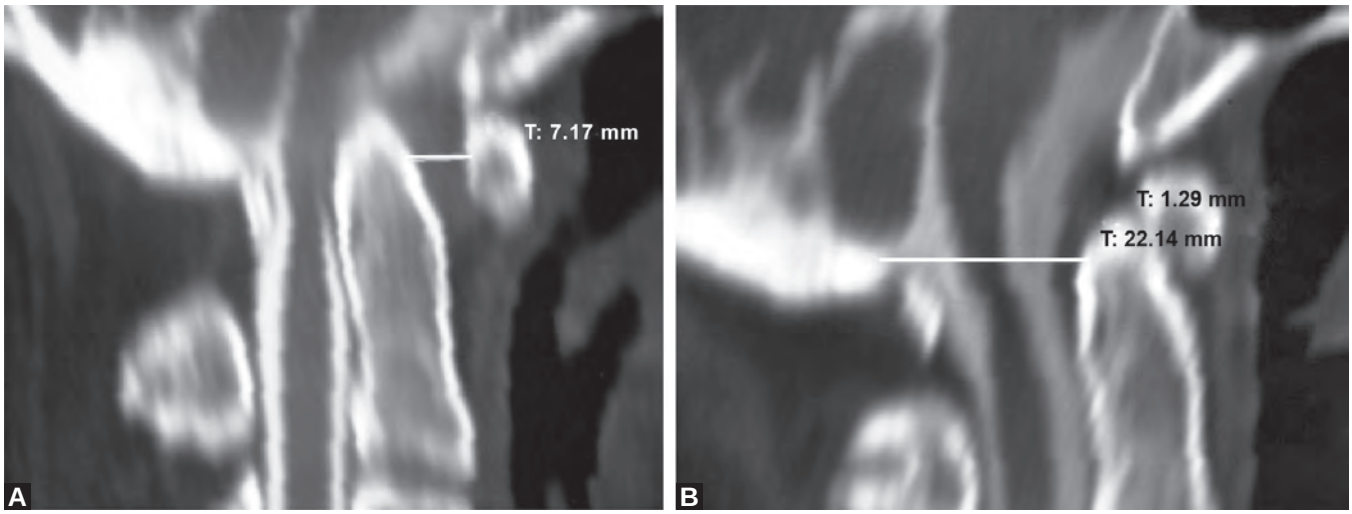
stability of the atlantoaxial joints is dependent primarily on the integrity of the transverse axial ligament (TAL) that limits excessive anterior translation of the axis while allowing rotation of the atlas on the axis through an arc of 90 degrees. In case of an incompetent TAL, the atlantoaxial joint becomes unstable and is dislocated posteriorly resulting in atlantoaxial dislocation (AAD). The congenital disorders involving the atlanto-odontoid articulation include hypoplasia or absence of the odontoid as well as incompetence or absence of the TAL.[4,41] Depending on the reducibility of the dislocation, the AAD may be irreducible (Figs 3A to C) or reducible (Figs 4A and B). In a few patients with a dysplastic or a hypoplastic odontoid, a "*hypermobile*" AAD exists, that causes cervicomedullary compression both in flexion (that displaces the odontoid tip posteriorly relative to the C1 arch) and extension (that displaces the C1 arch posteriorly relative to the axis) movements of the neck. This subtype requires special care during intubation, positioning and stabilisation with the patient being maintained in a strictly neutral position.[4,39]

Atlantoaxial Rotatory Fixation

Atlantoaxial rotatory fixation is a rare disorder in which the atlas gets fixed in a position normally achieved during rotation. Patients present with painful torticollis and a typical '*cocked robin*' position of the head: rotation, slight flexion and with the head tilting contralateral to the direction of rotation. During childhood, laxity of the ligamentous apparatus and joint cups allows a wider range of motion and rotation within these joints. The largest rotation of the cervical spine occurs at the atlantoaxial joints. When the rotation exceeds 40 degrees, an interlocking of the lateral inferior facet of the atlas occurs over the superior articular facet of the axis vertebra. If the TAL is deficient, the anterior arch will sublux forward producing a dislocation with an interlock at much less than 40 degrees. Further rotation more than 30–35 degrees produces an angulation of the ipsilateral vertebral artery. This phenomenon has an implication in certain sports activity like football injuries and wrestling, as well as with children under general anaesthesia or those who undergo chiropractic manipulations.[11,32,34]

Os Odontoideum

Os odontoideum is an uncommon CVJ abnormality that exists as a separate ossicle apart from a hypoplastic dens (Fig. 5). It usually moves with the clivus (dystopic) or with the atlas and the axis vertebrae (orthotopic). Its genesis and natural history have been debated, and its proper treatment remains uncertain.[12] Sometimes,



Figs 4A and B: (A) Sagittal reconstructions of intrathecal contrast CT scan in flexed position of the neck showing an atlantoaxial dislocation with occipitalised atlas. (B) In extended position showing reduction of the C1-C2 dislocation

Fig. 5: An intrathecal contrast CT scan showing an atlantoaxial dislocation with os odontoideum

os odontoideum is associated with early childhood trauma and is postulated to be an acquired phenomenon. At other times, it is proposed to be a congenital sclerotomal segmentation defect. The latter hypothesis states that os odontoideum results from the failure of fusion and the hypertrophy of the proatlas.[40,42,51] The presence of abnormal motion dynamics necessitates surgical intervention, as do associated neurological deficits. Asymptomatic patients in whom os odontoideum is incidentally discovered and in whom no abnormal motion dynamics are demonstrated should be followed closely.

Os odontoideum may be distinguished from an acute fracture of the dens by the presence of a smooth cortical margin of the os as well as of the odontoid surface in close proximity to it; an associated hypertrophic rounded and prominent anterior arch of atlas; and other associated congenital anomalies like occipitalised atlas or Klippel-Feil anomaly.

Ossiculum Terminale

This is a dystopic ossiculum of the dens that could be classified as an ossiculum terminale persistens or as os odontoideum.[46] When the terminal ossification part of the odontoid process remains separated beyond the age of usual fusion (i.e. up to 13 years) and survives as a separate ossicle cranial to the tip of the dens, it is called ossiculum terminale. The clinical presentations and management issues are similar to that of os odontoideum. It is also called the terminal ossicle (of Bergmann).

Syndromic Abnormalities of Craniovertebral Junction

Mucopolysaccharidoses

Mucopolysaccharidoses (MPS) are primary metabolic abnormalities of carbohydrate metabolism. These diseases are inheritable storage disorders manifested by mental retardation, macrocephaly, corneal clouding, small stature, dwarfism and skeletal dysplasia. Generalised ligamentous laxity causes the development of atlantoaxial dislocation. In some patients, radiographic evidence of hypoplasia, absence of odontoid process or even os odontoideum has been found. Death is common in Morquio syndrome (Mucopolysaccharidosis type IV) by the age of 7 years.[38] Other described syndromes with similar manifestations are type VI mucopolysaccharidosis (Maroteaux-Lamy syndrome), mucopolysaccharidosis (MPS) Type VII (Sly disease) and Hurler's syndrome.[49] Bone marrow transplantation has been found successful in certain patients with these disorders. Spinal cord compression due to atlantoaxial subluxation[14] at the CVJ is a major cause of disability and death in these patients. Once cervical myelopathy appears, early posterior occipitocervical fusion has been advocated in order to arrest the progression of neurological disability and is successful in most cases.[2]

Down's Syndrome

This is the most commonly occurring chromosomal anomaly described in humans occurring in about 1.4/1000 live births. Atlantoaxial instability due to ligamentous laxity occurs in 15–20% of Down's syndrome patients.[10,17,29] Other bony abnormalities, like os odontoideum, hypoplastic odontoid process and rotatory atlantoaxial subluxation, have also been found. The most common clinical complaints include neck pain and torticollis. Cervicomedullary compression associated with hyper-reflexia, ataxia and progressive weakness are also documented in a majority of patients. Atlantoaxial fusion is required in the symptomatic group with instability limited to the atlas and axis.[31]

Grisel's Syndrome

This is a unilateral or bilateral atlantoaxial subluxation occurring as a result of parapharyngeal infections. The pathophysiology involves metastasic inflammation causing ligamentous stretching and subluxation, muscle spasm and regional hyperaemia with decalcification of ligamentous structures. The management of such lesions requires precise visualisation of the area by means of MRI. Elimination of the source of infection is the mainstay of treatment. The CVJ region must be stabilised with a Halo brace during the phase of active treatment. Most cases do well with conservative measures.[54,55]

Clinical Symptomatology

The symptoms and signs of craniovertebral anomalies[24] are diverse owing to compression of the medulla, spinal cord, cranial nerves, spinal roots as well as vascular compromise secondary to various bony malformations. The signs of myelopathy are variable both in severity and in symmetry. Similarly, the sensory disturbances are also diverse and may include posterior column as well as bladder symptoms. Various brainstem signs are common when there is compression of the cervicomedullary region which include horizontal and down beat nystagmus, dysmetria, vertigo, internuclear ophthalmoplegia and sleep apnoea. Cranial nerve dysfunctions of trigeminal, vestibulocochlear, glossopharyngeal, vagus, accessory and hypoglossal nerves have also been reported.

Rarely, deficits, like hemiparesis, visual field defects and sleep attacks simulating narcolepsy, have been reported in these disorders.[36]

Symptoms related to vascular compromise are rare, but include syncope, vertigo, episodic hemiparesis, altered consciousness and transient impairment of vision. Usually these symptoms occur as a result of chronic or repetitive vascular compression due to abnormal mobility of the sub-occipital spine.

The stigmata specific to CVJ anomalies include a small stature, short and webbed neck, low hairline, facial asymmetry, mirror movements of the hands and high arched palate.

The neurological symptoms are slowly progressive in most cases, but rapid progression of symptoms does occur with trauma or other catastrophes. Some of the symptoms may become static after sometime.

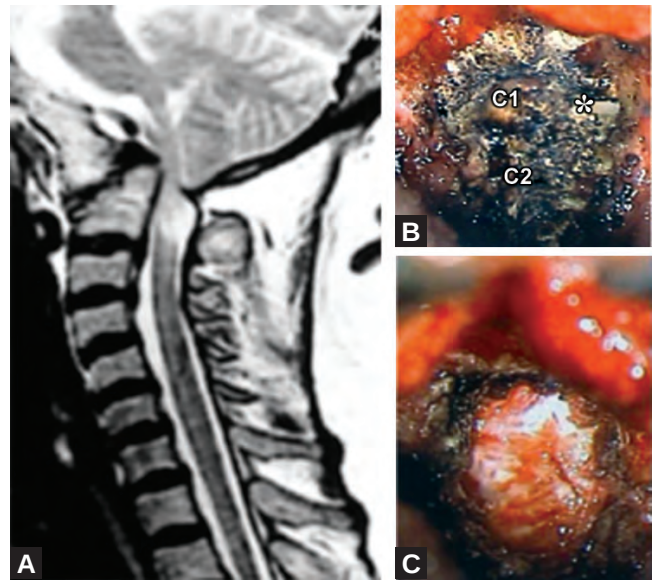
Investigations

The radiological investigations of CVJ anomalies must start with a good quality X-ray of the CVJ with active flexion, extension and transoral views. Numerous craniometrical reference lines were used to describe the atlantoaxial instability before the advent of CT and MRI scan. These measurements are meant to analyse the degree of medullary cord compression and other skull deformities associated with these bony anomalies. The basal angle is the angle formed by the line joining the nasion to the tuberculum sellae and the line joining the tuberculum sellae to the anterior lip of the foramen magnum. Normally, this angle should be about 132 degrees. When it exceeds 142 degrees, platybasia is present. McRae's line measures the sagittal diameter of the foramen magnum from the opisthion (the posterior lip of the foramen magnum) to basion (the anterior lip of the foramen magnum).[22,23] If the tip of the odontoid is above this line, BI is present. Chamberlain's line is drawn from the hard palate to the posterior margin of the foramen magnum, and the presence of more than a third of the length of the odontoid process above Chamberlain's line signifies the presence of BI. Wackenheim's clivus canal line is drawn tangentially to the posterior surface of the clivus; when BI is present the odontoid process intersects this line. Fishgold's digastric line, measured on frontal X-ray projections, connects the digastric grooves lying just medial to the mastoid processes. This line normally lies 11 ± 4 mm above the atlanto-occipital junction.[23] The normal atlantodental distance should be limited to 4.5 mm in children due to the relative resilience of the TAL, and in adults, its upper limit is about 3 mm. When the atlantodental distance exceeds the above-defined limits, AAD is said to be present. Another important measurement is the space available for the cord (SAC), which is the posterior dental distance between the posterior surface of the odontoid process and the posterior lip of the foramen magnum through which the neural structures pass. Normally, it should be more than 19 mm, otherwise cord compression is likely to occur.

Other important investigations include CT scan and MRI of the CVJ. The CT scan gives two- and three-dimensional projections of the CVJ, whereas the MRI scan is important to note abnormalities in the soft tissue as well as cord abnormalities in and around the cervicomedullary segment of the spinal cord.

Surgical Management

The surgical treatment of symptomatic CVJ anomalies requires a precise identification of the underlying pathophysiological conditions. The operative treatments include the anterior, posterior as well as the combination of both these approaches. Symptomatic patients with CVJ anomalies are divided into two groups: (1) with reducible deformity; and (2) with irreducible deformity. Some of the irreducible variety may be reducible with application of skeletal traction, especially under cover of muscle relaxants and general anaesthesia and in such situations these patients are grouped under the reducible variety. The principle of surgery in the reducible group is to fix the deformity in a perfectly reduced position by a posterior construct and bone grafts (Fig. 2C). In the irreducible group, the aim should be to attain a neural decompression if necessary with resections of misaligned fixed bony tissue using the anterior transoral approach (Figs 6A to C), and to stabilise the CVJ that is rendered unstable by the extensive osteoligamentous excision.[32] There are various procedures available for stabilisation of the CVJ like stabilisation with custom countered rods, various bone grafting techniques with plates and screws



Figs 6A to C: (A) A T2-weighted sagittal MR scan showing irreducible AAD with occipitalised atlas and C2-C3 fusion causing marked thecal compression. (B) An intra-operative view during the transoral decompression showing the anterior tubercle of the occipitalised atlas (C1) and the C1-C2 facet joints (*) seen from the anterior aspect (*). (C) The dura seen from the anterior aspect after transoral decompression of the odontoid and body of axis

as well as wires or cables (for more details, please check Textbook of Operative Neurosurgery).

CONCLUSION

The CVJ represents the mobile segment of the spine. It is developmentally also the most active region and is associated with numerous bony and soft tissue anomalies. Management of the myriad clinical manifestations and occasional catastrophic consequences due to CVJ anomalies represents one of the foremost technical challenges of neurosurgery. Future innovations in instrumentation and improvements in knowledge of its genetic associations may help in overcoming these challenges.

Note: There are many studies done by the Indian neurosurgeons which are now of historical importance.[3,6-8,16,33,37,44,45,53]

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24 Syringomyelia

Suresh Nair, Girish Menon, BRM Rao

INTRODUCTION

Syringomyelia is not a specific disease but rather a manifestation of various different pathologic processes with an estimated prevalence rate of 8.4 cases in 100,000 people.[6] The pathophysiologic and therapeutic modalities available in hindbrain related syringomyelia have been intensively analysed in recent times. Although several different hypotheses have been proposed for the mechanism of syringomyelia, the aetiology, pathogenesis and pathophysiology remain unclear and a subject of controversy. Over the years, attempts have been made to classify syringomyelic conditions in an effort to improve our understanding and management of this disease complex. Syringomyelia may be associated with different pathological conditions, both developmental and acquired. Because the natural history of the illness remains poorly understood, the true benefits of surgical intervention over what may be the natural course of the condition is also unclear. Patient prognosis and long-term response to surgery also remain highly variable. A thorough understanding of the pathologic process and treatment options are imperative for the neurosurgeon to determine appropriate treatment.

TERMINOLOGY AND CLASSIFICATION

Syringomyelia is defined as "tubular cavitations" (i.e. cyst) of the spinal cord extending over many segments. Many issues are controversial, especially the distinction between (a) hydromyelia and syringomyelia and (b) the terms communicating and non-communicating syringomyelia. Simon[59] introduced the term "hydromyelia" in 1857 to describe a spinal intramedullary cavity lined by ependymal cells and containing fluid identical to CSF, thus representing a dilatation of the spinal canal. This was distinguished from "classic syringomyelia" which was defined as being lined by glial tissue. The distinction between these two may be difficult to establish, even after histological examination. Although pure forms of hydromyelia may exist, hydrosyringomyelia is probably a more accurate term to describe the pathological findings of asymmetrical cavitations within the spinal cord lined by both ependymal and glial tissues.

Equally controversial is the terminology communicating and non-communicating syringomyelia. Although Barnett et al.[6] introduced the term communicating syringomyelia, with the assumption that in syringomyelia associated with Chiari malformation a communication between the fourth ventricle and spinal cord lesion, either exists or had existed at some time and then got blocked off, no such continuity of CSF flow between the fourth ventricle and syrinx could be demonstrated, even with high quality magnetic resonance imaging (MRI). This led Milhorat[36] to classify syringomyelia into three types: (a) communicating syrinx occurring with hydrocephalus and anatomically continuous with the fourth ventricle; (b) non-communicating syrinx which is separated from the fourth ventricle by a syrinx free segment of spinal cord and occurring with Chiari malformation, extramedullary compressive lesions, spinal cord trauma, intramedullary tumours, infections, etc. and (c) atrophic syrinx occurring with myelomalacia. This classification is quite different from what Barnett et al. described in their monograph on the subject, where communicating syringomyelia is the one occurring with developmental anomalies of the posterior fossa and non-communicating was equivalent of primary spinal syringomyelia due to tumour, trauma and infection. Syringomyelia associated with abnormal downward displacement of the tonsils has certain features which are distinct from cystic cavities occurring at lower spinal cord levels as a sequel to trauma or inflammation. But conditions that result in constriction of the subarachnoid space at the craniovertebral junction, i.e. impaction of the cerebellar tonsils, bony abnormalities at the foramen magnum or extrinsic compression by a extramedullary tumour all have some features in common. Hence, the classification put forward by Batzdorf[8] seems most simple: (a) syringomyelia related to anomalies at the craniovertebral junction (CV) and (b) syringomyelia related to abnormalities at the spinal level. Abnormalities at the CV junction that can result in the development of syringomyelia are those conditions that produce at least a partial block of the subarachnoid space at that level of the neuraxis.

AETIOPATHOGENESIS

Syringomyelia is associated with many different pathologic conditions.[13] The numerous causes of syringomyelia are listed in Table 1. The majority of cases are due to hindbrain descent of the Chiari malformation and the syrinx is usually in the cervical spinal cord

Table 1: Aetiology of syringomyelia

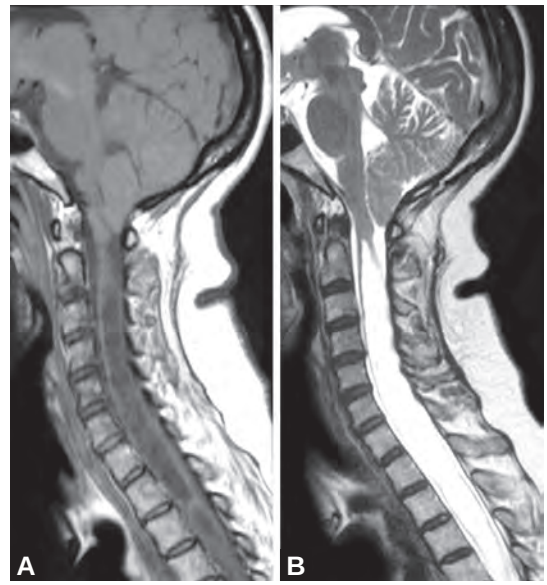
Abnormalities at Craniovertebral Junction
Bone abnormalities
Basilar invagination
Platybasia
Bone tumours
Arachnoid scarring
Trauma
Infection
Inflammation
Subarachnoid space compression (hindbrain impaction)
Fourth ventricular cyst
Dandy- Walker malformation
Tumours
Intrinsic
Extrinsic
Abnormalities at the Spinal Level
Arachnoid scarring
Trauma
Surgery
Infection
Inflammation
Subarachnoid space compression
Tumour (intrinsic or extrinsic)
Spondylosis

(Figs 1A and B). In the author's series of 206 operated cases of syringomyelia, an associated Chiari malformation was seen in 61% of patients.[47] Traumatic syrinx usually develops in the vicinity of the spinal injury and is most frequently located in the thoracic spine. Syrinx associated with occult spinal dysraphism usually occurs just rostral to the lipoma and is located in the lower thoracic and lumbar levels (Figs 2A to C). Myelomenigocoeles are associated with Chiari type II malformations and the syrinx is mostly in the cervical and thoracic levels. Although neoplasms, trauma, inflammation and displaced cerebellar tonsils are the most common causes of cyst formation within the spinal cord, most intramedullary tumour associated cysts are an entirely different condition, in which protein rich cyst fluid is generated by the neoplasm itself. Such tumour associated cysts are not discussed in this chapter, as their treatment is that of the neoplasm itself.

Mechanism of Syrinx Formation

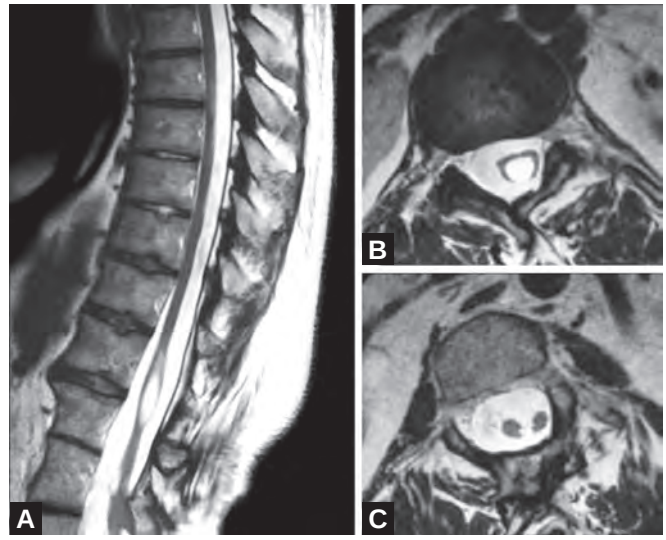
Syringomyelia Associated with CV Junction Anomaly

The most common CV junction anomaly associated with syringomyelia is Chiari malformation. In the author's published series of Chiari malformation more than 50% of patients had associated syringomyelia.[40,42,45,46] Chiari malformation represents a hind brain herniation from the posterior fossa into the cervical spinal canal. Even though four types of Chiari malformations are generally



Figs 1A and B: (A) MRI sagittal T1. (B) T2 showing cervicodorsal syrinx in a patient with Arnold Chiari Malformation

described, the fourth type merely represents agenesis of the cerebellum and thus doesn't represent true Chiari malformation. Type III is a rare variation, which is actually an encephalocoele in the occipital cervical junction. Type I Chiari malformation consists of herniation of the cerebellar tonsils into the upper cervical spinal canal. The medulla is essentially normal. The herniation may extend below the C2 lamina. The remainder of the brain is quite normal without any associated anomalies. Only in 10% of cases there is hydrocephalus. In Chiari type II malformation, in addition to the herniation of the tonsils and vermis, there may be buckling of the medulla because of the caudal herniation of the brainstem as well. There are associated anomalies in the brain, such as beaking of the tectum, presence of large



Figs 2A to C: MRI of a patient with diastematomyelia with syrinx. (A) MRI sagittal T2 showing syrinx at D12-L1. (B) T2 axial at D12-L1 showing the syrinx. (C) T2 axial at L1 showing the split cord malformation

massa intermedia, etc. Chiari II malformations are associated with a meningocoele and the majority of them have hydrocephalus as well as 88% of these patients have syringomyelia.

The exact mechanism of entry of the cyst fluid in most cases of syringomyelia is not known. Chiari[12] believed that the fluid was present in the cord due to the persistence of an embryonal state (hydromyelia) associated with hydrocephalus; the syrinx in his model would be of the communicating variety. Gardner[20] proposed the hydrodynamic theory to explain the association of hydrosyringomyelia with Chiari malformation. He postulated that arterial pulsations of the choroid plexus induced pulse waves of cerebrospinal fluid (CSF) that forced open and progressively distended the central canal, because of impaired outflow from the fourth ventricle. Normally, the foramina of Magendie and Luschka open during the 5th month of foetal life, allowing the pulse wave to be transmitted to the subarachnoid space. In Chiari malformations, the caudally displaced tonsils obstruct the foramen of Magendie and continue to direct the pulse wave into the central canal. Although this mechanism may have a role in the foetal development of hydrosyringomyelia, the arterial pulse wave is not likely to continue later in life. Williams[70] proposed a modification of the hydrodynamic theory, in which venous pressure changes were responsible for the formation of hydrosyringomyelia. During coughing or Valsalva manoeuvre, venous engorgement of epidural veins forces CSF into the spine rostrally. The herniated contents of the posterior fossa then act as a ball valve to trap the fluid intracranially. After the intracranial pressure dissipates, there is a craniospinal pressure dissociation that tends to suck the CSF caudally through the patent central canal. Likewise, the increased intraspinal pressure could force the intracavitary fluid within the syringomyelic cavity to dissect upward, extending the cavity and creating syringobulbia. These theories suggested that the syrinx developed and progressed from expansion of the central canal of the spinal cord, by CSF pulse pressure waves or craniospinal pressure differentials transmitted from the fourth ventricle to the syrinx. Surgical treatments were devised to reduce pressure transmission through the central canal of the spinal cord to the syrinx. Although treatments based on these theories met with moderate success, autopsy and radiographic studies rarely demonstrated a patent spinal canal in adult patients with syringomyelia and thus it became clear that development of syringomyelia must occur through some other mechanism. A relative obstruction at the foramen magnum has been supported by the clinical work of Tachibana[64] who showed that elevated intracranial pressure induced by a compressed jugular vein is not transmitted into the spinal canal of patients with Chiari malformation during neck flexion. Pre-operative MRI studies of these patients with syrinx done with cine mode MRI in cardiac gated phase contrast scanning have shown a significant reduction in CSF flow at the foramen magnum, anterior to the medulla, as well as rostrally into the fourth ventricle and even posteriorly over the cerebellar tonsils and the cisterna magna. Because expulsion of CSF into the cervical subarachnoid space is the normal compensatory mechanism in response to brain expansion during cardiac systole, brain expansion forces the cerebellar tonsils into the partially enclosed spinal subarachnoid space. Because the partially enclosed spinal subarachnoid space has low compliance to abrupt changes in volume, tonsillar descent results in enlarged cervical subarachnoid pulse pressure waves that compress the surface of the spinal cord. This causes progression of syringomyelia by abruptly compressing the cord and propelling the fluid in the syrinx longitudinally with each pulse. According to this widely accepted concept of Oldfield,[50] these pulsatile pressure waves, by forcing the CSF into the cord through the perivascular and interstitial spaces, are responsible for the origin and maintenance of syrinx. This movement of the syrinx fluid inferiorly during systole and superiorly during diastole can be demonstrated by cine MR imaging. This theory differs from that of Williams because it proposes that the CSF movement into the spinal cord is propelled by the systolic pressure wave and not by the increased venous pressure from the Valsalva manoeuvres. Stoodely et al.[63] using horse radish peroxidase as a tracer in sheep, demonstrated that reducing arterial pulsations would decrease the flow into the central canal. Their findings supported the hypothesis that there was a unidirectional flow of fluid from the perivascular spaces, across the interstitial space and into the central canal, driven by arterial pulsations. Under normal circumstances, presumably, the fluid would travel through the central canal to the fourth ventricle and into the subarachnoid space. This model helps to explain the accumulation of fluid in non-communicating syrinx, where there are isolated spinal segments due to scaring and other causes. Stoodely et al. proposed two distinct mechanisms for the normal migration of fluid through the perivascular spaces: (a) systolic expansion of the arteries in the perivascular space may force fluid through the surrounding basement membranes, while in diastole, fluid may enter the perivascular spaces from the subarachnoid space and (b) pulsation in the subarachnoid space transmitted through perivascular spaces acts as an impetus for flow.[62] Milhorat et al.[37] proposed that CSF was continually produced by the ependymal cells lining the central canal and the expansion of the central canal occurred in segments isolated by occlusion or stenosis at each end, such as occurs with viral ependymitis. A non-pathogenetic ageing mechanism may also lead to obliteration of the central canal in many people. Ball and Dayan[5] proposed that the subarachnoid fluid dissects into the spinal cord parenchyma along the Virchow Robin space, when tonsillar impaction prevented the upward escape of CSF. The intramedullary fluid in this theory would gradually enter the central canal. Aboulker[2] proposed a

similar theory with fluid entering along the dorsal nerve roots.

Why some patients with significant tonsillar herniation remain asymptomatic, whereas others have symptoms that frequently appear in adulthood is poorly understood. It has been suggested that gradual development of arachnoid adhesions near the foramen magnum, possibly secondary to mild yet repeated trauma caused by tonsillar motion with Valsalva manoeuvres, plays an important role. Such adhesions and arachnoid scarring, frequently observed during surgery, are thought to lead to progressive deterioration of the CSF space, altered CSF dynamics and increased compression of the spinal cord. Moreover, altered CSF dynamics, which plays a central role in several theories on the pathogenesis of syringohydromyelia, could explain its subsequent development. The relative importance of these factors remains poorly understood. Non-invasive methods for their detection and consideration in clinical decision making are currently inadequate. Neither arachnoid adhesions nor altered CSF dynamics are directly visualised on conventional CT or MRI. No specific risk factors for the development of syringomyelia in Chiari malformation had been known until 1992, when Stevens et al.[61] reported that syringomyelia is apparently more frequent in those with Chiari malformation who have a moderate degree of cerebellar herniation (9–14 mm) and less frequently with mild or severe herniation. This study further confused our understanding of the pathogenesis and pathophysiology of syringomyelia associated with Chiari malformation, by demonstrating that the completely tight compression in the advanced stage of cerebellar tissue herniation is not the condition that leads to the fluid circulatory change, which creates a syrinx in the cord. The development of syringomyelia is absolutely not the result of concentrated mechanical forces in the spinal cord, but obviously the product of disturbed fluid dynamics. It may be speculated that a threshold point exists for the central canal along with some degree of narrowing of the subarachnoid spaces, to balance patency of the obex at and around the foramen magnum. Stevens suggested that syringohydromyelia might occur less frequently with extreme degrees of herniation, where the obex lies below the level of the obstructing tonsils. This presupposes a communicating form of syringomyelia that is not universally accepted; however, it is not clear whether a low obex is present at all times.

Syringomyelia Related to Primary Spinal Abnormalities

The mechanism proposed for the development of post-traumatic syringomyelia is that the necrotic tissue and the haematoma within the injured spinal cord are resorbed and replaced by a cystic cavity,[69] but this theory is challenged by findings that a syrinx may occur after minor trauma. A proposed mechanism related to scar formation is the "spinal-spinal pressure dissociation" model, where subarachnoid scarring after trauma, in a fashion similar to that in hindbrain descent, impedes rapid pressure equilibrium in the subarachnoid space proximal and distal to the scar, which causes the CSF to move into the lower pressure environment of the central canal region of the spinal cord.[30] It is not known exactly why the fluid enters and accumulates within the spinal cord, but a common feature of the associated conditions is a focal or diffuse obstruction of the subarachnoid space, preventing the normally near instantaneous pressure equilibrium under various physiologic conditions, such as coughing or straining.

Spinal syringomyelic cavities may develop and fluctuate during the course of demyelinating diseases, like multiple sclerosis as a consequence of CSF dynamics imbalance.[60] Multiple sclerosis plaques are frequently found in areas adjacent to CSF pathways. These plaques can undergo degenerative change with resultant syrinx formation, involving areas of plaque and spinal cord rostral and caudal to the plaque.[14] Alternatively, a syrinx like lesion can develop, following atrophy of the swollen spinal cord which has undergone demyelination.[18,27] The predilection of inflammatory lesions of the spinal cord to produce secondary necrosis and subsequently syrinx may be a consequence of the tight investment of the cord by pia.[52]

Mechanism of Syrinx Propagation

There are various theories explaining the expansion of the fluid cavities. Gardner proposed that the high pressure waves from the fourth ventricle passing through the opening at the rostral end of the central canal produced progressive enlargement of the fluid collection. Ball and Dayan[5] and Aboulker[2] proposed that the fluid entering the spinal cord parenchyma, driven by the arterial pulsations, would coalesce and rupture into and therefore enlarge the central canal. Williams[70] proposed that the pressure differentials initiated by epidural venous distension after normal physiologic events, such as coughing and straining caused to and fro fluid dissection within the spinal cord referred to as slosh. Oldfield[50] proposed that the systolic pressure wave of the subarachnoid CSF applied against the surface of the spinal cord forces the syrinx fluid to move caudally within the cyst.

SYMPTOMATOLOGY

Most patients with hind brain related syringomyelia become symptomatic in young adulthood. Rarely, syringomyelia may develop in childhood or late adulthood. In a series by Thrush and Foster[65] of 100 patients with syringomyelia, the mean age at onset of symptoms was thirty one years. In the author's series the majority of the patients were in the third decade.[6] Syringomyelia is generally more common in males and has been the same at our institute. Even though familial cases have been described, occurrence in different races is unknown. Syringomyelia usually progresses slowly and the course may extend over many years. The condition may have

a more acute course, especially when the brainstem is affected. Syringomyelia usually involves the cervical area. Symptomatic presentation depends primarily on the location of the lesion within the neuraxis. The majority of cases of syringomyelia are associated with Chiari malformation. Therefore, it is essential to differentiate symptoms predominantly due to central spinal cord cavitations from those due to hindbrain descent.

Symptoms Predominantly Due to Central Spinal Cord Cavitation

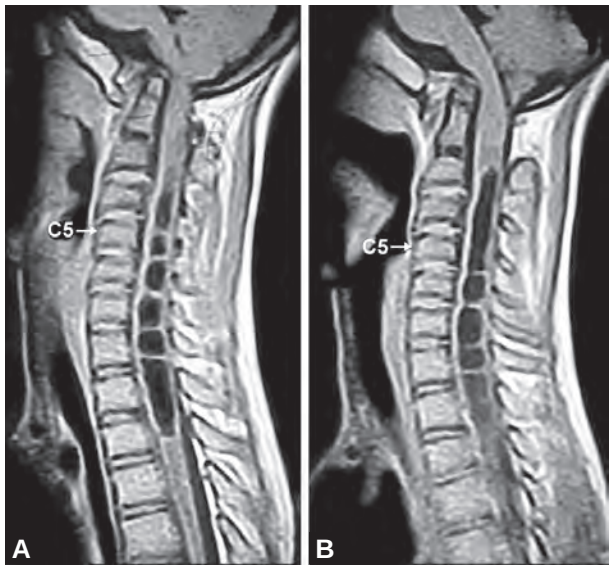
The classic symptoms of a syrinx[13] within the spinal cord include dissociated sensory loss, amyotrophy and spastic paraparesis (upper motor neuron symptoms in the lower extremities and lower motor neuron symptoms in the upper extremities). In later stages, with a larger syrinx, the symptoms may become bilateral. The dissociated sensory deficit is due to damage of the spinothalamic fibres (conveying pain and temperature sensation) in the anterior commissure. The ascending sensory fibres involved with light touch and proprioception are usually spared. The anterior commissure is damaged at the levels of the syrinx but remains intact rostrally and caudally. The resulting sensory deficit has been described as "cape like" or as a "suspended sensory level of cuirasse" because it typically involves the breast-plate distribution. If the syrinx extends laterally to involve the spinothalamic tracts, there will be analgesia in the lower limbs. When the cavity enlarges to involve the posterior columns, position and vibration sense in the feet are lost and astereognosis may be noted in the hands. Amyotrophy of the muscles is due to damage of the anterior horn cells. It usually begins in the hands and extends into the proximal upper extremities. Damage to the nerve bodies innervating the lumbricals may cause a claw hand deformity. Lower extremity motor symptoms are due to destruction or compression of the corticospinal tracts in the lateral columns. Typically, this results in asymmetric spastic paraparesis with absent superficial reflexes, increased deep tendon reflexes and extensor plantar responses. Respiratory insufficiency, which usually is related to changes in posture, may occur. Sphincter disturbance may occur as a late finding. Sexual dysfunction occurs in some. When sympathetic neurons in the intermediolateral cell column get involved, Horner's syndrome occurs. Scoliosis may develop and is due to damage to the dorsomedial and ventrolateral spinal nuclei. The site of the convexity of the scoliosis appears to correspond with the laterality of the syrinx as seen on MRI. Patients with syringomyelia frequently suffer from deep aching pain, usually in the neck and shoulders that may be due to dural distension or a central mechanism. Finally, neurogenic arthropathy (Charcot's joints) develops in 25% of patients with syrinx.[8] They form in areas of analgesia, usually involve the humeral head and result in gross deformity of the shoulder, elbow, hand and wrist. Charcot joints are also associated with tabes dorsalis, syphilis and diabetes, but in these conditions usually the joints in the lower extremities are involved. Syringomyelic patients can develop complex regional pain syndrome (CRPS), formerly known as reflex sympathetic dystrophy. CRPS is a pain syndrome that develops after an irritating noxious event. Typically, evidence of oedema, changes in skin blood flow, abnormal pseudomotor activity in the region of the pain, and allodynia or hyperalgesia is observed. The site is usually the distal aspect of an affected extremity.[14] Of the wide variety of precipitating factors that can cause injury to peripheral or central neural tissue, syringomyelia is a central nervous system cause of CRPS. Due to syrinx formation, the intermediolateral column of the spinal cord is stimulated rather than inhibited by branches of second order sensory neurons. The hyper-responsive sympathetic vasoconstrictor motor fibres severely restrict blood flow to the affected area, resulting in cyanosis, mottling and hypothermia.

If the syrinx extends into the medulla, syringobulbia develops, with symmetric limb weakness, palatal weakness, wasting of the tongue, dissociated trigeminal sensory loss and nystagmus. Lower cranial nerve signs and symptoms are seen particularly with basilar invagination. Rarely, the syrinx cavity can extend beyond the medulla in the brainstem into the centrum semiovale (syringocephalus).

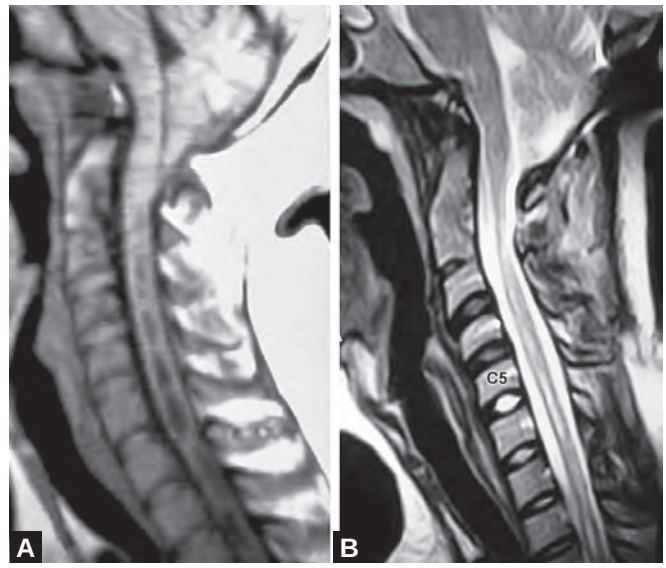
Clinical symptoms associated with Chiari malformation include headache, neck pain, cerebellar dysfunction, nystagmus, spasticity, ataxia, diplopia and bulbar palsies (dysphagia). These symptoms tend to develop in adolescence and early adulthood. The most common symptoms are occipital headache and pain in the distribution of the occipital nerve that may be exacerbated by coughing or sneezing and relieved by lying supine. Pain was the presenting symptom in 50% of patients with syringomyelia seen by the author. Fifteen percent of our patients did not have any sensory loss.[47] While evidence of motor dysfunction was noted only in 70% of the patients with syringomyelia with Chiari malformation, it was noted in as high as 91% of patients without associated Chiari malformation.[40,41,45] We also could identify various clinical syndromes as described by Saez et al.[55] when we analysed the presenting clinical picture of 252 patients of Chiari malformation. One hundred and eighty two patients in this group had syringomyelia. While a foramen magnum compression syndrome was seen in 36% of patients, it was central cord dysfunction in 55%. Approximately 4% of patients who presented with incordination, ataxia and nystagmus were categorised as cerebellar syndrome group. A small percentage (3%) presented with spasticity only and the remaining 2% had miscellaneous presentation.[40,41] Many authors have recognised the prognostic value of certain clinical variables, including the above mentioned clinical syndromes.

IMAGING

Magnetic resonance imaging is the best imaging modality for syringomyelia. It is able to demonstrate the extent of syrinx along with associated soft tissue abnormalities

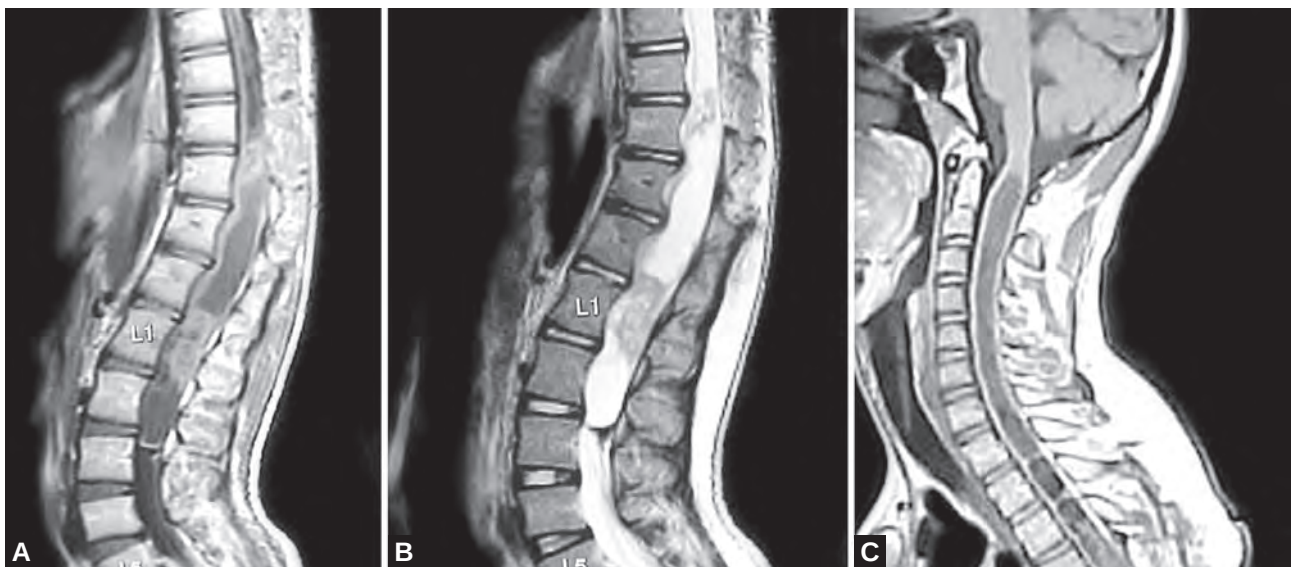


Figs 3A and B: (A) MRI sagittal T1. (B) T2 showing cervicodorsal syrinx in a patient with CV junction anomaly



Figs 4A and B: MRI sagittal T1 showing cervicodorsal syrinx in another patient with CV junction anomaly

of the craniovertebral junction [Figs (3A and B) and (4A and B)], neoplasms (Figs 5A to C), stenosis and arachnoid scarring. Imaging of the entire rostrocaudal extension of the cyst or cysts is important. It also helps to see the flow and septations inside the syrinx. Gadolinium enhanced images are indicated if a tumour is suspected. Magnetic resonance angiography may be helpful in cases of syringomyelia associated with vascular lesions. Myelography with delayed CT performed after 4–12 hours may be used in patients who are unable to tolerate MRI and may demonstrate contrast accumulation in the cyst. Batzdorf[17,42] has successfully used this technique in the evaluation of patients with posttraumatic syringomyelia where associated scar tissue obliterated the local anatomical details on the MRI and in cases where the level of subarachnoid scarring and obstruction was not well delineated. More recently, cardiac gated cine mode T2 weighted MRI has been used to demonstrate CSF flow patterns and it has been proposed that less pulsatile flow within the syrinx is associated with a decreased likelihood of benefit from surgery.[50] This modality may also be useful in distinguishing patients with asymptomatic tonsillar descent from those with abnormal flow dynamics who are more likely to benefit from surgery.[3] Since the development of MRI, real-time ultrasonography is rarely used for imaging syringomyelia. It is technically more feasible in young children or in thin patients. Routine radiographs may demonstrate a widened cervical canal, bony abnormalities of the skull and CV junction, platybasia, midline keel and assimilation of the atlas. Twenty percent of our patients had associated basilar invagination.[40,41]



Figs 5A to C: MRI of the dorsolumbar region; (A) T1. (B) T2 showing intramedullary lesion. (C) Cervical T1 imaging in the same patient showing syrinx

NATURAL HISTORY

The natural history of syringomyelia varies from spontaneous and complete regression to progressive devastating neurologic deficits. There are no large series delineating the natural history of untreated syringomyelia. Boman and Livanainen[10] reported the natural history of 55 un-operated patients with a diagnosis of syringomyelia, seen at the University of Helsinki from 1920 to 1965. It is not clear how many had an associated Chiari malformation. They reported relatively slow progression in all cases. Only 3 had a disability, preventing them from working within 5 years of onset. Twenty-eight had slow progression with worsening. Twenty-seven had a stationary period without progression for more than 10 years. Clearly, although the disease was often progressive, it was also often intermittent in its development with long periods of stability. In spite of this lack of information on the disease's course, it is usually viewed, as Lord Brain[11] described it, "relentlessly progressive". Although there have been case reports, it appears that spontaneous resolution is the exception. The unpredictable clinical course of syringomyelia causes difficulties and controversies regarding management. The possibility that a syrinx may spontaneously disappear may warrant a more conservative approach in certain instances. It was noted that patients with a nearly normal sized spinal cord were more likely to have a benign clinical course and if significant spinal cord dilation was seen, the symptoms tended to progress. These findings suggested that it might be reasonable to consider surgical intervention in those patients, noted to have clear radiological progression of their syringomyelia, even in the absence of significant progression of symptoms.

MANAGEMENT

There is no currently clear consensus about the optimal therapy and differing opinions are found in the literature. Syringomyelia is caused by many different conditions and thus may require different treatments. Another problem, encountered in interpreting the available information, is that a fairly long follow-up is needed because syrinx progression may occur slowly over time.

SELECTION OF PATIENTS FOR SURGERY

Operative management of syringomyelia should be considered when there are progressive neurological deficits by clinical criteria or when sequential imaging techniques show progressive enlargement of syringomyelia.[9] With the availability of high resolution MR images more and more non-distended intramedullary cavities are detected. We have no idea at present whether all such cavities ultimately enlarge or whether cerebellar tonsillar impaction is progressive in all patients. All the available data in literature predates the availability of high resolution MR and, therefore, does not provide an accurate picture of the spinal cord cysts. So, until the question of inevitability of progression can be answered with more certainty, patients with little or no neurologic impairment and non distended syrinx cavities should be followed-up with serial neurological examination and imaging before surgery is recommended. Size of the syrinx cavity alone should not be used as an indicator for surgery, as shown by Nair[49] and Grant,[22] where no correlation existed between cyst size and neurological deficit. As there is no evidence at present that a cyst can continue to enlarge without producing new deficits, surgical therapy should be considered for all distended cysts.

Nair et al.[48,49] have devised a simple clinical and radiological grading system for assessing the severity of the illness and to establish a uniformity in the clinical and radiological evaluation. Our clinical grading system takes into account the subjective, as well as the objective status of the patient with the clinical score ranging from 0–15 with a score of 0 for an asymptomatic individual and 15 for a severely disabled patient (Table 2). The patients were then graded into four clinical grades, depending upon the score (Table 3). Based upon the post-operative clinical score, the percentage clinical improvement (CI) can be calculated from the formula:

Table 2: Clinical scoring system

Clinical Feature		*Score*
Pain	Absent	0
	Mild-Moderate	1
	Incapacitating	2
Sensory	Asymptomatic	0
	Symptoms + No deficit	1
	+/–Symptoms + < 50% deficit	2
	+/–Symptoms + > 50% deficit	3
Cranial Nerve	Asymptomatic	0
	Symptoms + No deficit	1
	+/–Symptoms + Unilateral deficit	2
	+/–Symptoms + Bilateral deficit	3
Cerebellar	Asymptomatic	0
	Symptoms + No deficit	1
	+/–Symptoms + Unilateral deficit	2
	+/–Symptoms + Bilateral deficit	3
Motor	Asymptomatic	0
	Proximal/Distal only	
	Grade IV	1
	Grade III	2
	Grade II/I	3
	Proximal and Distal both	
	Grade IV	2
	Grade III	3
	Grade II/I	4

Table 3: Clinical grades

Grade 0	Asymptomatic	Score 0
Grade I	Mild	Score 1–5
Grade II	Moderate	Score 6–10
Grade III	Severe	Score 11–15

%CI = preoperative score - postoperative score/ preoperative score x 100

Our study proved that patients in mild clinical grade (grade I) had a much better chance of good to excellent outcome than grade II patients.

Radiologically syrinx size was assessed by cyst:cord and cord:canal ratios and a radiological grading system was devised with a score range of 0 to 8. (Tables 4 and 5). These radiological scores are based on the maximum anteroposterior dimensions of the syrinx, cord and canal at the same level. Percentage radiological improvement (RI) can be calculated by the formula:

%RI = Preoperative score - postoperative score/ preoperative score x 100

Our study[48,49] revealed lack of correlation between the clinical and radiological grades pre- as well as post-operatively. A radiological reduction in the syrinx size far outweighed the clinical improvement. On the basis of pre-operative clinical grade, one can predict the clinical outcome after surgery, whereas radiological grade fails to prognosticate the clinical outcome.

The likelihood of improvement of a symptom or symptoms following surgery should influence the decision to recommend surgery. It is known that not all the clinical manifestations of syrinx, which occur, with abnormalities of the CV junction respond equally to surgery. The main goal of surgery is to arrest progression of neurological deficits. Many authors[16,41] have recognised the prognostic value of certain clinical variables including clinical syndromes. Suboccipital headache caused by tonsillar impaction responds well to adequate decompressive therapy. Pyramidal tract manifestations and spinothalamic sensory loss improve, as the pressure of the cysts on these pathways is reduced. Weakness and atrophy of the hands show little improvement because of destruction of corresponding anterior horn cells.

Table 4: Radiological scoring system

		Score
Cyst:Cord	0.76–1	4
	0.51–0.75	3
	0.26–0.50	2
	0.01–0.25	1
	0.0	0
Cord:Canal	0.91–1	4
	0.81–0.9	3
	0.71–0.8	2
	0.61–0.7	1
	< 0.6	0

Table 5: Radiological grades

Grade 0	No cyst	Score 0
Grade I	Mild	Score 1–4
Grade II	Severe	Score 5–8

Similarly, dysaesthetic pain, which is a form of denervation dysaesthesia due to destruction of ascending spinal pathways with a thalamic projection, responds poorly to decompressive therapy. Each patient must be judged individually, keeping in mind that progression of symptoms can sometimes occur rather abruptly. Because some of the neurologic deficits tend to become fixed once they develop, most patients with Chiari malformation and a distended syrinx must be candidates for surgery. Chiari malformation presenting with lower cranial nerve involvement or symptoms of direct brainstem compression must also be candidates for surgery.[40,41]

Surgical Management of Syringomyelia Associated with Craniovertebral Junction Anomalies

Management of Chiari malformation with associated syringomyelia continues to pose a great challenge to physicians. Treatment of symptomatic patients is strictly surgical. Meadows et al.[35] and Nair et al.[43,44] in recent reviews had published the pros and cons of various surgical options. The management strategy follows a "top down" rule.[39,54] Treatment always begins by addressing hydrocephalus, if it is present. A VP shunt placed in patients with hydrocephalus may relieve both cerebellar ectopia and dilatation of the central canal as well. Early surgical techniques attempted to address syrinx and Chiari malformation separately with a decompressive procedure directed at the foramen magnum for Chiari and a myelotomy or shunting procedure directed at the syrinx. However, after the elucidation of the relationship between the syrinx and the pathology at the foramen magnum, surgeons now prefer to reserve shunting for patients who fail to respond to initial posterior fossa decompression. Most patients with Chiari malformation and syringomyelia are treated with a sub-occipital decompressive craniectomy, as well as cervical laminectomy to the distal tips of the cerebellar tonsils. The goal of the surgery is to relieve cord compression and to re-establish adequate CSF flow. The specific surgical steps in this operation continue to undergo modification, as surgeons attempt to identify the optimum treatment. This is usually dictated by patient characteristics and the surgeon's experience. The occipital bone may be considerably flattened and can have a rostral tilt at the foramen magnum. The dorsal ring of the atlas may be incomplete or thin. Most of the time, a markedly thick dural band is found at the foramen magnum that may conceal or contain aberrant veins. The dura is usually incised in a standard Y pattern, although some authors[26,38] have stressed that dural opening may be unnecessary. They contend that simple bony decompression without intradural exploration alone relieves the ball valve effect of Chiari malformation. There is controversy regarding the extent of decompression required to alleviate symptoms. Dural bands and arachnoid adhesions maybe freed, although several surgeons have stressed the importance of avoiding undue manipulation of the

subarachnoid space. Manipulation of the tonsil has also become a matter of considerable debate. Whereas several authors have suggested some form of manipulation ranging from simple retraction to bipolar coagulation or resection, only one study[23] has shown any additional benefit to such methods. In comparison to adults where the cerebellar tonsils may be necrotic secondary to chronic compression, there is rarely a need to excise the cerebellar tonsils in children. Occasionally, a thin membrane is found to occlude the foramen of Magendie, in which case the membrane is excised to establish communication with the fourth ventricle. If the tonsils cannot be mobilised, a tube or silastic wick is placed to maintain the patency of the fourth ventricle outlet in the midline. In the presence of dense arachnoid adhesions, some surgeons keep a shunt tube between the fourth ventricle and the intact subarachnoid space around the spinal cord. Gardner[19] had suggested the practise of plugging the obex with a small strip of muscle to prevent communication with the fourth ventricle. A number of authors have reported encouraging early results with this practise. This technique went into disrepute as several studies have shown the long-term results to be less encouraging with late neurological deterioration reported in many cases.[43] Intractable vomiting and respiratory embarrassment were also reported after plugging of the obex. The opened dura is later reconstructed in a capacious manner using a graft. In a review of patients who underwent decompression with and without duraplasty, Matsumoto and Symon[44] noted no difference in the reduction of hydromyelia. However, regarding improvement of symptoms, patients without duroplasty had a significantly worse outcome compared to those with duraplasty. Even though surgeons differ on the usefulness and safety of additional procedures like duraplasty, excision of tonsils and obex plugging, there is general consensus on the importance of CV junction decompression in the treatment of Chiari malformation with syringomyelia. In patients in whom there is no neurological improvement without radiological collapse of the syrinx cavity, 3–6 months after foramen magnum decompression, a syringoperitoneal shunt is inserted.

Management of Syringomyelia Related to Primary Spinal Abnormalities

The indications for surgery in patients with primary spinal syringomyelia are debatable. The natural history of these lesions is not known. As a rule, relatively rapid loss of neurological function facilitates the decision for surgery. The various management options for primary syringomyelia include syringostomy, shunting to the subarachnoid, pleural or peritoneal spaces and endoscopic release of septations. Syringostomy is the oldest and simplest surgical method. It involves a laminectomy at the appropriate level and a dorsal longitudinal incision through the thinned out spinal cord into the syrinx cavity. Incisions are usually made in the midline or just posterior to the dorsal root entry zone. Intra-operative real-time ultrasonography is useful in locating the largest section of the syrinx and where it is most superficial and in guiding the drainage/shunt catheter into the optimal position.[15] Problems with syringostomy include locating the optimal myelotomy site, minimising the risk of tissue damage and keeping the stoma patent. A technical variation was recently introduced by Ventureyra et al.[66] to solve the problem of stoma closure by scarring or gliosis. They proposed introducing a myringostomy tube through a small 3 mm midline myelotomy at the level of the maximum syrinx enlargement, to maintain the syringosubarachnoid communication. Shannon et al.[58] reported on a series of syringostomies and noted that patients whose main symptom was pain all improved, while patients whose predominant symptom was sensory loss did not. In their review of world literature from 1971 to 1991 including 1,301 operative cases, Aschoff and Kunze[4] found 176 syringostomies reported by eight different authors; the results were 41% improvement, 25% stabilisation and 34% deterioration.

Shunting procedure may achieve syrinx drainage into the pleural, peritoneal or subarachnoid spaces. The technique involves exposing the spinal cord by laminectomy or hemilaminectomy over the area where the syrinx has the largest diameter. A small myelotomy is performed, either in the midline or at the dorsal root entry zone.[53] A variety of valveless silastic catheters have been used. The catheter may be inserted cephalad or caudal, depending on the neurosurgeon's preference. The distal end of the catheter may then be placed in the subarachnoid space or tunnelled into the pleural or peritoneal space. The success rates of various shunting procedures are very different among the series and this has led to shunt advocates and shunt detractors.[31,57] Another procedure which was tried in the past is terminal ventriculostomy. The terminal ventricle is the dilated portion of the central canal that extends below the tip of the conus medullaris into the filum terminale. A laminectomy is performed over the caudal limit of the fluid sac and the filum is opened. This procedure is suitable only in patients with symptoms of syrinx without Chiari malformation. It is inappropriate in cases in which the hydromyelic cavity does not extend into the lumbar portion of the spinal cord or into the filum terminale.

Another surgical option is to attempt to recreate the normal CSF flow pattern and thus remove the impetus for syrinx formation. At the spinal level it involves open or endoscopic dissection of subarachnoid adhesions and the enlargement of the local subarachnoid space by expansile duroplasty or creation of a pseudomeningocoele. To increase the local CSF flow area, Wiart et al.[68] suggested tacking the dura open to create a pseudomeningocoele. Levi and Sonntag[32] suggested using an expansile duroplasty with a synthetic patch to help prevent a CSF leak. A final procedure used to recreate a more normal spinal CSF flow is spinal cord transection in complete paraplegia with an ascending syrinx.[57] As microsurgical skills progress lysis of local adhesions may prove to be an excellent treatment option

for syringomyelia that can prevent the need for implantation of a foreign body.[13] More minimally invasive treatments for syringomyelia have been evolving. Because many of the syrinx are septated, a shunt may not communicate with all of the fluid containing chamber, which can be seen with an intra-operative real-time ultrasound imaging and treated accordingly. Huewel et al.[25] used the endoscope to divide the septations and create a continuous pathway. Goldstein et al.[21] described CT guided percutaneous drainage of syringomyelia. Further studies will help to determine the value of these minimally invasive techniques.

Given a patient with syringomyelia, how are we to decide which is the optimal management for that patient. On the basis of MRI characteristics, Abe et al.[1] have classified syringomyelia into five types and have suggested the most appropriate treatment for each type. Type I has associated Chiari malformation and MRI, shows wedge shaped herniated tonsils to be occupying the cisterna magna with the rostral end of the syrinx looking conical and there is no obliteration of the caudal part of the fourth ventricle. As these findings suggest the herniated tonsils to be compressing the brainstem and spinal cord and mechanically obstructing the CSF flow at the foramen magnum, a foramen magnum decompression with or without duraplasty alone is required. Type II patients have basal arachnoiditis, usually with a history of difficult labour. MRI of these patients reveals the cisterna magna to be narrowed by scar tissue or by herniated tonsils. However, the tip of the tonsils is rounded and a cavity resembling the subarachnoid space may be seen in the region of the cisterna magna. In addition, the upper end of the syrinx is rounded and the lower part of the fourth ventricle will be well visualised. These MRI findings suggest that the foramen magnum is not mechanically obstructed by herniated tonsils but rather by arachnoid scarring due to arachnoiditis. As treatment, the authors have suggested foramen magnum decompression followed by placement of a shunt tube from the fourth ventricle to the ventral cervical subarachnoid space to prevent reobstruction of the foramen of Magendie. In patients with type III syringomyelia, MRI reveals a direct communication of the syrinx with the fourth ventricle via a patent central canal and is associated with hydrocephalus. The treatment suggested is foramen magnum decompression followed by opening of the membrane obstructing the foramen of Magendie, which will equalise the pressure between the ventricular system and the subarachnoid space. In addition, to prevent refilling of the syrinx, Abe et al.[1] have suggested plugging of the obex with a Dacron fabric. Type IV patients of syringomyelia have obliteration of the subarachnoid space around the spinal cord due to arachnoid scarring with a normal craniovertebral junction. There is extension of the syrinx both rostrally and caudally from the site of scarring. When scarring is localised, a syringosubarachnoid shunt rostrally from the site of scarring is advised. When the scarring is not localised a syringoperitoneal shunt is the treatment recommended. For type V patients in whom no associated lesions could be found on MRI or with cine MRI, either a syringosubarachnoid shunt or a lumboperitoneal shunt is suggested as the most effective treatment.

Results of Surgery

The results of surgery for syringomyelia associated with Chiari are variable and some signs and symptoms show a characteristic response to surgery. In the review by Levy et al.[33] patients presenting with exertional headache, as the dominant feature, showed the best results with 60% showing improvement. While 47% of patient presenting with mixed signs of cerebellar and lower brainstem and cervical cord involvement showed improvement, only 30% of patients with symptoms attributable to intrinsic cord lesions had any improvement. Dyste and coworkers[16] found that pain improved in 81.5%, worsened in 7.4% with 11.1% having no change. Motor strength improved in 70%, became normal in 21%, worsened in 6% and remained unchanged in 3%. Sensation by contrast improved in only 6%, remained unchanged in 61%, became normal in 29% and deteriorated in 4%. Analysis of the long-term results at our institute[29] with a mean follow-up of 58 months and a minimum of 12 months showed overall improvement in 60% of patients. While symptoms remained static in 24%, these deteriorated in 16%. Suboccipital pain improved in 72% of cases. While spinothalamic pain and motor symptoms improved in 57.6% and 47.6% of patients, cerebellar symptoms and cranial nerve deficits improved in 60% and 72%, respectively. The five most common clinical manifestations in Batzdorf's series[9] of syringomyelic patients were sensory deficit, motor weakness, sub-occipital pain, dysaesthetic pain and spasticity. Of these, headache and spinal pain responded best to surgery, presumably because pressure and distension of the dura were relieved. Weakness of lower limbs and spasticity improved in two thirds of patients but weakness with atrophy of hands often failed to improve. Relieving pressure on the corticospinal tracts relieves symptoms in the lower extremities, whereas destruction of anterior horn cells rarely improves. Dysaesthesia and sensory deficits improved in only 20% of patients. Mild scoliosis (less than 35) may improve or stabilise, but severe deformities progressed. Out of the 93 patients of syrinx with Chiari malformation treated over a ten year period at the All India Institute of Medical Sciences, New Delhi,[51] 76% of the patients who underwent modified William's procedure demonstrated clinical improvement, as opposed to the improvement seen in 55% of patients who underwent Gardner's procedure and 53% who underwent just foramen magnum decompression with or without duraplasty.

In 1996, Vernet et al.[67] compared syringopleural to syringosubarachnoid shunting in 31 children with five years follow-up. Of the 19 patients treated with syringopleural shunts, 11 improved and 8 remained stable. Of the 13 patients treated with syringosubarachnoid shunts, only one improved, eight remained stable and three deteriorated. They concluded that it was best to shunt the

syrinx fluid outside of the subarachnoid space. Klekamp et al.[28] in 1997 reviewed 107 patients who had syringomyelia associated with subarachnoid scarring due to arachnoiditis or trauma. Twenty nine patients remained stable and thus required no treatment. The 78 patients with progressive neurologic deterioration underwent 121 procedures with a follow-up of 32 months; all had arachnoid scarring near the syrinx, 52 from trauma and 69 from inflammation. Patients treated with shunting fared poorly. Those with focal scarring had recurrence of the syrinx in 92% and those with extensive scarring had recurrence in 100%. Microdissection of the scar and decompression of the subarachnoid space with fascia lata graft produced stabilisation in 83% with focal scarring, but in only 17% with extensive scarring. In this series, with associated scarring, the syringopleural and syringoperitoneal shunts fared better than the syringosubarachnoid shunts. The authors concluded that scar resections were the best treatment option if a focal area is involved and that no procedure is effective if diffuse scarring exists.

CAUSES OF SURGICAL FAILURE AND THEIR PREVENTION

Patient prognosis and long-term response to surgery remain highly variable, which proves the wide divergence in clinical presentation and surgical management.[35] Many patients who initially improve with surgery frequently return to their pre-surgical state or sometimes even become worse and continue to deteriorate. Whether this denotes the natural course of the condition in a subset of this patient population is not known. Because the natural history of this condition is poorly understood, the true benefits of surgery over what may be the natural history of this condition are poorly understood. Progressive neurological deficits after the initial operation should lead one to suspect post-operative cerebellar ptosis with tethering and scarring of the cervical spinal cord and recurrent syringomyelia.[24] Rarely, deterioration is due to instability at the craniovertebral junction, or even in some cases due to regeneration of the foramen magnum. Patients develop cerebellar ptosis when the craniectomy is too large for the specific patient. The herniated tonsils and vermis become adherent to the duroplasty, leading again to obstruction of CSF flow and reappearance of syringomyelia. These patients present with new onset of severe headache located in the frontal and vertex region which is not associated with Valsalva manoeuvres. This pain is due to stretching of an inadequately supported duramater of the posterior fossa, which is innervated by nociceptive fibres, which has contribution from the trigeminal nerve. This pain is different from the one attributed to attachment of nuchal muscles to the duramater of the posterior fossa, which occurs with neck movement. What is the optimal size of the craniectomy to prevent cerebellar ptosis? Samii et al.[56] have advised that the size of the craniectomy should be limited to the width of the spinal canal and not to extend further upward than 2 cm from the rim of the foramen magnum. The importance of performing a small craniectomy is magnified in patients with Chairi malformation, because a significant proportion of these patients have small posterior fossa volume. Apart from an oversized craniectomy, there are other possible causes for scar formation between the dural graft and the cord. Post-operative arachnoid scarring can be caused by insufficient haemostasis, obex plugging with muscle or autologous graft material or a large pseudomeningocoele. Blood and its breakdown products or muscle proteins may cause severe arachnoiditis. This may be provoked by William's technique of leaving the dura open after decompression. Plugging the obex with muscle may also create severe arachnoid scarring, particularly at the foramen of Magendie. Autologous graft may receive pial vascularisation, leading to dense adhesions of such grafts to the cerebellar cortex. Pseudomeningocoele or epidural CSF collection due to insufficient dural closure can create epidural pressure high enough to press the graft against the underlying cord and cerebellar cortex leading to scar formation. Apart from reducing the size of the craniectomy, this post-operative tethering can be prevented by suturing the duroplasty with running sutures to prevent any large CSF collection. A devitalised or artificial graft material should be used rather than autologous graft, such as fascia lata or galea which shows greater tendency for scarring. Other than utilising measures to prevent post-operative tethering, how and in what circumstances should a post-operative tethering at the foramen magnum be treated? Treatment of post-operative tethering at the level of the foramen magnum is possible, but can be extremely dangerous and can lead to life-threatening complications. It is recommended under certain circumstances. Post-operative adhesions of artificial graft material to underlying structures and adhesions related to pseudomeningocoele can be released by sharp dissection. But patients with a history of meningitis or with dense adhesions of autologous grafts are poor candidates for re-operation. Dissection of severe and extensive adhesions anywhere along the spinal canal is dangerous and, even if successful, the overwhelming majority of patients will only have a short life as scarring is likely to reappear. In cases of cerebellar ptosis due to an oversized craniectomy, Holly and Batzdorf[34] have suggested partial suboccipital cranioplasty to alleviate the stretching of the duramater.

Shunting procedures for syringomyelia are associated with potential complications. The tube may become kinked or displaced. It may be blocked internally by arachnoid scar, proteinaceous fluid or tissue debris. Over drainage of CSF may induce hindbrain herniation and in cases with pre-existing Chiari malformation, may lead to cardiorespiratory arrest. CSF leaks and fatal infection may develop. Batzdorf et al.[7] in 1998 reported on a follow-up analysis of 42 patients shunted for syringomyelia, with a 50% recurrence of cyst expansion representing shunt failure. There

were 18 patients with shunt obstruction and three patients with functioning shunts that had deterioration related to tethering of the spinal cord. Long-term follow-up is needed to determine the future adverse effects of a tethered catheter in a mobile spinal cord.

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SECTION

4

Head Injuries

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25 Epidemiology of Head Injury

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INTRODUCTION

Head injury is one of the most important public health problems today. The incidence of head injuries is steadily increasing all over the world and our country has the dubious distinction of having the highest incidence in the world of head injuries due to road traffic accidents per 1,000 vehicles or deaths per 1,000 accidents. The care of head-injured patients forms an important part of neurosurgical management in all countries. The modernisation of industries as well as modes of transport have increased the incidence and the severity of injuries. The management of severe head injury is a major challenge to neurosurgeons and basic neuroscientists, as the consequent mortality and morbidity is depressingly high. There is a need for an extensive multidimensional effort to improve the prognosis of head-injured patients and provide them a better quality of life. To achieve these aims, the epidemiology of head injury needs to be known especially the incidence and its burden on society.[17]

The literature review reflects that the epidemiology has been an oft-neglected area of study with very few epidemiological studies pertaining to head injuries.[4,5,8,10-12,25] The majority of the injuries reported in India are from the cities, which reflects not just their higher incidence in these areas but also the lack of reporting from rural areas. Another facet to such reporting is that most of the reports are based on medicolegal reports and hence may not be indicative of the true incidence. So, it can be appreciated that the majority of head injuries go unreported and the reported incidence may just be the tip of a huge iceberg[3,6,23,26] (Table 1).

Table 1: Incidence of brain injury, selected reports

Authors	*Year*	*Study from*	*Rate per 100,000*
Jennett and MacMillan	1981	UK	270
Klauber et al.	1981	San Diego, USA	294
Selecki et al.	1981	New South Wales, Australia	377
Kraus et al.	1984	San Diego, USA	180
Edna and Cappelen	1984	Norway	200
Fife et al.	1986	Rhode Island, USA	152
Razzak and Luby	1994	Pakistan	185
Wang et al.	1996	China	56

The incidence of head injury is mentioned as per 100,000 persons per year and has a wide range from 56 to 430.[4,5,8,11,12,22,25] The incidence is related to the characteristics of geography, climate, social activity of people, the sense of traffic safety, the basic traffic construction and management. The incidence varies widely in the urban and the rural populations. The incidence also relates to the adequacy of the reporting and is better in the developed countries vis-à-vis the developing countries. The highest incidence has been reported from the study by Field who reported an incidence as high as 430/100,000 persons in 1976.[5] The recent data suggests a decline in incidence per 100,000 persons with Fife et al. 1986[11] reporting the lowest incidence of 152/100,000 persons. The overall incidence in the US is around 200 per 100,000 vehicles per year[10] and nearly 1.6 million people per year suffered from head injury in the US.[7,20,30] In Spain, the incidence of head injury was 91/100,000 persons as reported in 1988. However, a report from China recorded the lowest incidence of 56 per 100,000 persons in 1986.[33]

The extensive studies even from small areas, like San Diego and Wales, have contributed enormously to the existing epidemiological data set for head injuries.[4,5,12] The epidemiological studies may be hospital based or based on traffic police records.[14,21,23] Both have their own advantages as well as pitfalls and formulating data based on both sources may not be practical most of the times.

The incidence of accidents and the deaths related to them have steadily been increasing over the years. Over the last 3–4 years, the incidence has, however, shown a decline in some parts of the country as is reflected in the incidence in Delhi (Table 2). Even in the US, there has been a 50% fall in head injury admissions in 2002 as compared to 1980.

The urbanisation and increased vehicular load has contributed significantly to the tremendous rise in the incidence of head injury in India.[14,23] Nearly 70% of the road traffic accident patients have head injury and amongst the deaths in road accidents, 70% are due to head injury[21] and most of these deaths occur during the first 2–3 days of sustaining injury.

In the New York Times, the fatality rate in India for 10,000 vehicles was reported as 55 in 1987, which was the highest in the world at that time.[19] Currently,

Table 2: Road accidents and fatal accidents in Delhi

Year	*Number of non-fatal accidents*	*Number of deaths*
1991	6,414	1,651
1993	6,815	1,686
1995	7,216	2,003
1997	10,548	2,176
2001	8,113	1,778
2003	6,700	1,645
2005	6,450	1,575

annual road accidents in India are over 600,000 and every minute there is an accident and every 8th minute there is a death. India has the highest accident rate in the world with a 6% reported incidence in 1991.[3] This is despite the fact that the total numbers of vehicles in India are only 1% of the world's total vehicles.

In 1986, Baker et al.[1] reported that over 8% of total deaths in the US were related to injury. Overall the annual numbers of deaths per year in the US are nearly 50,000.[29,31]

The development of roads has not kept pace with the number of vehicles that are plying on the roads. This has been the hallmark of the urbanisation of our country and especially of our metros. The number of accidents is directly proportional to the number of vehicles on the road. At the time of independence, the total vehicles in India were 300,000 and, in 1995, the number had increased to nearly 27,000,000. In Delhi alone, the vehicles have increased tremendously whereas the expansion of roads and the construction of flyovers have lagged behind. The motor vehicle registration in Delhi is the highest in India with nearly 500 registrations per day, and the number of vehicles reached almost 3 million in 1997 as compared to 0.5 million in 1980 (The Times of India, 27th December, 1997). This represents the exponential growth of vehicular load and reflects on the increased accidents and deaths.

Even though the overall incidence of deaths due to vehicular injuries has increased, the number per 1,000 vehicles has decreased to 14.7 in 1990 as compared to 80 in 1970. This incidence, however, is still very high compared to other countries.[21] The figures from Table 3 show that the number of accidents per 1,000 vehicles in India was nearly 2.5 times more compared to the US. However, in comparison, the numbers of deaths were 10 times more. This data is based on a report published in "Indian Auto", December 1991.[26]

Table 3: Indian statistics

Parameters	*1970*	*1980*	*1990*	*2000*
		(Numbers in thousand)		
Number of accidents	114	153	282	340
Number of injured	70	109	224	290
Number of deaths	14	24	54	70
Number of accidents per 1,000 vehicles	80.3	33.8	14.7	14.0
Total number of vehicles	1,401	4,514	19,177	29,180

Table 4: Number of accidents and deaths per 1,000 vehicles in different countries

Country	*Accidents per 1,000 vehicles*	*Deaths per 1,000 vehicles*
Australia	3.1	0.39
Brazil	1.3	0.34
France	8.7	0.40
Japan	9.8	0.20
UK	14.0	0.52
USA	12.2	0.25
India	31.8	2.5

TYPE OF INJURY AND DISABILITY

The majority (75–80%) of head injuries are minor or moderate[4,6,10] and, fortunately, only a minority are severe injuries. The incidence of severe head injury increases with age and about 5–10% of total injuries are fatal (Tables 3 and 4). In 1980, Besse[2] reported that 90% of head injuries in children were minor. There is a marked variation in the relative incidence of the types of head injury and this is primarily due to the protocols and criteria of hospital admission at various centres. This occurs especially in cases of mild injuries and thus the hospital data can be fallacious due to this. This is reflected by the following data: National Hospital Discharged Survey (NHDS) of the US in 1985 showed 50% of all head-injured patients discharged from the hospital had concussion. The data from the US reported an overall mortality of 20–30 per 100,000 persons. Several studies from the US (e.g. San Diego, Minnesota and Chicago) reported that 63–86% of head injuries were mild.[10,11] An incidence of 30 deaths per 100,000 persons has been reported. In India, over 60,000 people die due to road accidents every year.

Head injury has become a major health hazard in India and presently most of the cities in India report a rising trend.[14,19,21,23,26] An enormous loss of productivity occurs due to the mortality and morbidity associated with such injuries, and one of the major challenges that confronts a healthy society is its prevention. Kalyanaraman (1971)[9] reported head injury death to be the fourth most common cause of death in Madras General Hospital, next to malignancies, tuberculosis and myocardial infarction. Sano[28] reported head injury to be the seventh most common cause of death in Japan.

It was estimated by Lewin[13] in England and Wales that every year 1,200 new head-injured patients were added to the group of moderately disabled who could not return to their jobs. These figures are difficult to estimate in the developing countries due to various factors but the incidence is likely to be much higher. In the US, Walker[32] estimated that one person in every 200 would require medical care for head injury each year, which would result in 1% of the working population being disabled on any given day. It has increasingly been realised

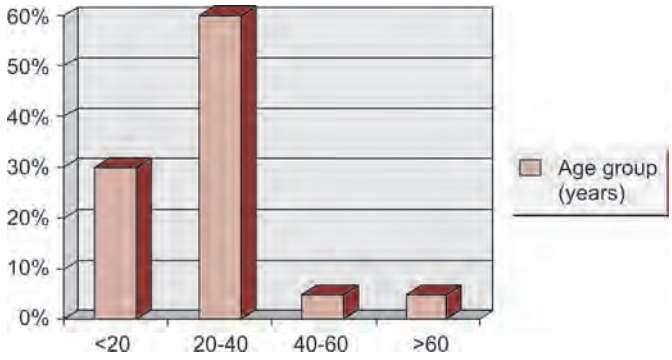

Fig. 1: Group affected by head injuries in terms of years

that minor injuries may result in functional disabilities way out of proportion to the severity of the trauma.

AETIOLOGY OF HEAD INJURY AND AGE DISTRIBUTION

The most common group affected by head injuries are the young people between 20 years and 40 years (Fig. 1) and the incidence is lowest at extremes of age, i.e. below 5 years and above 60 years.[10] From the total percentage of patients with head injury, this age group forms about 60–70% by itself. This may have multifactorial linkage and is primarily related to the social, cultural and demographic practises of this age group. In India, 40% of the total population belongs to the paediatric age group and around 25–27% of all head-injured patients are children under 16 years of age.[15,27] Studies from other countries, like the USA, also show a peak incidence of head injury in the third decade and the head injury rate ranged 300–600 per 100,000 persons.[10]

The most common cause of head injury is road accidents contributing to about 60% of injuries.[10-14,21,26] Injuries due to falls constitute the most frequent cause in children and they contribute to nearly 25–30% of total injuries.[24] Birth trauma is the most frequent cause in the neonatal age group.[27] There is a considerable variation in the aetiology of head injury in the paediatric age group.[24,27] Among the children, most injuries range 3–10 years of age.[24] A frequent cause is bicycle injury which occurs in older children and contributes around 10% of all head injuries in children.[24]

There are certain types of head injuries peculiar to the different regions of the country like the fall of a coconut on the head in Kerala and the Kolhu injury during the sugarcane crushing season in Punjab. Gunshots as a cause of injury are also prevalent in some parts of India and so are the injuries due to *Lathi* and *Gandasa*.

GENDER AND HEAD INJURY

The number of accidents is directly proportional to the type and number of driving and outdoor activities. Understandably so, the incidence is more in males as compared to females and most of the studies quote an incidence of 3:2 in favour of males.[10,24] This incidence reverses in infants and elderly patients above 65 years of age and this is also the age group where females are least cared for in comparison. The peak incidence for males is in the age group of 15–25 years with an incidence reaching 600–700/100,000 persons.[10] In comparison to the females, even though this is the most frequent affected age group, the incidence is about 40% (500–700 in males vs 150–250 in females/100,000 persons). In the paediatric age group, the incidence is again higher in males overall with a ratio of 1:1.6–1.9 in favour of boys.[24]

REASONS FOR ROAD ACCIDENTS IN INDIA

A variety of causes contribute to road accidents and the common causes in the Indian set up are presented in Table 5. The recent trend has, however, shown a decline in the relative incidence of accidents, especially in the developed countries. This has largely been due to thorough understanding of epidemiology of head injuries related to road accidents. Improved highway engineering leading to well-designed roads and improvement in safety measures in motor vehicles has led to such a decline. Public awareness of prevention of accidents has also played an important role and, amongst them, the use of helmets, seat belts, knowledge of traffic rules and understanding the long-term implications of severe accidents have been the most contributory. India has lagged behind primarily due to the poor understanding and implication of all such factors. The reluctance on the part of the people and the authorities has also contributed; however, the recent declining trends have been heartening and one does indeed see a silver lining.[3,19,23]

Only 1% of the total 43,000 km of National Highways in India meets international standards. The safest highways in the world are considered to be in the US, and there is an incidence of 1 death per 160 million kilometres driven in the US. Whereas, in India, comparably there

Table 5: Reasons for increasing number of accidents in India

Road related problems
• Poor road design
• Inadequate lighting
• Improper maintenance
• Lack of adequate road breadth and area
• Lack of bilane system
Vehicle related problems
• Poor vehicular standard
• Improper brake system
• Lack of seat belt
• Continued usage of old vehicles with inadequate safety devices
• Running of other non-motorised vehicles like bicycle, cycle-rickshaw, bullock cart, camel cart, etc. coupled with stray animals on roads
Driving related problems
• Inadequate training
• Easy availability of driving license
• Flexible and oft-broken traffic rules
• Poor visual acuity of drivers
• Consumption of drugs and alcohol

are 6 deaths per every 1 million kilometres driven. Thus, the number of deaths in India is about 960 times more frequent than in the US. The primary factors responsible for such an incidence are poor road design, improper maintenance, poorly maintained vehicles with no safety facilities, apathetic attitude of authorities and, above all, poorly trained and reckless drivers. The procurement of driving license in India is not very difficult even for the untrained drivers and these add on to the onus of vehicular accidents. Moreover, poor vision, old age and intoxicated drivers also cause vehicular accidents in India. A multidirectional approach, considering all the above factors, can reduce the number of accidents in India.

FINANCIAL IMPLICATION OF HEAD INJURY

Most people sustaining head injuries are young people in the productive part of their life and the loss of life and rehabilitation of these victims costs a lot of money and incurs a significant economic burden to the country. One of the WHO reports mentioned that out of 3.5 million injuries related deaths all over the world in a year, 700,000 were due to road accidents and nearly 1.5 million injured people required medical care. In 1993, Nakajima[18,21] reported 5,000 billion US dollars being the cost of medical bills and rehabilitation costs.

The loss of life or the associated morbidity not only reflects on the patient but also on the concerned family or rather society as a whole. They contribute to a significant financial burden as well. Ramamurthi[21] stated that a 350 crore rupees financial loss per year occurred due to accidents a few years back and the present estimate is nearly double that of the quoted figure.

Currently, the number of deaths due to road accidents alone in India is over 60,000. There are many other causes of head injuries apart from road accidents and a rough figure of around 100,000 is mentioned presently. A significant number of cases still go unreported and if included would inflate this figure even further.

CONCLUSION

A thorough understanding of epidemiology of head injury is central to their prevention. There has been a progressive increase in the total incidence of deaths related to head injuries over the years and across the globe. The relative incidence has, however, shown a decline in the recent years. India has been a major contributor to the overall global incidence of road traffic accidents as well as the related deaths.[16]

The majority of head injuries occur in the 2–4 decade and children constitute 25–30% of all head injury victims. Mortality and morbidity due to head injury are very high and associated with a significant financial burden all over the world. Prevention of head injury is a highly desirable aim and this can be achieved by improving road conditions, educating the public and conforming to safety measures.

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26 Biomechanics of Head Injury

Deepak Agrawal, Ashok Kumar Mahapatra

INTRODUCTION

Head injuries are very common and, apart from treatment, a very important area to which attention must be given is prevention. Prevention has three stages: (i) to stop the accident from occurring; (ii) to reduce the injuries on impact and (iii) to minimise the risk of subsequent complications. Understanding the biomechanics can go a long way in planning better prevention strategies for all the above three stages. In this chapter, we will review the current understanding of the biomechanics of head injuries and the application of this knowledge towards decreasing the incidence of head injuries.

TYPES OF MECHANICAL FORCES

Mechanical forces leading to head injury can be categorised as static or dynamic[9] (Fig. 1).

Dynamic Loading

Dynamic loading is more commonly seen and is defined as input force applied to the cranium over a very short period of time (usually less than 50 ms). Dynamic loading may further be subclassified as "impact loading" and "impulsive loading".

Impact Loading

Impact loading, which is the more common type, is a combination of contact and inertial forces. A sudden impact causes the head to accelerate, resulting in inertial forces coming into play, increasing the severity of injury. The inertial effects may be minimised if the head is immobilised at the time of the impact. Head rests in cars can play an important role in minimising the inertial forces during an impact in car accidents.

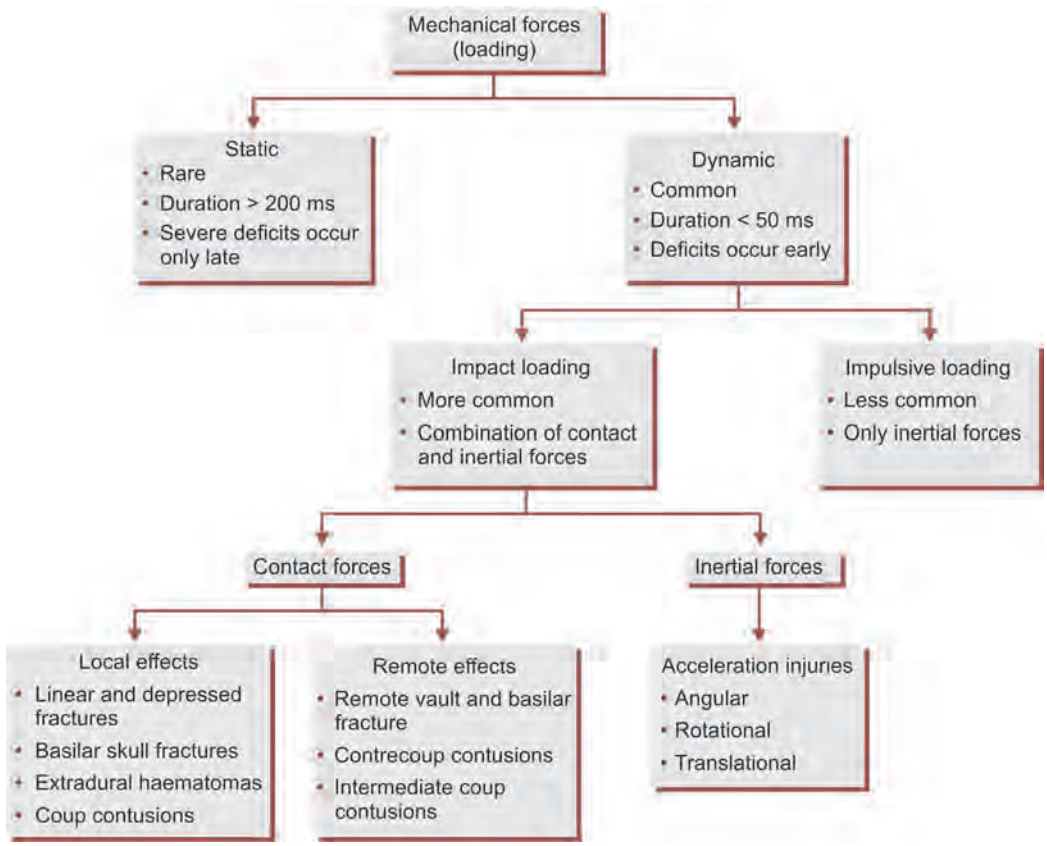

Fig. 1: Types of mechanical forces involved in head injury

Contact injuries: Contact injuries result from forces that occur during direct impact.[11,12] The impact results in complex mechanical events that occur both near and distant from the point of contact (contact phenomenon). Contact injuries typically cause focal injuries, but they do not cause diffuse brain injury. Neural brain damage by this mechanism is typically superficial and localised to the immediate vicinity of the skull injury. Since most impacts set the head into motion, these injuries are associated with acceleration injuries which may result in remote effects.

Local effects of contact injuries: These include depressed fractures, linear fractures, basilar skull fractures, extradural haematomas and coup contusions.[13] Depressed skull fractures are a result of a concentrated force immediately beneath the impacting object. The surface area of the hitting object should be small enough to cause concentration of stress and strain. The momentum of the object is borne by the localised area of the skull and not the remaining skull as in linear fractures. When local skull bending at the site of impact exceeds the strain limit for the bone, it results in the bone bending inwards like a cone. The apex of the bone which is formed by the inner table breaks first and results in a linear fracture.[19] The fracture tends to follow the path of least resistance and is complete when the energy in the impact process is dissipated completely.[11] In children, sutural diastasis may occur. Direct impact to the face, mastoid or occiput, therefore, results in basilar skull fractures.[14] Local bending of bone also results in tearing of dural vessels, leading to epidural haematomas. When the in bent skull recoils back to its position, negative pressure is created which results in tensile strain on the underlying pial vessels and brain resulting in a focal contusion[13] (Table 1).

Remote effects of contact injuries: These are due to skull distortion and stress waves. If the impacting object is broad and the impact occurs over a thick portion of the skull, a remotely placed thinner portion of the skull, with its decreased tensile strength, may fracture. Stress waves may also account for the remote contact effects such as basilar fractures, potential haemorrhages and intracerebral haematomas.[1,13]

Table 1: Clinical classification of head injuries[1]

Skull fractures	*Focal brain injuries*	*Diffuse brain injuries*
Vault	Contusion	Concussion
Linear	Coup	Mild
Depressed	Contrecoup	Classic
	Intermediate	
Basilar injury	*Haemorrhagic*	*Diffuse axonal*
	Extradural	
	Subdural	
	Intracerebral	
	Petechial	
		Other

Inertial injuries: These are commonly called acceleration and deceleration injuries. Acceleration injury of the head causes either a functional or a structural failure of neural and vascular structures, where the severity and extent of disruption are linked to the magnitude, rate, duration and type of inertial loading.[1,9]

Three types of acceleration may occur in inertial injuries:

1. Translational acceleration occurs when the brain moves in a straight line at its centre of gravity, i.e. pineal gland.
2. Rotational acceleration occurs when brain tissue moves around its static centre of gravity.
3. Angular acceleration occurs when there is movement of the centre of gravity in an angular manner. Angular acceleration is a combination of both translational and rotational acceleration.

Angular acceleration is most commonly encountered clinically and the centre of angulation is usually the mid-cervical and lower-cervical regions. The higher the centre of angulation, the greater is the rotational component. As the centre of gravity shifts inferiorly in the cervical spine, the translational component increases.

Three zones of the brain (e.g. surface, intermediate and deep) can be affected differentially as the duration of acceleration increases. At short acceleration duration, the brain experiences very little strain resulting in only surface zone injury. However, at longer acceleration durations, the inertial effects increase and the resulting strains penetrate deeper into the brain tissue. Hence, structural damage to superficial vascular tissue (bridging veins and pial vessels) occurs in short acceleration duration with a large acceleration magnitude, whereas deeper brain tissue injury occurs in longer duration acceleration with lesser acceleration magnitude.[13]

Impulsive Loading

Impulsive loading occurs when the head is put into motion or when the motion of a moving head is suddenly arrested without the head itself being struck or impacted. As there is no direct impact on the head, no contact forces are involved and injury is caused purely by inertial forces. A blow to the thorax or face can set the head into violent motion without direct impact of the skull. Other examples include fall from a height or being thrown off a moving vehicle.

Static Loading

Static loading is uncommon and is defined as input force applied to the load relatively slowly (over 200 ms). Typical examples of static loading are injuries from slowly moving vehicles or earthquakes that trap the head against rigid structures resulting in slow crushing of the skull. Static loading causes multiple comminuted fractures of the vault or base of skull. Severe neurological deficits, although uncommon, may be present if the brain is also distorted and compressed directly due to static loading. Duhaime et al.[8] reported a series of seven

children with head injuries caused due to static loading. Patient ages ranged from 15 months to 6 years. In four cases, the child's head was run over by a motor vehicle backing up in a driveway or parking lot. In the other three patients, the static loading occurred when the child climbed or pulled on a heavy object, which then fell over with the child and landed on the child's head. One child with cervicomedullary disruption died shortly after his arrival at the hospital. The others showed varying degrees of soft tissue injury to the face and scalp, with Glasgow Coma Scale scores ranging from 7 to 15. Computed tomograms (CTs) and magnetic resonance images (MRIs) showed multiple and often extensive comminuted calvarial fractures, as well as subarachnoid and parenchymal haemorrhages. All patients had basilar cranial fractures. There was one cervical spine injury but no major vascular injuries. One child had pituitary transection, four had cranial nerve palsies and another developed a delayed cerebrospinal fluid rhinorrhoea 18 months after injury. All children made good cognitive recoveries, with some having relatively mild fixed focal deficits.

MECHANISM OF SPECIFIC INJURIES

Concussion and Sports Injuries

Concussion, or mild traumatic brain injury (TBI), occurs in many activities, mostly as a result of the head being accelerated.[5] Angular or rotational head motions cause transient electrophysiologic dysfunction of the reticular activating system in the upper midbrain, caused by rotation of the cerebral hemispheres on a relatively fixed brainstem. In this type of injury, most of the strain is insufficient to cause structural damage, but results in biochemical and ultrastructural changes such as mitochondrial ATP depletion.[13] However, the physiological basis of amnesia remains unclear. Recent sophisticated laboratory research has better elucidated injury biomechanics associated with concussion in professional football players. This data has led to changes in helmet design and new helmet technology, which appears to have beneficial effects in reducing the incidence of cerebral concussion in high school football players. In a prospective study on 2,141 athletes, Collin et al.[6] showed that improved helmet design resulted in a 31% decreased relative risk and 2.3% decreased absolute risk for sustaining a concussion, as compared to standard helmets.[6]

Contrecoup Contusions

The predominant mechanism for contrecoup contusions is head acceleration (inertial effects). The term is a misnomer, as actual impact is not necessary.[7,16] In situations where the head undergoes impulsive loading, contrecoup lesions occur solely due to acceleration effects.[11,12]

Subdural Haematoma

Acute subdural haematoma is due to disruption of surface vessels, usually bridging veins. Disruption of bridging veins mostly occurs from inertial force and not from contact force. The acceleration is of short duration with a high strain ratio loading. Hence, acute subdural haematomas are usually associated with diffuse axonal injury (DAI) and cerebral contusion.[9]

Diffuse Axonal Injury

Diffuse axonal injury is considered as an extreme form of concussional injury and may be caused by long duration rotational or angular acceleration.[2,3,10] The extent of axonal damage depends upon the magnitude, duration and rate of angular acceleration. Neuronal damage occurs in a centripetal fashion, from the cortex inwards to the brainstem, as the force of injury increases. The direction of acceleration is important in the production of DAI. Pure sagittal acceleration may result in a milder DAI, whereas angular acceleration in the coronal plane is associated with a higher incidence of severe DAI.

Shaken Baby Syndrome

Shaken baby syndrome (SBS) is characterised by a constellation of clinical findings, including subdural bleeds, retinal haemorrhages and fractures of the extremities and ribs, with no external evidence of cranial trauma. Interestingly, attempts to reproduce this injury using biomechanical models have not yet succeeded.[15,18] Bandak[4] carried out injury biomechanics analysis of the reported SBS levels of rotational velocity and acceleration of the head for their injury effects on the infant head-neck. Resulting forces were compared with experimental data on the structural failure limits of the cervical spine in several animal models as well as human neonate cadaver models. Their study clearly showed that cervical cord and brainstem damage would occur prior to and, more importantly, at lower levels of rotational velocity and acceleration then purported in SBS. The very basis of SBS therefore remains controversial.

FUTURE RESEARCH

Presently, the controlled cortical impact model is used to study focal TBI. Although the impact variables can be well defined, little is known about the biomechanical trauma as delivered to different brain regions as well as the response of neurons to mechanical trauma. This knowledge, however, could be valuable for interpretation of experiments (e.g. immunohistochemistry, etc.), especially regarding the comparison of the regional biomechanical severity level to the regional magnitude of the trauma sequel under investigation. Finite element (FE) analysis,[20] using high resolution T2-weighted MRI images of rat brain, to simulate displacement, mean stress and shear stress of brain during impact has recently been used as a tool for biomechanical simulation and holds considerable promise, especially if complemented with the use of MR elastography.

Also, at the cellular level, plasma membrane disruption may be the earliest cellular outcome from a mechanical trauma. The increase in membrane permeability due to such disruptions may therefore play an important role in the initiation of deleterious cascades following brain injury.[17] Researchers have used novel devices capable of applying stress at high rates to neuronal cells cultured on a microelectrode array to simulate TBI. Spontaneous electrophysiological activity of injured cultures can then be monitored to get an insight into the neuronal effects of TBI.[17] The outcome from such ongoing research may help in our knowledge of the pathophysiology and biomechanics of head injury leading to improvement in preventive measures.

CONCLUSION

The mechanical forces causing head injury can be classified into dynamic and static in nature. Dynamic loading is further subclassified into impact and impulsive loading. Direct injuries are a type of impact loading which may result in linear fractures, extradural haematomas and coup contusions. Both impact and impulsive loading can lead to acceleration injuries which can be angular, translational and rotational. Cerebral concussion, contrecoup contusions, DAI and subdural haematoma are typical examples of acceleration injuries.

Although much insight has been gained into the biomechaincs of head injury, a lot remains to be done. FE analysis and neuron tissue culture are the thrust areas of ongoing research in biomechanics of head injury.

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27 Pathology

Sankar SK, Anita Mahadevan

INTRODUCTION

Socio-technological and economic progress in the developed and developing countries have brought about a significant change in the health related problems in their communities. Due to massive international and national commitment there has been a significant decline in infectious and communicable diseases. According to recent reports by The World Bank, WHO and Harvard School of Public Health, morbidity and mortality related to injuries has been recognised as the third major public health problem across the globe in the new millennium.[131,194] Traumatic brain injury (TBI) is a major condition affecting all aspects of human life, contributing to mortality, morbidity, disability and the resultant socio-economic impact on the family and society. The epidemiology of TBIs provides insight into the magnitude of the problem, population-ethnic characteristics, risk factors, mode, pattern and nature of injuries, the survival and the outcome, and the long term sequelae.[78,76,136,150] This type of information is crucial in designing, implementing and evaluating intervention programmes in terms of feasibility, affordability, sustainability and cost effectiveness, and evolve policy strategies beneficial to both the citizen and society.[75,77] A comprehensive epidemiological study of head injury from a South Indian city, Bangalore, indicated that the incidence and mortality rates were 160 and 20 per 100,000 population, respectively per year.[26,78] The extent of neurotrauma registration in Indian hospitals constituted approximately 25% of all registrations at casualty emergency services. Severe, moderate and mild injuries were seen in 69%, 15% and 16% of patients, respectively and the case fatality rate is 9.6%.[26]

It is estimated that, in India, of the 1,440,000 TBIs per year, nearly 180,000 succumb. Road traffic accidents and falls are the major cause of traumatic injuries in 62% and 22% respectively, followed by violence in 10% of cases. People in their prime and in the productive age group of 20–30 years are affected maximally, men being at greater risk.[26,75] Alcohol has been a major risk factor for traffic injuries, falls, violence, work related accidents and others (Table 1). Alcohol consumption also poses a significant influence on the evolution of the pathology, diagnosis and management as well. A point of major concern is that, in the majority of developing countries, the vulnerable road users are the pedestrians, motorised two wheeler users, and bicyclists, unlike car occupants in the Western countries. Among falls that cause brain injuries, the large majority (70%) are domestic falls, followed by others in schools, agricultural land and construction sites. Emergence of communal and political violence has become a matter of great concern for policy makers, and has resulted in bizarre forms of injury complicating the mechanics of brain injury.

Table 1: Factors modulating primary brain injury

a.	Precise type, location, extent (size) of injury		
b.	Type	→	Moving vehicle
		→	Missile—gun shot, stone throw
		→	Fall or assault (blunt/sharp/size of impact)
	Blunt Injury	→	Wide damage, long-term psychological impairment, poor recovery
c.	Biological factors in victim	–	Pre-existing disease
		–	Psychological status
		–	Nutritional status prior to injury
		–	Consumption of sedative, alcohol, psychoactive drugs

In India, unlike the Western countries, neurotrauma due to violence is inflicted by piercing and blunt objects than by firearms, constituting 2–23% of TBI across studies. Neurotrauma due to sports and recreational activities is found to vary from 4–10% and due to fall or hit by objects about 4% (cricket ball, cement, brick, ceiling fan, heavy utensils, coconut, etc.). We have no realistic estimate of TBI related to natural disasters, though it is a common feature year after year. In India, it is estimated that nearly 1% of the population is disabled and nearly 30–40% of these disabilities are due to TBI. Only 10% of the disabled receive adequate rehabilitation. Till date the study of head injury was confined to neurosurgeons, orthopaedic surgeons and forensic pathologists to meet the treatment requirement and medico legal aspects related to it. The Indian literature had a major limitation in that the problem of head injuries was studied in individual centres on issues of specific interest to the researchers.[13,15,96,154,155,158,177] Information is available only on motor vehicle injuries, thus it is a gross underestimate of the problem. The cultural and socio-economic aspects of society and genetic polymorphism also influence the biology of head

injury. It is essential to have an understanding of the evolution of pathology and pathophysiology, for timely and effective management of cases of TBI.

CAUSES OF BRAIN DAMAGE—TRAUMATIC BRAIN INJURY

The different causes of TBI are listed in Table 2.

Focal Brain Injury

Brain damage in non-missile head injury is classified as "focal" or "diffuse". The focal damage includes contusion and lacerations on the surface of the brain and intracranial haematoma and raised ICP as a secondary phenomenon. Focal injuries result from localised damage, found in nearly 58% of patients with severe head injuries and 66% of deaths associated with head injury.[71]

Contusions

In 1930, Spatz[171] characterised contusion and described the gross and microscopic features. Lindenberg and Freytag[105] carefully delineated the various topographic patterns and tissue responses in blunt trauma of the head and defined contusion as a bruise of the surface of the brain, which is covered by intact dura. Contusions are caused by blunt contact of the brain with various bony surfaces of the skull. According to Graham,[67] the pia arachnoid is intact over a contusion, but is torn in a laceration.

Table 2: Causes of brain damage—traumatic brain injury

A. Focal lesions:
- Fracture of the skull
- Scalp laceration
- Surface contusions/Lacerations of the brain
- Intracranial haemorrhage
  - Extradural
  - Subdural
  - Subarachnoid
  - Intracerebral
- Damage secondary to raised intracranial pressure (ICP).
- Damage to vessels due to trauma → dissection → thrombosis → large territory infarction

B. Diffuse lesions:
- Diffuse axonal injury (DAI) (secondary to stretching/rupture of axons)
- Diffuse brain swelling (Secondary to vasomotor paralysis → vasodilatation → vasogenic oedema)
- Diffuse small vessel injury—(Secondary to acceleration/deceleration → rupture of small vessels)

C. Sequelae of head injury:

DAI + hypoxic brain damage → Severe disability, vegetative state.

(Traumatic injury to the scalp and skull are not dealt with in this chapter)

Fig. 1: Severe contusion of the orbital surface of the frontal lobe more on one side, indicating angular impact against the anterior cranial fossa

Editors' comment: The pathological clinical and prognostic significance of cerebral contusion was a subject of a comprehensive study reported by Kristiansen and Tandon in 1960.[104]

Recent contusions are haemorrhagic (Figs 1 and 2) and, when superficial, are characteristically restricted to the crests of the gyri, but often extend into the sulci and the underlying white matter (Figs 3A and B). When located deep in the Sylvian fissure, they are visible on slicing the brain (Fig. 4). They develop rapidly by rupture of pial vessels soon after impact. With time, they are seen as shrunken brownish areas on the crest of gyri.

Healed contusions are commonly found in chronic epileptics, with repeated history of falls and are of medico legal importance. Unlike in all other age groups, the contusion in infancy (battered baby syndrome) results in tears in the sub-cortical white matter and inner layers of the cortex, particularly in the frontal and temporal lobes and the cortex above and below the Sylvian fissures. The most common sites of contusion in closed head injuries are the under surface, and polar regions of the frontal

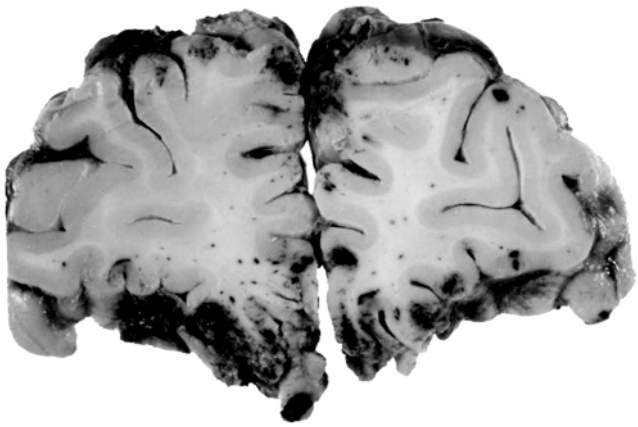
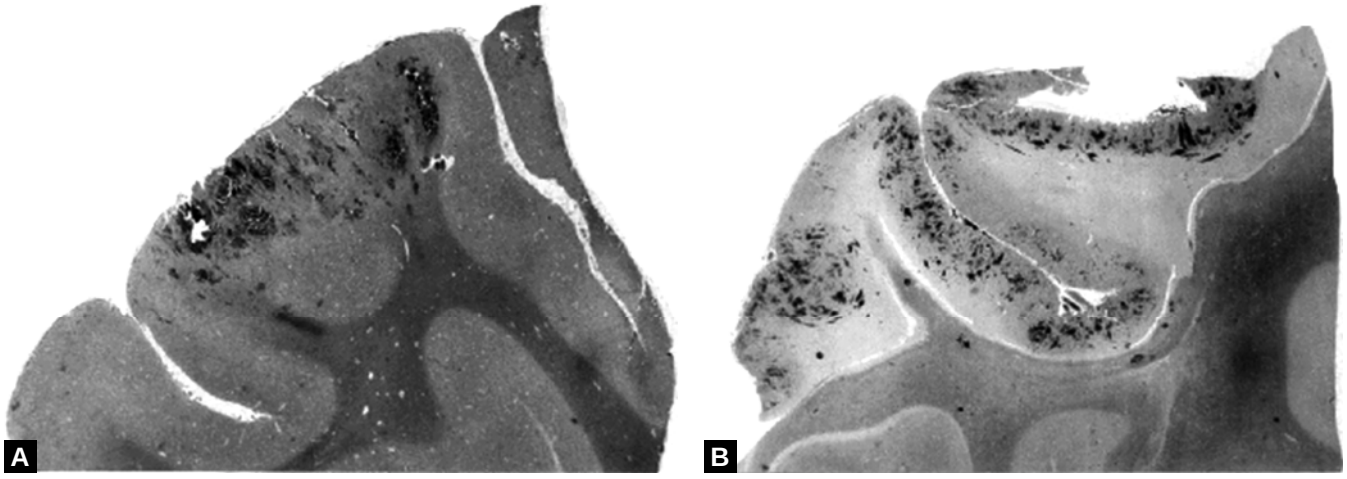


Fig. 2: Contusions along the orbital surface of the frontal lobe and adjacent white matter and also on the surface of the superior frontal gyrus and along the medial surface — gliding contusion



Figs 3A and B: (A) Recent contusion, haemorrhagic and confined to the crest of a gyrus. (B) Contusion involving the crest of gyri and extending into the depth of sulci, usually visible after 48 hours

and temporal lobes followed by their lateral surfaces. Contusion of the parietal and occipital lobes and cerebellum are rare and usually associated with local fracture. The surrounding brain shows focal reactionary oedema. Various forms of contusions provide clues about their evolution:

Fracture contusion: It is related to the site of fracture, common in the frontal lobe.

Herniation contusion: Parahippocampal gyrus and cerebellar tonsils impacting against the tentorium and foramen magnum, respectively, follow blunt impact on the vortex.

Gliding contusions: Adjacent to the superior sagittal sinus, (Parasagittal contusions) haemorrhages in the superficial cortex and white matter, caused by anteroposterior gliding movement of the brain with respect to the dura and falx cerebri. The parasagittal bridging veins entering the sinus may be torn with haemorrhage. They are usually bilateral and asymmetric, and associated with diffuse brain damage and DAI.

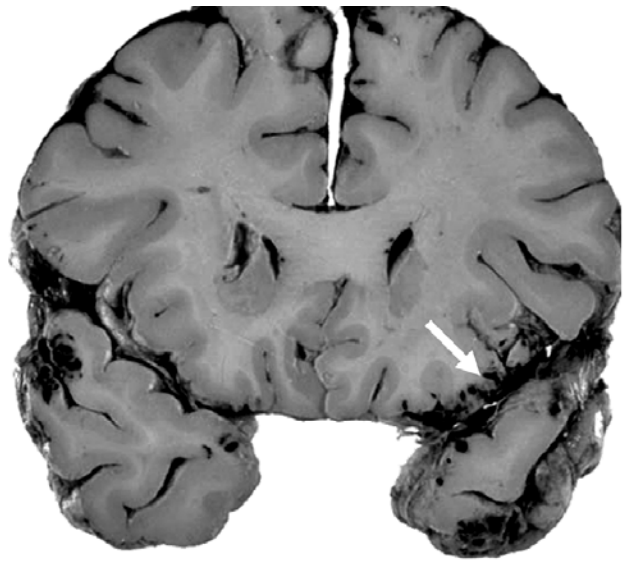


Fig. 4: Contusions along the Sylvian fissure due to impact against the sphenoid wing and temporal poles

Coup contusion: It occurs at the site of impact in the absence of fracture. The extent depends on the size of contact between the skull and the striking object and the accelerating force transmitted to the underlying brain.

Contre coup contusion: It occurs in the brain away from the site of impact, usually in a diagonally opposite anatomical area, caused by deceleration of the moving head against bone. Because of the complex nature of head motion in any accident and the anatomical irregularities of the inner surface of the skull, contre coup contusions may not be exactly opposite the point of impact. Hence, a contre coup contusion can be defined as a contusion not below the site of impact, irrespective of its exact location. Contusions are more severe in patients who have fracture of the skull in comparison to those who do not; contusions are more severe in patients who do not experience a lucid interval than those who do; contusions are less severe in patients with DAI than those without.[4,110]

Contusion index: For an objective evaluation of the extent of contusion and for clinical correlation, Adams et al. developed a quantitative approach. The index is the product of the extent and depth of contusional damage.[4] The extent includes both haemorrhagic and non-haemorrhagic necrosis, evident only on histology. The clinical usefulness of this contusion index is doubtful.[122]

Intracranial Haemorrhage

It is a common complication of severe forms of blunt head injury where the patient deteriorates after a period of lucid interval.

Editors' note: The classical lucid interval is not a consistent feature even in extradural haematomas (EDHs) and is an exception than a rule in acute subdural and intracerebral haematomas.

It has been noted in 55% of cases in the Glasgow database. The majority of patients who develop a haematoma have a skull fracture. Though, clinically, the haematoma may not be apparent until it causes mass effect and raised ICP, imaging techniques can detect them before they become apparent clinically. In traumatic intracranial haemorrhage there may be bleeding into the extradural, subdural or subarachnoid space, into the brain parenchyma and into the ventricles.

Extradural haematoma: EDH occurs in approximately 2% of all forms of head injury[91] and in 5–15% of fatal head injuries.[51,115] In the majority, there is associated skull fracture and usually follow a fall or road accident, but, in children, it can occur in the absence of a fracture. The haemorrhages originate from the ruptured meningeal vessels and enlarge by stripping the endosteum and dura from the skull and indenting the brain. Nearly 50% of EDHs occur in the region of the squamous part of the temporal bone, which is thin and easily fractured by blunt impact, tearing the middle meningeal artery.[126] In 20–80% of cases, it can occur in the frontal and parietal areas. Posterior fossa EDH can also occur and follows injury to the middle meningeal vein, diploic vein, dural sinuses or tear of the carotid artery before it enters the intracranial dura along the base of the skull.[31] Contrary to the generally held view, EDH is usually associated with contusions, influencing the clinical course.[177]

The size of the EDH can increase by up to 50% till the end of the 2nd week following the injury, after which it starts shrinking by organisation and may be resolved completely by 6–8 weeks after injury. However, most patients with significant EDH deteriorate rapidly and require early surgical intervention.

Following fire accidents at home/industrial zones or arson, fissure fracture of the skull and extradural heat haematomas may occur. The haematomas have a pink spongy appearance like "cooked meat", indicative of thermal injury, unlike the usual dark colour. For it to develop the victim needs to be alive and the EDH follows the pattern of external charring. A combination of EDH and fracture of the skull in fire victims may pose difficulty in interpretation, with medico legal implications. EDH can occur without fracture, following contact related skull deformation alone and vessel tear.

Subdural haematoma: Subdural haematoma (SDH) is caused by rupture of bridging veins, connecting the superior surface of the brain to the sagittal sinus. These types of lesions are common in adults and the elderly following even trivial trauma or whiplash movement of the head. Some SDHs are of arterial origin. It may occur in combination with intracerebral haemorrhage, and the two can communicate with each other, when it is referred to as "burst lobe".[177] Unlike EDH, SDH tends to spread diffusely to cover the entire hemisphere. In young adults they are common following falls, assaults and vehicular accidents. Occasionally, interhemispheric SDH may occur after minor injury in association with anticogulant therapy. Acute SDHs are found in approximately 10–30% of all patients with head injuries.[8,151,156,176,179]

Fig. 5: Subdural haematoma encapsulated by a membrane. Note the brownish discoloration of the underlying leptomeninges due to haemolysis. The brain is irregularly compressed (2 weeks after injury)

The SDH is defined as being acute, subacute or chronic based on histological features, but the classification is found to be unsatisfactory. Subdural haematoma is considered acute by the clinicians when composed of clotted blood and subacute when it is symptomatic within 3 days of injury and is usually composed of clotted blood. It is classified as chronic when it is already encapsulated which takes more than 3 weeks after injury. Most chronic SDH consist of fluid blood. On gross examination in case of a chronic SDH, a subdural membrane forms around 3 weeks after the injury (Fig. 5). It must be emphasised that acute and chronic SDH are distinct entities on the basis of their aetiopathogenesis, clinical picture and treatment (see individual chapters). The SDH causes compression of the brain to leave a smooth indentation, more often in old age, due to slow progression (Fig. 6). During the acute phase it may stain the

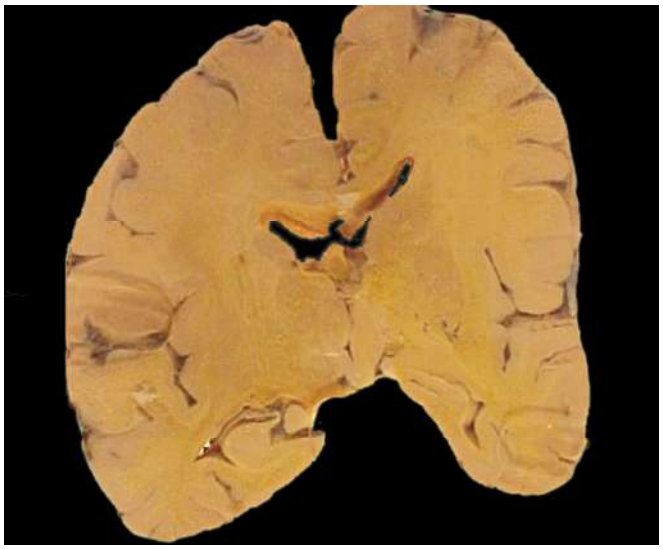


Fig. 6: Extradural haematoma causing flattening of the underlying brain. Note the absence of damage to the brain

adjacent arachnoid by haemolysis and release of haeme pigments. Most SDHs resolve spontaneously and do not progress to chronic SDH. Occasionally, an SDH may get encapsulated between the dura externally and subdural membrane internally and grow slowly due to repeated leak from the newly formed vessels during the healing phase, following vigorous movement of the head or trivial trauma. Following absorption, sometimes, a thin translucent membrane may be left adherent to the leptomeninges over a wide area, causing impedance to cerebrospinal fluid (CSF) flow. Histologically the subdural membrane resembles a flat membrane of granulation tissue with haemosiderin containing histiocytes or extra cellular clumps of haemosiderin. In nearly 15–20% of cases a variable eosinophilic leukocyte infiltration may be seen admixed with other chronic inflammatory cells and mast cells. The relationship of the eosinophilic reaction, either to evolution or chronicity, is not clear.

In aged individuals with cerebral atrophy, the haematoma expands slowly, and the period of spatial compensation may take so long that the cerebral hemispheres may be markedly distorted, but without significant increase in ICP. Death is usually due to secondary events, and not the initial impact, that results in brainstem distortion and compression.

Occasionally, clear or xanthochromic fluid may accumulate in the subarachnoid space resulting in hygroma and compression of the underlying brain (Fig. 7). This is considered to be due to a valve like arachnoid tear causing unidirectional flow of CSF into the subdural space that mixes with liquefied blood.[166] These subdural hygromas are reported in 7–12% of all intracranial mass lesions.[8,172] Kudesia et al.[105] reported subdural haematomas in 25.8% of cases. In this series, there was associated cerebral contusions in 94% of cases and skull fracture in 53%. Nearly 25% of cases with SDH had associated DAI. Adams et al.[8] reported SDH in 11% of cases with DAI.

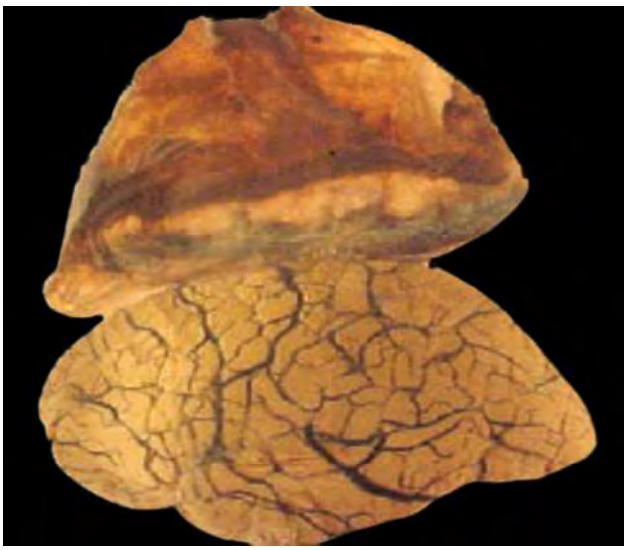


Fig. 7: Subdural membrane, covering the brain with almost total resorption of the blood clot (10 weeks after injury). The anterior part of the brain is compressed on both sides

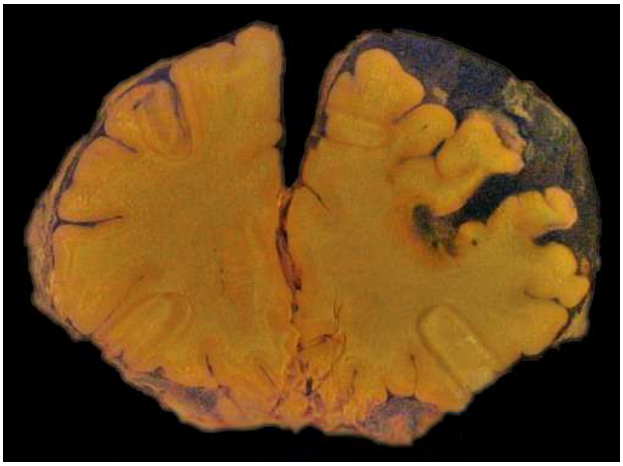


Fig. 8: Severe degree of subarachnoid haemorrhage mimicking subdural haematoma. Note the extension of haemorrhage into the sulcus indicating its plane in the subarachnoid space

Some amount of subarachnoid haemorrhage (SAH) is present almost invariably in any acute head injury in which there are cerebral contusions (Fig. 8). Intracerebral haematomas are present in 15–20% of all patients of traumatic injury in the Glasgow database.

Intracerebral haemorrhages: They are often multiple and most frequent in the white matter of the frontal and temporal lobes and, occasionally, the cerebellum. Intracerebral haematomas need to be distinguished from tissue tear haemorrhages noted in the severe form of DAI.[66] The latter are usually multiple, linear, small, parasagittal in location and caused by tensile tear of both vessels and axons in the white matter.

Post-traumatic deep intracerebral haemorrhage in the region of the basal ganglia (Fig. 9) is recognised to occur more frequently than thought of previously, with the advent of superior imaging techniques. However, the commonest sites of intracerebral haematoma are temporal, followed by the frontal lobe, the same sites

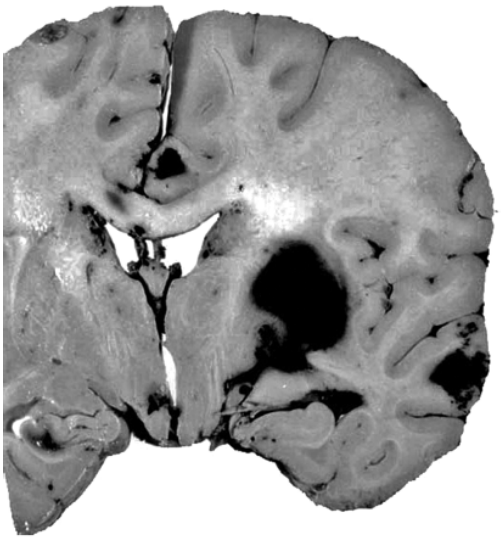


Fig. 9: Basal ganglion haematoma. A small haematoma in the cingulate gyrus with mild transfalcine herniation and another in the middle temporal gyrus, due to direct impact

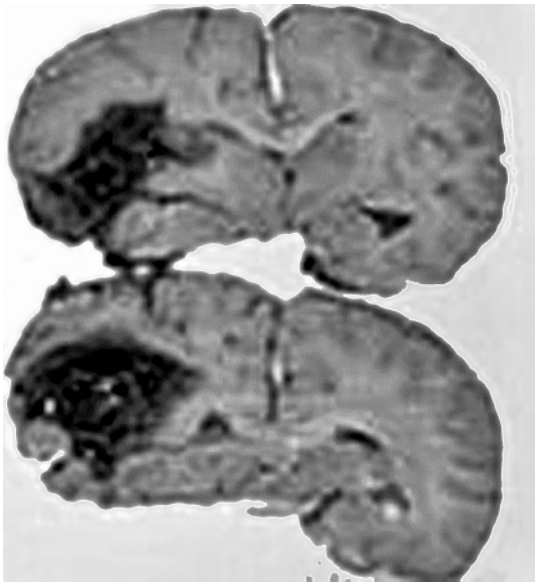


Fig. 10: Burst lobe. The haematoma in the left temporal lobe has ruptured into the subarachnoid space

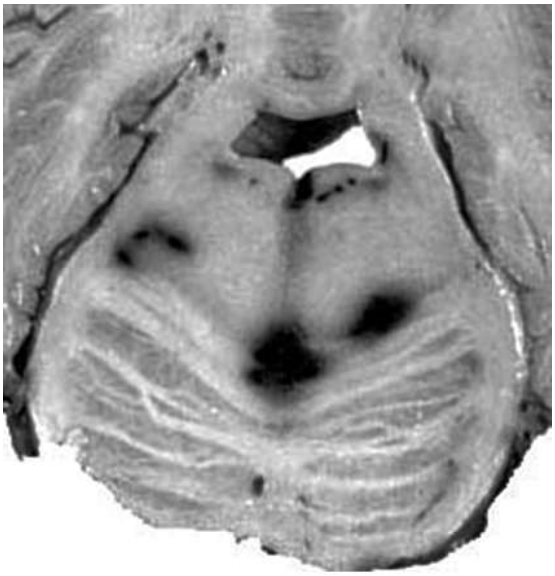


Fig. 11: Periaqueductal, subependymal haemorrhages in addition to primary and secondary pontine haemorrhages

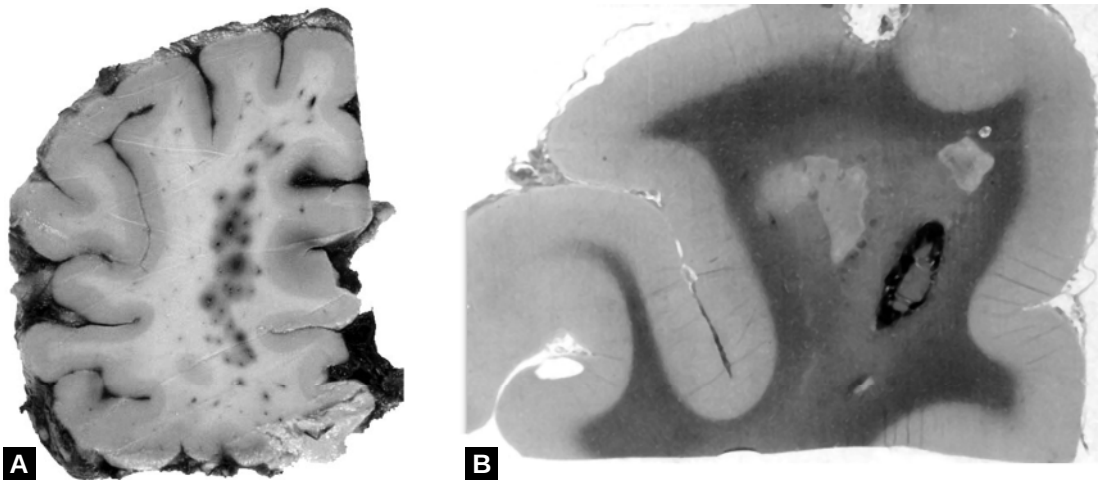
where contusions occur most frequently. Macpherson et al.[113] reported that computed tomography (CT) scans demonstrated basal ganglionic haematoma in 61 out of 2,000 head injury patients. Patients with basal ganglionic haematoma form a subgroup within head injury patients, because of their association with diffuse brain injury, surface contusions, gliding contusions and DAI. Adams et al.[5] reported the incidence of patients with deep intracerebral (basal ganglionic) haematoma to be 63 out of 635 cases of head injury. Lee and Wang[107] in a retrospective study of 52 cases of closed head injury, found the haematoma to be located in the putamen in 74.9%, caudate in 77% and thalamus in 17.4%. Kudesia et al. from India,[105] reported intracerebral haematoma in 24.4% and it was located in the basal ganglia in 11.4% of cases of head trauma. When an intracerebral haematoma destroys the parenchyma and communicates with the overlying subarachnoid and subdural haematoma, it is referred to as "burst lobe" (Fig. 10).

Histological examination of the brains with basal ganglionic haemorrhage (BGH) resembles those noted following DAI, although both these pathological entities can coexist. Vascular damage and microhaemorrhages predominate, the area bordered by zones of axonal pathology. These suggest that the haematomas in the deep cerebral parenchyma are caused by rupture of cerebral blood vessels at the time of impact. The frequent coexistence of DAI and BGH suggests that the biomechanics of the evolution of the two lesions is essentially similar, requiring angular acceleration of the head as in the case of a road traffic accident than in a free fall. Experimental studies on primates[10,59] have revealed that the blood vessels are likely to be affected only by injuries of greater severity than that involved in shearing of axons in the white matter. The anatomical location of the haemorrhages and haematoma following trauma are to an extent similar to areas manifesting hypertensive haematomas due to rupture of thin, long end arteries and also highlighting the vulnerability of these vessels to sudden alteration of pressure gradients and shearing forces. Hence, discriminating an intracerebral haemorrhage due to a hypertensive episode or ruptured saccular aneurysm and fall from an accidental injury with haemorrhage may not be possible and a definite opinion cannot be offered. This has medico legal implications.

Intraventricular haemorrhages: Intraventricular haemorrhages (IVH) are also usually associated with DAI.[10,32] Kudesia et al. from India,[105] in a study of 30 patients with severe head injury, noted IVH in nearly 50% of cases with radiological evidence of DAI. In these cases, subependymal haemorrhages due to rupture of veins with a breach of the ependyma (Fig. 11) and corpus callosal haemorrhages related to DAI extending to the fornix and septum and rupturing into the ventricle were common. In cases of IVH, the axonal bulbs are particularly observed in the subependymal area.

Diffuse (Multifocal) Brain Damage

Diffuse brain damage, following TBI, becomes evident by instantaneous loss of cerebral function and long lasting disturbances of consciousness with residual sequelae in patients rendered unconscious at the time of impact.[183] This diffuse pathology is the cardinal mechanism for prolonged unconsciousness in nearly 50% of patients with no expanding intracranial mass.[7] These diffuse lesions are seen in nearly one third of all head injury deaths.[58] Further, some patients who sustained minor injury may have diffuse damage in the brain that manifests later when subjected to mild cerebral ischaemia.[47] Among the four types of diffuse cerebral injury that follow trauma: (1) diffuse vascular injury, which is most serious and is found in patients who succumb soon after head injury.[183] The other three forms which manifest in



Figs 12A and B: (A) Multiple small haemorrhages in the parietal white matter. Survival 1 hour. (B) Histological preparation showing white matter haemorrhage and two ischaemic pale lesions. Survival 24 hours

those who survive longer and seek hospitalisation are: (2) DAI; (3) diffuse ischaemic brain damage and (4) diffuse brain swelling.

Diffuse Vascular Injury

Multiple small haemorrhages are frequently seen in the brains of patients who succumb very soon after a head injury, especially those who die instantaneously after impact. These haemorrhages, although considered a manifestation of severe degree of DAI,[8] are likely to be mechanical in origin caused by mechanical stretching and shearing of small blood vessels.[138] As they are usually seen in the brainstem, Tomlinson[183] suggested that they are indicative of brain damage that is incompatible with life. However, there is a spectrum of lesions that can result and can be compatible with life if located in the cortical white matter. They are usually conspicuous in the white matter of the anterior frontal (Figs 12A and B) and temporal lobes, periventricular white matter, thalamus and brainstem. In the brainstem they are numerous in the periaqueductal and fourth ventricular subependymal area (Fig. 11) and rarely seen in the caudal pons and medulla oblongata. Though some considered them to be primary brainstem haemorrhages, they essentially represent diffuse brain damage of vascular origin, in view of their widespread nature. When located in the corpus callosum and dorsolateral quadrant of the brainstem, they can be mistaken for DAI, but they are not restricted to these sites when present.

Many of these haemorrhages can be observed grossly, but many more, like perivascular haemorrhages, become evident on microscopic examination. These microscopic haemorrhages are, especially, present around small arterioles and venules with disruption of the vessel wall (Figs 13A to C). Kudesia et al.[105] reported these haemorrhages in more significant numbers in patients with gross evidence of DAI (42%) than in those without DAI (7%), suggesting a close association between these haemorrhages and DAI. The perivascular distribution of

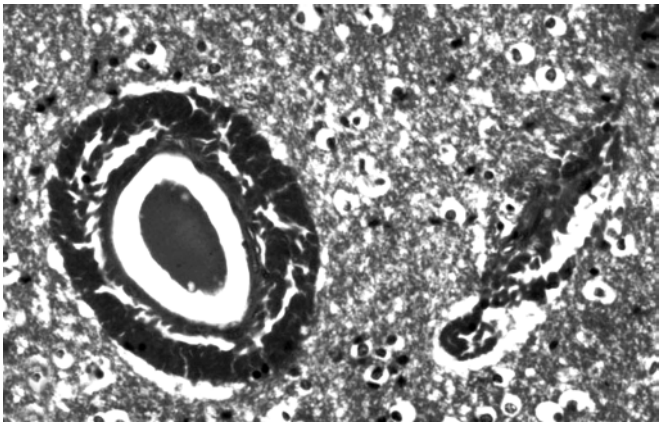


Fig. 13A: Perivascular acute haemorrhage due to tear of the vessel wall. Survival 30 minutes (HE × 160)

axonal retraction bulbs (Fig. 13C) in these cases suggests shearing and stretching of the axons by the mechanical forces, though vessels themselves were not torn, because of the differential threshold of reaction to acceleration deceleration impulses.[11,105] These observations provide evidence that shearing strains, especially rotational, as seen in road traffic accidents, are likely to disrupt the

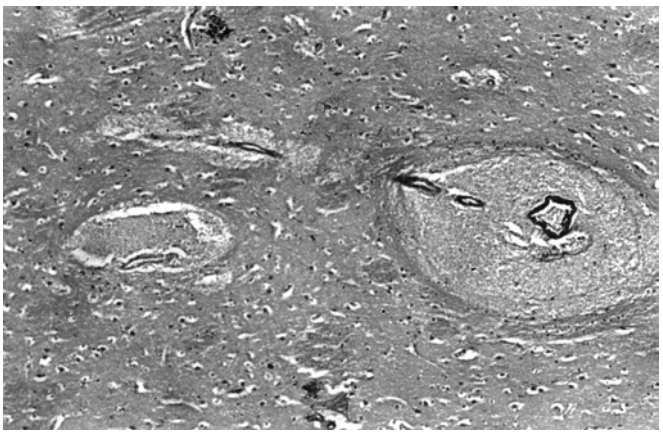


Fig. 13B: Perivascular haemorrhage around a vein. Survival 30 minutes. Note absence of white matter lesion due to acute nature of evolution (HE × 80)

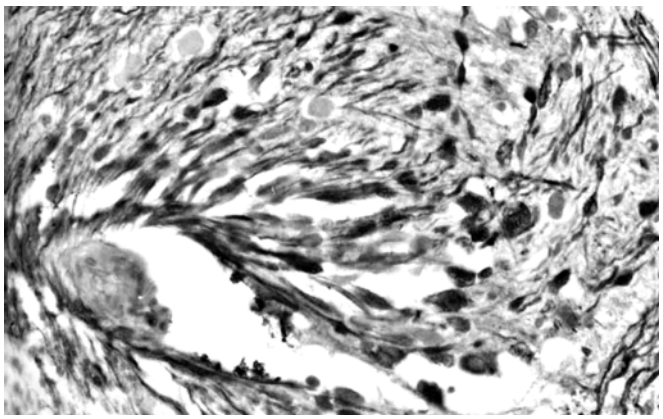


Fig. 13C: Wind blown appearance of perivascular axonal retraction bulbs, suggesting shearing and stretching of axons by the mechanical forces (Immunoperoxidase—NF × 200)

vessels and axons. Due to differential mobility of structures during acute displacement of the head, the blood vessels with firm collagenous walls lag behind.[163]

In conclusion, our study supports the hypothesis that TBI is characterised by frontomedian dysfunctions, which may be responsible for clinical deficits in the long-term and which might be modified by rehabilitative strategies in the future.[156,161]

Damage to blood vessels following injury: In addition to small vessel rupture due to mechanical avulsion, ischaemic damage as an accompaniment of DAI following trauma, medium sized and large vessels also can be damaged. The main vessels that show evidence of tear are the vertebral and the internal carotid arteries. The internal carotid artery can get traumatised in the sigmoid portion as it traverses the bony canal in the base of the skull following a fracture (Figs 14A and B). It can manifest as a pseudo aneurysm, the blood accumulating between the media and the adventitial sheath or dissecting the media, into two layers. Carotico-cavernous fistula is another rare sequel of head injury. The vertebral artery can get damaged in the canal in the first cervical vertebra, even without fracture of the transverse process or in the space between the transverse process of the axis and atlas as it emerges from the canal and penetrates the spinal dura below the foramen magnum. Occasionally, the vertebral artery can be traumatised in the subarachnoid space as it courses through the foramen magnum. More than real traumatic tear of the vessel, of great clinical importance is the not so well recognised vascular spasm and new imaging studies will assist the clinician in recognising them.

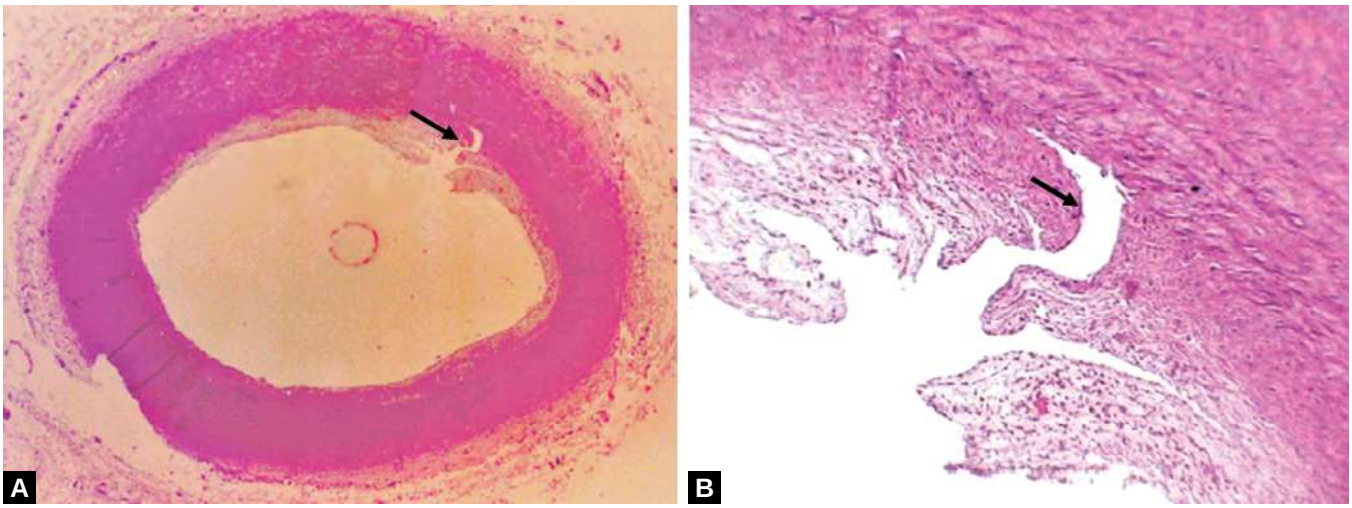
Features of Raised Intracranial Pressure and Brain Swelling

Following TBI, three types of brain swelling are observed:

1. Swelling adjacent to a contusion and intracerebral haemorrhage
2. Diffuse swelling of the unilateral cerebral hemisphere
3. Bilateral diffuse brain swelling.

The essential mechanism for all the types appears to be vasogenic, due to deranged vasotonicity or vasoparalysis, mediated by neurotransmitters, ionic imbalance and physical injury.

Consequent to contusion and haemorrhage, the breakdown in the blood brain barrier (BBB) causes localised vasogenic oedema.[41] Diffuse swelling of one side of the hemisphere is usually seen in relation to an ipsilateral acute subdural haematoma.[9] When the haematoma is evacuated, the adjacent brain swells to fill the void and may herniate through the craniotomy wound. This also appears to be vasogenic in pathogenesis and contributes to rapid clinical deterioration. An epileptic seizure alone or a large supratentorial tumour pre-existing alters the BBB further, aggravating the oedema and herniation. These events have medicolegal implications.



Figs 14A and B: (A) Road traffic accident, with injury to internal carotid artery without fracture. An intimal tear is seen due to impact. Following vasospasm the patient had ACA, MCA territory infarct on the side of impact and injury to the internal carotid artery. Survival 3 days (HE × 10); (B) Higher magnification showing the intimal tear. Note the sub-intimal thickening and proliferation of medial muscle cells (HE × 200)

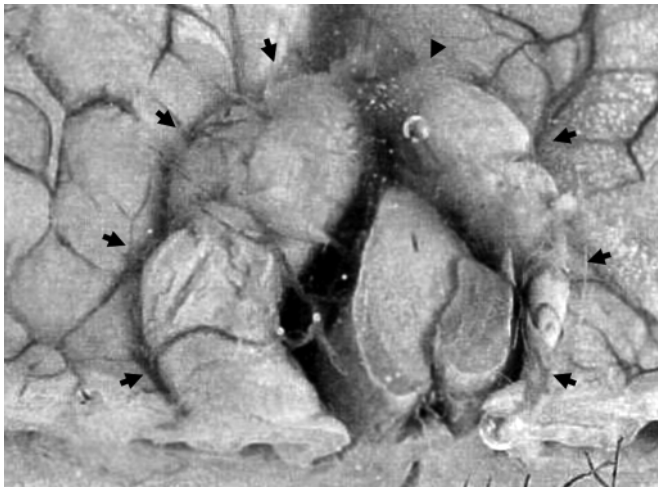


Fig. 15: Bilateral parahippocampal gyrus herniation through the tentorial hiatus forming a ring (arrow heads) and compressing the mid brain

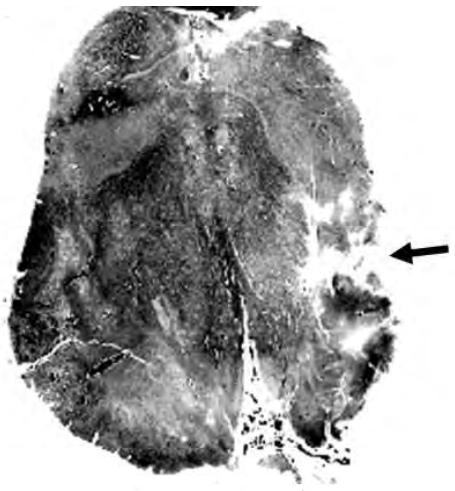
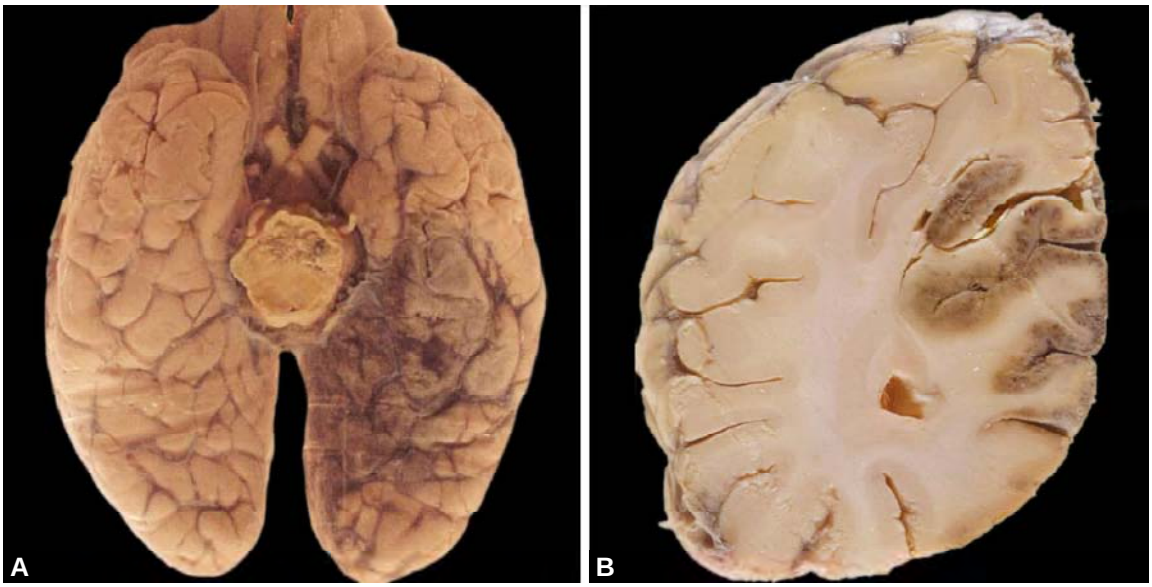


Fig. 16: Kernohan's notch — tear of contralateral aspect of crus cerebri against sharp tentorium (arrow) due to oedema. Ischaemic and demyelinating lesions seen (LFB × 4)

The supratentorial-expanding lesion, with raised ICP, causes downwards displacement of the brain, the parahippocampal gyrus (Fig. 15) and uncus herniating down with pressure necrosis. The pressure necrosis is evident only when the raised ICP is of some hours' duration. If the ICP rises rapidly and death supervenes soon, the parahippocampal herniation may not be seen. Furthermore, when the ICP is due to an expanding lesion infratentorially, no pressure necrosis of the hippocampi may be found but, on the other hand, there is upwards herniation of the vermis, the tentorial margin producing a groove. The other neuropathological features of raised ICP include supracallosal transfalcine cingulate gyrus herniation, contralateral grooving of the cerebral peduncle (Kernohan's notch), (Fig. 16) due to compression against the sharp tentorial margin, infarction in the territories of the anterior and posterior cerebral arteries (Figs 17A and B), anterior choroidal artery and superior cerebellar arteries. Some of the lesions can be haemorrhagic due to pressure on the veins around the brainstem, resembling a venous infarct. Rapid downwards displacement of the cerebellum and brainstem manifests as cerebellar tonsillar herniation (Fig. 18), compression of the medulla and death. An atrophic brain in old age may not manifest the features of herniation, despite raised ICP following trauma, due to available intracranial space for expansion. Kotapka et al.[103] in an analysis of 112 fatal cases of non-missile head injuries recorded hippocampal damage in 84% of cases. Kudesia et al.[105] in a study of 356 brains of TBI from India, noted features of raised ICP in 292 brains (82%). They observed pressure necrosis of the parahippocampal gyri in 88%, subfalcine herniation in 10.6%, calcarine infarction in 7.5% and Kernohan's notch in 2% of cases. All the cases showed



Figs 17A and B: (A) Right side posterior cerebral artery territory haemorrhagic infarct due to downward herniation and compression of PCA against the tentorium. Note ischaemic softening of tectum of mid brain. (B) Haemorrhagic infarction of calcarine cortex and adjacent gryi due to reperfusion following compression of PCA

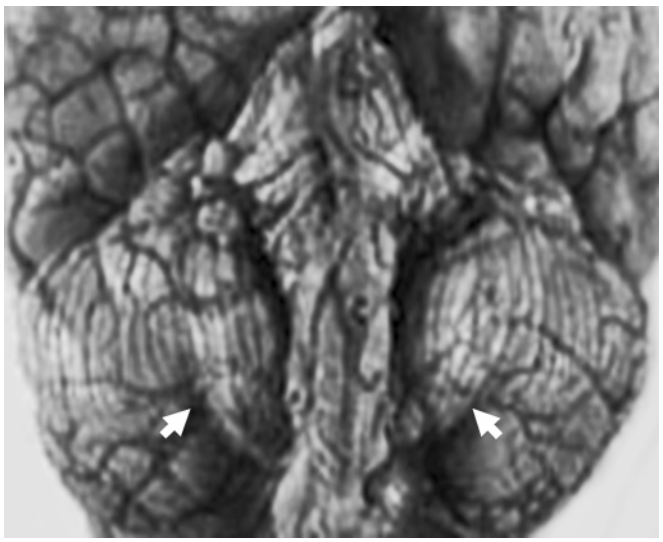


Fig. 18: Bilateral cerebellar tonsillar herniation (arrow heads) into the foramen magnum compressing the medulla oblongata

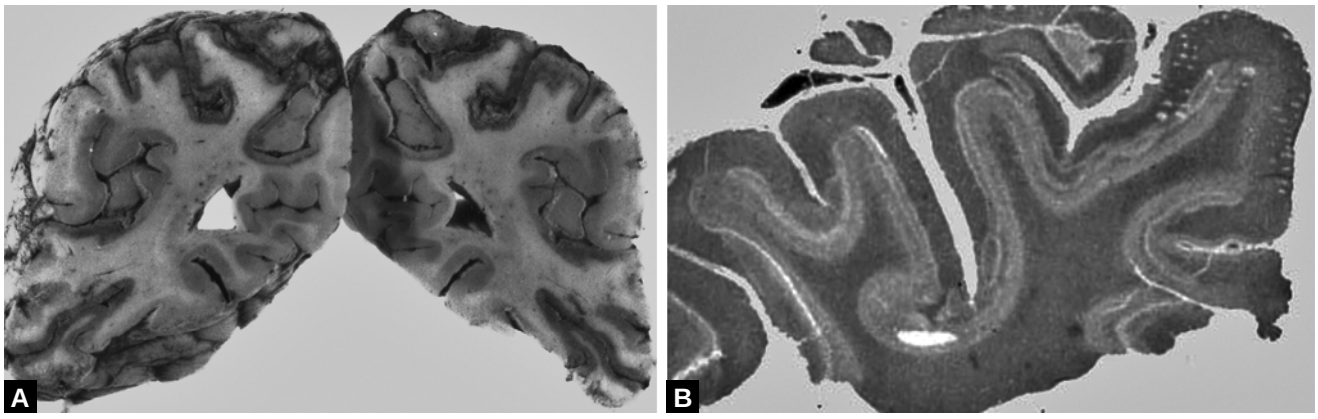
features of infratentorial herniation. A close association between DAI and ICP was observed (89% cases), suggesting a causal relation and synergistic effect in determining a poor prognosis.

Ischaemic Brain Damage

Ischaemic damage to the brain is common in fatal head injuries. The lesions are more common in the hippocampus and basal ganglia than in the cerebral cortex and cerebellum. Episodes of hypoxaemia, raised ICP, transient failure of cerebral perfusion pressure due to fall in cerebral blood flow (CBF), associated cardiac arrest and status epilepticus at the time of injury contribute to the ischaemic insult and form an important cause for mortality and morbidity. The hippocampus is selectively vulnerable to a variety of hypoxic events like cardiac arrest, status epilepticus and hypoglycaemia and is involved in nearly 84% of cases.[103] A post-traumatic electrical storm, flood of excitatory neurotransmitters-like glutamate and vascular leak are some of the events contributing to the ischaemia.[49] Regional or global reduction in CBF following trauma, usually occurring within 8 hours, has an important effect on brain viability and neurological consequences.[117] Following TBI, the brain may be at risk to even minor alterations in CBF, increase in ICP and apnoea. The ionic fluxes, like raised extracellular K+ results in increase in glycolysis and accumulation of lactic acid and acidosis.[197] During these periods of relative ischaemia, intracellular Ca++ increases. By 6 hours post-injury, the brain undergoes metabolic depression with reduction in CBF, glucose and oxidative metabolism, in experimental conditions.[88] In patients who make a good recovery, the CBF recovers sooner and to a greater extent. Using transcranial Doppler ultrasonography, vasospasm has been demonstrated in severely head injured patients, which contributes to post-traumatic hypotension.[24,25] These events of hypotension, and reduced CBF cause ischaemic lesions in the cerebral arterial territories, especially at the watershed zones of the anterior cerebral artery (ACA), middle cerebral artery (MCA) and posterior cerebral artery (PCA) territories (Figs 19A and B). Gross examination of the brain may look normal, but histological examination reveals laminar necrosis (Fig. 19B). These patients have relatively normal CT features, but the recovery is poor and they may become vegetative.

Diffuse Axonal Injury

This diffuse form of white matter damage, leading to post-traumatic dementia, was initially called "diffuse degeneration of cerebral white matter" by Strich.[173] Adam et al.[10] recognised this diffuse lesion in the white matter of patients who survived with vegetative or severely disabled state more than 4 weeks after injury due to impact and shearing forces. Initially, the clinical syndrome of primary brainstem injury was considered to be an expression of DAI, but now the two are recognised as distinct entities, though they can coexist or occur concurrently during the mechanics of impact. As the axonal damage can be identified on postmortem, by



Figs 19A and B: (A) Ischaemic softening with discoloration involving the cortical ribbon, on both sides due to prolonged hypotension and attempts at reperfusion (Survival 76 hours). (B) Histological preparation showing continuous laminar necrosis of the lower layers of cortex due to hypotension and hypoxic injury (Survival 8 days)

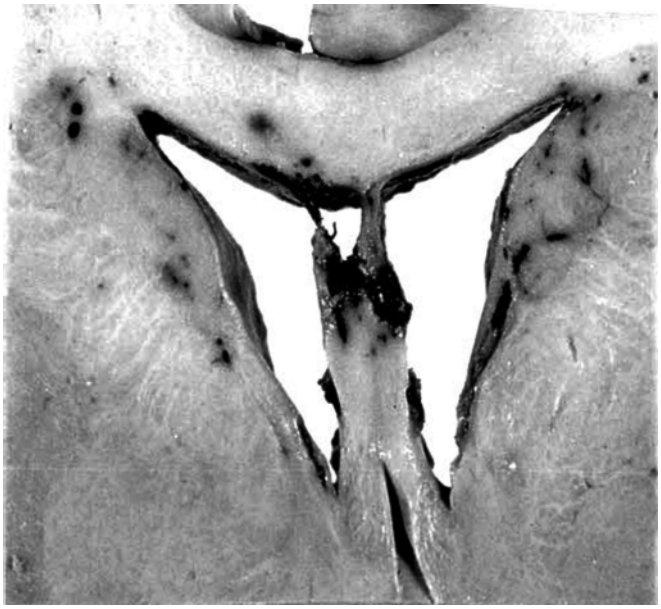


Fig. 20: Early diffuse axonal injury involving corpus callosum focally, but affecting the septum and formix more (Survival 28 hours)

microscopy, the term DAI is better used as a histological entity as defined by Adams et al.,[3] reserving the term, diffuse brain injury (DBI) to connote the clinical state. Sahuquillo et al.[157] also advocated the use of the term DBI to describe patients rendered immediately unconscious on impact and do not show any mass lesion on the admission CT scan. DAI is now defined as the occurrence of diffuse damage to the axons in the cerebral hemispheres, in the corpus callosum, in the brainstem and, occasionally, in the cerebellum resulting from head injury. Three distinct structural abnormalities are recognised in the pathology of DAI:

1. Focal lesions in the corpus callosum (Figs 20 to 25).
2. Focal lesions in one or both dorsolateral quadrants of the rostral brainstem adjacent to the superior cerebellar peduncle (Figs 23 and 24).
3. Diffuse damage to axons, especially in the corona radiata and other long fibre tracts (Fig. 21).

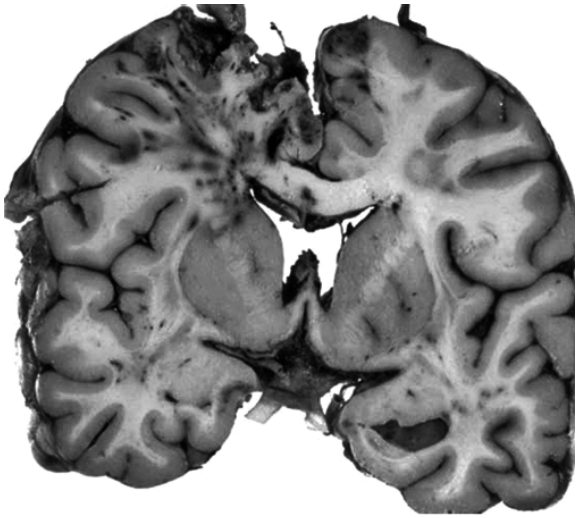


Fig. 21: Contusions and diffuse axonal injury involving the corpus callosum and frontal white matter (Survival 48 hours)

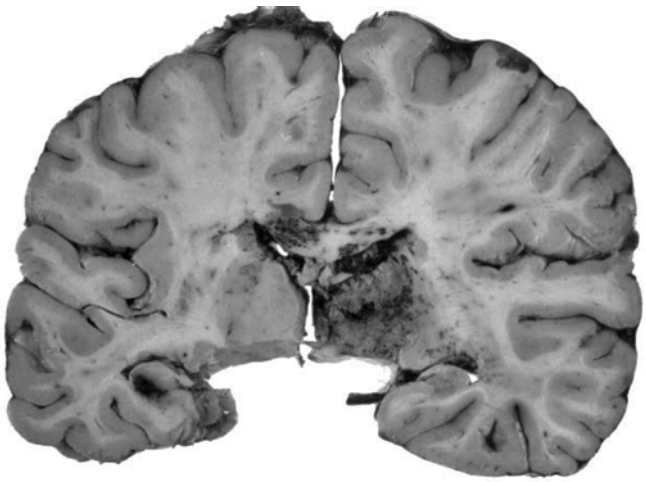


Fig. 22: Acute haemorrhagic lesion in the left half of corpus callosum. The right thalamus and left hippocampus have haemorrhagic lesions due to asymmetric venous compression along the base due to down ward displacement of brain (Survival 4 days)

It is conceivable that DAI encompasses a spectrum of pathological changes, correlating with severity of injury, beginning with the concussive syndrome leading to minor cerebral injury to severe forms of brain impairment, which include immediate coma with decerebrate posturing, prolonged coma and incomplete recovery. This assumption is further supported by the identification of axonal damage in humans with minor head injury and concussion, as well as in experimental minor head injury produced in animals by percussion.[137] These observations have led to grading of DAI for clinical correlation (Tables 3 and 4).[3]

In the initial stages after injury, the focal lesions in the corpus callosum and dorsal brainstem are haemorrhagic, usually unilateral and asymmetric when bilateral. From the corpus callosum they may extend down to involve the septum and fornix (Fig. 20). With progression of time, the lesions become brown leading to gliotic scars and tiny pale infarcts. On histological

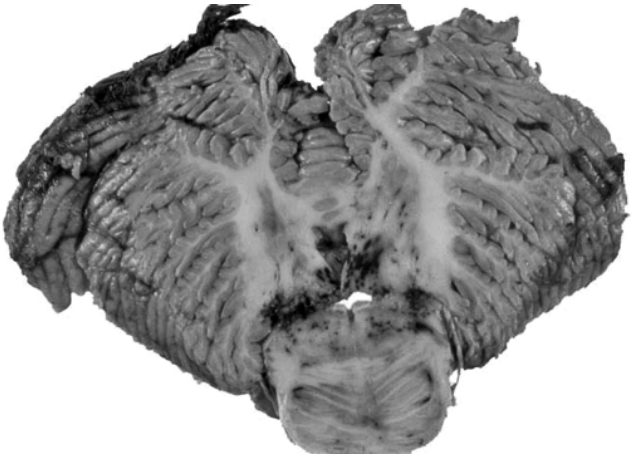


Fig. 23: Diffuse axonal injury-haemorrhagic lesion in the rostral pons, involving the tectum, middle cerebellar peduncle and cerebral vermis (Survival 24 hours)

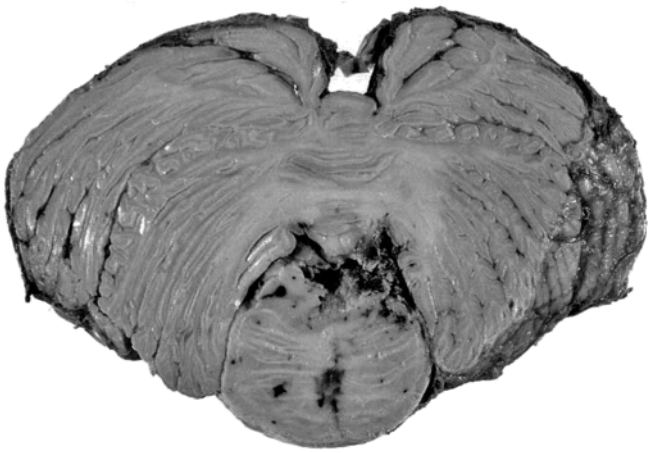


Fig. 24: Diffuse axonal injury lesions in the rostral pons involving the tectal area. Note multiple Duret haemorrhages in the midline involving paramedian vessels and lateral tectal zone due to rupture of long circumferential vessels

Table 3: Grading of diffuse axonal injury[3,59]

Grade I	Only histological evidence of axonal damage in white matter without focal lesions in corpus callosum, brainstem.
	Complete or partial lucid interval.
Grade II	Widely distributed axonal injury along with focal lesions in corpus callosum.
	Partial lucid interval
Grade III	Diffuse axonal damage with focal lesions in corpus callosum and brainstem.
	Did not talk—No lucid interval.
Identification:	Survival for 18–20 hours: visible axonal pathology—Silver stain (30%).
	Survival for 2–3 hours: visible axonal pathology by antibody to beta β-APP (92% cases).
Pathogenesis:	Primary axotomy—shearing of axolemma and resealing in 60 minutes after acceleration/deceleration injury at Node of Ranvier
	Secondary axotomy—Multiple foci of axonal injury
	→ At Node of Ranvier form Nodal bulbs
	→ At Internodes form axonal swelling 15 minutes after injury.

Table 4: Diffuse axonal injury

Evolution:	Early—Haemorrhagic
	3 days—Pale, rarefied
	Weeks-Months—Residual haemosiderin.
Axonal injury:	Disruption of axolemma (in the absence of infarcts and axonal swelling other lesions)
Survival days:	Multiple axonal swellings and oval/round bulbs at the end.
Survival weeks:	Clusters of microglial cells in white matter
Survival months:	In vegetative state—Wallerian degeneration in white matter

- Lower incidence of lucid interval
- Skull fracture, surface contusions, basal ganglia haematomas: common

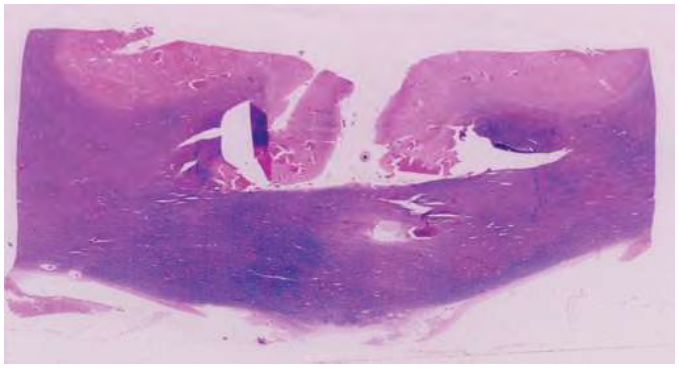
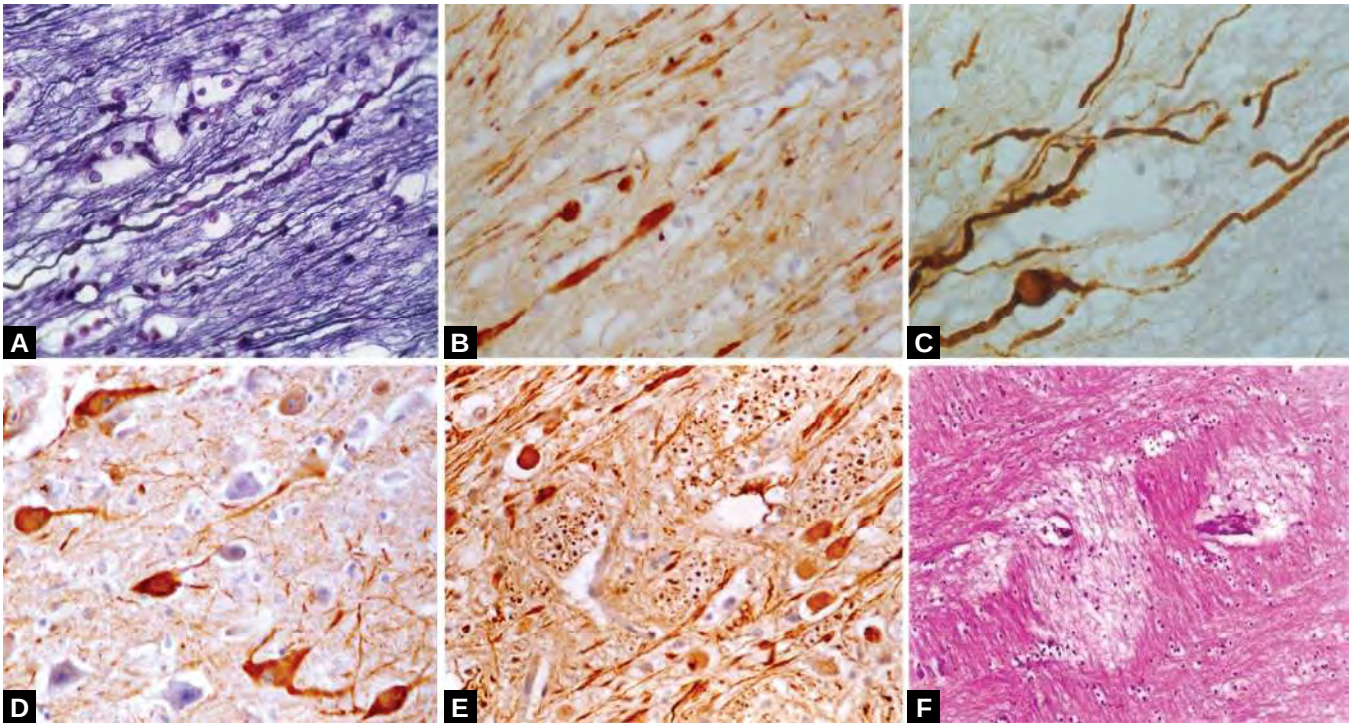


Fig. 25: Healing DAI lesion in the corpus callosum. Note small haemorrhage and adjacent pale ischaemic lesion (Survival 6 days LFB × 2)

examination the initial haemorrhage is perivascular, later extending to the surrounding tissue. Silver impregnation and immunohistochemical stain using antibody to neurofilament (NF) reveals numerous axonal swellings adjacent to the focal lesion 15–18 hours after injury (Figs 26A to F). Kudesia[105] has shown a spectrum of changes in the axons that correlate with the temporal evolution of the lesions. At 6 hours post-injury, the axons were only swollen and varicose without disconnection while, at 24 hours, they appeared grossly swollen and formed bulbs/spheroids, indicating disruption and interrupted axoplasmic flow. The axonal pathology was evident within 6 hours in 80% of cases with DAI who survived 8 hours or more. The axonal pathology in those surviving less than 8 hours could be identified only by immunohistochemical staining with NF antibodies, but not by silver stains.[65,132] Recent studies highlighted the utility of immuno-histochemistry using antibodies to ubiquitin[162] and beta amyloid precursor protein (β-APP).[125,165] Axonal APP immunoreactivity was present in all patients who survived 3 hours or more, thereby demonstrating that expression of β-APP is upregulated following injury and is useful as an early marker. It is important to realise that accumulation of β-APP is not restricted to head injury patients and can be observed in dystrophic axons of elderly subjects and in association with cerebral infarcts.[62,166] In addition to dystrophic axonal bulbs, Kudesia et al.,[105] also observed NF antibody immunolabelled neurons close to the dystrophic axons, indicating extension of pathology to the respective neurons in a retrograde fashion. In an evaluation of time course events in the axonal pathology, he observed a larger proportion of axonal swellings and varicosities than axonal bulb formation in patients surviving up to 8 hours. Later, by 10–15 hours survival, the axonal swelling increased only slightly, but axonal bulbs with disconnection were identified in most cases. This suggests that, the stage of axonal swelling may be a reversible phase, while disconnection and bulb formation indicates irreversible axotomy. Though more work is needed, it is plausible to think that by timely appropriate therapy at this stage, there is a likelihood of



Figs 26A to F: (A) Diffuse axonal injury focal axonal swelling without disconnection (Bodian × 460); (B) Axonal swelling in corpus callosum 8 hours after injury (× 460); (C) Disruption and globular swelling of axons in fornix. Survival 12 hours (× 460); (D) Dystrophic changes in cortical neurons proximal to damaged axons (× 460); (E) Dilated axonal spheroids in thalamus. Survival 36 hours. (× 240). (B-E: Immunostain with phosphorylated NF Ab); (F) Rarefied lesion in superior cerebellar peduncle. Survival 4 days (H and E × 160)

recovery in many of the traumatised, yet not disconnected axons. With longer survival, the axonal bulbs diminish in number, and can persist up to 3 months following injury. During this phase microglia, macrophages and astrocytes become prominent, indicating scavenging and scar formation at the site of injury.[62] Later, rarefied lesions resembling small ischaemic infarcts can be seen as tell tale evidence of DAI.

Kudesia from India,[105] in a study of 356 brains, noted macroscopic markers of DAI lesions in 57 cases (16%); corpus callosum alone was involved in 18 cases, dorsolateral brainstem in 10 cases and both corpus callosum and brainstem in 29 cases. In 8 cases, only microscopy revealed features of DAI, while on gross examination the brains failed to show any lesions, except for oedema. Similarly, Adams et al.[3] identified 10 cases of histologically recognisable lesions among 122 cases of DAI. In general, DAI can be found in any patient injured accidentally with high inertial loading as in road traffic accidents.[28,60]

Frequent involvement of the brainstem in cases of DAI indicates that this lesion is probably the common structural basis for persistent disability or the vegetative state so often seen in severe DAI. The involvement of the brainstem is almost always accompanied by similar lesions in the corpus callosum and deep cerebral white matter and less frequently related to haemorrhagic areas. Frequent involvement of the fornices, an important hippocampal projection pathway involved in memory mechanism, may underlie some of the persisting memory disturbances in survivors of mild forms of DAI following blunt head injury.[109] Similarly, a more widespread functional derangement of the axonal projections of the reticular activating system may account for transient loss of consciousness in cerebral concussion, a milder form of DAI.[18,109] The medulla oblongata is relatively spared in DAI.[11,35]

The direction in which the head moves following impact plays an important role in the degree and distribution of axonal damage. According to Graham and Generelli,[66] although some degree of axonal damage can occur in any directional movement, the full blown picture of widely distributed axonal damage in cerebral white matter and brainstem can occur due to geometrical change in the strain pattern induced by the falx and tentorium during lateral motions of the head during rotational acceleration. Certain anatomical areas in the midline, like the corpus callosum, basal ganglia, internal capsule and the brainstem, move in the opposite direction to the rest of the structures, thus generating maximum shear and tensile strains. These areas along the midline where the white fibres diverge out show maximal degree of axonal damage consistently. The brain tolerates best, movement in the horizontal or sagittal plane that causes less damage than lateral displacement.

The other pathological hallmark of DAI is diffuse microglial proliferation, at places forming clusters that resemble the early encephalitic process. These aggregates of microglial cells are thought to be a cellular reaction at the sites of minute tissue tears,[11] seen earliest at 15 hours

post-trauma. Cytokines secreted by these cells further aggravate tissue damage through Ca^{++} ion influx. This feature may persist for a few days to assist in scavenging the tissue breakdown products.

Kudesia[105] has shown ultrastructural evidence of DAI, as early as 3 hours following injury. The most characteristic findings on EM study of human DAI were separation of the myelin sheath and detachment of the axolemma from myelin, swelling of axons filled with cytoskeletal components and mitochondria, and extrusion of axonal contents through the tear to the exterior.[195] With progression, in long-term survivors, the swollen axons contain granular material and only a few organelles. The severity of ultrastructural lesions in humans is usually more when compared to experimental material, probably due to technical limitations in specimen collection and processing, and fixation artifacts.

Fat embolism (small haemorrhages): Fat embolism is a well-recognised, though relatively uncommon cause of progressive neurological deterioration without an acute intracranial expanding lesion. Usually one finds multiple petechial haemorrhages in the white matter.[9,97] These need to be differentiated from severe degree of DAI with white matter haemorrhages and vascular congestion in cases of cerebral malaria in tropical countries. Occasionally, the classical petechial haemorrhages may be absent in spite of extensive fat embolism. In patients with multiple injuries with fracture, the brain needs to be scrutinised for fat embolism by staining a frozen section of the suspected area with Oil Red O.[130] The intravascular fat stains bright red. In pregnant women, amniotic fluid embolism needs to be suspected. In addition, multiple haemorrhages may be found due to thrombocytopaenia secondary to drug reaction, sepsis and small vessel diseases.

PATHOLOGY OF TRAUMATIC HEAD INJURY IN CHILDREN

The pattern of intracerebral injury in infancy differs from that described in adults due to:

- increased elasticity and moldability of the infant's skull due to suture patency
- softer consistency of brain due to incomplete myelination
- shallow cranial vault

In children, fracture of the skull is not uncommon as the skull is thin and breaks easily with impact. The finding of a subdural haematoma suggests "shaken baby syndrome"; a form of child abuse, though perinatal trauma needs to be kept in mind.

Subdural haematoma can occur due to rupture of bridging superficial cerebral veins, tentorial laceration with rupture of the straight sinus, transverse sinus, vein of Galen and laceration of falx with rupture of the inferior sagittal sinus. Occipital osteodiastasis due to traumatic separation of the cartilagenous joint between the squamous and lateral aspects of the occipital bone (common with breech delivery) results in posterior fossa subdural haematoma. Other causes of subdural haematoma in children include birth trauma, bleeding diathesis, meningitis (Haemophilus influenzae) and shunt surgery.

Epidural haematomas are infrequent in infants, possibly due to the intradiploic course of the middle meningeal artery until the skull is fully ossified and the fontenelle are closed.[108]

Head trauma in infants is characterised by haemorrhagic tears in the cerebral white matter, unlike in adults who develop surface cortical lesions only following contusion. This is probably due to lack of support to vessels in the immature white matter, which easily rupture following rapid acceleration-deceleration movements of the head. These lesions can be associated with DAI and axonal retraction bulbs.[191] DAI may occur in the absence of skull fracture or grossly visible parenchymal lesions in the brain. Unlike in adults, DAI is not seen in the brainstem of infants.[191]

Sarala Das et al. made similar observations based on the study of 40 brains from cases of traumatic injury in the paediatric age group (unpublished). The impression that contusions of the brain are less common in children following head injury than adults based on CT scans is incorrect, as autopsy studies revealed their presence in 90% of cases.[68] Zimmerman et al.[199] reported fewer incidences of DAI in children than in adults. The incidence of ischaemic brain damage is essentially similar to that noted in adults. Diffuse bilateral cerebral oedema with deep coma is more common in the paediatric age group, especially in infants, than adults following traumatic injury, without overt gross damage.[22]

Epilepsy has long been established as a late consequence of head injury and is related to the severity and type of injury. Depressed skull fracture, cortical laceration and parenchymal haematoma contribute to increased risk of post-traumatic epilepsy. Early epilepsy occurring during the 1st week of injury is more common in children and may progress to status epilepticus resulting in irreversible ischaemic damage if not controlled adequately. The occurrence of early epilepsy also enhances the chance of developing late epilepsy, delayed by a year or more, in children. However, the risk of late epilepsy after head injury is less common in children than adults.

OTHER AREAS

Brainstem[114,175,178,180]

The clinical features of altered sensorium, hypertonicity, decerebrate rigidity, bilateral dilatation of pupils and absence of cold caloric response following traumatic injury indicate the anatomical localisation of damage to the brainstem. Deteriorating state of consciousness, decerebration and depression of vital signs represent significant caudal displacement of the upper brainstem towards the tentorial hiatus. Shearing of the brainstem

is maximal in the region of the aqueduct with the fibres of the medial longitudinal fasciculus being vulnerable resulting in internuclear ophthalmoplegia.[40] Oculomotor nerve palsy is common with brainstem injury due to damage either at its exit from the midbrain or fascicular injury in the midbrain. "Locked in syndrome" due to traumatic basilar artery dissection or direct impact following clival fracture have been reported.[187] In the midbrain, the haemorrhagic lesions are in the dorsolateral part, almost always involving the superior cerebellar peduncle.

The brainstem can be involved by any one of the following mechanisms:

1. Primary brainstem injury—not so rare as considered.
2. As a part of DAI.
3. Secondary brainstem injury—due to downwards herniation, torsion, lateral displacement.

Primary Brainstem Injury

Similar to the spinal cord, the brainstem is a relatively fixed structure tethered by cranial nerves and has restricted movement because of the investing meningeal coverings in close proximity (Figs 27 to 30).

In a series of 988 autopsied cases of road traffic fatalities, Simpson et al.[169] found gross primary damage to the brainstem in 36 (3.6%) cases. Some of these could be under diagnosed as the changes may be attributed to artifactual damage occurring during removal of the brain at autopsy.[48]

Mechanical effects on the brainstem and its surrounding structures due to rotation acceleration of the head along the transverse, vertical and sagittal axis cause primary injuries, without the association of lesions in the supratentorial compartment. During the initial impact, due to its inherent inertia, the brain remains relatively stationary, though the brainstem, because of its long axis oscillates. This results in microscopic and macroscopic haemorrhages in the isthmus cerebri, the cerebral peduncles, cerebellar brachium conjunctivum and tear of the long fibre tracts. The location of the lesions in the brainstem with tears and haemorrhages in the tentorium suggest that the brainstem injury is primary. Improperly used automobile seat belts can result in whiplash injury, with rotational movement of the brainstem alone, leading to severe morbidity or fatality.[42] Hyperextension of the neck with stretching of the brainstem can result in tissue tears and haemorrhages in the dorsal area of the midbrain and pons. If the shearing trauma or anteroposterior brain movement is severe, there can be supratentorial

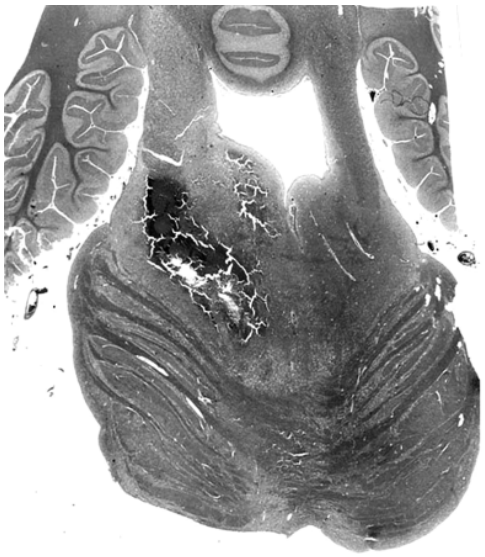


Fig. 28: Whole mount preparation of rostral pons. Fresh haemorrhage extending towards the superior cerebellar peduncle suggesting angular movement and rupture of vessels. The pallor of the adjacent white matter indicates ischaemic injury. HE × 4

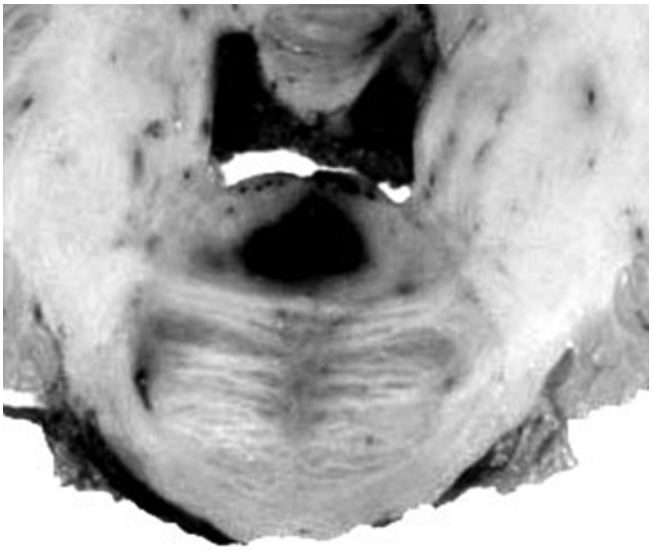


Fig. 27: Road traffic accident, impact on parietal region. Survival 6 hours. Pontine haematoma in tegmentum and periventricular area

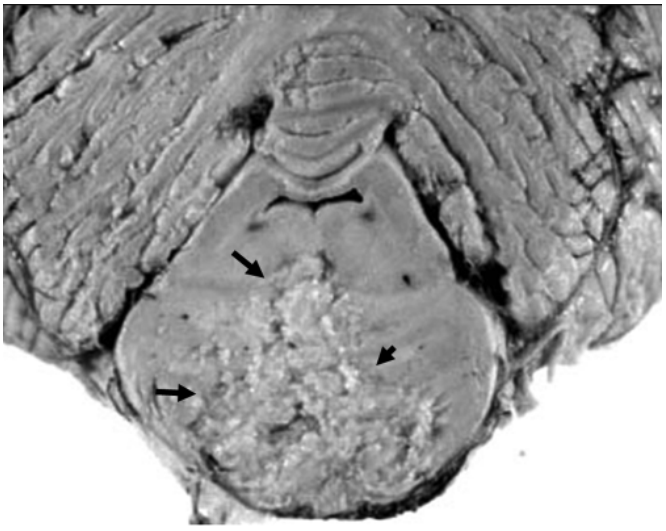
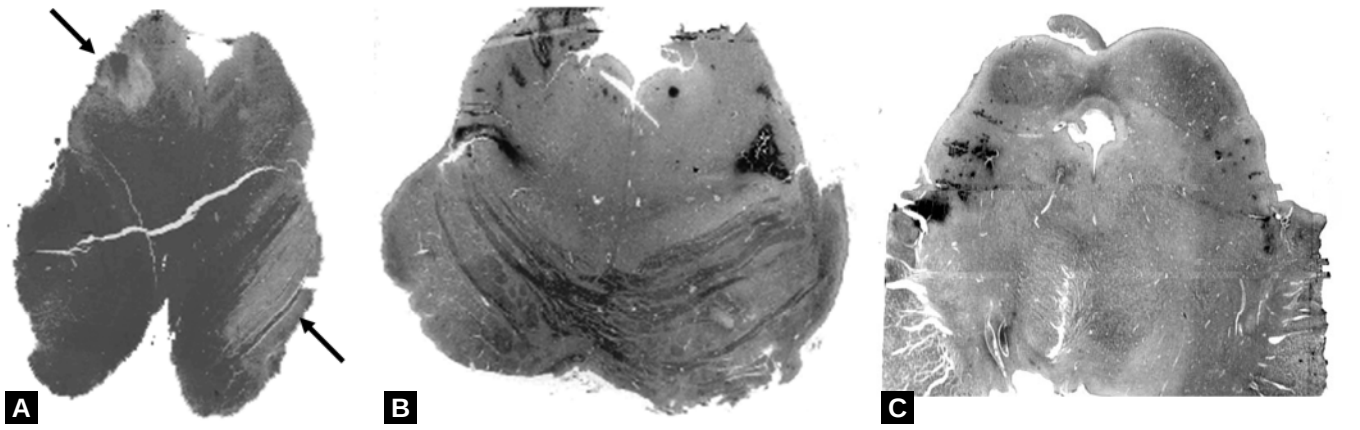


Fig. 29: Large, pale ischaemic infarct of ventral pontomesencephalic junction due to compression and prolonged vasospasm. Survival 4 days, road traffic accident with extensive subarachnoid haemorrhage



Figs 30A to C: (A) Localised pale infarcts (arrows) involving the right crus cerebri and left tectal area due to compression and prolonged vasospasm. Survival 5 days (LFB × 2); (B and C) Multiple duret haemorrhages involving the long circumferential vessels asymmetrically due to angular momentum and oscillation. Survival 18 hours (HE × 3)

injury, overshadowing the brainstem injury in clinical practice. Rotational forces produce axonal shearing, ischaemic necrosis and microhaemorrhages of the tegmental areas, while a forward thrust results in laceration of the upper brainstem against the sharp edges of the tentorium damaging the long tracts resulting in clinical signs on the opposite side of the body.[16]

The commonest primary brainstem injury is the pontomedullary rent that follows circumferential fracture through the petrous bones, ring fracture around the foramen magnum or fracture dislocation of the cervical vertebra. Similar lesions can be caused as a consequence of angular acceleration of the head as a form of DAI. Pontomedullary rents could be under diagnosed, as a partial rent is compatible with survival.[48] The second distinct form is massive laceration at the ponto-mesencephalic junction, usually found in association with pontomedullary rents in one-third of cases.[21,121] The third variant is direct contusion with focal laceration of the striate pons and is usually associated with clival fracture. The fourth distinct type is traumatic laceration or complete transection of the medulla from the cervical spinal cord. McCormick reported ten cases of spino medullary separation.[121] This is common in "dead at the scene" trauma victims, associated with separation of the atlas from the skull.[189]

In patients who survive for a few days following injury, one can find small ischaemic lesions, microhaemorrhages confined to the tegmentum of the lateral and superior margins of the mesencephalon and rostral pons revealing a spectrum of ages, without features of elevated ICP, thus qualifying them to be called post-traumatic primary brainstem lesions.

In a study of 45 cases of non-missile traumatic cranial injuries at NIMHANS, Bangalore,[168] primary brainstem injuries were observed in 7 cases and secondary brainstem injury in 29 cases. One-third of these cases with secondary brainstem injuries had hypothalamic damage indicating the widespread and dynamic nature of the injury. The patients with midline pontine haemorrhages had shorter survival than those with midbrain lesions,

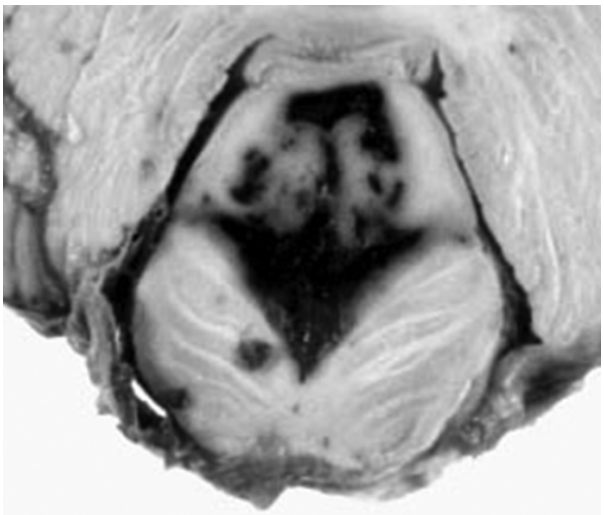


Fig. 31: Fall from a height, survival 16 hours. Large midline haematoma in the pontine tegmentum, reticular formation, medial longitudinal fasiculus, trapezoid body, nuclear areas. Note associated secondary haemorrhages

probably due to involvement of the medial reticular nuclei (Fig. 31).

Secondary Brainstem Injury

This is the commonest form caused by expanding supratentorial oedema or haemorrhage that results in downwards displacement and shearing strain on long fibre tracts and the perforating vessels (Figs 30A to C and 32A and B). Disruption of the perforating arteries entering the rostral brainstem from the basilar artery and posterior cerebral arteries due to sudden caudal displacement at the moment of impact results in multiple haemorrhages. These lesions, commonly referred to as "Duret haemorrhages", result from occlusion/shearing of paramedian short and long circumferential arteries, especially at the pontomesencephalic junction due to sudden and marked elevation of supratentorial pressure. The lesions are overtly haemorrhagic, though localised pale infarcts of the brainstem do occur in

Figs 32A and B: (A) Haemorrhages along the midline due to rupture of paramedian vessels due to sudden downward displacement. (B) Large midline haematoma involving decussation of superior peduncles, medial longitudinal fasciculus and dorsal tegmental nucleus. Survival 18 hours

patients with transtentorial herniation secondary to vasospasm and vascular compression (Fig. 29).[121] Most of the brainstem injuries defy classification due to complex dynamic impact and movement of the internal structures. Occasionally, lateral pressure exerted by the herniating medial temporal lobe on the midbrain can compromise the regional blood flow and cause local infarcts without necessarily being haemorrhagic. Rarely, entrapment of the posterior inferior cerebellar artery can result in medullary infarcts.[80,93]

The brainstem shows features of DAI, as an extension from other areas, following severe degree of injuries. Lateral aspects of the tectum and the superior and middle cerebellar peduncle show linear haemorrhages extending into the cerebellum. However, to establish DAI as the cause of brainstem injury tissue from the parasagittal white matter, corpus callosum and several levels of brainstem need to be studied.[66] Secondary brainstem haemorrhages are found in about 3% of all autopsies. Their frequency comes down with advancing age as a consequence of cerebral atrophy and increased pericerebral capacity. Similarly, brainstem haemorrhages rarely occur in infants and young children who die of head injury due to greater pliability of the calvarium and a wider tentorial hiatus.

Hypothalamus

Hypothalamic dysfunction following head injury may lead to aberrations in homeostatic functions including appetite and satiety mechanism and the thermoregulatory process. Injury to the hypothalamus produces dissociated ACTH-cortisol levels with no response to insulin-induced hypoglycaemia, hypothyroxaemia with preserved TSH response to TRH, low gonadotrophin levels with normal response to gonadotrophin releasing hormone, variable GH levels with paradoxical rise of ADH secretion, disturbed glucose metabolism, loss of thermoregulation, etc. Most severe injuries involving the skull base are sufficient to damage both the hypothalamus and pituitary causing a mixed endocrine picture. Increased ICP can alter the hypothalamic anatomy, releasing vasopressin and contributes to adrenal gland stimulation, a mechanism requiring intact brainstem function. Hypothalamic involvement is commonly associated with pituitary pathology following head trauma as a part of multifocal brain damage.[118,102,185] Post-traumatic long lasting diabetes insipidus indicates damage to the infundibulum or tuberal hypothalamus. In some instances of post-traumatic hypothalamic injury, disruption and haemorrhage in the supraoptic nuclei and optic tract may develop.[37,87] This form of hypothalmo-visual injury is a reflection of the close proximity of these structures and the fact that the lateral group of hypothalamic nuclei tethered to the visual tract may be exposed to the shearing stress and rupture of the thin penetrating vessels in the anterior perforated substance. The ischaemic lesions almost certainly are due to shearing of small perforating vessels at the time of impact. The microhaemorrhages localised to various hypothalamic nuclei bear a remarkable resemblance to lesions found in fatal cases of ruptured cerebral aneurysm. The pathogenesis of the lesions in hypothalamus following ruptured aneurysms and SAH in the chiasmatic cistern is probably due to vasospasm and reperfusion injury than evulsion as in traumatic injuries. Venous engorgement due to raised ICP or downwards displacement of the brain compressing the veins around the tentorial hiatus can also contribute to hypothalamic haemorrhages, especially the posterior group along the midline. Thus, not all the hypothalamic lesions found at autopsy have resulted from injury due to primary impact. It is

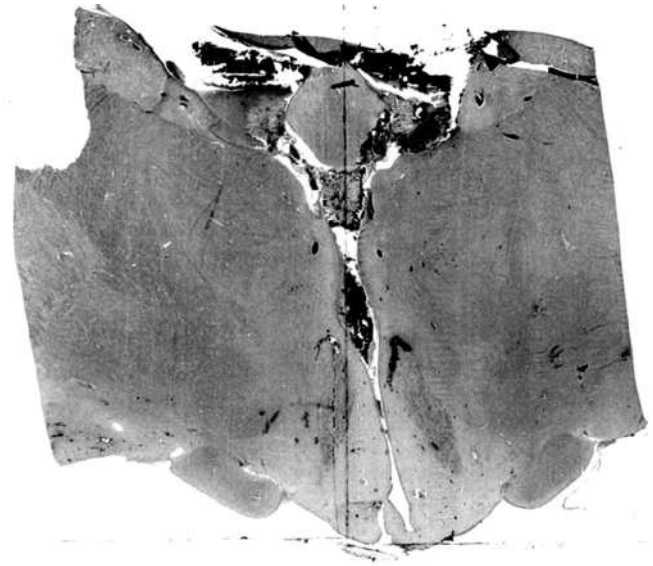


Fig. 33: Fall from height and impact on the vortex in an adult. Whole mount of coronal section of hypothalamus through infundibular area. Note haemorrhages in periventricular hypothalamic nuclei, in addition to involvement of fornix. Survival-3 hours (LFB × 5)

noted that temporo-parietal rather than fronto-occipital blows lead to hypothalamic lesions, suggesting lateral displacing forces shear the hypothalamic vessels, the upper hypothalamus moving more than the lower.[36] Downwards displacement of the brain towards the sella, by an impact on the vortex, can result in damage to the lower hypothalamus, infundibulum and upper half of the pituitary stalk, shearing the perforating vessels of the anterior cerebral arteries (Fig. 33).

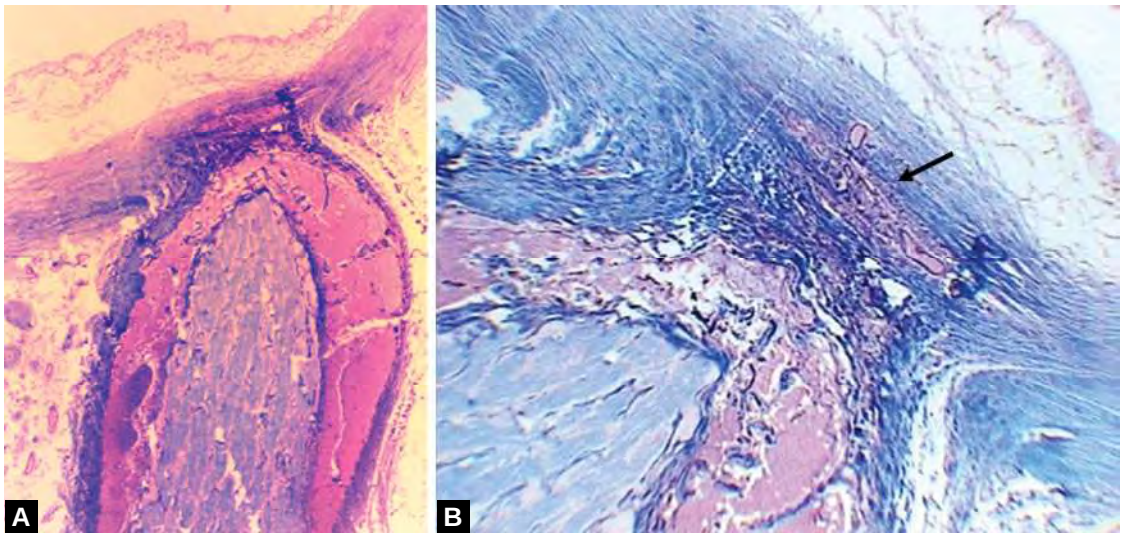
Post-traumatic hypothalamic injuries are more common in the young. In an autopsy study of 106 patients dying soon after closed head injury, Crompton recorded a hypothalamic lesion in 42.5% with it being bilateral in 22.6% of cases.[36] The pathological lesions were microhaemorrhages and ischaemic lesions involving various groups of nuclei. The microhaemorrhages were seen discreetly involving the subependymal paraventricular nuclei, lateral hypothalamic nuclei amongst the fibres of the median forebrain bundle and supra optic, but rarely in the region of the median eminence or infundibulum. Many of these are usually associated with cortical contusions indicating the diffuse and severe nature of injury though, rarely, isolated hypothalamic lesions may be seen.

Pituitary

Although an array of potential neuroendocrine problems can occur after TBI, most of the commonly encountered problems are transient in nature.[1,2] Panhypopituitarism is actually a rare post-traumatic phenomenon, but may be responsible for significant alterations in the level of the patients' consciousness. Direct pituitary trauma as an aetiology of hypopituitarism is less common than hypothalamic injury. Yuan and Wade[198] presented an overview of hypothalamic and pituitary alterations in brain trauma, the incidence of hypothalamic pituitary damage, mechanism of injury and features of hypothalamio-hypophysial defects. While hypothalamic-pituitary lesions have been commonly described at postmortem examination, a limited number of clinical cases of traumatic hypothalamo-pituitary dysfunction have been reported, probably because head injury of sufficient severity to cause hypothalamo-pituitary damage usually leads to early death. Most frequently seen are anterior lobe infarction, posterior lobe haemorrhage and destruction of the pituitary stalk.[81,87] Avulsion of the pituitary stalk with resultant interruption of pituitary blood supply is seen more often than direct injury to the pituitary. Post-traumatic haemorrhage into the neural lobe occurs, but extensive infarction is rare and, thus, post-traumatic diabetes insipidus is transient. Permanent diabetes insipidus indicates damage at a higher level; either at the infundibulum or at the hypothalamus. However, most of the damage to the pituitary is secondary to raised ICP, resultant ischaemic events reflecting multifocal brain damage. In a series of 434 traumatic victims from UK,[121] pituitary lesions, mostly consisting of haemorrhages into the posterior lobe (37%), infarction in the anterior lobe (17%), and a small number with capsular and anterior lobe haemorrhage and stalk laceration were observed. In McCormick's series of 110 cases of closed head injury, various types of pituitary lesions were seen in a large number (85% of cases).[121,122] From New Delhi, Prasad et al.[146] studied pituitary glands collected at postmortem from patients who died of head injury (n = 60) and other systemic injuries (n = 32%). They recorded capsular haemorrhage in 50%, haemorrhage and ischaemic necrosis of the anterior lobe of the pituitary in 25%, posterior pituitary haemorrhages in 20% and combined lesions in the rest. Ischaemic necrosis of the pituitary was also noted in cases with non-cranial injuries secondary to hypovolaemia, sepsis, diabetes mellitus and other systemic causes. Traumatic skull fracture was found to be associated with higher incidence of all types of pituitary haemorrhage and necrosis, though no distinct correlation with the location of the base of the skull fracture was evident.

Cranial Nerves

Trauma to the cranial nerves is not uncommon during TBI. Following gliding contusion of the orbitofrontal area or fracture involving the anterior cranial fossa, loss of olfactory sense is common. The most vulnerable part of the optic nerve is the portion traversing the optic canal. Following traumatic SAH the blood extends into the orbital portion of the optic nerve causing vasospasm. Rarely, the haemorrhage may dissect the scleral collagen and spread inside (Figs 34A and B). Severe trauma to the apex of the orbit or fracture in the middle cranial fossa extending medially can cause injury to the III, IV and VI cranial nerves and, occasionally, the Gasserian ganglion. Injury to the petrous temporal bone by lateral



Figs 34A and B: (A) Fall from height, with diffuse subarachnoid haemorrhage in the base, extending into the orbit along the subarachnoid space around the optic nerve. Note stretched dura externally (× 10); (B) Higher magnification showing haemorrhage separating scleral collagen (arrow), indicating the severe impact on the orbital cone (× 120). Masson's Trichome stain

impact can cause facial and VIII cranial nerve injuries of varying degrees. Damage to the lower cranial nerves is common following gunshot wounds or severe angular injury to the occipital bone and impact against the clivus. The injuries to cranial nerves are relatively ignored, being overshadowed in the attempt to save life.

CELLULAR/MOLECULAR RESPONSE TO BRAIN INJURY

A wide range of pathological insults to the brain, including mechanical injury, ischaemia and seizures induce the immediate early genes (IEGs), *C-fos*, *C-jun* and *jun B*. The members of the *fos* and *jun* families function as transcription factors, mediating long term adoptive responses of neurons to acute stimuli.[129,148] TBI induce changes in electrical properties of cell membranes and cytoskeletal structures that most likely result in aberrant cellular signalling pathways, which may subsequently be translated into an acute genomic response. Since these biochemical, molecular, anatomical and behavioural responses manifest as pathological damage and behavioural deficit, the study of genomic responses will help to understand the pathophysiology and evolution of traumatic injury. Most of the information available is from animal model systems and data on the human system needs to be generated. In the rat lateral fluid percussion model, the immediate early genes, *C-fos*, *C-jun* and *jun-B* were found to be increased bilaterally in the cortex and hippocampus.[141,149] The levels of *C-fos* and *jun-B* and RNA levels return to the control level in 6 hours, but *C-jun* mRNA remains elevated. Inducible heat shock protein (HSP 78, grpa4) can be observed up to 12 hours post-trauma, on the ipsilateral cortex of the impact site—which indicates stress response.[112] This stress protein can be immuno-localised in neurons, glia and endothelial cells.[181] *C-fos* and *C-jun* regulate nerve growth factor, amyloid precursor protein, opioid precursor proteins and modulate synaptic plasticity—and thus the recovery.[39,123,129,147] Further work is needed to extrapolate these observations to human beings.

Inflammation and Cytokines

Recapitulating the acute inflammatory process following acute focal brain injury like contusions, polymorphonuclear leucocytes accumulate in the damaged tissue temporarily coinciding with cerebral oedema[123] (Table 5). These cells find their way into CSF and peripheral blood to cause leucocytosis, leading to erroneous diagnosis of an infectious process. In experimental models, induction of neutropaenia has not shown a beneficial effect on the progression of oedema and tissue damage.[160,188] The macrophages replace the polymorphs to initiate the repair process and scavenging of the necrotic debris.[74] These macrophages also secrete cytokines, like 1L-1β, 1L-6 and TNF-α,[63,196,197] that initiate an excitotoxic neurodegenerative process with upregulation of

Table 5: Pathophysiology of head injury

Early traumatic process (not an event)
Traumatic brain injury → Acute perturbation → Mechanoporation in neurons lasting from minutes to 3–4 hours
Transient separation of cell membrane lipid layer from protein Components—receptors, channel proteins
↓
Sonic influx of K^+ inside and Na^+, Ca^{++}, Cl^- to outside
↓
Closure of defect by Ca^{++} activated lysolecithin patching and membrane fusion
Mild injury: Return to normal after few seconds to a few minutes (mild contusion)
Severe injury: Ca^{++} $\uparrow\uparrow\uparrow$ → severe cell toxicity

their receptors to find their way into the CSF. Thus, CNS derived cytokines may play a role in the pathophysiology of TBI.[128] This is further confirmed by the protective effect of endogenous 1L-1 inhibitors and 1L-1 receptor antagonist during the acute phase of head injury.[159,184] The cytokines, however, also produce a protective effect by induction of growth factors, astrocyte proliferation, inhibition of Ca^{++} currents and promote macrophage migration to the site as a defence mechanism.[153]

Traumatic brain damage being a dynamic process with a temporal evolution, various cellular components are involved with inflammatory damage being one of them.

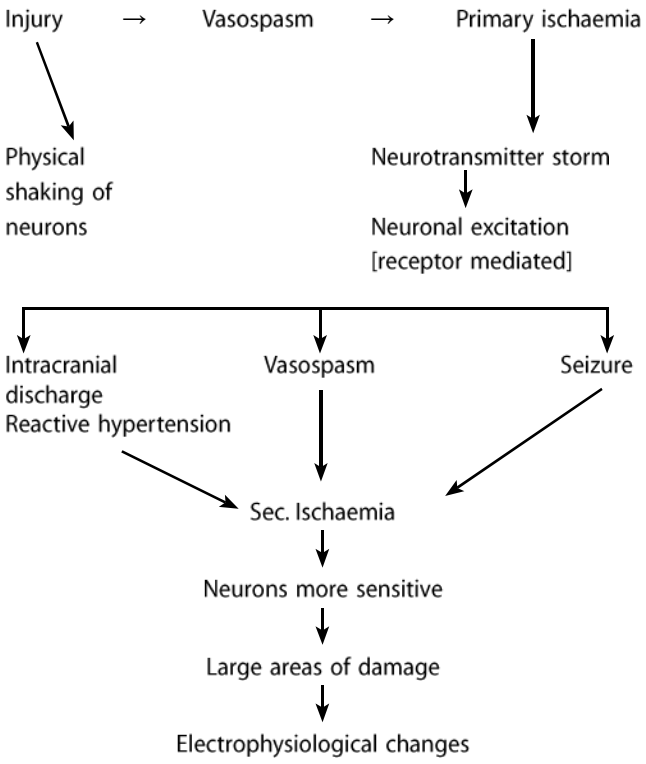
The direct impact mediated transient mechanoporation of the cell membrane and voltage channel dependent electrical activity at all cell membranes cause an influx of extracellular calcium. Similarly, NMDA receptor mediated, inositol-3-phosphate and G-protein coupled activation can cause release of intramitochondrial/intracellular calcium following trauma.[164] This causes activation of phospholipases, free radical generation through arachidonic acid metabolism and activation of deleterious proteases.[124] The protease activation in turn causes damage to the cell membrane and neuronal cytoskeleton, leading to delayed cell death. Sequestration and pumping out of the intracellular calcium may facilitate recovery. The total brain calcium concentration has been found to increase following focal or diffuse injury at the injured site, the high ionic level persisting for 48 hours in the rat model.[88,89] In the first 24 hours following injury, the axonal cytoskeletal elements, the neurofilaments, microtubules and associated proteins, their cross linking/stabilising phosphokinases get affected resulting in axonal swelling, dissolution, reduced axoplasmic flow and finally secondary axotomy. The demonstration of β-amyloid precursor protein in axons as early as 2 hours after brain injury is a reflection of these post-traumatic events.[140,166] Focal brain injury causes primary axotomy. The events of secondary axotomy are dependent on the degree of injury, mechanical distortion caused and the metabolic state of the brain at the time of injury. Though it is advocated that the node of Ranvier with a high density of ion channels is the site of injury due to high sensitivity,[6] it appears that the axons fail at the site of maximal tensile loading—the nodal, paranodal, internodal domains and not at any preordained site. Following trauma, most of the fibres undergoing reactive changes are of large calibre, long tract axons that are most likely subjected to maximal strain at some point along their length. In these fibres, reactive axonal swellings are seen at points where the axons decussate, cross blood vessels or change their intra-axial course, suggesting that sites of maximal tensile loading are prone for failure.[140,145]

Hypersensitivity of Traumatised Brain to Secondary Cerebral Ischaemia

Hypersensitivity of traumatised brain to secondary cerebral ischaemia is illustrated in Tables 6 and 7.

Table 6: Pathobiological changes caused by traumatic brain injury

Post-traumatic brain hypersensitivity to ischaemic and chemical insults



Non-traumatised brain—Tolerates same degree of ischaemia better

- Secondary ischaemia—starts 1 hour post-trauma → Brain hypersensitivty lasts for 24 hours post-trauma
- Secondary ischaemia starts → Beyond 24 hours post-trauma → Brain hyposensitive

Table 7: Neurochemical/neurotransmitter changes

Traumatic brain injury

- Injury induced membrane depolarisation
- Activation of voltage dependant channels
- Acetyl choline ↑↑↑—brain, cerebrospinal fluid
- Reduced binding or low affinity → Cholinergic receptors (muscarinic)
  → In Hippocampus, brainstem, for 2 weeks
- Acetyl choline excitation → Behavioural abnormalities and cognitive deficits
  (R_X: Anticholinergic drugs useful !!!)
- Catecholamine/monoamine—alterations proportional to degree of injury
- Levels and receptor binding
  ↓
  Vasomotor changes
- 5HT levels ↑↑↑↑ — cerebral hemisphere—same side of injury
  ↓
  Glucose internalisation reduced
  ↓
  Anoxic injury
- Dopamine levels (transporter ↑↑↑↑)
  - Down regulation of dopamine receptor (↓↓)

Contd...

Contd...

- Excitatory amino acids ↑↑↑ (hippocampus, neocortex)
  - Immediate lasts for 4–6 days
- Fall in Mg^{++} levels → secondary damage via neurochemical path and influx of Ca^{++}
- Rise in Ca^{++} levels → lasts for 2–4 days

↓

Cytoskeletal damage (within 24 hours)

- Accumulation of amyloid precursor protein (within 24 hours) for repair

Secondary insults like hypertension, hypoxia and global ischaemia worsen the bioenergetic, electrophysiologic and behavioural status of humans or animals subjected to TBI. Mild TBI or transient forebrain ischaemia, by themselves, do not result in appreciable histological changes, but when mildly traumatised brain is subjected to ischaemia, sequentially enhanced selective vulnerability and regionally restricted (like hippocampus) delayed ischaemic neuronal cell death can be noted in the absence of any initial overt pathological changes.[20,90] This exemplifies the phenomenon of brain hypersensitivity to secondary cerebral ischaemia, which is well studied in the fasting cat[92] and rat model.[44]

It is now becoming well established that a mild TBI, not capable of evoking overt structural cell change, can elicit a net phase of neuroexcitation by release of multiple neurotransmitters. These neurotransmitters in turn lead to receptor mediated calcium channel gating and calcium influx, disturbed neuronal ionic homeostasis, yet not enough in magnitude and duration to result in lethal injury.[44] Paralleling these traumatically induced changes, it is now well established that during ischaemia, extensive ionic shifts occur, including calcium homeostasis. This is related to energy failure, inactivating energy dependent ion membrane pumps, fall in cellular membrane potential and calcium influx via the voltage gated calcium channel (NMDA). This is further aggravated by post-ischaemia excitatory neurotransmitter release (similar to traumatic injury) and calcium influx as mentioned earlier.[30] When these compounding events occur in tandem, they result in significant tissue damage. But, when they manifest in sequence, the deranged calcium homeostasis can cause delayed and diffuse neuronal damage. This sequence of events can be reduced or abrogated in animal models by use of drugs competitive to muscarinic acetylcholine receptors (scopolamine) and the noncompeting NMDA antagonist, phencyclidine.[92] These cellular events can manifest, especially in some neuronal populations like the hippocampus, with long lasting changes in excitability thresholds and abnormal neuronal function as a consequence of aberrant stimulation of key regulatory calcium response elements. This trauma induced calcium influx mediated hypersensitivity to secondary ischaemia appears to persist for at least up to 24 hours post-injury. Interestingly, if more than 24 hours elapse between the traumatic and ischaemic insults, the brain becomes hyposensitive.[144] Though many of these observations are made in animal models, they have significant clinical relevance. In traumatically brain injured patients, ischaemic events can be precipitated by vasospasm and secondary intracranial hypertension. If the injured patient was fasting, was hypoglycaemic due to diabetes or in shock the resulting ischaemia during the window period may significantly and adversely alter the clinical course. Whether pharmacokinetic alteration of receptor mediated ionic imbalance during the critical period will be of use needs evaluation.

Ionic Events and Role of Excitatory Amino Acids in Traumatic Brain Injury

TBI, during the evolution, depending on the site, diffuse or focal and the severity, pass through different stages of physiological progression. The knowledge has been accrued through different experimental models. The ischaemic changes in the hippocampus, noted at postmortem following TBI, need not be caused by actual hypoxic or anoxic insults. Following a focal injury, either in clinical TBI or in the experimental setting, the adjacent brain shows decrease in CBF. A global decrease in blood flow with ischaemic changes rarely manifest, unless ICP rises uncontrollably.[186] One major event that occurs at the moment of impact in neuronal cells is the sudden and massive ionic influxes across the cell membrane of Na^+, Ca^{++} and Cl^1 and efflux of K^{+134}. In close impact injury, proportional to the degree of impact the shear, tensile or compressive strains generated, the ionic fluxes could be over wide brain areas.[98,99]

Following sudden efflux of K^+ $[(K^+)_e]$ a sequence of events are observed immediately in animal models, that probably occur in clinical practice as well.

1. As the magnitude of trauma crosses a threshold, an abrupt efflux of K^+ occurs from a baseline of 3–6 mM to a maximum of 60 m with membrane electrical changes and traumatic depolarisation (TD). As long as a large strain is generated, the K^+ efflux occurs over a wide area of the brain simultaneously. This can be observed bilaterally in the cortex, hippocampus and brainstem, especially following a blunt injury causing oscillation of the brain. In a restricted injury, this sequence of events could remain unilateral.[45] The recovery from the increase in K^+ to the baseline level takes a variable period of time, from 3–8 minutes.
2. Localised mechanical or K^+ ionic membrane stimulation induces other ionic events called spreading depression (SD), a pattern identical to $[K^+]_e$ with a threshold. The SD causes sudden disruption of other ionic homeostasis. The SD is usually localised, spreads slowly to adjacent areas and recovers soon unlike TD.[133]
3. Following injury, energy failure and anoxia, abrupt and rapid ionic fluxes occur with a short latent period of a minute, called anoxic depolarisation (AD).[79]

The three events TD, SD and AD, either in tandem or in various combinations, can disrupt the powerful mechanisms maintaining ionic homeostasis.

During traumatic brain and ischaemic injury, concomitant with a large increase in K^+ efflux, excitatory amino acids are released as a result of depolarisation at nerve terminals.[98,99] Denervation of the glutaminergic afferents have been shown to delay ionic changes in the hippocampus during ischaemia.[14] Receptor ligand gated ion channels opened by sudden indiscriminate release of EAA causes sudden influx of calcium, further enhanced by TD, SD and AD, thus a malignant cycle ensues. The massive ionic fluxes lead to cytotoxic oedema.[190] During this period the energy metabolism of the brain increases to activate energy-dependent ion pumps and ATP hydrolysis to restore the ionic homeostasis. This energy dependent ion pump activation and glycolysis, in TBI, causes accumulation of lactate and free fatty acids within minutes after injury.[46] This TBI is severe in states of low energy stores like hypoglycaemia, starvation, cold temperature and diabetic state. With the occurrence of TD following injury, in addition to the neurons, the astrocytes and microglia also get activated in an hour and start proliferating.[99] The activated astrocytes mop up extracellular K^+, convert excitatory glutamate to glutamine and try to envelop the neurons to guard against the ionic flood. The microglial cells, the macrophages of the brain are sensitive to depolarising events and become activated, releasing cytokines.[100] These cytokines can further damage the already injured neurons. The microglial activation can be prevented by antagonists to receptors of excitatory aminoacids.[99]

Role of Apolipoprotein E in the Outcome of Head Injury

Apolipoprotein E (ApoE) is a key component of the system involved in lipid transport in the nervous system. It transports cholesterol and phospholipids to the injured neurons and helps in repair of the cell membrane, neurite growth, dendritic remodelling and synaptogenesis.[142] Following injury there is a coordinated increase in the expression of ApoE by astrocytes and LDL receptors by neurons, facilitating the transport. Transient global ischaemia is found to dramatically increase ApoE immunoreactivity of neurons within a few hours after injury in the rodent model.[86] In man, there are three common alleles of ApoE gene located on chromosome 19, designated E_2, E_3 and E_4. The association between ApoE-E_4 and Alzheimer's disease has been confirmed worldwide. A tenfold increase in the risk of Alzheimer's disease was associated with ApoE-E_4 and history of traumatic injury. Head injury in the absence of ApoE-E_4 allele did not increase the risk. Given the similarities between Alzheimer's disease and dementia pugilistica, recent studies suggest that possession of ApoE-E_4 allele is associated with increase in the severity of chronic neurologic deficit in high exposure boxers.[95] Deposits of amyloid β protein (A beta) are found not only in cases of dementia pugilistica but in nearly 30% of patients with a single episode of severe head injury.[69] However, one study from Rotterdam, the Netherlands did not find trauma to be a major risk factor for dementia or AD in the elderly and ApoE genotype may not be associated with the clinical outcome.[127] This could be related to ethnic variability and needs further evaluation.

Polymorphism of ApoE gene appears to influence the neuropathological findings in a patient who dies of head injuries. More people who die from head injuries compared with non-head injured controls have deposits of amyloid beta-protein in the cerebral cortex, the amyloid β-protein deposits being present predominantly in patients with the ApoE-E_4 allele.[182] This shows a significant genetic association of ApoE polymorphism with outcome after TBI. Patients with ApoE-E_4 are more than twice likely to have adverse outcome 6 months after head injury than those with other genetic alleles. These observations have provided the first evidence for a link between a genetic susceptibility (ApoE-E_4) and an environmental trigger (head injury) to the development of Alzheimer type pathology[70] and also a genetic susceptibility to the outcome of brain injury.[52] Experimental studies have shown that following subdural haematoma, a rapid cellular redistribution of ApoE occurs and precedes a significant elevation in the levels of ApoE. These alterations in ApoE may occur initially as a part of the brain protective response to injury.[84]

Recent animal model studies using ApoE-deficient (knock out) mice revealed that these mice have memory deficits and neurochemical derangement and poor recovery following closed head injury than control mice.[85] This response appears to be due to reduced ability of ApoE deficient mice to counter antioxidative damage and further confirms the protective role of apolipoprotein in traumatic injury to the brain.[111]

Recently, a higher frequency of ApoE-E_4 was reported in patients who did not recover from post-traumatic coma than in those who recover consciousness soon.[170]

Ethanol Potentiation of Central Nervous System Trauma

Alcohol consumption has been a major risk factor in occurrence of neurotrauma. A study from Bangalore has noted that 16% of TBIs were related to the effect of alcohol consumption and the mortality was two times higher in this group.[26,27] A series of counter measures like education and legislation enforcement have yielded results in reducing alcohol related TBI to a variable degree.[75] A growing body of evidence indicates that moderate ethanol intake, even in the presence of adequate nutrition, may result in cell injury and cell death in the myocardium, liver and nervous system. Ethanol and its principal metabolite acetaldehyde, because of their lipophilic nature, get intercalated into the cell membrane, altering the biochemical and biophysical properties. In addition, the free radicals generated damage the cell membrane and other structures like mitochondria, depleting the

energy system.[23] To understand the pathology further, Flamm et al.[50] studied a cat model where the spinal cord and brain were subjected to impact injury in animals infused with alcohol. At the time of impact the blood alcohol was 450 mg% and after 24 hours, alcohol was not detectable. The animals which received the impact injury after alcohol infusion, showed disappearance of evoked potentials immediately after injury, and haemorrhages and oedema involving both grey and white matter 5–24 hours after injury. Nearly 80% of animals remained paraplegic, while a few regained the evoked potentials and recovered partially. The control animals, which had not received alcohol, had normal evoked potentials immediately following the injury. The spinal cord, 5–24 hours after impact, was essentially normal or had small haemorrhages. After 5 days the animals were mobile and 6–9 weeks after injury, they exhibited difficulty in walking. With minor injury to the brain, the control and alcohol infused animals were essentially normal. With greater impact, the alcohol infused animals had three to four times more extensive oedema and haemorrhages when compared to non-alcohol infused control animals. Altered platelet function, acetaldehyde induced mitochondrial damage and deranged adrenergic vasotonic activity following alcohol administration could be responsible for haemorrhagic lesions and oedema.[34,192] Free radical induced inhibition of Na+/K+—ATPase activity in the membrane could contribute to depressed evoked potentials. Synergistic action of alcohol and trauma produce the effect in neural conduction and late deleterious sequelae, which either of them individually could not produce. These features observed in the canine model appear to have significant relevance to human TBIs following alcohol consumption.

USE OF MRI IN ASSESSING THE TRAUMATIC BRAIN INJURY

MRI and related magnetic resonance techniques are more sensitive than CT in detecting and defining the focal and diffuse brain injury following trauma. Prediction of the outcome by imaging is dominated by a few variables like intracranial haemorrhages, brain swelling and DAI. CT may show petechial haemorrhages, but these punctuate lesions may resolve quickly and less than 20% of DAI is macroscopically haemorrhagic.[56] Small lesions and non-haemorrhagic lesions in the lobar white matter, corpus callosum and brainstem are detected in the MRI due to its excellent resolution. In adults, continued restlessness and agitation 2 months following TBI is associated with delayed T1 and T2 weighted signal abnormalities in the frontotemporal area and poorer outcome beyond 6 months after injury and some remain in persistent vegetative state.[17] Similarly, in a large study of children following TBI, the presence of large volume lesions in the frontal lobe correlated with defect in learning and memory function.[43] It appears that atrophy and compensatory hydrocephalus may be associated with bad outcome and long-term sequelae[82] detected on MRI, especially the frontal horn and III ventricle. During the acute phase, MRI image hypodensities noted in the deep dorsal brainstem indicate a poorer prognosis than those in the ventral and superficial brainstem, correlating with the pathological changes described.[167] Essentially, the late imaging correlates better with prognosis than the early MRI findings. Gadolinium enhancement of MRI in the acute phase highlights the injury to the BBB and the evolution of the lesion following injury.[174]

The features like small haemorrhages not detectable on T1 or T2 weighted imaging become evident in the gradient spin echo sequence. In children, especially, the abnormalities detected in gradient spin echo sequences at 3 months after injury correlate with both the severity of initial injury and also the outcome at 1 year.[64] In adults also, abnormalities may be noted in the gradient echo sequence within 5 days, but may not correlate with the outcome.[83] Diffusion weighted imaging sensitive to random movement of water molecules shows initially restricted diffusion (representing cytotoxic oedema) followed by unrestricted diffusion (vasogenic oedema) highlighting the evolution of dynamic events in the acute phase. The features are essentially similar to the evolution of clinical stroke. In a study of five severely injured patients in the first few days following TBI, restricted diffusion was noted in the brain surrounding focal lesions, which had normal signal intensity on T2 weighted imaging.[94] Lagares et al. found the anatomical substrate of TBI depicted by MRI to be a useful prognostic tool in patients with moderate and severe head injury. Patients with a score of 4 or less on the motor subscale of the GCS scale were those who benefited most from the prognostic information provided by MRI.[106] In paediatric TBI, assessment of DWI and ADC values is useful in evaluation, especially in those areas of brain that appear normal on conventional imaging. Early identification of children at high risk for poor outcome may assist in aggressive clinical management of paediatric TBI patients.[53]

Perfusion weighted imaging shows regional reduction in CBF and is sensitive to microscopic tissue level blood volume changes. Recent studies by perfusion weighted imaging have revealed reduced cerebral perfusion, both in the regions of contusion and also apparently normal surrounding brain, bringing to light the widespread nature of damage, which has a bearing on outcome.[55]

Bosnell et al.[19] studied the application of diffusion tensor imaging in recovery from TBI and summarised its uses as below:

- Monitoring pathological change
- Predicting recovery
- Identifying individual targets of therapy
- Providing outcome measures
- Providing measures of potentially compensatory structural changes
- Understanding of normal brain anatomy to aid in interpretation of the consequences of localised damage

Proton magnetic resonance spectroscopy (MRS) in clinical studies revealed reduction in N-acetyl aspartate in the white matter, reflecting DAI and poorer clinical outcome.[12,54] The occurrence of choline and myoinositol peaks reflect the reactive astrocytosis accompanying the DAI, neuronal damage and oedema.[54] Lactate is seen in severely injured adults within the first few hours in the contused brain. In children, visible levels of lactate indicate a poorer prognosis.[12] One recent phosphorous MRS study in severely injured patients during the acute phase revealed increase in phosphocreatine: inorganic phosphate ratio and alkaline pH in the regions of normal appearing brain, reflecting the depleted energy state of neurons and reactive astrocytosis.[57]

Single photon emission computed tomography may be the only examination to reveal perfusion abnormalities which are related to symptoms in the absence of other objective findings, such as post-traumatic amnesia, vertigo or personality change.[101]

Functional MRI, sensitive to the oxidative state of haemoglobin, reflecting oxygen extraction and regional activation, has not been widely used to study TBI. In one study of a patient with mild TBI, within 1 month, the regions of activation for memory were found to be similar to control subjects, but an altered degree of activation was noted with increasing processing load for memory, especially in the frontal lobes.[120]

Mamere et al. used a set of quantitative MR imaging techniques which could non-invasively demonstrate the neuronal and axonal damage in the normal appearing white matter and corpus callosum of human brains, secondary to moderate or severe TBI. The quantitative techniques used by them included: bicaudate and bifrontal ventricle-to-brain ratios, T2 relaxometry, magnetisation transfer ratio, apparent diffusion coefficient and proton spectroscopy by using an NAA/creatine ratio.[116]

Neuropathology of Post-Traumatic Sequelae

Severe disability after head injury is usually associated with abnormalities in the rostral brainstem, intracranial haematoma (SDH and intracerebral), cerebral oedema, circulatory and respiratory disturbance—thus, indicating the role of secondary events in the evolution during the first 1 month. These secondary events persist and are seen more frequently in patients who were vegetative for more than 1 month, especially with DAI and ischaemic damage. In patients with persistent vegetative state, widespread bilateral neocortical and white matter lesions are seen, some of them are cavitatory.

Late traumatic epilepsy is by far the most frequent complication of blunt head injury, the risk being higher in patients with intracerebral haematoma or compound depressed skull fracture and surface contusion. In adults, early epilepsy (occurring during the 1st week after head injury) is rare unless it is associated with depressed fracture, dural penetration, cortical laceration, intracerebral haematoma, retained foreign body and post-traumatic amnesia. Early epilepsy is common in children. This suggests a close association between focal brain damage and traumatic epilepsy. The epileptogenesis results from a combination of glial scar,[139] ischaemic lesions and disordered neuroglial function.[143] Willmore[193] postulated that the presence of blood in the neuropil is a critical aetiological factor. Iron liberated from haemoglobin and transferrin may be important in epileptogenesis based on the experimental evidence in cats and rats that had focal epileptiform seizures following injection of ferrous chloride into the sensorimotor cortex.

Temporal lobectomy specimens from cases of post-traumatic epilepsy, unlike idiopathic TLE, show less of Ammon's horn neuronal loss and gliosis and the outcome is better with temporal lobectomy.[119]

Neurologic diseases with possible connection with head injury include Alzheimer's disease,[33,135] Parkinson's disease[73] and motor neuron disease. Association with the occurrence of Creutzfeldt Jakob disease has also been suggested. A large number of concussive or subconcussive blows, as common in boxers, induce the development of progressive dementia.[29,61] In a detailed study of brains from ex-boxers, the pathological features noted were cavum septum pellucidum, fenestration of the septum, thinning of the fornix and corpus callosum, neuronal loss in the cerebellum and loss of pigmented neurons in the substantia nigra.[38] Numerous neurofibrillary tangles distributed diffusely in the cerebral cortex and in the brainstem and conspicuous scarcity or absence of neuritic plaques classical of Alzheimer's disease is observed. The brains of boxers[29] and those subjected to prolonged domestic violence[152] have numerous non-neuritic diffuse plaques not identifiable by congo-red or silver stains, but labelled by antibody to β amyloid protein. This is probably mediated by upregulation of glial cytokines and β amyloid precursor protein as a protective stress response.[72] Post-traumatic SAH may cause impedance to CSF circulation and can lead to communicating or obstructive hydrocephalus. Reduction in brain volume due to multiple ischaemic lesions and diffuse DAI may contribute to further normal pressure hydrocephalus manifesting with dementia.

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Pathology and Pathogenesis of Spinal Cord Injury

INTRODUCTION

Injury to the spinal cord is not just an acute disease. Long after the initial injury, the chronic long-term effects on the body are staggering because, although the pathology that occurred in the cord itself may have become fixed or static, the other organ systems including sensorimotor, respiratory, gastrointestinal, urinary and reproductive systems in the body undergo progressive changes that adversely affect function.

Initial research in spinal cord injuries (SCIs) was focused on detailing those pathological events responsible for the irreversible cord damage following injury. Now, renewed interest in the field has followed spectacular progress in inducing central nervous system (CNS) repair and regeneration that may make a "cure" for spinal paralysis a reality in the near future. But, for these discoveries to be applied to human SCIs, an in-depth knowledge of the pathology and pathophysiology is essential. In order to fully appreciate the pathological sequence of structural alterations in SCIs, it is also essential to keep in mind that the response of living tissues to injury undergoes continual changes with time. The key to the development of treatment strategies is dependant on the elucidation of the various sequential steps involved at the molecular level so that the process can be arrested or reversed before the onset of irreversible damage.

The annual incidence of SCI in various countries ranges from 15 cases to 40 cases per million population.[55] In civilian life, the most common causes are road traffic accidents, sports and recreational activities, accidents at work, falls and violence. SCI is the price we pay for modernisation and advent of industrialisation.

CLASSIFICATION OF SPINAL CORD INJURIES

SCI can be classified as "open" and "closed" injuries depending on the dynamics of the force, the separation into the respective categories being dependant on the integrity of the dura. In general, open injuries result from sharp or penetrating injuries while blunt force causes indirect or closed injuries by transmission of the mechanical impact to the cord without injury to the spine. A combination of the two may also occur as in fracture dislocation resulting from blunt force, wherein the dislocated bony spicules can cause penetrating injury and tear of arachnoid/dura.

Mechanisms of Closed Injuries

The mechanisms and classification of injuries of the spinal column have been a controversial issue with many differing views, as the forces generated produce not only displacement but also a combination of three-dimensional linear and rotational forces. Roaf[45] proposed that the mechanism of injury and the anatomical lesion that results is best described by indicating the direction of the resultant vector and the axis of rotation. Unlike the moveable head, the spinal cord is rarely submitted to acceleration injury. Accordingly, SCI are most often classified into four groups according to the most predominant factor at the time of injury as: (1) flexion and deflexion injuries; (2) vertical compression; (3) rotational injuries and (4) those with a combination of forces. All these mechanisms, except vertical compression, are associated with crushing of the cord. Vertical compression injuries often produce incomplete cord lesions.

Flexion and Deflexion Injuries

Ventroflexion and dorsiflexion forces produce deformities of the spine with or without accompanying cord injury. In this form of trauma, three types of forces come into play: (1) transverse shear; (2) longitudinal shear and (3) torsion. Among these, transverse shear is the most important. Flexion and deflexion injury is the most common mechanism of neck injuries (e.g. whiplash injuries) and results in anterior and posterior longitudinal ligament tears. The cord gets stretched diagonally upwards resulting in a transverse tear if there is a fracture dislocation or protrusion of the disc just above the fulcrum in both types of injury.

Flexion (anteroflexion/hyperflexion) injuries: Minor degrees of anteroflexion forces produce only dislocation or deformities of the spine without any cord lesion unless the cervical spine is pathologically stiff, but extreme hyperflexion injuries result in severe spine deformities leading to fracture, fracture dislocation of vertebral bodies, prolapse of discs, dislocation of articular processes, and is associated with severe local damage to the cord causing central necrosis and haemorrhage.

Acute anterohyperflexion of the neck in infants causes fatal central cerebral haemorrhage or haemorrhagic necrosis of the medulla or upper cervical cord.

Hyperextension injuries: The term "hyperextension injuries" encompasses retroflexion or dorsiflexion forces, and fracture dislocations caused by facial or frontal injuries. Roaf[45] was of the opinion that this term is inaccurate as extension would literally mean longitudinal distraction. Such forms of pure extension injuries are rare and happen with excessive skull traction[25], which causes fractures of the neural arches and, rarely, cord damage. But the majority of injuries to the cervical cord result from facial or frontal trauma as in a blow to the forehead or diving into shallow water and, in this form of injury there is retrohyperflexion of the head and neck

with or without rotation. As the mechanism involved is not pure longitudinal distraction, it forces the articular processes of the mid cervical vertebra backwards to cause separation of the body from the intervertebral disc or fracture dislocation with compression of the articular processes. Further separation will lead to tear of the anterior longitudinal ligament. The posterior longitudinal ligament buckles up, squeezing the cord backwards over the lower vertebra causing partial or complete transection of the spinal cord. The correct biomechanical term proposed for this form of injury is "deflexion"[45] or "retro-deflexion"[11] as disruption of the ligaments can only be produced if there is rotational force in addition to flexion and hyperextension.

In elderly persons with cervical spondylosis, dorsiflexion causes significant cord damage by tearing of the intervertebral disc and angulation of the cord already narrowed by ankylosing spondylitis.

Retroflexion of the head and neck causes central cord injury which can take the following forms:

- Small intramedullary haemorrhages with oedema (focal haematomyelia, representing butterfly-like central haemorrhage or haemorrhagic necrosis in the grey matter)
- Direct contusion of the cord (ischaemic malacia caused by squeezing of the cord)
- Central concussion with surrounding oedema and central ischaemic infarct due to vascular insufficiency caused by compression of the vertebral arteries.

Compression Injuries

The vertebral body absorbs compression injuries caused by vertical impact and cause vertebral fractures while the ligaments are intact. Such injuries follow a fall on the head or neck, car accidents, etc. resulting in flattening of the vertebral body, fracture of end plates and rupture of the nucleus pulposus.

Such injuries affect the thoracolumbar junction (most moveable part of the thoracolumbar spine) or lower cervical spine. Protrusion of the fractured vertebral body (posteriorly more often than anteriorly) or the intervertebral disc (acute retropulsion) in the transverse plane causes compression of the spinal cord.

Rotation Injuries

This can affect any part of the vertebral body, its articulations and the ligamentous complex to cause fracture dislocations (unilateral/bilateral, stable/unstable) and displacement of the intervertebral discs. This most often involves the thoracolumbar junction and the upper lumbar spine. Compression leads to cord injury and this type of injury is also associated with lesions in the cord and roots in the region of the cauda equina.

Combined Mechanisms

Pure extension or flexion injuries do not produce ligamentous rupture, disc destruction or fracture dislocations and requires coexisting rotational forces. Dislocations are the most common in the cervical spine due to its marked mobility, followed by the lower thoracic and thoracolumbar spine.

Flexion-rotation injuries produce unstable fracture dislocations that are associated with rupture of the posterior longitudinal ligaments, separation of spinous processes and unilateral or bilateral facet dislocations. Bilateral dislocations are more often associated with compression or crush injury of the cord.

In hyperextension (retroflexion) injuries of the neck, the anterior longitudinal ligament ruptures with posterior dislocation of the vertebral body that compresses the cord. In patients with cervical spondylosis, even minor injuries can cause subluxation without rupture of the anterior longitudinal ligament.

In the so-called "whiplash injuries", there is ventro/dorsiflexion of the cervical spine with rotation, compression and anteroposterior angular acceleration. This causes excessive distortion with soft tissue damage, in addition to damage to both anterior and posterior ligaments, the nerve roots and disc with or without cord injury.

Types of Cord Lesions in Closed Injury

For the pathologist, a classification based on the nature of the lesion is more meaningful rather than one based on the mechanics of trauma and is similar to that used for craniocerebral injuries:

- Primary traumatic lesions—which are the immediate result of direct trauma on the cord
- Secondary traumatic lesions—that develop from non-traumatic secondary sequelae resulting from the circulatory alterations, oedema, etc.
- Late sequelae of both primary and secondary traumatic effects that include repair, regeneration and secondary tract degeneration. Late complications and delayed progression (myelopathies) that occur at various intervals.

Primary Traumatic Lesions

This includes all local lesions at or adjacent to the site of impact caused by direct trauma as in laceration of the cord coverings, extradural, intradural and subarachnoid haemorrhages. The damage to the cord ranges from petechial haemorrhage and oedema to central necrosis, and damage to the vasculature or nerve roots.

Extramedullary haemorrhages: Traumatic epidural, subdural and subarachnoid haemorrhages are uncommon in adults and, also, rarely severe enough to cause cord compression. Subarachnoid and extradural haematomas are more common following birth injury and perinatal distress. Spinal subdural haematomas, similarly, are rare in adults except if there is associated bleeding tendency and more common in neonates following obstetric trauma. This is an important cause of perinatal paraplegia.

Concussion of the cord: Concussion is by definition a functional disorder, which is reversible and is produced by blunt direct injury without anatomically discernible damage to the cord. Like its cranial counterpart, it is associated with transitory changes in the nerve cells (neuronal chromatolysis and necrosis), fibre tracts, focal myelin and axonal breakdown, small haemorrhages, oedema and microscopic foci of ischaemic necrosis. The pathological events in concussion of the cord is focused in the grey matter, and results in haemorrhagic necrosis. Hypoperfusion of the grey matter, which is the initiating factor along with increase in intracellular calcium and reperfusion injury, plays a key role in cellular injury. The extent of necrosis depends not only on the amount of initial force of trauma but also the concomitant compression, perfusion pressures and blood flow, and administration of pharmacological agents. Preventing these mechanisms in the initial stages will limit the cascading effects.[50]

Compression: This may result from fracture dislocation of the vertebra, prolapsed disc, exostosis and spondylitic changes and, rarely, from extensive extramedullary haemorrhage. Compressive effects are more often encountered in the cervical region than the thoracolumbar, which has greater degree of space within the spinal canal.

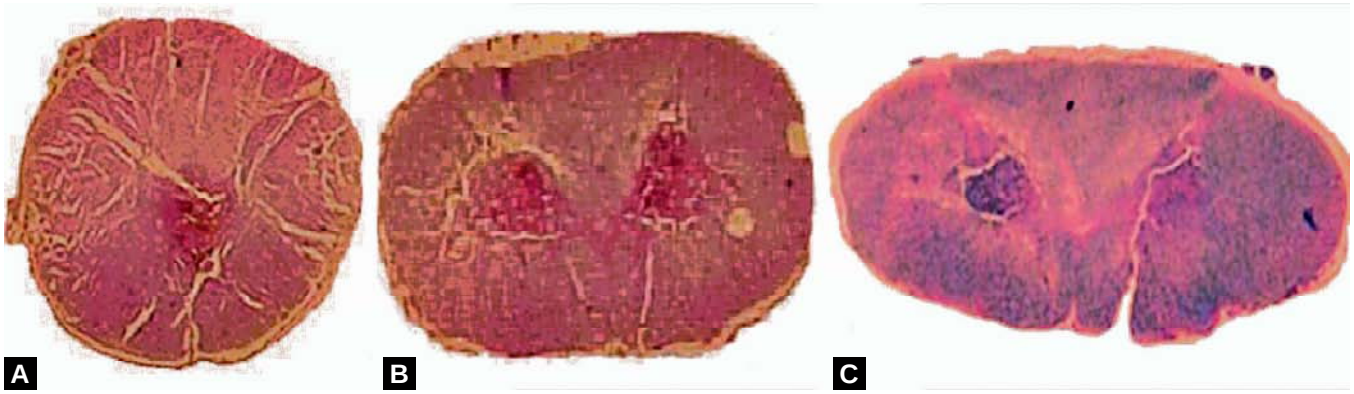
The pathological changes caused by compression include necrosis with or without haemorrhage or non-necrotic changes depending on the duration. The effect of short duration compression on the cord and its vasculature is almost the same as that found in concussion, while compression of greater intensity and duration produces marked oedematous swelling both above and below, and complete transverse necrosis at the level of compression. On sectioning there is central haemorrhage and softening occupying the central grey matter with variable spread into the white matter. The central necrotic tissue can extend in either direction in the posterior columns. These can later be transformed into cystic cavities. Ischaemic infarcts can occur rarely in the segments remote to the site of impact due to compression of radicular or anterior spinal arteries. In compression injuries, wherein the patient survives for longer duration, the acute phase subsides and is gradually replaced by a reparative process that causes demyelination and cavitation of the central grey matter, which is eventually replaced by a glial or collagenous scar. In cases surviving for months or years, the level of impact is marked by a dense scar that is adherent to the meninges obliterating the arachnoid space. The cord itself becomes thinned out and sclerotic or is converted into a fibrous or gliotic band. Apart from gliosis and demyelination as described above, axonal loss is also observed. This occurs in the white matter, whereas grey matter structures are relatively preserved. Critical compression of the cord will result in collapse of the venous side of the microvasculature, resulting in vasogenic oedema, which in turn may lead to rapid progression of dysfunction.[36]

Contusion of the cord: The term connotes all primary injuries to the spinal cord and its coverings caused by indirect blunt violence transmitted to the cord. It includes all non-disruptive injuries without evidence of continuing compression. It ranges from small petechial haemorrhages and oedema to extensive crush injuries wherein the cord tissue is pulped, but complete tears are rare. The pathology, similar to cerebral contusions, evolves over three consecutive stages:

1. An early phase of haemorrhage and necrosis
2. An intermediate stage wherein the process of resorption and organisation begins
3. The final stage of scarring or syringomyelia.

Acute stage: The immediate changes that follow acute injury are oedema and intramedullary haemorrhage, tissue disruption, inflammation, vascular alterations and effects on the preserved axons and myelin. Initially the most obvious abnormality is tissue disruption, which is followed by oedema, which appears within minutes and takes an hour or two to develop fully. Grossly visible bleeding may not always be present. At the site of impact, the cord is flattened and grooved transversely (Fig. 35) or swollen and bluish-red, but intact. On cross-section, the cord shows haemorrhage within the central grey matter, which can either be confined to only the central part or extend into one or both posterior horns or assume the typical H-shaped configuration of butterfly haemorrhages (Figs 36A and B).

Fig. 35: Road traffic injury with upper cervical cord injury (arrow). Survival up to 5 days



Figs 36A to C: Cervicomedullary. (A) Upper cervical segments. (B) Showing haemorrhagic necrosis of grey matter (HE × 10). Myelin stain. (C) Showing widespread demyelinating ischaemic lesions (LFB × 10)

Microscopically, petechial haemorrhages are the first to appear within the central grey matter caused by extravasation of erythrocytes from thin-walled vessels. Haemorrhages occur initially around the ventral part of the posterior horn and around the central canal. Differential vulnerability of the central grey matter of the cord is attributed to the grey matter being softer and more easily expandable as well as the differential vascularisation of the grey over white matter.

The initial leakage of RBCs is followed by engorgement of the capillaries and veins, which is seen as early as 2 hours post-trauma leading to rupture with leakage of plasma into the tissues. In crushed areas, there is fibrinoid necrosis or occlusion, and thrombosis of the intramedullary veins with compression of arteries and meningeal vessels within 24 hours of injury.[59] In addition to haemorrhages within the central grey area, there is also a zone of mechanically disrupted tissues causing rupture of cell membranes and liquefaction necrosis caused by dissolution and disintegration. The neurons in the adjacent grey matter show chromatolysis and progressive ischaemic cell death attributed to a disorder of the microcirculation as the endothelium of the intact capillaries swell reducing perfusion through the injured segment causing local tissue hypoxia.[57]

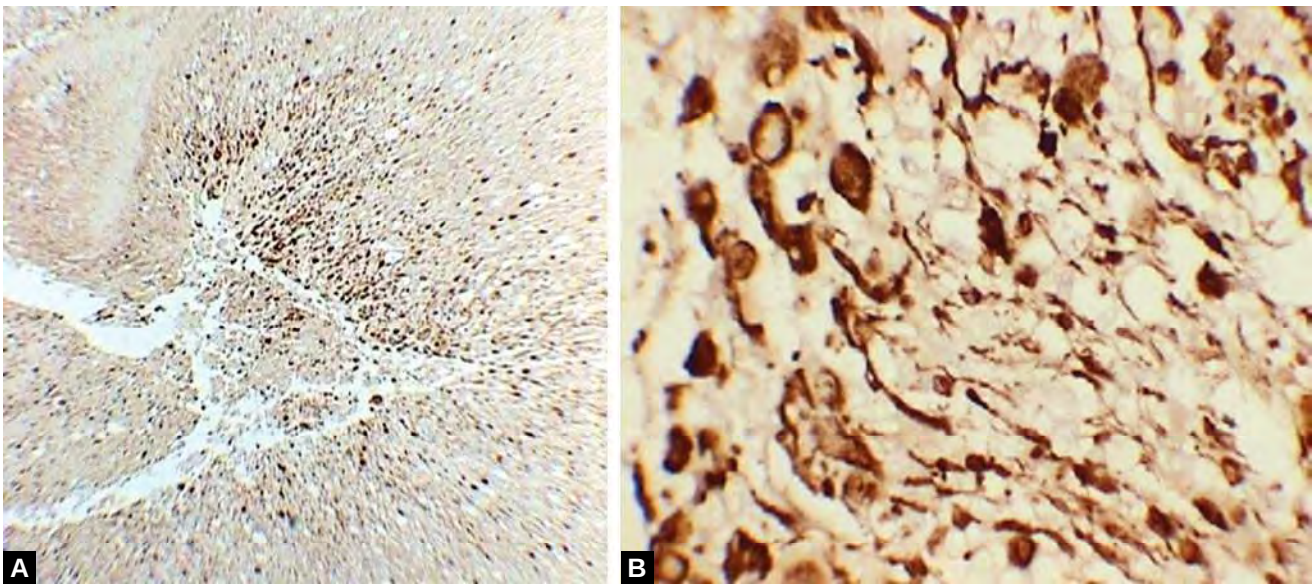
The haemorrhagic necrosis is accompanied by oedema that expands and loosens the neuropil, and distends the white matter causing separation of the fibre tracts giving it a honeycomb appearance. Both haemorrhage and oedema show a centrifugal pattern of spread from the central grey matter to the adjacent posterior and posterolateral columns of white matter to eventually involve the entire transection of the cord, which becomes round and tense within the covering meninges obliterating the subarachnoid and the subdural spaces. These then tend to spread longitudinally upwards and downwards rather than in a transverse direction and are responsible for deterioration following injury. The tendency to spread in the longitudinal axis is explained by the looser texture and greater vascularity of the grey matter enclosed by linear compact fibre tracts. The resultant centrally located, but elongated solid clot extending over several segments is termed "haematomyelia".

Apart from the haemorrhage and oedema, exudation of polymorphs followed by monocytes begins from the vessel walls into the damaged parenchyma within 24–48 hours. These are brought in by the cytokines released from injured and reactive astrocytes and microglial cells.[47,48,57] The granulocytes are soon replaced by lymphocytes and macrophages that induce the resorptive changes by scavenging the damaged tissue components.

The acute lesion is also characterised by traumatic changes of demyelination and Wallerian degeneration of the axis cylinders, which have escaped total disruption. Immediately following injury, there is complete disruption of a proportion of nerve fibres and partial injury to others. In the former the damage is permanent, while, in the latter, it is still reversible. Axonal damage can be detected within hours of injury by immunohistochemical methods using antibodies to the βA4 moiety of the amyloid precursor protein. This highlights two types of axonal damage:

1. Irregular varicosities appear within 30 minutes of injury and indicate a failure of the rapid anterograde axonal transport.
2. The axonal spheroids ("retraction bulbs") become apparent within 24 hours of injury suggesting that varicosities may progress to total axotomy and spheroid formation (Figs 37A and B).

It is interesting to speculate whether some of the varicosities recover and not progress. Spheroids are the equivalent of embryonal growth cones and so is the source of regeneration although abortive. These lesions are identical to the diffuse axonal injury occurring in the brain in the supratentorial compartment and evolve early on in the evolution of traumatic injury. Curiously, the term "diffuse axonal injury" however, is not applied when the lesions appear in the spinal cord. The changes in the cord involve only a few segments in proximity, unlike in the brain, where the changes are diffuse. Traumatic demyelination follows within a few hours of injury (Fig. 36C). Kakulas et al. observed that remyelination



Figs 37A and B: (A) Immunostain for neurofilament showing axonal bulbs along the periphery of ischaemic haemorrhagic lesion in the cord. Note the centrifugal nature of axonal damage with sphenoid formation due to disruption of axons (× 20). (B) Higher magnification showing axonal disruption and spheroids (× 400)

found in long-term survivors was not of the central oligodendrocytic type, but of peripheral myelin produced by Schwann cells.[29] This form of remyelination was found in 16 out of 27 patients who survived 6 months or more.

Intermediate "repair" phase: Within 24–48 hours post-trauma, the transverse progression of acute haemorrhagic necrosis, extravasation of RBCs and local blockage of blood flow begins to subside, but the oedema reaches a peak within 3–6 days after the injury. Within 2–3 days following the contusion, the haemorrhagic necrosis is gradually resorbed and a reparative process begins. The early polymorphs are replaced by lymphocytes and macrophages, which invade the margins of the necrotic area. Within the first 2 weeks after injury, the oedema subsides and the smaller foci of haemorrhages are resorbed leaving behind only a few haemosiderin laden macrophages while the lipid filled histiocytes in the necrotic area tend to surround the small vessels in an attempt to release the debris into the vascular channels. The next stage is heralded by the appearance of astrocytic gliosis, which depends on the degree of damage, such as with mild injury, reactive gliosis begins within 24–36 hours, but when there is severe damage, astroglia also disintegrate along with the nervous tissue. Therefore, in these areas, the mesenchymal elements, which originate from the blood vessels and leptomeninges aid in the process of repair. The central necrotic area progressively undergoes cystic dissolution. Along the margins, vessels proliferate and the resolving central necrotic area is soon surrounded by a zone of highly vascularised granulation tissue ("proliferation zone"). This gradually replaces the defect in a centripetal direction progressing from the preserved peripheral areas to the central necrotic foci. The central area of haemorrhagic necrosis is eventually replaced by a multilocular cyst traversed by gliovascular bundles. The surviving axons bordering the lesion are swollen, but simultaneously, secondary degeneration of the spinal nerve roots and the long fibre tracts begins. The anterior nerve roots are more affected than the posterior.

The vascular changes that occur in this stage include thrombosis of the pial and intramedullary vessels with subsequent organisation and recanalisation.[28] These can cause secondary ischaemic damage to the cord at sites remote from the original injury.

Late stage: Months to years after the injury, damaged parts of the cord are totally replaced by connective tissue. The zones above and below develop dense isomorphic gliosis, which replaces the lost neurons and nerve fibres. At the level of the lesion, all that remains is a dense fibrous scar that is formed by fusion of the periosteum and dura mater. The leptomeninges are thickened, discoloured from sequelae of haemorrhage and adherent, obliterating the subarachnoid space while the cord tissue is converted into a narrow fibrous band. On transverse sectioning, the cord tissue is found to be reduced to a thin rim that surrounds small gliotic islands of cord tissue that are separated by strands of highly vascularised connective tissue and dense collagenous bands. Cavitation involves the central grey matter and the posterior funiculi, the inner walls of the cavity being lined by gliomesenchymal cicatrised tissue with macrophages and occasional deposits of calcium and iron. With time, the iron and haemosiderin deposits disappear. Features of regeneration may be seen. The spinal roots appear thin and demyelinated and are also surrounded by fibrous scars. Above and below the lesion, patchy areas of gliosis and demyelination or scarred areas with dense gliosis and small cystic cavities with necrotic contents

and gliomesenchymal walls maybe found. Wallerian degeneration of tracts also progresses with subsequent gliosis. Changes in the vasculature of the cord in the late stages include organisation and recanalisation of occluded intramedullary and pial vessels, an obliterative vasculopathy.

Late sequelae (Post-traumatic syringomyelia): A nidus of traumatic haematomyelia or myelomalacia followed by liquefaction and cavitation, instead of solid scar formation is the initiating lesion. Further, a communication between the syringomyelic cavity and the subarachnoid space can act as a valve-like promoter, once the original cavity has been established. Histologically, post-traumatic syrinx is not any different from an idiopathic syrinx.

Sharply circumscribed areas of necrosis resembling infarcts are more readily identifiable in the chronic phase. These occur at considerable distances from the injury site and may conform to the distribution of anterior sulcal arteries,[33–35] while others may be of venous origin. The pathophysiology of these lesions is not definite, but is of clinical importance as they can explain some of the clinical deficits that are remote from the lesion site.

A less common type termed "microcystic myelomalacia" (marshy cord syndrome) described by MacDonald and his co-workers[37] is post-traumatic central degeneration without frank syringomyelia. Arachnoiditis has been seen with this condition. This may play a role in the progression of both post-traumatic syringomyelia and cystic myelomalacia.

In the absence of a dural tear, intramedullary scarring is usually minimal as is the astrocytosis or gliosis.[55] Due to Wallerian degeneration involving both rostral and caudal axons, the cord in the chronic stage is atrophic at the injury site as well as rostrally and caudally.

A range of regenerative changes have been described with in growth of Schwann cells and peripheral myelin with axons from the ventral and dorsal nerve roots. The proliferation may be extensive enough to produce intramedullary neuromas.[27]

PATHOPHYSIOLOGY OF ACUTE SPINAL CORD INJURIES

A fundamental observation in both clinical as well as experimental SCI is that the pathological appearance of the lesion changes dramatically over the first few days after injury. Experimental models have been developed that can simulate almost all forms of human SCI.[21,55] From the observation that myelotomy and removal of the central haemorrhagic necrotic material results in improvement in neurological function, Allen[5,6] proposed the concept of a secondary mechanism of injury. He believed that a noxious agent present in the necrotic material was responsible for further damage to the cord. Numerous processes that contribute to the pathophysiology of SCI have now been identified that are similar to head injuries, cerebral ischaemia and subarachnoid haemorrhage.

The secondary mechanisms involved in the pathophysiology of SCI include both local effects on the components of the cord itself such as neurons, astrocytes, microglia and blood vessels and systemic effects that include shock, hypoxia or other complications.

Systemic Effects

Neurogenic Shock

Spinal cord injury is one of the common causes for neurogenic shock, which results from a combination of decreased sympathetic tone, unopposed vagotonia and possible secondary changes in the heart.[24,31] The magnitude of the shock is directly related to the level (more common in complete cervical injuries) and the severity of the injury. The peripheral resistance and cardiac output can remain depressed for long periods of time following the injury.

Local Effects

Damage to the Microcirculation

A common feature of SCI is the development of central haematomyelia. This is attributed to the mechanical disruption of the capillaries, arterioles and venules due to the mechanical force of injury and distortion by impact, compression or laceration.[18]

Biochemical Changes

Of the biochemical derangements that occur in acute SCI, the key event is damage caused by the excitatory neurotransmitter glutamate that mediates injury through elevation of intracellular calcium. Increased levels of intracellular calcium sets into motion a chain of events, all of which acting via different pathways cause cell death and tissue necrosis. These processes include activation of proteases that degrade neurofilament proteins; lipases that cause dissolution of cell membranes, and release of free radicals that cause lipid peroxidation. Lipases also cause release of prostaglandins and eicosanoids from damaged neuronal membranes that can, in turn, induce vasospasm.

Inhibitors of these pathways appear to be a logical way to arrest damage caused by these secondary mechanisms. Experimental studies have attempted to examine this issue. For instance, blockage of the NMDA receptor through which glutamate acts using MK-801 (a receptor antagonist), has been shown to have a protective effect.[19] Similarly, methylprednisolone probably exerts its cytoprotective effect by inhibition of lipid peroxidation and reducing the release of free radicals.[26]

Electrolyte Shifts

The most important is increase in intracellular calcium that plays an important role in pathogenesis in acute SCI similar to ischaemic injuries and head trauma. Calcium enters either through disrupted cell membranes or through voltage gated calcium channels following

depolarisation or via receptors activated by glutamate. Increase in calcium within the vascular smooth muscle can result in tetanic contraction or vasospasm causing ischaemic damage.

STRATEGIES FOR TREATMENT OF SPINAL CORD INJURY

SCI is one of the most physically, psychologically, as well as, socially devastating afflictions. With remarkable advancements in critical care and rehabilitation, many patients who sustain SCI are surviving and have extended life spans up to 40 years post-injury.[8,55] But as there are currently no regimens to successfully enhance recovery of function, these individuals remain severely disabled. It's therefore imperative to discover ways to achieve both functional restoration and repair. This would have a powerful effect not only in the quality of life of the afflicted but also their families and health care costs.

The approaches vary from:

- Arresting the immediate effects of injury so that secondary damage to the cord is prevented or arrested
- Induce axonal regeneration to re-establish pathways so that functional restoration is possible
- Reconstruct the injured segment by transplantation or grafting.

Initial interest was focused on developing pharmacological regimens that can protect the cord at the time of the acute injury. These operate by suppressing some of the secondary processes that are activated following the trauma. For instance, methyl prednisolone[26,61] and the ganglioside GM-1[22], inhibit the inflammatory reaction and generation of free radicals. Use of antioxidants for countering the free radical damage has also been proposed. Antisera to nitric oxide synthase have been shown to have a protective effect.[48] The GABA inhibitors, such as Riluzole or Gabapentin, may be useful in limiting the damage caused by excitotoxicity.[52,53] The benefits of this form of approach are, however, limited and no functional improvement has been recorded in the chronic stages of SCI.

Following traumatic injury in the spinal cord, as in other organs, tissue repair begins, the difference being that in the spinal cord and brain it is not a regenerative process but a fibroproliferative event that progresses into a glial scar that "patches", but does not restore the damaged tissue. In the CNS, this can have potentially devastating functional consequences.

In the CNS, wound healing follows a very precise sequence of events that are grouped in order of progression as: inflammation, tissue formation and remodelling in which there is glial scar formation, and deposition of extracellular molecules.[14]

The glial scar that results, however, thwarts axonal regeneration acting as a physical barrier. Additionally, recent work suggests that orderly regrowth may also be adversely influenced by molecules within the glial scar that in some way signal neurons to stop growing (axonal outgrowth) or alter their direction of growth.[16] The molecules most strongly implicated in directing axonal growth are found in the extracellular matrix of the glial scar.[51] Most often upregulated are Tenascin C[12] and Chondroitin sulphate,[38] closely associated with Laminin. Laminin is permissive to growing axons and, *in vitro*, stimulates neurite growth. Tenascin C is inhibitory, but its effects vary depending on the microenvironment. Therefore, with proper molecular tools it maybe possible to manipulate the extracellular matrix so that a supportive environment for sprouting and regeneration is created.

Regeneration of the CNS axons is the prime target for treatment of end stage lesions. Much interest in regeneration followed the experimental study, which showed that a piece of sciatic nerve when inserted into the lesion site formed a conduit for the elongation of axons in the adult rat.[3,15,44] This was the first demonstration that CNS axons did have the capacity to regenerate if they were provided a permissive milieu in which to grow.

Following closely on the heels of this discovery, numerous methods of achieving the primary goal of promoting regeneration by transplantation have been tried out. Peripheral nerve grafts were developed by Aguayo et al.[1,2] Other techniques involve grafting of embryonic tissues or Schwann cells,[39,42,58] olfactory ensheathing cells,[30,43] and cells genetically engineered to produce neurotrophins[23] and even inert substances, like polyethylene glycol,[49] have produced exciting results with remyelination.

Anderson and his colleagues[7] assessed the feasibility of grafting foetal neural tissues taken from the foetal spinal cord (embryonic days 2–24), foetal brainstem (E21–38), foetal neocortex (E38) and a mixture of foetal spinal cord and brainstem into adult cat spinal cord. Chronic lesions that resemble human SCI (i.e. single/multicystic cavity surrounded by a peripheral rim of spared white matter) were produced by using static loading forces. They demonstrated that transplantation of foetal CNS tissue into these chronic compressive injuries did survive, integrate and show connectivity with host tissue. In addition, under appropriate conditions, these were capable of enhancing the recovery of locomotor function. Additionally, the capacity for homotypic transplants to promote recovery of function is greater than heterotypic transplants. The functional capacity of the graft depended on the time interval between injury and transplantation, and if the lesion cavity was debrided prior to grafting.

Falci et al.[20] went one step further and introduced human foetal spinal cord into the post-traumatic cysts with the intention of preventing development of post-traumatic syringomyelia rather than inducing regeneration, with some success.

Whether foetal tissue transplant will ever be applicable to human SCI is debatable given the ethical and procedural problems that arise with procurement of

foetal tissue, non-invasive monitoring of the graft site, assessment of outcome, etc., but this is an important stepping stone in the treatment of chronic SCI.

Neural stem cells have been the focus of intense research in recent times aimed at developing transplantation strategies to promote neural recovery in the injured nervous system. Neural stem cells have the capacity of self-renewal to generate progeny that are capable of differentiating into both neurons and glia. Transplantation of human neural stem cells obtained from embryonic tissue has shown both neuronal and astrocytic differentiation.[13,41,54] Remyelination and recovery of impulse conduction has also been demonstrated following transplantation into demyelinated rat spinal cords.[4] But relative inaccessibility of these cells for autologous therapy, the ethical and practical problems in obtaining embryonic tissues with their inherent problems of host incompatibility, and rigorous testing for viral screens make this an unpopular choice of therapy, forcing investigators to look further for alternate sources of neural precursors.

Recent work by Bjornson and his colleagues[9] demonstrated that neural stem cells could generate a variety of haematopoietic cells *in vivo* including myeloid and lymphoid cell lineages. This revealed the startling fact that the neural precursor cells are not restricted to purely neural lineage. The reverse was soon demonstrated when bone marrow stromal cells were shown to differentiate into astrocytes when injected into the lateral ventricle of mice[32] and into neurons both in *in vitro* culture systems[60] and in x-irradiated mice.[10,40] This raised the intriguing possibility of using bone marrow stromal cells as an alternative source of neural cells in traumatic and neurodegenerative diseases of the CNS for repair strategies. Bone marrow is easily accessible and more importantly will allow autologous transplantation obviating host incompatibility, and need to screen for viral and foreign antigens. Sasaki and his co-workers successfully demonstrated that transplantation of bone marrow cell fraction into demyelinated spinal cord caused extensive remyelination, albeit of peripheral Schwann cell myelin type.[46] Notwithstanding exciting results of a variety of transplantation techniques in the rodent model of SCI and some recent experimental attempts in humans so far the restoration of useful function has not been achieved.

Although many encouraging experimental models have been developed, all modalities of therapy tried so far address only axonal regrowth and not restoration of physiological function. As the neurological disability in SCI is a combination of motor (pyramidal and extrapyramidal), sensory and autonomic dysfunction, each of these must be corrected in order to achieve a complete cure. This contrasts with the simplistic view that all that is required for a cure is independent ambulation. The autonomic dysfunction that affects bowel, bladder, reproductive and cardiovascular systems is much more distressing than dysfunction of the motor system, which has received the maximum attention till date. "Restorative Neurology" is a clinical specialty that seeks to improve residual neurological function unlike conventional "rehabilitation" that focuses on enhancing the function of uninjured parts in order to make up for lost function. Dimitrijevic[17] was the first to make pioneering efforts in this important specialty. Approaches towards improvement of residual function include physical, pharmacological, electrical or neurophysiological methods (epidural stimulation, functional electric stimulation, computer modelling, etc.).

There is also the problem of CNS plasticity to be considered, because of which, isolated segments of the cord get subjected to abnormal inputs causing physiological aberrations and derangements, which means that simple reconnection of the transected segment by regeneration may not restore normal function. A better appreciation of the neurophysiology will be an important factor in restoring functions once central regeneration is achieved by whatever means.

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28 Concussion Brain

Sandeep Vaishya, Khan Z

INTRODUCTION

Concussion, derived from the Latin concutera ("to shake violently")[38] or the Latin concusses ("action of striking together")[6] is the most common type of traumatic brain injury. The term "concussion" has been used for centuries and is still most commonly used in sports medicine,[2] while the term mild traumatic brain injury (MTBI) is preferentially used in general medical contexts. Concussion is frequently defined as a head injury with a transient loss of brain function and is known to cause a variety of physical, cognitive and emotional symptoms.

The most widely accepted definition is the one proffered by The Committee on Head Injury Nomenclature of Neurological Surgeons in 1966 and defines it as "a clinical syndrome characterized by immediate and transient post-traumatic impairment of neural function such as alteration of consciousness, disturbance of vision or equilibrium, etc. due to brainstem dysfunction".[13,55] The more recent description, as given by The American Academy of Neurology, states that "concussion is the trauma induced alteration in mental status that may or may not include loss of consciousness".[26] The recent modification stems from the understanding that the injury is not restricted to the brainstem only.

MECHANISM

The brain is anatomically designed to prevent damage from light trauma, as the surrounding cerebrospinal fluid acts as a cushion for absorbing the impact while it is ill suited to bear more severe impacts or the forces associated with rapid acceleration. Concussion may be caused by impact forces, in which the head strikes or is struck by something or impulsive forces, in which the head moves without itself being subject to blunt trauma (for example, when the chest hits something and the head snaps forward).[50]

Forces may cause linear, rotational or angular movement of the brain or a combination of these types of motion.[50] In rotational movement, the head turns around its centre of gravity and in angular movement it turns on an axis not through its centre of gravity. Amongst all these forces, the amount of rotational force is considered the major type of force to cause concussion and the largest component in its severity.[42] Studies with athletes have shown that the amount of force and the location of the impact are not necessarily correlated to the severity of the concussion or its symptoms and have called into question the threshold for concussion previously thought to exist at around 70–75g.[19,21,48]

Rotational forces primarily affect the midbrain and diencephalon and the subsequent injury is thought to disrupt the normal cellular activities in the reticular activating system located in these areas, which eventually produces the loss of consciousness often seen in concussion.[38,46] Other areas of the brain that may be affected include the upper part of the brainstem, the fornix, the corpus callosum, the temporal lobe and the frontal lobe.[3]

PATHOGENESIS AND PROPOSED THEORIES

Most of the theories proposed to explain the genesis of concussion rely on the understanding of the post-traumatic responses of the various parts of the brain, towards different types of force employed for causing the injury. Some of the authors have also dwelled upon the consequent metabolic changes occurring in the brain's milieu. Below is a summation of the various theories along with the proposed reasons which are generally based upon the aforementioned explanations.

Ricker, as early as in 1919, suggested that concussion could be due to extreme vascular dilatation followed by constriction,[44] while Duret, in 1921, proposed that it could be due to the forces of CSF impinging on the floor of the fourth ventricle and sudden compression of the cerebral hemispheres. Trotter, in 1932, as quoted by Symonds,[51] suggested that it could be the result of a momentary cerebral anaemia, due to compression or indentation of the skull. Subsequently, in the year 1940, Scott[49] suggested that temporary rise of intracranial pressure above the systolic pressure with sudden cerebral anaemia could be one of the causes.

Denny Brown and Russell[14] in the year 1941 suggested acceleration to be responsible for "concussion". It was observed that in experimental studies on cats and monkeys, the sudden acceleration produced changes in brainstem function. This was categorically defined as acceleration concussion. It was further reported that since this injury is dependent on the rate of increasing velocity, anything which dampens the blow will prevent it. This remains the principle underlying the use of crash helmets.

Walker et al.[54] in the year 1944, proposed that the underlying reason for concussion could be the presence of pressure waves which cause primary intense neuronal stimulation followed by a temporary paralytic phase. Bronstien[5] in 1946 was perhaps the first researcher to suggest the role of acetyl choline, which is normally absent in CSF and was present in large quantities in experimental and clinical head injuries. Acetyl choline in high quantities can block synaptic transmission by depolarisation of the post-synaptic membrane.[53] This remains the basis of the hypothesis regarding changes in the reticular system during concussion. Foltz and Schmidt[17] proposed, in 1956, that concussion was due to reversible blocking of the functional integrity of the brainstem reticular system. In the year 1960, Dott[15] suggested that stretching of perforators causes vasospasm, resulting in brainstem anoxaemia. Symonds, in the same year, proposed that the instantaneous loss of cerebral function was the result of sudden direct damage, either by stretching or by compression of the nerve cells or fibres in the brain. Rowbotham[47] (1964) believed that less force might cause temporary derangement of fibre conduction or synaptic transmission, without actual anatomical disruption of fibres. The experimental concussion study conducted by Ommaya and colleagues[37] in the year 1964, found slowing of circulation and disruption of blood brain barrier as perhaps the primary cause of concussion. Kaplan[25] (1966) divided the entity into two subdivisions, as physiological concussion with reversible changes and pathological concussion with irreversible changes and permanent neuronal cell damage. Kristiansen and Tandon[27] (1960) considered the latter to represent a transitional stage between concussion and contusion.

PATHOPHYSIOLOGY

Most of the clinical studies proposed that concussion is caused by acceleration and deceleration forces.[18,36] It may be considered as the mild end of the traumatic brain injury continuum with loss of consciousness and post-traumatic amnesia being brief in duration and with minimal axonal stretch. Limited stretch of axons leads to initiation of a pathophysiological process that leads to very limited cell death, depending upon the morphology of the cell. The majority of these changes are a reversible series of metabolic events.

As per Giza and Hovda,[20] the primary mechanism includes ionic shifts, abnormal energy metabolism, diminished cerebral blood flow and impaired neurotransmission. Stretching of axons often invariably results in an indiscriminate release of neurotransmitters and uncontrolled ionic fluxes. With changed ionic gradients, the cell responds by activating ion pumps to restore the normal membrane potential. Pump activation increases the glucose consumption, leading to increase in local cerebral metabolic rate of glucose in tandem with decrease in cerebral blood flow, causing disparity in supply and demand of glucose. There also appears to be impaired oxidative metabolism and decreased mitochondrial function. This leads to over utilisation of the anaerobic energy pathway and elevated lactate levels as a by product. As is well known, magnesium is necessary for ATP generation, protein synthesis and maintenance of cellular membrane potential. The intracellular magnesium level decreases in such a state and remains low for some days, leading to derangement of these functions. The sustained calcium influx results in metabolic dysfunction and energy failure. High levels of intracellular calcium combined with stretch injury can lead to an irreversible process of destruction of microtubules within the axons.[20,24]

CLINICAL PICTURE

Concussion is a short lasting event and a neurosurgeon rarely sees the patient during the period of concussion. Immediately after the injury, the patient may experience brief loss of consciousness. The muscles become hypotonic and the respiration is slowed with an imperceptible pulse and fall of blood pressure which starts returning to normal within a few seconds or a minute. The stage of confusion may last for a few minutes and the patient often complains of severe headache.

Amnesia is emerging as perhaps the most important sign for careful assessment after concussion. It may present as retrograde amnesia or anterograde amnesia. The presence and duration of amnesia, disorientation or mental disturbance has been associated with an immediate good outcome or slower recovery. The period of amnesia shrinks over time with recovery.[12,31,34]

The most common symptom associated with concussion is headache or dizziness which may last for three hours to seven days. Most frequently, it presents as concussion headache, which is a feeling of constant localised or generalised pressure in the skull. The patient may also complain of blurring of vision and increased fatigue or feeling sluggish.[1,12,22]

There may be cognitive changes with problems of attention, concentration, short-term memory, learning and multitasking. Another commonly reported symptom is that of emotional changes which may present as irritability, sadness/depression, nervousness/anxiety or silliness and euphoria. These symptoms may be brief or may last for long, in case of more significant injury.

STRUCTURAL AND FUNCTIONAL IMAGING

Concussion presents itself largely as a metabolic event and not a structural injury, therefore limiting the role of conventional neuro-imaging techniques, like CT and MRI which are almost always unremarkable following simple concussion.

Recently, functional MRI and Blood Oxygen Level Dependent (BOLD) activity have been used to study the functional changes after concussion injury. They showed decreased activity in the mid dorsolateral prefrontal

Table 1: Comparison of concussion grading scales

	Grade I	*Grade II*	*Grade III*
Cantu guidelines	Post-traumatic amnesia <30 minutes, no loss of consciousness	Loss of consciousness <5 minutes or amnesia lasting 30 minutes–24 hours	Loss of consciousness >5 minutes or amnesia >24 hours
Colorado Medical Society guidelines	Confusion, no loss of consciousness	Confusion, post-traumatic amnesia, no loss of consciousness	Any loss of consciousness
American Academy of Neurology guidelines	Confusion, symptoms last <15 minutes, no loss of consciousness	Symptoms last >15 minutes, no loss of consciousness	Loss of consciousness (IIIa, coma lasts seconds, IIIb for minutes)

cortex. Increased activity was seen in the temporal and parietal lobes after concussion, as compared to controls.[10] PET/SPECT studies done in concussed patients showed a pattern of frontal hypoactivity.[45]

Electroencephalography done in post concussion patients revealed amplitude reduction in all standard frequency bands, especially during standing.[52] N2/P3 or P300 responses have been used in cognitive event related potentials for evaluation of patients with concussion.[16,28,41,43] Auditory P3 paradigm showed mixed results with decreased P3 amplitudes.

CUMULATIVE EFFECTS

The cumulative effects of concussion are poorly understood. The severity of concussion and its symptoms may worsen with successive injuries, even if a subsequent injury occurs months or years after an initial one.[23] Symptoms may be more severe and changes in neurophysiology can occur with the third and subsequent concussions.[35] Studies have had conflicting findings on whether athletes have longer recovery times after repeat concussions and whether cumulative effects such as impairment in cognition and memory occur.[40]

Cumulative effects may include psychiatric disorders and loss of long-term memory. For example, the risk of developing clinical depression has been found to be significantly greater for retired football players with a history of three or more concussions than for those with no concussion history. Three or more concussions is also associated with a fivefold greater chance of developing Alzheimer's disease earlier and a three-fold greater chance of developing memory deficits.[7]

SECOND IMPACT SYNDROME

Second impact syndrome is related to an extraordinarily rare cascade of events in which a patient experiences a catastrophic brain injury, following a seemingly mild concussion. Sustaining a second brain injury during a period of recovery from first concussion has been linked to second impact syndrome. The pathophysiological basis of this syndrome is cerebrovascular congestion or loss of cerebral auto-regulation, leading to brain swelling and oedema.[9,11] If a second injury is inflicted within 24 hours, there is a marked breakdown of the blood brain barrier which may be the possible mechanism for the rapid swelling and oedema.[29]

RECOVERY TIME

Single concussion typically resolves in less than two weeks.[4,30-33,39]

GRADING SCALES

Three grading systems are followed most widely: One was developed by Robert Cantu, one by the Colorado Medical Society and a third by the American Academy of Neurology.[26] Each divides concussion into three grades, as summarised in the Table 1.[8]

TREATMENT

Pure concussion, being a self limiting and an extremely short lived phenomenon, does not need any treatment. When concussion merges with traumatic unconsciousness, which is a phenomenon of longer duration, investigation with CT is necessary and the appropriate treatment may be given. All patients must be kept under observation. Post-concussion syndromes like giddiness, light-headedness or difficulty in concentration may require symptomatic treatment and reassurance. The preventive measures need emphasis.

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29 Cerebral Contusions

Ravi Ramamurthi, Nigel Peter Symss

INTRODUCTION

Cerebral contusion (in Latin *contusio cerebri*) is a bruise of the brain parenchyma. Localised contusion, laceration or intracerebral haematoma may occur after a head injury in any part of the brain, either singly or in combination. These may be due to coup/direct or contrecoup injury, and may be caused by the brain striking or being squeezed against dural partitions. When occurring in non-vital areas, even a large contusion may not be troublesome, while a small contusion in a vital area, like the hypothalamus, pons or medulla, may be fatal.[10] In closed head injuries, the accelerating and decelerating forces make the brain move within the cranial cavity under shearing strains. The cortex gets bruised or contused at the site directly under the force of trauma, at the opposite end (contrecoup) or in remote areas. Dural partitions play an important role in causing localised contusions.

CONTUSION

Cerebral contusion is the most frequently encountered lesion following head injury, occurring in 20–30% of severe head injuries.[28,47] Contusions are wedge shaped, with the apex pointing towards the white matter.[1,38,43] In a contusion, the pia is intact and, if the pia is torn, it becomes a laceration. Contusions can occur without laceration, but a laceration is always associated with contusion.

Based on the mechanism of injury, McCormick[43] divided contusions into various types:

- Coup
- Contrecoup
- Intermediate coup
- Gliding
- Herniation
- Fracture contusion.

Coup contusion occurs beneath the area of impact. *Contrecoup*[25] contusion occurs in remote areas, particularly in the area diagonally opposite to the site of impact (Fig. 1). *Intermediate coup* occurs within the brain and is located between coup and contrecoup contusions (Fig. 2).[36,37] Gliding contusions occur on the vertex due to the rostrocaudal movement of the brain. These contusions involve the deeper layers of the cortex more than the surface gyrus, with extension into the convolutional white matter.[44] Herniation contusions occur at the site of subfalcine, tentorial or tonsillar herniations. Medial temporal and hippocampal contusions are commonly associated with tentorial herniation. Fracture contusions

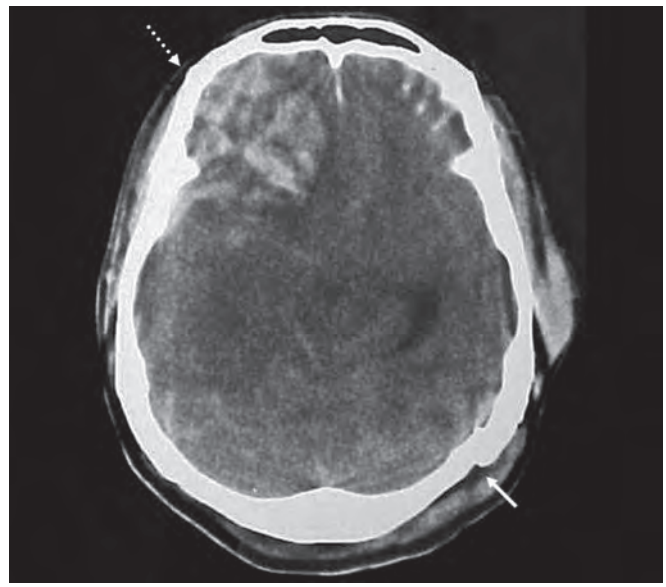


Fig. 1: Contrecoup contusion: The site of injury is shown by solid arrow. Haemorrhagic contusion is diagonally seen opposite to the site of injury—dashed arrow

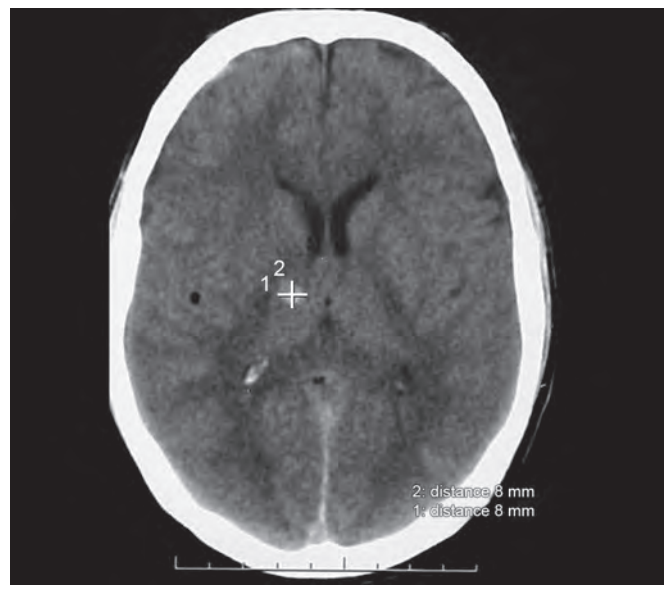


Fig. 2: CT scan showing intermediate contusions

are coup contusions that lie under the fracture line. Extensive contusion associated with subdural haematoma is called burst lobe. A burst frontal or temporal lobe is associated with high mortality and morbidity.[17]

Pathology

The gross appearance of a contusion is an area of haemorrhage beneath the pia extending, usually through the cortex, into the convolutional white matter. Severe brain contusion is often associated with non-haemorrhagic mass effect that rapidly progresses within 12–48 hours after the trauma. The pathogenesis underlying such a rapid progression of mass effect cannot be fully explained by vasogenic and cytotoxic brain oedema. Kawamata and Katayama[65] proposed that the high osmolality within the contused brain tissue generates an osmotic potential across the central and peripheral areas, causing the brain to accumulate a large amount of water. To determine the role of tissue osmolality in contusion oedema, they studied changes in tissue osmolality, specific gravity and ion concentration in contused brain in both experimental and clinical settings. They found the total ionic concentration $[Na^+] + [K^+] + [Cl^-]$ did not significantly alter at any given time. They concluded that inorganic ions do not primarily contribute to the rise in osmolality, suggesting that the increase in colloid osmotic pressure through the metabolic production of osmoles or the release of idiogenic osmoles could be the main cause of contusion oedema.[67] Hypoxia and hypotension still cause a substantial proportion of secondary injuries and many reports associate secondary brain injury with neuroinflammatory responses. Chemokines have been found in the cerebrospinal fluid but not in the brain tissue of patients following head injuries. Stefini et al., in their study, analysed if chemokines were expressed in pericontusional brain tissue in patients with moderate or severe head injury undergoing surgical evacuation of their contused brain. They found CCL2, a monocyte chemo-attractant produced by activated astrocytes, was the most strongly expressed chemokine, followed by CXCL8, CCL3 and CCL4. The chemokines CXCL10 and CCL5 were expressed at very low levels, and XCL1 was not detected. They concluded that chemokine activation occurs early following moderate or severe head injury and is present for several days after the trauma, and may contribute to neuroinflammatory exacerbation of post-traumatic brain damage in the pericontusional brain tissue.[63]

Just as in subcutaneous bruises, in brain contusion also, breakdown of erythrocytes takes place and haemosiderin pigments are released. Phagocytosis of the haemosiderin granules occurs. Macrophage activity is intense, as also the activity of compound granular corpuscles. Reactive gliosis occurs at the edges. Thus, over a period of 48 hours to several months, healing takes place in a graded manner and the contused area begins to look almost like normal tissue, yet some scarring and gliosis remain. Secondary degenerative changes following cerebral trauma include axonal disruptions, reorganisation of neuronal circuits and new growth of viable connections. Such changes may not be discernible in computed tomography (CT) scans, but may prove to be important in determining the clinical course.

Li et al. studied the effects of ginsenoside Rg1 on the expression of insulin-like growth factor-1 (IGF-1) in the brain of rats after experimental brain contusion, and concluded ginsenoside Rg1 enhances the recovery of the contused brain through increasing the expression of IGF-1.[35]

Chieregato et al. evaluated the response to an acute elevation of cerebral perfusion pressure (CPP) of the regional cerebral blood flow (rCBF) measured in the oedematous area of traumatic contusions. Their findings suggest that CPP elevation induced by norepinephrine is effective in improving contusional rCBF only in selected cases, which are represented by a subset of contusions with critical perfusion, which can be identified by rCBF measurements. Conversely, in contusions with rCBF higher than critical low values, the CPP elevation could probably induce a temporary breakdown of the blood-brain barrier, and norepinephrine leads to a vasoconstriction with a worsening of regional perfusion.[8]

LACERATION

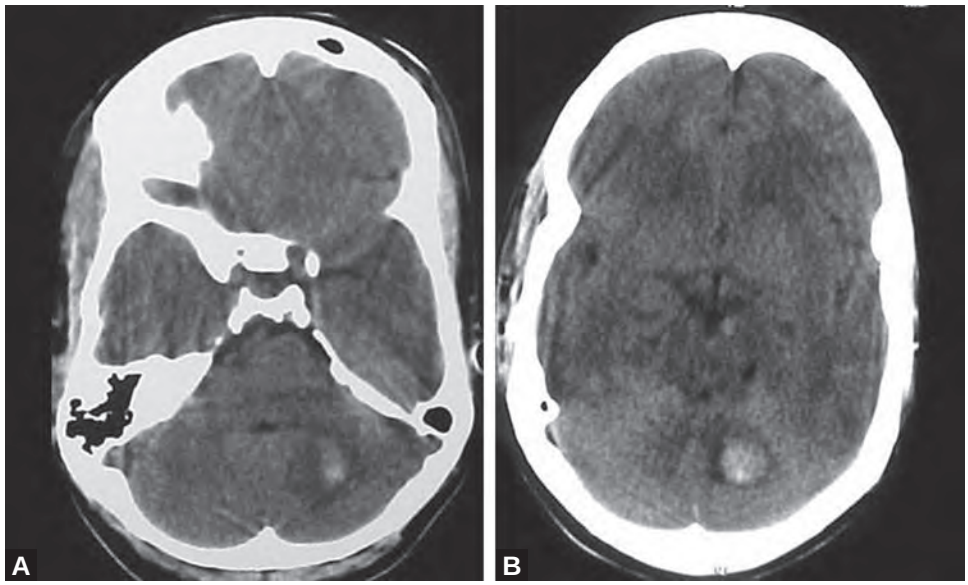
Laceration of the brain may accompany a contusion. It could be cortical-subcortical. In tangential craniocerebral wounds and in depressed fractures, bone fragments tear the dura and the subjacent brain is lacerated. The laceration varies in depth and is associated with perifocal oedema. A penetrating type of laceration is produced by high velocity missiles, the laceration taking a tubular pattern with its diameter increasing towards the exit wound. An extensive shock wave results in damage extending radially around the tubular laceration. This may involve the ventricles which may also be penetrated directly and the CSF escapes along with brain matter through the wound.[49]

Indirect injury causes lacerations due to translational impacts inside the cranial cavity. Thus, following an occipital impact, lacerations may occur in the frontal, orbital and temporal poles.

In the lacerated area, there is extensive damage to tissues. Extravasation of blood adds further damage. Degenerating brain tissue and products of blood degradation release many substances which can produce vasospasm, damage to the blood-brain barrier and cerebral oedema. The devitalised area is susceptible to infection and may result in a brain abscess, unless early antibiotic therapy is started. Contiguous areas of contusion may coalesce and form a localised intracerebral haematoma.

Clinical Features

Contusion can present with limb weakness, lack of motor co-ordination, numbness, aphasia, and memory



Figs 3A and B: Cerebellar contusion

and cognitive problems, depending on the contusion's location in the brain.[30] When the injury is moderately severe and the level of consciousness is good, a localised contusion can often be suspected from the clinical picture produced. It must, however, be emphasised that there is no consistent diagnostic feature of a contusion. It may produce no clinical deficit, depending upon its size, location, extent of associated oedema and haemorrhage and it may result in a rapidly deteriorating clinical course indistinguishable from an expanding intracranial haematoma.[16] Contusions are often multiple and frequently associated with other lesions, and hence their clinical picture is quite confusing. Large or multiple contusions involving the frontal and temporal lobes may produce raised intracranial pressure (ICP), midline shift and associated coma. Also, when the level of consciousness is depressed, the clinician has to rule out an expanding intracranial haematoma. Intracerebral haematomas are often associated with loss of consciousness due to the severity of the injury.

The CT scan and magnetic resonance imaging have made a tremendous difference to the diagnosis and subsequent management of all aspects of head injuries. Still it is essential for the neurosurgeon to recognise the clinical picture of localised damage to different parts of the nervous system, to be able to make correct judgments as to therapy and to assess progress. Hence, the clinical syndromes are discussed in detail.

Contusions of the frontal lobe, temporal lobe, sensorimotor cortex, cerebellar hemisphere and hypothalamus can clinically be made out as characteristic syndromes.

Frontal Lobe Injury

Prolonged post-traumatic confusion or a state of delirium in the earlier stages and a Korsakoff-like state in the later stages may result from contusions and laceration of the frontal lobe.[34] The patient may be disoriented and may have a memory disturbance and confabulation. Persistent nocturnal and occasional diurnal incontinence, as well as euphoria and disinhibition may closely resemble the clinical picture seen in frontal tumours. Focal motor or adversive fits with or without generalisation may occur. Often the seizures appear generalised from the onset.

Sensorimotor Contusion

Some form of pyramidal deficit is a common accompaniment of moderately severe head injuries. Upper motor neuron type of facial weakness, fall of the outstretched hand, weakness of handgrip, dragging of the foot while walking and an extensor plantar response may often be seen on one side.

Sometimes the hemiparesis is more marked and requires exclusion of an intracranial haematoma or middle cerebral or carotid artery occlusion. A detailed neurological examination may reveal varying degrees and types of cortical sensory loss. Special tests may be required to bring out associated parietal lobe dysfunction.

Cerebellar Injury

Contusions of the cerebellum or of the cerebellar peduncles are not common (Figs 3A and B). Occasionally, following a blow to the back of the head and in association with an occipital fracture, obvious unilateral cerebellar signs, like hypotonia, nystagmus and inco-ordination, are observed. When these signs occur without any impairment of consciousness or evidence of increased ICP, a space occupying posterior fossa haematoma is unlikely. Cerebellar dysarthria and an ataxic broad-based gait may also be seen. Recovery is spontaneous, early and generally almost complete.

Hypothalamic Injury

Hyperpnoea and excessive pulmonary secretions indicate associated hypothalamic damage. Unexplained severe and irreversible shock may indicate primary hypothalamic damage, but is very rare. Persistent hypothermia has been noted following widespread damage to the periventricular grey matter around the third ventricle.[68] Diabetes insipidus may follow bilateral infarction of the supraoptic nuclei and hypernatraemia may result from bilateral damage to the ventromedial nuclei.[68] Treatment of these manifestations is purely symptomatic until spontaneous recovery occurs, but severe hypothalamic damage almost always leads to a fatal outcome.

Usually contusions, lacerations and small haematomas can be treated conservatively with the patient under close observation for signs of increasing ICP. If a large intracerebral haematoma develops it needs evacuation.

Radiology

CT scanning is the imaging modality of choice for traumatic brain injury[69] because of its widespread availability, the rapid imaging time, the low associated costs and its safety. To standardise the imaging procedure, 5-mm slices should be obtained from the foramen magnum to the sella and 10-mm slices should be obtained above the sella, parallel to the orbitomeatal line.

Cerebral contusion is the commonest traumatic lesion visualised on CT scans. Dublin et al.[14] reported a 40% incidence while Zimmerman et al.[68,74] reported 21%.

The CT scan appearance in cerebral contusion depends on the presence of oedema and haemorrhages in the contused region and hence, presents a variable appearance depending on the predominance of either factor. Thus, there is a combination of high attenuation and low attenuation areas, described as 'salt and pepper appearance' by French and Dublin.[15] There is enhancement with contrast in an area of contusion due to vascular disruption. The high attenuation areas due to haemorrhage are short lasting while the low attenuation due to oedema may persist for a long time. In large contusions, ventricular displacement or compression may be seen. Chesnut et al. found the following early CT scan findings to correlate with outcome: (a) status of the basal cisterns; (b) midline shift and (c) subarachnoid haemorrhage in the basal cisterns.[7] Perfusion CT (PCT) has been found to be better in the evaluation of tissue viability than non-contrast CT, suggesting that PCT could be implemented for the early assessment of patients with traumatic brain injury.[61]

In the MR, there is a combination of different signal intensities. In non-haemorrhagic contusions, hypointense signals on T1 and hyperintense signals on T2 are observed. Haemorrhagic contusions show marked variability in signals depending on the age of the contusion.

Management

The management of patients with cerebral contusion depends on the location and extent of the contusion, and the neurological status of the patient. Patients with small or deep seated contusions can be managed without surgery, and can be followed with frequent assessment of their neurologic status. The ICP should be monitored and, if raised, should be treated accordingly. However, ICP monitoring is not mandatory in all cases.

The development of raised ICP from larger contusions may result in secondary brain injury, placing the patient at risk of further neurological deterioration, tentorial herniation and death. Rehman et al. recommend using ICP monitoring or blood flow measurements to trend patients with bifrontal intraparenchymal contusions and Glasgow Coma Scale (GCS) greater than eight to prevent clinically undetected deterioration from transtentorial/central herniation (Fig. 4).[54]

Since contusions tend to evolve, the timing of surgery with respect to the occurrence of neurological deterioration clearly affects the outcome.[42] Becker et al.[3] advocated early evacuation of traumatic intracranial haematomas and contusions for the purpose of avoiding secondary complications. Patients with GCS scores 6–8 with frontal or temporal contusions greater than 20 cm^3 in volume with midline shift of at least 5 mm and/or cisternal compression on CT scan, and patients with any lesion greater than 50 cm^3 in volume should be treated surgically, as an emergency.[55] Based on their CT classification, Marshall et al.[41] defined a mass lesion as a lesion of volume greater than 25 cm^3. They showed differential outcome between patients with evacuated and non-evacuated mass lesions (23% vs 11% favourable outcome, respectively) in their series of severe TBI patients, after resuscitation (GCS 8 or less). In contrast, Servadei et al. in their paper from the European Brain Injury

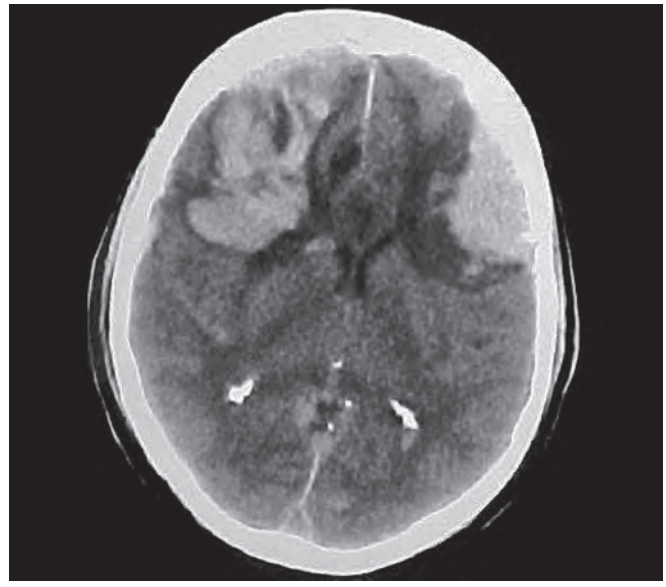


Fig. 4: CT scan of a patient with bilateral frontal contusions

Consortium[59] evaluating a series of 724 TBI patients with a GCS of 3–12 showed a 45% rate of favourable results in evacuated mass lesions versus 42% in non-evacuated mass lesions using the same classification system.

There is reluctance in operating on contusions involving a dominant lobe, and medical therapy along with frequent assessment of the neurological status can be tried in an attempt to tide the patient over the period of maximum oedema.[66] Large decompressive craniectomy with opening of the dura mater without resecting the contused brain has been performed as a treatment for cerebral contusion.[19,40] Decompressive procedures, including subtemporal decompression, and temporal lobectomy are other surgical options for patients with refractory intracranial hypertension and diffuse parenchymal injury with clinical and radiographic evidence for impending transtentorial herniation.

Lee et al.[32] reviewing 29 patients undergoing operation for a combination of acute subdural haematoma and severe contusion and swelling of the temporal lobe with uncal herniation reported a significant improvement in outcome with the combination of temporal lobectomy, subtemporal decompression and debridement of contused brain. Mortality decreased from 56% to 8%, with a concomitant increase in average GOS from 2.2 to 4.0.

Kawamata et al.[68] analysed the results of surgical excision of necrotic brain tissue in 182 patients with cerebral contusion registered with the Japan Neurotrauma Data Bank. Of these, 121 patients (66%; Group I) were treated conservatively, and 61 (34%; Group II) were treated surgically. Most Group II cases (90%) underwent complete excision of necrotic brain tissue and evacuation of clots. They found Group I demonstrated higher mortality at 6 months post-trauma when compared to Group II (48% vs 23%; p = 0.0001; n = 182). The results of their study do not directly confirm the superiority of surgical therapy for cerebral contusion, but shows that patients who underwent conservative therapy had a poorer outcome. They concluded that this also supports their hypothesis that early massive oedema is caused by cerebral contusion accompanied by necrotic brain tissue, indicating that surgical excision of necrotic brain tissue provides satisfactory control of progressive elevation in ICP and clinical deterioration.[68]

Prognostic Factors

These include age,[24,46,48,60] admission or post-resuscitation GCS,[18,20,46,48,53,60] presence of pupillary response/brainstem reflexes,[6,46] respiratory insufficiency,[9] raised ICP[5,6,20,46,63] and the status of the basal cisterns or third ventricle[42,68] on CT scan. Other variables significantly correlate with outcome. These include location of the lesion,[51,60] ICH volume,[9,68] GCS at time of follow-up CT,[68] lowest recorded GCS,[6] severity of surrounding oedema,[5] timing of surgery,[42,53,56] occurrence of pre-operative neurological deterioration,[42] and presence of acute hemispheric swelling or concomitant subdural haematoma.[6]

Outcome

The mortality from cerebral contusion has been reported to be from 25 to 60%.[57] Patients who are comatose at the time of surgery generally have a poorer outcome.[68]

Temporal Lobe Contusion

On account of its vulnerable situation, contusion of the temporal lobe is frequent in head injuries. Courville[11] found contusion of the temporal lobe in 70% of fatal head injuries. The pulped necrotic brain in temporal lobe contusion swells and is capable of producing a fatal increase in ICP.[4] Focal oedema and contusion of the temporal lobe may also be so severe as to compress the blood vessels in the middle fossa and lead to extensive secondary ischaemia.[34] The majority of temporal lobe injuries are associated with injuries to the frontobasal region, brainstem and other parts of the brain. However, in a few cases the injury to the temporal lobe is the major component and produces a characteristic clinical picture, justifying its description as a separate syndrome.[2,13,21,27,45,62] Temporal lobe contusion may mimic the clinical picture of an extracerebral haematoma and may present acutely or subacutely. It is frequently associated with a varying degree of subdural haemorrhage. Kristiansen and Tandon[29] pointed out that, from a pathological standpoint it is difficult to draw a clear-cut line between a lesion which could be called cerebral contusion with haemorrhage and a real intracerebral haematoma. This explains the variety of names given to these lesions like traumatic intracerebral haemorrhage,[11] pulped temporal lobe,[4] intradural haematomas,[52] exploded temporal lobe,[23] traumatic encephalomalacia[33] or simply temporal lobe lesions in head injury.[64]

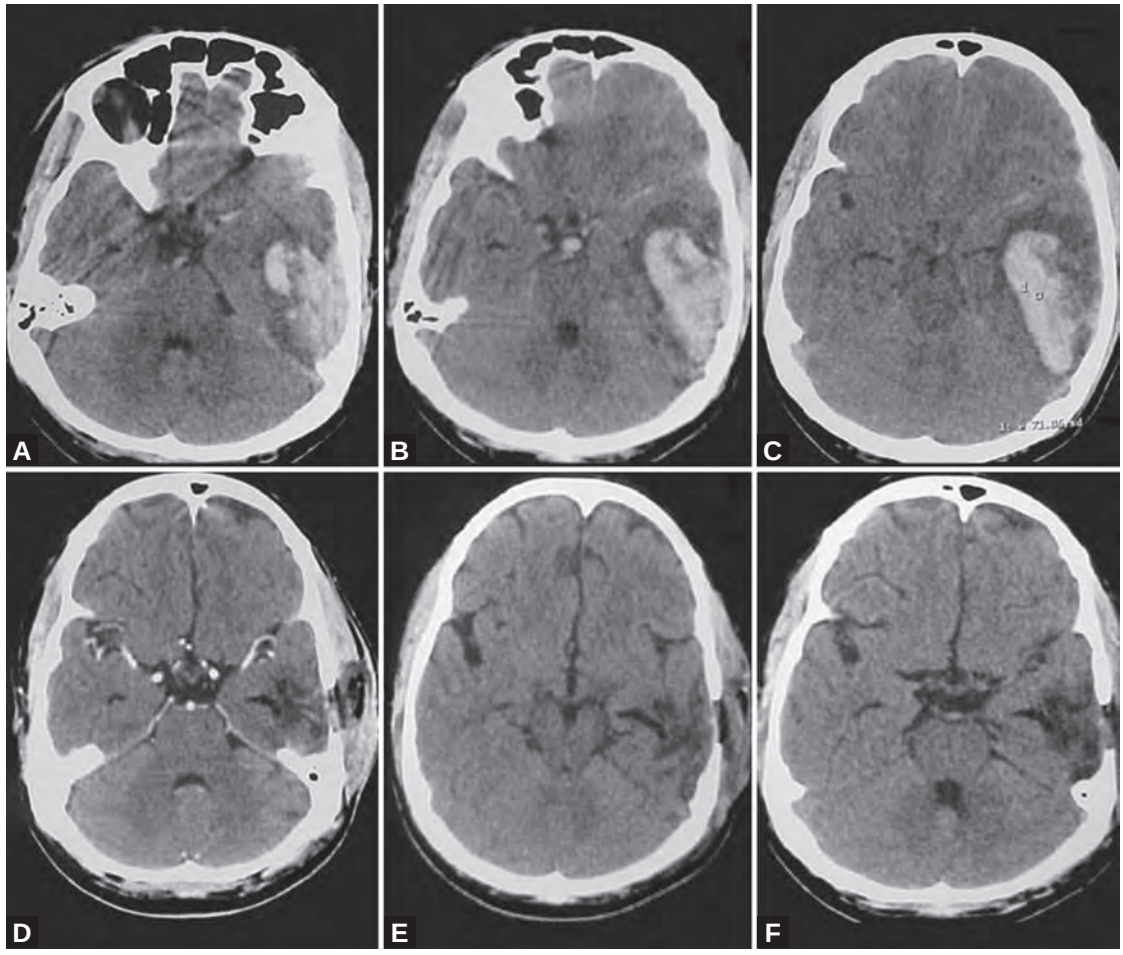
A detailed analysis by Tandon[65] of 236 surgically treated cases of post-traumatic temporal lobe lesions revealed the following important features. The lesion commonly affected persons between the ages of 20 years and 50 years (72.9%); 11.9% were below 20 years and 15.7% were above 50 years. Two-thirds of the patients were unconscious from the moment of injury till operation or death, while 17.7% had a lucid interval. Nearly two-thirds (64.2%) had hemiparesis: contralateral in 122 and ipsilateral in 30 cases. About one-half of the patients had pupillary abnormality, one pupil dilated and fixed in 28.3% and both in 19.5%.

In subacute and chronic cases, the clinical manifestations are slow in evolving. There is usually a history of a blow to the side or back of the head. The patient shows rapid improvement from the initial unconsciousness but does not progress to complete recovery. He may continue to be mildly restless, but co-operative. Often he is mute or just able to say a few words and obey simple commands. The level of consciousness may remain stationary at this stage for several days or may deteriorate following any respiratory complication or after the administration of excessive fluids.[34]

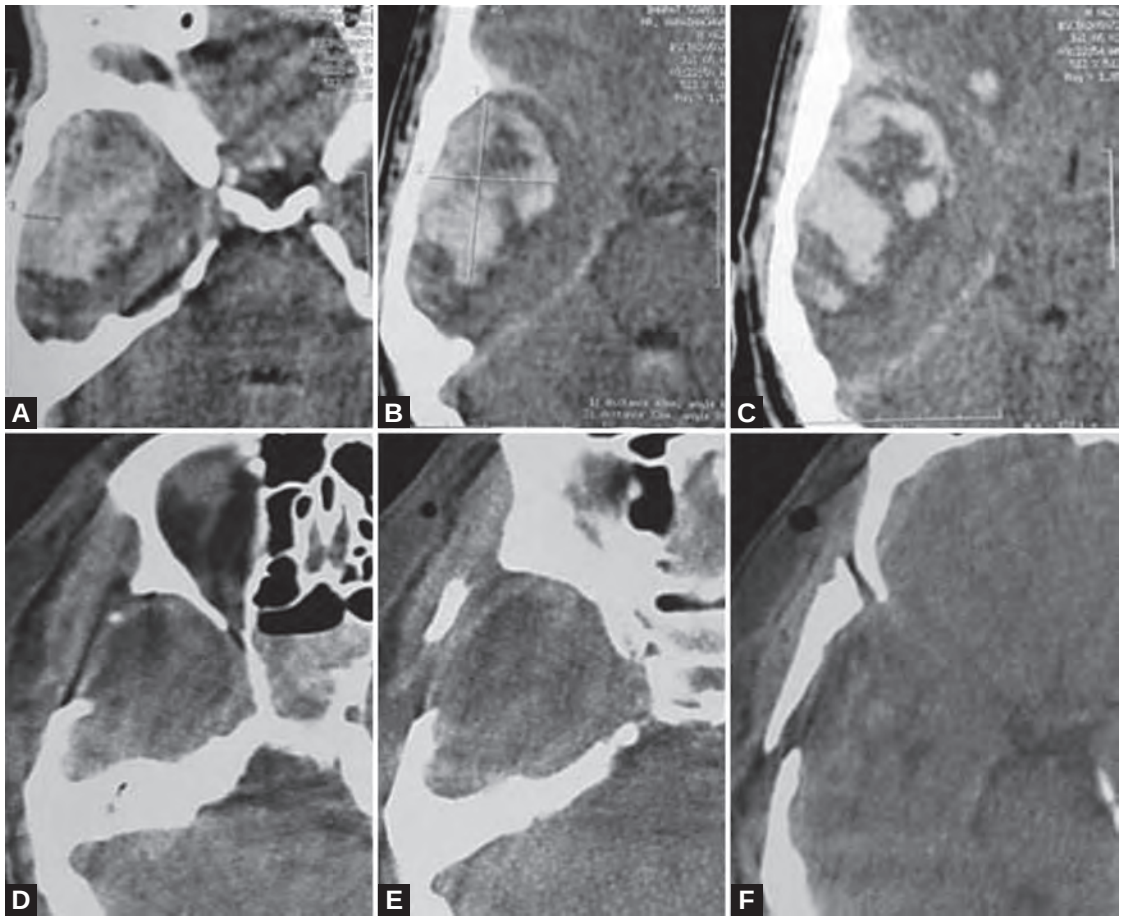
In the initial stages, the pupils are equal and reacting but later there may be a little transient dilatation and sluggish reaction on one side, or alternatively on both sides. A mild hemiparesis, with central weakness of the face, may become slowly evident. Dysphasia may be present if the dominant hemisphere has been affected. These findings suggest a mass lesion in the cranium. CT scan helps to exclude extracerebral haematomas and confirm haemorrhagic contusion with local oedema. Frank intratemporal lobe haematomas are also common. CT reveals the age and extent of the contusion, the presence of necrosis and oedema and any shift of the midline structures.

In mild cases of contusion, when the clinical condition is satisfactory, one is justified in using anti-oedema measures and keeping the patient under observation. These measures are not useful in laceration with oedema or with an intracerebral haematoma. In such cases, if the neurological condition worsens and if the CT shows a large lesion, craniotomy is indicated to decompress the temporal lobe or to remove any associated haematoma (Figs 5A to F and 6A to F). It should be stressed that temporal lobe haematomas and contusions are potentially dangerous due to the possibility of rapid herniation into the tentorial hiatus. If parts of the temporal lobe, usually the pole and anterior part, are lacerated, necrotic and non-viable, the necrotic portions are removed. If the swelling is marked and the affected side is non-dominant, sometimes one may be justified in doing partial anterior temporal lobectomy, as a method of internal decompression.[45] Patients with sizeable and acute progressive lesions requiring surgery (excluding those with small contusions seen on CT) carry a risk of mortality of 41–57%.[26,50,58,65] Those requiring surgery within 24 hours of injury also have a high mortality, prompting de Vet,[12] Vigouroux and Guillermain,[42,68] Lanksch et al.[31] and Papo et al.[50] to consider surgery within 24 hours to be futile. However, Seeling et al.[58] reported that early surgery, especially within 4 hours after injury, reduced the mortality to 30%. Tandon[65] observed that younger age, history of lucid interval and absence of pupillary abnormality are favourable prognostic factors.

The use of lobectomy in the management of severe closed head trauma[22] has been stressed by Litostky et al.[39] who found this useful, especially in younger patients with a relatively high initial GCS score who subsequently deteriorated or developed increased ICP. Basauri et al.[2] found that old age and alcoholism influenced the ultimate recovery adversely. Recovery is quite slow. Profound disturbance of recent memory is seen out



Figs 5A to F: (A to C) Pre-operative CT scan of the brain showing haemorrhagic contusion in the temporal lobe causing mass effect and midline shift. (D to F) Post-operative CT scan of the brain showing complete resolution of the contusion



Figs 6A to F: (A to C) Pre-operative CT scan of the brain showing haemorrhagic contusion in the temporal lobe. (D to F) Post-operative CT scan of the brain showing complete resolution of the contusion

of proportion to other mental changes. Dysphasia may recover only partly.

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30 Diffuse Axonal Injury

Rajkumar, Vivek Kumar Vaid, Ashok Kumar Mahapatra

INTRODUCTION

Diffuse brain injury is defined as the pathology of head-injured patients who are unconscious from the moment of impact without any evidence of space occupying intracranial lesions on computed tomography (CT) scan or magnetic resonance imaging (MRI).

Diffuse brain injury can exist in four principle forms, viz.

1. Diffuse axonal brain injury
2. Diffuse hypoxic/anoxic/ischaemic injury
3. Diffuse swelling
4. Diffuse vascular injury

Of these four forms, diffuse axonal injury (DAI) is the one that is gaining the most attention particularly because of its relationship in its less severe forms to the sequelae of subtle brain injury.

Traumatic TDAI was first described by Strich[38] as "diffuse degeneration of white matter following severe head injury". This was a study on patients having severe dementia following head injury and the term DAI was not used by her. In a later publication she described shearing of nerve fibres as a cause of brain damage due to head injury.[39] This was based on the observation of retraction bulbs on microscopic examination of autopsy material. Two decades later, Adams et al.[1] in a paper entitled "Diffuse axonal injury due to non-missile head injury in humans: an analysis of 45 cases" described the pathological hallmarks of this condition. They went ahead to study the condition in subhuman primates and compared the lesions to those observed in humans.[2] Since then, a number of terms have been used to describe (TDAI) and include "shearing injury", "diffuse white matter shearing injury" and "inner cerebral trauma". The current definition includes severely head-injured patients with normal scans, tissue tear haemorrhages, traumatic subarachnoid and intraventricular haemorrhages, diffuse brain swelling and unilateral swelling with midline shifts.

PATHOPHYSIOLOGY

It is caused by angular or rotational acceleration and deceleration inertial effects and not by contact phenomena.[47] The severity of axonal damage is related to the magnitude, duration and onset rate of the angular acceleration.

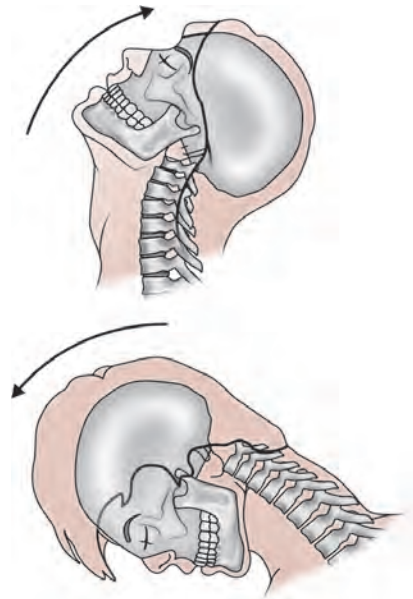

Fig. 1: Sudden acceleration-deceleration impact can produce rotational forces that lead to diffuse axonal injury

The pathophysiology of DAI was first described by Holbourn in 1943,[21] using two-dimensional gelatin moulds. His work led to the understanding that shear injury is not induced by linear or translational forces but rather by rotational forces.[14,47] Sudden acceleration-deceleration impact can produce rotational forces that affect the brain (Fig. 1). The injury to tissue is the greatest in those areas where the density difference is the greatest. For this reason, approximately two-thirds of DAI lesions occur at the grey-white matter junction (Fig. 2).

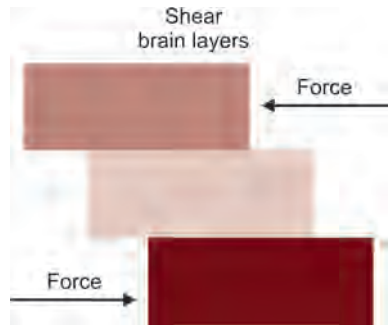

Fig. 2: Shear injury greatest in areas where the density difference is the greatest such as the grey-white matter junction

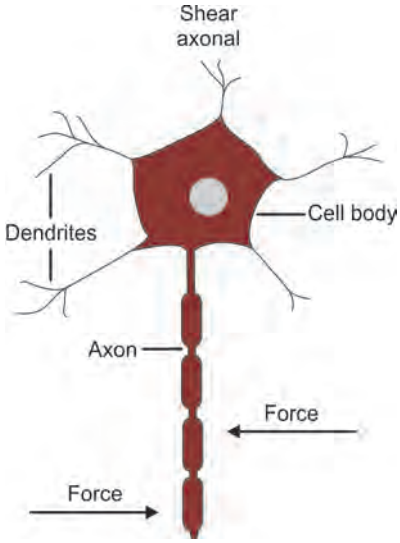

Fig. 3: Shear injury causing primary injury (axotomy) to the neuron

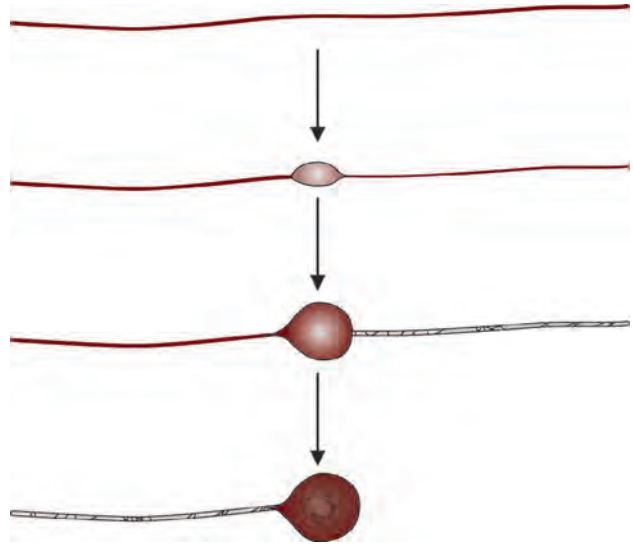

Fig. 4: Shear injury causing focal alteration of the axoplasmic membrane, leading to impaired axonal transport, axoplasmic swelling, with the axon subsequently splitting into two pieces and formation of a retraction ball

When shearing forces occur in areas of greater density differential, the axons suffer trauma (Fig. 3); this results in oedema and in axoplasmic leakage (which is most severe during the first 2 weeks following injury). The exact location of the shear-strain injury depends on the plane of rotation and is independent of the distance from the centre of rotation. Conversely, the magnitude of injury depends on the following three factors:

1. The distance from the centre of rotation.
2. The arc of rotation.
3. The duration and intensity of the force.

The true extent of axonal injury typically is worse than that visualised using current imaging techniques. On the microscopic level, the axon may not completely be torn by the initial force, but the trauma still can produce focal alteration of the axoplasmic membrane, resulting in impairment of axoplasmic transport. This would lead to axoplasmic swelling, with the axon subsequently splitting into two pieces and forming a retraction ball—a pathologic hallmark of shearing injury.[25,36-38,40-43] The axon would then undergo Wallerian degeneration (Fig. 4). Dendritic restructuring might occur, with some regeneration possible in mild-to-moderate injury.

Within the basal ganglia, the effect of DAI produces parenchymal atrophy brought on by shrinkage of astrocytes in the lateral and ventral nuclei, with sparing of the anterior and dorsomedial nuclei, the pulvinar, the centromedian nuclei and the lateral geniculate bodies. Cholinergic neurons have been found to be slightly more susceptible to trauma than are neurons belonging to other neurotransmitters. Peripheral lesions usually are smaller than central lesions. The lesions typically are ovoid or elliptical, with the long axis parallel to the direction of the involved axonal tracts. A high association is seen between thalamic injury and DAI.

Remaining surviving axons may be vulnerable due to secondary events leading to hypoxia, ischaemia and subsequent release of excitatory amino acids and free radicals. The ultimate event in neuronal death appears to be the influx of calcium ions.[40] Büki et al.[10,11] had demonstrated calpain-mediated spedin proteolysis in the pathogenesis of traumatically induced axonal injury. In another study they reported Cytochrome C release and caspase activation in TDAI.

Both silver staining and beta-amyloid precursor protein immunohistochemical staining have proven useful in the pathologic identification of DAI lesions.[9-11,19,20,29]

Diffuse axonal injury was classically believed to represent a primary injury (occurring at the instant that the trauma occurred). It has become apparent, however, that the axoplasmic membrane alteration, transport impairment and retraction ball formation may represent secondary (or delayed axotomy) components of the disease process. Accumulation of the precursor protein of amyloid[9,20] within 2 or 3 hours of injury indicates the beginning of delayed axotomy. The process may continue for 24 hours or more. The exact mechanisms causing secondary injury are not yet known, but it is postulated that there may be increased permeability to Ca^{2+} in the region of Ranvier's node or, alternatively, within the internal cytoskeleton itself.[40] This leads to disorganisation of microtubules and neurofilaments, hence a block in axonal transport resulting in axonal focal swelling. Later on, the classical axonal bulb appears (Figs 5A and B). Any measure which prevents or minimises secondary axotomy can improve clinical outcome.

PATHOLOGY OF TRAUMATIC DIFFUSED AXONAL INJURY

McCormick[27] described three "classic" lesions which characterise severe TDAI. These were earlier described as characteristic pathological lesions in TDAI in 1981 by Adams et al.[1]

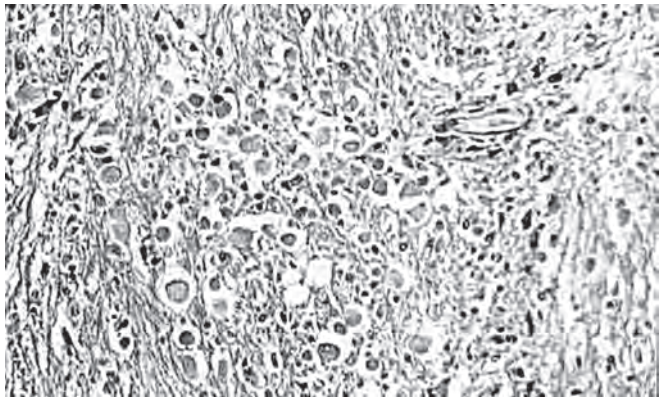

Fig. 5A: Shear injury leading to focal alteration of the axoplasmic membrane, leading to impaired axonal transport, axoplasmic swelling and subsequent formation of retraction balls as visible under the microscope (20x)

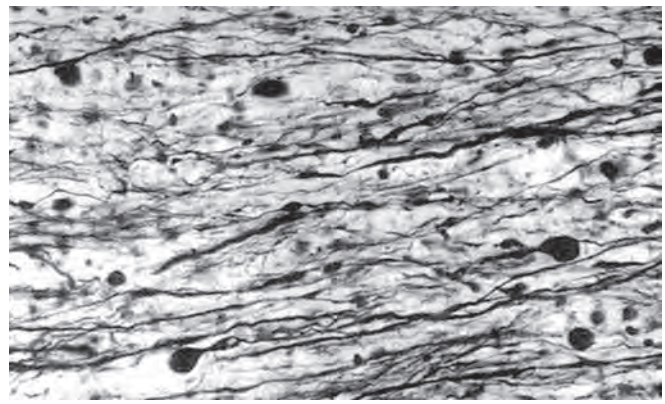

Fig. 5B: Shear injury leading to focal alteration of the axoplasmic membrane, leading to impaired axonal transport, axoplasmic swelling and subsequent formation of retraction balls as visible under the microscope (40x)

- Reactive axonal "retraction" balls.
- Haemorrhagic necrosis in the dorsolateral quadrant of the rostral brainstem.
- Haemorrhagic necrosis in the corpus callosum.

The axonal swellings are the microscopic hallmark of TDAI. They become apparent within hours after injury and may persist for a year or more. Typically, the process is diffuse and bilateral, involving the lobar white matter at the grey-white matter interface. The most commonly involved area is the frontal and temporal white matter. Microglial stars develop in these damaged sites and may eventually replace the swollen axon. Degeneration of long tracts will evolve and ventricular dilatation will follow.[25,27,36,37]

The lesion in the dorsolateral quadrant of the rostral brainstem is usually haemorrhagic and involves the dorsolateral/lateral part of the midbrain and the rostral pons, almost always involving the superior cerebellar peduncle.

The lesion in the corpus callosum usually lies lateral to the midline and affects the inferior and posterior part of the corpus callosum. These lesions may extend over several centimetres. The callosal injury may be focal, segmental or may extend from the genu to the splenium.

Other sites of involvement are the caudate nuclei, thalamus, tegmentum and internal capsule. Internal capsule lesions are associated more frequently with haemorrhage than are with other lesions and are secondary to the proximity of the lenticulostriate vessels.

Adams et al.[3] described the stages of involvement according to the anatomic location of the lesions:

- Stage I—This involves the parasagittal regions of the frontal lobes, the periventricular temporal lobes, and, less likely, the parietal and occipital lobes, internal and external capsules, and cerebellum.
- Stage II—This involves the corpus callosum in addition to the white-matter areas of stage I. Stage II is observed in approximately 20% of patients. Most commonly, the posterior body and splenium are involved; however, the process is believed to advance anteriorly with increasing severity of disease. Both sides of the corpus callosum may be involved; however, involvement is more frequently unilateral and may be haemorrhagic. The involvement of the corpus callosum carries a poorer prognosis.
- Stage III—This involves the areas associated with stage II, with the addition of brainstem involvement. A predilection exists for the superior cerebellar peduncles, medial lemnisci and corticospinal tracts.

INCIDENCE OF TRAUMATIC DIFFUSED AXONAL INJURY

The incidence of TDAI will be higher at autopsy than would be obvious on radiographic (e.g. CT and MRI) examination.[25,36-38,40-43] Adams et al.[3] found TDAI in 28% of non-missile head injuries histologically at autopsy. In 20% of these cases, the diagnosis of TDAI could not have been made without microscopic examination. The CT incidence of TDAI in various series varies from 2.4% to 15.5%.

Diffuse axonal injury represents approximately one-half of all intra-axial traumatic lesions.[14,15,18,25,33,43] No racial or sex predilection exists. DAI can occur at any age. Some studies suggest that DAI may occur *in utero*, if a pregnant woman is subjected to sufficient force.[49]

CLINICAL PRESENTATION

Patients with severe TDAI present in an unconscious state from the onset of trauma, with the majority of severely injured patients showing a combination of generalised extensor posture or flexion. About one-third of TDAI patients may recover sufficiently from the initial head injury to talk before lapsing into coma.

Classically, DAI has been considered a primary-type injury, with damage occurring at the time of the accident. Research has shown that another component of the injury comprises the secondary factors (or delayed component), since the axons are injured, secondary swelling occurs, and retraction bulbs form.[25,36-38,40,42,43] Of patients

with DAI, 80% demonstrate multiple areas of injury on CT scans.

The degree of microscopic injury is usually considered to be greater than that seen on diagnostic imaging and the clinical findings reflect this point. DAI is suggested in any patient who demonstrates clinical symptoms disproportionate to his or her CT scan findings. DAI results in instantaneous loss of consciousness and most patients (> 90%) remain in a persistent vegetative state, since brainstem function typically remains unaffected. DAI rarely causes death.

Compared with patients who have an epidural haematoma, patients with DAI are less likely to have a lucid interval. There is little association between DAI and the presence of skull fractures; in addition, the existence of DAI has no bearing on whether a subarachnoid or subdural haemorrhage is present.

The chance that a patient will remain in a persistent vegetative state is greater when lesions are observed in the supratentorial white matter, corpus callosum and corona radiata. The prognosis also worsens as the number of lesions increases. For the almost 10% of patients who experience a return to any form of normal function, this improvement will be seen within the 1st year. DAI lesions can result in deficits in information transfer between the two hemispheres through the corpus callosum, commonly resulting in auditory deficits.

DIAGNOSTIC STUDIES

Magnetic resonance imaging is the preferred examination for diagnosis of DAI (particularly with gradient-echo sequences), although CT scanning may demonstrate findings suggestive of DAI and is more practical and available.[13,16,17,30,32,34,50] Studies have indicated that MRI can play a role in predicting the length of coma in DAI patients.

Conventional Radiography

No specific findings related to DAI can be made using conventional radiography; however, other signs of head trauma can be appreciated, such as facial bone fractures or fluid levels within the paranasal sinuses. The degree of confidence is low, since conventional radiography cannot demonstrate subtle soft-tissue changes. While radiographs can clearly demonstrate skull fracture, this is not helpful in DAI, since DAI is rarely associated with skull fracture.

Computed Tomography Scan

Among patients eventually proven to have DAI, 50–80% have a normal CT scan upon presentation. Delayed CT scanning may be helpful in demonstrating oedema or atrophy, which occurs later. Small petechial haemorrhages, located at the grey-white matter junction, as well as in the corpus callosum and brainstem, are characteristic of CT scan findings in the acute setting (Fig. 6).

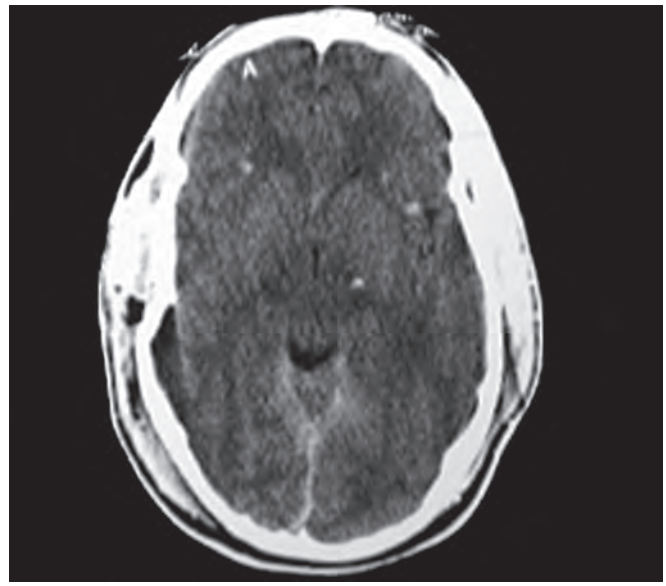

Fig. 6: Non-contrast CT scan of a trauma patient demonstrates multiple petechial haemorrhages consistent with DAI, characteristically located at the grey-white matter interface

The following CT scan criteria have been suggested by Wang et al.[43]

- One or more small intraparenchymal haemorrhages less than 2 cm in diameter, located in the cerebral hemispheres
- Intraventricular haemorrhage
- Haemorrhage in the corpus callosum
- Small focal areas of haemorrhage less than 2 cm in diameter, adjacent to the third ventricle
- Brainstem haemorrhage.

One may also observe small focal areas of low density on CT scans; these correspond to areas of oedema occurring where shearing injury took place.

MRI is more sensitive in the detection of subtle soft-tissue abnormalities; however, CT scanning is more available and practical in the current medical environment and is, therefore, the "mainstay of acute investigation of head injury" according to Teasdale.[41]

The degree of confidence in CT scanning is moderate, since the only finding may be petechial haemorrhage, and fewer than 20% of patients with DAI demonstrate this finding on CT scanning alone. When petechial haemorrhages are observed with the appropriate clinical findings, the sensitivity of CT scanning in the detection of DAI is high.

Magnetic Resonance Imaging

Recommended sequences include T1-weighted, T2-weighted, T2-gradient-echo, proton density-weighted and diffusion-weighted images.[5,6,12,30,35,46,50]

- T1-weighted images are helpful for anatomic localisation; however, non-haemorrhagic lesions may be isointense to surrounding tissue. Haemorrhagic lesions appear hyperintense on T1-weighted images. Non-haemorrhagic lesions appear hyperintense

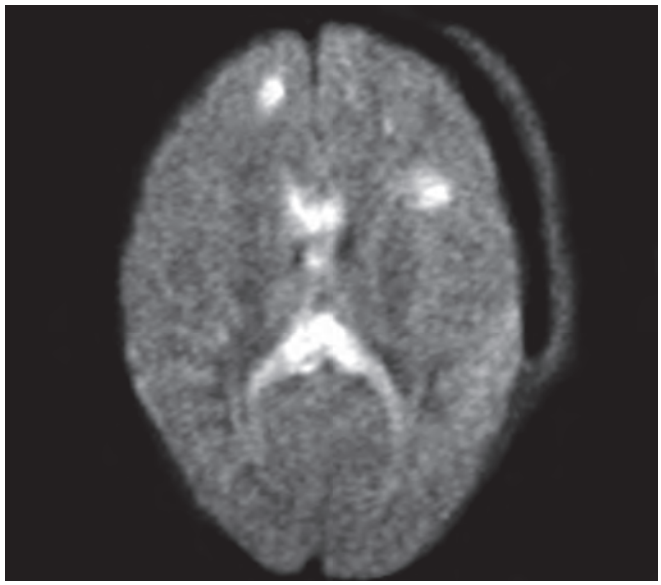

Fig. 7A: MRI diffusion sequence demonstrating multiple foci of abnormal increased signal at the grey-white matter junction and within the corpus callosum in a patient with DAI

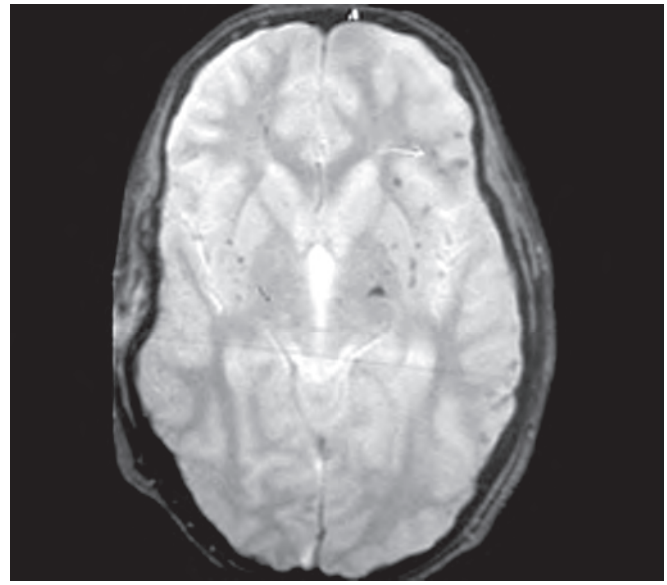

Fig. 7B: Gradient-echo axial MRI demonstrating numerous small foci of diminished signal consistent with the paramagnetic effect of the haemoglobin content of many acute haemorrhages

on T2-weighted sequences. Diffusion-weighted sequences can reveal hyperintensities in areas of axonal injury (Fig. 7A).

- Gradient-echo sequences are particularly useful in demonstrating the paramagnetic effects of petechial haemorrhages. Gradient-echo imaging can often demonstrate signal abnormality in areas that appear normal in T1-weighted and T2-weighted spin-echo sequences (Fig. 7B). For this reason, gradient-echo imaging has become the mainstay of MRI examination for patients with suspected shearing-type injuries. The abnormal signal on gradient-echo images can persist for many years after the injury.
- The most common MRI finding is the presence of multi-focal areas of abnormal signal (bright on T2-weighted images) in the white matter in the temporal or parietal corticomedullary junction or in the splenium of the corpus callosum.
- Other areas that are frequently abnormal include the dorsolateral rostral midbrain and the corona radiata. Eventually, non-specific atrophic changes are observed.

One area of research has been magnetisation transfer imaging. Studies have reported that the magnetic transfer ratio has shown promise in identifying areas of injury not visible on the above MRI pulse sequences. This may allow the radiologist to appreciate a truer representation of the degree of microscopic injury. Studies have indicated that MRI can play a role in predicting the length of coma in DAI patients. The volume of white-matter lesions has been correlated to the degree of injury, as measured by MRI. MRI has also been used to quantify cerebral blood flow in damaged areas of the brain, thus predicting injury severity. The degree of confidence is high, since abnormal signals in the characteristic locations discovered in the clinical setting of recent trauma, leaves little doubt about the diagnosis of DAI.

A novel MRI technique, diffusion tensor imaging (DTI),[4,7,8,22,24,26,28,31,45,48] permits the examination of white matter integrity *in vivo* through observing the amount of water diffusion within biological tissues.[11,30] A direct comparison between DTI-detected white matter integrity changes and histological findings in an animal model of axonal injury[26] suggests that DTI may become a valuable imaging tool for detecting DAI.

Two diffusion parameters[8] are used for characterising white matter integrity, namely fractional anisotropy (FA), a ratio from 0–1 that represents the degree of alignment of the underlying fibres[31] in a voxel, and mean diffusivity that represents the presence of overall restrictions to water diffusion (Fig. 8).

Nuclear medicine currently has no role in the routine diagnostic workup of patients with possible DAI; however, studies have suggested that iodine-123 single-photon emission CT (SPECT) imaging[23] demonstrates areas of hypoperfusion in regions of known injury and reveals additional areas of injury not visualised with MRI.

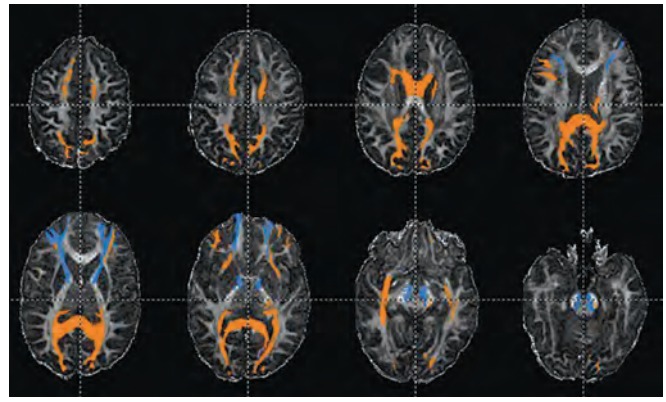

Fig. 8: Diffusion tensor imaging "a newer concept" in radiological assessment of diffuse axonal injury

DIFFERENTIAL DIAGNOSIS

One must consider the following in the differential diagnosis of TDAI:

- Cavernous angioma of the brain
- Embolic and/or haemorrhagic stroke
- Multiple sclerosis.

MANAGEMENT OF TRAUMATIC DIFFUSE AXONAL INJURY

The following basic principles are applicable for managing patients with DAIs:

- Immediate establishment of ventilation and circulation at the site of accident
- Aggressive monitoring and control of intracranial pressure (ICP)
- Intensive care to achieve neuronal recovery.

The patency of the respiratory tract must be maintained or established and restoration of adequate ventilation should have top priority. Endotracheal intubation is often necessary to protect the airway and maintain ventilation.

Cerebral perfusion pressure (CPP) is defined as mean arterial pressure (MAP) minus ICP. CPP = MAP - ICP. The initial approach to maintain MAP (hence CPP) is the establishment and maintenance of circulatory volume by administering an adequate volume of crystalloids, colloids or blood products, as appropriate.

It is important to identify the patients who are at risk of developing increased ICP. Risk factors which can predict intracranial hypertension are:

- Subarachnoid haemorrhage
- Midline shift
- Abnormal mesencephalic cistern

Patients with subarachnoid haemorrhage are twice as likely to develop increased ICP. Detection of an abnormal mesencephalic cistern in the CT scan indicates that patients are thrice as likely to develop increased ICP. The more the midline shift more is the chance of developing raised ICP.

Severe head-injured patients with a normal CT scan have a 10–15% chance of developing intracranial hypertension after 72 hours, hence serial follow-up CT scans are necessary. Most investigators report improved outcome with treatment at 15–20 mmHg levels. ICP may be measured from intraventricular, intraparenchymal, subdural and extradural sites (Fig. 9).

Various medical methods for controlling increased ICP are:

- Position of the patient's head
- Osmotherapy and diuretics
- Hyperventilation
- Barbiturates
- Cerebrospinal fluid drainage.

PROGNOSIS

In TDAI, little can be done about the primary axonal injury. Measures to reduce ICP and measures to prevent or reverse the secondary insults (such as oedema, ischaemia and secondary neuronal death) should be taken aggressively as it may improve the mortality and morbidity in TDAI.

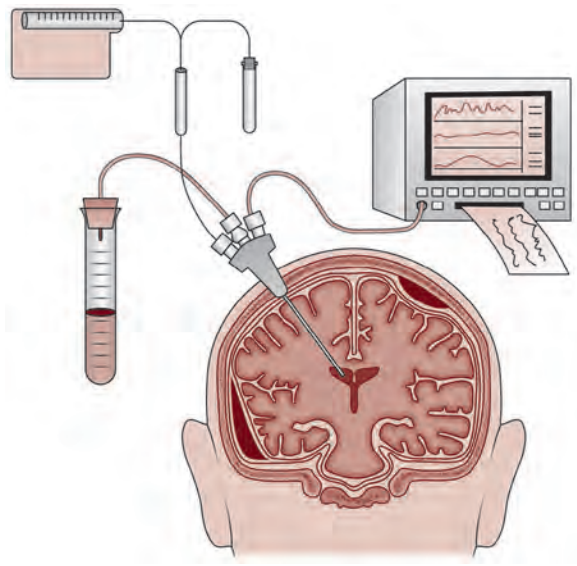

Fig. 9: Mechanism for intracranial pressure monitoring; also helpful to drain cerebrospinal fluid so as to lower intracranial pressure

Wilberger et al.[44] found a correlation between the admission GCS score and the eventual outcomes of patients with DAI.

In severe head injury, 42% of the patients died or were severely disabled or vegetative at discharge. Mild-and-moderate head injuries did well; no patient was severely disabled or vegetative at discharge, and no patient died. In patients with brainstem or corpus callosum tissue tear haemorrhages, the outcome was especially poor. Paterakis at al.[35] in 2000 had reported the outcome in patients with TDAI and highlighted the prognostic role of MRI.

CONCLUSION

Traumatic diffuse axonal injury is characterised by reactive axonal "retraction" balls, haemorrhagic necrosis in the dorsolateral quadrant of the brainstem and haemorrhagic necrosis in the corpus callosum. DAI is caused by angular acceleration or rotational acceleration and the extent of axonal damage depends upon the magnitude, duration and rate of angular acceleration. Classically, these patients become unconscious immediately upon impact, and the CT scan shows focal punctuate haemorrhages in the cerebral white matter, basal ganglia, corpus callosum or dorsal part of the brainstem. MRI is superior to CT scan in demonstrating non-haemorrhagic contusions. Maintenance of cerebral perfusion and aggressive monitoring and control of ICP is the mainstay of medical management.

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31 Fat Embolism

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INTRODUCTION

Fat embolism is a pathological entity characterised by occlusion of multiple blood vessels with fat globules, which presents clinically with manifestations of diffuse pulmonary insufficiency causing hypoxia, neurological dysfunction, pyrexia, tachycardia, tachypnoea and petechiae occurring 12–48 hours after trauma. The incidence of fat embolism presenting clinically varies between 0.5% and 2% of patients with long bone fractures and 5–10% of patients with multiple fractures. Subclinically it is present in almost all cases of long bone fractures. Drummond and his co-workers reported an incidence of 0.5% in 1800 children with pelvic and long bone fractures.[6]

Zenker,[28] in 1862, was the first to report the presence of fat in the lungs of a trauma victim. In 1865, Wagner, who produced fractures in dogs, was the first to recognise that the fat actually originated from the bone marrow. Von Bergmann,[4] first recognised the entity clinically in 1873. Lehman and Moore[17] suggested a metabolic origin of this complication in 1927. Sevitt,[26] a British pathologist, proposed a distinction between pulmonary and systemic fat embolism and emphasised the more serious clinical consequences of the latter. Peltier,[23] an American surgeon, suggested that the morbidity from fat embolism is in large part a result of hydrolysis of neutral fat to highly toxic fatty acids and that the inflammation produced by these substances is the primary cause of the clinical manifestations.

AETIOLOGY

The causes of fat embolism syndrome (FES) are as follows:

Traumatic Factors

- Fractures
  - Long bone
  - Pelvis
- Burns and subcutaneous adipose tissue injuries
- Surgery
  - IM nailing
  - Total hip and knee arthroplasty

Non-Traumatic Factors

- Procedures
  - Cardiopulmonary resuscitation (CPR)
  - Cryosurgery of bone
  - Intraosseous fluid and drug
  - Administration
  - Liposuction
  - Intra-operative autotransfusion
  - Lymphangiography
  - Hysterosalpingography

Diseases

- Sickle cell anaemia
- Acute pancreatitis
- Fatty liver
- Diabetes
- Immunosuppression.

Drugs

- Lipid emulsions
- Intra-arterial cisplatin
- Long-term steroid administration.

PATHOPHYSIOLOGY

Two theories have been proposed to explain the pathophysiological basis of the FES:

1. Mechanical theory of Guass
2. Biochemical theory of Lehman and Moore.

According to the mechanical theory, FES results because of physical obstruction of the pulmonary and systemic vasculature by the embolised fat which is liberated into the circulation from the bone marrow at the site of the fracture. This theory basically explains the FES of traumatic origin. The presence of cardiac septal defects will increase the incidence of systemic embolism.

According to the biochemical theory, which explains the non-traumatic origin of FES, fat globules in the pulmonary or systemic circulation originate from the lipids normally present in the blood. Physiochemical alterations of these compounds can lead to FES by two mechanisms: toxic and obstructive. Circulating free fatty acids (FFAs) are directly toxic to the pneumocytes and the capillary endothelium. However, controversy exists with regards

to the origin of the FFAs.[13] Peltier[23] proposed that they are produced by the action of the pulmonary lipase on the circulating neutral fat. Others have postulated that the offending FFAs originate from the body fat. FFAs are usually cleared by the liver and in the presence of shock and associated hypovolaemia and sepsis, the blood flow to the liver is reduced, which leads to the exacerbation of the toxic effects of the FFAs.

The obstructive mechanism attributes the development of FES to the coalescence of chylomicrons into fat globules, which is triggered by the mediators released at the site of fracture.

Neither the mechanical nor the biochemical theory alone can provide an entirely satisfactory explanation for the genesis of FES and it is therefore proposed by Peltier that shortly (hours) after an initial obstructive process, a second phase begins during which FFAs exert their toxic effect on the organs where neutral fat had embolised initially. Currently, this seems to be the most widely accepted view.

Additional mechanisms appear to contribute to the pathophysiology of FES. These include activation of the platelets, coagulative and fibrinolytic cascades.

Pathological examination revealed alveolar oedema and haemorrhage with multiple fat droplet depositions and fibrin thrombi. Fat droplets were also found in the arterioles and/or capillaries in the lung, kidney and brain. Immunohistochemical staining identified inducible nitric oxide synthase (iNOS) in alveolar macrophages.[14]

CLINICAL FEATURES OF FAT EMBOLISM SYNDROME

There are several puzzles in this otherwise distinctive clinical syndrome. It strikes the young and healthy, whereas older patients do not seem to carry any risk. It usually occurs after lower limb and pelvic fractures and not with upper limb fractures. It is more frequent with closed fracture and after multiple fractures. Although FES usually presents as a multisystem disorder, the most seriously affected organs are the lung, brain, cardiovascular system and skin.[24]

Fat embolism syndrome is a serious manifestation of fat embolism that involves a cascade of clinical signs, such as petechial haemorrhages, deteriorating mental status and progressive respiratory insufficiency, usually occurring within 24 hours of injury.[1]

Clinically, FES consists of a triad of hypoxia, confusion and petechiae appearing in a patient with fracture, 1–2 days after the trauma.[10] Sixty percent of all cases of FES are seen in first 24 hours after trauma and 90% of all cases appear within 72 hours. The various clinical forms of FES are summarised in Table 1.

NEUROLOGICAL ABNORMALITIES

Neurological impairment occurs in about 85% of cases who die of FES. The incidence in survivors is quite variable. It begins as an acute confusional state and then progresses to stupor and coma. Seizures have been

Table 1: Various forms of fat embolism syndrome

Clinical form	*Occurrence after injury (%)*	*Onset after injury*	*Clinical presentation*	*Mortality rate (%)*
Subclinical	60	12–72 hours	Non-specific or absent symptoms Moderate hypoxaemia (PaO_2 < 80 mmHg on room air) Moderate elevation of $AaDO_2$ (> 20 mmHg on room air) Moderate hypocapnia ($PaCO_2$ < 30 mmHg during spontaneous breathing) Moderate decrease of platelet count (<2 lakhs/μL)	0
Non-fulminant subacute (classic form)	Single fracture (1–5) Multiple fractures (5–10)	12–96 hours	Dyspnoea, fever, tachycardia, petechiae, cerebral signs, hypoxaemia (PaO_2 < 60 mmHg on room air), anaemia, thrombocytopenia and coagulation abnormalities, lung opacities on chest X-ray	0-5
Fulminant	< 0.2	Few hours	Acute cor pulmonale, frank pulmonary oedema, moderate to severe hypotension, cerebral signs, severe hypoxaemia, acidosis	> 50

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reported. Focal neurological deficits can be identified, including anisocoria, hemiplegia, scotomata, apraxia, aphasia and conjugate eye deviation. In spite of the severe initial neurological impairment, clinical recovery usually occurs and permanent deficits are infrequent. Focal neurological findings typically follow the encephalopathy. Focal lesions, such as pontine haemorrhage have been described. Cerebral oedema and decorticate posturing have been reported in severe cases and are reversible, suggesting that in certain cases, intracranial pressure monitoring may be beneficial. Focal neurological findings should be investigated to rule out lesions caused by associated head injury. Persistent alteration of consciousness or seizures are bad prognostic signs.[16]

Pathologically, diffuse petechial haemorrhages are present, predominantly in the white matter of the cerebral cortex. Ischaemic lesions are present and fat globules are demonstrated in the micro-vessels. A less frequent lesion is a non-haemorrhagic ischaemic micro-infarct that is randomly distributed and not regularly associated with intravascular fat globules.

DIAGNOSIS

Diagnosis of this syndrome is mainly a clinical one, that requires accumulation of clinical and laboratory findings and exclusion of other diagnostic possibilities. Several diagnostic criteria have been reported in the literature, of which two have found wide acceptance:

Gurd and Wilson's Criteria[12]

- Major clinical features: petechial rash, respiratory insufficiency and cerebral involvement.
- Minor clinical features: pyrexia, tachycardia, retinal changes, jaundice and renal changes.
- Fat macroglobulaemia.

Presence of one major clinical feature, four minor clinical features and fat macroglobulaemia, gives a positive diagnosis.

Lindeque et al. Criteria[18]

- PaO_2 < 60 mmHg in room air
- $PaCO_2$ > 55 mmHg or pHa < 7.3
- Spontaneous respiratory rate > 35 breaths/min (even after adequate sedation)
- Clinical signs of increased work of breathing (dyspnoea, accessory muscle use) and tachycardia.

The presence of at least one of these findings in a patient with long bone fracture(s) establishes the diagnosis of FES.[5]

Laboratory Tests

Cytological examination of urine, blood and sputum after Sudan or Oil Red O staining may permit detection of fat globules, either free or in macrophages, within 2–3 hours after collection of the specimen. Lipiduria, although it indicates a significant degree of fat embolism, cannot reliably identify patients with FES. Examination of the blood for fat globules by cryostat test helps in the diagnosis when it is performed on the blood obtained from the pulmonary vasculature, where a large amount of fat globules are trapped.

Quantification of the cells containing fat droplets in broncho-alveolar lavage material was helpful in diagnosing clinical fat embolism. At least 63% of the captured cells contained fat globules in patients with proven FES, whereas lipid was present in less than 2% of lavage cells in those without the clinical syndrome. The lavage is to be done with the help of a fibreoptic bronchoscope that is wedged in a sub-segmental bronchus, preferably in the one with maximal infiltrates on the chest radiograph.[9] Other laboratory tests like measurement of blood lipids, activated complement levels and coagulation parameters will not help in the diagnosis of the FES.

Chest radiograph abnormalities are non-specific, lag 12–24 hours behind clinical symptoms and occur in only 30–50% of affected individuals. Diffuse, evenly distributed fleck like shadows and increased interstitial and alveolar densities are the typical findings and give the radiograph a snow-storm appearance. Ventilation/perfusion scans show sub-segmental perfusion defects, a finding highly suggestive of FES. The typical mottled appearance of these scans may be present even in the absence of the radiographic signs. Most patients presenting with a normal initial radiograph develop radiographically evident abnormalities within 72 hours of injury and most cases showed radiographic resolution within 2 weeks of hospitalisation, although chest imaging plays little role in the clinical management of fat embolism.[20,25]

CT scan of the brain in cases of cerebral fat embolism may demonstrate diffuse oedema and low density areas with haemorrhages. Focal abnormalities on the scan may correlate with focal neurological signs. Despite encephalopathy and focal abnormalities, CT scan may be normal in some cases.

MRI is indicated in any patient with orthopaedic injuries who manifests an unexplained acute alteration in mental status, despite a normal head CT[14] MRI of the brain may show hypointense signals on T1-weighted images and hyperintense signals on T2-weighted images. On the diffusion-weighted scans, areas of fat embolism were revealed as bright spots on a dark background ("starfield" pattern). High-intensity lesions in the brain on diffusion-weighted images may serve as an early-appearing and more sensitive indicator of the diagnosis of fat embolism, in the clinical context of long bone injury without head trauma.[15,21,27] MRI with T2 and diffusion-weighted images revealed multiple, reversible brain lesions, suggesting vasogenic oedema and is consistent with this entity. At present, MRI is the most sensitive technique to evaluate cerebral fat embolism.[7] The diagnosis of cerebral fat embolism is shown here to demonstrate infarcts, secondary to fat emboli more intensely than T2 weighted sequences 24 hours after

the onset of symptoms. Embolic foci are hypointense on apparent diffusion coefficient mapping, consistent with cytotoxic oedema associated with cell death and restricted water diffusion. This technique increases the sensitivity for detecting cerebral fat embolism and offers a potentially important tool for its diagnosis.[19]

Single photon emission computed tomography may demonstrate hypoperfusion in areas of fat embolism.[5,8] Transcranial Doppler was found to be useful for monitoring of the microemboli moving in the cerebral vessels. Embolus monitoring may thus serve as a diagnostic tool in evaluation of cerebral fat embolism after long bone fractures. In addition, intra-operative monitoring with transcranial Doppler may identify the emboligenic surgical manoeuvres during the surgical procedures of cardiopulmonary bypass and carotid endarterectomy.[2]

DIFFERENTIAL DIAGNOSIS

Several of the cardiac, respiratory, neurological and haematological conditions need to be differentiated clinically from the FES. Careful review of the symptomatology, laboratory and radiological findings and monitoring of the haemodynamics and oxygenation status will help in the diagnosis of fat embolism. However, pulmonary abnormalities are difficult to differentiate. Pulmonary infiltrates appearing within hours of injury were caused by contusion and/or aspiration of gastric contents, those between the 1st and 2nd post injury day were primarily due to FES and/or ARDS and a delay of more than 2 days in the appearance of infiltrates indicated an infectious aetiology.[5]

MANAGEMENT

Prevention

Most authors recommend early fixation of all fractures after stabilisation of the systemic complications, although this approach has neither decreased nor worsened the incidence of FES in these patients. In a patient who had a concomitant head injury—some studies suggest that early definitive stabilisation is safe, while others have indicated that it is deleterious. Surgery can best be carried out after the patient has been fully resuscitated. There are theoretical concerns regarding occurrence of cerebral fat embolism during fixation of fractures. Most cerebral fat embolism, however, appears to occur at the time of fracture and is not necessarily produced during its stabilisation.

Treatment of Established Fat Embolism Syndrome

Treatment is largely symptomatic with therapy for respiratory failure similar to that used in the management of acute respiratory distress syndrome. Corticosteroids have not been found to be of significant benefit.[11]

The mainstay of treatment of FES is supportive. Administration of adequate humidified oxygen (titrated against the patient's needs by monitoring the arterial blood gas levels), together with fluid replacement and physiotherapy to the chest to minimise the risk of secondary infection, are instituted when FES is suspected. Mechanical ventilation is advocated wherever there is an indication. The hypoxaemia is addressed by manipulating the concentration of inspired oxygen and using positive end expiratory pressures. Antibiotics may be required for secondary infection and tracheostomy and nutritional support may be needed if prolonged ventilation is necessary.

Specific methods of treatment like administration of heparin, dextran and anticytokines have been tried with some encouraging results, but none of these interventions has been widely adopted, because each has a substantial risk of harmful and occasionally catastrophic side-effects.

Corticosteroids most likely decrease the incidence of FES by limiting the endothelial damage caused by the FAAs, but they are associated with significant risk of complications of infection and gastrointestinal bleeding, as many of the patients have multiple injuries. Clinical trials in which steroids were effective used a dose of 30 mg/kg body mass of methyl prednisolone administered on admission and repeated once at 4 hours or 1 gm on admission and two more doses at 8 hour intervals. However, FES is primarily a disease of the respiratory system and current treatment is therefore mainly with oxygen and meticulous mechanical ventilation.[22] Evidence suggests that corticosteroids may be beneficial in preventing FES and hypoxia but not mortality in patients with long-bone fractures. The risk of infection is not increased with the use of corticosteroids. However, methodological limitations of these trials necessitate a large confirmatory randomised trial.[3]

PROGNOSIS

Mortality from FES is usually between 5% and 15%, but it may be as high as 36% in patients who require mechanical ventilation. Patients with FES may have persistent neurological deficits, although spontaneous recovery may occur gradually over many months. Approximately 25% of patients experience permanent neurological deficits. Restoration of normal arterial oxygen levels commonly provides little relief from the CNS signs and symptoms, which usually resolve only 24–48 hours after pulmonary manifestations. Severe hepatic and renal involvement may result in permanent impairment in function of these organs.

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32 Paediatric Head Injuries

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INTRODUCTION

"A neonate is not a small child; neither is a child a small adult."

Trauma has become a leading cause of mortality and morbidity the world over. Although children and adults are affected by traumatic injuries the problems are worse in the paediatric age group due to the long-term implications of the mortality and morbidity. In our country, we are winning the war against infections and malnutrition as in most countries. This means trauma will soon become a serious public health problem—just as infections and malnutrition were several years ago.[83] Not only is the spectrum of injuries in children different from those encountered in adults, the overall spectrum of injuries varies from region to region around the world too, to cite an example, child abuse, —mercifully, —is not as prevalent in India as it is in the West, but falls from a height seem to be more common in our country.

Central nervous system (CNS) injuries are the most common among the various system injuries and, among the various system injuries these are the leading cause of mortality. Measurable deficits occur even after mild to moderate head injury but are markedly greater after severe injury.[35,103] In addition, the presence of an intracranial injury contributes significantly to the mortality resulting from polytrauma.[20,98]

In the United States, 52% of the total mortality in children is due to trauma, making it the leading cause of death in children.[83] More than half the patients who come to the emergency department for the management of head injuries are children.[29] Duhaime and his colleagues have reported that non-accidental injuries account for nearly 25% of all head-injured children under the age of 2 years.[27] The problem seems to be no less in our country,—in the year 1990, in Rajasthan alone, 10,456 accidents were reported.[83] Around 50,000 deaths occur every year as a result of traffic accidents. "The death rate per 10,000 vehicles in India is 45 while it is only 3 in developed countries".[78] The number of traffic accidents in our country is increasing. From 55,478 in 1960 it had increased to 220,000 in 1990.[79]

In a retrospective study spanning three years, 23.6% of all admissions to the paediatric surgical ward were for the management of trauma. In this analysis 2,100 children who were 13 years or younger admitted for the management of trauma, the commonest injury was cranial injury which constituted 84.3% of all cases (78.9% had isolated cranial injury while cranial with extracranial injuries formed 5.4%). This was followed by abdominal injury and skeletal injury. In this study not only was head injury the commonest nature of injury, it was also the leading cause of mortality. Around 161 out of these 2,100 (7.7%) children died, the cause in 145 of these 161 being head injury.[83]

In a study of 100 children admitted consecutively for the management of head injury, 50% were in the age group of 1–4 years while 33% were in the group 4–10 years.[95] Some significant and interesting facts have emerged from this study. A sizable percentage of the injuries were clustered around the weekend (15% on Friday, 18% on Saturday and 24% on Sunday) and half the injuries occurred between 4 PM and midnight. Around 73% of the injured children hailed from nuclear families; this may be a reflection on the breakup of the joint family system which has been the norm in our country for centuries. The spectrum of injuries in our country is different from that seen in other countries. While traffic accidents are more common in the Western countries, falls are more common here.[83,95] Fall from a height,—which was the leading cause of the head injury,—was seen in 68 out of the 100 children studied and falls from balconies were seen in 31 of this group of 68 children. Traffic accidents were the cause of the head injury in only 28%. In an analysis of 22,215 cases of head injuries seen over a period of a quarter of a century, 2,666 (12%) were in the age group 0–15 years with a male-female distribution almost equal. The distribution was as follows: Falls 1,173 (44%); Road accidents 988 (37%); Birth injuries 112 (4.2%); Coconut injuries (i.e. coconut falling on the head) 60 (2.2%); Miscellaneous injuries 335 (12.5%).[78] In an analysis of 297 children (0–10 years) admitted to a neurosurgical unit, the incidence of head injuries was found to be 22%. But the male to female ratio was found to be 2.5:1. 67% were due to falls while 24.4% were due to traffic accidents.[9] "...given the human and economic importance of head injury, there is an urgent need to acquire more epidemiological information on the management and outcome of head injury of all grades of severity."[22,91]

From the foregoing it is apparent that the incidence of traumatic injuries of the brain are on the increase in our country and may soon be the leading cause of mortality and morbidity.

GROWTH AND DEVELOPMENT

The child, and in particular the brain, undergoes constant and dynamic changes from birth to adulthood. These changes have serious implications when the brain suffers a traumatic injury. The changes are seen in body weight, head size, blood volume, tracheal size, etc. These have direct implications on the management of the child who has sustained a polytrauma or head injury.

First is the fact that the child's brain has just commenced the process of "growth" and any insult at this stage may leave lasting deficits. "In the adult, the insult takes place in a developed organ system, whereas a child's injury affects the brain and also the subsequent maturation process",[30] but this process is not without its own advantages. It is comparatively easier for the uninjured parts of the brain to "take over" the functions of the injured portions. Neuronal plasticity which, in simple terms, is the process by which the CNS develops and recovers from an insult is active till growth is complete. In spite of neuronal plasticity coming into play in the recovery process, the outcome depends on the age at the time of injury, severity and the location of the injury.[30] The two other important factors which have a direct influence on the outcome are the increased water content in the child's brain and the process of myelination which continues past the second year.

The other, which is equally important, concerns the changes which take place in the growing child,—for instance the size of the head in relation to the size of the body. These changes are to be factored into the equation when dealing with a child who has sustained an isolated head injury or polytrauma. A consideration of these will help in understanding the implications of the trauma as it concerns the child as a whole and in particular with reference to the brain and the response of the child to the trauma.

The physiologic differences between a child and an adult and the changes which take place as the child grows can be considered with reference to the whole body, i.e. airway, breathing, etc. and the CNS. A consideration of the former is of fundamental importance in the management of the injured child since the requirements change as the child grows.

The child's airway shows many differences as compared to the adult airway. The airway is small not only because children are smaller, but also because of anatomical factors. The tonsils and adenoids are large and contribute in no small measure to narrowing the airway, particularly if they are enlarged. In addition, the nasal passages are smaller as is the mouth and the supraglottic area. The practical implications of these are the need for the availability of different sizes of endotracheal tubes at the time of intubation.[20] The larynx, in addition to being soft, is also more anteriorly placed; this makes it more susceptible to narrowing when the neck is flexed or extended. Since the head is large compared to the body size in a child, the laryngeal dimensions are not at their maximum when the child lies supine. Distally, the anatomy of the trachea, too, has similar implications. The trachea is narrow at the level of the cricoid and the soft vocal cords are highly prone to damage at the time of intubation. A trauma victim with loss of the airway dies in 3–4 minutes. However, if the airway is patent and the patient is unable to breathe, death ensues in 5–7 minutes, whereas untreated hypovolaemic shock leads to death in 10 minutes. The impact of these on the day to day management are as follows: (a) the presence even of a small amount of food, blood or mucus can compromise an already small airway; (b) the neck needs to be only slightly flexed,—if needed at all,—so that the head is in the sniffing position for intubation. The presence of spinal cord injury without radiologic abnormality (SCIWORA) has to be borne in mind when intubating.

The consumption rate of oxygen in children is twice that of adults. The infant heart can increase the output, in a state of shock, only by increasing the heart rate and not the stroke volume. So, in situations of hypoxia/hypovolaemia the blood pressure and perfusion are maintained only by an increase in the heart rate.[11,20] Hence, the child may go into irreversible hypovolaemic shock without manifesting hypotension. Overt clinical features of shock are seen when around 25% of the circulating volume is lost and a loss of 50% results in death.

The relative surface area of children is greater than adults. So, hypothermia is a real danger when the clothes are removed to evaluate the injuries in a child who has sustained polytrauma.

The changes in the CNS parallel the changes seen in the rest of the body. The head and the brain of infants and children are larger and heavier with respect to the body compared to adults. This, combined with soft cervical vertebrae and a supple neck, leads to an increased susceptibility to injuries of the upper cervical spine. These also explain why shearing injuries are more common in children. Although the cerebral blood flow (CBF) and cerebral metabolic rate of oxygen ($CMRO_2$) are lower than the adult rate, in infants these increase to more than 50% the adult values by the age of 3–4 years. These reach the adult values by the mid teens.[11]

From the above discussion it will be apparent there are differences between the CNS of children and that of adults. These exist not only at the anatomic level but also at the physiologic level.

CLINICAL ASPECTS

Evaluation and Management of the Injured Child

Under this section, the author will discuss the basics of clinical evaluation of the injured child—particularly the head-injured child. The important physiologic aspects have already been discussed and the specific entities will be covered subsequently.

The care of the head-injured child follows the basic principles of polytrauma care. The child with a head

injury may have also suffered damage to other systems that can be life threatening and will affect the outcome. Immediate management consists of the Primary Survey and Initial Resuscitation. The purpose of the Primary Survey is to rapidly identify and treat the life threatening injuries. In the absence of signs of cerebral herniation or progressive neurological deterioration, no specific steps are recommended for the treatment of intracranial hypertension at this stage.[12] The steps in assessing and evaluating a child who has suffered a traumatic injury are as follows: (a) airway, (b) breathing, (c) circulation, (d) disability (neurologic) evaluation, (e) exposing and evaluating all injuries and (f) fluid therapy for resuscitation. Hypoxia and hypotension have been shown to be associated with increased morbidity and mortality and should, therefore, be treated aggressively.[51]

Airway management takes priority over all others. The specific aspects of the paediatric airway have been discussed earlier. If an oral airway has to be passed, occlusion by the tongue is avoided by passing the airway sideways along the tongue and then rotating it by 90°. The head is maintained in a position of slight flexion to avoid compression of the larynx. If there is any doubt about securing the airway the child is intubated immediately. A seriously head-injured child is assumed to have cervical spine injury as well, and it may be impossible to rule this out immediately. Care should be taken, while clearing the airway and during further manoeuvres, not to flex or hyperextend the spine. The airway should be cleared by a "jaw thrust" technique, rather than a "head tilt–chin lift" manoeuvre.[7] A hard cervical collar of the appropriate size should be applied and, whenever this is removed, the cervical spine must be stabilised manually by an assistant. The child's neck should not be hyperextended for intubation nor is it necessary. The neck is slightly flexed— "sniffing position"— prior to intubation. Gentle pressure on the cricoid not only facilitates intubation it also prevents distention of the stomach by the air entering the stomach during preoxygenation and also aspiration of the stomach contents. A non-cuffed endotracheal tube is preferred because the narrow cricoid acts as a natural cuff and also to prevent pressure necrosis by the cuff. There is no quick way or short cut to intubation; all precautions are to be taken. Hundred per cent oxygen is administered immediately after clearing the airway. Bag-valve-mask ventilation should be avoided unless there are signs of impending herniation. The following guidelines can be used to decide which patients should receive assisted ventilation with an endotracheal tube[5,31] (Table 1).

In suspected anterior skull base or facial fractures an orogastric rather than a nasogastric tube is passed lest the latter enter the intracranial cavity through the fracture site. The patient is assumed to have a full stomach and therefore is at risk of vomiting and aspiration.

Table 1: Guidelines for intubation

- A GCS of 8 or less
- A decrease in the GCS >2, irrespective of the initial GCS
- Anisocoria >1 mm
- Cervical spine injury compromising ventilation
- Apnoea
- Loss of the cough and/or gag reflexes
- Inability to clear upper airway secretions
- Uncontrollable seizures

In addition, since cervical injury cannot be ruled out (even if the child has a normal cervical spine X-ray) adequate precautions must be taken during intubation to maintain spinal immobilisation.[66] This is best done by having an assistant perform in-line manual stabilisation. The preferred technique of intubation is rapid sequence orotracheal intubation under direct vision by an experienced person. The size of the endotracheal tube can be determined using the formula "(age in years + 16) ÷ 4". Endotracheal intubation is a noxious stimulus that results in increased intracranial pressure (ICP). Unless the patient is in a state of cardiopulmonary arrest, he should always be prepared with adequate pre-oxygenation, sedation and neuromuscular blockade. The drugs used should be chosen after considering the haemodynamic stability of the patient, since some will cause or exacerbate hypotension. These have been elaborated in Table 2. If the patient has signs of increased ICP, and is haemodynamically stable, a combination of fentanyl, lidocaine, vecuronium and thiopentone sodium may be used. Thiopentone sodium causes dose dependent hypotension and should be used with caution if the blood pressure is already low. Lidocaine is used because it blunts the rise in ICP during intubation.[41] Succinyl choline is contraindicated since it can increase the ICP. Similar to the adult patient, avoidance of hypotension and hypoxia are the key to decreasing mortality.

Table 2: Drugs for intubation of the head-injured child

• Haemodynamically unstable	Fentanyl 2–4 mcg/kg
	Lidocaine 1 mg/kg
	Vecuronium 0.2–0.3 mg/kg
• Haemodynamically stable	Fentanyl 2–4 mcg/kg
	Lidocaine 1 mg/kg
	Midazolam 0.1–0.2 mg/kg
	Vecuronium 0.2–0.3 mg/kg
• Raised ICP	Fentanyl 2–4 mcg/kg
	Lidocaine 1 mg/kg
	Thiopentone sodium 4 mg/kg
	Vecuronium 0.2–0.3 mg/kg

Once the patient has been intubated, the child should be ventilated with 100% oxygen and maintained

normocapnic, unless there is evidence of intracranial hypertension. The patient should be sedated adequately with short-acting agents, such as midazolam. Neuromuscular paralysis should generally be avoided, unless it is required to provide safe transport or resuscitation.

Breathing is best evaluated by observing the chest movement. The two common factors which compromise breathing in children are: (1) soft chest wall which makes them more susceptible to chest visceral injuries and (2) gastric distension resulting from aerophagy. The cardiovascular system should be rapidly assessed by examination of the heart rate, blood pressure, quality of the peripheral and central pulses, peripheral perfusion and cerebral perfusion.[7] Patients with isolated head injuries seldom are in shock except in certain special situations. Therefore, if a child with head injury is in shock, other sources of blood loss, such as intra-abdominal injuries, should be sought. The primary objective in the patient with shock is to restore the intravascular volume as quickly as possible. Fluids should not be withheld in the patient in shock due to concerns of worsening cerebral oedema. If intravenous (IV) access cannot be established quickly, an intraosseous needle has to be inserted to administer fluids. As soon as IV access is established, a bolus of an isotonic crystalloid (normal saline or lactated Ringer's solution), 20 ml/kg, should be given rapidly. Dextrose containing fluids should not be used for boluses since they will lead to hyperglycaemia, which is associated with a poor outcome. If the patient does not respond after two 20 ml/kg boluses of crystalloid, a colloid or blood can be administered. Patients can also be in shock due to cardiac contusion or spinal cord injury, which may require inotropic therapy. There is strong evidence, in both adults and children, to suggest that even brief periods of hypotension are associated with a poor outcome. Therefore, hypotension must be treated aggressively, initially with fluids and then with inotropic support if required. The following table (Table 3) gives the 5th percentile of systolic blood pressure at different ages—these are the minimum acceptable.

As discussed earlier, the cardiac response to a fall in the circulating volume is different in children and adults. Further, the non-atherosclerotic vessels of children respond well to pressor agents resulting in a normotensive response rather than the hypertensive response seen in adults. In cases of polytrauma or severe head injury, as soon as IV access is established, blood is drawn for basic investigations. The neurologic evaluation is done next (the details of neurologic evaluation will be discussed subsequently). In a child with a Glasgow Coma Score (GCS) of 8 or below, intubation is carried out in the emergency room and good IV access is established. At times the child may be brought to the emergency department with signs of raised ICP. Clinical signs of increased ICP, such as unilateral or bilateral pupillary dilatation, asymmetric pupillary reaction, posturing or other evidence of neurological deterioration, should be treated aggressively. The patient should be hyperventilated acutely and, if the intravascular volume has been replaced adequately, mannitol administered intravenously (up to 1 gm/kg). Anti-oedema measures are commenced if clinically indicated even before a CT scan is obtained. Urinary catheter is placed to assess the urine output even if anti-oedema measures are not instituted in the emergency room. The clothes are then removed and the child is evaluated as a whole. A good look at the spine, posterior chest and abdominal walls can be obtained by logrolling the child keeping in mind the possibility of spinal injury. It is important to avoid hypothermia when doing this since hypothermia is tolerated poorly. The relatively large surface area in children predisposes not only to hypothermia but also to increased insensible water loss. In addition, under conditions of increased stress hypothermia results in acidosis and a worsening of the metabolic status. After resuscitation, basic investigations should be done, including electrolytes, glucose, haematocrit and blood gases. After the initial resuscitation the patient is transported to the nearest available CT scanner. If sedation is required, a short-acting agent should be employed. Paralysis is used only if sedation alone prevents safe transport to the scanner. Paralysis should never be used alone since it has no sedative effect.

Even under the best of conditions the neurologic evaluation of a child is not as easy as that of an adult. A good history should be obtained after the child has been stabilised. The mechanism of injury should be noted. In addition the behaviour immediately after the injury is important. If the child had been unconscious from the time of injury it indicates a serious injury like diffuse axonal injury. This is only more difficult in a child, as the parents and the doctor are under stress when dealing with a child who has sustained an injury. The ubiquitous GCS and the AVPU scoring systems have been evolved to make objective assessment easier. The GCS is a more comprehensive scoring system although AVPU may be easier to use. The AVPU scoring is as follows: A—Alert; V—Responds to verbal commands; P—Responds to pain and U—Unresponsive.[7] The GCS is more popular and more comprehensive. The adult scoring system has been modified for use in children. In this scoring system the best response in three categories [Eye opening (E), Motor response (M) and Verbal response (V)] is noted and a score is given to each of the responses and the individual scores are totalled. The highest score is 15/15 and the lowest 3/15. A score of 8 or below indicates a state of coma and 3/15 "death". The adult and the paediatric score are as indicated in Table 4.[58]

Table 3: Systolic blood pressure at different ages

Age	*Systolic BP*
0–1 month	60 mmHg
>1 month to 1 year	70 mmHg
>1 year	70 + (2 x age in years) mmHg

Table 4: Glasgow coma score in adults and children

Score	*Adults*	*Children*
Eye opening:		
4	Spontaneous	Spontaneous
3	To command	To sound/speech
2	To pain	To pain
1	None	None
Motor response:		
6	Obeys spontaneous	Spontaneous/ obeys
5	Localises	Localises
4	Withdraws	Withdraws
3	Abnormal flexion	Abnormal flexion
2	Abnormal extension	Abnormal extension
1	None	None
Verbal response:		
5	Oriented	Appropriate for age
4	Confused	Crying but consolable
3	Inappropriate words	Irritable/Restless
2	Incomprehensible sounds	Lethargic
1	None	None

It has to be emphasised here that children cannot be expected to respond in the same way adults do. This is so because the motor and verbal skills are age dependant.[74] A child who is "normal" may not have a score of 15/15. Based on a 14 point GCS scoring system the best response which can be expected in the various ages has been enumerated. This has been given in Table 5.[74] The GCS, it will be apparent, is not as reliable in children as it is in adults. It is "not accurate for children less than 5 years of age and is even more limited in children less than 3 years".[74] But the GCS scores have been shown to be inversely related to the number of positive findings on CT, i.e. patients with low GCS have more abnormal CT findings than those with higher GCS.[45] In children, absence of physical signs does not exclude an intracranial injury.[38] It has also been found that there may be a disparity between the clinical and the CT findings. No single clinical feature can predict what abnormality the CT may disclose in children. In addition, it is difficult to correlate the clinical findings with the CT findings.[25,70,73] These go to show the difficulty in evaluating an acutely head-injured child as opposed to adults where evaluation is easier. This brings to the fore that CT should be done even if there is a suspicion of abnormality and the neurosurgeon should be "liberal" in ordering a CT.[85] Assessment is more difficult in infants and the clinical signs may not reflect an intracranial injury. Only a CT scan will demonstrate an intracranial injury in a substantial number of infants.[36] Castellani et al. have evaluated the importance of Serum S-100B level as a serum marker of head injury and found that values below the cut-off safely rule out intracranial lesions. By using this serum marker, unnecessary CT scans may be decreased.[13]

Table 5: Best scores in various ages

Age	*Best motor*	*Best verbal*	*Best overall*
0–6 months	2 or 3	2	9
6–12 months	4	3	11
12–24 months	4	4	12
2–5 years	4 or 5	4	13
>5 years	5	5	14

To simplify the scoring in children younger than 2 years "a score of 5 is given if the there is any vocalisation at all and 1 if no crying is elicited". In children younger than 1 year of age, a stereotypic eye opening may be seen. This is not a normal response.[11] A severely head-injured infant can exhibit certain stereotyped movements which on initial evaluation appear to be purposeful but, in reality, these are reflex movements.[10]

Additional points to be noted in the examination are palpation of the fontanelles and sutures. The former may be bulging or tense in the presence of raised ICP while the latter may be splayed. These are applicable only to young children. Examination of the ocular fundi may not be possible in all children, particularly so if the child is crying.

Vomiting is very common after head injuries in children. Although vomiting is a hallmark of raised ICP in adults who have sustained a head injury, it may follow even trivial injuries in children. It, often, is a source of concern particularly for the anxious parents. Vomiting may be limited to one or two episodes or may be protracted. In addition, the vomiting may start a day or so after the injury. Although a CT should be done to rule out an intracranial mass lesion it often is normal. Intravenous antiemetics are given if the vomiting is protracted or oral antiemetics fail. Once the vicious cycle is broken, the vomiting stops. Insertion of a nasogastric tube in this situation only serves to increase the discomfort.

Seizures too are common in the head-injured child and like vomiting may follow even trivial injuries. These may be limited to a single episode of generalised seizures, a brief spell of tonic seizure or a vacant stare. Many a time these are self limiting and need no specific therapy. A CT should be done to rule out a focal injury or a mass lesion, but very often it is normal. No specific therapy is needed, nor are long-term anticonvulsants indicated. If, however, these are prolonged, focal or occur several hours or days after an injury it is usually indicative of a serious injury. These children may need long-term anticonvulsants. Anti-seizure prophylaxis is beneficial only for early post-traumatic seizure prophylaxis, i.e. seizures occurring within the first week after injury.[12] The following group of children are at increased risk for post-traumatic seizures: "those with diffuse cerebral oedema, acute subdural haematoma,

compound depressed skull fracture with parenchymal damage, or severe head injury (GCS ≤8)".[39] Children less than 3 years old and those suffering prolonged unconsciousness (>12 hours) are also at increased risk.[19,72] The routine use of anti-seizure prophylaxis for late post-traumatic epilepsy has not been advocated.[12]

Acute deterioration may follow moderate to severe head injuries and this may be due to seizures, brain oedema or intracranial haemorrhage.[11] Intracranial haemorrhage is not the commonest cause of hypotension or hypovolaemic shock in a trauma victim. It is usually the result of bleeding elsewhere—long bone fractures or visceral injury. The blood loss resulting from scalp injury can be severe enough in children to precipitate hypovolaemic shock. Even subgaleal haematomas can be large enough to cause significant blood loss. There are two instances where an intracranial haemorrhage can cause hypovolaemia. The first is the situation where an epidural haematoma "decompresses" itself through a wide linear fracture resulting in a large scalp haematoma. The second instance is in a child with hydrocephalus. Here the cerebrospinal fluid (CSF) is "pushed" out through the shunt by the expanding clot resulting in hypotension and anaemia from the blood loss. These may be the only manifesting symptoms.[11]

There are a few factors which make evaluation of children difficult in the emergency room or casualty. These are:

- *Pain and anxiety*: The child who has suffered an injury is oftentimes anxious and inconsolable. These are made worse when there is also an associated painful injury like a fracture of a long bone.
- *Separation anxiety*: Examination is easy if one of the parents is allowed to be by the side of the child. This will not be possible if the child is being resuscitated or the child is being evaluated for polytrauma. If possible the child must be allowed to sit on the parent's lap. The presence of too many well meaning relatives results in an anxious doctor.
- *Hostile environment*: The injured child perceives everyone in the busy emergency department to be "enemies" and hence the child must be made to feel comfortable before the examination can be carried out if the injury is not too serious.
- *Assessment of the higher functions*: This is made difficult by the fact that the motor and language skills are constantly changing with age and due allowance has to be given for this.

Injuries in the Various Age Groups

No age group is exempt from head injuries. The pattern of head injuries and the spectrum vary in the various ages but a certain degree of overlap is often present. For instance, depressed fractures are seen in almost all the ages from the newborn to well into adulthood (Figs 1 and 2). In the first few years of life, however, falls are common. These may take place when the child is learning to walk or when the child is engaged in play.

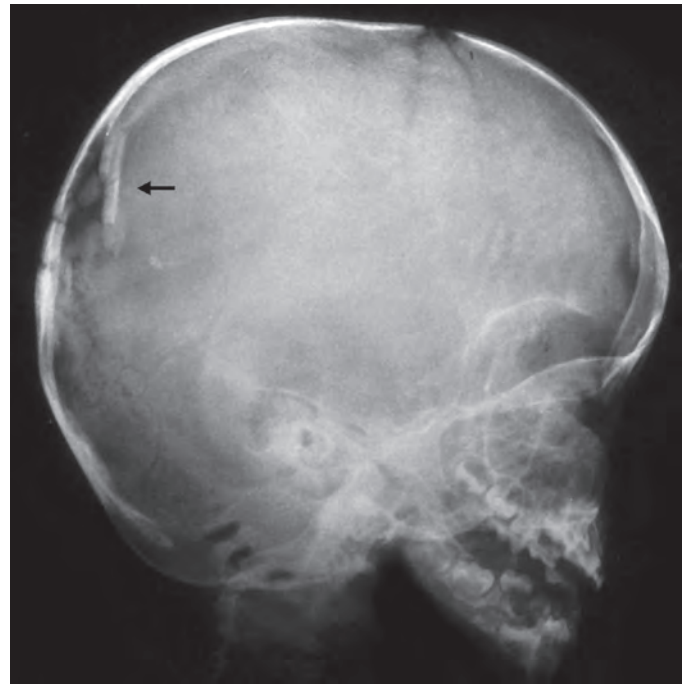

Fig. 1: Depressed fracture X-ray

The older child is more prone to injuries sustained as a result of a traffic accident on the way to or from school. Falls from balconies, too, are seen more often in this age group.

Injuries in neonates are due to two factors: (1) those caused by the natural forces of labour and (2) those produced by obstetric intervention.[11] There is some overlap between the two groups. The injuries involve the scalp, skull and the intracranial compartment. Major intracranial injuries in neonates are uncommon. These constitute 1–3% of trauma cases in busy paediatric neurosurgical units and are associated with 10% mortality and 30% morbidity.[11] Although open scalp injuries are uncommon, scalp haematoma may be present. These are self

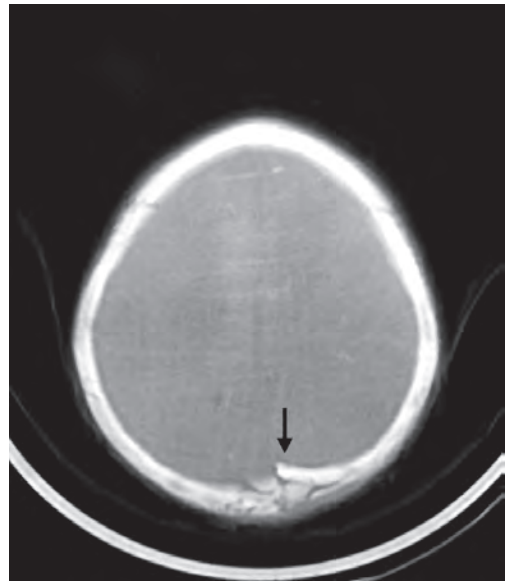

Fig. 2: Depressed fracture CT

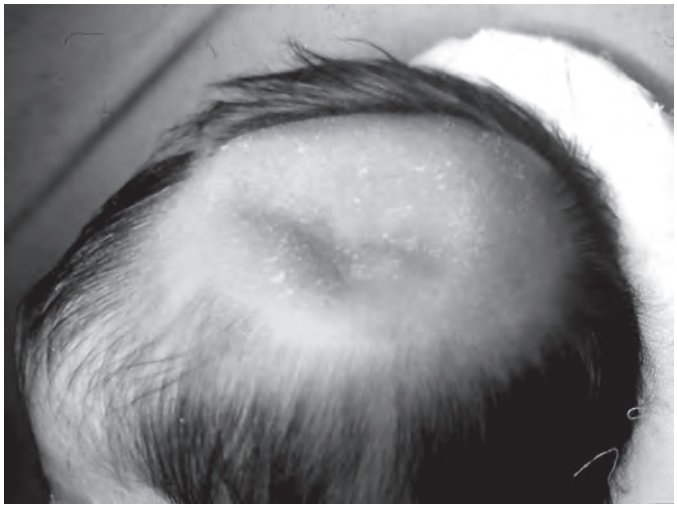

Fig. 3: Pond fracture clinical

limiting and resolve in a few days. Closed depressed fractures referred to as "ping pong" or "pond" fractures are seen in the parietal region usually at the parietal eminence (Fig. 3). These fractures may result from the soft cranium being pressed against the sacral promontory or ischial tuberosity of the mother. This injury may also be seen when forceps have been applied. The scalp is intact and a small amount of scalp haematoma may be associated with it. Clinical examination reveals the extent of the injury. Although plain skiagrams reveal the amount of depression, a CT scan is needed to evaluate the degree of underlying brain damage (Fig. 4).

Parenchymal injuries or bleeds are uncommon in neonates. Epidural, subdural and subarachnoid haemorrhages again are not very common. Intraventricular haemorrhage from germinal matrix haemorrhage is seen in premature infants but not in term infants. The other cause for intracranial bleeds is clotting disorders. Most of these bleeds are not very big and may be treated conservatively. The common manifestations of intracranial

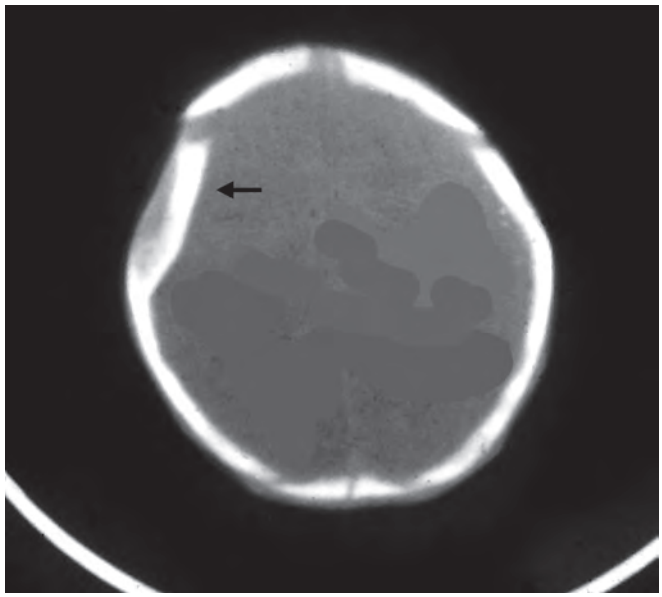

Fig. 4: Pond fracture CT

haemorrhage in neonates are seizures, low APGAR, bradycardia, poor cry and poor respiratory efforts.[20] Extreme care has to be exercised if surgery is to be carried out and only the minimum required is done. As mentioned earlier, these children should be cared for only in neonatal units by a dedicated team. Even though the procedures as such may appear simple, these surgical operations should be undertaken with caution. The margin for error is very small. Even a small volume blood loss may be large in terms of percentage of blood volume and can prove disastrous. The team (neurosurgeon and anaesthetist) must be trained or experienced in the care of neonates, and post-operatively these infants must be cared for in the neonatal unit.

Posterior fossa haemorrhage can occur in neonates as a result of birth trauma. During the process of labour the skull is compressed in the anteroposterior direction. This results in stretching of the falx and also compression of the cerebellum. The result is rupture at the falcotentorial junction and consequent bleeding from the venous sinuses and bridging veins. In addition, parenchymal cerebellar haematomas may occur. A constellation of clinical features is seen ranging from lethargy to features of raised ICP, brainstem dysfunction and seizures. The decision to operate is a difficult one to take and during surgery the team must be prepared for profuse bleeding.

Injuries in infants resulting in diffuse axonal injury are unusual. Shaken baby syndrome refers to the infants with acute subdural haematoma and subarachnoid haemorrhage, retinal haemorrhages and periosteal new bone formation at epiphyseal regions of long bones resulting from to and fro shaking of a child's body producing a whiplash motion of the child's head on the neck. Head-injured infants are likely to have undergone shaking followed by sudden inertial injury from impact. The most important finding was that the predominant neurohistological abnormality in cases of non-accidental injury in infants is due to hypoxia and not diffuse axonal injury.[35]

Injuries in toddlers result from a variety of causes. This is the age when children are learning to walk and explore their surroundings. Fall from a cot and stumbling and falling when learning to walk are the commonest causes. Many of these falls are a cause for concern to the anxious "new" parents and grandparents. Often, many of these falls are not witnessed. The common symptoms which prompt the parents to seek medical attention are vomiting, seizures and the appearance of subgaleal haematoma a few days after the fall. Sometimes, the parents may recall the history of fall or it may be so trivial that they may not recall it at all. The subgaleal haematoma often enlarges in size over a day or two and becomes softer as it liquefies. The parents have to be reassured that the haematoma will clear in about two weeks. The indications for aspiration are persistent fever, suspicion of infection or large size. In the latter instance, coagulopathy has to be excluded, for instance haemophilia in boys. Vomiting may also occur several hours after

the fall. Antiemetics given intravenously usually suffice. Anticonvulsants are indicated only for short-term prophylaxis.

Falls, minor or major (like from the first floor balcony), may not cause significant intracranial problems,[11] but a skull fracture may be seen in many instances. These fractures may be extensive and may extend bilaterally.

Epidural haematomas may occur in this age group without any skull fracture or only an insignificant fracture. This is because the skull, being soft, may bend in and out without fracturing. In this process it may injure the meningeal vessels or, if the skull fractures, the bleeding may be from the skull itself since the child's skull is very vascular.

Rotational acceleration in children due to blunt trauma to the ear may result in "tin ear syndrome" which comprises of unilateral ear bruising, radiographic evidence of ipisilateral cerebral oedema with obliteration of the basilar cisterns, and haemorrhagic retinopathy. Similar trauma may also result in shear stress and tearing of the subdural veins, loss of cortical vasomotor tone, cerebral hyperaemia, herniation and death.[42]

Subdural haematomas (SDH) usually follow a severe injury like falls from the first or second floor, traffic accidents, etc. The presentation is more acute and these children deteriorate faster. In children, the subarachnoid spaces are prominent particularly in the frontal and parietal regions. A small or minor bleed may occur in these regions following even a trivial injury. These do not require any specific treatment.

Injuries in older children and teenagers are usually the result of falls from balconies, injuries sustained when playing and traffic accidents on the way to and from school. The major cause of serious injuries in this age group is acceleration-deceleration injury. Hence, diffuse injuries are commonest in this age group among children.[11]

Head Injuries in Haemophiliacs

Bleeding is the most frequent cause of death in children with congenital coagulation disorders, and intracranial haemorrhage accounts for the majority of mortality in all age groups.[24] Haemophilia A and B are the most common inherited bleeding disorders. Even a minor head trauma may produce significant intracranial pathology. Immediate diagnosis and rapid medical management are mandatory if morbidity and mortality are to be minimised.[24] Among all haemophiliacs approximately 3.5–4.0% had intracranial haemorrhage during the neonatal period which is considerably (40–80 times) higher than expected in the normal population.[99] In haemophiliacs who have suffered from intracerebral haemorrhage, more than 40% had it within 1 week of birth. Birth trauma was identified as an important risk factor for intracerebral haemorrhage in patients with haemophilia.[50] Haemophilia in the newborn can be a challenge in terms of both diagnosis and management. In the presence of a family history of haemophilia, safe outcome of these patients is achieved by mutual cooperation and optimal management by obstetricians, haematologists and neonatologists. When a family history is absent, haemophilia in the neonate may not be suspected. Diagnostic difficulties may then arise due to failure to recognise the presence of abnormal bleeding, which is often different from that typically observed in older children with haemophilia. In addition, diagnostic investigations are complicated by physiological differences in the neonatal haemostatic system.[14] Intracranial haemorrhages in older children are rare, and a better outcome may be expected.[50]

The most important aspect of intracerebral haemorrhage management is early replacement therapy in haemophilic patients. This prompt treatment will increase the chances of a better prognosis. Administration of the deficient coagulation factor after every head trauma, even when considered minor is advocated by a few authors. Recombinant factor VIIa can enhance haemostasis in patients with FVII deficiency and other coagulopathic conditions.[8,22,75]

SPECIFIC INJURIES AND PROBLEMS

Even though there is an overlap between the problems in adults and children, the latter present certain features which are unique. Not only is the pathologic process different, even the clinical features and management are different too. Similarly, the problems encountered in neonates are different from those seen in older children.

Scalp injuries are seen commonly in all age groups and are a part of almost all traumatic injuries involving the head and neck. A certain amount of scalp haematoma is seen even at the time of birth—caput succedaneum—which resolves over a few days. The blood loss can be very profuse from scalp lacerations since the scalp is very vascular. If the laceration is large the child can exsanguinate. Even subgaleal haematomas associated with simple linear fractures of the skull may be associated with a significant blood loss. Palpation of the edge of the haematoma gives the feeling of palpating the edge of a depressed fracture, but often times this is not the case.

Fractures are seen in all paediatric age groups. They are present in up to 20% of children admitted for the management of head injuries.[80] Despite this high prevalence many of the fractures do not need any treatment. The fracture is a good indicator of an underlying parenchymal injury. To detect these injuries a plain X-ray of the skull is enough in most of the instances. However, parenchymal injuries cannot be seen on the plain X-rays at all. Hence, CT is the preferred mode of investigation. It has to be emphasised that fractures, not detected on the CT, hardly influence the outcome or management.[80] The point worthy of note is in children, as in adults with acute head injury, the presence of a skull fracture increases the probability of developing an intracranial haematoma significantly.[60,88]

In adolescents, the presence of a skull fracture is the only significant risk factor for predicting an ICH.[16] In

a child who has a simple linear fracture and a normal clinical and CT examination the chances of developing an intracranial haematoma or a complication later on is next to nothing.[56,59,86] Also if a child is seen a day or later after the injury and a linear fracture is discovered, if the child has no neurologic symptoms the chances of the child harbouring an intracranial haematoma becomes very low. Hence, a CT may not be indicated.

Linear fractures are the commonest variety of skull fractures in children. Certain unique features are seen with respect to such fractures in children. Linear fractures can cross suture lines and some of the fractures may extend bilaterally (at times even across the sagittal suture). Since the frontal sinus does not develop till the end of the first decade, a fracture involving the frontal region may extend into the roof of the orbit or even up to the clinoid process because the force of the impact (which is transmitted to the base of the skull) extends for quite some distance (Figs 5 to 7). The unpneumatised sinus does confer an advantage in that post-traumatic CSF leaks are uncommon in children. Growing fractures, a rare complication of fractures, are also peculiar to the paediatric age group. These are also referred to as enlarging/expanding skull fractures, leptomeningeal cysts and post-traumatic meningocoeles.[59] Usually a wide linear fracture is seen at the time of injury as the first manifestation. A dural laceration beneath the fracture is mandatory for this to occur. The dural laceration and the fracture result in the "amplification of the ICP pulse wave", which in turn results in herniation of the arachnoid and brain. Over a period of time, due to the transmitted pulsations of the brain, the edges of the fracture separate and the fracture "grows". These manifest clinically as a pulsatile swelling at the site of injury a few months after the injury. In addition, hemiparesis and seizures may be present. Since this entity is associated with a severe injury, a meningocerebral cicatrix

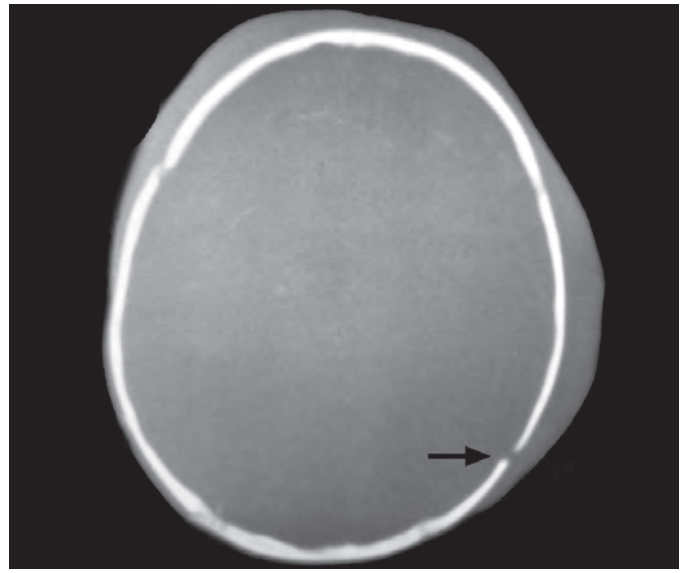

Fig. 6: Linear fracture CT

is usually also seen at the site of injury. The treatment is surgical. The fracture margins are exposed and the dura and arachnoid are exposed. These are separated from the site of incarceration. Watertight dural repair is mandatory to prevent further incarceration and growth of the fracture.[92] The calvarium is then reconstructed preferably using autogenous bone grafts.

Depressed fractures in the paediatric age group are usually green stick fractures unlike those in adults. This is because the skull of children is softer than the skull of adults. Being soft, the calvarium of the child can undergo distortion without fracturing. When the calvarium is distorted or deformed as a result of an injury the dura can be stripped away or the middle meningeal vessels injured, resulting in the formation of an extradural haematoma or, at times, because of the bending, the inner table may fracture without the

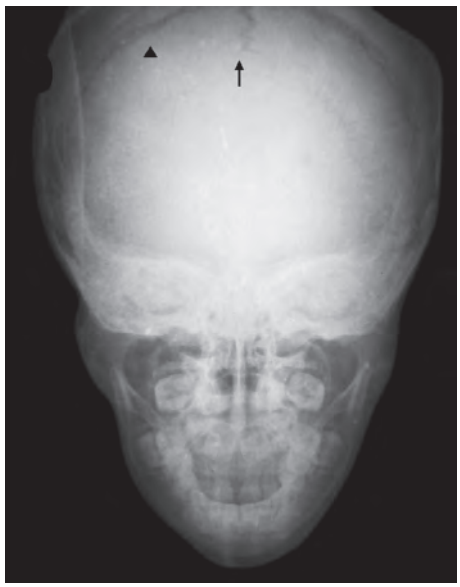

Fig. 5: Linear fracture X-ray
arrow head diastatic arrow

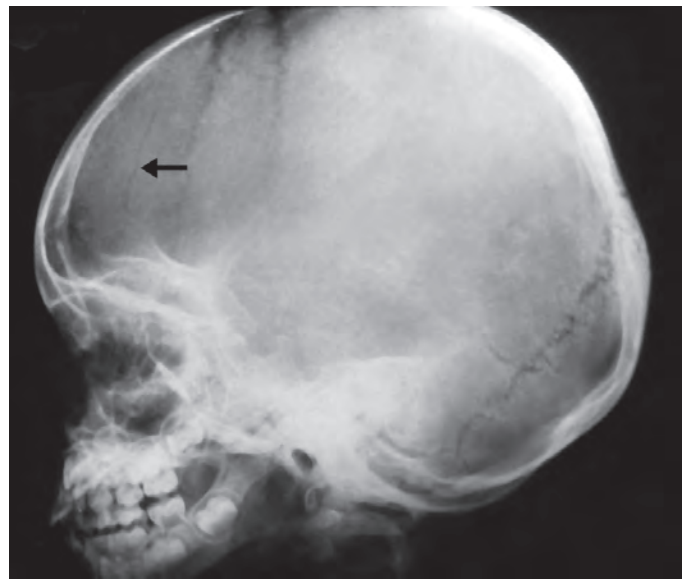

Fig. 7: Linear fracture X-ray

outer table exhibiting any sign of fracture. In neonates the skull is "soft" and membranous, hence it does not fracture so easily. A linear fracture is uncommon and is usually the result of pressure or battering against the maternal pelvis. A depressed fracture results from pressure against the sacral promontory, ischial tuberosity or forceps application. A scalp haematoma may mask the underlying fracture. The investigation of choice is a CT scan. Small fractures do not need any specific treatment since the growing brain "pushes" the depressed segment out. The indications for surgical elevation are similar to those for other closed depressed fractures, namely large diameter of the depression (>3–4 cm), significant depression, pressure on or deformation of subjacent brain, focal deficit, seizures or cosmetic disfigurement. Surgery, if it is to be performed, is best done within the first week. This will make elevation easier since the depressed segments would not have fused. The technique of elevation is simple. Through an incision placed close to the margin of the depression a small burr-hole is made. A periosteal elevator is gently introduced epidurally under the fractured bone up to or just beyond the point of maximum depression. The depressed bone is gently elevated by levering the periosteal elevator over the surgeon's finger. This manoeuvre will avoid pressure on the edge of the bone by the periosteal elevator which can deform or fracture the underlying bone. A vacuum device (i.e. obstetric vacuum extractor) has also been used to elevate these fractures.[59,80]

In a child who has an acute severe head injury and also a depressed fracture, the former takes precedence over the latter. This rule can be applied even if the fracture is compound. Here the skin can be closed to provide a cover for the fracture, and the dura and the fracture can be addressed electively. Basal fractures and those involving the frontal air sinuses are commoner in adults. If there are clinical indicators of basal fractures or fractures involving the frontal air sinus (like raccoon eyes or Battle's sign), the presence of these fractures must be assumed to be present until proved otherwise and all precautions must be taken during management. To cite an example, an orogastric rather than a nasogastric tube must be placed if an anterior skull base fracture is suspected lest the tube enter the intracranial compartment through the fracture. Controversy surrounds the issue of antibiotic prophylaxis in the management of skull base fractures. Since there are recommendations for and against the use of prophylactic antibiotics, the decision to use (or not to use) should be based on the clinical scenario and the neurosurgeon's judgement. The need for admitting all children with an uncomplicated skull fracture has been questioned, if the family are dependable and the child can be brought to the hospital quickly, admission may not be needed in all.[96]

Contusions of the brain in children as in adults may be a cause for delayed deterioration. Small contusions are known to enlarge after resuscitation. Those that exert a mass effect, especially those in areas which can easily lead to herniation, may need to be treated surgically even prophylactically.[59] The incidence of seizures in a child with a contusion is not greater than in the child who has developed an extradural hematoma (EDH) or one who has a normal CT after a head injury.[39]

Concussion, which is basically a transient loss of consciousness followed by normal function, can manifest in a wide variety of ways in children. At one end is the mildest form where the child recovers without any deficit whatsoever, while at the other end is the child who is neurologically devastated from diffuse axonal injury. Concussion is considered to be a mild form of diffuse injury of the brain and diffuse axonal injury as the extreme form with a whole range of severity lying in between.[58] Not only can these follow a trivial injury, they can also be disproportionate to the severity of injury.[20] The clinical picture of concussion does not always follow a severe head injury. This condition often follows injuries sustained at play, or even minor falls. Often the imaging studies may not disclose any abnormality unless the patient manifests serious symptoms. The basic pattern and clinical manifestations are the same as in adults, but some of the features not seen in adults are encountered. In the most benign form the child may be stunned soon after a head injury only to "regain consciousness" soon and act normally. After recovery the child may be irritable, have headaches or have difficulty concentrating for a few weeks if the concussion had been severe.[59]

Cortical blindness is an entity peculiar to children. Immediately, or soon after a fall, the child complains of loss of vision.[69] The pupils will be reacting normally to light. The blindness recovers without any treatment. Associated features are headache, nausea, vomiting and irritability.[77] The aetiology has been attributed to concussion of the occipital lobe and transient "kinking" of the posterior cerebral arteries. Vasospasm has also been proposed as a cause.[15] This condition has to be differentiated from post-traumatic optic neuropathy where the blindness is unilateral and recovery is poor. The following have been associated with a benign outcome "mild head trauma, brief or no LOC, onset of blindness occurring within hours of the head injury, absent optokinetic nystagmus, duration of blindness less than 24 hours, agitation and restlessness, absence of skull fracture or visible cerebral injury on CT scan, absence of other neurological deficits, and EEG findings that initially show posterior slowing with subsequent normalisation". An increased awareness will result in more cases of this kind being diagnosed.[101]

Paediatric concussion syndrome is a dramatic event but with a good outcome. A child who had been well after a minor head injury becomes somnolent and irritable. A few hours after the event, pallor, cyanosis and vomiting develop. A hypotensive episode may also be present. Imaging studies are normal and the child regains normalcy in a few days. The aetiopathogenesis is poorly understood. Other conditions, like expanding intracranial haematoma, fits, brain oedema and

electrolyte imbalance (sodium in particular) have to be ruled out. The diagnosis of this condition is by a process of exclusion.[59] Children who do not show the expected recovery or who recover slowly may have post-traumatic subarachnoid haemorrhage or even a mild form of diffuse axonal injury.[59]

Diffuse brain swelling is a condition seen in children, but not commonly in adults.[58] It is 2–5 times commoner in children.[102] This may be seen after a mild head injury. Following a lucid interval the level of consciousness rapidly deteriorates with an associated increase in the ICP. Even though the child may be clinically normal, the initial CT may show changes like compression of the perimesencephalic cisterns, absent third ventricle and diffuse cerebral swelling.[10,52,58] The treatment has to be initiated on a high index of suspicion. Aggressive and early initiation of therapy results in a good outcome. The aetiology of this condition is supposed to be a post-traumatic vasoreactive phenomenon resulting in a significant rise in ICP.[58] There is increased cerebral blood volume resulting from hyperaemia and engorgement which in turn results in raised ICP. These have been shown by blood flow studies.[52] Since children have a wide range of CBF this hypothesis has been questioned.[102] The exact aetiology is unknown till date. This clinical entity has been described in adults too but the outcome is better in children.[52]

Diffuse axonal injury, which is an injury resulting essentially from angular acceleration/deceleration forces, is uncommon in infants while in older children it is the result of a fall or traffic accident where the child is knocked down by a vehicle. The child is rendered unconscious from the time of the accident. A variable motor response ranging from abnormal flexion/extension to a withdrawal response is encountered. In addition abnormalities in pupillary size and response and other brainstem signs including posturing and abnormalities of eye movement may be encountered, but these responses "do not reflect a significant trend".[59] The CT may be "disproportionately" normal compared to the clinical severity of injury. The CT may at times show petechial haemorrhages in the deep white matter, haemorrhages in the region of the splenium, thin SDH, subarachnoid haemorrhage, intraventricular haemorrhage and small contusions. The management of this condition is along the lines of management of the severely head-injured patient.

Post-traumatic intracranial haematomas are seen from as low as less than 0.1% to as high as 35% of patients with head injury.[74] The three varieties of post-traumatic haematomas EDH, SDH and intracerebral haematomas (ICH) have different aetiologies depending on the age of the child. In neonates it is trauma related to birth, while in toddlers and older children it falls, and in adolescents it is related to traffic accidents in addition to accidents sustained during play and falls. The manifestation, too, varies with age. Neonates present with anaemia, bradycardia, irritability, tense fontanelle, focal deficits and altered consciousness. The older children, however, have other features of raised ICP like headache, vomiting, alteration in level of consciousness and focal deficits.[74] The location of the intracranial haematomas depends to some extent on the age of the child (Table 6, Fig. 8).[67]

Table 6: Location of the intracranial haematomas

Neonates	*Infants*	*Toddlers*	*Adolescents*
Posterior fossa Supratentorial	SDH (Acute/ chronic)	EDH	ICH SDH (Acute EDH

Extradural haematomas in infants are venous in origin unlike those in older children in whom it is arterial. The other sources of bleeding are the fractured edge of the bone and from venous sinuses (Fig. 9). The latter is often the source in posterior fossa haematomas. In older children the aetiology is as in adults, bleeding from the middle meningeal artery. In infants needle aspiration of these haematomas has been recommended as a treatment modality.[74] Conservative management of EDH in children has been described. Criteria have been described for conservative treatment and also termination of conservative treatment.[65,74] For nonsurgical treatment the indications are children with no neurologic deficit but with headache, nausea, vomiting and lateral rectus palsy in supratentorial clots. Conservative treatment is terminated if the patient develops a focal deficit, the level of consciousness deteriorates, pupillary changes develop, headache, or vomiting persists or rebleeding occurs. Delayed epidural haematoma is usually seen following a severe head injury. The diagnosis is made on a high index of suspicion in the absence of neurologic deficit. The outcome is good if timely intervention is carried out, even in delayed EDH.[33,67] The source of bleeding in a posterior fossa EDH is usually venous—from a venous sinus. An associated fracture is seen in a significant number of children. At times the clot can extend to the supratentorial compartment as well. Rapid deterioration is a hall mark of this condition.

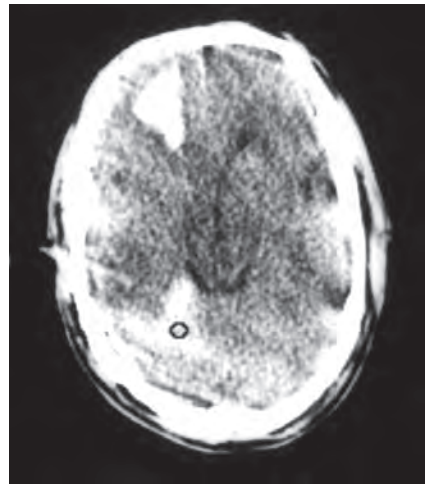

Fig. 8: Post-traumatic ICH

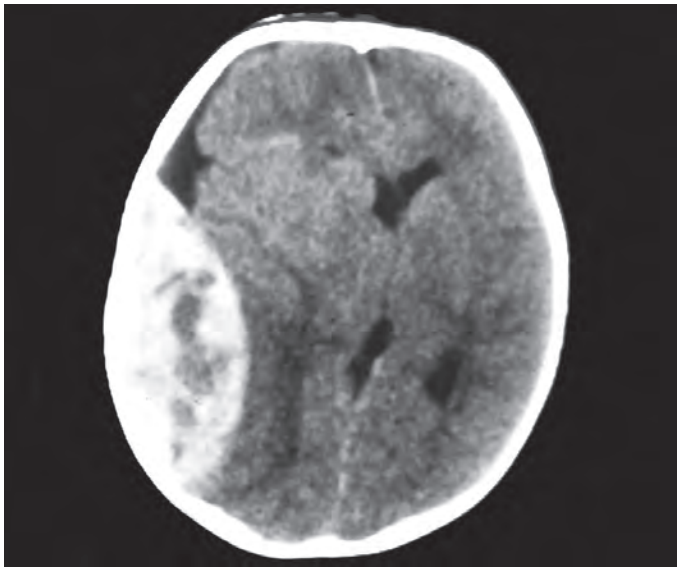

Fig. 9: EDH

SDH in older children generally present as they do in adults—as an acute event following trauma. In neonates, due to enlarged subarachnoid spaces, the bridging veins snap easily and may lead to a subdural collection. Small haematomas may occur even after a trivial injury. This is because the subarachnoid/subdural spaces are wide in this age group and the bridging veins are relatively unsupported, but a significant haematoma never results from a trivial injury unless there is an associated medical problem like coagulopathy. These are often accompanied by other injuries in the intracranial compartment. In managing these lesions, due to the frequent association of other traumatic lesions, treatment should also be directed at raised ICP. The posterior fossa is a common site of SDH in neonates. These are usually due to tears of the tentorium or rupture of the bridging veins. Chronic SDH are known to occur in children, but the classical picture seen in adults is absent. These are usually the result of over drainage following a shunt or bleeding into a subdural collection. Careful radiologic evaluation will aid in differentiating SDH from other subdural collections.

ICH occurring in childhood has certain features which are not encountered in adults. Since the aetiopathogenesis, clinical features and management of germinal matrix haemorrhage are completely different, they will not be considered here. In a child who presents with an intracerebral haemorrhage even with a history of trauma an underlying cause for the bleed other than trauma has to be kept in mind if dictated so by the clinical picture. These include bleeding as a result of coagulopathies, vascular malformation or tumour (Table 7).[67] In such instances, the size and location may not correspond to the severity of the injury; screening for coagulopathy and appropriate radiologic studies will help in differentiating these conditions from post-traumatic haematomas. These lesions can be large and can be differentiated from haemorrhagic contusions by not being cortical in location and having a more or less uniform density on the initial CT. The management of these lesions is along the same lines as in adults. However, even if there is a suspicion of viability of the brain, it is better not to remove the affected area since children recover better than adults, and the "damaged" area may recover its functions well.

Table 7: Spontaneous intracranial haemorrhage: causes

Structural causes:
• Bleed into a tumour or an infarction
• Vascular malformations: AVM; aneurysms; cavernomas
• Vasculopathies: Inflammatory; moyamoya syndrome
• Dural sinus thrombosis
• Venous infarcts
Non-structural causes:
• Coagulopathies: Haemophilia; vitamin K deficiency
• Liver disorders
• Anticoagulation therapy
• Disseminated intravascular coagulation: Due to any cause
• Platelet disorders
• Fulminant sepsis
• Unknown aetiology: Germinal matrix haemorrhage

CRITICAL CARE

The critical care of children has evolved into a distinct specialty. The problems in children and the needs of children are entirely different from those of adults; hence children requiring intensive care have to be cared for in special dedicated units. Nowhere is this more apparent than in neurologic and cardiac care. It has been estimated that children with head injuries account for 10% of all ICU admissions and 10% of all ICU days.[28]

Indications for Admission to the ICU

Not every child who has sustained a head injury needs be admitted to the ICU. Guidelines have been proposed for admission criteria to the ICU.[6] The reason for admission to the ICU may be for the management of a neurosurgical problem or the treatment of other problems. In simple terms, the following groups will need to be admitted to the ICU for care or, at least, observation.

Neurosurgical Indications

- Post-operative patients
- Seriously head-injured children—even if the child in neurologically intact, i.e. child with multiple contusions
- Children with impending neurologic deterioration
- Children with proved or suspected raised ICP
- Children with more than one episode of seizure even if the seizures are mild.

Non-neurosurgical Indications

- Intubated children—intubated for any reason whatsoever

- Polytrauma victims
- Children with compromised cardiopulmonary status.

Care in the ICU

The question of who is in charge of the child in the ICU may come up. Intensive care management of children should be a combined effort between the neurosurgeon and the paediatric intensivist. Anything else will result in a poor outcome.

There are two aspects to the care of the child in the ICU: (1) Monitoring and (2) Managing.

Monitoring in ICU

There are two parameters which are routinely monitored in the ICU. The non-neurologic monitoring, i.e. haemodynamic and other parameters like fluid and electrolyte therapy. The other is the neurologic part which consists of clinical examination and ICP monitoring.

Haemodynamic: In addition to routine PICU monitoring (heart rate, respiration, pulse oximetry and non-invasive blood pressure), all patients with serious head injuries should have invasive monitoring of the central venous and arterial blood pressures. This is especially true if they are receiving mannitol therapy or other therapies to reduce raised ICP. Arterial BP monitoring allows changes or falls in BP to be noted in real time (which may occur if the child is receiving diuretics or barbiturates) so that appropriate measures, like fluid boluses or pressor support, can be instituted. In addition, in ventilated patients, drawing blood samples, particularly for blood gases, is rendered easy. A central venous line is very useful to titrate fluid balances, especially in children who have the syndrome of inappropriate ADH secretion (SIADH) or cerebral salt wasting syndrome (CSW). In certain situations a child may be adequately hydrated, but may still be hypotensive—as in a child receiving barbiturates. In such situations the need for inotropic support will be dictated by the CVP and arterial pressure.

In ventilated patients, end tidal carbon dioxide ($ETCO_2$) monitoring is invaluable. This allows non-invasive breath-by-breath measurement of the exhaled CO_2 and detects large swings in the CO_2 tension immediately. It also allows less frequent measurement of arterial blood gases and thus reduces the overall cost of therapy.

Fluids and electrolytes: The aim of fluid therapy should be to maintain euvolaemia. If for some reason crystalloids are to be withheld, colloids can be administered to maintain euvolaemia (euvolaemic dehydration). Traditionally, head-injured patients have been fluid restricted due to the risk of cerebral oedema and SIADH. However, the administration of large volumes of isotonic fluids does not result in cerebral oedema.[5] It is important to maintain an adequate preload so that the cardiac output and blood pressure are sufficient to maintain optimal cerebral perfusion. A central venous pressure monitor is invaluable in guiding therapy and should be inserted in all seriously ill patients, especially those receiving mannitol or other diuretic therapy. Large volumes of hypotonic fluids should not be administered. Additional dextrose should not be administered since the head-injured patient is often hyperglycaemic to begin with, and hyperglycaemia has been linked with poor outcome in head injury.[18] Our current practice is to give the patient normal maintenance requirement of fluids as normal saline with potassium or lactated Ringer's solution and monitor the serum glucose frequently. Dextrose is added only if the patient develops hypoglycaemia. Additional fluid administration is guided by CVP, blood pressure, heart rate and perfusion, and is administered as boluses of either isotonic crystalloid (normal saline or lactated Ringer's solution), or colloid. In a child who is critically ill, a child who is being ventilated or receiving anti-oedema measures, serum electrolytes are to be checked at least twice a day and, if mannitol is being given, serum osmolarity should be checked, ideally, before every dose of mannitol.

Patients with head injury are at risk of developing the SIADH. This manifests as a decreased urine output, despite adequate filling pressures and hyponatraemia, and is managed by fluid restriction. An important differential diagnosis for hyponatraemia in head injury is the CSW, which is caused by an excess of atrial natriuretic peptide and results in massive urinary losses of sodium and water, resulting in severe hyponatraemia and volume depletion.[26] It is vital to differentiate between the two conditions since the therapy is different (Table 8).

Hypertonic saline has been used in the management of head-injured patients, with various reports claiming that ICP is decreased; patients have shorter ICU stays and fewer complications.[49,84] However, there are still no well performed prospective randomised controlled trials which show that this modality is superior to conventional treatment. Therefore, the routine use of hypertonic saline is not recommended at this time. It may, however, be used in individual circumstances at the physician's discretion.

Nutrition: Early nutritional support is extremely important. Head-injured patients, like all trauma victims, have a hypermetabolic state with increased nitrogen excretion that can last for several weeks. Undernutrition in head injury has been linked to increased mortality.[71] When the management of nutrition in a brain-injured child is

Table 8: Differential diagnosis of SIADH and CSW

Parameter	*SIADH*	*CSW*
Volume depletion	No	Yes
Plasma volume	Isovolumeic or ↑	↓
Serum sodium	↓	↓
Serum osmolarity	↓	Normal or ↑
Serum uric acid	↓	Normal
Serum ADH	↑	↓
Urine sodium	↑	↑
Sodium loss	Normal	Very high
Urine output	Low	Very high

Table 9: Equation for predicting BMR from body weight (W = body weight in kg)

Age (Years)	*Males (Kcal/day)*	*Females (Kcal/day)*
0–3	60.9 W–54	61.0 W–51
3–10	22.7 W + 495	22.5 W + 499
10–18	17.5 W + 651	12.2 W + 746

(From: WHO: Energy and Protein Requirements. Report of a Joint FAO/WHO/UNU Expert Consultation Technical Report Series 724. Geneva, WHO; 1985)

being planned, the requirements of a normal child in that age group and the additional allowances needed by a child who has sustained an injury need to be assessed and then plans are made to ensure the total requirement is met.[99]

Current adult recommendations are to provide 140% of the resting metabolic expenditure in non-paralysed patients and 100% of the resting metabolic expenditure in paralysed patients, with at least 15% of the calories as nitrogen, by the seventh day following head injury. Although it may be difficult to measure the resting metabolic expenditure routinely, the basal metabolic rate (BMR) can easily be calculated and used as a guide (Table 9).

Enteral nutrition has significant advantages and is much cheaper than parenteral. If the patient does not tolerate orogastric or nasogastric tube feedings, the tube can be advanced into the jejunum with the aid of prokinetics or under fluoroscopy and continuous drip feeds administered. Several paediatric enteral nutrition formulas, including a semi-elemental formula, are available. Parenteral nutrition is started only if the patient does not tolerate enteral feeds or if there are injuries which preclude enteral feeding. Although studies comparing enteral and parenteral nutritional support have not been conducted in children they both have certain limitations and advantages. The principles of tube feeding may be summarised as follows:[99]

- Allow 2–5 days to meet full nutritional requirements
- Use isotonic feeds initially
- Careful adjustments to be made in children who are chronically/critically ill and also in malnourished children
- If intolerance develops to feeds the last tolerated formulation is restarted and changes are made slowly
- Continuous feeds are stated at 1–2 ml/kg/hr and increased slowly till full requirements are met
- If the child is also receiving parenteral fluids, fluid overload may occur.

ICP monitoring has come to stay in the management of a head-injured patient, but the use of ICP monitoring in adults has only been recommended as a guideline.[12] There are insufficient data concerning ICP monitoring in children and this has not been considered as a part of standard care in children.[2] Monitoring of ICP is one of the more controversial issues in the management of head-injured patients. This therapy is not used universally and there is evidence both for and against monitoring. The issue has not been studied in a properly conducted prospective randomised clinical trial. Nevertheless, it has become standard practice in most large head injury centres.

Rationale: All therapies used in the treatment of severe head injuries are potentially harmful and can adversely affect the outcome. In order to scientifically apply the therapies and thus minimise adverse effects, it is necessary to monitor ICP. High ICP correlates with poor outcome in severe head injury. Lowering the ICP reduces the risk of herniation, helps optimise cerebral perfusion and oxygenation and may thus improve outcome. When the ICP is monitored using a ventricular catheter, CSF can be drained through the catheter to reduce ICP. In addition, ICP data correlate strongly with outcome—patients with normal ICP have the best outcome, those with elevated but controllable ICP do less well and those with uncontrollable ICP have the worst outcome. Therefore, the data can be very useful in counselling families.

Indications for ICP monitoring: There are no specific recommendations for children, but the adult guidelines are to monitor the ICP in all patients with severe head injury and an abnormal head CT scan on admission.[12] ICP monitoring is also recommended for patients with severe head injury and a normal head CT scan if they have hypotension or unilateral or bilateral motor posturing. Severe head injury is defined as a GCS of 3–8 after cardiopulmonary resuscitation. An abnormal head CT is one that shows a haematoma, oedema, contusion or compressed basal cisterns.

Using ICP to guide therapy: Normal ICP in adults is 0–10 mmHg. In the absence of good data for children, these adult baselines are often used. However, more important than the actual ICP is the blood flow to the brain. This is reflected by the cerebral perfusion pressure (CPP), which is the difference between the mean arterial pressure and the ICP (CPP = MAP – ICP). Therefore, even if the ICP is elevated, it may be possible to maintain adequate blood supply by increasing the MAP. It must be borne in mind that these numbers apply to the entire brain and do not reflect what is happening in individual areas. Although the exact level at which one should intervene is being debated, most centres intervene when the ICP is greater than 15–20 mmHg. A strategy of targeting the CPP is more physiological, rather than treating the actual ICP. A CPP target of 70 mmHg is often used in adults. Good guidelines are not available for children, but a CPP target of 40–50 mmHg in infants and toddlers and 50–60 mmHg in older children are recommended.[31] If the ICP is high, it may be necessary to use inotropic support to elevate the blood pressure in order to meet these CPP goals.

Techniques of ICP monitoring: A ventricular catheter connected to a standard pressure transducer is the gold

standard. In addition to measuring ICP, it allows CSF drainage for reducing the ICP. This can be placed at the bedside in the ICU. However, ventricular drains can sometimes be difficult to insert in patients with cerebral oedema in whom the ventricles are compressed. The catheter should be connected to a closed drainage system and the transducer must be maintained at a fixed level with respect to the patient (generally at the level of the external auditory meatus). The risks associated with a ventricular catheter are misplacement, haemorrhage, obstruction, migration of the catheter and infection. The risk of infection increases significantly after the fifth day and, therefore, the catheter should be changed after every 5–7 days.

The other devices used commonly are fibre optic catheters with a pressure transducer at the tip. These can be placed in the parenchyma and are thus easy to insert, especially if the ventricle size is small. They are also significantly more expensive. Subarachnoid, subdural and epidural devices are not accurate and should not be used.

Monitoring cerebral metabolism: Various techniques, including jugular venous saturation, near-infrared spectroscopy, cerebral parenchymal pO_2 monitoring, cerebral microdialysis and positron emission tomography have been used to monitor the cerebral metabolism.

Of these, jugular venous saturation has been used extensively. A special catheter is inserted in a retrograde manner through the neck into the jugular vein and threaded up to the jugular bulb. Venous saturations are monitored via a probe at the catheter tip. The amount of oxygen remaining in the blood after supply to the brain reflects oxygen utilisation by the brain and is indicative of the state of the cerebral metabolism. The minimum value is taken as 50% and values lower than this have been reported to be associated with increased mortality in adults.[34] The arteriojugular venous difference in oxygen content can also be calculated from the information provided by this technique. This information can be used to titrate therapies such as barbiturate coma. One limitation of this technique is that it measures only global oxygen utilisation, which may not be representative of the state of the injured areas.

Monitoring cerebral blood flow: Cerebral blood flow can be measured by techniques such as: (1) stable Xenon-enhanced CT; (2) radioactive ^{133}Xenon scanning; (3) transcranial Doppler and (4) cerebral thermal perfusion.

Of the three, stable Xenon-enhanced CT is the simplest and can be performed using almost any of the recently introduced CT scanners with slight modifications. It provides important information about the regional blood flow and may be coupled to interventions such as altering the arterial blood pressure or $PaCO_2$ level to see the effect of such physiological manipulation on blood flow.

Radioactive ^{133}Xenon scans can be performed at the bedside and gives information about regional blood flow. It can also be performed before and after physiological manipulation, as described above. Transcranial Doppler is sometimes used in adults, but has very limited application in children.

A cerebral thermal perfusion probe consisting of two thermistors is placed intracerebrally via a burr hole in the vascular area of interest in the brain. The probe is connected to a probe monitor that continuously displays the perfusion data. This provides the details of CBF.[90]

Managing in the ICU

As in monitoring, there are two broad divisions: (1) raised ICP and (2) associated problems (like seizures) and each one influences the overall outcome.

Therapy for raised ICP is one of the basic management problems in the ICU. Raised ICP contributes to a poor outcome in more than half of all the severe head injuries.[2] As in any situation in neurosurgery, the cause is an increase in the volume of the brain, CSF, blood or a mass lesion. Increase in CSF volume and a mass lesion are best treated by surgical measures and the techniques will not be elaborated here. Increase in blood volume (as in hyperaemia) has been discussed earlier. Raised ICP has to be carefully managed. A variety of methods is available to manage the raised ICP. A single method very seldom suffices. The raised ICP might have to be managed using various combinations of the several techniques available. The combination of therapies to be adopted will be dictated by the clinical scenario, experience of the team and the facilities available.

The strategies may be divided as follows:

- General
  - Head positioning; haemodynamic (regulating CPP); sedation and paralysis
- Barbiturate
- Diuretic
- Ventilatory
- Surgical
  - CSF drainage; removal of mass lesions; decompressive craniectomy.

General

Head position plays a role in reducing the ICP. Elevation of the head to 30° lowers the ICP. In addition the head has to be kept in the neutral position lest turning the head result in kinking and compression of the jugular veins.

Cerebral perfusion pressure (CPP which is the Mean Arterial Pressure—ICP, i.e. CPP = MAP – ICP) and ischaemia are intertwined and, since the latter has a significant influence on the outcome, it is important to ensure CPP is adequate in a head-injured patient.[2,12] Following a traumatic injury to the brain there is a global fall in the CBF and in areas adjoining contusions it is even lower than the global fall in CBF.[12] The ideal values of MAP and CPP have not been defined in children. Since the normal ICP of 20 mmHg in adults is high for the paediatric population, a "working value"

of 15 and 17–18 mmHg is taken for infants and children respectively.[2] A corollary of the foregoing is the values are only very general and each child has to be treated on a case-by-case basis. This is because the blood pressure of a child varies with age and in some a normotensive status will suffice while another may need mild hypertension.[2] If there is loss of autoregulation it will only serve to worsen the cerebral hyperaemia and raise the ICP further. The extension of the above discussion is hypotension should be avoided and, if present, should be treated with fluid boluses of crystalloids/colloids and the possible addition of pressor agents.

Sedation and paralysis are employed primarily in children who are being ventilated. Agitation and muscular activity result in an increase in the ICP and should be controlled. All patients who are being mechanically ventilated should be sedated adequately. The ideal sedating agent should be a short acting one since frequent neurological assessment is mandatory. An infusion of midazolam, 0.1–0.3 mg/kg/hr can be used safely. Fentanyl, 1–4 mcg/kg/hr, can also be added. Opiates cause miosis and this should be kept in mind during the neurologic assessment.

Routine paralysis has been linked to longer ICU stay and a higher incidence of pneumonia.[44] Neuromuscular blockade should only be used when excessive muscular activity cannot be controlled with sedation alone. Once pharmacologically paralysed, the neurological examination is limited to checking the pupillary size and reaction. In addition, the occurrence of seizures will be masked. If deemed necessary, infusions of vecuronium (0.1–0.2 mg/kg/hr) may be used. The dose should be titrated using a peripheral nerve stimulator to maintain 1–2 twitches on train of four stimulations. If this is not available, the infusion can be stopped every morning to allow the patient to recover from paralysis and then restarted, if necessary. The longer acting drug pancuronium can also be used, but it causes tachycardia. The initial dose of pancuronium is 0.1–0.15 mg/kg IV followed by an infusion at 0.02–0.04 mg/kg/hr, if needed.

Sometimes, children who are not intubated and ventilated may be irritable or agitated. However, they should not be sedated unless absolutely necessary since this will affect the neurological examination and can mask a deteriorating neurological status. If such a clinical situation warrants sedation, a CT has to be done to make sure there is no pathology which can explain the irritable state. It has to be emphasised here that trials have been conducted comparing intermittent versus continuous paralysis and sedation. No single regimen has proved superior. There are advantages and disadvantages in both regimens. The best regimen is probably what the doctors caring for the child are used to or comfortable with.

Barbiturates

Barbiturates are effective in lowering raised ICP by their effect on altering the vascular tone, lowering cerebral metabolism and inhibition of free radical peroxidation. Their primary effects may be by reducing the cerebral metabolic demands, thereby reducing the blood flow, which in turn results in a reduction in cerebral blood volume and perfusion.[12] They may be useful in hemodynamically stable children with refractory raised ICP. Since barbiturates have potent cardiovascular side effects, CVP and arterial pressure monitoring are mandatory and hypotension should be treated aggressively with additional volume and inotropic support, if required. Most patients with barbiturate-induced hypotension will respond to dopamine infusion after adequate volume replenishment. All patients should ideally have continuous EEG monitoring and the dose titrated to achieve burst suppression. Although pentobarbital is the commonly used drug, thiopentone sodium is used in our country since the former is not available. It has to be added here that the use of thiopentone has also been advocated.[31] Thiopentone sodium can be given as a loading dose of 3–5 mg/kg. Then a maintenance infusion of 1–2 mg/kg/hr may be continued. An intermittent dose of 5 mg/kg 4–6 hourly has also been advocated to achieve the same end point.[2] The end point of barbiturate is to achieve a burst suppression pattern on EEG. Their use prophylactically has not been proven to be useful. The use of barbiturates is usually a "last resort" therapy.

Diuretic

Both loop and osmotic diuretics have been used in the management of head injury.

Mannitol is useful to control raised ICP after severe head injury. The exact mechanism of action of mannitol is still unclear, but it probably has two separate actions:

1. Through its rheological properties, it reduces blood viscosity and produces an increase in the CBF and also oxygen delivery to the brain. The increase in plasma volume after the administration of mannitol may raise the blood pressure and increase the CPP.
2. Its osmotic effect occurs in about 15–30 minutes after administration. Mannitol creates an osmotic gradient across the blood-brain barrier, which results in dehydration of the brain and thus reduces the ICP.

Mannitol is excreted entirely through the kidneys and causes a pronounced osmotic diuresis. A Foley catheter is necessary when mannitol is used. There is a risk of acute renal failure due to acute tubular necrosis, especially when used in large doses or the serum osmolality is allowed to exceed 320 mOsm/L. Mannitol should not be used when there is pre-existing renal failure.

In the absence of ICP monitoring, mannitol can be given when there are signs of transtentorial herniation or progressive neurological deterioration. The initial dose is usually 0.5–1 g/kg body weight given intravenously. The child is then given mannitol at a dose of 0.25–1g/kg. Intermittent bolus doses (administered 4–6 hourly) are thought to be safer and more effective than a continuous infusion.

Care should be taken to maintain euvolaemia since the brisk diuresis can quickly cause dehydration. Serum sodium and osmolality should be checked one hour before each dose and the dose omitted if the sodium exceeds 150 mEq/L or the osmolality exceeds 320 mOsm/L (serum osmolality is best measured with an osmometer, and not calculated). Mannitol has been advocated as a "small volume resuscitation fluid" to be used in the initial fluid resuscitation of patients with head injury and hypovolaemia.

Loop diuretics can be used in combination with mannitol. The drug of choice is furosemide. In addition to causing diuresis, furosemide has been shown to decrease CSF production. The recommended dose is 1 mg/kg/day. Furosemide can be used in addition to mannitol. No matter which diuretic is used, it is important to maintain euvolaemia since hypovolaemia and even brief episodes of hypotension are associated with poor outcome. These two drugs may have a synergestic action if used in combination. If used in combination with mannitol severe dehydration and electrolyte imbalances may result. So, very careful monitoring is essential in such situations.

Ventilatory Support

The concept of hyperventilation was built on the foundation of the response of the cerebral vasculature to CO_2. The logical extension of this was the use of hyperventilation to reduce ICP. Since raised ICP and brain swelling occur in up to 40% of patients with severe traumatic brain injury it was assumed hyperventilation would benefit all with raised ICP.[12] Hyperventilation, however, is a double edged sword. It reduces the ICP by vasoconstriction but this vasoconstriction also worsens the already existing cerebral ischaemia which is almost an inevitable occurrence of severe head injury. So the use of hyperventilation is limited to brief periods when there is an acute deterioration or "for longer periods if there is intracranial hypertension refractory to sedation, paralysis, CSF drainage and osmotic diuretics".[12] The use of chronic prolonged or prophylactic hyperventilation should be avoided.[12]

Modes: No single mode of ventilation has been shown to be superior to another in the care of head-injured patients. However, it is prudent to use the lowest mean airway pressures possible, since this will minimise the intrathoracic pressure and thus prevent further increases in the ICP. Either a pressure controlled or volume controlled mode of ventilation can be used. If pressure control is chosen, just enough pressure to move the chest adequately should be used. Care should be taken to avoid large tidal volumes as this will increase the incidence of barotrauma and volutrauma to the lungs, and will increase the intrathoracic pressure. Generally, a tidal volume of 7–10 ml/kg should be sufficient. Similarly, inspiratory times should be age appropriate and generally ranging from 0.6 seconds in the newborn to 1 second in older children and adults.

High levels of positive end expiratory pressure (PEEP) should also be avoided because it will raise the intrathoracic pressure and may impede venous return, thus affecting the ICP. In the uninjured lung, a PEEP of 2–4 cm H_2O is used. Using no PEEP can be detrimental since it may lead to lung collapse at the end of expiration. However, if there is lung damage and oxygenation is impaired, as much PEEP should be used as is necessary to maintain optimal oxygenation.

Routine nursing procedures, such as endotracheal suctioning, cause an increase in the ICP. Therefore, the patient should be disturbed as little as possible. IV lidocaine (1 mg/kg) has been advocated prior to suctioning in order to blunt the centrally mediated increased ICP.[41] However, this has been questioned recently and, if used, it should not be administered more often than every 4 hours to avoid over dosage.[76] If intermittent paralysis is used, the suctioning can be timed to immediately follow the dose of paralysing agent to abolish the cough response.

Surgical Measures

Surgical measures include CSF drainage, removal of mass lesions and decompressive craniectomy.

CSF drainage: Although the indications and guidelines for ICP monitoring in children are still being worked out, ICP monitoring has almost become a standard of care in adults. Monitoring through an indwelling ventriculostomy catheter is probably the best. If such a device is available it can be used to monitor the ICP and also vent CSF whenever the ICP rises. The volume of CSF to be drained will depend on the clinical scenario and the protocol followed by the team in charge of the child. The CSF can be removed manually every time the pressure rises beyond a set level or the drainage chamber can be positioned in such a way that the CSF drains automatically when the pressure goes above the set level.

CSF drainage through the lumbar route has its advocates too and it has been successfully employed. This has been tried not only in those with subarachnoid haemorrhage, but also in those with "refractory intracranial hypertension".[63] In a study of adult patients who had refractory intracranial hypertension, even after conventional therapies had failed, lumbar CSF drainage was instituted if the basal cisterns were seen on CT. The conclusions of the study were, "Controlled lumbar cerebrospinal fluid drainage significantly reduces refractory intracranial hypertension. The danger of transtentorial or tonsillar herniation is minimised by considering lumbar drainage in the presence of discernible basilar cisterns only". Similar work has also been done in children and the results have been good.[54]

Removal of mass lesions, if they are responsible for raised ICP, should be done promptly. The management issue of these has been addressed in the appropriate chapters.

Decompressive craniectomy, which was initially described by Cushing, is now staging a resurgence, but it is mired in debate and controversy. It is used in cases of refractory intracranial hypertension where conventional therapies have failed. The technique involves removal of a large bone flap and opening the dura. The dura may be left open as it is or a patch may used to "enlarge" the volume of the dural compartment. Once the period of intracranial hypertension has settled and the patient has improved, cranioplasty is done. There are proponents and opponents to this method of managing "malignant" raised ICP. The decompression may be bifrontal or temperoparietal.

Bifrontal decompressive craniectomy has been shown to reduce the ICP and also the amplitude of the ICP waves.[100] In children, unilateral decompressive or bilateral craniectomy has been shown to be associated with a good outcome.[43,87] This has been shown to be useful even in the presence of associated intracranial lesions and the recommendations are to perform it sooner rather than later.[23] The experience of one and all has not been so gratifying. The observations have shown "there was a significant decrease in midline shift after craniectomy, but this did not translate into decompressive craniectomy demonstrating a beneficial effect on patient outcome".[62] Observations have also shown that there is "a significant decrease in expected mortality, but severe morbidity in the survivors".[94] Correlation of the clinical and experimental findings also does not show that this procedure confers an excellent benefit on the outcome.[21]

What has to be borne in mind is that this procedure does not always translate into a good outcome for those with refractory raised ICP. Until randomised studies are done this has to be considered a last ditch effort to salvage a limited group of patients who have failed all other therapies to control the raised ICP. The results in terms of improved mortality and particularly morbidity remain unproven at the present time.

Corticosteroids have been utilised as a standard form of treatment in the management of head injury until recently. There is a large volume of literature regarding their use in head-injured patients, both adults and children. However, none have shown conclusively that the administration of steroids is beneficial or has any adverse effects.[4] Therefore, steroids are not recommended in the treatment of head injuries at this time.[12]

Therapy for associated problems too cannot be taken lightly. These may appear simple at first glance, but often have far reaching consequences.

Hypo/Hyperthermia

Hypothermia as a therapeutic measure to combat raised ICP was proposed initially in the 1950s.[2] Mild to moderate hypothermia (32–34°C) has been advocated in the management of severe head injury. Several studies in the past have shown beneficial effects, such as lower incidence of seizures, decreased ICP and an improved neurological outcome. Its beneficial effect in children was reported, but due to "lack of scientific methodology" this did not gain widespread acceptance. Even in adults this has not proved useful.[2] A review has concluded that there is no evidence that hypothermia is beneficial in the treatment of head injury.[32]

In contrast, hyperthermia (even 1–2°C for brief durations) has marked deleterious effects on neuronal recovery and blood-brain barrier integrity and should be controlled immediately.[31] Fever is a serious problem in the ICU. The cause may be neurogenic, i.e. related primarily to the injury, or it may be the result of polytrauma or sepsis. The cause for the fever should be established and treated vigorously. Every degree centigrade rise in temperature increases the $CMRO_2$ by 9%. So it is clear why fever is deleterious in the head-injured child.

Seizures

Between 6.5% and 10% of children with head injury develop post-traumatic seizures. Post-traumatic seizures are further divided into early onset (occurring within one week after injury) and late onset (occurring later than one week after injury). Children are more prone than adults to develop early onset seizures. Seizure activity has multiple adverse effects in head injury. They can affect ventilation and oxygenation, thus leading to secondary damage and increased ICP. In addition, they also increase the metabolic demands of the already injured brain. Therefore, seizures must be treated aggressively.

Immediate control of seizures can be achieved with either lorazepam or midazolam, 0.1 mg/kg IV. The dose may be repeated if needed. In addition, the patient should also be started on a longer acting drug, such as phenytoin (loading dose of 15–20 mg/kg followed by a maintenance dose of 5–8 mg/kg). Phenobarbital, although effective, is not recommended because it depresses the sensorium and can mask a deteriorating neurological status. For uncontrolled seizures or status epilepticus the child may require thiopentone sodium.

Certain patients are more at risk of developing early onset seizures. These include those with a GCS less than 10, EDH or SDH, penetrating head injuries, intracerebral haematomas and depressed skull fractures. Such patients may also be given anticonvulsants prophylactically. However, although prophylactic administration of anticonvulsants is effective in preventing early onset seizures, this does not prevent late onset seizures nor does it have any effect on the incidence of death or neurological disability.[81] Therefore, prophylactic anticonvulsants are recommended only during the first week in patients at risk of developing seizures.[12]

Complications

Disseminated intravascular coagulation (DIC): Brain tissue is a rich source of tissue thromboplastin. Following a severe traumatic brain injury there may be a significant

outpouring of thromboplastin from the injured brain. The released thromboplastin initiates the coagulation cascade which results in the scenario of a "runaway" consumptive coagulopathy or DIC. In one study, one-third of paediatric patients with head injury had evidence of DIC.[61] This can occur as early as one to two hours following the injury and the patient can have profuse bleeding that is difficult to control. Therefore, all patients with severe head injury should have their coagulation status monitored at admission and also as indicated clinically, regularly, and any bleeding tendency must be treated aggressively with fresh frozen plasma and cryoprecipitate, as appropriate.

Neurogenic pulmonary oedema (NPE) generally occurs 2–12 hours after injury, although its onset can be delayed further. It manifests as hypoxia, hyperventilation and hypercarbia, with bilateral fluffy infiltrates on the chest X-ray. This oedema is non-cardiogenic and is due to increased pulmonary permeability. Medullary ischaemia causes a sudden massive surge in sympathetic activity, which leads to increased pulmonary vascular pressures and shifts blood from the systemic into the pulmonary circulation. There is increased permeability in the lungs, which allows the transudation of fluid into the alveoli.

NPE generally resolves spontaneously if the patient survives. However, it may complicate patient management because the hypoxia can lead to secondary injury. In order to overcome the oedema, high levels of PEEP may need to be applied. This, in turn, can interfere with cerebral venous drainage and thus increase ICP. The presence of NPE in any head injured or polytrauma victim results in a poor prognosis.

SUMMARY

The management of a child in the ICU is a dynamic process, in the sense that no one rule or therapy can be strictly adhered to in a given child since the clinical scenario may change frequently. The management has to be changed as per the dictates of the clinical situation. The management in the ICU has been stratified into three tiers which serve as a foundation for guiding the treatment.[55] It should be emphasised that there is no "water tight" division between the various levels and there is a considerable degree of overlap between the various tiers. It is worthy of note here that a lot of the management strategies have evolved from the studies of head-injured adults (since the incidence of head injuries is more in adults, various modalities can be evaluated by clinical trials) and the child admitted to the ICU for various other causes. What should also be borne in mind is, if the child is treated merely as a small adult it would amount to courting disaster.

Treatment has been divided into basic, escalated and intensive tires (Table 10). Two rules are to be observed in following these guidelines before "escalating therapy to any higher level":

Table 10: Different treatment therapies

Treatments	*Monitoring*
Basic level therapy:	
• Elevation of head end of bed	• Systemic BP and oxygenation
• Keep head in neutral position	• Intracranial pressure
• Sedation ± Paralysis	• PaO_2; $PaCO_2$; pH
• Mechanical ventilation to keep $PaCO_2$ between 35 and 40 mmHg	• Intake/output; pulse; pulse pressure; weight
• Maintain euvolaemia to slight hypervolaemia	• Haemogram; serum electrolytes; blood glucose and blood urea nitrogen
• Maintain normal fluid and electrolyte status; No fluid restriction; avoid anaemia and hyperglycaemia	• Monitor for sepsis/fever and if present treat aggressively
• Temperature: maintain euthermia; treat hyperthermia	• CT scan
Escalated therapy:	
• Ventricular CSF drainage	• Ventricular catheter
• Mannitol	• Central venous pressure
• Maintain $PaCO_2$ between 30–35 mmHg	• Serum osmolality
Intensive therapy (for refractory raised ICP):	
• High dose barbiturate therapy	• Continuous EEG, serum level of barbiturates
• Lumbar CSF drainage	• Jugular venous O_2 saturation, CBF
• (? Decompressive craniectomy)	
• Hyperventilation for acute rise in ICP	

(Source: Modified from Leurssen[55])

- "one must confirm that the current therapy is being correctly applied"
- "prior to any escalation of therapy, escalation of systemic and neurologic monitoring must occur."[55]

OUTCOME

Head injuries have been divided into two broad categories: (1) primary and (2) secondary. The former occurs at the time of the injury while the latter occurs later on as a result of a compromise in A, B, C, D, E and F which have been discussed earlier. A compromise in any of these ultimately results in neuronal hypoxia, leading to injury or death of the neurons and this is the reason for the poor outcome. Nothing can be done about primary injury apart from prevention and prophylaxis, while preventing the latter is very much in our hands and every effort has to be taken to minimise it, if not prevent it all together.

Using the GCS scoring system about 80% of head injuries in children are mild (GCS 13–15), while 10% are moderate (GCS 9–13) and 10% are severe (GCS 3–8).[58] Using the above criteria, the incidence of severe injuries in children is half that of adults.[58] Severe brain injury is commoner in the "older" population than it is in children. It has also been observed that the outcome in children is better than it is in adults.[3,57,58]

Factors associated with a poor outcome include low GCS and prolonged impairment of consciousness.[58] These were seen not only at the time of discharge but also at 6 months post injury and several years after the injury.[58] The GCS alone is a good predictor of outcome in children. Hyperglycaemia, and especially its persistence over time, appears to be an important negative prognostic factor in children with head injury.[19] The factors which result in a poor outcome include presence of hypoxia on admission and CT scan features of subarachnoid haemorrhage, diffuse axonal injury and brain swelling.[64] In those with a minor head injury, no clinical sign is absolutely indicative of an ominous outcome. We have to depend on imaging studies to identify those children with mild head injury who are at risk.[48] The morbidity and mortality are higher in infants and young children than in older children.[2,58]

The data generated by the Traumatic Coma Data Bank have shown very important and interesting features. About 103 children (0–15 years of age at the time of injury) treated at four centres were evaluated at 6 months (92 children) and 1 year (82 children) post injury. The Glasgow Outcome Scale was used to assess these children. Children 0–4 years fared the worst (62% mortality at 1 year) whereas children 5–10 years fared the best (2/3 good recovery at 1 year), the others were in between these two groups. A low GCS score concomitant with non-reactive pupils was particularly predictive of poor outcome. Bilateral brain swelling with or without midline shift and the presence of a mass lesion seen on CT were also predictors of a poor outcome. The Kings Outcome Scale for Childhood Head Injury (KOSCHI) is a specific paediatric adaptation by Crouchman et al. of the original adult GOS. The GOS category of "persistent vegetative state" was replaced by vegetative. "Good recovery" was allocated two categories, keeping in mind the relatively minor sequelae in a developing child. They have also elaborated in detail the definition of each category for easy adaptation in children.[93]

In short, the outcome after a severe head injury depends on age, neurologic state and CT findings as have been discussed above.[53] Not only the mortality is less in children compared to adults, the outcome in survivors is better too. In a series of 330 patients, the mortality in children was 24% as opposed to 44% in adults. One year post injury, 55% of children and 21% of adults had a good outcome.[2] Even though the overall outcome in children is better than adults, children do not always emerge "unscathed" after a severe head injury. A variety of anxiety symptoms have been recorded in children 1 year following severe head injury.[93]

CONCLUSION

Most of the literature suggests children fare better than adults after a head injury. "The significant influence of age on outcome is not explained by the increased frequency of systemic complications or ICH with age."[12] Children do not react or respond to an injury, whatever be the nature of the injury, the way adults do. The fundamentals may be same in all age groups, but the problems in children are unique; even clinical assessment is fraught with difficulties. As has been mentioned earlier, infants may manifest few clinical features in spite of harbouring an intracranial pathology.[69] A CT should be done in all symptomatic children although this may not be true for their adult counterparts.

In the light of the rising cost of medical care, the routine scanning and admission of all children who have sustained a head injury has been brought under scrutiny.[1,37,82] A prospective study has shown the need for CT even in children with mild alterations in mental status (GCS 13–14).[97] More studies are mandatory to come to a firm conclusion and, if done prospectively, firm conclusions/guidelines can be proposed.

In an analysis of a large series of head-injured children, two factors which determine the presence of an intracranial complication have been identified and these can be identified by the primary care taker, these are impaired consciousness and skull fracture.[17] An increased awareness should be created to prompt early referral for a better outcome.

Children present problems that are unique and completely different from those of adults. The aetiology of injury, the difference in physiologic parameters, possible interference with growth and development, and the requirement of different set of facilities in terms of personnel and equipment present facets and cannot be compared to the larger adult population.[46] The question of who should care for children with a head injury has been the subject of many a debate. The data show children who have suffered a blunt trauma have a better outcome when treated at a paediatric trauma centre.[40] This better outcome has been shown not only with respect to trauma in general but also head injuries in particular. Children brought to a paediatric trauma centre have had a better outcome than those who have been referred to another hospital and then transported to a paediatric centre.[47] The improved outcome in head injuries has contributed significantly to the overall better outcome.[68]

A poor outcome in severe head injury is not unknown or it, probably, is only to be expected. But the incidence of disability after a mild head injury in young people and adults seems to have been underestimated.[91] So much so the very concept of mild head injury seems to have been questioned. Whether this can be extended to children needs to be evaluated.[89]

The development of a treatment strategy for a severely head-injured child involves a synthesis of the known clinical and radiographic classification of the

injury with the nature of mitigating systemic injuries and complications. It also involves the continuous reassessment of the evolution of the injury, both expected and unexpected, and the responses to each therapy. Selecting a therapy is still a matter of experience.[58]

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33 Clinical Assessment of a Head Injured Patient

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INTRODUCTION

The successful management of patients sustaining head injury requires careful assessment of the details and diligent anticipation of forthcoming sequelae. A comprehensive neurological evaluation of the head-injured patient remains the single-most efficient factor in their diagnostic evaluation. A correct assessment not only helps in better management but also enables us to do a judicious triage of such patients.[8,9] The clinical evaluation provides an index of local and generalised dysfunction of the nervous system and repeated assessment indicates the ongoing neurological state and the response to treatment. The clinical assessment thus is central in the initial evaluation and subsequent management of all head-injured patients.[10,11]

Such an assessment requires a careful general examination to look for associated injuries and other sources of bleeding helping in prioritising the treatment and carrying out requisite investigations. The patients may present in a conscious state or with altered consciousness, and the major goals of assessment[12] are:

- To determine the presence of an intracranial mass lesion requiring operative removal.
- To have a baseline evaluation of clinical parameters for future comparison.
- To define an abnormal intracranial mass lesion for institution of appropriate operative or non-operative therapy.
- To diagnose associated injuries.
- To carry out necessary investigations.
- To prognosticate patients and apprise them or relatives of the possible course of illness.
- To allow statistical analysis and comparative studies.

However, before any clinical evaluation, it is important to assess and ensure the patency of the airways, and ascertain the systemic circulatory status by recording the blood pressure and pulse.

CONSCIOUS LEVEL

The initial evaluation should be as thorough as possible whether the patient presents in a conscious or an unconscious state. The anatomical, as well as physiological parameters are assessed on examination. The anatomical parameters are assessed by the abbreviated injury scale and the injury severity score. The Glasgow Coma Scale (GCS) and the Revised Trauma Score (RTS) are commonly used to measure the physiological derangements. The internationally accepted standard scale to quantify the neurological state after head injury is the GCS and the numerical scores used for assessment in this score have demonstrated their practicability and validity in prognosticating patients of head injury over the years.[16] The RTS provides an assessment of the physiological state by including respiratory rate, systolic blood pressure and GCS. The trauma score and injury severity score and a severity characterisation of trauma are the recent introductions to the scoring assessment scales. The GCS still remains the most widely used and has stood the test of time over the years.[10,12,16] The most important fact in respect to consciousness is not the findings of the initial observation but its dynamic changes virtually from the moment of injury and especially in the early post-traumatic period.

GENERAL EXAMINATION

The first concern of the physician after having assessed the level of consciousness is to assess the respiration and ensure a clear airway and oxygenation. The establishment of adequate alveolar ventilation assumes top priority. All accumulated secretions, blood or vomitus should be sucked away and associated jaw, tongue, throat or chest injuries should be looked for as all of these impede respiration.[9,12,17] The respiratory abnormalities should be attended to expeditiously to prevent further injury to the already insulted brain. Endotracheal intubation is often necessary to protect the airway and maintain the ventilation. As a rule, intubation requires ventilation.[2,12,17]

The vital parameters including the pulse rate, blood pressure and respiration should be assessed. Head injuries associated with raised ICP may manifest Cushing's response of raised blood pressure and bradycardia.

Editorial note: In clinical practise, this is extremely rare and not a helpful feature for assessment or management of acute head injury.

The patients who present with shock usually have associated visceral injuries or fractures of long bones as the cause of their blood loss and they manifest with hypotension associated with tachycardia.[7,9,12] The presence of shock, however, is observed in the initial period

following head trauma and it generally recovers spontaneously. An association of hypotension with bradycardia is suggestive of cervical injury.[5,10,12] It is important to recognise that in infants and young children even a small amount of blood loss, as in a scalp haematoma, could result in hypotension.

CLINICAL HISTORY

The history is the next step in evaluation after having stabilised the respiratory and vascular status of the patient. A complete history can be given by a conscious patient and should be obtained. Information regarding the precise time of injury and mechanism of injury should be elicited. The feedback from the attendants, relatives, police or any eye witness who brought the patient should also be obtained regarding the scene of the accident and the course of events following injury.[2,8,12] Their account of the accident becomes absolutely important in patients who are in an unconscious state. A report from the referring hospital, if any, should actively be sought. The information regarding drug or alcohol intake and the past medical history is also valuable. The history of bleeding from the ear, nose or throat should be sought. The duration and timing of loss of consciousness has to be asked for. The associated co-morbid conditions and any significant concurrent or past illness (e.g. diabetes, hypertension, ischaemic heart disease, etc.) should be enquired for and taken note of. They are important in management and prognosis. The history regarding leak of cerebrospinal fluid (CSF) from the nose or ear must be asked for.[3,5,12]

Post-traumatic amnesia is an index of the severity of injury and should be asked for. It is also a significant risk factor for the occurrence of post-traumatic seizures.[18] In conscious patients, memory regarding the accident and recent events should be tested. The duration of retrograde and post-traumatic amnesia should also be recorded. Post-traumatic amnesia is a useful index of severity of the injury and a good guide to the period of rehabilitation necessary before return to full work. In children this assessment, however, becomes difficult.[9,12] Brachial plexus or peripheral nerve injuries are also sometimes associated and should be ruled out historically.

A history of seizures should be enquired into and recorded. The seizures occurring following trauma may be of three types:

1. Immediate seizures; occurring within 24 hours.
2. Early seizures; occurring within 7 days.
3. Late seizures; occurring later than 7 days.

The diagnosis of head injury is usually straightforward and stabilisation of the patient assumes highest priority. Due to these factors, a detailed history is not taken in these patients and is mostly missed. This tendency should be condemned and one must be aware of the importance of a detailed history in these patients. All such information is valuable not only for diagnosis and management but also may be required for medico-legal purposes.[10,12]

GENERAL PHYSICAL EXAMINATION

The patient should systematically be examined after appropriate resuscitative measures and detailed history have been obtained. The examination should be comprehensive and must include the general physical condition as well as neurological status. The vital parameters should be recorded and, importantly, for temperature recording, the rectal temperature should be obtained. This is reflective of the central body temperature and not affected by external factors. The chest, abdomen, pelvis, spine and long bones should also be assessed for associated injuries and an effort should be made to have a comprehensive whole-body examination. All scalp wounds, lacerations and avulsions should be inspected. The forehead should be palpated for signs of a depressed fracture or frontal sinus injury. Associated CSF rhinorrhoea or otorrhoea are usually secondary to basal skull fractures and should be sought. Bilateral periorbital haematomas (raccoon eyes) result from fractures of the orbital roof. Associated bleeding beneath the pericranium over the mastoid (Battle's sign) usually appears after 2–3 days.[10,12] Dental occlusion should be checked to rule out a mandibular fracture. A high index of suspicion should be kept for an associated cervical injury. The auscultation of carotid arteries and the eyes should be done to rule out an associated carotid dissection and traumatic carotid cavernous fistula, respectively. A careful examination of the chest and abdomen is mandatory.

NEUROLOGICAL ASSESSMENT

The single most important parameter of neurological examination is the state of consciousness. This should be recorded meticulously as per the GCS as already discussed. The score was first introduced in 1974 and then revised in 1977 by the addition of another motor response.[5,10,12,16] The score includes eye opening, best motor response and best verbal response (Table 1).

Table 1: Glasgow coma scale

Eye opening:
1. No eye opening
2. Opens eyes to pain
3. Opens eyes to verbal commands
4. Spontaneous eye opening
Best motor response:
1. No movement
2. Extensor response
3. Flexor response
4. Withdraws to pain
5. Localises to pain
6. Obeys commands
Best verbal response:
1. No sounds
2. Incomprehensible sounds
3. Inappropriate words
4. Confused conversation
5. Well oriented speech

The patient is examined vis-à-vis the above list and each patient is given a score after adding the three parameters. A fully conscious patient has a score of 15 and a deeply comatose and areflexic patient would have a score of 3. A GCS of 8 or less is consistent with coma. The GCS has been adopted by neurosurgical units all over the world to evaluate head-injured patients. The score also helps to classify the types of head injury into three categories namely:

1. Mild head injury; GCS 13–15.
2. Moderate head injury; GCS 9–12.
3. Severe head injury; GCS 8 or less.

The score, however, has a few pitfalls despite its wide acceptance. They are:

- Eye movements and other brainstem reflexes are not taken into account.
- Patients with dysphasia or with bilateral ecchymosis have inaccurate recording.
- GCS does not take into account the pupillary status and vital parameters.
- Facial fractures or lip and tongue injuries may impede patients from talking.
- The usefulness in children is limited and a modified scale called the "children coma scale" is used for them.

The children coma scale has the same three parameters used in the GCS and only the verbal response is different from the GCS. This is best used in children below 4 years of age. The verbal response is as follows (Table 2):

Pupillary Status and Optic Nerve Function

The pupillary status constitutes an important part of the neurological examination and the size, shape, position, reaction to light and the pupillary reflexes should be recorded in all cases. An attempt to see the fundus is also made at this time along with the observation of the iris margins and evidence of local injury to the eye.[10,12,15] The pupillary examination provides important clues to the diagnosis and treatment and is a sensitive indicator of a developing intracranial mass.

The pupillary size depends upon a balance of tonic forces constituted by pupilloconstrictor parasympathetic and pupillodilator sympathetic controls. The pupillary status and their changes are related to the brainstem and both II and III nerve activity. In an unconscious patient, the direct and consensual reflexes are most important aids to assess optic nerve function.[15] In patients having hemianopias, the signs are elicited from the blind side of the visual field. The direct and consensual reflexes should both be elicited as they help to distinguish between II and III nerve injuries. A unilateral dilated and non-reactive pupil with absent consensual reflex points towards an underlying optic nerve injury. The interruption of oculo-sympathetic neurons may result in Horner's syndrome.[9,12,15] This syndrome is characterised by unilateral miosis, facial anhidrosis, ptosis, pseudo-enophthalmos and loss of ciliospinal reflex.

Bilaterally dilated pupils are indicators of a poor prognosis and are early harbingers of brain death.[6,15,19] There are certain conditions like bilateral glaucoma with blindness, drugs like atropine, datura and glutethimide poisoning which can lead to bilateral pupillary dilatation and such entities should be kept in mind when one sees a patient with bilaterally dilated and non-reactive pupils.

The patients with accidental or post-surgical aphakia may have irregular pupils. Colobomas of the iris may lead to irregular pupils as well. Opiate and barbiturate poisoning lead to small-sized pupils. All such abnormalities of the pupil should also be borne in mind during the pupillary examination.

Table 2: Verbal response

Points	*Best verbal response*	
5	Smiles, oriented to sound, follows objects and interacts	
	Crying	*Interaction*
4	Consolable	Inappropriate
3	Inconsistently consolable	Moaning
2	Inconsolable	Restless
1	No sound	No sound

Eye Movements

The eye movements are commonly affected after structural lesions and can easily be tested in conscious and cooperative patients. For unconscious patients, the "Doll's head ocular movement" and oculovestibular reflex (caloric response) can be elicited. These are amongst the most important signs for assessment of brainstem function.[4,11] Sinha et al.[13] were the first to study this systematically in a large series of unconscious patients. Its value was later confirmed in an autopsy study.[14]

The "Doll's head ocular movement" is performed in the supine position and rotating the head horizontally or vertically to 30° from the neutral position. The eyes normally maintain their position in space by moving to the side opposite to the direction of movement of the head and absent movement indicates brainstem insult. The test is not performed in cases with suspected cervical spine injuries.

The "oculovestibular reflex" is elicited by caloric stimulation of the labyrinth. The patient is supine with head flexion of 30° so that the horizontal semicircular canal lies in the vertical plane, with the ampullae at the highest point. The ears are irrigated with water, first at 30°C and then at 44°C for 40 seconds. In comatose patients, irrigation of the external auditory meatus is done with at least 20 ml of ice cold saline. The presence of nystagmus in the same direction as the warm saline and in the opposite direction to the cold saline (well-known mnemonic: COWS) is indicative of the integrity of the brainstem. It also helps to evaluate abnormalities of the ocular nerves or gaze paresis.[4,11] It also helps to

predict the prognosis and in case the reflex is not elicited, brainstem injury can be inferred.

Patients with head injury can also have upward or downward gaze palsies. The upward gaze palsies occur in compressive or destructive lesions involving the pretectal area of the midbrain, posterior commissure and dorsal midbrain tegmentum.

Lesions in the pons involving the pontine paramedian reticular formation (PPRF) produce conjugate deviation of the eyes towards the opposite side. Internuclear ophthalmoplegia is due to a lesion in the medial longitudinal fasciculus (MLF) of the midbrain. In this condition, there is impaired adduction of the ipsilateral eye with nystagmus of the abducting opposite eye during attempted lateral gaze to the opposite side. The so-called "one and a half syndrome" is due to a lesion involving both the PPRF and the MLF on the same side and is associated with ipsilateral gaze paresis with impaired adduction of the ipsilateral eye and nystagmus on abduction of the opposite side. It is possible to ascertain these deficits by using the cold-caloric (vestibulo-ocular reflex) test in unconscious patients.

Skew deviation in which one eye is directed upwards and the other eye is directed downwards may also be noted. They are indicative of lesions of the brachium pontis or dorsolateral medulla and point towards a grave prognosis.

Other Cranial Nerves

It is impossible to examine the olfactory nerve in unconscious patients. Fractures of the anterior cranial fossa may be associated with loss of smell and, so, the sense of smell should be examined in all conscious patients.[10,12]

The V cranial nerve may be injured in fractures of the middle cranial fossa. The corneal reflex tests the integrity of the V and VII cranial nerves and is done with a moist light cotton wisp. The VII and VIII cranial nerves may also be affected in fractures of the petrous pyramid. The more common longitudinal fracture of the petrous bone is due to a lateral blow to the head and may result in facial nerve injury and CSF leak. The less common transverse fracture results from occipital blows and is associated with a higher incidence of facial nerve injury and other complications.[12] There may be associated CSF otorrhoea, deafness or vertigo. Patients may also have vertigo on account of micro-haemorrhages in the vestibular system. It is impossible to test the auditory component of the VIII nerve directly in the unconscious patient (except by evoked potential using audiometric inputs). The vestibular component is tested using the caloric test.

Posterior fossa fractures involve the lower cranial nerves. A haematoma below the mastoid is seen as a skin discolouration. The assessment of vocal cord function, gag and swallowing evaluates glossopharyngeal and vagus nerve functions. The endotracheal tube in an unconscious patient can be manipulated to elicit these responses.

Motor Examination and Reflexes

In conscious and alert patients, muscle tone can be evaluated by passive range of movement and muscle power by assessing voluntary movement. The Medical Research Council Grading is used to grade muscle function:

Grade 0: Complete paralysis
Grade 1: Flicker of contraction
Grade 2: Muscle contracts, but cannot overcome gravity
Grade 3: Muscle contraction against force of gravity only
Grade 4: Some degree of weakness can be overcome with resistance
Grade 5: Normal power

The assessment of motor power in an unconscious or unco-operative patient is done by observing the characteristics and strength of response to painful stimuli. The painful stimulus used is pressure applied with the thumb in the supraorbital groove thereby pressing on the supraorbital nerve. The responses of the two sides are compared.

Mass effect on one side produces pupillary dilatation on the same side with hemiplegia of the opposite side.[2,15] This is the usual situation and is due to the involvement of the III nerve, and the pyramidal tracts in the cerebral peduncle. There are exceptions to this axiom and the dilated and non-reactive pupil may be associated with ipsilateral hemiplegia due to the indentation of the contralateral cerebral peduncle by the edge of the tentorium cerebelli (Kernohan's notch). The "decorticate posture" indicates severe supratentorial damage. This is represented by patients in abnormal flexion with adduction and internal rotation of the shoulders, slow flexion of elbow, wrist and fingers with flexion or extension of the lower limbs. The "decerebrate posture" indicates a lesion in the midbrain between the superior and the inferior colliculi. There is extensor motor response with the head extended backwards and extension of all limbs and internal rotation of the arms and opisthotonus position.

Deep tendon and superficial reflexes should be examined. The common tendon reflexes include biceps, supinator, triceps, knee and ankle jerks. The abnormal reflexes may be exaggerated, diminished or absent. The superficial reflexes include the plantar reflex and the superficial abdominal reflex. Patients with corticospinal tract involvement have an extensor plantar response. In patients with suspected spinal cord injury, anal wink and bulbocavernous reflexes are also checked. The tests for co-ordination, involuntary movements and gait should be included as a part of the examination whenever feasible. They may also give an important insight to the prognosis of head-injured patients.

SENSORY AND LOCAL EXAMINATION

The sensory examination should include tests for pain, touch, temperature, vibration and sense of position.

This part of the examination should not be neglected. The local examination should include looking for any external swelling, laceration or avulsion. It should be detailed and comprehensive as well, looking for the sites of fractures and scalp haematomas. A simple depressed fracture can often be seen and palpated, except when covered by a scalp haematoma. Local deformity and tenderness should be sought. The examination of the neck for tenderness and stiffness should be performed as a routine and there should be a high index of suspicion of an associated cervical injury in all cases of head injury.

BRAIN DEATH

The crucial point in determining brain death is the cessation of all brainstem functions. The aim of neurological examination is to prove death of the whole brainstem and to detect any evidence of persisting function. The causes of brainstem death can be either related to primary damage of the brainstem itself or secondary damage resulting from increased intracranial pressure with compromised blood supply.[1,12] A better understanding of brainstem death has clearly increased the number of patients in whom mechanical ventilation has electively been stopped, avoiding both an excessively long and tragic waiting period for the family and the enormous costs of intensive care. The concept of brain death became a legal issue and, in India, it was defined in 1995 in "The Transplantation of Human Organ Act, 1995". There are various criteria used differently all around the world to define brain death. Each brain dead patient is a potential donor for organs and all neurosurgeons must be well aware of the rules, regulations and the essential criteria required for such a diagnosis.

SUMMARY

Head injury is a significant public health problem today. It is a dynamic phenomenon and the initial assessment of a head-injured patient is highly dependant on a thorough clinical assessment. Despite a few drawbacks, the GCS has widely been accepted as an index of evaluation of these patients. The scheme of examination follows a strict protocol and has to be tailored according to the neurological status of the patient. Following systematic guidelines helps in examining unconscious and uncooperative patients and a wealth of information can be derived. Most of the cranial nerves can also be and should be assessed in these patients. A comprehensive sensorimotor examination follows assessment of cranial nerves. Detailed neurological evaluation helps in prognosticating and prioritising the treatment and helps in deciding further investigations. Better management can be accorded in case such a schema is followed.

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34 Fluid and Electrolyte Balance in Head Injury

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INTRODUCTION

In the setting of head injury, the incidence of significant fluid and electrolyte imbalance increases with the severity of injury. Though it is very rare in minor head injury (1–2%) and infrequent in moderate head injury (5–8%), it is very frequent in severely head injured patients (8–25%). Principally, polytrauma patients with severe head injury, especially central neuraxis damage and hypothalamic insult, usually develop fluid and electrolyte disturbances. Fluid and electrolyte imbalances have major implications for the management of these patients as the severity of the disturbance also increases proportionally to the severity of head injury. Minor fluid and electrolyte disturbances are self correctable, moderate disturbances get corrected with routine therapy, whereas the management of severe disturbances may be extremely challenging even in neuro-intensive care units (NICUs). Interestingly, unresponsiveness to treatment also increases with the severity of injury. Before one gets entangled in the vicious circle of intractability and clinical irreversibility, appropriate steps in the management may help in salvaging the patient.

Currently, the overall outcome of primary brain injuries is improving with the use of a structured management plan including active resuscitative measures (ABCDE), use of GCS for initial and subsequent clinical evaluations, controlled ventilation, computerised tomography (CT) scan to study the intracranial status on a periodic basis, emergency neurosurgical intervention, NICU and intracranial pressure (ICP) and cerebral perfusion pressure (CPP) monitoring for physiologic management. Prevention of secondary brain damage is one of the main goals of modern management. Therefore, the management of arterial blood gases, coagulation profile and fluid and electrolyte balance are of paramount importance in these patients to prevent secondary brain injuries, intrahospital morbidity and mortality. Clinical manifestations of fluid and electrolyte disturbances may resemble those due to raised ICP with or without a space occupying lesion such as an intracranial haematoma/contusion. Therefore, periodic CT brain scans and laboratory investigations are utilised to ascertain the appropriate cause and to sort out its management.

GENERAL CONSIDERATIONS

Head Injury Patients

In head injury patients, maintenance of precise fluid balance is of paramount importance in preventing hypovolaemia, electrolyte imbalance and intravascular coagulation. Inadequate fluid therapy results in hypotension and underperfusion of the vital organs, whereas excessive fluid therapy results in cerebral, pulmonary and peripheral oedema. The body's mechanisms are usually adequate for correction/compensation of fluid imbalance of minor and moderate severity, but in the severely or critically ill patients, the mechanisms are usually compromised. These latter cases need intensive care management.

Normal Homeostatic Mechanisms

Normal homeostatic mechanisms maintain intracellular fluid (ICF) and extracellular fluid (ECF) volume, tonicity and composition in healthy individuals (Table 1). However, in patients with acute head injury, alterations in fluid volume, tonicity and composition occur due to an emergent neuroendocrine surge [antidiuretic

Table 1: Composition of ECF and ICF compartments (mmol/l)

Sr. No. Cations	*Ions*	*ECF (plasma)*	*ECF (ISS)*	*ICF*
1.	Na^+	135–145	135–140	5–10
2.	K^+	4.5–5.5	4.5–5.5	156–160
3.	Others	2–3	2–3	14
Anions				
1.	Cl^-	101–105	115–120	3–4
2.	HCO_3^-	26–28	26–28	10
3.	PO_4^- & Others (non-diffusible)	1	1	106
4.	Protein (non-diffusible)	15–17	0	64–66
	Total	292	302	368

hormone (ADH) to retain water, Renin-Angiotensinogen II-Aldosterone to retain sodium, and catecholamines to support the vascular system], which is mainly aimed at maintaining an effective intravascular volume for adequate cerebral blood flow at the expense of ICF and ECF fluid tonicity and composition [Na^+, K^+, HCO_3^- and H^+].[1,5,28,29] Disturbances of ICF/ECF tonicity and composition are often associated with a worsening neurological status. Excessive capillary leakage in the brain is well recognised as a cause of acute cerebral swelling and its association with high morbidity and mortality. Inappropriate fluid therapy is, therefore, potentially harmful in such patients with acute cerebral trauma. The maintenance of a stable ionic concentration in the body fluids is necessary for normal cellular functions and metabolism.[43,45] Many of the potentially serious complications due to improper fluid and electrolyte therapy are largely preventable and, therefore, should be recognised early in the clinical course and treated in time.

BASIC PHYSIOPATHOLOGICAL FACTS

Fluid and electrolyte imbalance in patients with severe head injury more often present with a diagnostic dilemma and, therefore, precise diagnosis is established by periodic laboratory investigations and neuroimaging studies.

Water Distribution in the Body

A 70 kg person has 42 litres of body water; 28 litres (66%) in the intracellular space (ICF) and 14 litres in the extracellular space (ECF): 10.5 litres in interstitial space and 3.5 litres in plasma. Water is obtained from the diet (1.5–2.1 litres/day) and oxidative metabolism (400 ml/day) and is lost (2–2.5 litres/day) through the kidneys (sensible loss of 1.5 litres/day), lungs, gut and skin (sum total insensible loss of 1 litre/day). Its distribution in ICF and ECF is determined by the osmolalities of these compartments. Osmolality is the sum of the total solute particles in the solution and is expressed as the molal concentration of all solutes in water (mOsm/kg). The normal serum osmolality ranges from 280 mOsm/kg to 295 mOsm/kg. Normally, ICF and ECF are isotonic. Any change in osmolality of a compartment results in the net to and fro movement of water between the ECF and the ICF to restore isotonicity. The minimum volume of urine necessary for normal excretion of metabolic waste products is about 500 ml/day (20 ml/hr), and minimum daily dietary water intake is about 1100 ml.

Free-water deficit = (0.6 × body weight in kgs) × current serum sodium/1.40–1.

Sodium Distribution in the Body

The majority of exchangeable sodium is extracellular: the normal ECF sodium concentration is 135–145 mmol/l while that of the ICF is only 4–10 mmol/l. Most cell membranes are permeable to sodium and the gradient is maintained by active pumping of sodium from ICF to ECF by Na^+/K^+-ATPase pump. The normal daily intake of sodium is about 100–200 mmols, but the daily obligatory loss is less than 10 mmols. Sodium balance is maintained by regulation of its renal excretion; 70% of glomerular filtrate is absorbed in the proximal convoluted tubules, 25% in the loop of Henle and nearly 5% in the distal convoluted tubules and collecting ducts (Renin-Angiotensinogen II-Aldosterone mechanism).[1,5,28,29,43]

Na^+ requirement is usually calculated by the following equation:

0.6 × body weight × serum Na^+ deficit = mmol of sodium × 0.05 = gm of salt required.

1 gm of NaCl gives 44 mmol of Na^+.

Na^+ deficit in mmols × 2 = ml of 3% saline.

1 ml of 3% saline provides 0.5 mmol of Na^+.

Osmolarity of the ECF

The osmolarity of the ECF is normally maintained in the range 280–295 mmol/l of water. Increase in ECF osmolarity in comparison to ICF osmolarity causes three main effects:[4,28,29,43,45]

i. Stimulation of the hypothalamic thirst centre promoting dietary water intake.
ii. Movement of water from ICF to ECF in order to maintain isotonicity, and
iii. Stimulation of hypothalamic osmoreceptors causing the release of ADH for effective renal water reabsorption and minimising urinary water output and, therefore, resulting in a concentrated (low water-high solute) urine.

Osmoreceptors

Osmoreceptors are highly sensitive to the increased ECF osmolarity even by 1% more than the ICF osmolarity and, therefore, stimulation of these osmoreceptors results in immediate release of ADH in the circulation.[4,12,23,29,43,45] They are located outside the blood-brain barrier in the anteroventral region of the third ventricle of the hypothalamus. If the ECF osmolarity falls, then there is no sensation of thirst; ADH secretion is inhibited (and a dilute urine is produced) allowing increase in renal water loss to restore ECF osmolarity (by raising it) to a normal level. If an increase in ECF osmolarity occurs as a result of a solute, such as urea, which readily diffuses across cell membranes, the ICF osmolarity is also increased. In such cases, the ECF and the ICF remain isotonic and, therefore, osmoreceptors are not stimulated.

Hypovolaemia

Significant hypovolaemia (10%) is a powerful stimulus (via angiotensinogen, arterial and venous baroreceptors and volume receptors) to ADH release to restore effective ECF volume even though there is a decrease in osmolarity.[4,8,12,23,29,43,45] Maintenance of volume takes precedence over the maintenance of serum osmolarity. ADH is synthesised in the supraoptic nuclei of the

hypothalamus and passes down the nerve axons into the posterior pituitary from where it is released into the circulation.[1,28,29,43]

Antidiuretic Hormone

Antidiuretic hormone is essential for life as it maintains serum osmolarity by enhancing renal water reabsorption as it increases the permeability of the renal collecting tubules to water in response to increase in ECF osmolarity (above 285 mmol/kg). However, if ECF osmolarity is below 285 mmol/kg ADH secretion is strongly inhibited.[15,28,29,31,35,43]

Mechanism of action of ADH on renal tubules is interesting[27,31] ADH attaches to a specific vasopressin receptor on the contraluminal side of the renal medullary tubular cell. This attachment activates renal (medullary tubular) cellular adenyl cyclase. The latter stimulates production of cyclic AMP. Abundant cellular cyclic AMP then activates a protein kinase on the luminal side of the cell causing phosphorylation of membrane protein leading to an increased permeability of the tubular cell to water, facilitating its transport into the renal medullary circulation and then back into the general circulation. Steroid replacement therapy lowers plasma ADH to normal and inhibits the secretory activity of the supraoptic neurons, and therefore has some role in the syndrome of inappropriate ADH (SIADH) secretion.

ADH plays a vital role in the control of the tonicity of the ECF[8,12,15,23,27,31,35] and indirectly of the ICF and, therefore, overall control of water balance in the body. Excessive ADH secretion results in dilutional hyponatraemia (SIADH) with a risk of water intoxication while decreased ADH secretion results in excessive renal water loss (diabetes insipidus—DI) causing hypernatraemia with a risk of severe dehydration (Table 2).

In the setting of head injury: Minor head injury patients rarely, moderate head injury patients infrequently and severe head injury patients very frequently develop fluid and electrolyte disturbances. In general, patients with brain damage with preservation of the hypothalamo-pituitary axis develop SIADH, whereas DI is due to hypothalamo-pituitary axis disturbance/damage.[1,4,11,22,28,29,43,45] Damage to the posterior pituitary gland may also cause temporary failure of ADH secretion/release.

In head injury patients, ADH is released in response to the clinical status (raised ECF osmolarity, raised ICP, hypovolaemia, nociceptive stimuli, emotional stress), drug therapy (barbiturates, morphine, carbamazepine, chlorpropamide, angiotensin, thyroxin, glucocorticoids, cholinergic and beta-adrenergic stimulations) and mechanical ventilation (positive airway pressure), whereas ADH is suppressed by phenytoin, ethanol, anticholinergics, atropine, alpha adrenergic stimulation, reserpine, chlorpromazine, besides increased plasma volume (hypervolaemia) and reduced plasma osmolarity.[8,12,23,28,29,31,43] Steroid replacement therapy lowers plasma ADH to normal and permits the normal diuretic response to hydration by inhibiting the secretory activity of the supraoptic neurons (a weak response).[28,29,43] Antinatriuretics (catecholamines, Renin-AngiotensinogenII-Aldosterone, cortisol) help in volume restitution or expansion following trauma.

Atrial Natriuretic Peptide (ANP) and Brain Natriuretic Peptide (BNP)

Brain natriuretic peptide (largely of cardiac ventricular origin) has biological effects on the control of blood volume, blood pressure and electrolyte composition. ANP/BNP induce natriuresis through direct tubular effects or by inhibition of the Rennin-Angiotensinogen II-Aldosterone mechanism.[2,22,42]

Hypervolaemia is also kept under check as there is no appreciable ADH secretion in such circumstances and the excess of water is therefore lost from the kidneys. It is routinely measured by central venous pressure monitoring. Moreover, natriuretic peptide hormone (ANP, a 28-amino acid peptide) is produced by the cardiac atria when hypervolaemia exerts excessive stretch on the sensitive atrial stretch receptors. It antagonises the Renin-AngiotensinogenII-Aldosterone mechanism which leads to natriuresis and hypovolaemia.[14,25,42]

Table 2: Clinical manifestations of Na^+ imbalance

Sr. No.	*Organic systems/ clinical state*	*Hyponatraemia*	*Hypernatraemia*
1.	Neurological	Cerebral oedema, disorientation, lethargy, apathy, impairment of consciousness, seizures, coma, Cheyne-Stokes respiration, hypothermia	Cerebral dehydration, restlessness, irritability, disorientation, ataxia, seizures, coma, intracranial haemorrhage
2.	Muscular	Cramps, hypotonic weakness, depressed reflexes, rhabdomyolysis.	Increased muscle tone, hyperreflexia
3.	Renal	Oliguria, concentrated urine or hypertonic urine	Polyuria, diluted urine or hypotonic urine
4.	Gastrointestinal	Loss of appetite, nausea, vomiting	Thirst

Serum Osmolality and Osmolarity

In clinical practise, serum osmolality and osmolarity are routinely measured using the following equations:

Osmolality (mOsm/kg) = 2 x [Na^+] + Glucose/18 + BUN/2.8.

Osmolality is a measure of solute concentrate per kilogram of solvent.

Osmolarity (mmol/l) = 2 x [Na^+] + [urea] + [Glucose]

Osmolarity is a measure of solute concentrate per litre of solution.[29]

ECF osmolarity, ICF osmolarity and the difference between these two are powerful stimuli for osmoreceptors to modulate ADH secretion for the maintenance of effective intravascular volume. In clinical practise, the difference between osmolality and osmolarity is negligible (Table 3).

In head injury patients, abnormalities of serum sodium (<125 or >150 mEq/l or <150 or >300 mmol/l) and serum osmolality (<260 or >320 mOsm/kg) should be avoided. Over hydration *per se* will not cause brain oedema if the serum sodium value is normal (135–145 mEq/l); however, it can cause brain oedema at brain injury sites only when it is combined with hyponatraemia (<130 mEq/l) because ECF water shifts to the ICF compartment in an attempt to maintain ECF/ICF isotonicity.

Loss of Fluid and Electrolytes

Loss of fluid and electrolytes without protein loss will raise the haematocrit and plasma protein concentration.[1,5,8,15,23,28,29,31,35,43,45] These two parameters provide a good guide to ECF losses. For example, an initial value of albumin (Pr1), if later, rose to Pr2 following loss of fluid (dehydration) then the percentage fall in ECF volume can be calculated as follows:

% fall in ECF volume = [1 - Pr1/Pr2] 100.

A fall in plasma volume can be more precisely calculated with the initial (Hct1) and subsequent (Hct2) haematocrit readings:

% fall in plasma volume = 100 [1-(Hct1/100-Hct2 x 100-Hct2/Hct2)] = [1-Hct1/Hct2] 100.

Haematocrit and plasma protein (albumin) are therefore more useful in the assessment of plasma volume and ECF fluid losses as compared to the Na^+ measurements where, although the Na^+ is being lost, it does not change in its serum concentration or in cerebral salt wasting syndrome (CSWS).[1,25,27]

By invasive haemodynamic monitoring, a low pulmonary capillary wedge pressure (<18 mmHg) or low CVP (<6 mmHg) implies volume depletion. Clinical evidence of dehydration, weight loss, orthostatic hypotension, CVP <6 mmHg and negative water balance are noted in CSWS. Moreover, elevation of haematocrit, the serum creatinine and serum protein concentration point to dehydration in CSWS. Increased natriuresis and elevated serum K^+ also suggest CSWS.[2,7,11,22,42]

Isotope-dilution techniques show features suggestive of CSWS, such as a decreased plasma volume (<35 ml/kg) and a decreased total blood volume (<60 ml/kg).

In the water loading test, increased free-water reabsorption in the renal tubules suggests increased ADH secretion.[2,27,38] Appropriate or inappropriate ADH secretion can be differentiated from one another by examining the urine volume, creatinine clearance, osmotic clearance and fractional water excretion.[2] If the overall clinicopathological results suggest dehydration, then increased free-water reabsorption in the renal tubules points to appropriate ADH secretion. On the other hand, increased free-water reabsorption in the absence of dehydration suggests inappropriate ADH secretion as in SIADH. Normal or reduced free-water reabsorption in the presence of dehydration (reduced creatinine clearance, polyuria and high fractional or osmotic diuresis) and inappropriate natriuresis (sodium excretion of >0.001 mmol/hour, which is inappropriate in the presence of severe hyponatraemia) are central features of CSWS. Disproportionate fractional water clearance relative to the free-water clearance suggests an osmotic

Table 3: Characteristics of parentral fluid therapy

Sr. No.	*Name*	*Concentration*	*Na^+*	*Cl^-*	*K^+*	*HCO_3^-*	*Ca_2^+*	*Calculated mmol/l*
1.	Normal saline	NaCl 0.9%	150	150	–	–	–	300
2.	Hartman's solution (Ringer Lactate)	Saline + K^+ + HCO_3^-	131	111	5	29	–	280
3.	5% Glucose	5% dextrose	–	–	–	–	–	280
4.	Dextrose saline	4% glucose, 0.18% saline	30	30	–	–	–	286
5.	Half normal saline	NaCl 0.45%	75	75	–	–	–	150
6.	Human plasma protein fraction	HPPF mol. wt 69000	150	150	5	–	2	314 or more
7.	Haemaccel polygeline	Degraded gelatin mol. wt. 24,500	145	145	5	–	6.25	310 or more
8.	Succinylated gelatin	Gelofusin mol. wt. 22,600	154	154	0.4	–	0.4	310
9.	Hetastarch	Hydroxyethyl starch 6% in saline mol. wt. 70,000	154	154	–	–	–	310 or more
10.	Blood	Whole blood constituents	140	102	4	26	2.4	285

Table 4: Clinical characteristics of common causes of Na^+ imbalance in head injuries

Sr. No.	*Clinical features*	*Hyponatraemia-SIADH*	*Hyponatraemia-CSWS*	*Hypernatraemia solute diuresis*	*Hypenatraemia DI*
1.	Intravascular volume	Hypervolaemia	Hypovolaemia	Hypervolaemia	Hypovolaemia
2.	Dehydration features	Absent	Present	Absent	Present
3.	Body weight	Increased	Decreased	Increased	Decreased
4.	CVP	Increased	Decreased	Increased	Decreased
5.	Haematology:				
	i. PCWP	Decreased	Increased or normal	Variable	Increased
	ii. Haematocrit	Decreased	Increased	Decreased	Increased
6.	Biochemical parameters:				
	i. S. osmolarity	Decreased	Incr./ normal	Increased	Increased
	ii. S. protein conc.	Decr./normal	Increased	Variable	Increased
	iii. BUN/Creatinine	Decreased	Incr./normal	Variable	Incr./normal
	iv. S. uric acid	Decreased	Normal	Decr./normal	Normal
	v. S. Na^+	Decreased	Decreased	Increased	Increased
	vi. Urine Na^+	Incr./normal	Increased	Increased	Decreased
	vii. Urine osmolarity	Increased	Increased	Increased	Decreased
7.	Management	Fluid restriction, salt replacement, loop diuretics, phenytoin, demeclocycline, lithium, fludrocortisone, haemodialysis	Fluid replacement with isotonic fluid therapy, blood transfusions. Fludrocortisone	Fluid replacement with hypotonic fluid, treatment of cause	Fluid replacement with hypotonic fluids, vasopressin, chlorpropamide clofibrate, thiazide diuretics, carbamazepine, steroids haemofiltration

diuresis. In DI, there is disproportionate free-water clearance.[2,7,11,15,18,31,32,35,37]

It is essential that appropriate fluid and electrolyte studies be done early in the course of management of the head-injured patient. Therapy is directed primarily towards the underlying cause of the fluid and electrolyte abnormality. In the potentially salvageable patients, optimal correction may occur spontaneously or may require cautious use of medical therapy to achieve a good outcome (Table 4).

MAIN CLINICOPATHOLOGICAL CATEGORIES

There are two main types of clinicopathological categories:

I. Hyponatraemia
II. Hypernatraemia

HYPONATRAEMIA

Maintenance of Volume in Hyponatraemic States

Hyponatraemia (a low serum sodium concentration) is a common finding in the intensive care unit due to disturbance of the hypothalamo-hypophysial axis, a metabolic response to trauma or a sick cell syndrome requiring principally management of the underlying cause.[1,5,6,11,17,18,22,27-29,32,35,43,45] It is commonly due to water excess than to sodium loss. The severity of hyponatraemia is divided into three categories: mild (Na^+ <135 to 125 mEq/l); moderate (Na^+ 120–124 mEq/l) and severe (Na^+ <120 mEq/l).

Aetiopathogenesis

The risk of developing significant hyponatraemia increases in cases of moderate and severe head injuries, fracture base of skull and subdural haematoma.[6,17,35,38]

Following acute injury, the body retains water and sodium as a consequence of an acute neuroendocrine surge in an attempt to maintain an effective extracellular volume and thereby intravascular volume. The water content of ECF increases as compared to its solute concentration, which results in dilutional hyponatraemia. Hyponatraemia lowers the seizure threshold, exacerbates cerebral oedema and causes impairment of the level of consciousness.[29,35,37] However, the degree of cerebral disturbances usually depends upon the rapidity of the development of hyponatraemia; a serum sodium level of 115 mmol/l may be asymptomatic if it develops slowly over a long period of time, whereas a rapidly developing serum sodium level of 120–130 mmol/l may have severe neurological consequences.

In the setting of hypervolaemia with hyponatraemia, initially the brain cells (e.g. glia and neurons) swell due to the increase in cellular volume following the movement of ECF water to the ICF compartment. The water movement from ECF to ICF compartment results due to the low ECF osmolarity as compared to the ICF osmolarity. Later, a gradually adaptive but down regulatory volume reduction is achieved mainly by the loss of intracellular ions, such as K^+, Cl^-, taurine, phosphocreatine and amino acids including excitatory neurotransmitters (e.g. glutamine and glutamate). This consequently causes neurologic impairment.[1,5,28,29,43,45] Hyponatraemia ultimately leads to cerebral oedema and raised ICP with deleterious consequences.

Water retention (not natriuresis) is a marked feature of ADH excess, whereas natriuresis (not water retention) is a prominent feature of ANP excess. Clinically, the intravascular volume expansion due to ADH excess is an important feature of SIADH. The intravascular volume depletion with natriuresis due to ANP and BNP excess

is a marked feature of CSWS. Interestingly, ANP can suppress ADH secretion while ADH may itself stimulate ANP secretion.

In SIADH, water retention (hyponatraemic hypervolaemia) inhibits aldosterone secretion and, therefore, relative natriuresis continues. CSWS causes high natriuresis due to high ANP/BNP and low aldosterone activity.[2,7,13,17,18,21,22,27,32,34,35,38,42]

Differential Diagnosis

Various hyponatraemic syndromes in head-injured patients may be differentiated primarily on clinical and laboratory grounds.[1,4,6,11,15-17,27-29,35,37,43,45] Sodium depletion is seldom due to inadequate input (nutritional restriction), but more often due to excessive renal loss of sodium (CSWS due to high ANP levels, or urinary sodium loss in diuretic therapy). The clinical features of sodium depletion are primarily as a result of decreased ECF volume. The plasma sodium will be normal if fluid is lost isotonically as in traumatic haemorrhage/bleeding, and increased if it is lost hypotonically (excessive sweating in hyperpyrexia, mechanical ventilation or gastrointestinal hyperkinesia). Thus, the plasma sodium concentration in various clinical conditions of sodium depletion may be variable (low, normal or high). Sodium loss never occurs alone but is always accompanied by some loss of water. The fluid lost may be isotonic or hypotonic with respect to the plasma.

Hyperosmotic Hyponatraemia

Head injury patients with hyperglycaemia, uraemia and prolonged mannitol therapy are more prone to develop hyponatraemia. When plasma solute concentrations (e.g. glucose, mannitol, urea, etc.) are increased, a shift of water from the ICF to the ECF causes cellular dehydration and intravascular volume expansion with dilutional hyponatraemia. Because of water shift from ICF to ECF, it is also called translocational hyponatraemia. In addition, increased serum osmolarity causes direct stimulation of osmoreceptors and ADH release. This leads to renal water retention and further worsens the dilutional hyponatraemia. Moreover, such an increase in ECF volume inhibits volume receptors, thereby decreasing aldosterone secretion. This, in turn, leads to renal loss of sodium (natriuresis). Mannitol is an osmotic diuretic which increases ECF volume and reduces ICF volume to treat cerebral oedema. Following mannitol infusion in high dose with low renal output, hyponatraemia may occur via the aforementioned mechanisms and may lead to pulmonary oedema due to rapid volume expansion, metabolic acidosis and hyperkalaemia. In hyperglycaemic hyponatraemia with high renal output, patients may have gastrointestinal symptoms such as dryness of mouth, nausea, vomiting and abdominal pains besides dry skin and low jugular venous pressure. Intensive management of hyperglycaemia is therefore of paramount importance in such clinical settings.

Isosmotic Hyponatraemia

Pseudohyponatraemia may result due to decreased fractional water content of the plasma in cases of hyperproteinaemia (two times the normal values) and hyperlipidaemia. An increase in positively charged paraproteins or a decrease in negatively charged albumin concentrations in plasma can displace Na^+ from the plasma or ECF to the ICF compartment causing hyponatraemia. Fractitious hyponatraemia with normal serum osmolality therefore requires special attention to correct the conditions responsible.

Hypotonic fluid therapy with dextrose saline, half strength saline or 5% dextrose in head injury patients may result in isosmotic dilutional hyponatraemia, which may in turn cause cerebral oedema. These patients may develop nausea, disorientation, confusion, convulsions and gastrointestinal disturbances. These solutions are better avoided; however, if needed, they should be used judiciously in head trauma patients.

Hyposmotic Hyponatraemia

Excessive water intake and/or water retention are responsible for hyposmotic (dilutional) hyponatraemia. This condition must be assessed and treated differently in different clinical settings.

In low dietary intake, depletion of both ICF and ECF solutes can lead to hyponatraemia. In true sodium depletion due to nutritional neglect, hyponatraemia is accompanied by evidence of a contracted blood volume (low blood pressure, decreased skin turgor and elevated haematocrit). Here correction is achieved slowly with careful dietary manipulations.

In dilutional hyponatraemia due to excessive hypotonic fluid infusion, peripheral oedema is a prominent feature and, in addition, there may be evidence of cerebral oedema, congestive heart failure or hepatic disease. Urinary sodium concentration will be less than 10 mmol/l in both the aforementioned conditions: chronic dietary salt depletion and dilutional hyponatraemia due to excessive hypotonic fluid therapy using dextrose saline, half strength saline or 5% dextrose.

The persistence of dilutional hyponatraemia implies either SIADH or renal impairment (acute tubular necrosis). Dilutional hyponatraemia with low serum proteins and low serum urea indicates SIADH. In normal subjects, osmolarity of the maximally dilute urine is about 50 mmols/l. In SIADH, osmolarity of urine is more than 50 mmols/l, and peripheral oedema is not a prominent feature, whereas dilutional hyponatraemia with a dilute urine with peripheral oedema indicates renal impairment. Hyponatraemia is common after infusion of hypotonic fluids (5% dextrose or dextrose saline), when the ability of the body to excrete water is depressed.

Common Hyponatraemic States in Head Injury Patients

Initially, CSWS was recognised in the early 1950s and later, the syndrome of inappropriate (excess) antidiuretic

hormone (SIADH) in 1957 by Schwartz.[10,24,36,43] The majority of head injury patients with hyponatraemia present with SIADH or CSWS. In a few cases, both conditions may coexist. CSWS and SIADH are characterised by hyponatraemia, hyperosmolar urine and hypernatriuresis in patients with normal renal, suprarenal and thyroid functions. The major distinction between these two conditions is the volume status of the patient. In CSWS, the ECF volume is contracted and the patient appears dehydrated; whereas in SIADH, the ECF volume is expanded and a clinical picture of fluid overload is often seen. Patients with CSWS respond to fluid and sodium administration while those with SIADH respond to fluid restriction. In neurosurgical patients, CSWS is more common than SIADH.

Syndrome of Inappropriate ADH Secretion

Syndrome of inappropriate ADH (SIADH) secretion[5,11,15,27,32,35,36] usually begins in the first or second week following head injury and with appropriate therapy lasts no more than one to two weeks. In SIADH, there is a continuous secretion of ADH even in the presence of conditions such as hyponatraemia, hypo-osmolar serum and hypervolaemia which normally inhibits ADH secretion.

The typical clinical features of SIADH are hyponatraemia, with concomitant hypervolaemic hyposmolar ECF, relative hypernatriuresis with hyperosmolar urine and absence of clinical evidence of volume depletion (normal skin turgor and blood pressure). The clinical symptoms include anorexia, nausea, vomiting, irritability, personality changes and neurological manifestations including seizures (bulbar or pseudobulbar palsy, stupor, muscular weakness, loss of reflexes, positive Babinski sign and convulsions).

Cerebral Salt Wasting Syndrome

Cerebral salt wasting syndrome (CSWS)[2,5,10,14,21,22,24,38,42,43] is due to an inappropriate/unregulated release of atrial natriuretic peptide. It presents with hyponatraemia, hypovolaemic hypo-osmolar ECF, hypernatriuresis with hyperosmolar urine and volume depletion (contracted intravascular volume). Persistence of high salt loss in the urine despite fluid restriction differentiates this condition from SIADH where salt loss depends on a liberal fluid intake. The estimation of intravascular volume (by CVP) and urinary sodium usually differentiates salt retaining state (SIADH) from salt losing state (CSWS). Initially, Peters et al.[24] and Cort[10] described CSWS as a condition with hyponatraemia with natriuresis and believed that the CNS normally influences the ability of the kidneys to reabsorb sodium in the proximal tubule and that a defect in this regulatory function can lead to natriuresis. Many workers have reported a reduction in the red cell mass in patients with CSWS. Vingerhoets and de Tribolet[41] distinguished between two clinical syndromes of hyponatraemia and natriuresis, which differed in the interval between the neurological insult and the emergence of hyponatraemia: the acute syndrome (<3 days) and the delayed syndrome (>1 week). They found elevated serum ADH levels in patients with the acute syndrome and depressed or normal levels in the chronic syndrome. SIADH is commonly seen in the acute and CSWS in the chronic syndrome.

The main diagnostic criteria of SIADH and CSWS are outlined in Table 4.

Management[2,5,12,19,20,27,33,35,41]

Hyponatraemia is basically treated according to the underlying disease process, serum osmolarity/osmolality and clinical estimates of total body sodium. The cornerstone of therapy in SIADH is fluid restriction, whereas in CSWS volume replacement and correction of the haematocrit.

SIADH[19,20,33,41]

Patients with SIADH are basically treated with fluid restriction usually below one litre/day until serum Na^+ returns to normal levels with some salt supplement or replacements. The free-water restriction should be sufficient to decrease total body water by 0.5–1.0 litre/day. The resultant reduction in glomerular filtration rate enhances proximal tubular absorption of salt and water as well as stimulates aldosterone secretion.

Mild cases (Na^+ >125 mEq/l) are best treated with fluid restriction, whereas moderate cases (Na^+ <125 mEq/l to 120 mEq/l) with water restriction to 600–800 ml 5% dextrose in 0.45% saline per 24 hours, with or without normal saline; diuresis usually occurs in 36–48 hours. Patients with severe hyponatraemia (Na^+ <120 mEq/l) or in coma or with seizures may require hypertonic saline, with furosemide; 20–40 mg.[14] Diuretic therapy is used with utmost caution and monitoring to promote water loss. When hypertonic saline therapy is considered, it should be given only to restore Na^+ concentration to levels that no longer represent a hazardous state. The endpoint of hypertonic saline therapy is generally a serum Na^+ level of 120 mEq/l or absence of overt symptoms. Initially, plasma Na+ may be increased by 1–2 mEq/l/hr. Care should be taken to avoid hypernatraemia by cautious correction so that the plasma Na^+ should not be increased more than 12 mEq/l in 24 hours or 25 mEq/l in 48 hours, or to a concentration greater than 130 mEq/l.[2,9,29] Demeclocycline (anti-ADH synthetic hormone) antagonises the action of ADH on the renal collecting ducts and, therefore, may be used (600–1200 mg/day) to induce nephrogenic resistance to ADH.[2,20] Phenytoin is used as an antiepileptic drug with an added benefit as an anti-ADH agent.[19] Fluorocortisone (0.3–3 mg/day) is mainly used to inhibit action of ADH on the aldosterone mechanism, and to help in raising serum Na^+ levels.[26]

Cerebral Salt Wasting Syndrome[2,3,5,10,21,24,25,27,36,42,45]

The principles of managing hyponatraemia associated with CSWS consist of the treatment of an underlying cause, restriction of intravascular volume, isotonic fluid (e.g. normal saline, plasma and blood) infusion and fludrocortisone.[2,3,11,22,26,27,35,40,44] These measures are effective without jeopardising ICP control in most cases. CSWS is best managed with salt containing fluid orally, enterally or intravenously to maintain CVP around 10–12 mmHg. The patient's haemoglobin and haematocrit levels are measured daily and, if needed, packed cells with isotonic fluid or whole blood are given as per requirements.

Rapid correction of chronic hyponatraemia[9,12,27,35,40] using hypertonic saline has been associated with fatal central pontine and extrapontine myelinolysis; on the other hand, severe acute hyponatraemia can cause fatal cerebral oedema (tentorial herniation) and status epilepticus. Despite such concerns, the management of hyponatraemia with diuretic therapy (furosemide) and supervised saline infusion (isotonic/hypertonic) is safe.

HYPERNATRAEMIA

Common Hypernatraemic States

Clinically significant hypernatraemia (a high serum sodium concentration) is much less frequent in head-injured patients than hyponatraemia. It is either caused by the loss of water or an excess intake of sodium.

Aetiopathogenesis[2,4-6,11,15,17,22,27,30,35,37,39]

In hypernatraemic states, especially in head injured patients, water depletion mainly occurs due to an increased water loss as in DI (lack of ADH), renal DI (ADH insensitivity), mannitol therapy (osmotic diuresis), glycosuria (osmotic diuresis), prolonged hyperpyrexia (increased sweating), hyperventilation (increased insensible loss) and antibiotics related diarrhoea and, less commonly due to reduced intake of dietary water. The neurological causes of hypernatraemia include cerebral trauma, cerebral tumours (craniopharyngioma, pituitary tumours,), vascular disorders (Sheehan's syndrome, SAH-cerebral aneurysm), meningoencephalitis, surgery in the sellar-suprasellar-third ventricular region and an idiopathic variety. Despite the frequent pathological demonstration of pituitary and hypothalamic damage in head injury, the incidence of DI is relatively less common. However, DI is a mortal sign in patients with massive brain injuries and uncontrollable intracranial hypertension.

In clinical practise, excessive water loss without much sodium loss is unusual except in clinical DI. Pure water loss is borne by the total body water and not just the ECF, and therefore signs of a reduced ECF volume are not usually present. Severe water depletion causes cerebral dehydration that stimulates intracellular mechanisms for brain cells to synthesise osmotically active compounds and acute cerebral oedema may then follow rapid fluid replacement with deleterious consequences. Severe water depletion is therefore corrected in a cautious manner by 5% dextrose or hypotonic saline (2/3 deficits in the first 24 hours and 1/3 in next 24 hours).

Differential Diagnosis[5,7,11-13,15,27,30,35,39,42]

Serum hyperosmolarity, polydipsia (thirst leading to increased intake) and polyuria following hypothalamo-hypophysial trauma are the hallmarks of DI.

The differential diagnosis includes other conditions causing polyuria and polydipsia, i.e. renal DI, diabetes mellitus, chronic renal failure, hypercalcaemia, hypokalaemia and psychogenic polydipsia. Simple biochemical tests will easily eliminate many of these possibilities. Solute diuresis in hyperglycaemia, uraemia, osmotic or loop diuretics is diagnostic. Aldosterone deficiency presents with normal or slightly decreased serum sodium with only an occasional change in thirst mechanism. The urine specific gravity remains between 1.009 and 1.035 and urine osmolality between 250 and 320 mOsmol/kg, whereas water diuresis (DI) presents with normal or increased serum sodium levels and intense thirst and polyuria. The urine specific gravity remains between 50 and 150 mOsm/kg, whereas a normal (water deprived) individual will concentrate his urine with urine output of 0.5 ml/min and urine osmolality of greater than 750 mOsm/kg.

In DI, decreased ADH secretion results in uncontrolled renal water loss (dilute urine) with dehydrational hypernatraemia. Renal DI is due to renal insensitivity to ADH despite increased ADH levels in serum and urine, and psychogenic polydipsia-polyuria is due to a compulsive desire to drink. These conditions are differentiated with the help of either water deprivation tests or serum and urine ADH assays. Diabetes mellitus (hyperglycaemia), hypercalcaemia, chronic renal failure and hypokalaemia may also cause polyuria and polydipsia but are easily differentiated from central DI by routine biochemical tests. If it is due to the use of Demeclocycline (anti-ADH agent) then this drug should be discontinued. If random urine osmolality is greater than 750 mOsm/kg, DI is basically excluded.

Diabetes Insipidus[5,7,11-13,22,30,35,39,42]

Diabetes insipidus (DI) is a common condition after craniofacial trauma, skull base fractures and hypothalamo-pituitary injuries. It can be permanent or transient disappearing in a few days to a few weeks. Polytrauma, cerebral hypoxia, cerebral ischemia in haemorrhagic shock, neurosurgery in the suprasellar region, fat embolism, drug overdose, etc. may cause DI. Hypothalamo-hypophyseal injury poses a particular risk of developing transient or permanent DI. It is transient in the majority of patients lasting for 3–5 days; however, in one-fourth to one-third of cases, it may be permanent. Some patients show a triphasic response manifested by early transient DI, followed by

return of normal urinary functions for 1–3 weeks and then relapse leading to permanent DI.

Clinical Manifestations

Clinical manifestations of DI:[12,13,28,29,30,39,43] Polyuria, (>2–3 litres/day), polydipsia, hypernatraemia with hypovolaemia, high serum osmolality (320–330 mOsm/kg), low urine osmolality and a dilute urine (specific gravity less than 1005), and a urine to serum osmolality ratio of less than one, implying a negative water balance are characteristic features of DI.

Diagnostic Tests[1,5,28,29,30,35,39]

Serum and urine ADH assays and/or a water deprivation test are performed. A normal person on water deprivation for 8 hours will have urine output 0.5 ml/mt and will concentrate urine to preserve water. Urine osmolality will rise and become greater than 500 mOsm/kg. Patients with DI fail to concentrate their urine and the water loss continues as dilute urine.

During the water deprivation test, in patients with DI, the urine does not become concentrated and the serum osmolarity rises during the 8-hour test period. However, a normal person will maintain serum osmolarity below 295 mmol/l during this 8-hour period. Serum osmolarity above 285 mmol/l is a strong stimulus for ADH release to maintain serum osmolarity in the normal range by retaining more water. On administration of desmopressin in patients suspected of DI, if the urine becomes concentrated and the serum osmolarity falls then the diagnosis of DI will be confirmed.

Measurement of ADH levels in urine and serum in relation to plasma osmolarity is far more desirable than the water deprivation test in acute head injury patients as the latter may be highly inappropriate in many of these patients. If the ADH assays are not available then a therapeutic trial with desmopressin is highly indicated to resolve the diagnostic dilemma.

Management[1,2,5,7,11,12-14,22,25,30,39,42]

Daily measurements of body weight, fluid intake/output, haemoglobin, haematocrit, renal function tests (e.g. serum creatinine, BUN, electrolytes, etc.), serum sugar, serum osmolarity, urine specific gravity and urine osmolarity are performed.

Treatment of hypernatraemia basically consists of water and electrolyte replacement. Hypernatraemia is corrected slowly because of the risk of neurologic sequelae such as seizures and cerebral oedema. The water deficit is corrected over 24–48 hours and plasma Na^+ is gradually reduced by 1–2 mEq/l/hr.

The aim of the fluid therapy is to replace hourly urine output along with the usual estimate for the insensible loss, with hypotonic fluids. The volume depletion may lead to reduction in the mean systemic arterial pressure and subsequently a reduction in the CPP and, therefore, needs cautious correction.

Regardless of its cause, hypernatraemia should initially be treated by administration of hypotonic fluids such as water (orally) or 5% dextrose (parenterally). Urine output in DI may exceed 10 l/day, although less than this is more usual. Adequate fluid replacement, desmopressin [Desmopressin (1-desamino-D-arginine vasopressin) is a synthetic analogue of ADH] for severe cases and chlorpropamide (oral hypoglycemic agent) 50–200 mg/day or carbamazepine (antiepileptic agent 600 mg/day) for mild cases of DI may be used.

Desmopressin is indicated if urine output exceeds 6–7 l/day, or urinary output remains more than 250 ml/hr for consecutive 2–4 hours or the patient is unable to maintain fluid balance and the normal intravascular volume. Treatment with vasopressin should not be withheld in verified cases of DI. There are many preparations of vasopressin which are highly effective:

- Aqueous vasopressin (5–10 IU IM/IV, 4–6 hourly)
- Vasopressin tannate-in-oil (5 IU IM/daily as initial therapy once in 2–3 days)
- Lysine vasopressin nasal spray (2 IU/spray, 6–8 hourly)
- DDAVP (l-deamino-8-D-arginine vasopressin): 10–20 mg intranasally on OD or BD basis.

Care must be exercised during the active treatment of DI/hypernatraemia to prevent water intoxication (lethargy, confusion, seizures and coma) due to excessive administration of desmopressin, hypoglycaemia due to chlorpropamide therapy, and significant hypovolaemia following diuretic therapy (by further contracting ECF volume). While controlling post-traumatic seizures, carbamazepine stimulates ADH release in patients with DI. In patients with dangerously high serum sodium, the use of one of the methods such as peritoneal dialysis/haemodialysis/haemofiltration is strongly considered to remove excess of serum sodium. The patient does not respond to any treatment in terminal hypernatraemia, which has the worst prognosis. Haemofiltration employs a filter containing a membrane having characteristics similar to those of capillary endothelial cells. Water and smaller molecules (with a molecular weight ≤20,000) can pass freely across the membrane. The filter is connected to arterial and venous lines and the hydrostatic pressure drives a solution similar to the ECF across the cell membrane. Haemofiltration in NICU has advantages over conventional haemodialysis in fine control of fluid and electrolyte balance and removal of water soluble waste products and drugs.

CONCLUSION

A majority of the patients with mild and moderate head injury show no appreciable fluid and electrolyte abnormalities (normovolemic and normonatraemia); however, a subset of moderate and severe head injury patients suffer from fluid and electrolyte disturbances (commonly hyponatraemia and less often hypernatraemia).

The more severe the head injury, the higher the chances of serious fluid and electrolyte disturbances with more chances of unresponsiveness to the treatment. Therefore, recognition of common disturbances such, as hyponatraemia (SIADH and CSWS) and hypernatraemia (DI) is of paramount importance because of their different clinical presentations, disparate nature of appropriate treatment strategies and responsiveness to the protocol-based treatment in the early stages of occurrence.

Higher incidences of fluid and electrolyte disturbances occur especially in patients with injury to larger areas of the cerebral hemispheres, central neuraxis including the brainstem and hypothalamo-hypophyseal system and, therefore, these patients need intensive care. Neurological recovery in responsive patients occurs rapidly if appropriate fluid and electrolyte therapy is instituted in time. To institute appropriate therapy, a proper understanding of the aetiopathological mechanisms, their diagnostic parameters and treatment protocols is necessary. Inappropriate management worsens existing brain injury and results in otherwise avoidable morbidity and mortality with poor overall outcome. Therefore, clinicians must be aware of the fluid and electrolyte disturbances in head injury patients so as to recognise them early enough in time to treat appropriately.

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35 Scalp Injuries

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INTRODUCTION

The skin is the largest organ of the body and the scalp is the thickest component of the skin. The scalp plays its role in generalised functions like protecting the underlying calvarium and the brain, and specialised functions like regulation of body temperature, nourishment of the outer cortex of the skull and defining aesthetic characteristics of the patient's facial image.[18]

The scalp is in a vulnerable, exposed portion of the body and hence is prone to injury. Scalp laceration is the most common head injury requiring operative care.[18] Usually, primary healing occurs with infrequent complications. However, significant therapeutic problems can occur with avulsion, thermal, electrical injuries and post-malignancy and post-radiation defects.

Historical Aspects

3000 BC: Egyptians studied the natural history of extensive scalp injuries.[30]

2180 BC: Skulls dating back to this age have shown changes consistent with post-mortem scalping.

320 BC to 100 BC: Inflicting scalp wounds was a widely prevalent procedure among ancient dynasties as a method of marking slaves, a mode of punishment inflicting chronic suffering and slow death;[18] and war trophies.

17th century AD: Celsus first mentioned trephination of the exposed skull to allow formation of granulation tissue.[18,30,37]

1654: Augustine Belloste first performed 'Celsus' technique.[12,18]

1871: Netilitsky performed the first skin graft to resurface a scalp defect.[12]

1908: Concept of vascularity of pericranium recognised by Robinson.[45]

1911: Davis published a review of his management techniques of scalp trauma.

1918: Harvey Cushing studied over 250 cases of scalp injuries during World War I and established surgical treatment principles.[7]

1924: Mc Williams discussed four types of skin grafting with an improved method of treating total avulsion of the scalp.[37]

1944: Harold Gillies described the use of tubed pedicles, local flaps and the handling of scalp tissue in injuries.[14]

1946: Kazanjian and Webster described methods for reconstruction of extensive scalp loss.[26]

1953: Kazanjian described repair of partial scalp loss.[27]

1960: Jacobson and Suarez described microsurgery in anastomosis of small vessels, (about 1 mm in diameter) with more than 80% patency (13-SS). This has revolutionised the management of scalp avulsion.[21]

1969: Lu reported successful results with direct suturing of the avulsed scalp.[31]

1972: Mc Lean and Buncke performed the first successful covering of scalp with omental free tissue.[36]

1976: Miller reported the first successful replantation of avulsed scalp with microanastomosis.[38]

1982: Alpert et al. described the principles of surgery for scalp avulsion.[1]

1983: Argenta et al. described the use of tissue expansion in reconstructive scalp surgery.[2]

ANATOMY

The scalp extends from the supraorbital ridges anteriorly to the inferior nuchal line posteriorly and to the auriculocephalic angle laterally. Apart from the forehead, the scalp is completely covered with hair in most individuals. The thickness of the scalp varies from 3–8 mm, being thick over the occipital region and thinner over the frontal and temporal areas. The skin is the first layer and is 3–8 mm thick. The septa of the superficial fascia lie in the connective tissue layer. Numerous blood vessels and nerves course through this layer. The galea aponeurotica, the next layer, is characterised by a flat central tendon, attached between the frontalis and occipitalis muscles. The galea offers tensile strength to the scalp, failure of closure of which leads to contracture of attached muscles and a depressed appearance of a scalp wound. The subepicranium, containing loose areolar tissue and small vessels, provides scalp mobility. It is the usual plane of scalp avulsion, haematoma or infection. The pericranium is adherent to the skull, contains many small capillaries that pass through the underlying bone and has an outer layer of fibrous connective tissue and an inner layer of elastic fibres.[51]

DESCRIPTION OF SCALP INJURIES

Caput Succedaenum

It is due to scalp oedema which occurs in the newborn following trauma during prolonged engagement of the head at the pelvic outlet.[25] It presents as a boggy swelling seen at birth and usually subsides spontaneously within 2–3 days.[25]

Cephal-Haematoma

It is a subperiosteal haematoma occurring almost exclusively as a result of birth trauma. Since the pericranium meets the endocranium at the suture lines, this haematoma takes the shape of the underlying bone. It is seen usually following forceps delivery. It usually gets absorbed within a period of 2 weeks, failing which it may need aspiration. It may occasionally calcify and may require surgical excision.[25]

Abrasion

It is a destruction of the skin, usually involving the superficial layers of the epidermis only. It is caused by a lateral rubbing action by a blow, a fall on a rough surface, by being dragged in a vehicular accident, by fingernails, thorns or teeth bite. Pressure and movement by an agent on the surface of the skin is essential to cause this injury. The spectrum of injury may range from flattening of epidermal cells and elongation of nuclei to partial or complete removal of the epithelium and damage of the superficial layer of dermis. Many abrasions have some deeper areas of sub-epidermal damage, which may result in superficial scarring. Sometimes, full thickness of the skin may be damaged in places, but usually in an interrupted, irregular manner, and intact epidermis remains within the area of the abrasion. The rougher the surface, and the more rapid the movement of the skin over it, the deeper is the injury. The exposed raw surface is covered by exudation of lymph and blood which produces a protective covering known as a scab or crust. Abrasions vary in size, depending on the extent of the body surface exposed to the abrading force. They are simple injuries, bleed slightly, heal rapidly and scar is not formed. Large abrasions can cause severe pain and bleeding.

The main types of abrasions are:

Scratches: They are caused by a sharp or pointed object passing across the skin, such as fingernails, pin or thorn. The surface layers of the skin are collected in front of the object, which leaves a clean area at the start and tags at the end.

Grazes (Sliding, Scraping or Grinding Abrasion): The most common type occurs when there is movement between the skin and some rough surface in contact with it. They show uneven, longitudinal parallel lines (grooves or furrows) with the epithelium heaped up at the ends of these lines, which indicate the direction in which the force was applied.

Pressure Abrasions (Crushing or Friction Abrasions): They are caused by crushing of the superficial layers of the epidermis and are associated with a bruise of the surrounding area. It occurs if the movement of the instrument is around 90° to the skin.

Impact Abrasions (Contact or Imprint Abrasions): They are caused by impact with a rough object, when the force is applied at or near a right angle to the skin surface. The abrasion is slightly depressed below the surface, unless there is bulging due to underlying contusion or local oedema.

Impact abrasions and pressure abrasions reproduce the pattern of the object causing it and are called patterned abrasions.

Age of the Abrasion

The exact age cannot be determined, but a fair estimate may be done.

Fresh: Bright red

12–24 hours: Lymph and blood dries up leaving a bright scab

2–3 days: Reddish brown scab

4–7 days: Epithelium grows and covers defect under the scab

After 7 days: Scab dries, shrinks and falls off.

Contusion (Bruise)

A contusion is an effusion of blood into the tissues due to the rupture of blood vessels (venules and arterioles) caused by blunt trauma. The extravasated blood is diffusely distributed through the tissue spaces and the margins are blurred.

Age of the Contusion

Immediately:	Red
Few hours to 3 days:	Blue
4th day:	Bluish-black to brown (haemosiderin)
5–6 days:	Greenish (haematoidin)
7–12 days:	Yellow (bilirubin)
2 weeks:	Normal.

Laceration

Lacerations are tears or splits of the skin. These are usually caused by sharp objects. In a laceration caused by a blunt object, localised portions of tissue are displaced by the impact of the blunt force, which sets up traction forces and results in tearing of the tissues.

Split Lacerations

Splitting occurs by crushing of the skin between two hard objects. Scalp lacerations occur due to the tissues being crushed between the skull and some hard object, such as the ground or a blunt instrument.

Stretch Lacerations

Overstretching of the skin, if it is fixed, will cause a laceration. There is localised pressure with pull which

increases until tearing occurs and produces a flap of skin, which is peeled off the underlying bone or deep fascia. This is seen in the running over by a motor vehicle and the flap may indicate the direction of the vehicle.

Scalp lacerations are primarily troublesome because of bleeding. Infection is extremely rare because of the rich blood supply. One-layer closure with continuous monofilament suture and locking of alternating sutures to prevent edge inversion usually is adequate. Sutures are left in place for 10–14 days, to allow maximal wound tensile strength to develop in order to prevent spreading of the scar, since a wide, hairless scar is more visible than any potential suture marks except in a bald scalp. The tissue adhesive hair apposition technique also is effective in repairing scalp lacerations. The sting of local anaesthesia injections can be lessened by using smaller gauge needles, administering the injection slowly and warming or buffering the solution.[11]

Avulsion

An avulsion is a laceration produced by sufficient force (shearing force) delivered at an acute angle to detach (tear off) a portion of a traumatised scalp from its attachments along the path of least resistance, which is the loose areolar tissue layer. Scalp avulsion requires a strong tearing or shearing force. If the force is extensive enough, the scalping will progress to the boundaries of the galea at the supraorbital ridges and the zygomatic, mastoid and occipital nuchal line. Scalp avulsion is a threatening blood loss injury. Rapid cessation of bleeding, wound compression and aggressive fluid resuscitation are important. With adequate resuscitation, careful evaluation and replantation as soon as possible the outcome is usually good.[20,39,46]

Thermal Injury

Thermal injury may be caused by dry heat (burns), hot liquids (scalds) and steam. The depth of injury is directly proportional to the burning temperature and the time of exposure, and inversely proportional to the depth of the skin. In the scalp, deep injuries are less common due to thick skin and rich circulation. As the hair follicles are in the subcutaneous space, re-epithelialization of deep second-degree injuries also is rapid; provided there is no infection. Hence, conservative treatment is indicated where the injury is superficial or depth is questionable.[43]

Electrical Burns

Luce and Hoopes showed that the non-infected burnt skull can act as an *in situ* bone graft and regenerate, if covered by tissue of good vascularity.[32] The therapy for electrical burns therefore should consist of excision of the burnt scalp and pericranium, once the margins of the burn are established and before infection occurs (1–3 days) and immediate coverage with vascularised flaps, either local or distant. The burnt skull should be left intact, unless it is infected or underlying damage to the dura or brain is suspected.[53]

Grading of Electrical Burns

1. First degree	Superficial redness
2. Second degree	Partial thickness Blistering Regenerate spontaneously
3. Third degree	Full thickness Leathery skin Does not heal spontaneously Requires excision and grafting.

Chemical Burns

Injury by chemical agents can be accidental (more common, especially in children), homicidal (due to an assault) and suicidal (rare). Alkali burns are more common than acid burns. The damage caused to the scalp is determined by the duration of contact, the concentration, penetrance, quantity and the mechanism of action of the chemical compound. Copious irrigation of the injured part with sterile water helps in minimising the duration of contact. Neutralisation is the next step and is done by dilute acetic acid for alkali burns and with dilute sodium bicarbonate for acid wounds.[7] Extensive debridiment should be avoided, particularly when the depth is difficult to determine and a conservative approach is practised in such cases.

Radiation Injury

Ionising radiation may cause radiodermatitis or radionecrotic ulcer by microvascular damage and reduced cell turnover. Wound healing is also significantly affected in such scalps. The radionecrotic ulcer may further worsen the matter by undergoing malignant transformation. Treatment includes excision followed by grafting with fresh, uninvolved, vascularised tissue. Free flaps have the greatest success rate in the long run.[18]

MANAGEMENT

Resuscitation

When a scalp injury has occurred, the emergency facility receiving the patient should stabilise the patient's vital signs, determine the patient's tetanus prophylaxis status, do the necessary diagnostic procedures, and administer a broad-spectrum antibiotic and analgesics. Preparation for blood transfusion should also be made. The exposed cranium should be covered with saline moistened gauze. In case of scalp avulsion, the amputated scalp should be placed in a plastic bag and the bag placed in ice chips, awaiting replantation.[10,12,13,21,31,38]

Initial Evaluation of Scalp Injury

- Detailed history
- Detailed physical examination
- Assessment of mechanism of injury
- Evaluation of intracranial injury
- Evaluation of cervical spine injury, if any

- Appropriate neuro-imaging
- Additional history—male pattern baldness, Previous scalp trauma, Radiation injury.

Aims of Management of Scalp Injury

- Rapid and safe coverage of underlying structures
- Minimising the risk of infection
- Transforming a dirty wound into a clean wound
- Transforming an open wound into a closed wound
- Providing a durable tissue cover
- Restoring normal contour and function
- Achieving acceptable aesthetic result.

Assessment

Assessment of the Scalp Injury Includes the Following

- Duration since injury
- Environment of injury
- Wound characteristics:
  - Size
  - Shape
  - Depth
  - Margins
  - Presence of haematoma
  - Presence of foreign body
  - Necrosis
- Vascularity of local tissue:
  - Abundant
  - Poor
- Nature of the defect in the bed:
  - Pericranium
  - Cortical bone
- Character and abundance of the local tissue
- Potential for simple camouflage.

Duration since injury is an important determinant of wound viability and the outcome after surgical repair. It is now accepted that a wound exposed to the exterior for more than 6 hours has a four-fold increased risk of infection, compared to the one exposed for a lesser duration.[8,9,34] "The scientific basis of this time gap lies in the fact that doubling time of commonly found wound pathogens is an average of 30 minutes and 10,000 bacteria per gram of tissue is the microbiological representation of clinical infection." Hence, a primary closure of a scalp injury is ideally done within 6 hours. However, this time gap can be safely extended in the case of a clean wound and also to some extent in a wound with minimally devitalised edges.

An environment containing sand, mud, gravel, wood and metal particles significantly increases the risk of infection of the wound by the direct contact of exposed tissues to these substances.[6] Healing is thus naturally delayed in such cases, either by conservative treatment or surgical manipulation.

A scalp wound with a size more than 3 sqcm with a complex shape, irregular outline, charred, burnt or necrosed margins and those having an underlying haematoma or foreign body have a higher risk of infection and poorer healing.[8] Measurement of size should be done before excision of scalp injuries, with the slack in the edges taken up by gentle pulling. The real defect may be much smaller than is at first apparent, because the edges of the wound retract.[30] It has to be borne in mind that even minimal trauma must be evaluated and managed accordingly.[7,34] Cases of large subgaleal haematomas following trivial trauma like pulling of hair and bumping the head are rare, but significant enough to take note of and exercise caution.[40]

The choice of reconstruction and the wound healing depends upon the "vascularity" of the graft and wound, respectively. If the supply in the area of the defect is adequate, free grafting may suffice. If local supply is inadequate, either because of scarring, radiation effects or exposed bone, the graft must carry its own circulation for a successful take.

The nature of the bed of the wound relates both to the circulation available for the graft and to the need for protecting the underlying structures. Exposed diploic bone will easily support a simple skin graft, as will the dura; however, a skin graft on the dura would hardly suffice for long-term protection of the brain and hence calvarial reconstruction plays an important role.

The easiest reconstruction usually is accomplished with local tissue, and this has to be the first choice. The most efficient closure is accomplished if tissue can be mobilised by flap techniques to achieve a primary closure of the donor site.

The need for complex flap closure may be obviated if the defect can be covered by a simple change of hairstyle or by a hairpiece or a hat. Hence, the potential for simple camouflage plays a prominent role.[37]

Surgical Principles in Treating Scalp Injuries

- Large subgaleal haematomas should be evacuated early.[40]
- Meticulous haemostasis and approximation of wound margins is essential.[7–9,30]
- Local debridement to be done wherever necessary, to remove non-viable tissue and re-orient the wound.[8,34]
- Galea has to be closed with absorbable sutures for protection and retention of skin edges.[9,14,34]
- The flap should be taken from the scalp wherever feasible ("replace like with like").[6,9,14,30,34]
- Take the scalp flap from areas of relative excess (lateral and posterior), and place in areas of relative deficiency (anterior and medial).[9,30,34,41]
- Axial scalp flaps permit significant increase in length-base ratio, compared to the conventional random flaps.[18,26,30]
- During scalp replantation anastamosis should be done between two normal vessels.[4,21,38]
- The scalp can survive on one superficial temporal artery. But anastamosis of, as many arteries or veins as possible, has to be done during scalp replantation.[26,30]

- Veins should be anastamosed first during scalp replantation, unless there is significant ischaemia in which case anastamosis of arteries first is a priority.[13,21,31,38]
- Leeches have long been used to supplement venous drainage post-operatively for grafts,[30] but recently machines which perform controlled low suction of blood ("artificial leech") have undergone clinical trials successfully in the USA.
- In the presence of viable pericranium, split thickness grafts are used and free tissue transfer is indicated when viable pericranium is lost.[5,30,34]

Surgical Planning and Execution

Reconstructive Ladder: Options for Covering the Scalp Defect

- Primary closure
- Delayed primary closure
- Secondary intention healing
- Local transposition flaps – random axial
- Distant flaps – split thickness skin graft island pedicle flaps (trapezium, latissimus dorsi, temporalis)
- Free autogenous tissue transplantation (skin, muscle, omentum).

The reconstructive techniques for scalp defects are mentioned as follows, in general order of decreasing indications. These are:

1. *Split thickness grafts*: These are partial thickness of skin containing epidermis and variable thickness of dermis.
2. *Full-thickness skin grafts*: These consist of a complete thickness of skin with epidermis and dermis but without subcutaneous fat.
3. *Local attached flaps*: These flaps contain skin and subcutaneous tissue and carry their own circulation during transfer.
4. *Distant detached flaps*: Skin and subcutaneous tissue from a non-contiguous area is used that carries its own circulation during the transfer process until circulation is established in the recipient area.
5. *Distant re-attached flaps*: Tissue is harvested from a distant donor site with its vascular supply included and revascularised by microsurgical anastomosis at the recipient site.[12,21,47] Such flaps include skin and subcutaneous tissue, musculocutaneous flaps, muscle flaps with skin grafts and omentum with an overlying skin graft.[36]
6. *Scalp expansion*: Gradual expansion of adjacent scalp with subsequent advancement into the defect.[29,35]

Free Skin Grafts

These represent the first line of reconstruction of scalp defects. Two general principles govern their selection: (1) the thicker the graft, the lower the percentage of take and (2) the more dermis that is included, the less the contraction.[12] In large defects, such as in a granulating burn wound, initial closure may be done best by covering the wound with a thin, meshed graft even though reconstruction with flaps may be planned at a later date. The thickness of dermis in the graft determines the eventual contracture of the recipient bed. A thin split graft may contract 60–70% in area over the period of a year, gradually pulling in the edges of the wound to a degree that would be impossible to achieve at the time of initial closure because of suture necrosis.[12]

Free grafts can be harvested from any site. Grafts retain the characteristics of the donor site, therefore colour match and texture can sometimes be pre-selected.[48]

Free grafts in scalp reconstruction:

- Scalp
- Temporalis fascia
- Latissimus dorsi
- Parascapular
- Omentum
- Scapula
- Rectus abdominis
- Internal oblique
- Groin
- Radial aspect of the forearm.

Use of the superficial temporal artery and vein for scalp and face reconstruction is reliable and safe. The superficial temporal artery and vein should be considered as primary recipient vessels in microsurgical reconstruction of the upper two-thirds of the face and/or scalp.[16]

Compared to the omentum flap, the latissimus dorsi offers more tissue and has less donor site morbidity, and secondary surgery, such as cranial bone reconstruction, is possible. The preferred donor vessels are the maxillary artery and the external jugular vein and to avoid any vascular compression, a myo-cutaneous flap is used.[19]

Split Skin Graft

A split graft can be taken by any standard method, i.e. free-hand knife or one of the various dermatomes. Failure of the graft is due to interposition of pus, clot or serum between the graft and the bed and this must be prevented. Pressure on the graft is most easily achieved with a tied-over stent dressing, using enough bulk so that the resulting force is downward.[37]

The full-thickness graft is cut by standard scalpel excision and is clearly limited in size to those donor sites where primary suture closure is possible. These include the retro-auricular area where the maximal graft size permissible is 3 × 5 cm; the hairless supra-clavicular area and the groin crease. Application of acellular human dermis (AlloDerm) and split-thickness skin graft can be performed in a single phase. This shortens the treatment period and produces an excellent outcome.[23]

Techniques of Flap Transfer

Flap Theory

In the scalp the circulation is primarily axial, with the intervening areas between large known vessels being of random circulation. Large flaps are therefore successful, as long as the circulatory system between the galea

and the skin is not violated, either by poor flap design or by obstruction of venous return by tight closure or by the accumulation of fluid between the galea and the pericranium.[12,37]

Local Flaps

The basic concept of local flap transfer is to move available tissue with its circulation intact from an area of excess to an area of deficiency.[9,27] In the scalp, the only areas of excess are laterally and posteriorly, since the movement of tissue from the anterior scalp causes distortion of the forehead and hairline.[22,30,34]

Local Scalp Flaps with Galeal Scoring

Small Defects (<6 cm): The use of local (Fig. 1) flaps based on the major nutrient blood supply is the best method to close these wounds. The non-stretchable scalp can be made to cover a larger area by scoring the galea perpendicular to the direction of tension.[30] The galea can be cross-hatched to relieve tension.

Medium-Sized Defects (6–8 cm)

The best choice is usually a large scalp flap with skin grafting of the donor pericranium. In some cases, use of multiple axial flaps is helpful. This concept was initially described by Orticochea[42] as a four-flap technique, utilising the entire remaining scalp to close the defect. Orticochea[41] later modified this to a three-flap technique in which two smaller flaps adjacent to the defect are used to provide primary wound closure and a third larger flap, consisting of the entire remaining scalp, covers the donor defect, following rotation of the two smaller flaps. These flaps are based on known vascular territories and can be used to cover defects up to one-third of the scalp surface area.

Orticochea Flap Techniques

The width of the two smaller flaps should be at least one-half the width of the primary defect so that, when mobilised and juxtaposed, they automatically cover the raw surface.[34,41,42] The larger flap should cover the rest of the scalp (Fig. 2). If the defect is lateral to the midline, the base of the pedicle of the large scalp flap should be on the contralateral side of the defect. These flaps are elevated in the loose areolar plane, and will require extensive undermining of the remaining scalp, forehead and nape of the neck.[42]

Large Defects (8–10 cm)

When the defect is large, anterior and off to one side, a subtotal scalp flap can be raised based on the superficial temporal and posterior auricular arteries.[8,9,30] The remaining scalp can be transposed with a large donor deficit that must be grafted.

Pericranial Flaps and Overlying Skin Grafts or Local Flaps

Pericranial flaps are endowed with a rich vascular network that allows them to be used as pedicled flaps to cover denuded bone and act as a bed for skin grafting. They should be designed larger than the recipient site because of their elastic properties.[17,24,30]

Muscular Flaps

The latissimus dorsi muscle, which can be transferred as a myocutaneous unit or as a free muscle only and covered with a split-thickness skin graft, was first used in 1978 to cover a scalp defect. The muscle is large enough to cover the entire scalp and is reliable in its anatomy. In addition, the thoracodorsal artery and vein provide a long pedicle that aids in the utility of this flap.[8,18] The

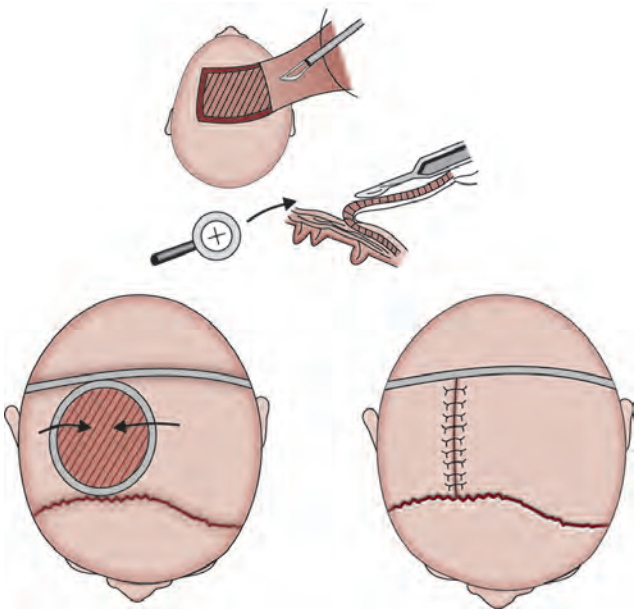

Fig. 1: Local flap with galeal scoring method

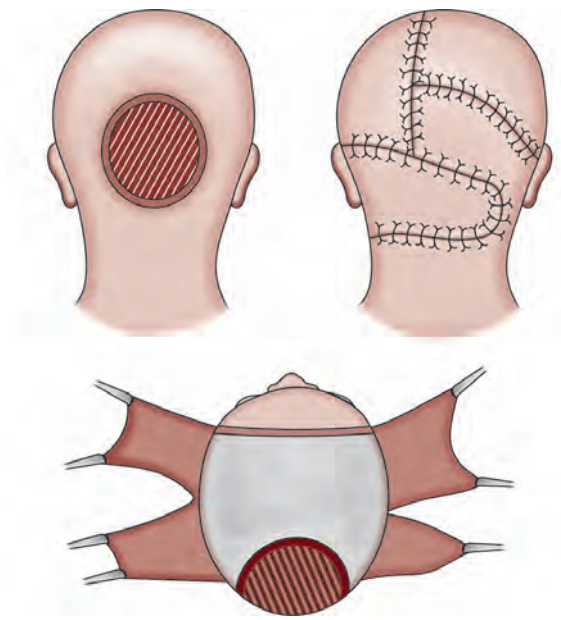

Fig. 2: Four flap method

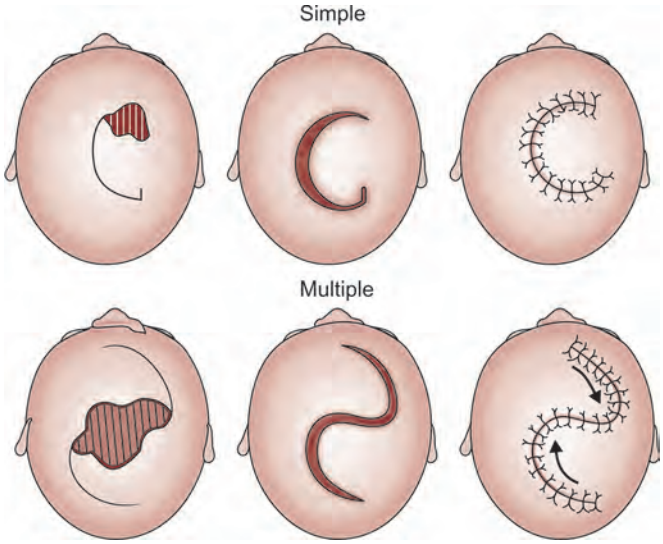

Fig. 3: Rotation flaps

parascapular flap is more bulky than the latissimus dorsi flap but does not sacrifice a functional muscle.[8,18] It cannot cover the entire scalp. These flaps are unsatisfactory from an aesthetic standpoint and do not restore hair-bearing tissue to the scalp.

Rotation Flaps

Planning a rotation flap (Fig 3) requires an understanding of a simple geometric concept. "Tissue is added to the defect subtracting from the flap donor area and this is achieved by changing the defect shape from non closable to closable."[30] For example, if the defect is a square 2 inches on a side, the area is 4 sq in, movement of a flap to fill a 4 sq in defect creates a 4 sq in donor defect. Primary closure will be impossible because of suture tension necrosis.

Now, consider making a 10 inch semicircular incision; which will result in the flap rotating into the defect, leaving an elliptical defect 10 inches long still having a total area of 4 sq in. Due to the change in shape of the donor defect, primary closure is then possible, since maximum width of the defect would be 0.5 inch or less.[30]

Calvarial Reconstruction

Calvarial reconstruction is undertaken to provide adequate protective coverage of intracranial contents and to restore calvarial contour. Defects of the frontal region warrant cranioplasty for both cosmetic and protective reasons. Autogenous bone is the material of choice in the growing craniofacial skeleton. Manson et al.[33] reported no statistical difference in the incidence of infection between the use of autogenous bone and mesh-acrylic in reconstructions involving the frontal region. If a frontal defect extends into the frontal sinus, autogenous bone should be used to decrease the risk of infection. Defects in the parietal or occipital region most often require cranioplasty for protective reasons. Defects in the temporal region need cranioplasty less often, because of some protection offered by the overlying temporalis muscle.

Materials Used for Calvarial Reconstruction

Autogenous material	***Alloplastic material:***
Split rib grafts	Acrylic[18]
Calvarial bone grafts	Hydroxyapatite cement
Bone paste	Vitallium
	Stainless steel
	Tantalum
	Titanium

Calvarial reconstruction can be done, beyond controversy, in the acute situation;[50] the only exception being the presence of local infection and devitalised tissue; in which case, soft tissue cover has to be done in the acute setting and bony reconstruction has to be postponed by one year.[50]

Dural Closure and Intradural Repair

Primary closure of a dural tear is mandatory in any scalp injury. When there is an associated loss of dura, a duroplasty is done with temporalis fascia, if the latter is viable and is not needed for scalp defect closure. Otherwise, fascia lata serves the purpose well.[30,48]

Tissue Expansion

In 1978, Radovan[44] and, in 1982, Austad and Ross[3] published reports on the first clinically successful techniques of tissue expansion (Fig. 4) and demonstrated the prototypes of expanders clinically useful today. "This method is based on the simple principle that the skin is capable of significant expansion, sometimes enormously" (one need not over-emphasise the enormous stretching of abdominal skin in pregnancy and extreme obesity). Up to 50% of the scalp can be resurfaced with expanded skin without changing the hair growth pattern or creating new donor defects.[28,29,52] The expander is a silicone bag with a self-sealing fill valve that is placed beneath the tissue to be expanded.[44] Expansion is then done percutaneously with incremental saline injections into the valve.[44]

"It has to be understood that the expansion is planned in the normal scalp adjacent to the defect and not under the graft or at the site within the area of intended primary closure". The prosthesis is placed beneath the galea and expanded over a few months at 6–80 days

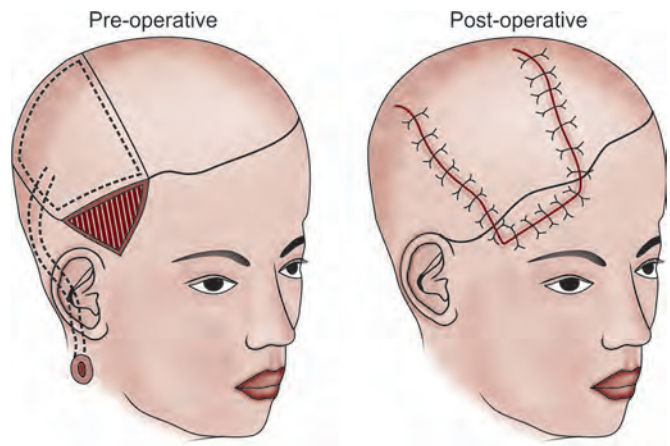

Fig. 4: Expansion flaps

intervals.[44] Following the desired expansion, the hairless scar is excised and primary closure accomplished by advancing the expanded scalp into the defect.[2] Intraoperative filling of the expander reduces the need for drains, by preventing haematoma and seroma formation. A good estimation of flap length is twice the height of the expander above the skin surface. Over-expansion by 30–50% makes the procedure more reliable.[44]

Replantation

Miller and associates were the first to report successful total scalp replantation by microvascular anastomoses.[38] The superficial temporal artery has the most reliable inflow and replantation of the entire scalp can be based on a single arterial and venous anastomosis,[32] showing that the midline of the scalp is not an absolute barrier for segmental blood supply. However, most reports of successful scalp replantation are based on multiple arterial and venous anastomoses.[14,38] As a rule vein grafts are used to avoid using arteries within the zone of injury.[31] There is no strict time frame for replantation of avulsed scalp, but successful replantation has been accomplished up to 18 hours after injury.[32]

Ideally, two operating teams should be available for the replantation surgery. One team identifies and tags the vessels on the avulsed scalp and the other team works on the patient's head identifying vessels and debriding the wound.

Locating the vessels on an avulsed scalp can be time consuming and should be done with the aid of magnification. The paired vessels that should be investigated are the supraorbital, temporal, postauricular and occipital. The diameters of the vessels in adults will range from 0.5 mm to 1.5 mm. A normal vessel has to be anastamosed to another normal vessel and to be sure, operative microscopic evaluation of the intima is mandatory.[14,38] Anastamoses should be performed outside the zone of injury and should be multiple, whenever possible.[14,38] The scalp is tacked exactly into place and drains are placed before suturing. The dressing should be light and non-compressive.

Most authorities recommend post-operative anticoagulation,[27] either in the form of heparin followed later by aspirin or low molecular weight heparin. Gregory Dostall et al. have recommended usage of low molecular weight dextran in a dose of 20 cc/hour for 3–5 days post-operatively.[15]

Post-operative assessment of replanted scalp:

1. Clinical examinationColour
   Capillary refill
   Temperature
   Capillary bleeding
2. Doppler[49]
3. Thermocouples
4. Fluorescein staining
5. Transcutaneous oxygen measurements
6. Impedance techniques.

Omental Transfer

McClean and Bunke described the free vascularised omental transfer (Fig. 5) for scalp coverage.[26] The

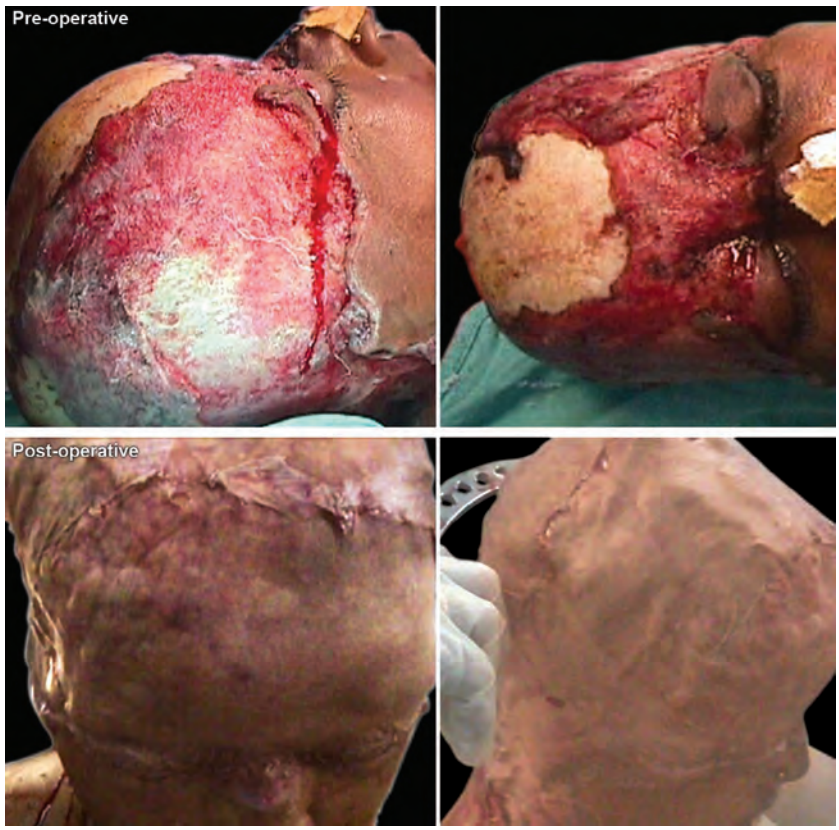

Fig. 5: Partial scalp avulsion, omental transfer for scalp avulsion

omentum was moulded to the scalp defect and then covered with a split-thickness skin graft. The necessity of laparotomy and the availability of less morbid flaps are limitations of this procedure.[26]

Complications of Scalp Injuries

- Infection
- Wound necrosis
- Calvarial, dural and brain injury
- Graft rejection
- Wound contracture
- Poor cosmetic result.

FUTURE PERSPECTIVES

Scalp Transplantation

The potential for scalp transplantation is tremendous in the years to come. Buncke et al. already have reported a case of scalp transplantation involving twins in whom one had suffered an avulsion injury, which was managed with the aid of a free flap harvested from her sister's scalp.[4] This case illustration goes a long way in proving that once the immunological barriers are resolved, allografts and even xenografts may be employed in scalp injury management.

Foetal Tissue Healing

Tremendous amount of time and dedication is being expended in research on foetal wound healing. As the results of the research on this apparently regenerative process unravel, they may be applied to scalp injuries.

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36 Acute Subdural Haematomas

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INTRODUCTION

Acute subdural haematomas (SDHs) are haematomas accumulating within the subdural space of the brain to become clinically symptomatic within 24–72 hours of injury. They are extracerebral, hyperdense, crescentic collections between the dura and the brain parenchyma and regarded as "acute" when diagnosed within 14 days of traumatic brain injury.[10] They are usually located over the cerebral convexities conforming to the convex brain surface. When extending along the tentorium or falx cerebri, their extent is contained by dural reflections.[15,20] There is a wide variation in the incidence of acute SDH (5–29%) as the primary lesion in patients admitted with head injury. Acute SDH often occurs in the fifth and sixth decades (mean age 31–47 years) and, therefore, the mean age of patients with acute SDH is older than with other types of head injury. Men are twice to four times more likely to be affected than women.[10,15]

AETIOPATHOGENESIS

Acute SDH is frequently due to falls, assaults or vehicular accidents. When the head lands on or strikes against a hard surface or when there is an assault to the head with a hard object, there may be avulsion of the bridging veins. The mechanism for this injury is often rapid deceleration of the cranium with a relatively low magnitude of the shear force applied. Rotational acceleration of the head, as occurs in boxing, may also produce these injuries.[20] Avulsion of parasagittal and Sylvian bridging veins is often accompanied by a degree of diffuse axonal injury and polar contusion. The low pressure venous bleeding accumulates to form a haematoma of sufficient size to compress the brain by two mechanisms. Episodes of coughing, straining or vomiting may cause sufficient bleeding to prevent progressive tamponade by the brain. The avulsion of veins directly attached to the sagittal sinus may be held open because of the high venous sinus pressure rather than be compressed by the haematoma. Cortical contusion with haemorrhage from a small cortical artery rupture is also a common cause of acute SDH. This results in a characteristic "burst lobe" injury with SDH, polar contusion, cerebral haematoma and hemispheric swelling. Occasionally, coalescence and rupture of parenchymal small vessel bleeding from a contusion may also cause an acute SDH. This may occur especially when consumption coagulopathy develops or in patients on anticoagulant therapy. Such a SDH is often associated with sizable intraparenchymal clots.[9,10] Maxeiner and Wolff[12] performed a post-operative analysis of size, space-occupying effect and form of the SDH in patients who had died due to acute SDH resulting from one of the three common causes namely: (1) cerebral contusions; (2) rupture of bridging veins and (3) rupture of small cortical arteries. They termed the bleeding from torn bridging veins, and rupture of small cortical arteries as "pure SDHs" as they occurred without any gross (focal or diffuse) damage to the brain itself. They found that the volumes of arterial and venous acute SDH and their relative areas in the horizontal planes were similar irrespective of the causal mechanism. The haematoma thickness and midline shift were higher in arterial SDH. On the other hand, in venous SDH, the difference between the midline shift and the haematoma thickness was lower than in arterial SDH (i.e. in venous SDH, a smaller acute SDH was associated with a greater midline shift) indicating a tendency towards more pronounced midline shift in venous, rather than arterial SDH of similar volumes. They also found that venous SDH due to bridging vein ruptures were generally located in the central frontoparietal, parasagittal region and had a comparatively smaller length and thickness than the arterial SDH which were more often located in the temporoparietal region.

Poor outcome following acute SDH may also be related to the ischaemic damage occurring in the hemisphere underlying the haematoma due to raised intracranial pressure producing impaired cerebral perfusion. Removal of an acute SDH often results in reversal of global ischaemia.[2,13,14] However, hemispheric oedema below the acute SDH may occur even when the haematoma is thin and may be related to an excitotoxic mechanism due to the massive release of excitatory glutamate and aspartate neurotransmitters. Excessive activation of excitatory neurotransmitter receptors, especially glutamatergic N-methyl-D-aspartate receptor, can cause neuronal damage closely resembling ischaemic necrosis.[20]

Howard et al.[5] found that 56% of acute SDH in the younger group (18–40 years) were caused by motor vehicular accidents and only 12% were caused by falls. Whereas, in the older groups (> 65 years), 22% and 56%, respectively, of acute SDH occurred due to the two conditions. In comatose patients, motor vehicular

accidents are responsible for acute SDH in 53–75% patients because these are often high-velocity accidents with associated diffuse axonal injury.

Associated intracranial injuries occur in more than 50% of patients with acute SDH and have a significant prognostic implication.[9,19] Associated lesions occur in 47–57% of patients presenting with Glasgow Coma Score (GCS) scores between 13 and 15, and in 65–82% of patients with GCS scores less than 10. In patients with acute SDH, contusion and fractures are the most frequent injuries encountered; associated subarachnoid haemorrhage has been seen in 14–25% of patients with SDH and epidural haematomas in 14–25% of patients. Extracranial injuries are seen in 18–51% of patients including facial fractures, limb fractures, thoracic and abdominal trauma. Around 70% of patients with other associated lesions have a contrecoup injury. Bilateral acute SDH occurs in 8–33%.

CLINICAL SPECTRUM

The clinical presentation is non-specific and occurs due to mass effect produced by the acute SDH as well as associated parenchymatous injury. It depends upon the severity of the primary injury, the associated parenchymal injuries and the rapidity of accumulation of the acute SDH. According to Jameison et al.[6] and Obana and Pitts,[10] the patients may remain unconscious throughout or may vary in sensorium from being totally unconscious to being lucid to unconscious, or may remain lucid throughout. About 40–50% of patients are unconscious at the time of their primary injury and remain comatose for prolonged periods. Stone et al.[18] showed that 53% of their patients with lucid interval neurologically deteriorated. Pupillary asymmetry ipsilateral to the side of haematoma with contralateral hemiparesis may be due to transtentorial herniation. However, false localising pupillary dilatation contralateral to the lesion may occur due to direct optic nerve, oculomotor nerve or brainstem injury on that side. Ipsilateral hemiparesis may be due to associated brain injury or due to Kernohan's notching produced by compression of the contralateral cerebral peduncle against the tentorial edge. The incidence of associated seizures has varied from 6 to 22%.[10,15]

Posterior fossa acute SDH is rare and occurs in 2.3–3% of patients who underwent surgery within 72 hours of injury. Occipital trauma and associated occipital fractures may be responsible. Posterior fossa acute SDH occurs due to tearing of bridging veins, laceration of the tentorium, contusion of the cerebellum or injury to venous sinuses. Cerebellar signs, neck stiffness and pain or symptoms of raised intracranial pressure due to the size of the lesion or the development of hydrocephalus may be the presenting features. Despite urgent surgical evacuation, the mortality ranges from 5 to 75%.[1,4,10]

IMAGING FEATURES

On CT scans, an acute SDH appears as crescentric, hyperdense collections that lie between the arachnoid and the inner meningeal layer of the dura that conform to and often exert a mass effect on the surface of the brain (Figs 1 to 3). It extends across sutural lines, but does not cross the falx or the tentorium (Fig. 4). In contrast to this, an extradural haematoma is biconvex, less likely to cross sutural lines and may cross the falx or tentorium. An acute SDH may occasionally be biconvex due to adhesions between the brain and the dura mater, or when it is thick. The exact thickness of the crescentric SDH should be measured by taking the CT images with a wide window to distinguish the hyperdense clot from bone.[20] According to Servadei et al., early CT scan (within 3 hours from injury) underestimates the size of the associated parenchymal contusions and the consequent oedema. Patients who show subarachnoid haemorrhage on early CT are those at highest risk for evolving contusions. The worst outcomes previously associated with acute SDH may, in many cases, be due to the concomitant presence of contusions in multiple areas of the brain and consequent development of oedema. Thus, the use of sequential CT scan should be included in the routine management of head-injured patients.[16,17] In the younger population, an associated swollen hypointense, ipsilateral hemisphere indicates a very poor prognosis.[20] In patients with acute anaemia and haemodilution (during resuscitation from multiple injuries), the acute SDH may appear as isodense to hypodense on CT.[3] A subacute SDH may also be isodense to the brain.

Magnetic resonance (MR) scan is a sensitive investigation for diagnosing an acute SDH (Figs 36.5A to D). The image acquisition time of an MR scan is more (30–60 minutes) than the CT scan and, therefore, a restless and irritable patient with a head injury may cause several imaging artifacts. Patients with ferromagnetic foreign bodies or electronic implants need to be excluded. Thus, MR is less preferred in the clinical setting in patients

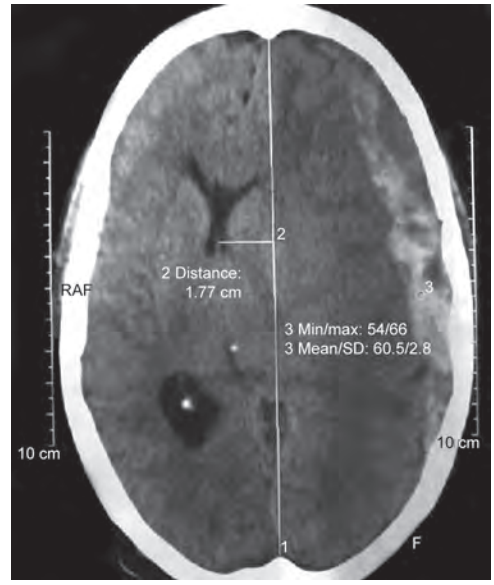
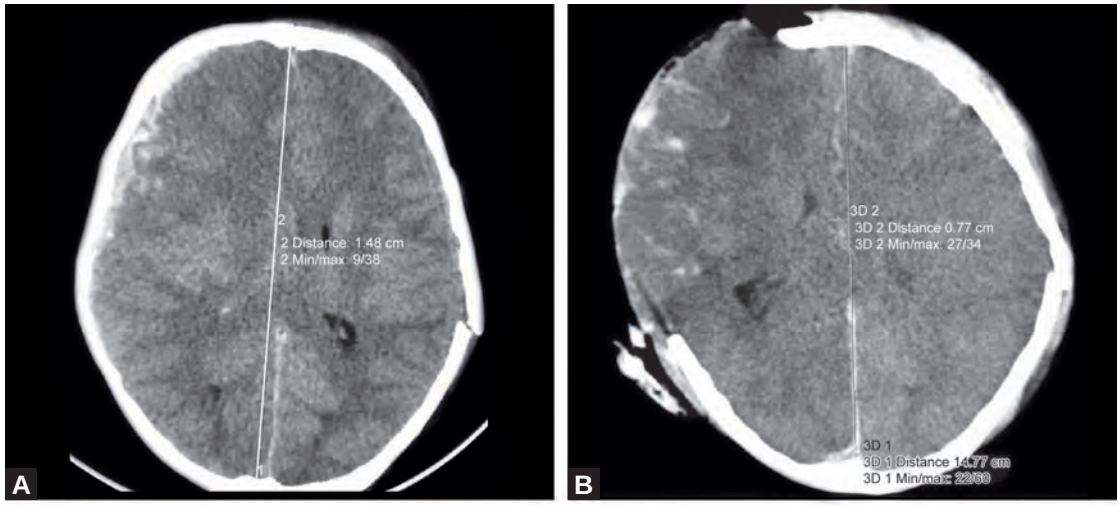
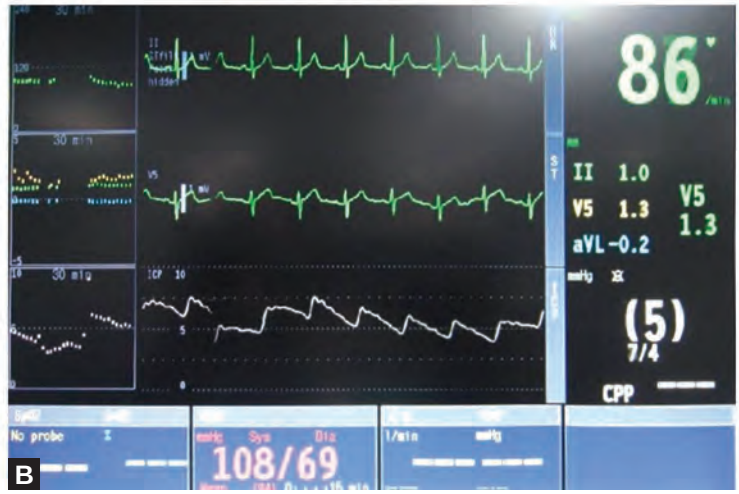


Fig. 1: Non-contrast axial CT scan showing a crescentric acute subdural haematoma causing midline shift





Figs 2A to C: (A) Axial CT scan showing a thin rim of subdural haematoma, with disproportionate midline shift and effacement of sulci and ventricular system. There is a parietal skull fracture contralateral to the side of the acute subdural haematoma. (B) Axial CT showing that following a large frontoparietal craniectomy, the oedematous brain herniates through the craniectomy defect. (C) Intracranial pressure monitoring. The lower-most wave is the characteristic waveform obtained on intracranial pressure monitoring. The systolic, diastolic and mean (in brackets) intracranial pressures are seen

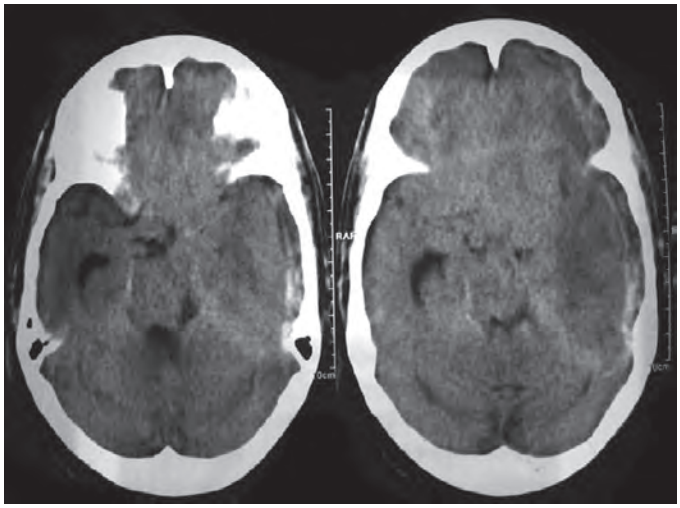


Fig. 3: Axial CT scan showing a tentorial subdural haematoma

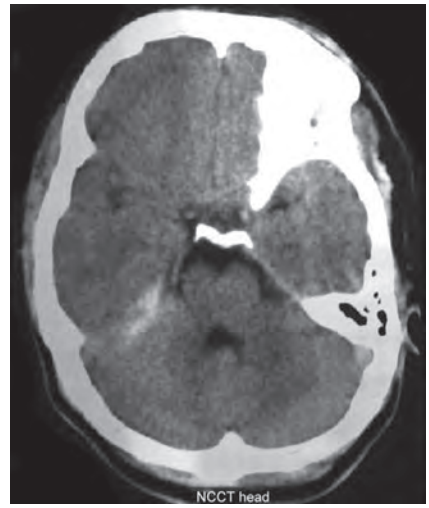
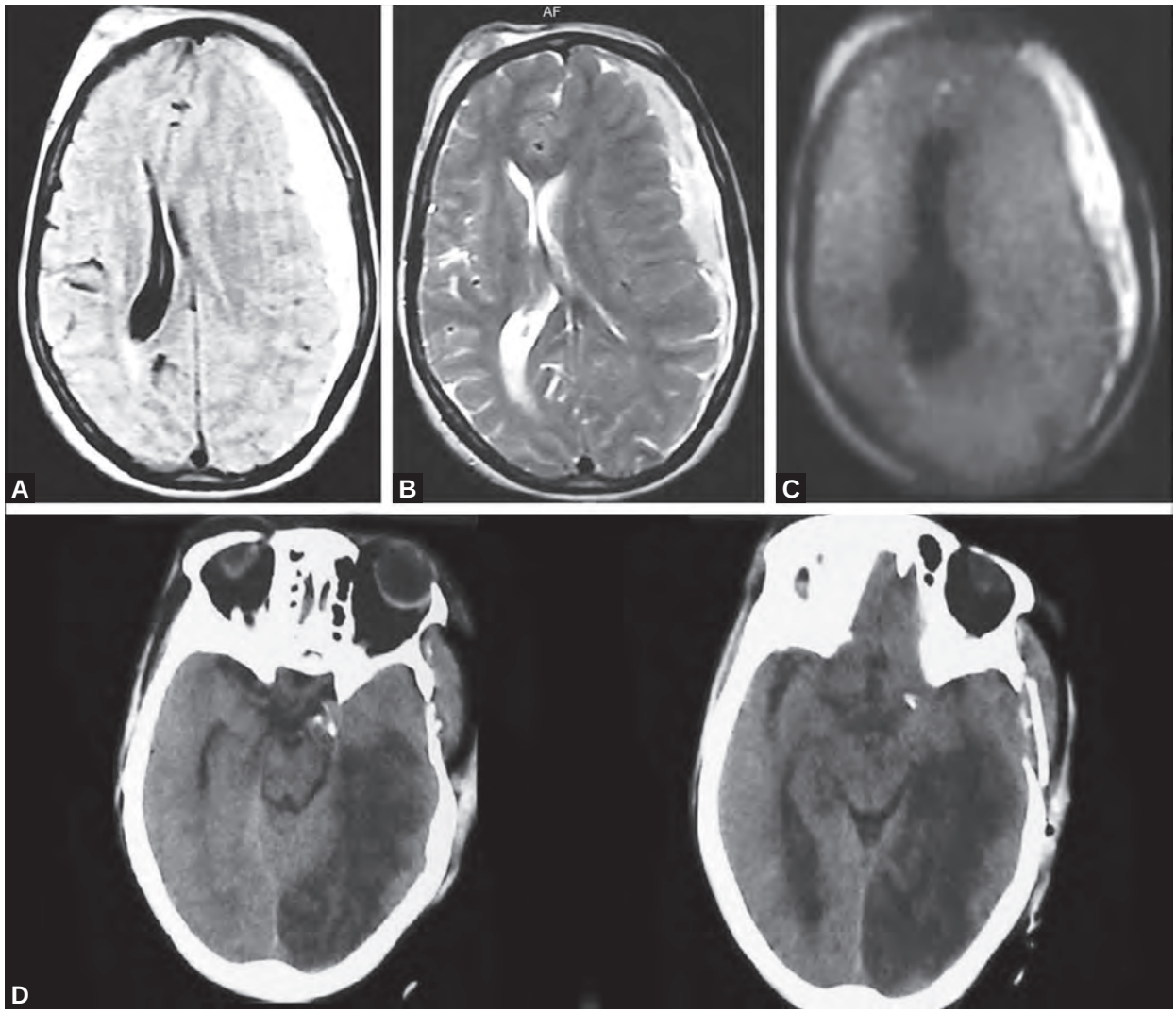


Fig. 4: Axial CT scan showing a thin rim of subdural haematoma causing uncal herniation and effacement of basal cisterns



Figs 5A to D: (A) Axial T1-weighted MR image showing a subacute SDH haematoma that is hyperintense and causing significant midline shift. (B) Axial T2-weighted image showing that the subacute SDH is still hyperintense. (C) Diffusion-weighted MR image showing the characteristic hyperintensity indicating the clot is solid in nature. (D) Follow-up CT scan after 20 days of haematoma evacuation. The patient did not improve following surgery due to the development of posterior cerebral artery infarct as a result of transtentorial herniation despite the subsidence of midline shift and opening up of the basal cisterns

with head injury as compared to a CT scan. The conventional long TR spin echo provides T2-weighted, and short TR spin echo or inversion recovery section demonstrates T1-weighted contrast differences. Gradient echo T2-weighted sequences highlight magnetic susceptibility changes making them sensitive to haemorrhage but at the cost of reduced definition close to the paranasal sinuses and other brain-air interfaces where there is an artifactual loss of signal due to diamagnetic susceptibility gradient effects. Ultrafast echoplanar imaging and other newer MR sequences have been developed that increase the speed of image acquisition. Cerebral diffusion, perfusion and functional studies at higher anatomical resolution show the presence of associated ischaemia.[20]

Bone generates a low signal on MR and, therefore, enables identification of even a small acute SDH associated with moderate to severe contusions. On MR imaging, the acute SDH ages in a similar way to intracerebral haemorrhage but its appearance in acute and subacute stages may be modified by decreased resorption of serum and liquefaction of the haematoma. Thus, in the hyperacute stage, lasting from minutes to a few hours, due to the oxyhaemoglobin content, the haematoma is dark on T1-weighted images and bright on T2-weighted images. In the acute stage, lasting for the next 1–12 hours, the presence of deoxyhaemoglobin causes the haematoma to be isointense on T1-weighted images and dark on T2-weighted images. The subacute stage that starts as early as 3 days and is established from a week may be divided into the early and late stages. In the early subacute stage, the methaemoglobin appears bright on T1-weighted and dark on T2-weighted images. In the late subacute stage, signals are bright on T1-weighted and T2-weighted images (Figs 5A and B). As the SDH become chronic (21–30 days) these signals become hypointense on T1-weighted and T2-weighted

images.[20] Fresh haemorrhage within a subacute SDH may give rise to the layering effect of the high and low attenuation clot. Occasionally, the presence of bilateral acute SDH may cause no midline shift despite the mass effect. The effacement of frontal horns, obliteration of sulci and gyri and compression of third ventricles points towards mass effect in these cases. An MR may also be more sensitive than a CT scan in picking up small gliding contusions, contrecoup injury or brainstem injury associated with the acute SDH. An extradural haematoma may be distinguished from an acute SDH by the sharply delineated, low intensity dura between the haematoma and the displaced brain in the former. Acute SDH is often associated with displaced cortical pial veins demarcated by flow voids. MR coronal imaging will also distinguish between the two entities.[20]

Radionuclide tracers, such as ^{99m}Tc hexamethyl propylene amine oxime (^{99m}Tc-HMPAO) and xenon-enhanced CT cerebral blood flow studies, may also give an idea about the regional cerebral blood flow and hypoperfusion below an acute SDH. Loss of autoregulation may cause the hypoperfused area in the subacute phase to appear hyperperfused. Severe continued hypoperfusion below an acute SDH eventually leads to tissue loss in that area.[14]

SURGICAL MANAGEMENT

The aim of surgery is to evacuate the haematoma and any associated underlying lesions in order to relieve the mass effect and improve the focal neurological deficits.[7] However, if the patient has no brainstem reflexes and is hypotonic with no motor response, surgery may not be useful. The size of the haematoma that should definitely be removed has not been ascertained. Removal of a very thin acute SDH may not be indicated as the clinical deterioration is usually due to associated lesions in this case and is not likely to improve with acute SDH evacuation. Although the current consensus is to have an acute SDH promptly evacuated through a craniotomy in 90–97% patients, conservative treatment of a small acute SDH in patients (approximately 3%) with contraindications for surgery have been reported. Some of these patients make a good recovery while some others require subsequent surgical evacuation of the haematoma. Non-operative therapy should only be considered in patients who are fully conscious, when the extra-axial mass is the single dominant lesion, that is, there are no multiple contusions or potentially significant contralateral mass lesions (which may be preventing midline shift), and when there are no features of mass effect such as a midline shift greater than 3 mm, or basal cisternal effacement. In such cases and, especially if the lesion is less than 10 mm at its thickest point, conservative therapy may be successful in most instances. The SDH will usually resorb within 1 month, although there are occasional instances of chronic SDH formation. Similarly, a deep-seated interhemispheric or tentorial SDH in a stable conscious patient may not need surgical evacuation.[7]

The guidelines for selecting patients for conservative management of the SDH proposed by Mathew et al.[11] include: (1) GCS score greater than or equal to 13 since injury; (2) absence of other intracranial haematomas or oedema on CT scan; (3) midline shift of less than 10 mm; and (4) absence of basal cisternal effacement. However, Wong[23] could not find the level of SDH volume, thickness or the associated midline shift beyond which failure of conservative treatment could be predicted. According to the recommendations of the Total Brain Injury Author Consortium[1] for the surgical management of acute SDH published in 2006, an acute SDH with a thickness greater than 10 mm or a midline shift greater than 5 mm on CT scan should surgically be evacuated, regardless of the patient's GCS score. All patients with acute SDH in coma (GCS score less than 9) should undergo intracranial pressure monitoring. A comatose patient (GCS score less than 9) with an SDH less than 10 mm thick and a midline shift less than 5 mm should undergo surgical evacuation of the lesion if the GCS score decreased between the time of injury and hospital admission by 2 or more points on the GCS and/or the patient presents with asymmetric or fixed and dilated pupils and/or the intracranial pressure exceeds 20 mmHg. An increase in haematoma size on CT scan with increasing intracranial pressure and decline in neurological status is also an indication for surgical removal of the lesion. Regarding the timing of surgery, it is recommended that in patients with acute SDH and with indications for surgery, surgical evacuation should be performed as early as possible. If surgical evacuation of an acute SDH is indicated in a comatose patient (GCS < 9), it should be performed using a craniotomy with or without bone flap removal and a duraplasty.

Since an acute SDH is composed of solid clots, a large craniotomy centred over the haematoma is the recommended technique for its evacuation.[7,19,21] If the haematoma is frontotemporal, a craniectomy centred over a temporal burr hole may be performed. The dura is opened and all accessible clot should be removed. Obana and Pitts[10] recommend a "95% operation" in which all easily accessible dark, clotted blood (usually under pressure) should be removed, but clots near dural venous sinuses or out of safe reach should not be pursued. Removal of the last bit of clot offers no added advantage and unnecessarily subjects the patient to the risk of catastrophic bleeding. It may sometimes be preferable to make several slits in the dura without joining them together as this will minimise herniation of the brain through the site of dural opening, which can be dramatic and may even prevent closure of the scalp. An attempt should be made to identify the parasagittal venous bleeder, if no cortical source of bleeding is evident. Parasagittal irrigation with depression of the medial cortex and raising the venous pressure by the anaesthetists are manoeuvres to identify the bleeding point. The latter may be controlled with bipolar coagulation or liga clips. If it is direct and profuse from the

sagittal sinus, then a muscle patch may be required for tamponade. Failure to identify and control the parasagittal bleeding source may cause recurrence of acute SDH. Removal of contused brain or even a frontal or temporal lobectomy may be considered when cortical damage and the mass effect are severe. A duraplasty using temporalis fascia, pericranium, fascia lata or dural substitutes such as lyophilised dura or woven collagen may be performed. If possible, the bone flap should be replaced and secured and scalp layer closed meticulously.[7] Intraoperative brain swelling is commonly seen with acute SDH. This may be the result of pre-existing multiple small gliding contusions and diffuse axonal injury. The potentially remediable causes of brain swelling after evacuation of an acute SDH include impaired ventilation (due to pneumothorax, endotracheal tube dislodgement or occlusion) requiring hyperventilation and change of airway; an intracerebral haematoma developing beyond the craniotomy margins or contralateral haematomas requiring evacuation and dehydrants; or, acute hydrocephalus developing due to coexisting intraventricular haemorrhage or due to midline shift causing contralateral foramen of Monro block that requires a ventricular drainage procedure. If intracranial pressure control is not achieved with maximum dehydrant therapy then consideration must be given to the removal of contused and swollen brain. The frontal and/or temporal lobectomy must be aimed at removing only the damaged brain and at avoiding eloquent areas. The drawback of a lobectomy is that removal of the brain tissue frequently does not control intracranial pressure.[7]

A wide decompressive haemicraniectomy/craniotomy with duraplasty (Figs 2A and B) may be useful in obtunded patients with intact brainstem function who subsequently deteriorate due to increased hemispheric oedema or the SDH. An intracranial pressure monitoring device and adjuvant medical management of raised intracranial pressure is useful in such cases.[7,13,21] The Medical College of Virginia criteria for performing this procedure is when intracranial pressure control is not achieved with maximum therapy using mannitol, ventricular drainage, pressors, moderate hyperventilation ($PaCO_2$ = 32 ± 2 mmHg) and moderate hypothermia (32 ± 2°C); pupils not fixed and dilated; and preserved brainstem responses and central conduction time on evoked potential testing.[7]

Burr-hole drainage of an acute SDH is usually unsuccessful because the underlying clot is solid. It may, however, be used to localise the site of clot in case imaging facilities are not available, following which the burr hole may be enlarged to a craniectomy.[7]

OUTCOME

The mortality from an acute SDH in all patients shows a wide range (42–90%); in all age groups with GCS between 3 and 15 requiring surgery ranges between 40% and 60%; and in comatose patients requiring subsequent surgical evacuation is between 57% and 68%. Residual or recurrent haematoma requiring evacuation has been seen in approximately 14% of patients.[10] Occasionally, removal of the mass effect caused by the acute SDH may increase the underlying intracerebral haematoma or contralateral acute or chronic SDH. Post-operative haematomas should be suspected and a post-operative CT obtained in patients who fail to improve or those who deteriorate and in whom the intracranial pressure monitoring shows persistently high intracranial pressures. The post-operative complications following evacuation of an acute SDH may include osteomyelitis, wound infection, meningitis, subdural empyema and ventriculitis.[1,10]

The factors determining outcome include:

1. The neurological status: This forms the most significant factor in determining outcome. In patients with acute SDH and GCS of 3–5, the mortality was 76% and good to moderate outcome occurred in 14% patients; those with GCS of 6–8 had a mortality of 36% and a moderate to good outcome in 40% of patients.[10] Pupillary asymmetry correlates with a poorer outcome. In bilateral pupillary abnormalities, the mortality is over 80%; in unilaterally dilated but reactive pupils, the mortality reported is approximately 50% and, in unilaterally dilated non-reactive pupils, the mortality reported is approximately 58%.[10,18] Decerebrate posturing, flaccid patients (mortality 77–95%), and patients with hemiparesis and hemiplegia (mortality 35–48%) also have a poorer prognosis as compared to intact patients.[10]
2. Age: Younger patients have a better outcome than older patients due to less comorbid conditions in the former. A number of authors have not found any significant correlation between age and mortality, but a significant association between age and functional recovery.
3. CT parameters: CT parameters such as clot thickness, haematoma volume, midline shift and patency of the basal cisterns: Howard et al.,[5] following surgery for acute SDH, found a significant correlation between poor outcome and the volume of SDH and the midline shift.[5] Servadei et al.[16,17] also found a correlation between outcome and clot thickness and the status of the basal cisterns. Kotwaca and Brezezinski[8] also found a significant relationship between midline shift and outcome in patients with GCS scores lower than 10, who were undergoing surgery for SDH. However, van den Brink et al.[22] found no difference in haematoma volume, midline shift and patency of the basal cisterns in surgical patients with favourable versus unfavourable outcome. Zumkeller et al.[24] revealed a 10% mortality rate in patients with a clot thickness of less than 10 mm and a 90% mortality for patients with clot thickness greater than 30 mm. Thus, these parameters do seem to influence outcome, but the specific threshold values need to be determined.
4. Timing of surgery: Usually conservative treatment is adopted and surgery deferred in patients with

less severe acute SDH and in better neurological status. Thus, mortality is less whenever timing from injury to surgery increases in most of the published series. In comatose patients, however, there was a significant decrease in mortality and increase in functional recovery in patients who underwent surgery within 4 hours of injury as compared to those in whom surgery was delayed beyond 4 hours of injury. The mechanism of secondary brain damage is direct compression of the underlying cortex and brain shift that causes local zones of ischaemia. If the elevated intracranial pressure is unrelieved, leading to reduced cerebral perfusion pressure, then global ischaemic brain damage may occur.[10]

5. Intracranial pressure: Persistently elevated (> 20 mm Hg) post-operative intracranial pressure is associated with a poorer prognosis.[1,10]
6. Associated lesions: An associated intracerebral haematoma or contusion did not influence mortality but the functional outcome was significantly better in patients without contusions. Associated diffuse axonal injury significantly influences outcome.[19] Jamieson and Yelland[6] classified acute SDH based on their associated lesions into: simple acute SDH without brain injury (mortality: 22%); acute SDH with contusion (mortality: 30%) and complicated acute SDH (with parenchymal laceration, intracerebral haemorrhage or burst temporal lobes; mortality: 53%).
7. Comorbid conditions: Lung infections, septicaemia, meningitis, shock, cardiac arrhythmias, upper gastrointestinal haemorrhage or cirrhosis may all influence outcome.[1,10]

According to the Traumatic Brain Injury Author group, the key issues for further investigation in cases of acute SDH include the influence of craniotomy versus decompressive craniectomy on the outcome; the impact of the timing of surgery, the pre-operative hypotension and hypoxia on outcome; identification of subgroups that do not benefit from surgery such as older patients with low GCS scores, pupillary abnormalities and associated intracerebral lesions; and investigating whether operating on all comatose patients regardless of their clot thickness would lead to a better outcome.[1]

In 2001, Tandon,[19] in a review article concluded that isolated acute SDH, acting as a compressive lesion, is an uncommon clinicopathological entity with the majority of patients having associated focal (contusion/laceration/intracerebral haematoma) or global (diffuse axonal injury, subarachnoid haemorrhage) involvement or both. Ischaemia underlying an acute SDH and hemispheric brain swelling may be superadded and self-perpetuating and may lead to uncontrollable elevations of intracranial pressure with consequent herniation, brainstem compression and haemorrhage. The molecular cascade initiated by the injury may lead to secondary brain damage. Thus, even with successful and early evacuation of the clot and aggressive intensive care management, mortality still remains high and functional status is often compromised. The future reduction in morbidity and mortality will depend upon the effective prevention, arrest or reversal of the molecular events that are responsible for the secondary ischaemia and cytotoxic oedema. Acute SDH should therefore be subclassified as SDH with or without associated parenchymal pathology in order to shift the focus from the haematoma to the brain injuries as that would lead to a more expeditious addressal of the entire coexisting pathology and the secondary changes. This would permit better comparison of different therapeutic modalities and better prognostication.

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37 Extradural Haematomas

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INTRODUCTION

Extradural haematoma (EDH) is a collection of blood between the potential space that exists between the inner table of the skull and the dura (periosteal layer). Extension of the haematoma usually is limited by suture lines owing to the tight attachment of the dura at these locations (continuation of periosteal layer of the dura with the pericranium at the sutures).

EPIDEMIOLOGY

Extradural haematoma occurs in approximately 2% of all patients with head injuries and 5–15% of patients with fatal head injuries. EDH is considered to be one of the most serious complications of head injury, requiring immediate diagnosis and surgical intervention. EDH may be acute (58%), subacute (31%) or chronic (11%). It usually occurs in young adults and is rare in children below 2 years of age[1,13,34] (due to the plasticity of the immature calvarium) or after age 60 (because the dura is adherent to the overlying bone). The incidence of delayed extradural haematoma (DEDH) following an initially negative CT scan is reported in 10–30%.[16]

PATHOPHYSIOLOGY

Extradural haematoma usually results from a brief linear contact force to the calvarium that causes separation of the periosteal dura from bone and disruption of interposed vessels due to shearing stress. Skull fractures are found in 85–95% of adult cases. Arterial or venous structures may be compromised, causing rapid expansion of the haematoma. However, chronic or delayed manifestations may occur when venous sources are involved. The haematoma arises from injury to the middle meningeal artery in over one half of the patients, from the middle meningeal vein in one third and from diploic veins or a torn dural venous sinus in the remainder.[44]

The temporoparietal region and the middle meningeal artery are most commonly involved (66%),[12,21,36,37,40,44–46,48] although the anterior ethmoidal artery may be involved in frontal injuries, the transverse or sigmoid sinus in occipital injuries and the superior sagittal sinus in trauma to the vertex. Bilateral EDHs account for 2–10%[19] of all acute epidural haematomas in adults but are exceedingly rare in children. Posterior fossa EDHs occur in 5% of all cases of EDH.[17,25,28,30,35,42,43,54] Associated intracranial injury occurs in a minority of patients thus implying a better prognosis for these patients, if managed emergently. The risk factors for DEDH include lowering of intracranial pressure (ICP) medically and/or surgically, thus reducing the tamponading effect, rapid correction of haemodynamic shock and coagulopathies.[19]

CLINICAL PRESENTATION

This classification was first described by Kristiansen and Tandon in 1960.[39] Patients with EDH may have the following five clinical presentations:[3,5–13,20,45,46,48,49,51]

- Conscious throughout (8–24%)
- Unconscious throughout (23–24%)
- Initially conscious and subsequently unconscious (20–28%)
- Initially unconscious and subsequently lucid (14–21%)
- The "Textbook" presentation consisting of brief post-traumatic loss of consciousness (LOC), followed by a "lucid interval" for several hours and then obtundation, contralateral hemiparesis and ipsilateral pupillary dilatation occurs in less than 10–27% of the patients.

A lucid interval is not pathognomonic for EDH; other post-traumatic mass lesions can also present in a similar manner. There are no definite symptoms of EDHs. The triad of head injury with lucid interval, mydriasis on the side of the haematoma and contralateral hemiparesis occurs in only 18% of the cases and mainly when the EDH is localised to the temporoparietal region.

The dilated and non-reactive pupil can be associated with ipsilateral hemiplegia. This is due to indentation of the contralateral cerebral peduncle by the edge of the tentorium cerebelli (Kernohan's notch). Initially, the pupil on the side of EDH contracts due to irritation of the oculomotor nerve and the opposite pupil will be normal in size. In the next stage, the ipsilateral pupil dilates due to paralysis of the oculomotor nerve. Finally, the pupils of both the sides become dilated and fixed (Hutchinson's pupil).

Editorial note: So called Hutchinson's pupils is neither characteristic nor follows the sequence originally reported. For good outcome the diagnosis and treatment of EDH should be carried out prior to the pupil becoming dilated and fixed.

Paralysis of extraocular muscles supplied by the oculomotor nerve occurs a little after pupillary changes as the pupillary fibres are more sensitive to pressure due to their peripheral arrangement in the oculomotor nerve.

Patients may also present with minimal complaints such as headache, nausea and vomiting. The variable appearance and progression of symptoms depend on the location, speed and growth of the haematoma. A post-traumatic disorder (a form of vagal syncope), described by Denny-Brown, consisting of "lucid interval" followed by bradycardia, brief episodes of restlessness and vomiting, without intracranial hypertension or mass, must be considered in the differential diagnosis.

DIAGNOSIS

The diagnosis of EDH must be considered when the plain skull X-rays show a fracture[1,3,5–11,13,34] and it must obviously be clinically correlated. A fracture is not identifiable in approximately 40% of the cases. If the clinical condition of the patient permits and a non-contrast computed tomogram (CT) scan is possible, it must be done urgently. The "Classic" CT appearance is seen in 84% of the cases and consists of a hyperdense, biconvex (lenticular) mass adjacent to the skull[4,13,32,52] (Fig. 1). Fracture lines will further be evident and mass effect appreciated. Generally the EDH is confined (restricted) within sutures, but this may not be the case every time. Occasionally, air may be visualised within the haematoma due to an associated internal or external compound fracture of the skull.[15,24] Magnetic resonance imaging (MRI) can also be done, but is time consuming and in no way superior to CT. Another diagnostic modality now under development is near infrared spectroscopy which can be used with reasonable sensitivity and specificity for detection of intracranial lesions in a short time[26,27] and could be informative when the patient is herniating, and urgent surgical intervention is required. Cervical spine evaluation usually is necessary because of the risk of neck injury associated with EDH.

MANAGEMENT

Laboratory investigations which are routine for traumatic brain injury patients are also done. These are as follows:

- *Complete blood count (CBC) with platelets:* To monitor for infection and assess haematocrit and platelets for further haemorrhagic risk.
- *Prothrombin time (PT)/activated partial thromboplastin time (aPTT):* To identify bleeding diathesis.
- *Serum chemistry, including electrolytes, blood urea nitrogen (BUN), creatinine, and glucose:* To characterise metabolic derangements that may complicate the clinical course.
- *Toxicology screen and serum alcohol level:* To identify associated causes of head trauma and establish the need for surveillance with regard to withdrawal symptoms.
- *Type and hold an appropriate amount of blood:* To prepare for necessary transfusion needed due to blood loss or anaemia.

In 1990, Pickard and co-workers[47] showed that surgical management of post-traumatic EDH is one of the most "cost effective" of all surgical procedures in terms of quality of life and work years preserved.[48] Management of EDH most of the time is surgical,[1,3,5–13,34,53] but, in a few selected patients, non-surgical management[13,14,32,38,48,49] may be attempted (Figs 2A and B). These are:

- Small EDH (≤1 cm maximal thickness)
- Subacute or chronic EDH
- Minimal neurological signs and symptoms.

These select few patients must be closely observed and surgery undertaken, if the patient fails to show progressive improvement. In 50% of the cases, there is a transient increase in size between days 5–16, and it is during this time period that most of the non-surgically managed patients need special attention.[16] Surgery should be done for most posterior fossa EDHs.

In a rapidly deteriorating patient with suspected EDH, a CT scan is inappropriate. The clinical triad of altered mental status, unilateral pupillary dilatation with loss of light reflex and contralateral hemiparesis is most often due to upper brainstem compression by

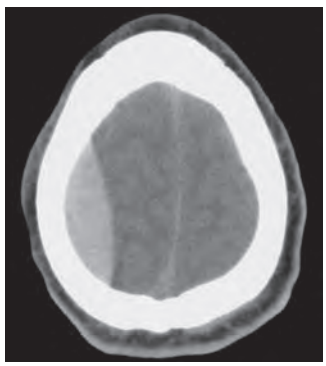
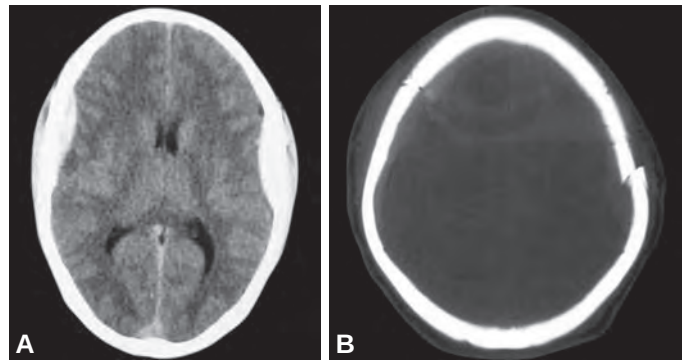


Fig. 1: Right frontotemporal EDH with mass effect managed by surgical intervention



Figs 2A and B: CT scan of the brain. (A) With bone windows. (B) Showing bilateral EDH with fracture calvarium managed conservatively

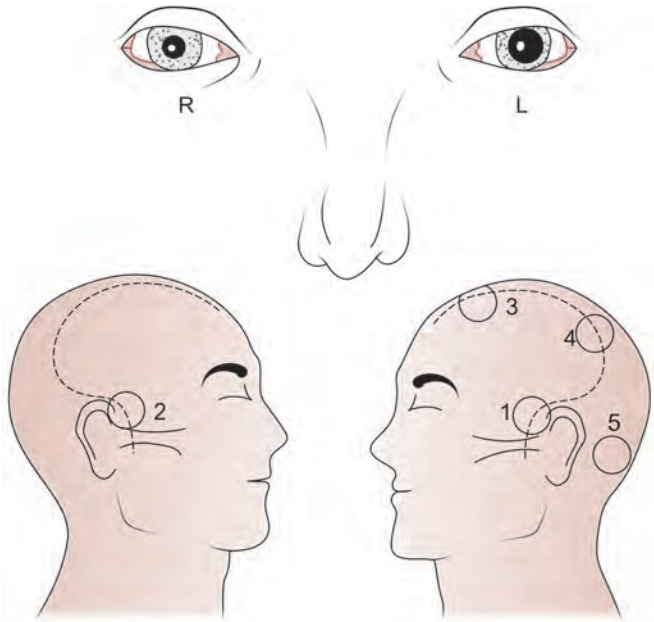


Fig. 3: Order of placement of exploratory burr holes: (1) temporal burr hole on the side of initial dilatation of pupil; (2) temporal burr hole on the opposite side; (3) frontal burr hole on the side of initial dilatation of pupil; (4) parietal burr hole on the side of initial dilatation of pupil and (5) occipital burr hole on the side of initial dilatation of pupil

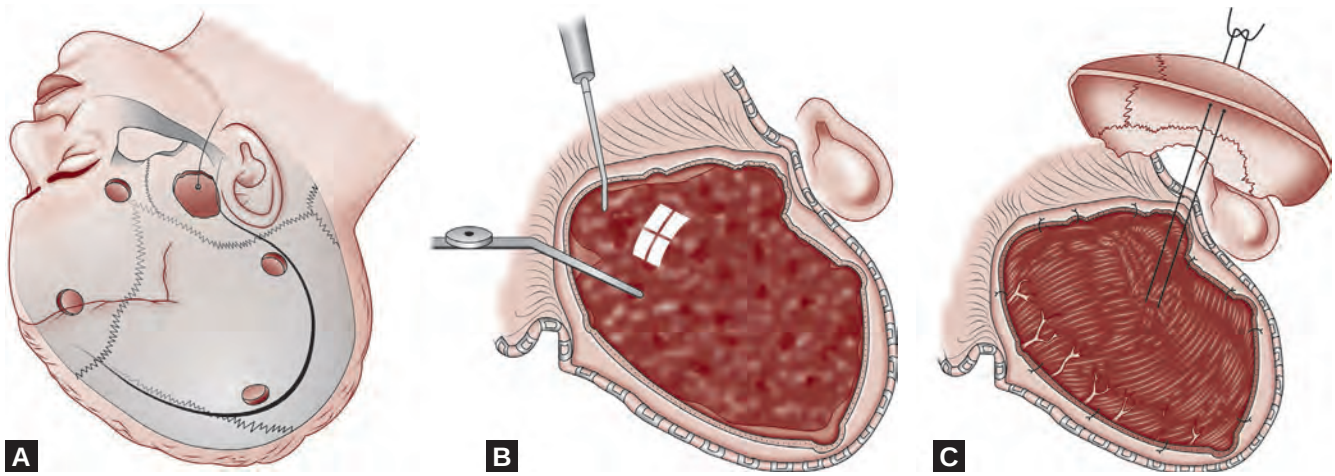
uncal herniation which, in the majority of trauma cases, is due to EDH. In such patients exploratory burr holes are indicated.[18,26,27,41,48–51,53] The choice of the site for initial burr hole placement are (Fig. 3) as follows:

- Start with temporal burr hole on the side
  - Ipsilateral to the dilated pupil (will be correct side in >85% of EDHs and other intra-axial mass lesions.
  - If both the pupils are dilated, use the side of the first dilating pupil (if known).
  - If the pupils are equal, or it is not known which side dilated first, place on side of obvious external trauma. For example, bruising and/or scalp haematoma.
  - If there are no localising clues, place holes on left side (to evaluate and decompress the dominant hemisphere).
- If no epidural haematoma is found, the dura is opened if it has bluish discolouration (suggests subdural haematoma), or if there is a strong suspicion of a mass lesion on that side.
- If completely negative, usually perform temporal burr holes on the contralateral side.
- If negative, further burr holes should be undertaken if CT scan can still not be done.
- Proceed to ipsilateral frontal burr hole.
- Subsequent burr holes may be placed at the parietal region and lastly in the posterior fossa.

If the burr hole is positive, then a modest bony decompression is performed around the burr hole and then the definitive craniotomy undertaken incorporating the burr hole(s).

Patients who are neurologically stable and can undergo CT scan should have this investigation done at the earliest. This avoids time consuming and often misleading diagnostic burr holes. If EDH is detected, then the indications for surgical management are given as follows:

- Any symptomatic EDH.
- An acute asymptomatic EDH >1 cm (containing more than 40 ml of blood) in its thickest measurement.
- EDH in paediatric patients (low threshold for sudden deterioration as there is less room for the clot to accumulate).
- Failure of non-surgical (conservative) management. There are mainly three surgical objectives (Figs 4A to C). These are as follows:
- To remove the clot, thus reducing the ICP and eliminating the focal mass effect.
- Achieve absolute haemostasis.
- Prevent reaccumulation by placing dural hitch sutures (tack-up sutures). A central tack-up suture (Poppen's suture) in the middle of the craniotomy flap is always advisable.



Figs 4A to C: (A) Skin incision for trauma flap with subtemporal craniectomy for initial rapid decompression of the haematoma. (B) Gentle evacuation of the EDH with irrigation and suction. (C) Adequate haemostasis with placement of dural hitch sutures at the margins of the craniotomy with a central hitch suture fixing the dura to the raised bone flap

POSTERIOR FOSSA EDH (PFEDH)

Among the posterior fossa post-traumatic haematomas, EDH is the most common lesion that requires surgery, followed by SDH and ICH, respectively. Infratentorial EDH is most often due to lateral sinus injury, but injury to sinuses deep to the skull base may be more frequent than is commonly realised.[2,17,22,25,28–30,43] Occipital fractures extend into the petrous bones in more than one third of the cases, resulting in significant hearing loss (mostly sensorineural) in 20% of cases and facial nerve injury in 9% of cases.

Clinically, deterioration may be rapid, with respiratory depression occurring without any pupillary change or motor signs. Headache, nausea, vomiting and neck stiffness are the most common signs. The patient may present with a classic lucid interval, but in acute cases, patients more commonly present with signs of brainstem compression of rapid onset.

Patients with posterior fossa EDH should intensively be managed with a low threshold for surgical intervention.[2,17,22,25,28–30,35,42,43,54] The principles and objectives of surgery remain the same as for supratentorial EDH, i.e. evacuation of EDH and reduction of ICP and mass effect, adequate haemostasis and placement of dural tacking sutures (Figs 5A to C). In view of obstructive hydrocephalus placement of a right frontal ventriculostomy is mandatory before surgery. Bone removal should include the rim of the foramen magnum inferiorly and go up to the edge of the transverse sinus superiorly, to allow identification and control of bleeding from the sinus. A rapidly performed craniotomy using a high speed drill and a craniotome is possible in place of the usually performed craniectomy, as the dura is already stripped from the overlying bone by the haematoma and there is minimal chance of dural injury.

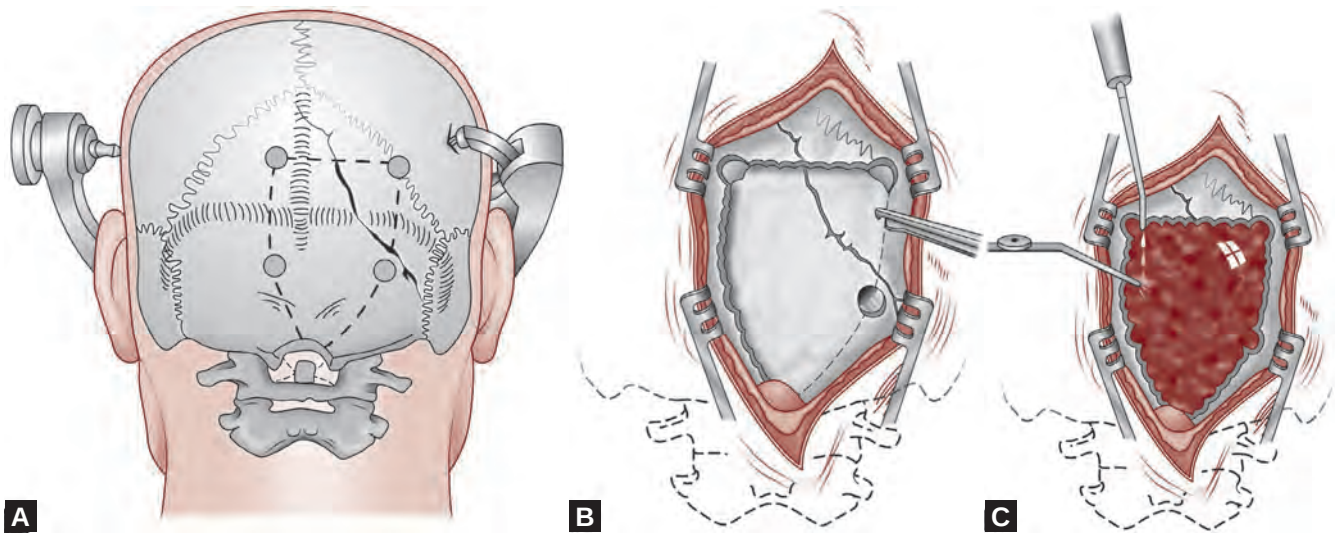
After emergent neurosurgical evacuation of the haematoma, the patient is transferred to the intensive care unit (ICU) for further care. Subsequent care generally includes the following:

- Serial neurological examinations
- Management of elevated ICP
- Avoidance of hypotension or hypertension [i.e. maintain mean arterial pressure (MAP) between 70–130 mmHg]
- Use of isotonic solutions, such as normal saline, to minimise cerebral oedema
- Avoidance of hyperthermia
- Treatment or prevention of post-traumatic seizures
- Observation and potential repair of CSF leaks
- Prevention and, when necessary, treatment of urinary tract infection
- Prevention of venous thrombosis
- Prophylaxis for gastric ulcers
- Physical, occupational and speech therapy as required
- Repeat CT scan for clinical deterioration.

MORBIDITY AND MORTALITY

Delay in diagnosis and treatment is the most common preventable cause of morbidity and mortality. Recurrent or residual haematoma may result from failure to gain full access to the haematoma and to the lacerated meningeal vessels or multiple small bleeders on the dura where it has been stripped off the inner table of the skull.

Mortality following treatment of EDH varies from 5 to 43%. Mortality is particularly low in children (5–10%) and increases sharply in those over age 40 (35–50%). Associated intracranial lesions, such as subdural haematoma (SDH), intracerebral haematoma (ICH) and cerebral contusion, carry a poor outcome and results in mortality rate four times greater when compared to those patients without such lesions. Older age, poor preoperative neurological condition, large haematoma volume, delay in operative evacuation, large midline shift and post-operative elevation in ICP are all associated with poor prognosis.[12,18,20,21,23,31,33,36,37,40,45,46,48,50,51,53]



Figs 5A to C: (A) Skin incision for evacuation of posterior fossa extradural haematoma (EDH). (B) Craniotomy done with underlying EDH being visualised. (C) Gentle evacuation of the EDH with irrigation and suction

In the present environment of consumer protection and awareness the medical/legal pitfalls to be considered are given below:

- Failure to consider diagnosis, especially in a conscious patient with normal pupils
- Failure to diagnose EDH in a patient with altered mental status (instead naming alcohol or another intoxicant as the cause)
- Failure to closely observe traumatic brain injury patients with frequent neurologic evaluations
- Failure to transfer expeditiously to a trauma centre with a neurosurgeon (delayed transfer and triage may be the principal determinant of death)
- Failure to consider EDH in all patients who have experienced head injury
- Failure to promptly evacuate the haematoma when surgically indicated.

CONCLUSION

EDH occurs in approximately 2% of patients with head injuries. EDH is considered to be the most serious complication of head injury, requiring immediate diagnosis and surgical intervention. It usually occurs in young adults, and is rare in children below 2 years or after the age of 60 years. The temporoparietal region and the middle meningeal artery are involved most commonly. EDH occurs due to vascular tear and dural stripping following trauma. EDH should be suspected in patients with progressive deterioration in level of consciousness and patients with a lucid interval. CT scan is the investigation of choice and shows a biconvex lenticular hyperdense lesion on plain CT. Early diagnosis and quick surgical evacuation is the key to good results. The outcome depends upon on the level of consciousness at the time of operation, and associated brain and systemic injuries. Quick diagnosis and early surgical evacuation lead to excellent results.

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38 Traumatic Intracerebral Haematomas

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Patients with head injury who sustain sublethal intracranial damage normally tend to recover unless certain secondary complications set in. These are often referred to as "epiphenomena" or "the second accident".[19] These "epiphenomena" signify the onset and perpetuation of post-traumatic intracranial hypertension. A common and treatable cause of post-traumatic intracranial hypertension is an expanding intracerebral haematoma. The survival rate of the victims sustaining a sublethal intracranial injury depends to a large extent on the early recognition and treatment of intracranial haemorrhage.

CLASSIFICATION

Traumatic intracranial haemorrhage may be classified on the basis of the anatomical location of the bleed as subarachnoid, extradural, subdural or intracerebral; and on the basis of the time factor as acute, subacute and chronic. The latter classification is arbitrary, but useful for diagnosis and prognosis.

Intracerebral haemorrhage can be either in the form of a haematoma or a contusion. Intracerebral haematomas are more common, occurring as the primary lesion in 10% of severe closed head injuries in the Traumatic Coma Bank (TCB) data study series.[10] It is difficult to distinguish between intracerebral haematomas occurring primarily and those associated with a contusion. Haemorrhagic contusions were present as the primary lesion in 3% of severe closed head injuries in the TCB data study.[10]

INCIDENCE

The incidence of intracranial haemorrhage in acute head injury is difficult to assess. There can be no reliable data available regarding those cases who die immediately after the accident and those that do not reach the hospital.

In India, the pattern of incidence of complications has shown an interesting variation. Three decades ago, acute subdural and extradural haemorrhages were less frequent as traffic accidents were mostly slow-speed injuries.[25] This picture has now changed with the increasing number of automobiles and motorized traffic in the cities. The high speed attained by vehicles on the highways of the West is not seen in India and the developing countries because of the type of roads and the type of traffic.[29,30] This is bound to change with the advent of world-class roadways in India such as the Golden Quadrilateral and similar roads. The existence of ambulances and the availability of first aid on these highways are but a small step in the right direction.

INTRACEREBRAL HAEMORRHAGE

Most severe head injuries have some degree of intracerebral haemorrhage which may be conveniently classified as follows:

1. Immediate
   a. Cortical and subcortical haemorrhage (local or diffuse) in association with brain laceration and contusion.
   b. Petechial haemorrhages – small, medium or widespread in the brain substance.
   c. Massive intracerebral haemorrhage.
2. Delayed intracerebral haemorrhage.

Immediate Intracerebral Haemorrhages

Cortical and Subcortical Haemorrhage

All lacerations or contusions of the brain, either due to direct injury as in a depressed fracture and penetrating injury or in a closed head injury due to an acceleration-deceleration type of trauma are associated with some amount of subpial and subcortical extravasation of blood. In the closed type of trauma, such lacerations are most marked in the frontal, temporal and occipital poles and their undersurfaces. These areas of the brain are more vulnerable as they strike the irregular inner surface of the skull and also because they impinge over the sphenoidal and petrous ridges of the base of the skull. The damaged capillaries in the surrounding area give rise to a number of small haemorrhages and the area of laceration is surrounded by an area of oedema. When extensive, this oedema may result in raised intracranial pressure (ICP). Traumatic basal ganglia haematomas are due to acceleration and deceleration injuries. A contusion index has been developed that grades contusions based on the depth of injury (1-superficial cortex, 2-full thickness of cortex, 3-cortex white matter junction) and extent of contusion (1-localised, 2-moderately extensive, 3-extensive).[13]

Petechial Haemorrhages

In many cases of acute brain injury where epiphenomena have not occurred, autopsy studies reveal small or moderate foci of haemorrhage in the white matter, basal ganglia, brainstem, corpus callosum and the cerebellum. Impairment of respiratory function due to any cause following a head injury leads to anoxia of the brain, which also results in petechiae. These are not unlike those found in cases of asphyxia and strangulation. These haemorrhages are also caused by distortion of the brain occurring at the time of the accident with consequent damage to the capillaries. The intracranial vessels are fixed either at the base of the skull or at the dural sinuses, while the substance of the brain is soft and floating in the cerebrospinal fluid (CSF). The shearing strain of the injury causes friction between the fixed vessel and the deformed brain substance – "neurovascular friction" of Shimizu et al.[27]

Small haemorrhages of this type attain clinical significance in critical areas like the pons or the midbrain.[30] When occurring around the aqueduct, they may lead to obstruction to the flow of CSF. Contusions in the brain with capillary haemorrhages may coalesce and form small haematomas. These are often multiple. Schneider et al.[26] found that 36% of contusion haematomas were multiple and 64% were solitary. These are often associated with other injuries to the brain like extradural or subdural haematomas and fractures. These small haematomas rarely require operative removal. After absorption some of them may coalesce and form cavities resulting ultimately in post-traumatic porencephalic cysts, which may or may not communicate with the ventricular system or the subarachnoid space.

Massive Traumatic Intracerebral Haematoma

Traumatic intracerebral haematoma as an isolated lesion is not common. However, those associated with contusion and laceration and acting as a significant mass lesion constitute one of the most common lesions requiring surgical relief.[28] More frequent in the older age group, they are situated mainly in the temporal and frontal lobes, due to the brain impacting against the rigid skull. Parietal and occipital lobe haematomas are much less common and are usually due to direct impact, as seen in assaults.[14] They rarely occur in the cerebellum (Figs 1 and 2). The source of haemorrhage is the rupture of an artery or vein. Multiple haematomas involving the brainstem and basal ganglia may occur.[2,23,30] Most intracerebral haematomas are visualised as hyperdense mass lesions and can be detected by computed tomography (CT) immediately after the trauma. It may be noted that in many, if not most cases of traumatic intracerebral hemorrhage (ICH), there is an accompanying, usually inconsequential, layer of subdural blood.

Intracerebral haematomas may co-exist with compound depressed fractures and may be revealed while the fracture is being treated. Some of them clinically simulate acute extradural or subdural haemorrhage or may be associated with them.[16] Others may present subacutely some days after the head injury with signs of increasing ICP. In subacute cases, CT scan is of great help in the diagnosis and localisation, as well as in detecting associated surface haematomas. The majority of acute cases are fatal if the haemorrhage does not stop. Kristiansen and Tandon[18] found (before the CT era) intracerebral haematomas in a series of 146 cases of post-traumatic intracranial haematomas of which only 50% could be saved. When encapsulated, the haematomas can be evacuated with benefit, through suitably placed burrholes.[25] Stereotactic evacuation can be done. In surface haematomas, if burrhole aspiration is not effective, the localised haematoma can be removed by a craniotomy. Tandon recommends that all patients with sizeable intracerebral haematoma require a large trephine or a formal craniotomy to achieve satisfactory

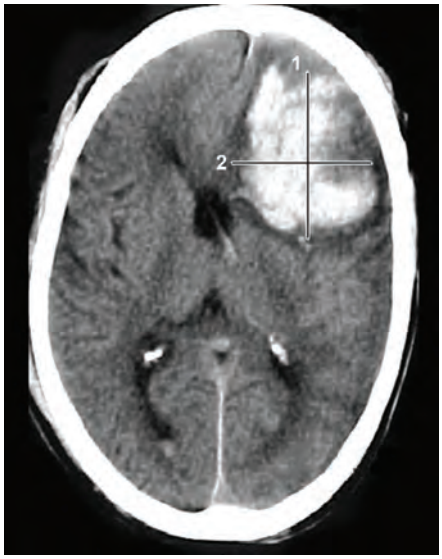

Fig. 1: CT scan of the brain showing post-traumatic haematoma in the frontal lobe

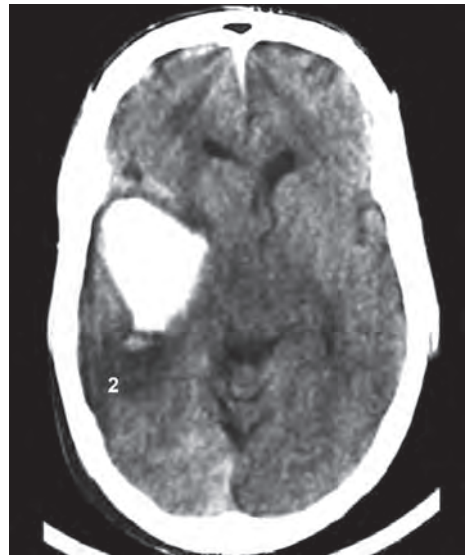

Fig. 2: CT scan of the brain showing post-traumatic haematoma in the temporal lobe

evacuation and decompression.[28,29] Small haematomas do not need surgical relief. Endoscopic evacuation of the intracerebral hematoma can also be done.

Delayed Intracerebral Haemorrhage

A delayed haematoma is one that is seen on a repeat CT scan within 24–48 hours of the injury, and was not present on the initial scan. A circumscribed haematoma may occur sometime after the original accident during the process of repair of the lacerated brain. This is due to bleeding from the necrosed blood vessels into the lacerated area. Originally described in 1891 by Bollinger[3] as "late traumatic apoplexy", this rare syndrome is interesting not merely as regards the time factor but also because of the "apoplectic" onset of symptoms.[11] Mertol et al.[20] found the average interval between the trauma and the delayed haemorrhage to be about 24 hours. Its pathogenesis is not clear.[1] The fact that these cases occur usually in the older age group may indicate that this may be a complication of a pre-existing vascular pathology such as atherosclerosis. There is renewed interest in delayed injury which is now known as the "concept of secondary autodestruction" as an area of research.[12] A probable explanation seems to be that the bleeding occurs slowly into a softened area of traumatized brain, the "apoplexy" occurring when a critical point is reached. During the intervening period the patient appears well and presents a picture resembling a chronic subdural haematoma. The diagnosis is difficult as the symptoms and signs, both focal and general, tend to wax and wane, and then all of a sudden the patient gets into the final state of coma. Clinical awareness of this possibility is important and when patients do not rapidly improve or continue to be ill, CT studies are to be repeated. The prognosis is poor even when the haematoma is evacuated by aspiration through a burrhole. Three of eight patients with delayed ICH seen by Mertol et al.[20] expired. Nineteen percent of patients with severe head injuries who deteriorated neurologically after admission to the hospital had large delayed intracerebral haematomas as reported by Clifton et al.[8]

In the course of an acutely enlarging space-occupying lesion, such as an intracerebral haematoma/contusion in the human or an extradural inflated balloon (a simulated lesion) in the experimental animal, four stages of evolution may be distinguished.

a. Stage of initial compression
b. Stage of venous congestion, oedema, anoxia and neuronal irritation
c. Stage of arterial obstruction, anaemia and neuronal paralysis
d. Stage of irreversible neuronal failure and death.

Stage of Initial Compression

Initially the rise in ICP due to an increasing mass lesion is compensated by the displacement of CSF, blood and brain itself. However, once these mechanisms prove to be inadequate, venous congestion leads to stasis of blood and an increase in tissue CO_2 and oedema. Clinically the signs are those of neuronal irritation, epileptic fits, constricted pupils and general irritability, with headache of increasing severity and vomiting. The patient may be drowsy or confused and boisterous. There is a distinct shift from orientation to confusion. There is no significant rise in the systolic blood pressure as yet. The deformed and displaced brain irritates the ipsilateral third nerve and then the contralateral third nerve followed by their paralysis resulting in sequential changes in the pupils. These changes herald temporal lobe herniation into the tentorial hiatus and compression of the upper brainstem.

Compression of the long tracts results in ipsilateral and then contralateral hemiplegia. With rapidly collecting haematomas, the brainstem is pushed and the contralateral cerebral peduncle is compressed against the free margin of the tentorium (Kernohan's notch) leading to an ipsilateral hemiplegia. Thus, the haematoma may be on the same side as the hemiplegia (Kernohan's phenomenon).

Stage of Anaemia and Neuronal Paralysis

At this stage, the ICP is raised high enough to cause a critical reduction in cerebral blood flow. This leads to abolition of vasomotor tone and further autoregulation of the cerebral circulation is not possible. The vasoparalysis results in the volume of the blood in the vessels passively following the changes in the arterial blood pressure, and haemorrhages may occur in the brain. The patient drifts into unconsciousness, the pulse pressure rises and the respiratory rate first becomes slow and then rapid. When both the cerebral peduncles get compressed, the patient goes into extensor rigidity that comes on as extensor spasms spontaneously or on stimulation. At this stage both pupils are dilated and nonreacting. As the ICP rises further, the lower brainstem begins to suffer. The patient may hyperventilate washing out the CO_2 and manifest Cheyne-Stokes periodic breathing. The respiratory centre gets deafferented and induces apneustic type of breathing. The autonomic nervous system is in disarray and there could be excessive secretions from the salivary and other glands, which trickle down the throat, making the respiration gurgling and noisy.

Stage of Irreversible Neuronal Failure

The blood pressure begins to fall and respiratory arrest and death supervene. Experimental studies have shown that the earlier the ICP is restored to normalcy by the removal of the acute compressing lesion, the greater are the chances that oedema and other tissue changes in the brain will get reversed. Irreversibility sets in between the second and the third stages, a transition which is marked by the onset of unconsciousness.

One would expect to note this orderly sequence of events in every case but for the following four important modifying factors:

Distribution of ICP: The increasing ICP is not uniformly distributed over the entire brain, the greatest pressure being exerted nearest the lesion with the zone of increased pressure successively spreading to the opposite side and then over the entire brain. Hence, in practise, a combination of symptoms of neuronal irritation and paralysis may occur simultaneously, as for example, a constricted pupil on one side and a dilated pupil on the opposite side.

Skull not a smooth sphere: This fact and the division of the cranial cavity into compartments lead to variations in the degree of ICP from area to area and to displacement of structures through anatomical openings. This results in the clinical picture of "coning" under the falx, through the tentorial hiatus and through the foramen magnum.

The rapidity and progress of compression: These influence the brain response. If the progress of space occupation is spread over weeks or months as in neoplasms or in a chronic subdural haematoma, several other compensatory mechanisms come into play and the clinical picture becomes different.[9] High blood pressure, for example, is not a usual feature even in large tumours of the brain though the ICP may be high.

Associated brain injuries: These modify all the processes enumerated so far making the clinical picture more complicated and more rapid in progress, the changes varying with the site and degree of injury.

CLINICAL FEATURES

Conscious Level

With the exception of penetrating injuries, like gunshot wounds, it is almost impossible for severe brain damage to occur without an alteration in the level of consciousness. No one dies of a damaged brain in a conscious state; a period of coma always precedes a fatal outcome. Thus, alteration in the level of consciousness is an important clinical entity. Its relationship to the time of injury and its progress with time and therapy give valuable information regarding the diagnosis.[18]

During the first two or three hours after a non-fatal head injury, the primary neuronal injury is the main, if not the only active lesion. One may assume that complicating epiphenomena take a little time to establish themselves. This assumption, though not always true, helps as a working clinical hypothesis. Unconsciousness, which supervenes immediately after the injury but clears in a few minutes, is usually explained as concussional. If such unconsciousness persists, it indicates the severity of the underlying primary neuronal damage. On the contrary, if the loss of consciousness occurs some time after the accident, the obvious conclusion is that the primary neuronal injury was not severe enough to render the victim unconscious and that this delayed loss after the "lucid interval" is due to the onset of the epiphenomena. The state of consciousness at the time of onset of the epiphenomena has a definite significance. The greater the depth of unconsciousness at the onset, the grosser is the primary neuronal damage.

Early Detection

In patients with intracerebral haematomas, perilesional swelling and enlargement of bleeding is the rule rather than the exception. Thereby, to achieve a low mortality rate, the development of the classical picture of severe compression has to be prevented by early recognition of rising ICP and prompt intervention.

Are there any clinical signs or symptoms of raised ICP which are earlier in their onset than changes in the level of consciousness? Any such pointers would be of immense value, because the most favourable time to initiate surgical or medical therapy is before unconsciousness sets in. In this context, apart from guidance from CT findings, many neurosurgeons advocate routine ICP monitoring to detect a rise in ICP before clinical signs become obvious.

Headache, which does not subside on routine analgesic administration, persistent vomiting and convulsions, especially in non-epileptics, must arouse suspicion, though they could be explained on other grounds. The earliest alterations in consciousness are subtle and must be looked for; inattention, lack of the usual alertness, and a delayed response to routine demands are extremely suggestive even though the patient may give satisfactory answers to specific questions. There is no clinical feature really pathognomonic of extradural, subdural or intracerebral haemorrhage. A direct injury, a fracture line across the vascular markings and a boggy swelling of the scalp indicate the possibility of extradural haemorrhage.

Careful neurological examination reveals subtle signs like an extensor plantar response and hyperreflexia on one side or diplopia. Involuntary micturition in a conscious adult with head injury is always a definite indication of raised ICP. Restlessness not subsiding easily may indicate the onset of cerebral compression. These various features either singly or in combination constitute grounds enough to get a CT done.

The most frequent clinical event that prompts the surgeon to operate is the deterioration in the level of consciousness. This may be with or without a lucid interval. Pupillary asymmetry and onset of hemiplegia and convulsions are events that appear later. Thus, their presence in a conscious patient requires careful assessment to exclude local injury or contusion. Changes in vital signs, like blood pressure, pulse rate except when slow, or respiration, hardly ever provide an indication for surgery. They are more useful in the assessment of the total injury to the body.

Volumetric Measurement of Intracerebral Haematoma[6]

Volumetric measurement on traumatic brain injury is calculated by the ellipsoid method (ABC method) (previously described for AVM) or by the direct estimation

method using a grid as described by Cavalieri et al. The ABC method described by Kothari et al.[17] has been proposed as a means of measuring ICH volume.

The first step is to identify the CT slice with the largest area of haemorrhage. The variables are given as follows: (A) the largest diameter; (B) largest diameter perpendicular to A on the same slice; (C) the total number of 10 mm slices. Compare each slice with the first slice. The haemorrhage is scored as follows: If it is more than 75% compared with slice 1, the slice is counted as 1, if the ICH is 25–75% of the maximum size count the slice as 0.5 and if the slice is less than 25% the slice is not counted. The total gives the value of the variable C. The volume is then calculated by the formula ABC/2.

REGIONAL CEREBRAL BLOOD FLOW (rCBF) MEASUREMENT

Chieregato et al.[7] evaluated regional cerebral blood flow (rCBF) by means of xenon-enhanced computerised tomography (XeCT) in 29 traumatic intracerebral haematomas, from 22 patients with severe head injury [Glasgow coma scale (GCS) < or = 8]. The rCBF was measured in three different regions of interest: The haemorrhagic core, the peri-haematoma oedematous low-density area, and a 1-cm rim of peri-haematoma normal appearing brain tissue, surrounding the oedematous low-density area. They found a centrifugal improvement of rCBF as well as a decrease in the rates of CBF levels below 18 ml/100 g/min from the core to the periphery ($p < 0.0001$), which persisted over time. Ischaemic rCBF values were detected in the peri-haematoma low-density area only in 24% of the traumatic haematomas. The time course of rCBF levels showed a reduced flow in the first 24 hours, with a recovery of flow from day 2 to day 4, followed by another reduced flow ($p <$ or $= 0.0001$) both in the peri-haematoma oedematous low-density area and in the non-lesioned tissue. Their findings suggest that the only area with persistent ischaemic values was the haemorrhagic core, and the low rCBF levels seen in the peri-haematoma low-density area can be ascribed partially to ischaemia, which can possibly recover over time. Their results could encourage a surgical approach based on an early evacuation of the haemorrhagic core with preservation of the surrounding oedematous tissue.[7]

GUIDELINES FOR THE TREATMENT OF TRAUMATIC ICH[5]

1. Patients with parenchymal mass lesions and signs of progressive neurological deterioration with reference to the lesion, those who develop medically refractory-raised ICP or those who show signs of significant mass effect on CT have to be managed surgically.
2. Patients with GCS 6–8 with frontal or temporal contusions more than 20 cc in volume associated with a midline shift of 5 mm or more, with cisternal compression on CT scan and with a lesional volume more than 50 cc are to be managed surgically.
3. Patients with parenchymal mass lesions who do not show signs of neurological compromise, who have a controlled ICP and with no significant mass effect on CT scan may be managed conservatively with intensive care unit (ICU) monitoring and serial imaging.

Treatment Strategies-Timing and Methods

Intracerebral haematomas generally do not require surgical evacuation unless there is significant mass effect or intracranial hypertension resulting in a poor GCS. They resorb in about 4–6 weeks by macrophage phagocytosis and gliosis.

1. Craniotomy and evacuation of the mass lesion is recommended for patients with the surgical indications listed above. A bifrontal craniotomy sometimes may have to be performed in cases of bifrontal haematoma as the procedure provides a larger area of decompression, through which the underlying haematoma and haemorrhagic tissue can be easily visualised and evacuated. For temporal lobe lesions, one requires temporal craniotomy. Ventricular drainage may be necessary when there is associated intraventricular haemorrhage causing hydrocephalus.
2. Bifrontal decompressive craniectomy within 48 hours of injury is a treatment option for patients with diffuse, medically refractive post-traumatic cerebral oedema and the resultant intracranial hypertension. Two studies showed better outcomes when the procedure was performed before irreversible ischaemic brain damage resulted.[15,24]
3. For temporal lobe lesions—contusion, laceration, haematomas, a temporal craniotomy and removal of the damaged tissue is the treatment of choice. In case the haematoma is circumscribed, it could be removed through a cortical incision. In cases with a more diffuse lesion, an anterior temporal lobectomy may be required.[28]
4. Decompressive procedures, including subtemporal decompression, temporal lobectomy and hemispheric decompressive craniectomy, are treatment options for patients with refractory intracranial hypertension with diffuse parenchymal injury with clinical and radiological evidence of impending transtentorial herniation.

To summarise, traumatic ICH of volume more than 50 cc or in any patient with traumatic ICH in whom there is progressive neurological deterioration, mass effect on CT, refractory raised ICP and with a shift of more than 5 mm, surgery is recommended.

OUTCOME

It is believed by many neurosurgeons that in addition to age and neurological status, the CT patterns of traumatic intracerebral haemorrhages are related to outcome. Wong et al.[31] analysed prospectively and collected data of patients with traumatic intracerebral haematomas. Logistic regression analysis showed that

age and GCS score/GCS motor component score were significant factors for inpatient mortality, one-year mortality and one year outcome. There was an association between temporal haematomas and inpatient mortality, subdural haematomas and inpatient mortality, and bilateral haematomas and unfavourable one year outcome. They concluded in patients with severe head injury, a traumatic haematoma of more than 50 ml was associated with higher inpatient mortality, and in addition to age and GCS score, the CT patterns of bilateral haematomas, temporal haematomas and associated subdural haematomas were suggestive of poor outcome or mortality.[31]

PREVENTION OF TRAUMATIC ICH

No discussion on traumatic ICH is complete without a note on prevention and the programs which have been implemented to lessen the sufferings of people affected by trauma. Neurosurgeons generally cry themselves hoarse about road safety, as they more than any other specialty in medicine see more often than not lives and families marred by trauma. Towards the goal of trauma prevention, the efforts of the World Health Organization (WHO) and the Accident Trauma and Life Support (ATLS) programs are to be lauded.

The ATLS was born through the untiring efforts of Dr JK Styner in 1978. Having suffered a family tragedy following a flight accident in 1977, he realised that the treatment of trauma could be made more efficient if the doctors were systematically trained. He patterned the ATLS on the already existing advanced cardiac life support (ACLS), which had made inroads into emergency cardiac care and was paying rich dividends. The first ATLS prototype program was started in conjunction with the Southeast Nerbraska Emergency Medical Services in 1978. The American College of Surgeons (ACS) committee on trauma (COT) adopted it in 1979 and ever since it has grown in stature and efficiency and is today considered the *sine qua non* in a trauma unit. It has brought about a uniformity world over in the treatment of the injured.[4]

The Essential Trauma Care Project (EsTC project) is a collaborative effort of the WHO together with the International Association for Trauma Surgery and Intensive Care (IATSIC), an integrated society as a part of International Society of Surgery. They have issued guidelines for essential trauma care.[21] The WHO also provides details about trauma care and recent advances on its website www.essential traumacare.org. They have stated in their guidelines what are known as "Rights of the injured"; in which head and spinal injury treatment find a special mention.[22]

The Indian Academy of Traumatology was among the first to implement these guidelines in 2003 even when it was in its nascent stages. This was done after a meeting in Gujarat. In 2005, the first National Consultation Meeting on Trauma System Development in India was held under the auspices of the WHO. The guidelines recommend 4 levels of trauma care with Level 1 being tertiary care hospitals with teaching programs in trauma and allied fields and with 24 hours service and the fourth level being the rural hospitals. But we in India indeed have "miles to go before we sleep" before quality trauma care on par with the Occident is available for all.

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39 Traumatic Brainstem Haematomas

Ashok Kumar Mahapatra, Deepak Agrawal

Traumatic brainstem haemorrhage is a rare condition. Prior to the availability of the CT scan, it was practically impossible to establish the diagnosis of brainstem haematoma (BSH) antemortem. Prior to the CT, diagnosis was suspected based on clinical findings like decerebrate rigidity and an inter-nuclear ophthalmoplegia. However, these findings can also be present due to functional disturbances, and it is not always necessary to have anatomical changes in the brainstem.[16,25,31] With the advent of CT scan, it has become possible to visualise and diagnose BSH in head-injured patients within 4–8 hours. This chapter highlights some aspects of traumatic BSH.

HISTORY

The occurrence of haemorrhages in the brainstem in cases of craniocerebral injuries was well documented by Duret in 1878. These came to be known as Duret haemorrhages.[20] Interestingly, Duret described most of them in the medulla while these generally affect the midbrain and pons. During the following years, Bollinger (1891), Attwater (1911), Martland and Beling (1929), Jefferson (1921), Bann-Worth (1935) and others discussed the various aspects of the problem. There was difference of opinion regarding the pathogenesis, the clinicopathological correlation and even about the site of the haemorrhages. For more details refer to Tandon (1964).[31]

INCIDENCE

The incidence of brainstem haemorrhage is difficult to determine. Tandon in 1964 reported 69 cases of brainstem haemorrhage among 132 autopsy cases of head injury.[31] Mahapatra et al.[16] had reported seven cases of BSH among 62 decerebrating head-injured patients. Tsai et al.[32] in 1986 reported brainstem lesions in 67 patients among 1,600 injured patients. However, the data also included indirect evidence of brainstem involvement such as obliteration of prepontine and perimesencephalic cisterns. Thus, only 19 patients in their study had brainstem injury and 12 of them had evidence of haemorrhage on the CT scan. Zuccarello et al.[37] in 1983 reported primary brainstem haemorrhage in 36 patients among 1,000 cases of head injury in whom CT scans were performed. In a study of 2,500 patients with head injuries, only 48 were found to have BSH.[19] With the advent of CT scan, the incidence of BSH has dramatically increased. Kalyanaraman and Ramamurthi[13] reported brainstem haematomas in 4.6% of all head-injured patients.

MECHANISM OF INJURY

Since Duret first described this condition in 1878, there are several pathological studies describing the details of mechanism, location and pathogenesis of BSH[6,15,25,34] (Fig. 1). Acceleration and deceleration injuries involve the brainstem to varying degrees, depending upon several factors. Mechanical effects of stretching and distortion further aggravate the damage due to vascular injury. Involvement of the brainstem can occur due to several mechanisms: (a) damage to the brainstem by direct force of impact; (b) due to flexion and distortion and (c) vascular involvement. Primary damage is also possible due to brain movement when the brainstem gets lacerated or contused by the tentorial edge.[11,25,31] While acute flexion is the most frequent cause, rarely hyperextension injury to the head can also give rise to brainstem damage.[15] Generally, primary brainstem injury can be in the form of: (a) laceration; (b) contusion and (c) BSH (Table 1). Frequently, brainstem injury is associated with injuries elsewhere in the brain. Isolated brainstem injury/haematoma occurs rarely.[3,11,15,17,22,25,31] Very rarely, traumatic brainstem transection has been reported.[10]

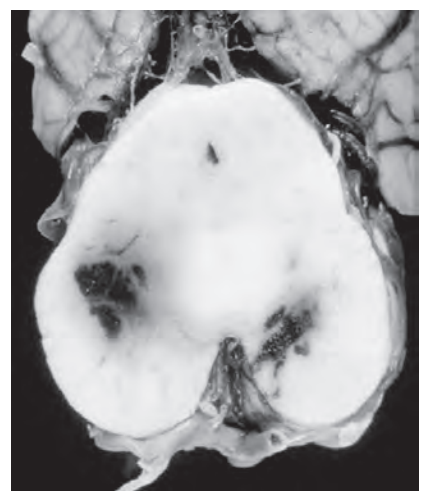


Fig. 1: Brainstem haematoma seen in bilateral paramedian location in diffuse axonal injury

Table 1: Pathology of traumatic brainstem lesions

(A)	Primary pathology
	(i) Laceration
	(ii) Contusion
	(iii) Primary brainstem haematoma
	(iv) Transection of brainstem
(B)	Secondary pathology
	(i) Oedema
	(ii) Ischaemia
	(iii) Infarction
	(iv) Secondary haemorrhage
(C)	Combination of primary and secondary pathology

Secondary damage to the brainstem occurs more frequently as compared to primary damage. Transtentorial herniation is the most frequent cause of brainstem damage. Secondary brainstem haemorrhage is more frequent in the tegmentum of the midbrain and the pons.[6,10,22,27,36] Multiple subependymal punctate haemorrhages may also occur secondary to transtentorial herniation. Secondary haemorrhages are often bilateral and paramedian in location.[5,7,15,25,27,36] Necrosis may occur in distorted areas. Secondary medullary lesions are also seen due to longitudinal buckling of the medulla. Frequently, both primary and secondary damage in the brainstem might coexist. Lesions, like ischaemic necrosis, small haemorrhages, microhaemorrhages and degeneration of axons, showing retraction bulbs can also be seen.

Subthalamic lesions are prone to microhaemorrhages and necrosis. Primary lesions are less common in the tegmentum. In the medulla, there is selective necrosis of the inferior olivary nucleus and vestibular nuclei.[25,27,31]

CLINICAL PRESENTATION

Patients with BSH are usually unconscious or in altered sensorium (Table 2). However, only on the basis of unconsciousness, a clinical diagnosis cannot be made. Rarely, patients may have GCS more than nine.[17,27,31] In our study, out of 70 patients 15 had no response to pain on admission and 35 (50%) were decerebrating. Tandon[31] reported that only two-thirds of cases were comatose from injury to death, while the remaining were unconscious. He also reported a lucid interval in 21% and no initial unconsciousness in 9% of patients. Mahapatra et al.[17] in 1990 reported five patients who were conscious at the time of admission. In a series reported by Tandon,[31] 7% of patients were conscious at the time of admission.

Table 2: Conscious state in brainstem haematoma (AIIMS experience)

Responses	*No.*
No response	15
Decerebrating	35
GCS 5–8	15
GCS ≥ 9	5
Total	70

Decerebrate rigidity is commonly observed in patients with BSH.[2,17,27,37] However, decerebrate rigidity can occur in the absence of a brainstem lesion. Rarely, patients present with hypotonicity.[27]

Other clinical findings which are typical of brainstem lesions are respiratory abnormalities, pupillary changes and temperature changes. Varieties of respiratory abnormalities have been reported depending on the site of the lesion. It could be classical Cheyne-Stokes breathing, hyperventilation or shallow breathing. Some patients rapidly deteriorate to brain death with respiratory arrest. Disturbances of temperature regulation lead to hyperpyrexia. In the past, hyperthermia was considered pathognomonic of pontine haematoma. Surprisingly, however, Tandon[31] reported hypothermia in 35% patients with brainstem haemorrhage, as compared to a 48% incidence of hyperthermia in patients with non-haemorrhagic brainstem involvement.

Pupillary abnormalities are well described in brainstem haemorrhage.[4,31,32] Fixed dilated pupils were frequently observed by Tsai et al.[32] Tandon[31] described the classical presentation of bilateral non-reacting pupils in patients with brainstem haemorrhage. Nevertheless, he found, in the same study, 26 normally reacting pupils and 65 patients clinically manifesting signs of brainstem dysfunction who on autopsy did not have brainstem haemorrhage. He also found that the so-called 'pin-point pupils' are very rarely observed in patients with BSH. Thus, pupillary changes are non-specific and not diagnostic of brainstem injury.

Disturbance of conjugated eye movement is more frequent. This is basically due to involvement of the medial longitudinal fasciculus (MLF). The disconjugate movement and abnormal oculocephalic or doll's eye movement are characteristic findings of brainstem damage.[12,21,29,32,34]

Cold Caloric Response (Vestibulo-Ocular Reflex)

Cold caloric response is an important test for assessing brainstem integrity.[12,16,17,18,29,30] Its utility in predicting the outcome in severe head injury is well established.[12,16,18,23,30] It is a simple bedside test. The head is raised by 30 degrees and the external auditory meatus is irrigated with ice-cold saline or water which stimulates the semicircular canals. The stimulus is carried by the vestibular nerve to the vestibular nuclei which are connected to the MLF, and 3rd and 6th nerve nuclei in the brainstem. Thus, by stimulating the vestibular nuclei, there is conjugate deviation of the eyes with nystagmus in normal individuals. Depending upon the site of brainstem involvement and the degree of damage, there may be absent or abnormal response of varying degrees[12,30] (Table 3). A complete absence of caloric response is indicative of a grave prognosis.[17,18] The study must be repeated several times to assess improvement or deterioration of brainstem function and is more predictive and reliable as compared to brainstem auditory evoked response.[4]

Table 3: Cold caloric response in brainstem haematoma (experience of 65 cases at AIIMS)

Responses	*No.*
Normal	20
Abnormal	24
Absent	21
Total	65

Brainstem Auditory Evoked Response

Brainstem auditory evoked response (BAER) is a reliable study assessing auditory nerve and brainstem function. BAER is frequently used as a prognostic test in severe head injury. Patients with normal BAER have a good prognosis and, on the contrary, patients with repeatedly absent BAER either die or remain vegetative. Only a few studies have reported the usefulness of BAER in BSH.[17,18,24,28,35] Sancesario et al.[28] reported BAER findings in six patients with BSH and found that abnormality of wave IV and V as well as delay in I–V interpeak latency is the most frequent finding. Tsutsui et al.[35] reported BAER in one patient with BSH, prior to and following haematoma evacuation. BAER normalised following surgery and preceded clinical improvement. Mahapatra et al.[17] emphasised the role of BAER in 70 patients with traumatic BSH. Patients with repeatedly absent BAER had a poor prognosis. On the contrary, improvement in BAER findings or normal BAER were associated with a favourable outcome (Figs 2 and 3).

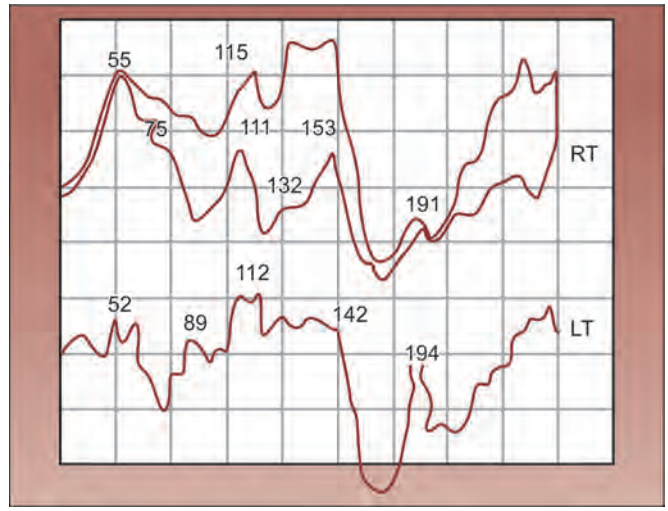
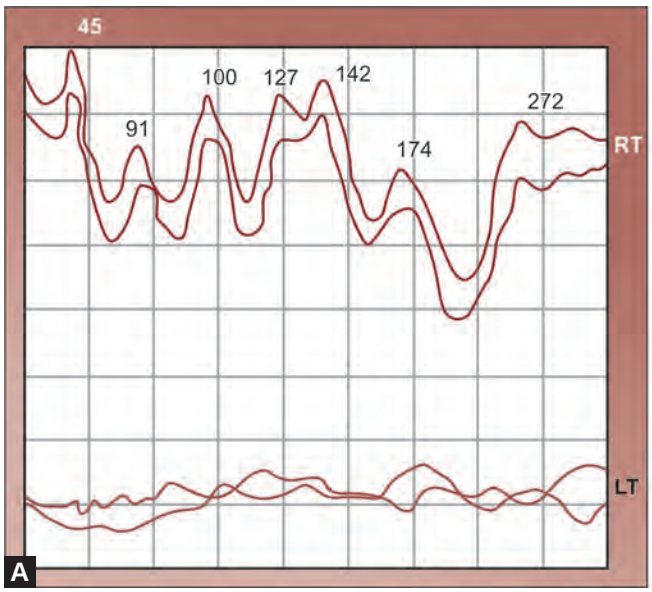


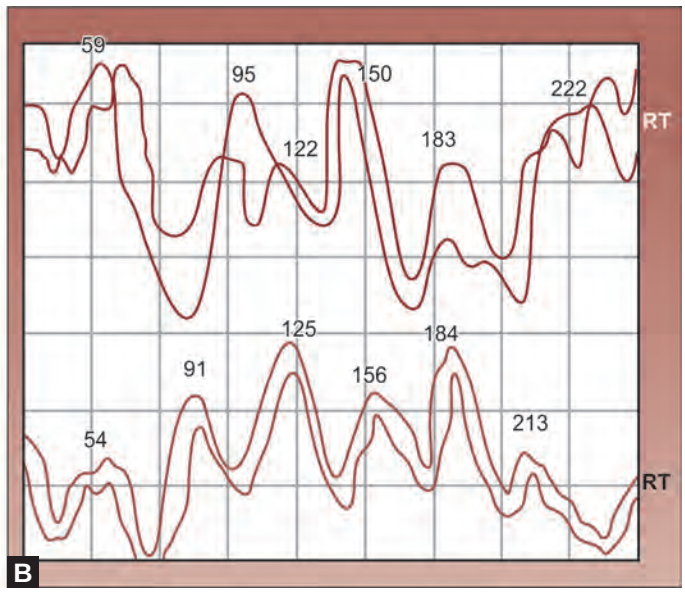
Fig. 2: BAER in a 13-year-old boy with brainstem haematoma shows normal wave pattern. The child had good outcome

RADIOLOGY

CT scan (Tables 4A and B) is a reliable imaging modality for post-traumatic intracranial pathology, because of its ability to demonstrate the extent, sites and nature of injury. Hence, today CT is the primary diagnostic method in patients with head injuries (Fig. 4). There are several reports dealing with findings in BSH.[17,24,28,32,33,35,37] CT scan not only shows the haematoma but it also shows the obliteration of the basal cisterns and the presence of blood in the prepontine or perimesencephalic cistern17 (Fig. 5). Tasi et al.[32] studied direct and indirect evidence of brainstem injury. Direct evidence was the presence of a haematoma. Among 67 patients diagnosed as brainstem injury, only 12 had haematoma, and 55 were diagnosed on indirect evidence. They also described unifocal or multifocal haematoma. The haematomas may be hyperdense, isodense or hypodense, depending on the extent of haemorrhage and oedema.

Mahapatra et al.[17] described their findings in 70 patients. Thirty-four patients had midline haematoma and 36 had a laterally placed haematoma. In 45 patients, haematomas were situated in the midbrain and in 25





Figs 3A and B: (A) BAER findings in a patient with brainstem haematoma show no wave on the left side. (B) BAER repeated one week later shows bilateral normal waves. Patient had good recovery

Table 4A: CT scan finding in patients with traumatic brainstem haematoma

	Midline	*Lateral*	*Total*
Midbrain	20	25	45
Pons	14	11	25
	34	36	70

Table 4B: Associated abnormalities along with brainstem haematoma (AIIMS experience)

Nature of pathology	*No.*
Extradural haematoma	3*
Cerebral contusion	22 (13*)
Midline shift	15

* Required surgery

patients the haematoma was in the pons. Surprisingly, there was no case of medullary haematoma (Table 4A). CT scan also demonstrated a remote haematoma in the brain in a significant number of patients.[17,32] The study reported from our department[17] showed associated focal abnormalities in 25 patients with 16 requiring surgery (Table 4B).

TREATMENT

There is no specific treatment for BSH. However, associated pathology may need surgery[17,32] depending on the size of the haematoma and the mass effect. Overall, 20% of patients with brainstem haemorrhage may have sizable haematomas elsewhere in the brain needing surgery.

As the patients with BSH are very sick and remain unconscious for long periods, they need longer intensive care management and ventilatory support. Nursing care, management of pulmonary problems and tracheostomy care need special mention. Moderate hypothermia and control of hyperpyrexia, if present, are important factors in survival. Hypothermia may enhance the chance of survival.[9]

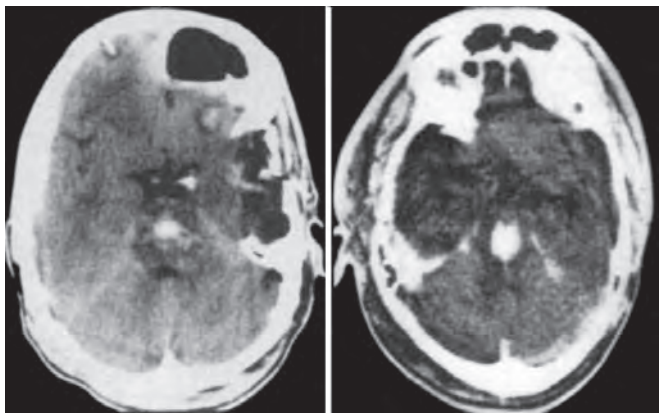


Fig. 5: CT scan in two different patients with head injury showing midline brainstem haematoma

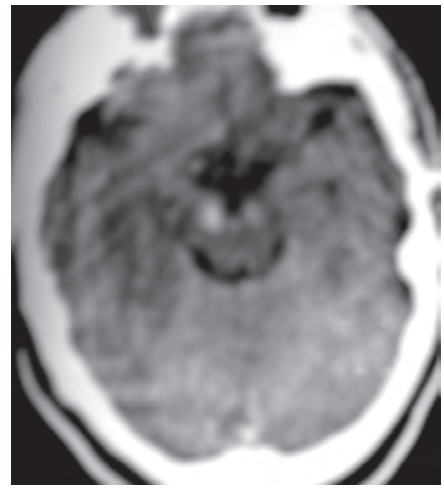


Fig. 4: CT scan of a patient with head injury shows bilateral anteriorly placed midbrain haematoma

Outcome in Patients with Traumatic BSH

Outcome of patients with traumatic BSH was considered to be grave two decades ago. With the availability of CT, diagnosis and follow-up of these patients has become possible and more reports are available regarding long-term outcome and quality of survival of these patients.[1,4,8,9,17,22,28,32,35,37]

Mahapatra et al.[17] had reported survival in more than 50% of cases studied. Among the 70 patients analysed, 38 survived and 22 patients had a good recovery. Six patients each were severely disabled or remained vegetative (Table 5). Stewart et al.[8] developed a prognostic model for head injuries and found brainstem haematoma to be an important variable in the prognostication. Age, associated skull fracture and other injuries were also significant factors for prognostication. Young patients had a good outcome. In a series reported by Tsai et al.,[32] mortality rate was 67% in patients with secondary brainstem injury. In another study the same authors reported 27% mortality in patients with transtentorial herniation, but without brainstem involvement, and 61% had mild to moderate deficits. The survival rate in transtentorial herniation alone was 73%. Of the 19 patients with primary brainstem injury only 5 patients survived. Thus, in their study, patients with primary BSH had a survival rate of 25%.

Other significant factors which help in predicting the outcome are cold caloric responses and brainstem auditory

Table 5: BAER and outcome experience in 32 patients at AIIMS

BAER findings	*No deficit*	*Mild deficit*	*Severe deficit*	*Vegetative*	*Dead*
Normal (8)	4	3	1	–	–
Abnormal (16)	4	6	5	–	1
Absent (8)	–	–	–	1	7
Total	8	9	6	1	8

evoked potentials.[4,17,18,30,35] Absent cold caloric response in patients with brainstem haemorrhage carries a grave prognosis.[17,18,30] Similarly, when repeated BAER recordings fail to show waveform or absence of wave III, IV and V, it denotes a poor outcome.[17,28,35] Presence of traumatic basal subarachnoid haemorrhage[26] in association with brainstem injury also carries a poor prognosis.

CONCLUSION

Traumatic BSH is not as rare a condition as was believed earlier. With the availability of CT scan more cases are being diagnosed to have BSH. The common sites for BSH are the pons or midbrain. Around 25% of patients are conscious at admission and 50% of patients are admitted in a decerebrating state. In more than 30% of patients, there are associated haematomas elsewhere in the brain. Caloric responses and BAER are two good prognostic tests. Repeated normal cold caloric response or BAER is indicative of a good prognosis. Survival ranges from 30 to 50%, and 25% may have good outcome.

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40 Complications and Sequelae of Head Injuries

Khosla VK, Gupta SK, Mukherjee KK, Chhabra R

INTRODUCTION

Head injury (HI) can account for a great deal of chronic disability. Common physical defects after HI include cranial nerve palsies, such as anosmia, oculomotor paresis, visual field defects, and motor disorders, resulting from cortical or brainstem lesions. The other more disabling effects of head injury include a group of syndromes for which there may not be a demonstrable pathological basis. Problems, such as cognitive incapacitation or personality change far outstrip the physical sequelae. These psychological deficits act as obstacles in rehabilitation and as a source of long-term disability. Decline in employment is more likely to be associated with mental than physical factors. These post-traumatic sequelae include:

- Post-traumatic amnesia
- Post-concussion syndrome
- Neurobehavioural sequelae
- Post-traumatic epilepsy
- Infections: Meningitis, osteomyelitis, abscess
- Post-traumatic CSF fistulae and pneumocephalus
- Normal pressure hydrocephalus
- Metabolic abnormalities[15]
- Vascular abnormalities like coagulopathies, carotid cavernous fistula, delayed intracerebral haematomas and others.

This chapter deals with the initial four post-traumatic sequelae in detail. Other conditions are dealt with in detail separately.

POST-TRAUMATIC AMNESIA

The length of post-traumatic amnesia (PTA) is defined as the time from the moment of injury to the time of resumption of normal continuous memory. It ends at the time from which the patient can later give a clear and consecutive account of what is happening around him. When the duration of PTA is noted, there may be two end-points—the first recollection after the accident or the first recollection after which the patient has continuous memory. The latter is the accepted end-point for PTA.

Usually, the termination is abrupt, except in patients with severe head injuries where memory impairment is likely to persist. The amnesic phase may last from several minutes to several weeks, yet finally ends sharply with the return of normal continuous memory. In a few exceptional cases, brief islands of memory emerge before the continuity of memory is restored. Behaviour during the PTA period varies from apparent normality to impaired memory and mental confusion. PTA includes any period of unconsciousness or overt confusion and, in addition, a further period during which outward behaviour has appeared to return to normal. The general behaviour may be surprisingly intact, so that one can be easily misled into thinking that full recovery has occurred. It is, thus, only in retrospect that the true duration of PTA can be determined with certainty.[86] In the majority of cases, the purely amnesic phase follows the clearing of overt signs of confusion or impairment of consciousness, but it may occasionally follow immediately after the injury and may be the only deficit.

The duration of retrograde amnesia (RA) is measured as the time between the moment of injury and the last clear memory from before the injury, which the patient can recall. In road traffic accidents, the journey may be typically recalled up to the accident point. Usually, RA is much shorter than PTA, although the reverse may occasionally be seen. Mostly, RA lasts for only a few seconds or minutes. Longer RA is usually seen in severe injuries and may be of many days or weeks duration. In mild injuries, there may be no RA and full details of the injury can be recalled up to the moment of loss of consciousness. With long RA, the amnesia is most dense for events immediately preceding the injury. RA, as determined shortly after injury, may be misleading, as it may shrink with time.

The duration of amnesia is taken as a guide to the severity of injury and prognosis. PTA is more valid and useful than RA in this regard.[85] In general, the duration of PTA may be related to the time likely to elapse before the patient can return to work. Broadly, in closed head injuries, a patient with PTA less than 1 hour will usually return to work within a month, with a PTA less than 1 day within 2 months and with a PTA less than 1 week within 4 months. PTA more than 1 week will be followed by disability of more than 1 year. The duration of PTA shows close correlation with objective evidence of damage to brain tissue, such as motor disorder, dysphasia, anosmia or memory impairment. The mean duration of PTA is significantly increased in patients who show post-traumatic personality changes. In penetrating

injuries, there is a tendency for the PTA to be very short or even absent in up to 50% of cases.[86]

Evaluation of Post-Traumatic Amnesia

Anterograde amnesia is evaluated by testing of impaired episodic memory for events that occur within a specific spatio-temporal context, which is reflected by difficulty in recalling events in the hospital environment and recount events in the news or in the patient's life. Traditional methods of assessing retrograde amnesia asked the patient to describe and date the last event in memory before the injury. More recently, lists of information in the public domain or an autobiographical memory questionnaire are used to assess retrograde memory loss. The sequence of recovery of orientation is person, place and time in about 70% of patients.[60] Serial administration of a brief bedside test, such as the Galveston Orientation and Amnesia Test (GOAT) can depict an early cognitive recovery curve that is related to long-term neurobehavioural outcome. Monitoring the resolution of PTA is useful for acute clinical management.

POST-TRAUMATIC (POST-CONCUSSION) SYNDROME

The post-traumatic syndrome is a constellation of symptoms that usually occur after a mild head injury. Historically it was called "shell shock".[52] Diagnosis may be made when symptoms resulting from concussion last for more than 3 months after the injury.[64] In late, persistent, or prolonged PCS (PPCS), symptoms last for over 6 months[31] or by other standards, three.[12] The patients frequently have few, if any, abnormalities on neurological examination; therefore, many of the patients are treated by physicians in other specialties. However, neurosurgeons are best able to evaluate these patients to recommend treatment and to perform the necessary research to determine the pathophysiology. Although much energy and considerable resources are devoted to the management of severe head injuries, it is evident that patients with mild head injury also constitute a significant problem in terms of socio-economic impact. Although the post-traumatic syndrome can occur in a patient who survives a head injury of any severity, it is far more common in those with mild brain injuries.

The incidence of post-traumatic syndrome varies from 24 to 84%[14,19,21,24,26] and its duration is usually 1–6 months.[40] Rutherford and associates studied head injury patients at 6 weeks and 1 year after injury and found that several factors are associated with a higher incidence of symptoms: (1) female sex; (2) headaches or abnormal central nervous system signs at 24 hours and (3) fall from a height.[87] However, the post-traumatic syndrome does not seem to be as prevalent in the paediatric population compared with groups of older patients.[43] Litigation and compensation seemed to play a minor role in the percentage that failed to return to work.[80] However, other studies contradict this, with one report claiming that litigation doubles the rate of complaints at a year.[87]

Pathophysiology

A paucity of information exists regarding the pathophysiology of the post-traumatic syndrome. Most of the current understanding is inferred on the basis of data from animal studies. Traditionally, diffuse axonal injury was believed to occur at the moment of impact and that this led to physical disruption and permanent damage; however, studies indicate that a sequence of events occurs that culminates in axonal fragmentation.[72] Because the axon does not necessarily sustain physical tearing initially and because the intra-axonal events progress over several hours, it is possible to arrest the process. The reason for the involvement of the brainstem in these very mild injuries is uncertain, as is the type of damage to the axons. Many neurosurgeons now think that many, if not most, symptoms result from microscopic structural changes. The fact that only a few axonal projections in any group or fibre tract are interrupted may be of functional importance. Loss of only a portion of the fibres in a tract may result in synaptic modulation, which alters the probability of certain responses.[2,3]

Many secondary injury events which include damage to the blood-brain barrier, release of factors that cause inflammation, free radical overload, excessive release of the neurotransmitters like glutamate (excitotoxicity), influx of calcium and sodium ions into neurons and dysfunction of mitochondria occur which injure the brain's white matter axons which may separate from their cell bodies and lead to cell death.[75]

There is, in addition, some early evidence of volume transmission through the extracellular space that may occur in combination with the usual synaptic transmission of information.[2,3] For example, a mismatch between the location of the transmitter release and receptors frequently occurs. Receptor up or down regulation may occur following brain insults, and such alterations of extra-synaptic receptors have been proposed as possible causes of alterations in vigilance, diaschisis, sleep and so forth. Volume transmission alterations may also be associated with neuronal damage with potassium ion or glutamate release into the extracellular fluid.[94] Hayes and co-workers have proposed that activation of an inhibitory system, such as the cholinergic system in the rostral pons, may cause behavioural suppression rather than interference with an activating system in the brain. More research is required to evaluate these potential injury mechanisms.[42]

Clinical Profile and Evaluation

The usual clinical profile of a patient with post-traumatic syndrome is that of mild head injury, minor or no significant abnormalities on neurological examination, and one or more of the following subjective complaints: Headache, dizziness, emotional lability, sleep

abnormalities, poor concentration, memory difficulties, personality changes, anxiety or depression.

Post-traumatic headaches are characterised by their variability. They range from mild to excruciatingly severe, steady to intermittent, throbbing to dull, burning to pressure-like and generalised to localised. Common causative factors are change in posture, stress, fatigue and effort.[16] Temporary respite can be usually obtained by rest or simple analgesics. The characteristics of the headache do not seem to be related to the length of persistence of the headache after the injury. Headaches lasting longer than 2 months are commonly accompanied by dizziness, anxiety, fatigability and impaired concentration. Prolonged headaches occur more often in patients with neurotic symptoms before injury, occupational difficulties, pending litigation, immediate emotional reaction to the injury and scalp laceration. Prolonged headaches occurred infrequently after very mild head injuries and recreational accidents.[16] Headaches persisting after head injury may also be due to tension in neck muscles, whiplash injuries, occipital neuralgia, migraine, depression, intracranial hypotension, injury to paranasal sinuses, scalp neuritis, hysteria, etc.

Post-traumatic dizziness is intermittent, with each episode lasting a few minutes usually.[39] A change in posture commonly initiates the attack, but stress is occasionally also a precipitating factor. The severity and frequency of attacks are largely variable. The symptoms usually subside with recumbence and with the eyes closed. Dizziness persisting longer than 2 months is associated with neurosis, anxiety, fatigability, impaired memory, occupational difficulties, pending litigation, retrograde amnesia, disorientation and definite loss of consciousness. True vertigo is much less common.

There is a marked and continuing decline in the percentage of patients displaying one or more post-concussional symptoms from 73% at 2 days to 24% at 3 months. Only about 1% of patients are still symptomatic after a year.[62]

Early after-injury organic contributions to the symptomatology have been suggested while non-organic factors appear to be operative when patients are still complaining of symptoms after 3–6 months. When persisting beyond a year, the evidence becomes overwhelming that such long-lasting post-concussion symptoms rest principally on psychogenic mechanisms.

Cognitive-behavioural factors, such as social stresses, personal resources and coping processes are influential over the entire time course of the syndrome.

Evaluation of a head injury patient with symptoms of post-traumatic syndrome should begin with a detailed history of the events surrounding the mechanism of injury.

Evaluation of pre-existing conditions, such as alcohol or drug dependency, psychiatric illness or endocrinological disorders, should be undertaken. The issue of ongoing or future litigation should be discussed to assess the potential for personal restitution in the situation. A thorough neurological evaluation should be performed by a neurosurgeon; cranial nerve examination should include testing for anosmia, visual acuity and field testing and a hearing evaluation. The neck and suboccipital area should be examined for muscle spasm, which may be responsible for the complaint of headache. Serial examinations should be undertaken at intervals to assess the consistency of findings and because many symptoms may dissipate with time.

Radiological evaluation should include a review of the studies obtained during the initial hospital stay, with careful attention to abnormalities that may have been overlooked initially. Follow-up computed tomography may show such lesions as chronic subdural haematoma, cortical atrophy (particularly in the frontal lobes) or hydrocephalus. Magnetic resonance imaging expands the diagnostic possibilities by demonstrating oedema, resolving contusions, effusions or evidence of diffuse axonal injury. PET scans showed reduction in glucose use by the brain and changes in cerebral blood flow have been found to exist for as long as 3 years after a concussion in studies using single photon emission computed tomography (SPECT).[41] Electroencephalography may be indicated, particularly in patients who have had seizure activity at some point in their clinical course.

Evoked potential studies, such as brainstem auditory evoked response analysis or visual evoked response analysis, afford yet another method for demonstrating evidence of underlying organic dysfunction. Although abnormal evoked potentials are indicative of altered brainstem function, their studies do not show a causal relationship between the test results and the subjective complaints of patients.[84]

Psychological testing is added to assess whether a patient has experienced memory alterations, personality changes, task-oriented difficulties and similar dysfunction. The Stroop Color Test and the 2 and 7 Processing Speed Test (which both detect deficits in speed of mental processing) can predict the development of cognitive problems from PCS.[41] The Minnesota Multiphasic Personality Inventory profile can identify characteristics of anxiety, somatisation and conversion mechanisms.[34] Other tests like Rivermead Postconcussion Symptoms Questionnaire[67], Hopkins Verbal Learning A test and the Digit Span Forward[41] examination are also helpful in assessing the psychological status of the patient. The Glasgow Outcome Scale is an accepted standard by which levels of recovery after head injury can be classified, whereas the Levels of Cognitive Function Scale have been adopted by the clinical departments of many rehabilitation centres for classifying patients, to plan their treatments and to track their progress throughout recovery.[107] It appears likely that the symptom complex of the post-traumatic syndrome is multi-factorial. There is accumulating evidence that neural changes actually accompany the injury. Most patients with minor head injuries have one or more of the above complaints early after their injuries. Patients' complaints lessen with time

and most patients are asymptomatic by 3 months; however, a minority may have persistent complaints at 1 year or beyond.[14,59,96] Rutherford and associates found that about one-third of patients had only one symptom, while another third had two symptoms. The remaining third had more than two symptoms.[87] Patients with post-concussion syndrome frequently manifest memory problems.

Some symptoms reported in a delayed fashion include irritability, sleeplessness, failure of concentration or memory and sensitivity to alcohol.[87] Most likely, new deficits are not added, but rather the recognition of the deficits is delayed. Initially, the patients and the family are preoccupied with the immediate events of the injury and it is only after the patient's return to a more normal environment that one notices the inability to handle the stresses of everyday life. Most patients improve with time, and Levin and associates thought that a single uncomplicated mild head injury would rarely result in permanent cognitive impairment.[59] Others have suggested that 3–7% of patients may have some permanent sequelae.[19] Rimel et al. observed that at 3 months after injury, about one-third of patients will not have returned to work.[80] These authors stated three reasons for persistence of problems: organic damage; psychological problems and secondary gain. Previous head injury increases the likelihood that another minor injury will result in post-concussion symptoms.

Treatment

Treatment of post-traumatic syndrome mandates recognition of the interplay of both organic and psychological factors.[103] Education of the family and patients about the condition and its outcome alleviates a great deal of apprehension and perhaps speeds improvement. Rehabilitation is intended to help the patient develop a sequence of adaptive behaviours that increase personal independence. This includes learning behavioural skills appropriate for independent daily living, such as use of public amenities, food, shopping and driving. As a result of the change in employment status of the patient, financial difficulties may complicate the rehabilitation period. Vocational difficulties may also affect marital relationships.

Many of the rehabilitative efforts for post-traumatic syndrome patients are directed at improving memory and attention.[103] Even acupuncture has been studied in patients with post-concussion headaches and many patients who have been treated by this modality have responded with favourable results.[26,103] Both physical and psychological factors are important in persistent post-traumatic headache and dizziness.[16] Mild analgesics, medicines for vertigo and dizziness, antidepressants or anti-anxiety drugs may be helpful. Fortunately, the post-concussion syndrome almost always resolves with the passage of time. In some cases, cessation of symptoms occurs only after the settlement of litigation.

NEUROBEHAVIOURAL SEQUELAE

Neurobehavioural sequelae refer to the cognitive and behavioural effects of brain injury. The range of mental sequelae is very broad and embraces most that can be found in psychiatric symptomatology.

There are a number of aetiological factors, which may contribute to post-traumatic neurobehavioural sequelae.[62] These are listed below:

- Mental constitution
- Pre-morbid personality
- Emotional impact of injury
- Circumstances, setting and repercussions of injury
- Iatrogenic factors
- Environmental factors
- Compensation and litigation
- Response to intellectual impairment
- Epilepsy after injury
- Amount and location of brain damage.

The different post-traumatic psychiatric sequelae can be broadly discussed under the following headings:

(a) Cognitive impairment
(b) Personality change
(c) Psychosis
(d) Neurotic disability
(e) Memory impairment.

Cognitive Impairment

This is the direct result of damage to the brain at the time of injury. The severity of post-traumatic cognitive disturbance depends on the degree of diffuse axonal injury, as well as the volume and location of focal injuries.[92] These cognitive impairments are due to cholinergic deficits following head injury.[8] A single, uncomplicated, minor head injury produces no permanent neurobehavioural sequelae in most of the patients, provided they do not have a pre-existing neuropsychiatric disorder.[59] Severe head injuries, especially with post-traumatic amnesia (PTA) more than 24 hours, are likely to be followed by persisting cognitive impairment. With penetrating injuries, the length of PTA is less reliable. Chance of intellectual impairment is higher with advanced age and with damage to the dominant hemisphere.[78,100]

Generalised Intellectual Impairment

After a closed head injury, the impairment of intellect is usually global. Marked dementia is usually accompanied by severe neurological disability and the patient may be in a persistent vegetative state.[48] Short of this state, the patient may be lethargic and apathetic, with incontinence and dysarthria. All intellectual processes are severely affected and recognition of relatives may be impaired. Emotional lability, with episodes of uncontrolled weeping or laughing, and outbursts of aggressive behaviour may also be there. The final level of incapacitation is characterised by mental slowing, impairment of memory, apathy and impaired abstract thinking. Loss of libido and paranoid behaviour are common. At the other

end, there may be only a very minimal degree of intellectual impairment, which may be apparent only when the patient resumes his job.[62] Between these extremes, all grades of intellectual impairment are seen. Complaints of forgetfulness and impaired concentration may be difficult to assess and may be attributable to depression, preoccupation or anxiety. There may be deficits in selective attention, vigilance and information processing. Such problems appear to be common even after minor head injury.[97] There may even be difficulty in maintaining their train of thoughts.[76]

Focal Cognitive Impairment

This is more likely to develop following penetrating head injury. Psychometric tests reveal disorders of memory, language and visuospatial competence. Deficits in sustained attention and mental speed may prove to be a great handicap.[69] Selective impairment of memory may persist despite excellent restitution of other intellectual functions. Localised damage to the diencephalon or medial temporal lobe may result in a post-traumatic Korsakoff syndrome.[62]

Dominant hemisphere injury may cause language difficulties such as impaired comprehension, speech production, reading, writing or spelling. There may be reduced verbal fluency, impaired arithmetical function or dyspraxia. Non-dominant hemisphere damage may result in visuospatial agnostic defects and disturbances of topographical orientation. Disturbances of body image, dressing apraxia and anosognosia may be marked in the early stages, but rarely persist in the absence of gross intellectual derangement.

Newcombe, studying men with focal injuries due to high velocity missiles, was able to demonstrate highly selective impairment in language, visual perception and spatial orientation persisting 20 years after injury, without any evidence of generalised intellectual deterioration.[68]

Recovery of Intellectual Function

Even after severe head injuries, some patients may slowly show improvement over time, so that a firm prognosis should not be attempted until 2–3 years after the trauma.

Most substantial improvement occurs during the 1st year, maximally usually within the first 6 months. Psychometric testing has shown that different components of cognitive function tend to plateau at different periods. Verbal test of the Wechsler Adult Intelligence Scale tended to approach those of a non-injured control group after 1 year, whereas recovery on performance subsets continued for about 3 years.[63] The slower restitution on performance tests depends upon their complex nature, requiring a synthesis of numerous capacities, such as perception, attention, learning and psychomotor speed. Surprising examples of apparent long-continued cognitive improvement have been recorded.[65] This is probably a measure of the plasticity of the human brain, i.e. re-education of the intact brain tissue to take over new functions. An additional factor may be that a part of dementia seen in the early phase of recovery is more apparent than real. This may be because of coincident affective disorder, which may be easily missed in the early phases or there may be marked motivational defect, which may be a result of dopaminergic under activity.[11] Later in recovery, psychological processes of readjustment and adaptation will play back powerfully to improve motivation.

Personality Change

This implies an alteration in the patient's habitual attitudes and patterns of behaviour, so that his reactions to events and to people are different from what they were before. Head injured patients are particularly prone to damage of the neocortical portions of the limbic system; frontopolar, orbitofrontal and temporal regions.[5] This may explain why behavioural problems are often out of proportion to the severity of neurological deficits.

Personality Change with Brain Damage

The personality changes, which accompany intellectual impairment, may be only a loss of refinement or lessened vitality of behaviour. With more severe dementia, there will be slowing, impairment in motivation, loss of libido and withdrawal of interest in surrounding events and people.

Frontal lobe lesions remain the best known examples of effects of regional cerebral damage on personality. These include lack of foresight, tact and concern, inability to plan ahead or judge the consequences of actions and a euphoric disposition. This leads to antisocial conduct, disinhibition, amorous advances and sexual innuendoes in conversation. Bilateral frontal lobe lesions, especially of the orbital parts, lead to the most severe changes. A combination of disabling euphoria and disinhibition associated with intense irritability is termed as "frontolimbic dementia".[82] Occasionally, patients could be said to have shown improvement in personality, being less prone to worry and becoming more outgoing and social.

Hypothalamic and basal brain injuries may be characterised by sluggishness and apathy, fluctuations of mood, sudden outbursts of irritability, disturbances of appetite, thirst and sleep rhythm, and varied sexual pathologies.[45]

Personality Change without Brain Damage

These include fluctuating depression, morbid anxiety, obsessional traits and persistent irritability. Often they represent an intensification of previous personality traits. In some cases, they conform to the picture of post-traumatic stress disorders (PTSD), with intrusive thoughts concerning the accident and avoidance of situations related to it.[66] The patient may dwell on the circumstances of injury or relive it in terrifying dreams. There may be marked startle response and phobic avoidance of situations, which bring the accident to the mind.

PTSD can be a long lasting source of chronic disability. Head injury may have profound sequelae in terms of career, marriage and lifestyle.[62]

Psychoses

Psychotic episodes may develop later in association with post-traumatic epilepsy (PTE).[47] The problem is more complex when schizophrenic, paranoid or affective psychosis develops in head injured patients. The causal role of injury may be far from clear, especially if considerable time has elapsed between the trauma and the onset of illness.

Brain disturbance may itself contribute directly to such developments or may act merely as a precipitant in someone already predisposed. The generally accepted view is that a constitutional predisposition to the psychosis is a major factor in most cases of schizophrenia or affective psychosis following head injury.

All forms of schizophrenia have been reported following head injury—hebephrenic, paranoid and catatonic.[30] The incidence of schizophrenia-like-psychosis after head injury is certainly greater than chance expectation and trauma may be often of direct aetiological significance, rather than merely a precipitating factor. The various factors which help in distinguishing TBI psychosis from schizophrenia include a later age of onset, less premorbid psychiatric disturbance, brief duration, a less common family history, better response to neuroleptics, less need for maintenance medication and a better prognosis.[88]

Paranoid disturbances may be the cause of much distress and disturbance after head injury. Ideas of persecution or of marital infidelity are prominent.[1]

Affective psychoses may be seen in all degrees of severity, both in the presence and in the absence of objective signs of brain injury, even after minimal trauma. Factors related to brain injury may be operative in both major depression and mania. Hypothalamic damage might play a part in lasting bipolar affective disorders.[45] Manic psychosis after head injury is much less common than major depression.[1]

Neuroses/Neurotic Disability

The post-traumatic neuroses represent the most common of the psychiatric sequelae of head injury.[73] These include a number of emotional disorders: minor depression; states of tension and anxiety; neurasthenic reactions; conversion hysteria and obsessional neurosis. Patients with post-traumatic stress disorders are increasingly being reported.[62] Severe neurosis is chiefly found in subjects prone to neurotic reactions generally, and post-traumatic neurotics, when compared to non-organic neurotics, have shown the same range of complaints and a similar degree of vulnerability. There is little to suggest that organic factors play a part over the years. There is a conspicuous lack of relationship between the severity of injury and severity of neurotic disability and neurotic symptoms are rare in the presence of marked intellectual or neurological disabilities.[62]

Depression in these patients is characteristic of neurotic depression. Anorexia, insomnia and early morning waking are rarely marked. The depression often fluctuates in severity and may be responsive to a change of activity and surroundings. Complaints of difficulty in concentration, lack of normal interest and minor forgetfulness may be marked. Anxiety may coexist with depression or occur alone. Persistent states of anxiety and tension tend to be seen after accidents of especially frightening nature.

A neurasthenic reaction may incapacitate the patient for months or years after the trauma. The patient complains that he is always tired, feels weak and lacking in energy. Fatigue, both mental and physical, is readily precipitated by effort and there is marked curtailment of activity.

Irritability is among the most common of the emotional consequences of injury. The patient is short-tempered, snappy and stricter in matters of discipline. It may be difficult to decide how far this represents an affective disturbance or personality damage due to brain damage. Hysterical symptoms are prominent among head injured patients during war.[6]

The dissociative states include fits, fugues, amnesia, motor paralysis, anaesthesia, disturbances of speech, sight or hearing. Obsessive compulsive symptoms may emerge in susceptible individuals. Typically, the patient is tense and ruminative, focussing his doubt, indecision and compulsive preoccupation on the injured head.[6] Compulsive disorders tend to occur after reasonably severe rather than mild head injuries.[44]

Memory Impairment

About one-half of survivors of severe closed head injury exhibit residual antero-grade memory deficit, as reflected by impaired learning and retention of new information.[86] Episodic memory for events with a specific spatiotemporal context is the most intensively studied form of memory in head-injured patients.[57] Tests involving verbal memory for word lists revealed that head-injured patients recalled about 50% fewer words. Recall declined with more severe impairment of consciousness in patients with at least one non-reactive pupil. However, verbal memory was unrelated to the Glasgow Coma Scale (GCS) in patients whose pupils reacted normally to light. Impaired recall of geometric designs was also related to the GCS and pupillary reactivity.[57]

Improvement in memory after severe closed head injury occurs primarily during the first 6 months on measures of verbal learning and memory and on visual recognition memory; whereas further gains are negligible.[56] Memory generally recovers to the normal range within 1–3 months after mild closed head injury. Moderate and severe closed head-injury groups exhibit impaired verbal and visual memory despite their relatively normal intellectual levels. The disproportionate impairment of memory was greater in the severely

injured patients than in the group with moderate head injury.[58] Patients will have difficulty with multitasking. Declarative memory for events is more affected than the implicit memory. Working memory and prospective memory (remembering to pay one's bills) are impaired, particularly after damage to the frontal lobes. Functional magnetic resonance imaging shows altered patterns of activation of the brain during memory tasks in patients with TBI.[76]

Although the neuroanatomic substrate for procedural learning is not well understood, the cerebellum and basal ganglia have been implicated.[27] To investigate procedural learning after closed head injury, Ewert et al. administered mirror reading, maze learning and visual tracking tests to patients.[32] Latencies of head-injured patients for reading words presented in mirror orientation decreased across the three sessions during post-traumatic amnesia, a pattern reflecting acquisition of this skill that was confirmed for maze learning and visuomotor tracking. Further increments in performance were obtained after resolution of PTA, suggesting transfer of training effects. In contrast, the patients' declarative memory for the proceedings of each session was grossly impaired. The potential for procedural learning demonstrated during post-traumatic amnesia could be exploited in rehabilitation to emphasise skill learning.

Neurobehavioural Sequelae in Children

The after effects of head injury in children differ from those in adults in certain important respects. There are several factors involved:

- Neural apparatus is more resilient to damage.
- Conversely, certain functions are more vulnerable during development.
- Compensation motive is absent.
- Cognitive and emotional aftermaths hamper school work.[62]

The overall incidence of sequelae is lower in children than in adults.[13] This may be due to the greater pliability of the skull and intracranial structures. In addition, the powers of restitution and compensation seem to be greater in the young nervous system.[100] Profound intellectual disability appears to be rare, following head trauma in children. More commonly, the child is observed to have setbacks only temporarily and recovers in the months that follow. However, while they persist, such factors can hamper education to a serious degree. Visuospatial and visuomotor skills tend to be more severely affected than verbal skills.[24] Recovery, sometimes, can extend up to 4–5 years.[54]

Among focal defects, dysphasia has been most closely investigated. A change in cerebral dominance is possible after unilateral brain injury in early life and this plasticity appears to persist to some degree in later childhood. A particular feature of childhood dysphasia is, often, the quantitative reduction of spoken and written language, extending even to gesture activities.[4] Spontaneous speech is sparse and the child must be strongly encouraged to reply to questions.

Behaviour disturbances are probably the most common and most disruptive of the head injury sequelae in children. They consist of hyperkinesis (restless overactivity), impulsive disobedience at home and at school, and explosive outbursts of anger and irritability. Marked delinquency may appear by way of stealing, cruelty and destructiveness.[13] The child may appear to be dominated by instinctual and emotional impulses, as though he has lost the inhibiting and restraining influences normally acquired during development. Sometimes, self-control is gradually re-established, as the child matures and hyperkinesis usually wanes as the child grows older. Neurotic disturbances are, by contrast, rare in children.

Boxing Injuries

Serious sequelae appear to follow repeated mild head injuries, each in itself leading to no more than brief concussion. The mechanisms of such a cumulative effect are unknown, although the findings of beta-amyloid deposition in the brain may be a pointer towards the pathophysiologic process.[62]

The picture of "punch-drunkenness" in retired boxers is widely recognised. In its fully developed form, the syndrome consists of cerebellar, pyramidal and extrapyramidal features, along with a varying degree of intellectual deterioration. Severe examples date mostly from boxing careers before World War II when medical control over boxing was less rigorous.[81] In mild examples, there is dysarthria, facial immobility, poverty and slowness of movement. At its most severe, there is disabling ataxia, dysequilibrium, festinant gait, tremors of the hands and head, and spasticity or rigidity of the limbs.

The prevalence of the syndrome increases with increasing exposure to boxing strongly upholding a causal relationship. The majority of cases remain static, once boxing is discontinued. In a few cases, there has been undoubted improvement after retirement from the ring.[81]

In addition to the neurological disability, there may be intellectual and personality changes indicative of dementia. There may be severe memory impairment, apathy, irritability, marked disinhibition and profoundly slowed thinking. The main psychiatric disturbances reported include a chronic amnesic state, progressive dementia, morbid jealousy and rage reactions.[51]

More recent studies have concentrated on "modern era" boxers who have fought under present medical controls. Evidence from brain imaging and psychometry is that, chronic as well as acute brain damage is still prone to occur. Cerebral atrophy has been found to antedate the development of overt signs of brain damage; and sometimes show association with the number of bouts fought rather than with the number of knockouts, suggesting a cumulative effect of multiple sub concussive blows to the head.[22] It is hoped that the introduction of new safety measures will diminish the risk of long-term boxing.[20]

Cerebral atrophy is commonly revealed on CT scanning, with dilatation of the ventricles, sulcal shrinkage and, sometimes, obvious cerebellar atrophy. A characteristic finding is perforation of the septum pellucidum. The EEG may be abnormal with flattening of the record, diminution of the alpha rhythm or diffuse slow waves.

At autopsy, cerebral atrophy and ventricular enlargement are obvious and ragged holes may be seen in the septum pellucidum. The most obvious abnormalities are in the deep midline structures, with tearing of the septal region and atrophy of the fornices. Severe gliosis is seen in these regions and also in the hypothalamus and thalamus. The cerebellum also shows gliosis and loss of Purkinje cells. In the substantia nigra, there is loss of pigmented neurons similar to that seen in Parkinson's disease.[28]

The cerebral cortex shows extensive loss of neurons, many of those surviving showing neurofibrillary degeneration of the Alzheimer type. The clinical features are probably related to damage to two main areas of the brain—the upper brainstem and the hippocampal-limbic system.[51]

In the occasional cases of severe and progressive dementia, it is hard to discount the possibility of coincident Alzheimer's disease. All cases with substantial neurofibrillary tangle formation showed extensive immunoreactive deposits of beta protein.[83] It is possible that frequent disruptions of the blood-brain barrier may allow leakage of beta-protein precursors from the serum into the brain.

Pathology of Traumatic Brain Injury

Evidence of neuronal and glial cell death and traumatic axonal injury contributing to the overall pathology of traumatic brain injury (TBI) in both humans and animals have been identified. Apoptotic and necrotic neurons were identified within contusions in the acute post-traumatic period and in regions remote from the site of impact in the days and weeks after trauma, while degenerating oligodendrocytes and astrocytes have been observed within injured white matter tracts.

It is generally accepted that a shift in the balance between pro-apoptotic and anti-apoptotic protein factors towards the expression of proteins that promote death may be one mechanism underlying apoptotic cell death. The effect of TBI on cellular expression of survival promoting-proteins, such as Bcl-2, Bcl-xL and extracellular signal-regulated kinases and death-inducing proteins such as Bax, c-Jun N-terminal kinase, tumour-suppressor gene, p53 and the calpain and caspase families of proteases have been studied.[79]

Treatment of Neurobehavioural Sequelae

Rehabilitation should be planned and supervised with care from the early stages of recovery. Fortunately, the majority of patients with mild head injuries make satisfactory progress without a great deal of specialised attention.[62] The initial convalescent period is usually undertaken in the hospital. Physical activities are beneficial, provided certain limits are imposed and the value of early mobilisation is recognised. Graduated exercises and games help to restore the patients' physical self-confidence and the morale is improved by opportunities for social interaction.[61] Usually, little is needed in the early phase by way of psychotherapy, but the value of doctor-patient relationship should not be overlooked. An appropriate period of time away from work will need to be advised, after taking into account the severity of injury, its complications and the patient's personality and the stresses of the work to which he will return to.

The main neurological sequelae, which require evaluation are locomotion, upper extremity function and impairment of communication. Visual acuity and visual field defects must also be assessed. Physiotherapy, occupational therapy and speech therapy have a role. The rehabilitation of cognitive functions presents a special therapeutic challenge.[69] Full psychometric assessment is the first step and serves both to highlight areas of deficit and areas of preserved function on which to capitalise. An optimistic and positive approach is required to instil enthusiasm, with ready allowance for fatigue and tolerance of shortcomings. The therapeutic program must be graded, with goals at any stage that are realisable, rational and acceptable to the patient.[53]

Emphasis should be placed upon:

- Re-education,
- Compensatory method, and
- Substitution, when a function is damaged irreparably.[92]

An important requirement is to separate primary defects, attributable directly to brain injury from the coping mechanisms adopted by the patient.[69] In the retraining of memory, it can be valuable to teach the use of visual imagery, verbal coding or other mnemonic systems.

Successful results have been described with a 5–10-week course of "attention training"[95] In this, a variety of tasks, including specially designed computer programs, were used to concentrate on five aspects of attention: focused; sustained and relative attention; alternating attention as needed for mental flexibility and divided attention which is required for simultaneous responses to multiple tasks.

Personality changes following brain damage are notoriously difficult to modify. Psychotherapy should aim at helping the patient to achieve some insight when this is lacking. A measure of control may sometimes be achieved in such matters as disinhibition, impulsiveness or emotional outbursts, although progress is usually limited. A valuable development is the application of behavioural modification techniques to brain-injured persons, with the aim of reducing disruptive behaviour and encouraging more constructive involvement in the rehabilitation process.

Tranquilizing drugs such as diazepam may help in tension and anxiety, and antidepressants should be tried if indicated. Low dose chlorpromazine is beneficial in patients with frontal lobe damage. Dopamine agonists, such as bromocriptine and lisuride have been found to be useful in patients with severe passivity and anergy.[9] There may be a place for a cautious trial of stimulating agents, such as methylphenidate or amphetamine in patients whose sluggishness and anergia are due to hypothalamic damage. Anti-convulsants are of doubtful value in preventing outbursts of aggression.[62]

Psychoses, which develop after head injury, require the same psychiatric management as the equivalent illnesses, which occur in other settings. For neurotic complications, the mainstay of treatment is psychotherapy and attention to the social problems that exist. Antidepressants and minor tranquilisers may be helpful. Post-traumatic stress disorder may require a cognitive-behavioural approach and phobic conditions will often respond to behaviour therapy.

Speedy resolution of litigation is to be desired, certainly in cases where brain damage does not play an identifiable part. Return to work should also be secured at the earliest possible opportunity.[62]

It is clearly advantageous to have centres for the rehabilitation of the more severely disabled patients. This need is widely recognised, but facilities are not equally widely available. Head-injured patients often present a combination of physical handicap with disturbances of intellect, mood and behaviour. Properly organised rehabilitation units allow a multidisciplinary approach, both in evaluation and in supervision of treatment with neurologists, psychiatrists and orthopaedicians, along with physiotherapists, psychologists, occupational therapists, speech therapists and social workers.

An essential part of the rehabilitation lies in the help and guidance offered when the time comes for preparation for return to work. Conditions usually to be avoided include shift or night work, noisy or oppressive conditions, high frequency vibration, working at heights or with moving machinery and work, which must be carried out under pressure of time.

Female patients more often need to be institutionalised, perhaps because a wife can more easily assume the major care of a disabled husband than vice-versa. Success can often be achieved by intensive rehabilitation, even among severely injured and behaviourally disturbed patients who would normally be considered to have a poor prognosis.[17] A designated case manager should be in a position to establish a continuous link among the various service providers, build up knowledge of what is available locally and coordinate input to the patient and the family.

Consideration of the sequelae of head injury is incomplete without mention of the broad effects on the quality of the patient's life and that of his family. Leisure and social activities are often profoundly disrupted. Family relationships can come under considerable strain.[37,71] Lack of comprehension of the patients' behaviour and its origins can lead to unhelpful responses on the part of those around. Anger may arise from a suspicion that the patient is not making proper effort or guilt that disappointing progress reflects the carer's own inadequacy.[37] The problems most frequently encountered by the family concerned are the patient's slowness, irritability, poor memory and emotional changes. Physical disability was less commonly a problem. Emotional lability and outbursts of pathological laughter were especially embarrassing features.[101]

POST-TRAUMATIC EPILEPSY

Definition

Post-traumatic epilepsy can be of two types: (a) One occurring within 7 days after injury is labelled as early PTE and (b) seizures occurring more than 1 week after head trauma are categorised as late PTE. Within the early epilepsy group, seizures occurring within the first 24 hours are labelled as immediate seizures.[98]

Incidence

The incidence of early epilepsy varies from 2.5 to 7%.[7,49] Young children, under the age of 5 years, have early seizures in about 7–9% of patients.[49] Late PTE ranges from 5 to 7%[7] being much higher in soldiers with missile wounds (34–53%).[90] Young children are more prone to early seizure and adolescents and adults to late seizures.[9]

Pathophysiology

The cascade of structural and physiological changes leading to PTE is still not well understood. The following different mechanisms may be responsible at different time intervals.[104]

- Direct neuronal impact
- Membrane depolarisation
- Acetylcholine release
- Temporary loss of inhibitory control from the mesencephalic reticular system
- Cerebral contusion and oedema with interference in cation transport
- Hyperexcitability of recovering neurons[93]
- Meningocerebral cicatrix and glial scar
- Dendritic depolarisation and post-synaptic hypersensitivity
- Genetic factors.

Even a single episode of experimental closed head trauma induces long-lasting alterations in the hippocampus. These persisting structural and functional alterations in inhibitory and excitatory circuits are likely to influence the development of hyper-excitable foci in post-traumatic limbic circuits.[91] The histopathological examination of brain tissue after trauma reveals reactive gliosis, neuronal and oligodendroglial loss, axonal retraction balls, Wallerian degeneration, neuroglial scar

formation and cystic white matter changes.[55,102] The deposition of iron liberated from haemoglobin may be an important causative factor.[33,48,89] Iron and other compounds have been found to affect intracellular calcium oscillation.

Pre-treatment of animals with antioxidants alpha tocopherol and selenium prevents seizures, suggesting that the initiation and the propagation of lipid preoxidation, especially of the arachidonic acid cascade, may play an important role in epileptogenesis.[25,36,105] The activation of the arachidonic acid cascade leads to formation of diacylglycerol and inositol triphosphate. This leads to elevation of intracellular calcium, which appears to be involved in excitotoxic damage to neurons. Neuronal death and reactive gliosis can lead to the formation of a glial scar, which becomes the epicentre of the hyper excitable focus.[106] The epileptogenic focus has been demonstrated to have biochemical defects in metabolism of acetylcholine, glutamic acid, gamma amino butyric acid and potassium. The epileptogenesis after chronic cortical injury could result from alterations of intrinsic membrane properties of pyramidal neurons, together with enhanced NMDA synaptic conductances.[18]

ApoE-ε4 allele and haptoglobin Hp2-2 allele may be a genetic risk factor in post-traumatic epilepsy.[29] Inhibitory GABAergic neurons were particularly more sensitive to cortical deafferentation than excitatory ones, leading to a progressively increasing ratio between excitation and inhibition towards excitation, which potentially explains the increased propensity to seizures.[10]

Early Post-Traumatic Epilepsy

The risk of early PTE is related to the type and severity of brain injury. It is much higher in patients with more severe injuries. Subdural haematomas and depressed skull fractures are major independent predictors of early seizures (24–27%).[49,99] In another study, subdural and intracerebral haematomas were associated with 30–36% incidence of early seizures,[48] while extradural haematoma, frontal and parietal depressed fractures, PTA more than 24 hours and focal neurological deficits were associated with an early seizure incidence of 9–13%.[23,48,49] Early seizures occur more frequently in children less than 5 years of age.[41]

About one third of early PTE occurs within the first hour, one third between 1 and 24 hours, and the rest between 1 and 7 days after injury, with adults having their first seizures somewhat later than children.[49]

Focal seizures account for most of all early seizures (from 50 to 80%), with the remaining being primarily generalised tonic clonic (25–50%). Most early focal seizures are focal motor seizures; being more frequent after missile injuries.[49,74] A generalised seizure occurring within a few moments of trauma is called immediate epilepsy.[98] This usually follows a mild injury. Immediate concussive convulsions are thought to be a brief traumatic functional decerebration that results from loss of cortical inhibition.[77] Patients with isolated concussive convulsions have no evidence of structural brain injury. The long-term outcome for these patients is universally good, with no long-term neurologic sequelae nor increased incidence of early or late PTE. It requires no specific therapy and anti-epileptic medication is not indicated.[77]

The main significance of early PTE is an indication of an increased risk for development of late PTE, being approximately 25%.[49] About 10% of adults and 22% of children under 5 years of age, with early seizures, go into status epilepticus.[50,74] Early seizures can lead to depression of consciousness and increased risk of aspiration pneumonitis.

Late Post-Traumatic Epilepsy

The highest risk factor for late PTE is missile wounds.[89,90] In blunt head injury, the main risk factors are haematomas, depressed fractures, focal signs and early seizures. Low GCS, subdural haematomas and cortical contusion, each provide independent additional risk of late seizures. About one-fifth of patients with epidural haematomas and almost one-half of those with subdural or intracerebral haematomas develop late PTE.[48] A patient with mild head injury, but having early seizures has a 25% chance of late PTE, while mild head injury without loss of consciousness and without early epilepsy has only a 1–2 % incidence of late seizures.[49] The frequency of late seizures varies within a wide range, from only a single seizure to so many that no effort is made to keep a count.

Seizure risk is initially greater. Eighteen per cent of epilepsy cases in the Vietnam Head Injury Study developed their seizure within one month and 57% developed seizures by 1 year.[90] Seizure risk remains elevated for many years, however. 60–70% of late PTE is generalised, with or without focal onset.[74]

Prophylaxis and Treatment

Natural cessation of PTE is likely to occur in patients with a low frequency of seizures, in those in whom fits started early and in those who have an early remission for more than a year.

An attack of seizures occurring within a few minutes after a head injury (immediate epilepsy) may not require any anticonvulsant medication. There is a lack of consensus on the usefulness of prophylaxis with anticonvulsants for the prevention of late PTE.[38,46] Considering the data available, prophylactic administration of phenytoin to prevent either early or late PTE is not recommended.[46] However, there are many reports, which conclude that phenytoin reduces the risk of early seizures by 67–73%.[70,99] If an early seizure occurs, intravenous phenytoin should be given with a loading dose of 18 mg/kg/minute, followed by a maintenance dose of 5–7 mg/kg/day. Prophylactic phenytoin can be stopped after about 1–2 weeks.

No prophylaxis should be given for late PTE. If a late seizure occurs, an anti-epileptic drug (e.g. phenytoin, carbamezapine or valproate) may be administered. The duration of treatment for late PTE follows the principles of treatment of all late seizures and is usually 2 years.

Resection of the epileptogenic focus is rarely required to control post-traumatic seizure intractable to medical management. Late PTE tends to diminish with time and surgery should not be performed for at least 2 years after the injury. When there are multiple epileptic foci or the focus cannot be localised and drug therapy is not effective, vagus nerve stimulation is another option for treating PTE.[35]

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41 Cranioplasty

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INTRODUCTION

Cranioplasty is defined as the restoration of a defect in the cranial bone or correction of a deformity of the bone that may happen after trauma as in depressed fracture. The replacement of a bone flap after a craniotomy would also be a cranioplasty. There is a feeling that cranioplasty connotes repairing the defect after a gap of sometime using material other than the original bone. However, we shall include any reconstruction of the skull defect/deformity under cranioplasty. The technique of cranioplasty is a fine mix of art and surgical science. The cranium has a well-defined topography and regions with specific contours. Some areas are hidden under the hair and some areas, like the frontal regions, are easily seen. An aesthetically pleasing result necessitates that we must have the proper contours of the calvarium restored while filling up the "holes" in the cranium. There has been an attempt to reconstruct the cranium from times immemorial and there are instances of its being reconstructed as early as 3000 BC by Peruvians using Gold/Gourds.[19] The first attempt to use bone for cranial reconstruction was made as far back as 1670 by Van Meekren[2] who repaired a cranial bone defect of a Russian soldier using bone from a dog. As the patient was excommunicated as a result of this procedure, Van Meekren removed the graft 2 years later so that the patient could return to his church.

AETIOLOGY OF THE CRANIAL DEFECT

The main cause of defects of the cranial and facial bones is trauma. Penetrating head injuries at times necessitate removal of bone (craniectomy). At times it may not be possible to replace the osteoplastic craniotomy flap due to either brain oedema or infection. The replaced bone flap may become infected and may need to be removed. Other causes are surgical bone excision for tumours (osteomas, meningiomas, haemangiomas, eosinophilic granulomas, epidermoids, metastases, fibrous dysplasia, chondromas, sarcomas, aneurysmal bone cysts); for infections (osteomyelitis, infected cranial flaps); for radionecrosis and electrical lesions of the skull and for congenital cranial and craniofacial anomalies (encephalocoeles, congenital parietal defects).

CRANIOPLASTIC MATERIAL

An enormous range of materials has been employed for the repair of cranial defects. These have included an autograft from the same individual, allograft from another individual of the same species, xenograft from other species and bone substitutes from outside the realm of living tissue. Whenever possible, the use of autografts is the most preferable, although this is sometimes impractical because of insufficient amount or their unmalleable property. The ideal substitute material should be strong, lightweight, malleable, thermally non-conductive, sterilisable, easily secured, inert, radiolucent, non-magnetic, aesthetically good, readily available and inexpensive. Needless to say, the search for such a material continues. The history of cranioplasty is filled with the introduction of the "ideal replacement" only to have its use abandoned for various reasons.

PRESERVATION OF AUTOGRAFTS

There are times when the surgeon cannot replace the bone flap after craniotomy. Various methods have been used in an effort to preserve the bone and maintain its sterility without losing its osteogenic potential. Boiling of the bone was suggested by Westermann (1916),[24] but this results in increased tendency for infection and bone resorption.[16] Other older preservation methods have included storing in alcohol or formalin and then boiling before implantation. It has become clear that boiling lessens the osteogenic potential of the flap and makes it prone to bone resorption and infection. Autoclaving bone flaps may also predispose them to similar complications, but this has not been a uniform experience. Autoclaved bone flaps, in some institutions, have been observed to heal without necrosis or resorption.[15]

Storing the bone flap in the abdominal wall until it was required for the cranioplasty was first described by Kreider (1920).[10] This technique is not widely used today, because it necessitates another operation and produces an unsightly scar and there is little evidence for better osteogenic potential of the bone. It is known that bone removed from its blood supply and replaced in fresh tissue dies, with the exception of a layer of superficial cells less than a millimetre in depth. Nevertheless, this method has its contemporary proponents.[13]

NEED FOR RECONSTRUCTION

Reconstruction of the cranial vault is often needed for protective and cosmetic reasons. The goals are to protect the brain and restore the normal contour with as few complications as possible. Other controversial goals are eliminating headache and apprehension and avoiding cere bral palsy, decreasing vibration and motion intolerance, and overcoming fatigue, insecurity and post-traumatic epilepsy.[5,22]

CRITICAL SIZE OF DEFECT THAT REQUIRES CRANIOPLASTY

It is commonly accepted that the fundamental indications for cranioplasty are bone defects larger than 2 cm situated on the cerebral convexity and bone defects of the glabrous frontal region. Defects below the temporal and occipital muscles and those in very elderly patients are not usually considered to require repair. Moreover, in children under 6 years of age in whom the dura is not damaged, regeneration of a portion of the skull may be observed. Thus, it is necessary to wait at least a year after craniectomy in a child before deciding whether reconstruction is necessary.

ANATOMY OF THE DEFECT

The defect may either be very small or be quite extensive. These may be classified into Type I, where the size may be less than 5 cm^2 or Type IV, where the size may be greater than 50 cm^2. Very small defects may not be reconstructed as far as protective function is concerned, but may need reconstruction if these are situated in frontal areas, especially the supraorbital and non-hair bearing forehead region. The frontal region has been divided into three regions:

1. Supraorbital
2. Prehairline
3. Within the hairline

Even small defects in zone 1 and 2 look unaesthetic and should be corrected (Figs 1 and 2).

The defect may be situated anteriorly in the frontal area, midway in the calvarium in the parietal area or posteriorly in the occipital area. The frontal defects may either be within the hairline or be in the visible forehead. Parietal area defects of less than 5 cm^2 may not require any reconstruction. Likewise, a small defect in the temporal region may not require reconstruction. In the occipital area, defects of moderate size may also not need any reconstruction as the thick musculature provides protection. In short, the need for reconstruction is dictated both by the size of the defect and the location of the defect (Fig. 3).

TIMING OF RECONSTRUCTION

A significant reduction in incidence of infection has been noted when sometime is allowed to elapse between the initial injury or infection and the subsequent reconstruction. It is generally believed that the interval between complex or contaminated wounds and definitive cranioplasty should be between 3 months and 6 months. Rish and his co-workers[17] reviewed 491 cranioplasties and concluded that it was necessary to wait at least a year after penetrating or complex head injuries to ensure a good outcome. If the frontal sinus has been opened, it may be prudent to perform cranioplasty after about a year. Similarly, in the presence of an infected open wound, one should allow the wound to heal and then embark on cranioplasty after about a year or so. However, if adequate vascularised tissue is available, immediate reconstruction is possible. It is important to separate the aerodigestive tract from the extradural space by the use of a vascularised flap like frontogaleal flap. If the conditions are favourable, a primary cranioplasty is always advisable.

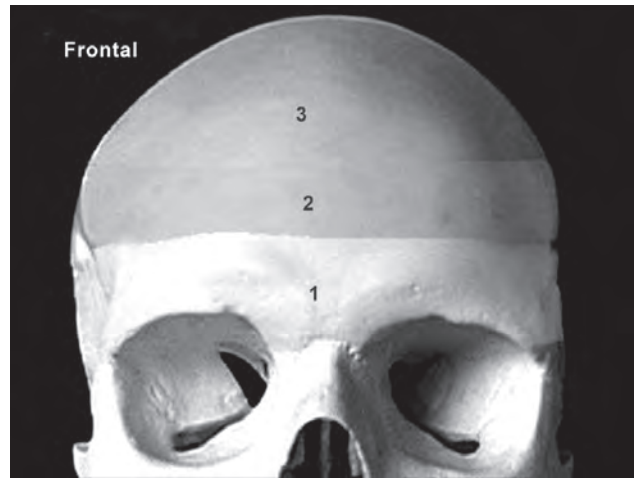

Fig. 1: The frontal region is divided into. (1) supraorbital. (2) Prehairline. (3) Within hairline

IMPORTANCE OF ADEQUATE SKIN COVER

Before undertaking cranioplasty, it is important to ascertain that there are no compromised areas in the scalp. If the scalp has unstable areas these need to be revised. The cranioplasty can be accomplished through existing scars and, if need be, additional incisions can also be made. It is very important to ascertain that there is sufficient skin available in the scalp; it is more so in large defects of long standing duration. The scalp tends to sag inside the defect and might be stretched once cranioplasty is done. This tight envelop can lead to exposure of the grafts/implants in the post-operative period (Fig. 4). If there is deficiency of tissue, it should be corrected before cranioplasty is contemplated. Smaller defects can be adjusted with local flaps, but larger defects will necessitate import of tissue from distant areas. Very large defects may require free tissue transfer (Fig. 5).

CHOICE OF MATERIAL FOR CRANIOPLASTY

There is almost unanimous agreement that autogenous calvarium possesses far better characteristics and quality

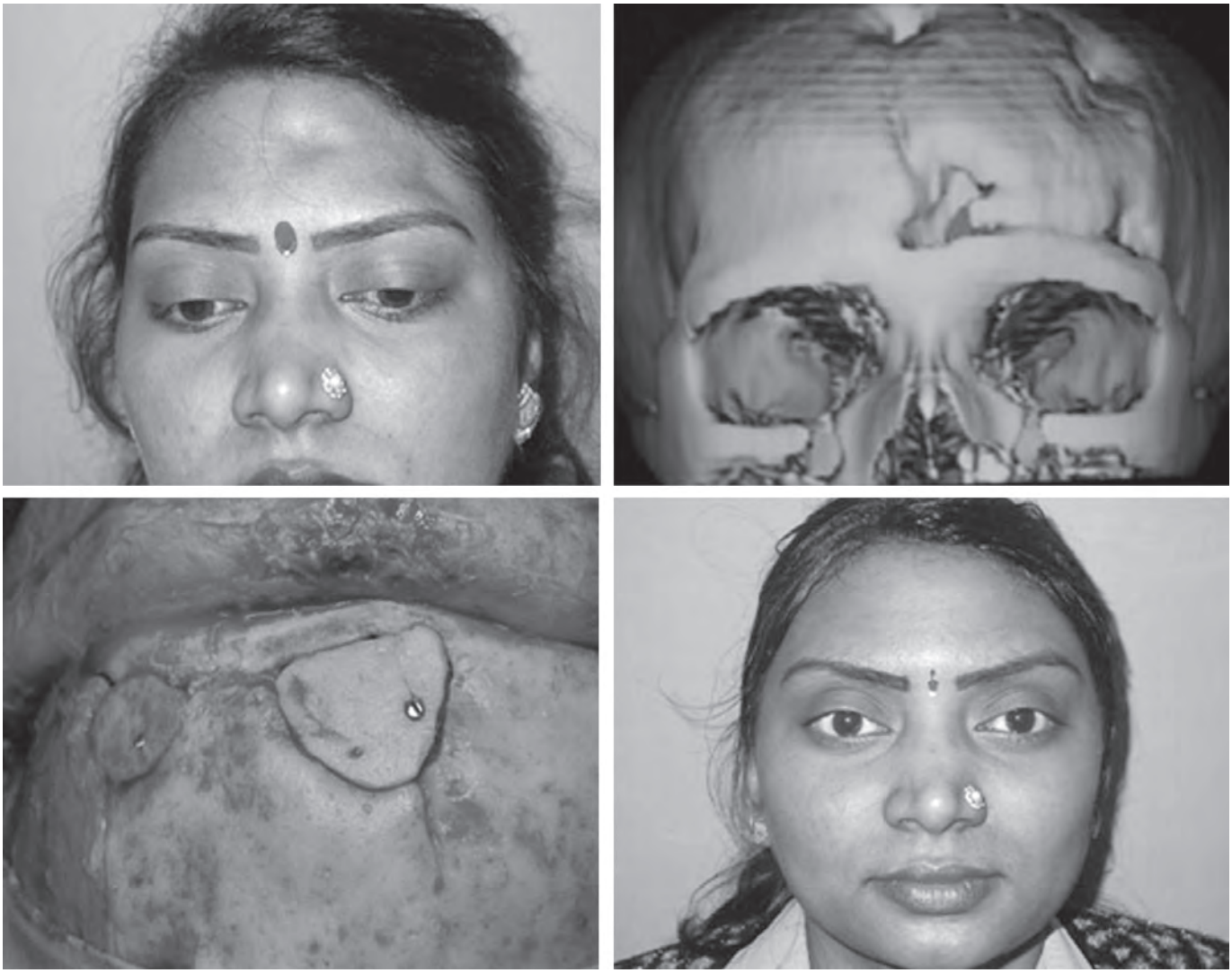

Fig. 2: Even small defects can be cosmetically disturbing in region 1 and 2

than any other currently available alloplastic materials. Calvarial autograft is the most "natural" material of all because not only does it possess all the ideal qualities for cranioplasty but it is also vital and has excellent biologic properties. It has good growth potential and resistance to infection. There can be no doubt that fresh autologous bone is the most suitable material for reconstruction of cranial defects in view of its perfect histocompatibility, optimal mechanical properties and good integration of the graft with the adjacent bone, as well as the possibility of partial or total revitalisation of the graft itself. Autologous bone also ensures the best possible physiologic and cosmetic results (in theory at least). In fact, autologous bone grafts usually display bone regeneration processes and there is a low incidence of infection.[1,4]

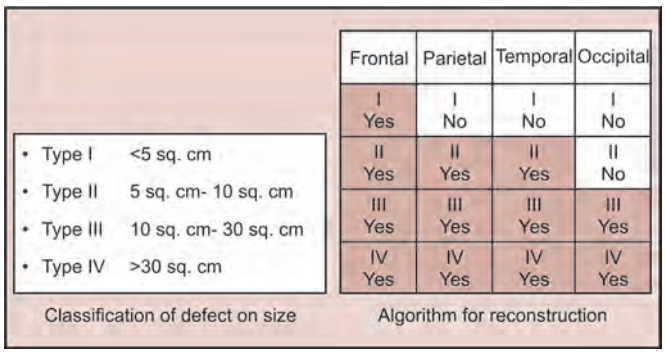

Fig. 3: Classification of defects and algorithm for reconstruction needs

The source of autologous bone can be the calvarium itself, ribs or iliac bone. The cranium is the preferred donor site for harvesting bone graft for cranioplasty. The donor area is in the vicinity of the defect and a large amount of bone can be harvested. The patient experiences much less pain at the donor site as compared to other donor sites like ribs and iliac bone. It has been consistently highlighted that the pain in the iliac crest and chest donor site often exceeds that of the primary procedure on the skull or face. In harvesting the ribs there is a possibility of injuring the pleura.

The cranium provides a large area for bone grafting. The bone can be harvested from an area which matches with the contour requirement of the defect. It requires training to obtain a cranial bone graft; however, the skill

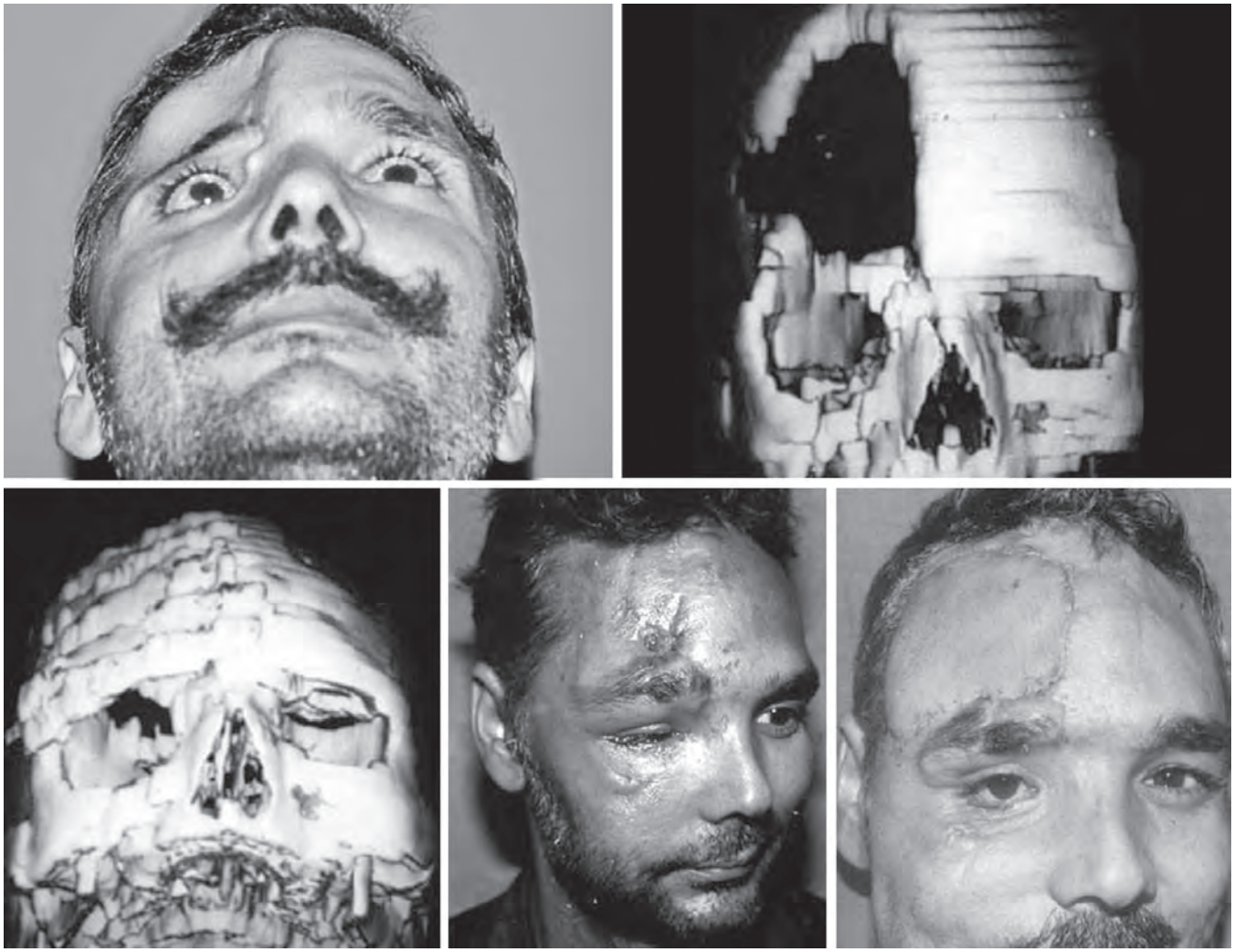

Fig. 4: Large defect in the frontal region of long standing duration. The envelop seemed tight after reconstruction; the underlying bones got exposed in the post-operative period and urgent cover had to be given with radial forearm flap for salvage of reconstruction

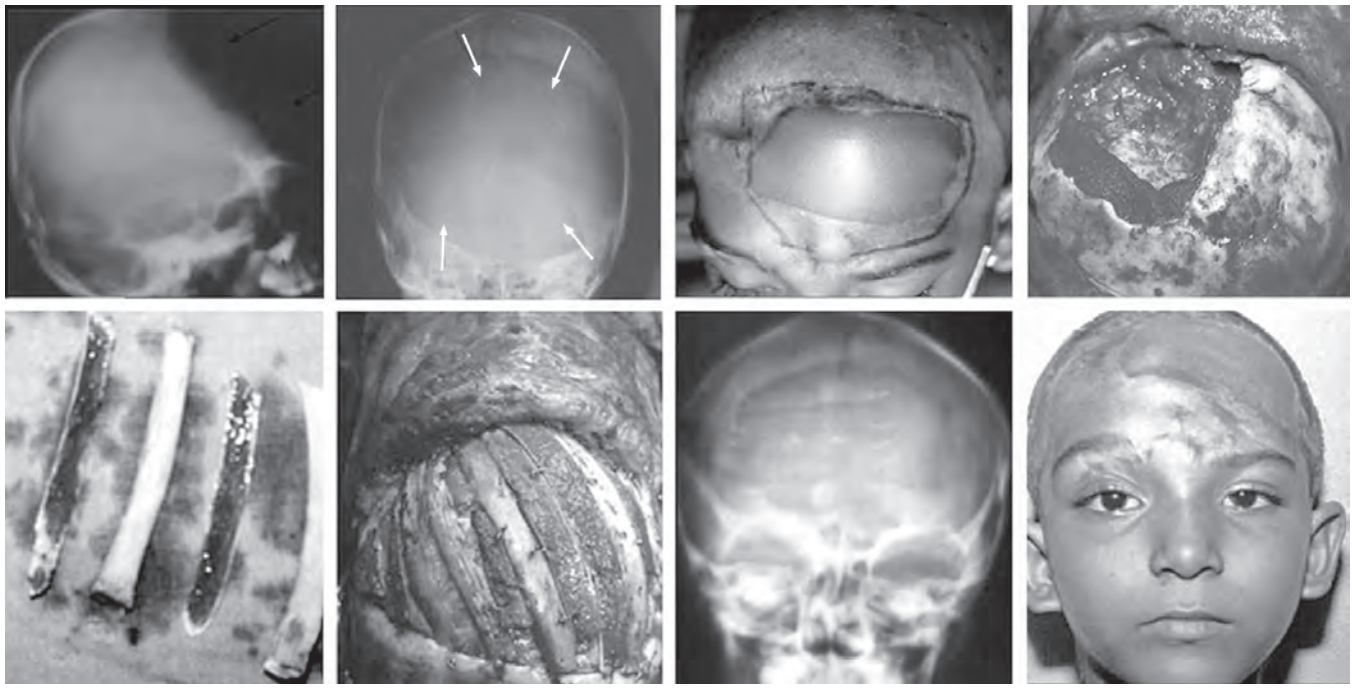

Fig. 5: Large defect in a child with skin loss. The skin defect was first resurfaced with radial forearm flap. The bony reconstruction was done using split ribs and cranial bone graft. The bones have been fixed with interosseous wires

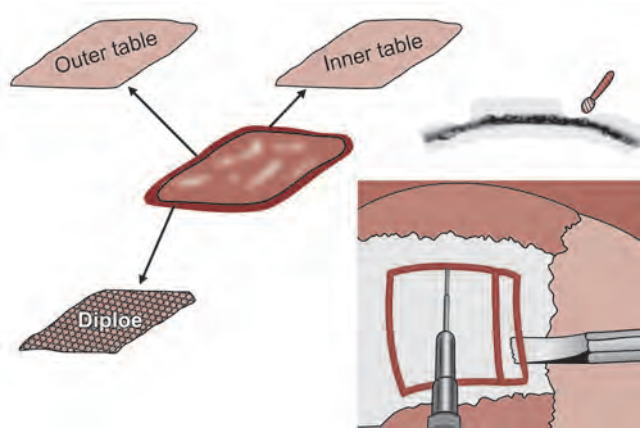

Fig. 6: The skull consists of outer and inner tables with diploe in between. The split cranial bone graft is harvested by creating a plane at the level of diploe with a burr. An osteotome has been used to harvest the cranial bone graft

is easily acquired. This may be done with a hammer and osteotome or even with a Gigli saw. The bone is generally, harvested from the non-dominant parietal area as it is technically easy and the thickness of the bone is adequate. It may be difficult to harvest split bone graft in very old and young patients as the dipole is not well-developed. A full thickness cranial bone graft may be harvested from the skull, and it can be split on a side table. More commonly, the bone is harvested as a split graft *in situ* (Fig. 6).

The cranium provides grafts of different contours to meet any reconstructive need. The graft may be oriented in any direction as dictated by the reconstructive need. The split graft can be harvested across the midline and suture areas. The template of the defect can be made and placed in an appropriate area of the calvarium to provide matching grafts (Fig. 7). With a little practise, a split cranial bone graft can be harvested even in children as young as 6 months to 1-year-old (Fig. 8).

If the need for bone graft is more than 50 cm^2 additional bones may be procured from other sources like ribs and iliac bone. The rib may be split into two for increasing the surface area. The volume loss in membranous bone[11] like the cranium is much less as compared to endochondral bone. The cranium can provide large areas of bone graft and, if it is harvested as a split table bone graft, there is no donor site morbidity. The operative site is the same so no further incision is required. It has been observed that there is little pain at the calvarial bone graft site as compared to other sites like ribs or iliac bone. Moreover, the site of the bone graft harvest can be chosen depending upon the contour requirement of the recipient site. Although some site the morbidity involved in harvesting cranial bone, it has been documented that with proper training, plastic surgeons can harvest bone grafts easily and comfortably with minimal morbidity.[9]

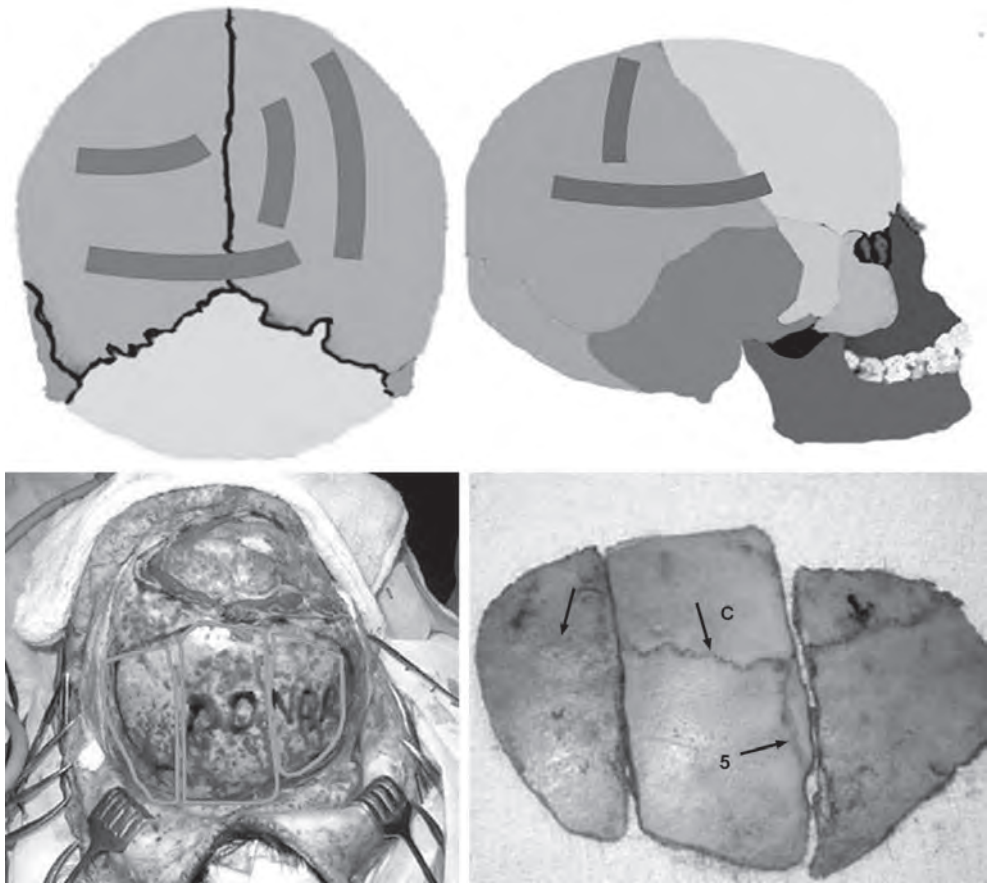

Fig. 7: The bone grafts can be harvested from the parietal region. The orientation of donor site depends upon the contour requirement at the recipient site. The graft can extend even beyond the midline or sutures

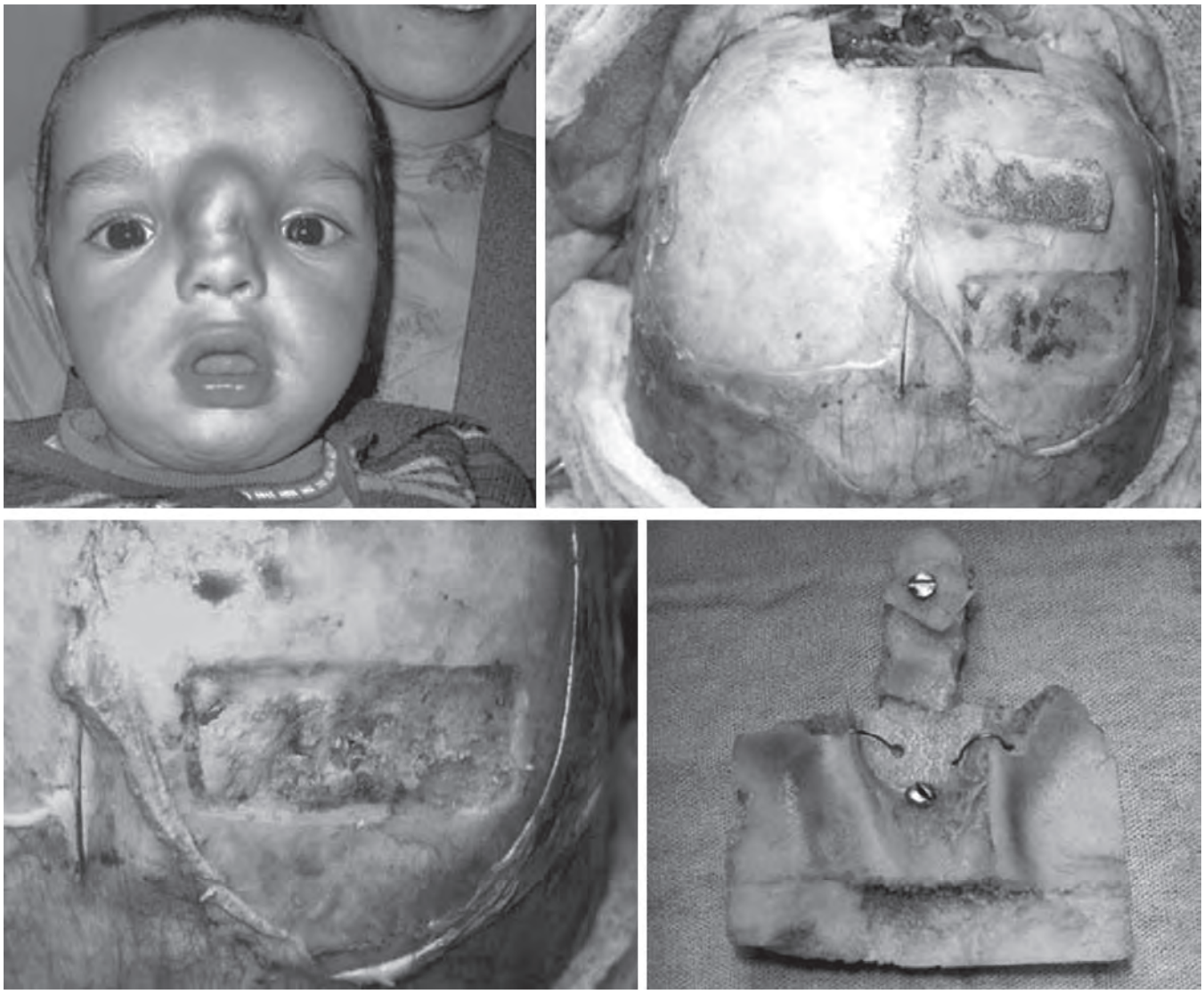

Fig. 8: The split cranial bone graft can be harvested even in small children. In this child aged 13 months, the bone graft has been used to reconstruct the encephalocoele defect. The bone graft has also been used to augment the nasal dorsum. Lag screws have been used for fixation

Autologous bone grafts from other sites can cause significant donor site morbidity, can prolong operative time, are limited in the quantity available for reconstruction and are difficult to contour.[14]

ALLOPLASTIC MATERIAL

Alloplastic material has the advantage of malleability, easy accessibility and durability. However, it has many inherent disadvantages. These include high-risk of infection, foreign body reaction, fibrous and capsular contracture of surrounding tissue and lack of incorporation in the cranium. There is also the danger of deeper migration of the implants. In experimental studies where alloplastic implants were removed, it was noted that the underlying recipient bone underwent transformation to a trabecular architecture with decreased bone density.[7] This may particularly be troublesome, if an alloplastic implant has to be removed following infection or dislodgement, which would result in greater deformity than was initially present.

The use of alloplastic implants for cranial reconstruction has a long history with numerous materials used with varying degrees of success. Currently, three different alloplastic alternatives are widely used: (1) methylmethacrylate (PMMA); (2) hydroxyapatite (HA) and (3) metal. Each has its own advantages and indications in contemporary cranioplasty. When employed with good surgical technique and in the appropriate patient, each material can lead to good clinical outcomes.

PMMA offers an inexpensive method. It is easily adapted and contoured intra-operatively to cover a defect of any size and provides great impact resistance. It does not integrate into the surrounding tissues and is reserved for use in adult and older patients. Custom preformed hard tissue replacement (HTR) implants, a modified porous PMMA material, provide a very accurate and rapid method for large full-thickness cranial defects. It requires pre-operative preparation utilising a 3D craniofacial model.

Hydroxyl apatite has excellent tissue compatibility and the advantage of being osteoactive, radiolucent and readily available. Osteoactivity is the ability of the biomaterial to be replaced with bone formation either through osteoinduction or osteoconduction. In addition, it is biocompatible and does not produce a chronic inflammatory response.[8] Unlike most other alloplasts that are inert, these materials are bioactive (capable of osteoconduction) and have the potential to develop tissue in-growth and integration into the recipient site after placement. These materials are not osteoinductive by themselves but they do provide a physical substrate onto which new bone from adjacent surfaces may be deposited and potentially guided into areas occupied by the material.

Nova Bone (Porex Surgical, College Park, GA) is a synthetic bioactive glass particulate consisting of 45% silica dioxide, 45% sodium oxide, 5% calcium and 5% phosphate, which is believed to be bioactive towards the production of new bone within the biomaterial. Most biomaterials, including bioactive glasses, are osteoconductive, serving as a biocompatible interface along which bone cells migrate. In addition, bioactive glasses are osteoproductive, which is defined as the process whereby a bioactive surface is colonised by osteogenic stem cells from the defect environment as a result of surgical intervention.[25]

A recent review of the experience with HA-cement cranioplasties revealed a high infection rate. During removal of these implants, all were loose and fractured. Forty per cent of these patients had a history of minor trauma at the site of cranioplasty before experiencing infection. Minor trauma may fracture HA cranioplasties and result in infection.[12]

Porous polyethylene (Medpor; Porex Surgical, College Park, GA) is commonly used for facial augmentation and to restore continuity to craniofacial skeletal defects.[3] Polyethylene resins are straight-chain aliphatic hydrocarbons that are inert and promote little tissue reactivity. Unlike bone grafts, porous polyethylene shows little evidence of implant degradation. Like HTR, this is a porous (100–250 mm) biomaterial that permits bone and soft tissue in-growth when placed on facial skeletal defects. There are reports of sufficient soft tissue in-growth with sufficient vascularity to allow skin grafts to be placed directly over the implant.[23]

Demineralised bone is another alternative for reconstruction of the craniofacial skeleton. Salyer and associates have studied the use of cortical demineralised perforated bone for reconstructions (produced by Pacific Coast Tissue Bank) in animal models and in the clinical setting.[18] Although all of the biomaterials discussed in this article seem to maintain their volume overtime, porosity of the biomaterial may be a significant factor in determining bone in-growth into the implant. Methyl methacrylate is non-porous, and no bone in-growth is expected. Cement paste implants tend to contain micropores, and experimental and clinical evidence indicates that there is less long-term bone in-growth into these biomaterials than in implants with macroporous architecture. Biomaterials presently reviewed that have a macroporous architecture and have demonstrated bone in-growth in clinical or experimental studies include ceramic and granular forms of HA, HTR polymer, porous polyethylene (Medpor), bioactive glasses (Nova Bone) and demineralised bone paste. Prefabricated biomaterials and those that set as a cement are not designed to change dimension overtime and are, therefore, best-suited for cranial vault reconstruction after completion of skull growth.[6,26] The most commonly used biomaterials in cranioplasty are HAs especially for contour irregularities and touch up surgeries following cranioplasty (Fig. 9).

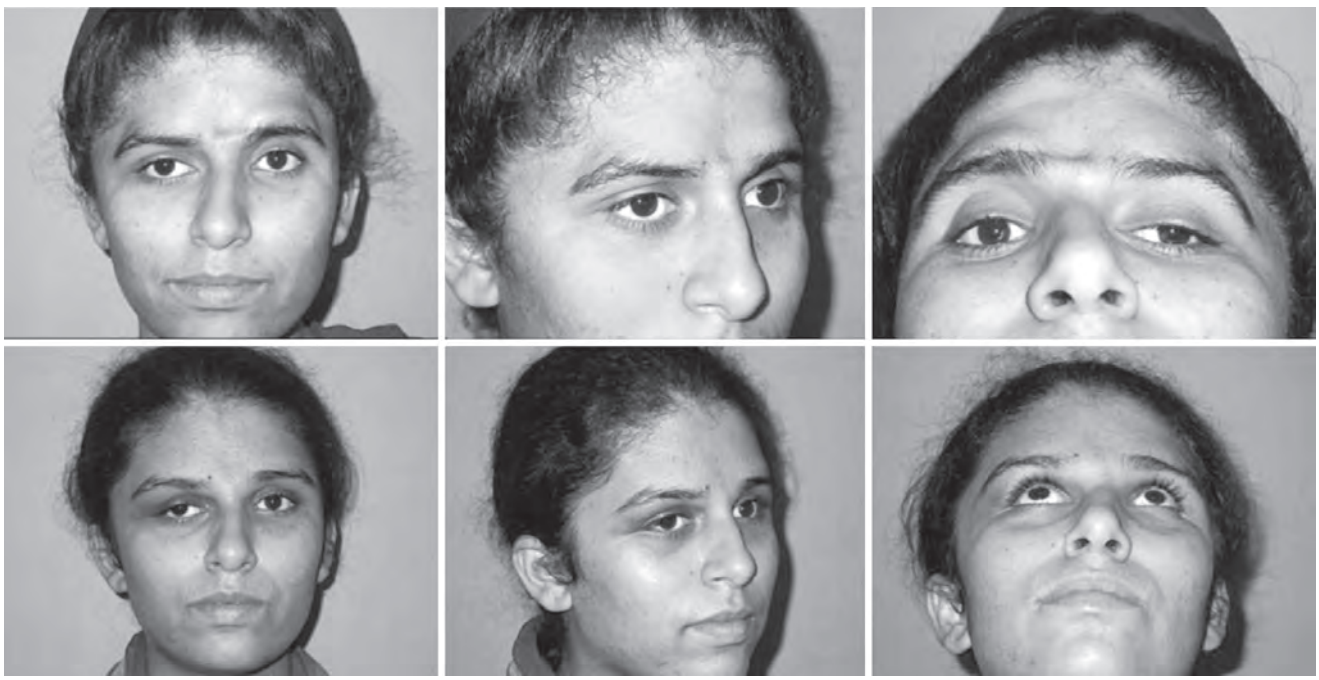

Fig. 9: Hydoxyapatite granules have been used for correction of contour defects in this patient who had undergone plagiocephaly correction in childhood

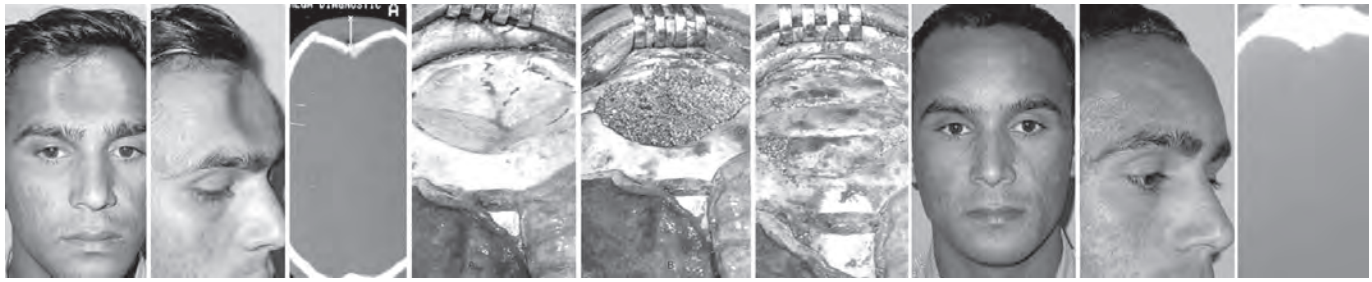

Fig. 10: Use of autogenous cranial bone graft and hydroxyapatite granules in correction of contour deformities of depressed fracture frontal bone. The granules fill up the depression and act like a paste in which bone grafts can be "set" as in a masonry job

A combination of autogenous bone and bioactive materials can be quite handy in the management of difficult contour irregularities, especially for a depressed fracture of the frontal region[21] (Fig. 10).

Metal (Ti) mesh is an historic method of cranioplasty that provides a rapid method for re-establishing an outer cranial cover. Its role today is more limited but is still selectively used in the older cranial defect patients where implantation times are shorter.

FIXATION

It is mandatory to properly fix the bone flap after bone flap craniotomy; an improperly fixed flap has a tendency to drift downwards because of the effect of gravity and pull of the temporalis muscle and leads to significant cosmetic and functional disability.[20]

A variety of techniques are available for fixation of the bone grafts. The edges of the cranial defect should be refashioned and the bone grafts should firmly be in contact with the defect edges. The fixation can be achieved quite satisfactorily with plates and screws (Fig. 11), but these need to be removed if they cause problems. The bone graft could also be pegged into the potential space between the outer and the inner table. The use of stainless steel wire is another way of fixation. The use of currently available absorbable plates may come in handy in future (Fig. 12).

CASE EXAMPLES

The following case reports will highlight the various aspects of cranioplasty:

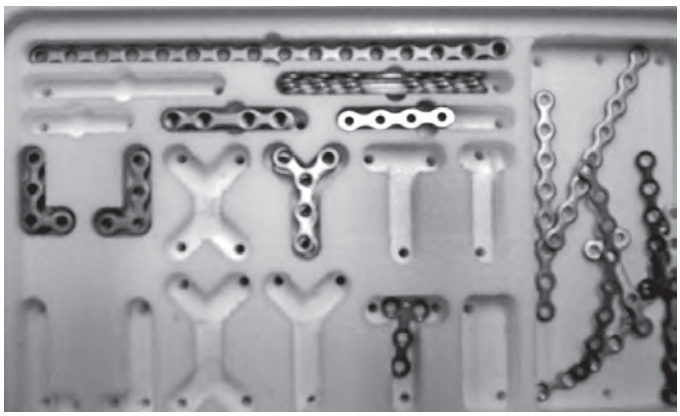

Fig. 11: Titanium plating set

Case 1: Small Defect Frontal Region (Burr Holes)

This young lady had a visible contour defect in the frontal region following frontal craniotomy for head injury many years ago. There were four burr hole defects and these were managed with autogenous split cranial bone grafts that were fixed with the help of lag screws (see Fig. 2). The post-operative appearance is quite pleasing.

Case 2: Sliding Bone Flap

The patient had undergone a right pterional craniotomy for clipping of a right anterior communicating artery aneurysm 8 months earlier. She presented with a slit-like deformity over the forehead running almost vertically over the centre of the right eyebrow. There was a palpable 2 cm wide gap between the edges of the bone. The two bony margins were at different levels leading to a contour deformity. CT scan with 3D reconstruction demonstrated that the pterional bone flap had migrated posteroinferiorly leading to a defect in the region of the forehead due to the over-riding of the bone edges posteriorly (Fig. 13). This was corrected by approaching the defect through a coronal incision. The bone flap that had malunited inferiorly was refractured and moved anterosuperiorly. This left a bone defect in the posteroinferior part and was corrected by using strips of split cranial bone graft taken from the adjacent area. The fixation

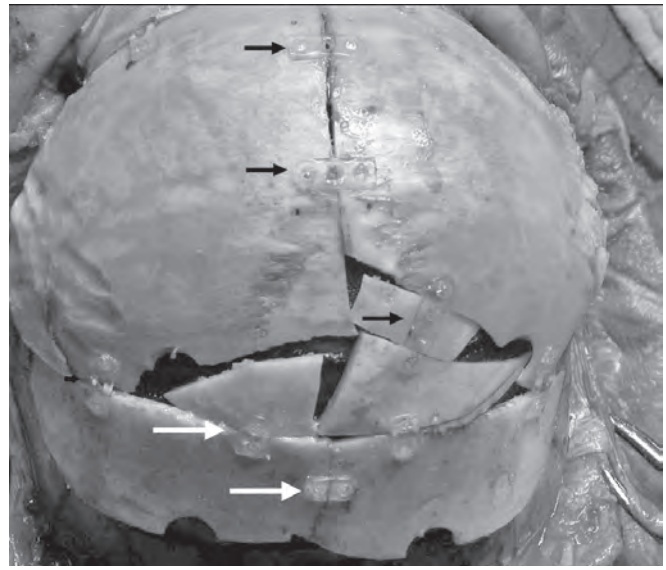

Fig. 12: Absorbable plates are very useful in growing skeleton

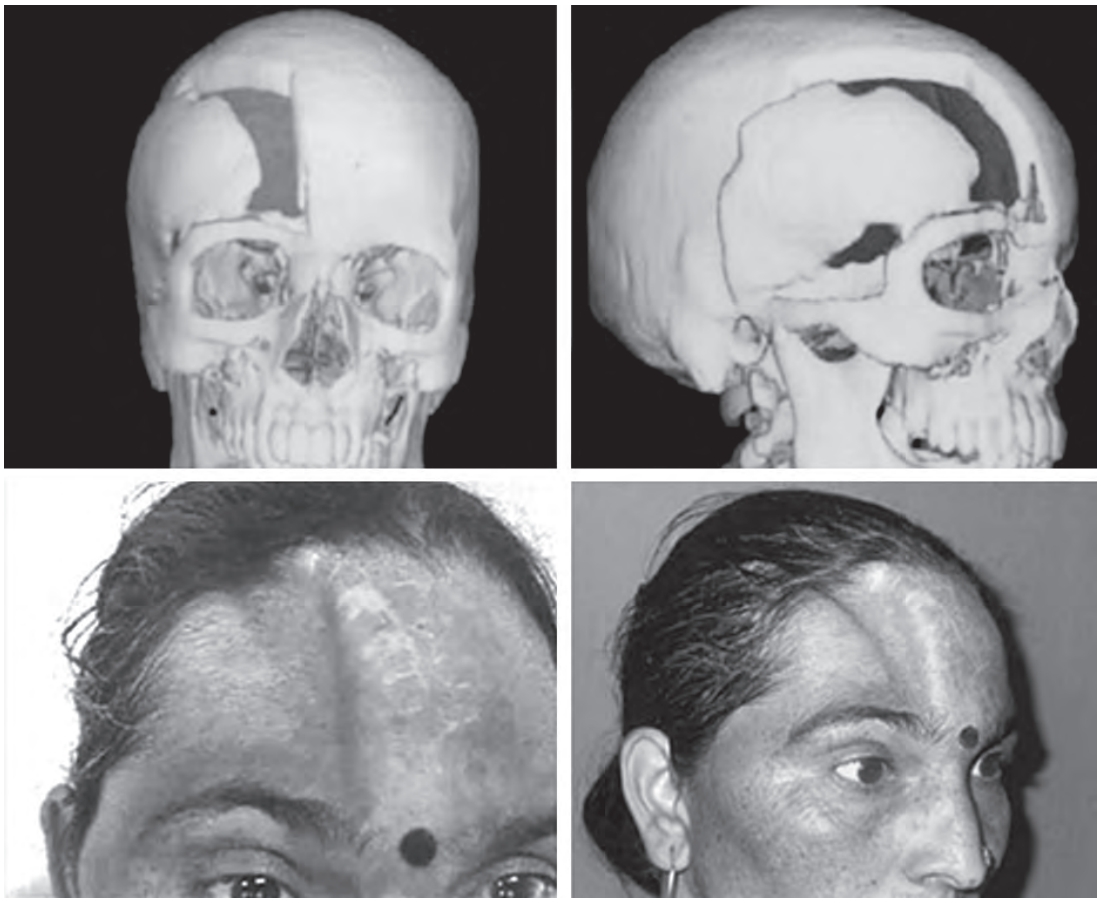

Fig. 13: Improperly fixed osteoplastic bone flaps tend to get pulled down by the temporalis muscle and can lead to significant cosmetic defects

of the bone flap and bone grafts was done using miniplates and screws. The post-operative appearance after 3 months is shown in Figure 14.

Case 3: Large Defect with Skin Deficiency

This patient had a post-craniectomy defect in the frontal region for 3 years. The reconstruction was done using autogenous split cranial bone graft. The skin envelop had, however, become tight and this resulted in exposure of the reconstructed region. This necessitated an immediate flap cover with a radial forearm flap for salvaging the reconstruction.[16] One must be very careful in assessing the adequacy of the overlying skin cover before undertaking bony reconstruction. Any shortage of skin has to be addressed before any reconstruction of the skeletal defect is undertaken. This is best exemplified in the patient shown in Figure 5.

Case 4: Large Defect in the Frontoparietal Region

This girl had a post-traumatic defect in the frontoparietal region. The donor site was selected adjacent to the defect and three large pieces of autogenous split cranial bone

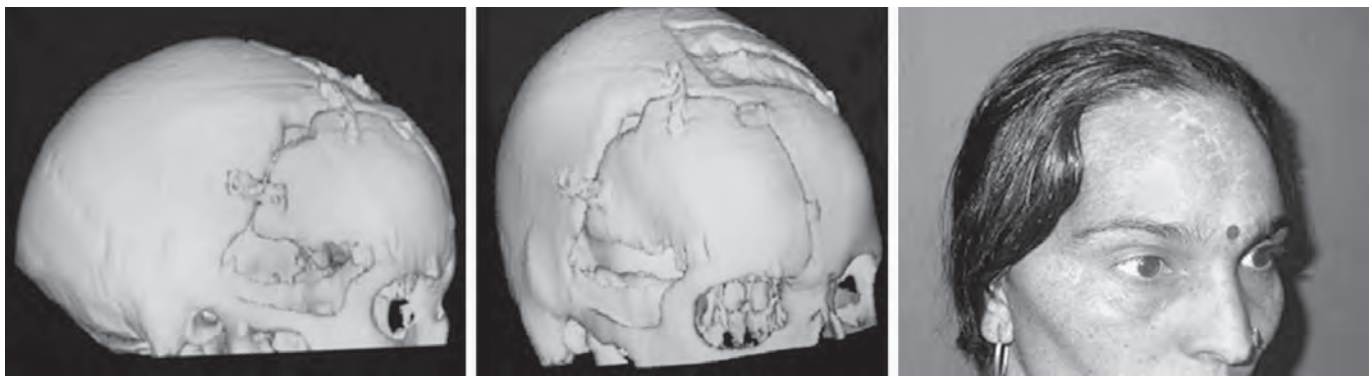

Fig. 14: Result of correction of sliding bone flap of Figure 13. The bones have been secured with titanium screws and plates

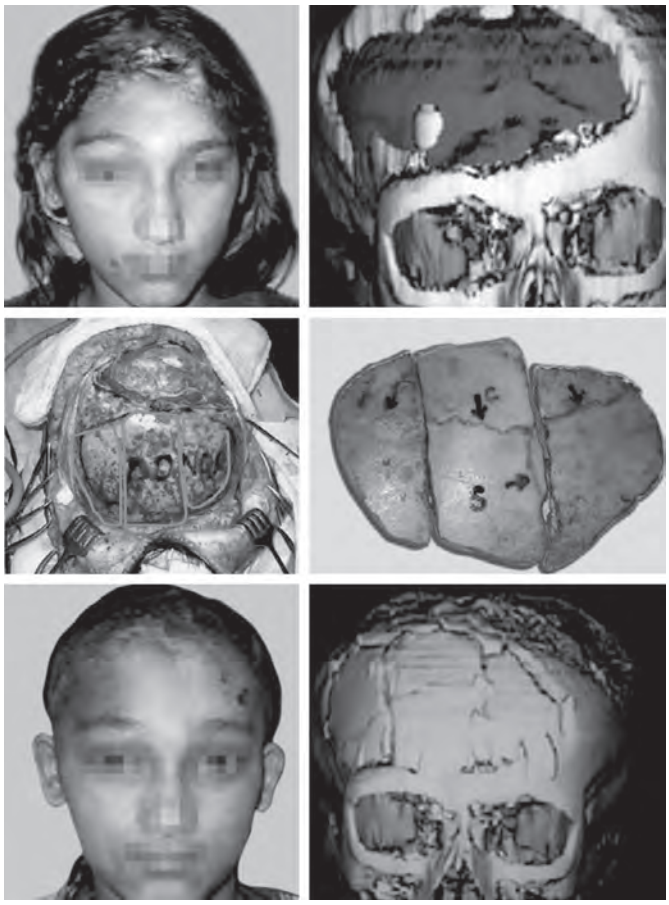

Fig. 15: Large defect in the frontoparietal region reconstructed with autogenous split cranial bone graft. Please note the grafts have been harvested across the suture lines. Three large pieces of bone were used for reconstruction

grafts were used for reconstruction of the bony defect (Fig. 15).

Case 5: Depressed Frontal Bone Fracture, Use of Autogenous Bone and HA

The patient had a depressed fracture of the frontal bone 2 years earlier. He had significant contour deformity in the forehead area. There were no neurological sign/symptoms. The contour correction was done with the help of HA granules and split cranial bone grafts. The granules were used to fill up the "crater" and cranial bone graft pieces were "set" in the mixture as a mason would do with bricks (see Fig. 10). The post-operative contour was quite satisfactory.

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42 Maxillofacial Injuries

Arun Kumar Singh, Upadhyay DN

INTRODUCTION

The incidence of maxillofacial injuries is on the rise owing to increase in automobile accidents. Better roads and faster vehicles have contributed their bit in the waxing trend seen in the occurrence of these injuries. Exact incidence figures for India are not available owing to a lack of a registry system.

Other causes of maxillofacial injuries include assaults, battery, domestic violence, fall from a height and gunshot or explosive injuries (war time and peace time both).

GENERAL PRINCIPLES

A vast majority of facial injuries occur due to automobile accidents, assault and fall from a height, bringing these patients under the purview of polytrauma. As always, managing polytrauma starts with ABC (airway, breathing and circulation). The patient has to be evaluated in toto, ruling out major and life-threatening injuries. Undiagnosed head injuries, blunt abdominal trauma and open chest wounds/haemo/pnuemothorax wounds and spinal injuries are the major causes of fatality in polytrauma patients. Such concomitant injuries have to be evaluated and managed primarily before one can proceed further with the management of facial injuries.

Facial injuries, however grotesque they may look, are not life threatening, except if the airway is compromised due to bleeding in the air passages, oedema or aspiration.

Evaluation of the polytraumatised patient should include a quick recording of the vital parameters, a systematic survey of the other organ systems and ensuring proper ventilatory and circulatory support. A rapid haemogram and plain X-rays of the chest, abdomen and cervical spine will avert many a diagnostic disaster and save many lives. Continued blood loss is indicated by a labile blood pressure, a thready pulse and a dyspnoeic, irritable patient. A Glasgow coma scale (GCS) score should be established, cervical spine injury excluded and the chest and abdomen examined thoroughly to rule out injuries in these areas. Continued nasopharyngeal bleed cannot only exsanguinate the patient but can also lead to respiratory compromise. A nasal pack or interdental stabilisation of the facial fractures can often arrest the bleeding at a dramatic speed. Continued bleeding even after these measures should force one to think of embolisation/ligation of the external carotid vessels and/or superficial temporal vessels.

In rare cases the nasal/pharyngeal bleed is often refractory to even ligation of the carotid vessels and may be due to laceration of the dural venous sinuses or internal carotid vessels. These will require a thorough evaluation for head injury/arteriography with arterial embolisation, but death from haemorrhage is frequent in these cases.

CLINICAL EVALUATION OF FACIAL INJURIES

A careful history and a thorough clinical examination form the basis for the diagnosis of almost all facial injuries. Facial injury presentation can range from superficial lacerations to very ghastly wounds with skeletal disarray. A careful examination in all the cases, however, will stand the surgeon in good stead as very minor wounds or laceration can be an indicator of an underlying skeletal injury. Minor cuts, abrasions or contusions should not be taken lightly and as much time should be devoted to their examination as to other injuries. Bone injuries are often suggested by overlying soft tissue swelling and distortion of facial features. A haematoma in the region of the eye should prompt one to think of a fracture in the region of the orbit or the zygoma. A blunting of the cheek bone prominence is a clear indicator of fracture zygoma. Nasal bleed may be the only indicator of a fracture of the maxilla, while fracture of the mandible may be indicated by an inability to clench the teeth or open the jaw. An orderly examination of all the facial structures should be done according to an individualised scheme, progressing either from superior to inferior or vice versa.

IMAGING

Most patients who present to the emergency department with facial injury will be required to undergo a "Facial trauma series", which consists of plain X-rays (PA view, Lateral view, Caldwell view and Water's view). However, plain X-rays do not give the extent of information required for the planning of surgery in terms of displacement. Also X-rays are particularly deficient at showing injury to areas like the floor of the orbit. In all patients with severe facial trauma a CT scan must be

performed. A 3D reconstruction should be done which is helpful in planning the surgery and show the fracture line and their displacements in great detail.

A panoramic view of the mandible supplements the information got on a CT and, therefore, must be requested. With newer CT software it is possible to image great details of the mandibular and dental anatomy (DentaScan).

SOFT TISSUE INJURIES

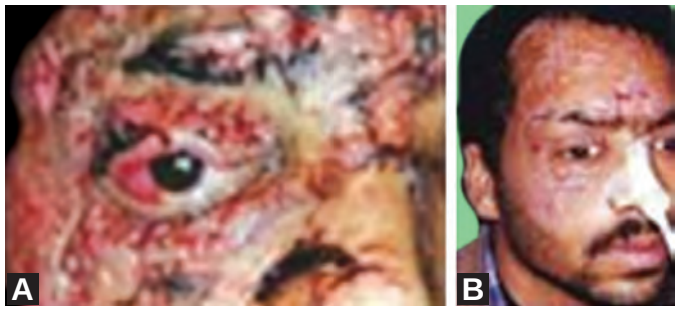
The face is blessed with a very good vascularity of the soft tissues and bones ensuring very good results if proper attention to certain details is paid during the primary care. The maxim—"first chance is the best chance"—holds especially true for the management of facial soft tissue injuries. There are certain fundamental principles of facial wound management which, if adhered to, give highly gratifying results.

The first and the foremost of these principles are a thorough cleaning and lavage of the wound. Facial wounds, depending on the mechanism of the injury, are often very dirty and have dirt and grit smeared into them. During the first surgery, the wound needs to be thoroughly cleaned with copious amounts of saline and needs to be freed of all the dirt and grit, with a wire brush if needed (however revolting it may sound). Contused and avulsed facial tissues need special consideration and need to be debrided conservatively. Facial tissues, owing to the excellent vascularity, often survive major avulsions even if attached to a minor skin pedicle. All that needs to be done sometimes is to reposition the tissues back into their place. This can be more difficult than it sounds, because the mechanism of facial injuries are often such that they lead to widespread disarray of the tissues and "putting the pieces of the jigsaw puzzle together" may be an uphill task (Figs 1A and B).

Thumb rules in facial soft tissue injuries are:

- Debride conservatively
- Clean thoroughly
- Reposition nicely
- Wait patiently

A word of caution;—seemingly harmless facial injuries—can have concomitant bony injury or injury to the facial nerve or the duct of the parotid gland. Be sure to rule them out before embarking on any definitive treatment.



Figs 1A and B: (A) Soft tissue laceration, fracture of zygoma. Branch of facial nerve identified and saved. Repair of all structures by aligning soft tissue landmarks. (B) Result tafter fixation of fracture

FRACTURE OF THE MANDIBLE

The mandible is one of the most common bones to be fractured in the face, due to its prominence in the face. The mandible is injured most commonly due to direct trauma to the face. Mandibular fractures typically result in some degree of malocclusion; therefore, a complaint by the patient of a change in their occlusal status after injury is a reliable indicator of fracture mandible (Fig. 2).

Mandibular fractures are almost always compound into the mouth as the mucoperiosteum on the inner aspect of the mandible is closely adherent and gets torn during any fracture leading to the compounding of the fracture into the oral cavity.

Fracture mandible can be classified in various ways depending on the arrangement of teeth around the fracture site, the direction of the fracture line and the region of the fracture. The goal of treatment of mandibular fractures is to not only restore the aesthetics of the face but also to restore the occlusion.

Mandibular fracture can occur in the subcondylar area (commonest), body, angle, parasymphysis area, symphyseal area, alveolar process and coronoid process (Fig. 3). Again, depending on the direction of the fracture line, a mandibular fracture can be either favourable or unfavourable. An unfavourable fracture is one in which the action of muscles acting on the mandible is such that it pulls the fracture fragments apart. A favourable fracture, on the other hand, is pulled together by the action of the local muscles. The fracture can be favourable or unfavourable either in the vertical plane or in the horizontal plane.

Symptoms of fracture mandible are:

- Malocclusion
- Pain
- Swelling

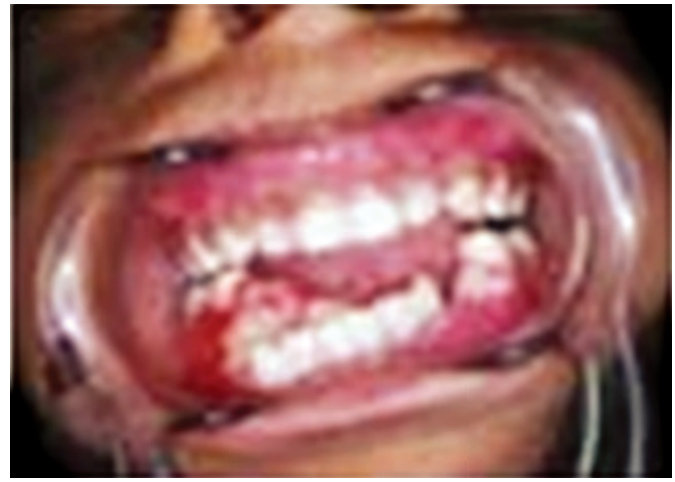


Fig. 2: Segmental compound fracture of mandible, showing malocclusion and gingival tear

Fig. 3: Common sites for fracture mandible

- Bleeding from the oral cavity
- Trismus

Signs of fracture mandible are:

- Crepitus
- Intraoral haematoma
- Gingival tear
- Anaesthesia/Hypoaesthesia lower lip
- Deviation of jaw on opening the mouth
- Loose teeth
- Difficulty in opening or closing the jaws
- Open bite
- Abnormal mobility

Investigations

- Plain X-rays mandible AP and oblique views
- Ortho pantomogram
- CT scan

Management

If a fracture in the mandible is suspected at one place, one should be wary of another fracture opposite the first fracture (much the same way as a coup-contrecoup injury in the brain). Typical areas to look for (and easily missed) are the subcondylar areas.

Fracture mandible can be managed in a number of ways, both operative and non-operative. Non-operative treatment is preferred in patients at extremes of age (edentulous arch and high operative risk) or in co-operative patients with stable fracture or in polytrauma patients with other life-threatening injuries which must be attended to first.

Non-operative treatments include:

- Soft diet only
- Interdental fixation with dental wires
- Maxillomandibular fixation with arch bars
- Splints for fracture stabilisation (Cap splint, Gunning splint).

Operative treatment includes open reduction of the fracture fragment and either internal or external fixation. Internal fixation can be achieved by means of dental wires or mini-plates and screws. External fixation can be achieved by means of rigid pin and frame devices which come in various shapes and sizes.

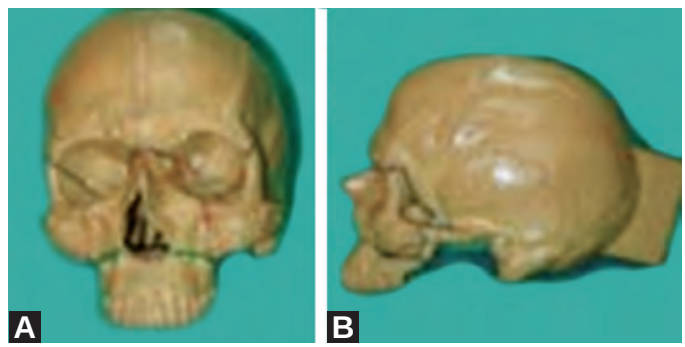
MAXILLARY FRACTURES

In a patient with multiple injuries the maxilla is almost invariably involved along with the mandible. The maxilla occupies an important position in the mid-face and articulates with the nasal bones anteriorly, the frontal bone superiorly, the pterygoid plates posteriorly, the temporal bone laterally, and also forms part of the floor of the orbit superiorly. It houses the all important antrum of the maxillary sinus which is the biggest of all the sinuses and the most prone to trauma and infection. Maxillary fracture is also, like mandibular fractures, almost always compound into the maxillary sinus due to the delicate mucosa there being torn by the trauma of the fracture. This leads to bleeding into the antrum which may or may not manifest as nasal bleed externally.

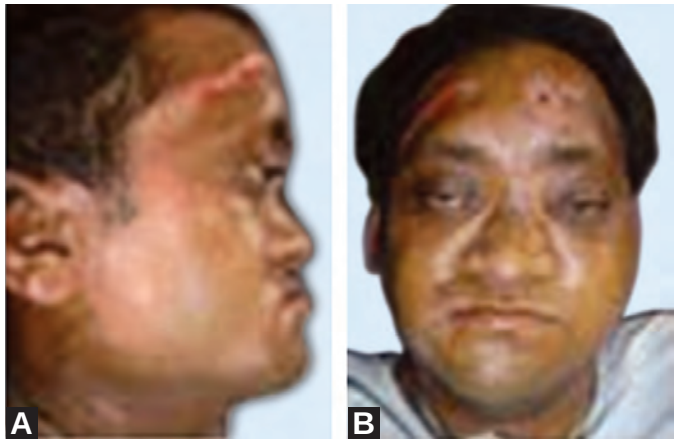
Maxillary fracture, like the mandibular fractures, almost always leads to malocclusion, the maxilla being part of the upper, tooth bearing arch. The similarity does not stop there. Entrapment of the infraorbital nerve in the fracture fragments may lead to loss of sensation or hypoaesthesia in the upper lip and lateral nose (compare Mental N. entrapment in mandible fracture).

Maxillary fractures have classically been classified along the Le Fort lines (Le Fort I, II and III) (Figs 4A and B). Le Fort lines are the lines of inherent weakness in the maxilla along which fracture lines run. The Le Fort fractures are those which tend to separate the maxilla from the skull base and they are classified according to their position. The Le Fort fractures must extend up to the pterygoid plates for them to be complete and cause a complete dysjunction. In practice, however, the classical fracture lines are rarely seen due to the complex mechanism of injuries that cause these fractures. They, however, serve as important yardsticks to classify, plan and prognosticate maxillary injuries.

The Le Fort I fracture classically passes through the maxilla transversely between the tooth apices and the infraorbital rim. The Le Fort II (or the Pyramidal fracture) extends through the nose and the infraorbital rim in a pyramidal fashion, separating a triangular segment of the face from the skull base. The Le Fort III fracture



Figs 4A and B: Le Fort I (in green), II (in red) and III (in blue) fractures of maxilla



Figs 5A and B: Malocclusion and long face

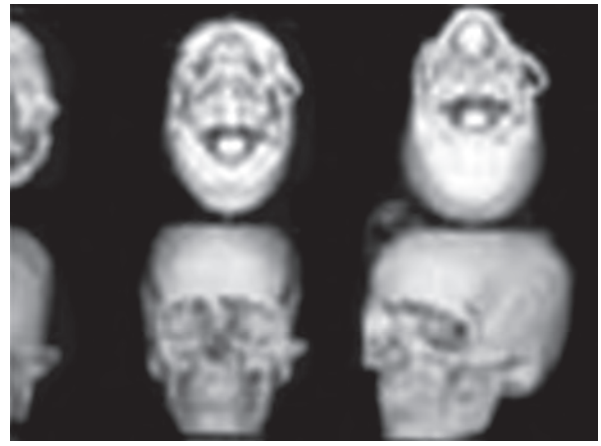


Fig. 6: Three-dimensional CT—zygomatic fracture with dislocation

is also called craniofacial dysjunction and in this the fracture line passes through the nasal bones, the zygomaticofrontal suture and the zygomatic arch and results in the face being separated from the skull (hence the name!) (Figs 5A and B).

Maxillary fractures will usually present as a combination of injuries on the two sides of the face. They are nearly always comminuted due to the thin plate of fragile bone in the area of the antrum and almost always compound into the antrum.

Maxillary injuries can be treated in a variety of ways including interdental wiring, arch bar fixation with maxillary mandibular fixation, transpalatal wiring and miniplate and screw fixation.

The surgical approach to the fractures can also be many. The Le Fort I injury is best approached through an intraoral, upper buccal sulcus incision. The Le Fort II fracture can be approached through a lower eyelid incision, a transconjunctival incision, and upper buccal sulcus incision or a local laceration.

The Le Fort III fracture can be approached via a combination of incisions—upper buccal sulcus and coronal.

While fixing the maxillary fractures it is important to keep in mind to fix the nasofrontal, zygomaticomaxillary and zygomaticofrontal buttresses.

FRACTURES OF THE ZYGOMA

The zygoma, also known as the cheek bone, is a pyramidal structure and articulates with the maxilla, the frontal bone and the temporal bone and also forms part of the floor of the orbit. Swelling in the malar area and hypoaesthesia in the distribution of the infraorbital nerve are prime indicators of fracture of the zygoma, although the swelling in the malar area often masks the zygomatic displacement except to the careful eye.

Injuries to the zygoma are often associated with injuries to the orbital area as the zygoma itself forms part of the lateral part of the orbital floor. These injuries are often together known as orbitozygomatic injuries (Fig. 6). These may be associated with ophthalmologic symptoms like diplopia and a downward tilt to the lateral canthus and merit a careful ophthalmologic examination.

Zygomatic fractures are also often compound into the antrum as the zygoma forms the lateral part of the antrum and may lead to bleeding inside the antrum, manifesting as ipsilateral epistaxis. An injury to the zygomatic arch may be the cause of trismus due to impingement of the fractured segment on the coronoid process of the maxilla.

Solitary, undisplaced fractures of the zygoma may be treated conservatively with rest and soft diet, but fracture of two of the three major articulations of the zygoma (to the maxilla, frontal bone and temporal bone) along with complicating factors, like displacement or rotation, are indications for operative treatment.

The signs and symptoms indicating an injury to the zygoma have been tabulated as under:

- Swelling and ecchymosis in the malar area
- Conjunctival haematoma
- Pain/anaesthesia over cheek/upper lip
- Nasal bleed
- Difficulty in opening the mouth/trismus
- Diplopia
- Downward tilt to the lateral canthal area

Fractures of the zygoma have been classified by Knight and North according to their displacement and the presence or absence of comminution, the discussion of which is beyond the scope of this chapter.

As already alluded to zygomatic fractures (solitary, undisplaced) and undisplaced arch fractures are treated conservatively. The zygoma has three very strong articulations with adjacent bones (maxilla, frontal bone and temporal bone) and unless two or more of these are disrupted the chances of rotational component to the displacement are minimal. Displaced zygomatic fractures, fractures with disruption of two or more buttresses, rotated fractures, fractures of the arch impinging on the coronoid and fractures with an orbital component leading to diplopia are indications for operative treatment with closed or open reduction and fixation of the fracture.

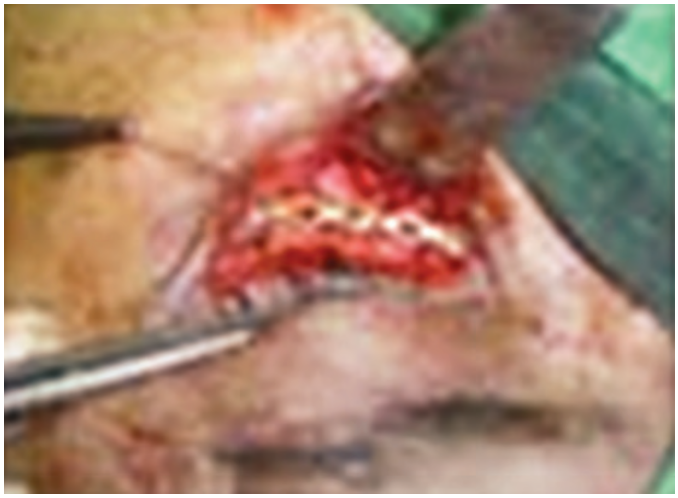
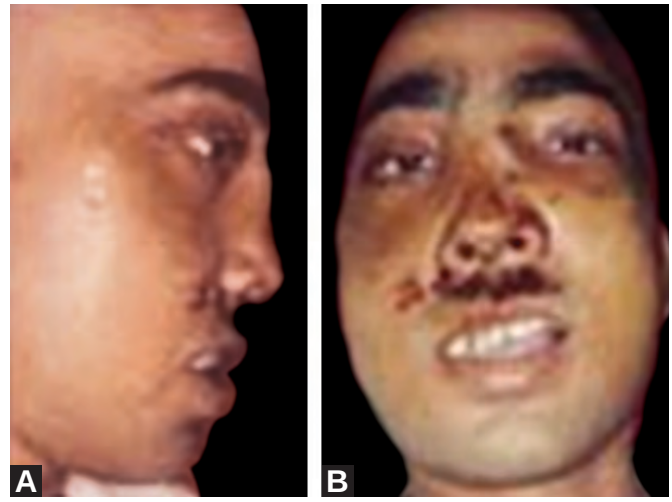


Fig. 7: Plating of orbital rim through subciliary approach



Figs 8A and B: Telescoping injury of the face. The naso-pyramid goes between the orbits into the ethmoids. May be associated with CSF rhinorrhoea. Early treatment is essential as malunion is specially difficult to treat

The zygomatic fracture lines can be approached through a variety of approaches including the intraoral, lower eyelid (Fig. 7) and temporal approach (Gillies). Fixation of two out of three buttresses ensures prevention of re-rotation of the injured zygoma.

NASAL FRACTURES

Nasal fractures occur as a result of direct violence to the nose (frontal or lateral). The diagnosis of a nasal fracture is usually straight-forward and is mainly clinical. History of trauma to the nose along with a deviated nose and/or oedema and intranasal bleed are indicators of nasal fracture. X-rays are needed only for confirming the diagnosis and for documentation purposes and usually consist of a plain X-ray lateral view of the face (soft-tissue). Nasal fractures are classified according to the extent of injury to the bony-cartilaginous pyramid (Stranc classification).

Emergency treatment of nasal fractures is usually straight-forward and consists of reduction of the fractured fragments and splintage (internal and external). Nasal packing in the acute situation helps in control of bleeding as well as provides support to the nasal splint that is placed outside. Although this can theoretically be done up to 2–3 weeks after trauma, excessive oedema and increasing union of the thin, soft, membranous bones of the face renders reduction difficult and a bloody procedure, if treatment is delayed. Later than 3 weeks, bony union of the fractured fragments renders simple reduction impractical and the treatment then consists of osteotomies and anatomical reduction of the deviated framework, akin to a formal, complete rhinoplasty.

NASO-ORBITO-ETHMOID/FRONTO-ORBITO-ETHMOID FRACTURES

The naso-orbito-ethmoid region includes the medial part of the orbits, the nasal bones and the nasofrontal area. The typical findings in case of a naso-orbito-ethmoidal (NOE) fracture are a depressed nasal area with loss of nasal support and telecanthus due to fracture of the bone bearing the medial canthi (Figs 8A and B). A depressed middle third of the face (dish face or pan face) is a diagnostic sign of a middle third fracture involving the nasoethmoidal area. The orbits are almost always involved in any frontal trauma involving the nasoethmoidal region and leading to a dish face. The supraorbital margins, owing to their prominence, are especially prone to frontal trauma. Besides fracture of the orbital margins, there can occur, fractures of the orbital walls, most commonly the floor. A frontal impact over the globe can also cause immense pressure to build up within the bony orbit in a short span of time leading to fracture of the weak areas of the orbit namely the medial wall (the lamina papyracea) or the floor. Fracture of the floor of the orbit can lead to orbital fat herniation (leading to decrease in orbital volume and enopthalmos), extra-ocular muscle entrapment and diplopia. Minor changes in the orbital volume are well tolerated by the globe and are not visible to the casual eye, but an enophthalmos of greater than 2 mm requires surgical reduction and repair of the orbital floor. Herniated fat can necrose and can get infected due to communication with the antrum leading to pan-ophthalmitis and loss of vision and, therefore, orbital injuries require careful evaluation and emergency treatment.

A CT scan of the face is the best radiological tool for visualising the floor of the orbit and the medial wall and also for calculating the loss of orbital volume and for documentation of herniated fat for medical records (Fig. 9).

The orbital floor can be approached via a number of routes, the most common of them being the 'Subciliary stair-step' incision which has the least incidence of post-operative ectropion and gives adequate exposure of the bony orbit. Another approach is the transconjunctival approach which uses an incision 4–6 mm below the lid margin.

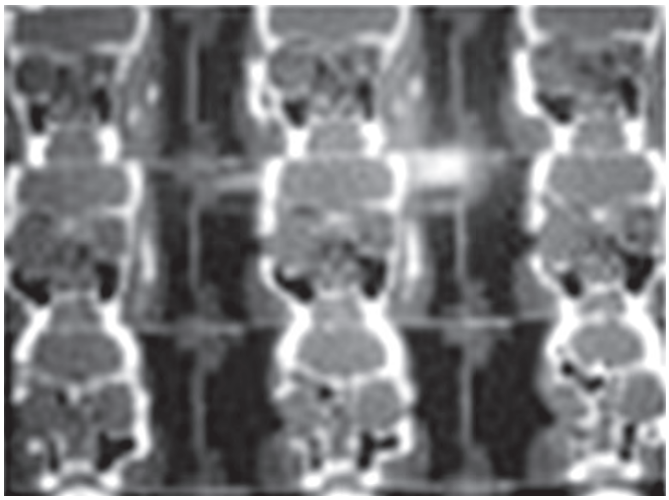


Fig. 9: Blow out fracture, herniation of contents into the maxillary antrum, incarceration of inferior rectus in the orbital floor

The orbital floor can be repaired by either autogenous or prosthetic materials. Various schools of thought favour either a bone graft or prosthetic plate for floor reconstructions. Both these materials have their pros and cons. If autologous tissue is chosen it is usually a cortical bone plate from the outer table of the skull or the iliac crest area. Prosthetic materials include polypropylene mesh, polyethylene plate or Medpore implants.

This type of injury is frequently associated with CSF rhinorrhoea. This should be carefully looked for since the associated nasal bleed or the nasopharyngeal route taken by the CSF leak may obscure its detection. The nature of management and timing of surgery would need to be decided (see chapter on "CSF Rhinorrhoea").

PAN-FACIAL FRACTURES

Pan-facial fractures are particularly tricky as most of the bones of the face are involved in the trauma. The face is conveniently divided into upper, middle and lower thirds. Any injury encompassing two or more of these regions may be classified as a pan-facial injury. Typically, in a pan-facial injury the major bones of the face are fractured leaving one with no stable platform to reduce the bones onto. These are usually the result of high speed frontal collisions or assault. Such patients have to be closely evaluated for other life-threatening injuries such as head injuries, major vessel ruptures, thoracic injuries, tracheal fractures, abdominal trauma and spinal injuries. Pan-facial fractures look particularly ghastly but are amenable to treatment and give good results, if the principles are kept in mind.

As in all facial injuries the ABC have to be secured first and then one must come to a thorough evaluation of the face. Clinical examination (inspection, palpation) must be supplemented by radiological survey. Besides the facial X-ray series, a CT scan of the face, preferably with 3D reconstruction, is a necessity.

Principles of fracture fixation remain the same as mentioned in other sections. For pan-facial fractures, however, the difficulty lies in assessing the normal contour or occlusion as all the major bones are traumatised.

One must remember to proceed either from above, below or vice versa reducing the unstable fragments over a stable bone which can serve as the reference or scaffolding to build the facial skeleton on. Comminuted fractures may require wide exposure and interfragmentary wiring or external fixation in major trauma. Patients usually will need secondary looks at revising the results (augmenting the nose, zygoma, etc.) after healing has occurred and the results of the first attempt are clear.

PAEDIATRIC FACIAL INJURIES

While managing paediatric injuries one must keep in mind that the facial skeleton is not yet mature and has a lot of growth left in it. While this may be an advantage in certain cases, in others it may be detrimental to the results in the long-term.

The facial tissues in children are blessed with a superb vascularity and, therefore, one has to be very conservative in soft tissue debridement or even in discarding small fragments of bone. Pieces of bone may show amazing take up and future growth even if they are attached by a flimsy soft tissue or a piece of periosteum.

Some surgeons now prefer resorbable plates and screws in paediatric injuries so as not to retard the growth potential of the paediatric skeleton with hardware.

Children's bones are also very soft and pliable leading to good moulding while fixing the fracture, but also necessitating gentle handling.

Facial scars in children tend to remain hard and red for a longer time than in adults but the results are far superior in terms of cosmesis. Also, due to the growth potential of the paediatric skeleton, minor discrepancies in fracture fixation can adjust themselves over a period of time so that the final result is good.

SUGGESTED READING

1. Nicolas Hardt, Johannes Kuttenberger. Craniofacial Trauma: Diagnosis and Management, 1st edition. Springer; 2009.
2. Peterson's Principles of Oral and Maxillofacial Surgery, 2nd edition. BC Decker Inc; 2004.

43 Traumatic CSF Fistulae

Ravi Ramamurthi, Amit Kapoor

CEREBROSPINAL FLUID RHINORRHOEA

Leakage of cerebrospinal fluid (CSF) through the nose following trauma has been reported to occur in 1–2% of head injuries admitted to hospital.[31,38] In 70%, the leak occurs within 48 hours of the injury. The leak will clinically be obvious in 98% within 3 months. The leak ceases spontaneously in 70% during the first 7 days. In most cases the leak will stop within 6 months. In a small group, after the initial arrest, the rhinorrhoea may recur a few weeks, months or even years after the original trauma.[32,44] In such cases the dural defect gets temporarily sealed by blood clot, brain, or a spicule of bone or by direct adherence of the sinus mucosa to the arachnoid. When such local factors resolve, or when there is an increase in intracranial pressure (ICP) due to post-traumatic hydrocephalus, a free pathway is opened up from the subarachnoid space to the exterior and a delayed CSF leak occurs. In some cases a leptomeningeal cyst may form, from which the leak may occur.[19] Rao[48] postulated that the mechanism of onset of late CSF rhinorrhoea is similar to that of growing fractures in children. The interposition of a piece of dura and arachnoid and possibly a bit of brain tissue trapped into the bony gap is the primary defect. The pulsations of the brain enlarge the bony and dural defect leading to a recurrence of the leak. If such interposition of the meninges into the bony gap does not occur in the immediate post-trauma period, the fistula heals spontaneously.

CSF fistulas may also be classified as low pressure or high pressure. This distinction is relevant for management, as when the CSF pressure is high as in associated hydrocephalus, the ICP has to be reduced by appropriate surgical intervention.

Pathophysiology

The CSF rhinorrhoea may be unilateral or bilateral. When unilateral, it need not necessarily be on the same side as the fracture and dural tear. The severity of the leak is also not always proportional to the size of the dural tear. Usually the leak is through a dural tear which is associated with a fracture of the anterior cranial fossa involving a paranasal air sinus or the cribriform plate of the ethmoid. Samii and Draf[51] are of the opinion that most leaks occur in the adjacent ethmoid roof. The next common sites for the fistula are fractures of the posterior wall of the frontal sinus and those involving the sphenoid sinus (tuberculum sella and anterior wall of the sella rather than the planum sphenoidale). Rarely, fluid leaking through a fracture of the middle cranial fossa into the eustachian tube may flow into the nose during forward bending of the head, i.e. paradoxical CSF rhinorrhoea.[8] A minor injury causing profuse rhinorrhoea through a large fistulous tract is due to the rupture of an associated encephalocoele projecting through a congenital defect in the cribriform plate.[42]

Diagnosis

A detailed history should be obtained in patients who do not have an obvious profuse leak. A salty taste in the back of the throat and salty fluid running down the back of the throat should be asked for. When the fluid is blood tinged, the fluid should be allowed to drip onto a piece of cloth. A ring of blood with an outer ring of fluid suggests the presence of CSF (ring sign). The fluid should be collected and sent for glucose and B2 transferrin estimation. Glucose levels above 30 mg% are indicative of CSF though it may be lower when there is meningitis. This test is more useful when it is negative as it may rule out CSF rhinorrhoea. B2 transferrin is present in CSF and vitreous fluid. It is absent in tears, nasal discharge, saliva and serum.[18,50]

Allergic rhinitis with sudden leak of clear fluid from the nostrils can be differentiated by: (1) the use of sterile cotton pledgets in the nose and soaking them later in water which is examined for glucose, (2) application of decongestant nasal drops and then attempting to provoke the rhinorrhoea by changes in the position of the head, (3) failure of nasal fluid to stain or stiffen a handkerchief and (4) the presence of eosinophils in the nasal discharge of allergic rhinitis.

Headache may be complained of and may be due to high or low ICP. Low pressure occurs when there is a profuse leak of CSF. High pressure headache is often relieved when there is fresh leak of CSF brought about by the high pressure. Meningitis may be the presenting symptom in about 20% of patients in the acute stage.[39,60] The risk of meningitis in delayed cases is 57%.[30,34,36,38,47] The most common organism is *Pneumococcus* and the mortality is around 10%.[24]

Associated symptoms help in locating the site of the leak. Anosmia would indicate a fistula near the

cribriform plate, whereas a leak through the sphenoid sinus may be suspected if there are signs of injury to the neighbouring structures, viz. visual field disturbance, diabetes insipidus or a carotid cavernous fistula. Retention of the sense of smell, demonstration of an ipsilateral middle fossa fracture and the absence of an anterior fossa fracture would throw strong suspicion on the Eustachian tube being involved in the rhinorrhoea.

Investigations

Searching for the site of the fistula during surgery can at times be time consuming and frustrating[45] and every effort must be made to locate the site by clinical and radiological means.

Plain X-rays of the skull, lateral, AP, basal and paranasal sinus views may be helpful in diagnosis, but may not always demonstrate the defect. Tomograms are useful in confirming suspected fracture sites. Radiological demonstration of a fracture involving a paranasal air sinus is strong supporting evidence that the nasal discharge is CSF. Occasionally, plain X-rays of the skull may show pneumocephalus, the air having gained access into the cranium through a fistula. Plain lateral films of the skull in the sitting position may show air in the chiasmatic cistern and a fluid level in the sphenoid sinus.

Computerised Tomography Scan

Fine 1–1.5 mm cuts in the coronal and axial planes should be done from the anterior cranial fossa base up to the sella and a fracture can be made out in about 50%[14] (Figs 1 and 2). On intravenous contrast administration there may be enhancement of the adjacent brain. Hydrocephalus can also be made out.

When the fracture site is not obvious on the plain CT scan, cisternography using water soluble non-ionic contrast, like iohexol or metrizamide, has to be done. When there is an active leak the site of leak can be made out 76–100% of the time.[2,10,46] In inactive leaks the site of leak can be made out in 60%. CT cisternography cannot differentiate between small ethmoid bones and leaking contrast as they both appear white. Bone can be separated from the contrast medium by using dual energy CT scanning.

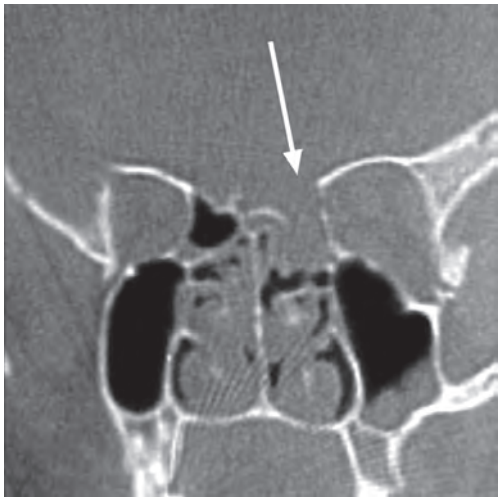


Fig. 1: CT bone cuts coronal views showing injury to the cribriform plate

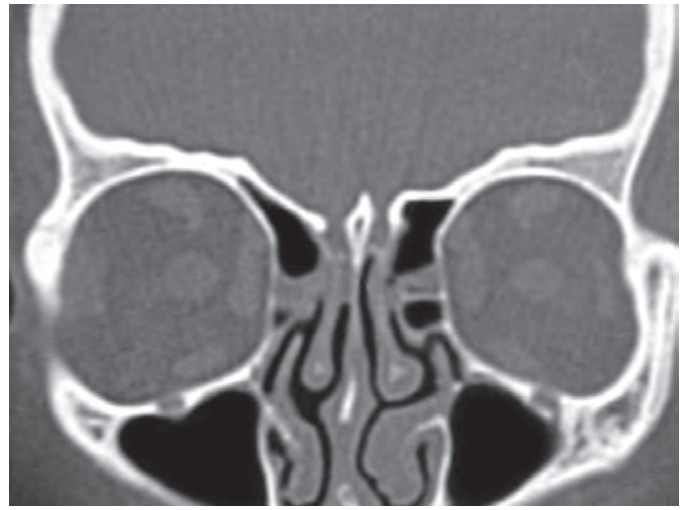


Fig. 2: CT bone cuts coronal views showing bilateral cribriform plate defect in a patient who presented with delayed post-traumatic CSF leak

Radionuclide Cisternography

Isotope studies are useful especially when the leak is minimal or intermittent.[3,12,28,55] The isotopes in common use are technetium-99 and DTPA. Cotton pledgets are placed in the appropriate areas of suspected leak like the roof of the anterior and posterior nares, sphenoethmoidal recess, the posterior floor of the nose and the middle meatus. The isotope is then injected by a lumbar puncture and counts are taken at various time intervals from the different cotton pledgets. In active rhinorrhoea, the site of leak can be located in 70% and in only 28% in inactive leaks.[17]

Magnetic Resonance Imaging

The usefulness of magnetic resonance imaging in finding the site of leak better than the other methods has been doubted.[5,22,25] One report found that magnetic resonance (MR) cisternography was superior to CT cisternography.[15] MR cisternography was done using T2-weighted sequences, a 3D PSIF (time-inversed fast imaging with steady-state precession, FISP) and a 3D constructive interference steady-state sequence. The sensitivity in detecting the site of leak was 92% as compared to 72% with CT cisternography.

Treatment

The patient is given prophylactic antibiotics and is cautioned not to sniff or blow his nose. The usefulness of prophylactic antibiotics has been questioned. There was found to be no difference in incidence or morbidity of meningitis when antibiotics were not given.[33,53] In a meta-analysis which included six series over a period

of 25 years, it was found that meningitis occurred in 10% of patients who were not on antibiotics and in 2.5% of those who were on antibiotics.[4] When the leak lasted for more than 7–10 days, the risk of meningitis increased 8–10 fold. Choi and Spann[9] reported that the incidence of meningitis was greater in patients receiving prophylactic antibiotics. The risk of producing resistant strains was higher with antibiotic prophylaxis.[53] The routine use of prophylactic antibiotics in patients with CSF fistulae in closed head injuries is not recommended.

The nose or ear may be covered with a light dressing, but the orifice should not be plugged tightly. A course of acetazolamide and oral glycerol for a week may be helpful. A period of one or two weeks is allowed to give a chance for the fistula to close on its own. In the presence of associated fractures of the face and extensive facial soft tissue, injury operative intervention cannot be delayed for too long. Repair of the CSF fistula, if required in such cases, should be performed after any surgical manipulations needed to correct mandibular or facial fractures.

Indications for Surgery

A persistent CSF fistula needs surgical closure because of the ever present risk of meningitis and brain abscess. The accepted indications for surgery are: (1) profuse rhinorrhoea; (2) delayed onset or recurrence of rhinorrhoea; (3) the presence of an intracranial aerocoele; (4) associated faciomaxillary injuries; (5) radiological demonstration of a spicule of bone projecting into the brain and (6) history of an attack of meningitis. Lewin[38] recommends that every case of CSF fistula must surgically be closed, on the argument that the temporary sealing of the leak may breakdown at any time by normal changes in ICP, as happens in straining, coughing, etc. Once meningitis sets in, it may be antibiotic-resistant or so virulent that it may prove fatal, and in surviving patients post-meningitic epilepsy is likely to occur. But even such advocates of aggressive surgery would prefer to wait for about 10 days after the injury to allow brain oedema to subside.[30] It may be mentioned that when cases of traumatic CSF fistula report for the first time with symptoms of meningitis, it is often seen that the CSF leak has stopped and does not recur after the meningitis has been controlled. However, Tandon[54] advises surgical closure of the fistula once meningitis has occurred.

Operative technique: The operative repair of CSF fistulae may be performed through an intracranial or extracranial approach.

Intracranial approach: The intracranial operation was described by Dandy,[11] Cushing and Cairns.[6] The currently used technique was first described by Taylor, as reported by Eden.[16] In case the fracture and the rhinorrhoea are on the same side, a unilateral frontal flap may be sufficient for exploration. Rhinorrhoea through either both nostrils or doubtful localisation of the site of leak dictates bilateral exploration. Good general anaesthesia with measures to relax the brain (intravenous mannitol, hyperventilation and/or lumbar drainage) is essential. This of course is not necessary, if profuse CSF leak has been present pre-operatively. An associated aerocoele is tapped to reduce the ICP.

The defect may be approached intradurally, extradurally or both ways. The most suitable plan is to look for the fistulous tract intradurally first. The protrusion through or adherence of the brain to the dural margins of the tract indicates the site of the fistula. After releasing this, the fistula is approached extradurally. A probe inserted into the fistula from inside the dura helps in identification of the tract extradurally. The dura is found adherent to the fracture line at the site of the fistulous tract. The site of the leak, along with a minimum margin of 1 cm of dura all round, is fully exposed.

Fascia lata or pericranium may be used to close the dural defect. It is advisable to place two flaps of fascia lata over the defect, one extradurally and the other intradurally. Fibrin glue can be used to promote adhesion of the graft. The use of cyanoacrylate adhesive for the dural defect[37,40,57] and methyl methacrylate for the bone defect[56] has been advocated. Sometimes, even extensive exposure may fail to disclose the site of the fistula. Ray and Bergland[49] recommended that nasal air insufflation during craniotomy may reveal the site of the leak. If the site is still unidentifiable they recommend covering the cribriform area and packing the sphenoid sinus. Mohanty and Tandon have described the steps of transcranial repair in detail.[43]

The patients are given antibiotics for at least 2 weeks post-operatively and are cautioned to avoid straining of any sort for 4 months. The intracranial route is advantageous[27] in that the surgeon has direct visualisation of the dural defect.[7] It allows inspection and treatment of any associated brain injury[29] and is necessary in the presence of intracranial haemorrhage[41] and in compound fractures. The disadvantages of the intracranial route include: (a) difficulty in reaching and dealing with sphenoidal sinus fistulas and (b) the risk of anosmia following the procedure.

Extracranial approach: The extracranial transnasal approach successfully used to repair CSF fistulae was first reported by Dohlman.[13] This has been followed by other surgeons who have successfully used the extracranial approach to treat CSF rhinorrhoea.[7,27,29,41] The approaches use mucoperiosteal or mucosal flaps, fascia lata or abdominal fat and fascia.[51] The endoscopic approach has become universally accepted and is the method of choice.[23,35,52] The advantages of the extracranial approach are: (a) it does not generally result in anosmia; (b) it produces the best exposure of the sphenoid, parasellar and posterior ethmoid regions, the posterior wall of the frontal sinus, cribriform plate and fovea ethmoidalis and (c) it produces less morbidity than the intracranial procedure. The disadvantages of the extracranial approach are: (1) it does not allow visualisation of the associated cerebral injury and (2) in the presence of comminuted fractures

of the skull base, the extracranial approach does not allow sufficient debridement to delineate the extensive dural tears which may be present.

A CSF diversionary procedure (lumboperitoneal shunt) is necessary when there is raised ICP without hydrocephalus, as measured by lumbar manometry or intracranial ICP monitoring.[21] A ventriculoperitoneal shunt should be done when there is hydrocephalus. It is wise to do the diversionary procedure after the CSF leak site has been identified and repaired. If the shunt is done first, the site of leak may be difficult to locate.

CEREBROSPINAL FLUID OTORRHOEA

This is rarer than rhinorrhoea, but in one series,[31] the incidence was equal in the immediate post-traumatic period. CSF otorrhoea occurs when there is a fracture of the petrous temporal bone along with injury to the tympanic membrane. The fracture can be longitudinal or transverse to the long axis. The incidence in longitudinal fractures is 29% and in transverse fractures 44%.[26] Ghorayeb and Rafie reported a 23% incidence in temporal bone fractures.[20] The dural tear in these cases is usually found on the anterior surface of the petrous ridge in relation to the tegmen tympani. The CSF leaks through the external auditory meatus only if there is an injury or a perforation of the tympanum. Otherwise, the fluid reaches the pharynx through the ear. Such patients complain of deafness after the injury and examination with an auroscope shows a fluid level behind the tympanic membrane. The leak in CSF otorrhoea is usually more profuse than in rhinorrhoea, but has a much greater tendency to cease spontaneously. The tear tends to heal permanently and rarely surgical repair is required. The leak can surgically be repaired by a mastoidectomy. If necessary, the mastoid cavity, middle ear cleft and the Eustachian tube may be obliterated. A limited craniotomy may also be done along with the mastoidectomy.[1] The dural defect after definition can be packed with fat and fascia. A pedicled temporalis muscle flap can be rotated.

Sudden arrest of CSF otorrhoea may be an indication of natural healing but may also be the first sign of the onset of meningitis. As CSF otorrhoea is caused by a fracture of the middle cranial fossa, the same injury may also result in an extradural haemorrhage. When such a combination exists, the CSF leak partly compensates for the rise in ICP, and masks the signs of the haematoma which may reach a large and fatal size before recognition, unless the neurosurgical team is alert to its possibility.

TRAUMATIC PNEUMOCEPHALUS

Following a head injury, air may enter the intracranial cavity through a tear in the dura and a fracture of the skull. This is most often preceded by a CSF leak which may be missed if heavily bloodstained. Occasionally, pneumocephalus may also occur in well-established CSF rhinorrhoea. Air may enter the cranial cavity immediately after the head injury or after a few days, and may be found in the ventricles, in the subarachnoid space or subdurally. In the usual course of events, the air gets absorbed without producing any symptoms. However, if there is a ball valve action which allows the entry of air, but prevents its exit, a condition of tension pneumocephalus may develop. Walker[59] states that Chiari was able to demonstrate what was probably the first reported authentic case of traumatic pneumocephalus.

Some patients present with no symptoms, the pneumocephalus being diagnosed accidentally during routine imaging. In other cases the patients may report with headache and irritability. There may also be vomiting and convulsions.[58] This clinical picture may appear immediately after the head injury or some time later. Infection may occur, leading to meningitis or brain abscess.

Treatment

If there is a tension, pneumocephalus or a trapped subdural aerocoele causing headache and vomiting, tapping and release of the air is essential. In most cases the air gets absorbed by itself. If it persists or recurs or is accompanied by a CSF fistula, then a repair of the fistulous tract is indicated after careful assessment of the patient and after accurate localisation of the tract.

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44 Missile Injuries of the Brain

Harjinder S Bhatoe

Missile injuries of the brain (CMI) have traditionally been viewed with pessimism due their supposedly poor outcome. While their incidence is rising all over the world, due to rise in ethnic armed struggle and militancy and terrorist related violence, civilian injuries are also showin g a rise due to easy availability of firearms.[23] There has been improved understanding of these injuries due to the pioneering work of Horsley, Cushing and more recently by experience in the Korean and Vietnam wars. Missile ballistics is now understood better and CT has revolutionised the evaluation and prognostication of these injuries. Multi- and univariate analysis of various factors influencing the likely outcome has been attempted and the Glasgow Coma Scale score has remained the most reliable predictor of the outcome. Surgical techniques have been standardised and post-operative monitoring is better. Outcome of such injuries, both during war or war-like situations and in civilian gunshot wounds has shown improvement and there has been rethinking on the problem of retained intracranial fragments. A better understanding of pathology and adherence to basic neurosurgical principles of definitive surgical management will ensure saving of more lives and improved neurological preservation. Nevertheless, mortality due to these injuries remains high a fact to be borne in mind by all those who attend on the victims of craniocerebral missile injuries.

HISTORICAL PERSPECTIVE

Penetrating wounds of the head have challenged physicians since medieval ages. Within a few hundred years of the Mongols' bringing gunpowder to Europe from China in the fourteenth century, a firearm (Spanish musket) was invented which could propel a projectile at 1,000 ft/sec and could inflict previously unimaginable wounds.[53] There was little attempt to treat these injuries over the next three centuries and until the turn of the twentieth century, missile injuries of the brain were considered to be almost universally fatal. Modern management of these injuries began with the experimental studies of Sir Victor Horsley,[30] in which he described the hydrodynamic nature of CMIs and cessation of respiration with rise in intracranial pressure. This was followed by application of antiseptic techniques to combat neurosurgery in the Anglo-Boer war (1899–1902). Management was further advanced and standardised by Harvey Cushing during his wartime service in France during the First World War, which resulted in a decrease in mortality from 54 to 28%.[18]

The literature on missile wounds sustained during war is more extensive than on peacetime injuries. Each war has furthered experience in this regard. World War I proved the efficacy of definitive surgical intervention. The Spanish Civil War showed that the blast effect was a significant component of craniofacial injury. During World War II, initial dural repair and antibiotic medication showed distinct improvement in outcome.[37] The Korean War confirmed the effectiveness of prompt evacuation of the patient to a neurosurgical centre, often by helicopters from the battle site, followed by definitive neurosurgical intervention. This resulted in improved survival and reduced infection.[38] The civil disturbances in Belfast took place close to a neurosurgical centre and the natural history of penetrating injury could be studied from the moment of injury.[10,41] During the Israeli expedition into Lebanon, all the victims of head injuries were brought to a single institution and for the first time, the place of CT scan in combat neurosurgery was established and a less aggressive debridement could be followed.[9] Finally, after the Vietnam conflict, the Vietnam Head Injury Study (VHIS) involving the US Army, Navy, Air Force and American Red Cross followed up the head injury survivors of war for 18 years and elicited valuable data.[40] Significantly, during the Gulf War (1991), there were only two cases of missile injuries of the brain among the American troops.[11] From India, Bajpayee[4] reported on missile injuries of the brain sustained during the 1971 Indo-Pakistan war. Experiences with civilian gunshot wounds too have been reported.[14,19,39,43] Experiences in management of low velocity missile injuries (LVMIs) to the brain during low intensity military conflicts and anti-militancy operations have recently been analysed.[8,20] Experiences with CMIs during OP VIJAY (Kargil) have been analysed and the role of conservative debridement and meticulous dural closure has been firmly established.[49] The management principles have been successfully extrapolated to the management of civilian casualties.

APPLIED BALLISTICS

Missiles

Projectiles travelling at less than 2,000 ft/sec fall into the category of low velocity missiles, while those travelling

above this speed are high velocity missiles. There is a distinct difference in the pattern of injury and the outcome of low velocity missile injuries (LVMIs) and of high velocity missile injuries (HVMIs). Most handguns and revolvers use heavy bullets weighing about 0.5 oz and have muzzle velocities ranging from 550 ft/sec to 900 ft/sec. In contrast, most rifles and small arms (rifles, stenguns, machine-guns, etc.) used in war use light bullets, having muzzle velocities averaging 3,000 ft/sec. High velocity missiles, as they reach the limit of their range become low velocity (spent bullet) and may inflict less severe wounds, as compared to that within their effective range. The handgun ammunition can achieve muzzle velocity of 1,200 ft/sec effective over a short distance. Pieces of shrapnel from exploding devices may have a velocity of 600 ft/sec, unlike rifled bullets; however, they rapidly lose energy due to their irregular shape and non-aerodynamic nature. The commonly observed CNS missile injuries are inflicted by one of the following missiles:

- The 7.62 mm bullet: This can be fired by the AK-47 assault rifle (Kalashnikov), self loading rifle (SLR), light machine gun or medium machine gun (LMG/MMG). The bullet weighs 150 grams and has a muzzle velocity of more than 2,000 ft/sec.
- The 5.56 mm bullet fired from the Indian Small Arms System (INSAS), M-16 rifle. The bullet weighs 55 grams and has a muzzle velocity of more than 3,000 ft/sec.
- Low velocity missiles fired from a variety of firearms, viz. revolvers, shotguns, handguns, 12 bore single/double barrel guns and country made weapons (katta, tamancha, etc. as prevalent in parts of Bihar and Uttar Pradesh).
- Fragments of exploding devices: The variety of exploding devices reflects the ingenuity of the minds that assemble them, often in innocuous looking forms. They may be made to look like toys, transistors, cassette players, etc. which are often detonated by handling or by remote access. A domestic LPG cylinder placed on its top often makes an innocuous looking but deadly combination for explosion. Other familiar sources of missiles are the HE 36 mm grenade, rockets and exploding artillery/mortar shells. Fragments of exploding devices initially travel at high speeds of over 3,000 ft/sec and then rapidly lose speed because of their volume, weight, irregular shape and become low velocity at distances of 10 metres or more.
- Glass fragments, nails, etc. may rarely act as missiles.[42,55]

Energy Transfer

A bullet is stable in its flight through the atmosphere, but becomes less stable on entering the tissues, when it tends to yaw, deform and tumble due to resistance offered by the tissues, thus releasing kinetic energy (KE). Injury to the tissues by a missile is a function of energy release over time and of the volume and location of tissue disruption. The amount of kinetic energy contained in the missile is defined by the formula $E = -1/2mv^2$, where m is the mass of the missile and v its velocity. Since energy contained in the missile varies directly with the square of its velocity, the latter is relatively more important in determining the energy transfer by the missile than the mass. The amount of tissue damage caused by a missile may be correlated with the amount of energy deposited within the tissues by the missile. The energy transferred can be expressed by the equation:

$E_t = E_{en} - E_{ex}$, where E_t = missile energy transferred, E_{en} = energy of entry at the time of impact, and E_{ex} = energy contained in the missile at the time of its exit from the tissues. If the missile exits, only part of its kinetic energy will be deposited within the tissues. The same amount of energy may be deposited by a missile of a smaller mass with a high velocity or a greater mass missile with low velocity. The amount of energy transfer to the brain is the difference of the energies of the missiles at entry into and exit from the skull. If the missile does not exit from the skull, the energy transferred is the energy contained in the missile at the moment of impact. Thus, lower the residual velocity, greater the energy liberated.[29]

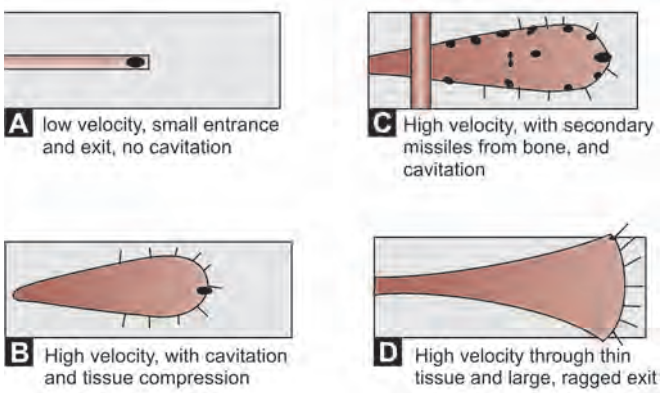
The extent and degree of damage in wounds are proportional to the amount of KE of the missile dissipated in the wound. The injury produced by the missile is increased by factors causing it to give up more of its energy intracranially. A missile that yaws will give up more of its energy. Similarly, a hollow point bullet that shatters upon impact will tend to give up more KE to the brain and is more destructive than bullets that do not shatter. Likewise, shotgun injuries caused by multiple pellets at close range, each with a relatively small amount of KE are extremely destructive; each of these pellets acts as an independent missile invested with KE according to its mass and velocity. Other factors that determine KE transfer by a missile are the resistance offered by the tissues and the tendency of the bullet to deform and increase the area, with which it impacts the brain with a consequent increase in energy transfer to the tissues. Bullets with a flat front and expansion on impact (dumdum bullets) present a large surface area to the tissues to transfer energy. A rifled bullet fired at low velocity, spinning with its long axis parallel to the trajectory may pass cleanly through the tissue and exit retaining much of its KE it had on impact. A high velocity rifle bullet of the same calibre, will more likely strike with its long axis at a slight angle to its trajectory[6] and as a consequence of this and its great velocity, deforms and may even disintegrate in the tissues. The much greater tissue resistance to this high velocity deformed and 'tilted' missile and its fragments leads to release of an enormous amount of KE. The tissue damage is proportionately greater. Transfer of energy is greatest in dense tissues with high water content. Thus, wounds of the brain (and those of liver, kidney, muscle and bone)

are more destructive than wounds of less dense tissue, such as lung or fat.

PHYSICAL EFFECTS OF MISSILE WOUNDING

Missile wounding can be understood in terms of physical interactions between the missile and the tissues through which it passes. The primary destructive effects of a missile interacting with tissues are caused by two mechanisms:

- *Crushing action of the missile*: There is fracture of the skull, laceration and fragmentation of brain tissue and injury to vascular structures.
- *Pressure waves and cavitation (Figs 1A to D)*: Besides the direct crushing action, a missile moving in water or tissue medium generates distinctive types of pressure waves within the medium it transits:
  a. *Juxta-missile pressure*: Extremely high pressures (thousands of atmospheres) are generated immediately in front of and at right angles to a moving missile, owing to the flow of medium (through which the missile is travelling) around the missile.
  b. *Longitudinal shock wave*: When a missile strikes animal tissues, a high-pressure compression front or shock wave is formed which moves spherically away from the point of impact. It is doubtful whether these shock waves result in any energy transfer to cause tissue damage.[28]
  c. *Pressure waves from KE transfer (Cavitation)*: Cavitation was first recognised as a pathological phenomenon in missile injuries by Woodruff.[54] At the same time, Sir Victor Horsley[30] demonstrated experimentally the cavitation in missile injuries of the brain by firing into clay models of brain. When a high velocity missile passes through tissues, KE is transferred to adjacent tissue elements, which are propelled radially, creating a large subatmospheric temporary cavity directly behind the missile. When the elastic limit of this outwardly displaced tissue is reached, it falls inward whence it was displaced. This cycle may be repeated several times before the deranged tissue comes to rest around the permanent track created by the missile. The oscillatory, outward and inward rush of tissue created a long lasting (milliseconds) lower amplitude (20–30 atmospheres) pressure wave, which propagates throughout the medium. It has been considered that these lower amplitude, longer lasting pressure waves are the cause of damage to the tissues at a distance from the site of actual missile injury. Kinetic energy deposited by a missile is partitioned between that which directly crushes tissues in its path and that which displaces tissues adjacent to the missile track. The latter is less destructive than the former owing to the elastic properties of the displaced tissue, which may be deformed without being irrevocably destroyed.[12,16]



Figs 1A to D: Passage of low and high velocity missiles through animal tissues

PATHOPHYSIOLOGY

The pathophysiology of CMI remains a complicated and poorly understood aspect of neurotrauma, although some deductions arrived at from head injury management can be applied to it. Absence of specific data and scant literature on experimental studies (unlike that seen in closed head injuries) are major limiting factors in further understanding of the pathophysiology of CMI.

Effect on ICP and Cerebral Perfusion

Experimental studies have revealed an instantaneous rise in ICP immediately after tissue penetration, due to shock waves lasting 15–25 microseconds; the magnitude of rise is determined by the amount of KE of the missile and can reach up to 80 kg/cm^2.[29] Such a rise in ICP may produce instant brainstem compression and internal brain herniations, resulting in death or decerebration, while there may be no demonstrable significant mass effect.[32] Such acutely raised ICP may be the cause of instant death in humans following CMI. Experimental studies have demonstrated a second rise in ICP to 60–100 mm Hg within two to five minutes of injury and a rapid rise in mean arterial blood pressure (MABP); MABP shows a subsequent fall and a low MABP with persistently raised ICP results in poor cerebral perfusion, decerebration and higher mortality.[12,17,34] Transcranial Doppler studies in patients with CMI have shown vasospasm in 37% cases; these patients have poor survival, as compared to those without vasospasm.[33]

Mechanism of Brain Injury

Immediate rise of ICP due to a shock wave lasting 15–25 microseconds may be transmitted to the brainstem and this factor along with internal brain herniations may lead to instantaneous death, especially if the missile is a high-velocity one.[32] As the missile penetrates the brain, cerebral parenchyma in its path is crushed and spread apart, creating a permanent cavity that is slightly larger than the diameter of the missile. Formation of a temporary cavity, which may be 30 times the diameter of the

missile (depending on the KE of the missile) stretches and tears the brain parenchyma. KE transfer to the brain may be cumulative with injuries from multiple pellets, secondary missiles or from internal ricochet and injuries remote to the observed missile track are quite common.

Contusion and haemorrhage may occur in areas distant from the missile track. Laceration of major vessels may produce large parenchymal haematomas, extending considerable distances from the site of the track. Patients who have no intracranial missile penetration may develop neurological deficit as a result of blast wave. They may suffer fracture of the skull as well. White matter oedema has been observed in experimental CMI in primates,[3] with widespread swelling of perivascular astrocytes within 30 minutes of injury.[2] Oedema has been observed in minutes in patients with CMI who died subsequently.

Experimental studies on cats have shown the early-stage changes in the cerebral microcirculation after a craniocerebral missile wound. The blood flow in the microvessels may increase progressively in the areas of concussion, contusion and laceration, induce reperfusion injury following ischaemia and hypoxia of the brain tissue resulting from a microcirculation disorder caused by the wound.[52]

EVALUATION AND INITIAL MANAGEMENT

Rapid neurological deterioration after missile injury to the brain can occur due to primary and secondary factors. Because the morbidity and mortality are significantly influenced by the patient's neurological status before reaching neurosurgical care, efforts should be made to minimise the time taken for transportation to a well-equipped neurosurgical centre.[31] Upon arrival in the emergency room the patient is completely evaluated after ensuring an adequate airway and haemodynamic stability. All external bleeding should be controlled and a search for abdominal, thoracic and extremity injury is made and their appropriate treatment is planned. The head is shaven completely and extruded brain matter or CSF leak, boggy scalp swelling, eye injury (indicating oculocerebral injury), bleeding or CSF leak from nose or ears, subcutaneous emphysema over the face and neck and pulsations in the carotids in the neck are carefully looked for. The mouth and oropharynx are cleared by suction and examined for bone fragments, splinters and brain matter.

A detailed neurological evaluation, as practical in the prevailing circumstances, is carried out, which will be the baseline for all subsequent evaluations. Rapid examination of sensorium by Glasgow Coma Scale (GCS) is done. Pupils and visual status and ocular movements are noted and facial paresis, focal motor deficit, etc. are looked for. An enlarging intracranial mass lesion should be suspected when there is progressive loss of brainstem function in a pattern consistent with herniation or if the brainstem examination is dramatically better than the overall GCS score.[25]

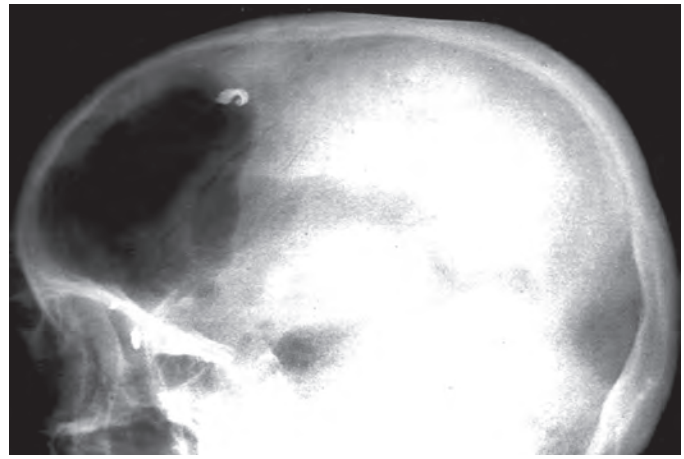


Fig. 2: Skull X-ray showing intracranial splinter with pneumocephalus and air ventriculogram

Imaging

Skull Radiograph

Skull radiographs are done routinely in all the patients. The most common finding is the presence of intracranial radio-opaque foreign bodies (Fig. 2). Their location and distribution can give an idea about the direction of the missile track and the structures likely to have been injured. Communited fractures, depressed fractures, stellate and linear fractures can be observed. Skull radiographs are superior to CT in delineating certain fractures, such as horizontal linear fractures and fractures in the same plane as axial CT slices that can be missed on CT. Another important finding is the presence of pneumocephalus and rarely an air ventriculogram if the ventricle has been entered. Other findings that may be present are opacification of paranasal sinuses and contralateral shift of calcified midline structures, if any.

Skull radiographs may also be done after CT, when trying to locate a single intracranial foreign body, which is suspected to have changed its position and in patients with post-operative neurological deterioration, when it may show a treatable lesion like pneumocephalus.

Computed Tomography

CT is the imaging procedure of choice for evaluation of these injuries, which can diagnose as well as prognosticate the injuries. Usually, a depressed comminuted fracture with in driven fragments is seen in LVMIs. On the other hand, HVMIs may result in extensive skull fracturing remote from the impact site. The parenchymal laceration is seen as a conical track with the base of the cone at the entrance site. Haemorrhage into the track outlines it as a high attenuating track (Fig. 3). However, the shape of the track is variable, according to the missile yaw and energy transfer to the tissues as mentioned earlier. CT will also show the ricocheted missile tract, intracranial haemorrhage, in driven radio-opaque material, pneumocephalus, cerebral oedema

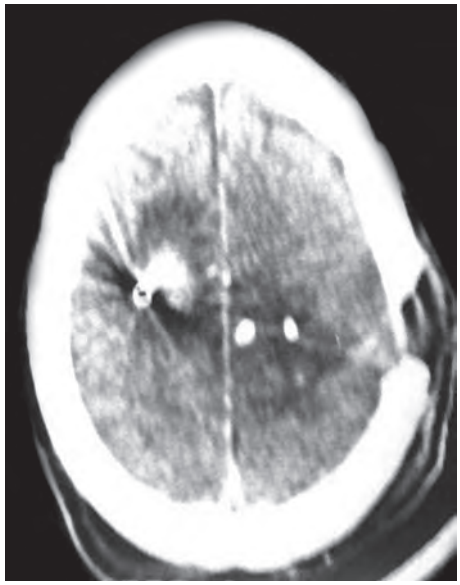


Fig. 3: CT brain showing the missile track

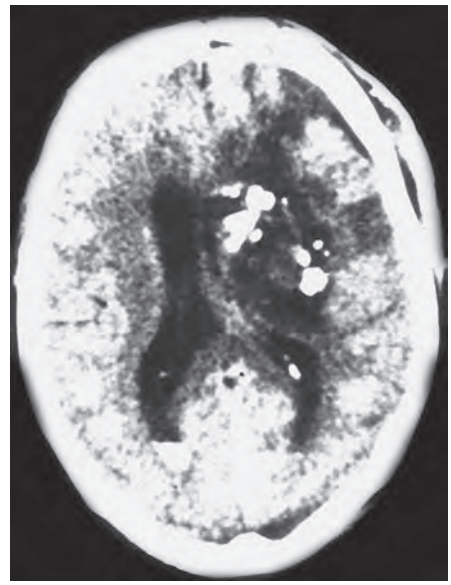


Fig. 4: CT brain showing intracerebral splinter, oedema and intraventricular haemorrhage

and brain contusion (Figs 4, 5A and B). Besides being the most important diagnostic imaging modality, CT is also valuable in prognostication of CMIs. Patients with multilobar injury, subarachnoid haemorrhage and cerebral infarction carry a worse prognosis, as compared to those with localised damage. CT is also valuable in serial evaluation of CMI patients, especially in the event of neurological deterioration.

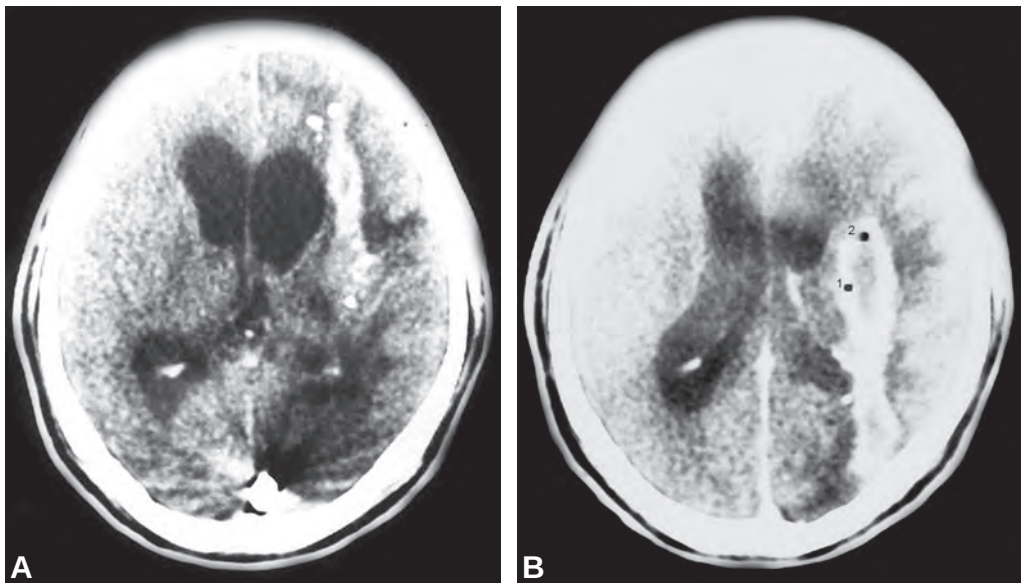
Carotid Angiography

Evaluation of CMI with carotid angiography in the acute phase is no more necessary. Angiography is, however, valuable in evaluation of certain sequelae of CMI like traumatic aneurysms, arteriovenous fistulae, etc.

OPERATIVE MANAGEMENT

The aim of surgical management in missile injuries of the brain is to improve the quality of survival by reducing the raised intracranial pressure and prevention of infection in as many patients as possible. The principles of surgery enunciated by various authors are:

a. The mass lesion consisting of intracranial haematoma and non-viable brain tissue along the path of the missile must be evacuated.
b. The missile and bone fragments, wherever feasible, must be removed, but without enhancing the pre-existing neurological deficit. The brain is usually swollen and retraction can be hazardous. Therefore, one should avoid digging into the brain to retrieve the elusive missile.



Figs 5A and B: CT brain showing intracranial splinters and haemorrhagic missile track

c. Dura and scalp must be closed over the brain in a watertight fashion.
d. Post-operative elevation of intracranial pressure should be minimised and adjunctive therapy (vide infra) should be instituted aggressively.

Availability of adequate anaesthesia support during and after surgery, good fibreoptic illumination, suction and bipolar cautery are mandatory prerequisites for optimum management.

The choice of approach is between debridement via small craniectomies[27] and large bone flaps centred over the wound of entrance.[26] The latter allows greater control of haemorrhage and better decompression[4] and lower infection rate.[44,45] Craniectomy should be wide enough to allow access to normal dura from all sides. Recent military data[9,21,50] indicate that an aggressive approach is not always necessary and efforts should be made to preserve as much neural tissue as possible. After debridement, missile and bone fragments should be retrieved, only if they are accessible without producing any further neurological damage. Exit wounds, if present, are also debrided and the dura is closed with pericranial graft, temporalis fascia or fascia lata.

Orbito-cranial injuries and fronto-orbito-maxillary injuries are usually associated with compound fracture of the skull base, resulting in profuse CSF rhinorrhoea and orbitorrhoea. Such injuries may not be accompanied by alteration in sensorium but are potentially dangerous due to their communication with the oral cavity or air sinuses. These injuries have to be recognised and repair of the dural defect (usually by bifrontal craniotomy) to stop the CSF leak should be carried out at the earliest. Pericranial flaps, mashed muscle and fascia lata are extremely useful in dealing with these CSF leaks.

Gunshot injuries to the paranasal sinuses and orbit are uncommon. Their severity depends on the missile track in the tissues. Such injuries can involve the orbit, paranasal sinuses or brain. Functional endoscopic sinus surgery is the most appropriate technique for removing projectiles.[5] Penetrating orbitocranial non-missile intracranial injuries caused by metallic foreign bodies are very rare among the civilian population. After careful radiological evaluation of the shape and position of the foreign object, a combined right frontal craniotomy and supraorbital osteotomy can be performed, in order to achieve safe removal of the metal bar.[41] Neuronavigation techniques have been utilised as a component of the surgical strategy for secondary removal of retained missile fragments.[47]

PROBLEM OF RETAINED INTRACRANIAL FRAGMENTS

It may not be possible to extricate all the metallic fragments lodged within the brain, due to the unpredictable trajectory of the missile and accompanying factors like brain swelling. Attempts to aggressively remove these missiles may aggravate neurological injury due to retraction, haemorrhage, etc. The problems to be kept in mind while dealing with retained fragments are:

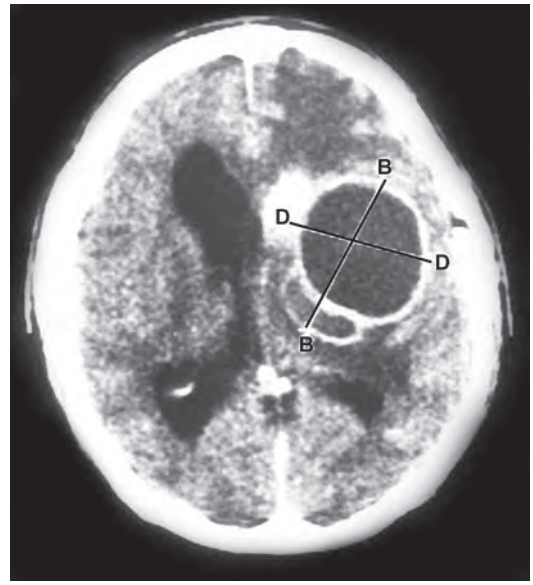


Fig. 6: CT brain showing retained intracranial splinters with cerebral abscess

Infection (Fig. 6)

In the past, military neurosurgeons believed that it was imperative to remove all the bone and metallic pieces. Re-operation was advocated if retained fragments were evident after initial debridement.[27,36] Retained fragments were believed to be fraught with intracranial suppurative complications.[38] Martin and Campbell[35] recorded an infection rate of 16% based on their World War II experience. Over 40% of their patients with retained fragments became infected. Re-operation in such patients was associated with increased neurological deficit.

Recent reports have advocated a more conservative approach. Brandvold et al.[9] while treating Israeli soldiers during their expedition into Lebanon, reported that 60% of the survivors had retained fragments and none of them developed suppurative complications. In the wartime experience of Bajpayee,[4] 22 patients out of 63 treated for missile brain injuries had retained intracranial missiles; two of these 22 developed brain abscess and two developed recurrent meningitis. In a recent series of patients with retained intracranial splinters in low intensity military conflicts,[7,8] there were suppurative complications in only four out of 37 cases with retained fragments; all the four had either orbitocranial injury or breach of paranasal sinuses. They had recurrent episodes of pyogenic meningitis; two of these developed brain abscesses and two developed hydrocephalus, requiring ventriculoperitoneal shunt (Fig. 7). Intraventricular fragments may be associated with meningitis and ventriculitis (Fig. 8). Metallic foreign body in the cavernous sinus causing delayed formation of brain abscess after missile injury has been reported.[48] It is now evident that the extent of brain damage as evident on initial CT is of

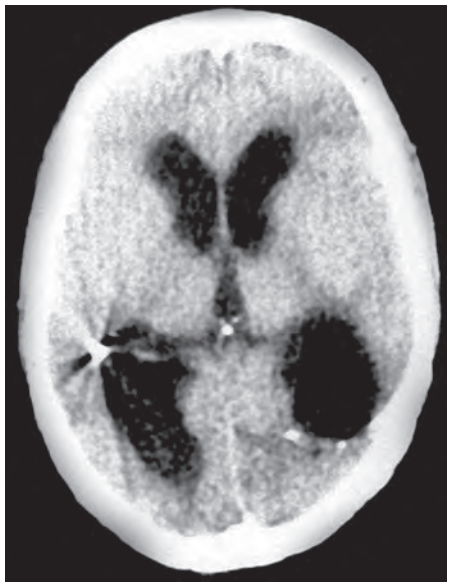


Fig. 7: CT brain showing intraventricular splinter with hydrocephalus

greater prognostic value than the fragment lodged in the brain *per se*. Suppurative complications are more likely if the paranasal sinuses or orbit has been breached or there is brain swelling and persistent external CSF leak.

Epilepsy

The epileptogenic effects of retained fragments, especially those containing copper have been mentioned.[15] However, the true incidence is difficult to assess, since these patients are routinely put on antiepileptic drugs.

Migration

Migration of retained intracranial fragments has been of considerable interest. Migration possibly occurs due to creation of paths wider than the diameter of the missile itself, the weight of the missile and pulsation of the brain. Migration can occur across the midline[19] and into the cervical canal.[56] Migration can lead to fresh neurological deficits, hydrocephalus and traumatic aneurysm.[26] Migrations of a bullet from the cranium to the lower end of the spinal canal after months of injury have been reported.

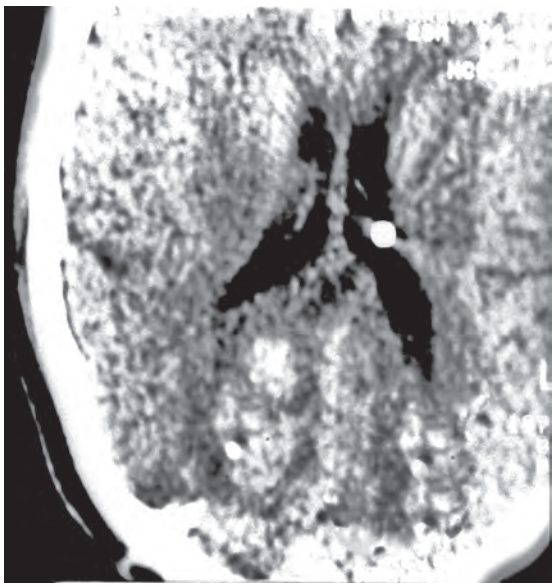


Fig. 8: CT brain showing retained intraventricular splinters

ADJUNCTS TO OPERATIVE MANAGEMENT

Anticonvulsants

The exact role of prophylactic anticonvulsants in CMI is not yet settled, although what is clear is that there is a higher incidence of post-traumatic epilepsy after CMI, as compared to that seen after closed head injury. Although anticonvulsants were used in the Korean and Vietnam conflicts, the incidence of PTE following CMI was the same as in earlier wars, where these were not used[13,15] In the VHIS, one half of the patients with early seizures had late epilepsy.[13,46] During the Iran-Iraq War, 32% patients developed PTE after CMI.[1] Thus, it would be reasonable to assume that approximately one-third of patients with combat CMIs develop seizures.[13] There are few series that document the incidence of PTE after civilian CMIs. Crockard.[17] reported a seizure incidence of 35% and Gordon,[24] an incidence of 40–50%. Thus, it would be reasonable to believe that all penetrating brain injuries must have anticonvulsant prophylaxis, since the true incidence of epilepsy in such injuries may be as high as 35%.[51]

Management of Raised Intracranial Pressure

Management of raised ICP in CMI is a source of trepidation because few of the therapies aimed at ICP reduction and maintenance of CPP are physiologically benign. While head elevation by 30 degrees in euvolaemic patients can significantly reduce ICP without altering CPP,[22] some of the other therapeutic measures used in routine management of head trauma, such as hyperventilation and diuresis risk converting relatively uncomplicated neurologic injuries into complicated multisystem injuries. Hyperventilation can result in alkalosis, which contributes to hypokalaemia and diuresis can provoke hypotension, hypovolaemia and hypokalaemia. Hence, the therapy for lowering raised ICP has to be carefully monitored, so that electrolyte disturbances are avoided or promptly recognised and treated and CPP is maintained. Current concepts in the management of missile injuries to the brain emphasise the frequent occurrence of raised ICP in the post-operative period. To a large extent, judicious debridement of injured cerebral tissue and evacuation of intraparenchymal and extra-axial haematomas can minimise ICP elevations. Medical management of raised ICP consists of proper positioning, ensuring adequate oxygenation and administration of osmotic and loop diuretics. Hyperventilation can be valuable in selected patients. ICP monitoring is a valuable adjunct in the post-operative management.

Antibiotics

Antibiotics that cross into the CSF should be administered in antimeningitic doses for 4–6 weeks. Previously, a combination of chloramphenicol and penicillin was widely used; at present, one of the third generation cephalosporins (cefotaxime, ceftazidime, ceftriaxome) along with an aminoglycoside (netilmicin, amikacin) are favoured. Metronidazole may be added, especially in the presence of extensive soft tissue injury.

CONCLUSIONS

Initial GCS is the single most important prognostic factor in predicting the outcome in missile injuries of the brain. Rapid evacuation of these patients to a neurosurgical centre, aggressive resuscitation in both the field and during transit and prompt correction of physiologic abnormalities are of paramount importance to clinical outcome. CT is the cornerstone in the diagnostic evaluation of these patients. The surgical principles of aggressive treatment of mass lesions, limited brain debridement, watertight dural closure and tension free scalp closure should be applied to all situations. Postoperative management of raised ICP, administration of antibiotics and anticonvulsants are required for optimising the outcome of victims of missile brain injuries.

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45 Endocrine Abnormalities following Traumatic Brain Injuries

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INTRODUCTION

Severe head injury still continues to be a great challenge for management as its outcome is still depressing. Concentration on injury to the brain results in neglect of other body systems. The marked improvement in life support measures for patients following traumatic brain injury (TBI) has kept more patients alive after injury than was the case earlier. Despite growing recognition among those who provide care for TBI patients, endocrine dysfunction following brain injury is an often under-recognised phenomenon. On the basis of earlier literature one would conclude that endocrine dysfunctions hardly ever occur following trauma to the head. However, recent studies suggest that a significant proportion of patients suffer some degree of hypopituitarism. To date, there are no clear predicting factors identifying patients at risk for developing hormonal disturbances and thus no parameters exist for screening. Despite a number of case reports of patients with post-traumatic endocrinal disturbances,[11,23,28,37,60] prospective studies or even large retrospective studies dealing with head trauma induced pituitary dysfunction are not available. Severe craniocerebral trauma very often results in persistent deficits and invalidity. The chronic neurobehavioural problems and quality of life complaints plague many patients of severe head injury, which are often strikingly similar to those of patients who have adult onset hormone abnormalities.[44] Cyran first made the association between head injury and development of hypopituitarism. Since then, till the last decade of the last century, sporadic case reports of endocrine abnormality following head injury have appeared. Pituitary function studies are infrequently considered in the acute stage or even in long-term management of patients with TBI, even though it is now a well-known fact that severe head injury results in considerable risk to pituitary function. Earlier autopsy studies had demonstrated anterior pituitary necrosis in as high as one-third of fatally head-injured patients.[16,48] It is thus obvious that TBI poses significant risk to the pituitary gland, leading to elevated risk of diabetes, hypopituitarism and other endocrinopathies. Signs and symptoms associated with hypopituitarism often mimic the sequel of TBI, although the severity of symptoms is not necessarily related to the severity of the injury. Patients with TBI-induced hypopituitarism may benefit both physically and psychologically from appropriate hormone replacement therapy (HRT).

Anterior pituitary insufficiency due to pathologic causes was first reported by Simmonds[73] in 1914, thus it is sometimes referred to as Simmonds' disease. The first report of anterior pituitary insufficiency as a result of head trauma was published in 1918.[21] A complete literature review of Simmonds' disease in 1942 found that of the 595 cases included, only four (0.7%) were related to brain trauma and the others were related to other pathologic causes.[30] Subsequent reviews and case reports identified additional instances of hypopituitarism following head injury.[10,50,75] Benvenga et al.[10] found that 'the anatomical integrity of the pituitary' varies from 14% to 74% in cases of head injury.

TBI poses a significant risk to hypothalamic and pituitary function. Structural abnormalities in the hypothalamus and the pituitary are commonly, anterior lobe necrosis, posterior lobe haemorrhage or stalk laceration.[47] Trauma-mediated vascular injury to the hypothalamus may be the basis of TBI-mediated hypopituitarism, although pituitary lesions are also a prominent factor. Hypothalamic lesions have been reported in greater than 50% of head trauma cases, affecting hypothalamic nuclei and resembling the lesions found in ruptured cerebral aneurysms.[19,24] Pituitary function is at particular risk because of the vulnerable physiologic location of the gland within the sella turcica as well as its delicate infundibular hypothalamic structure and its fragile vascular supply.[43] At present, there are no studies that suggest head injuries of a certain type or in a certain location are more likely to produce hypopituitarism.

Growth hormone deficiency (GHD) is most often seen in patients with TBI because the growth hormone-secreting somatotrope cells are located in the wings of the pituitary gland and the vascular supply and oxygen they receive come from the hypothalamo-pituitary portal vessels. Consequently, damage in this area impairs the blood and oxygen supply resulting in cell death. In contrast, the cells that secrete adrenocorticotrophic hormone (ACTH) and thyroid-stimulating hormone (TSH) are located ventrally in the more protected, medial portion of the pituitary, and they receive blood from the portal vessels and the anterior pituitary artery branch, which provides nutrients and oxygen to this area and to all the cells located in the sub-capsular part.[43] Evidence

from previous and current studies on pituitary deficiencies following TBI demonstrate that total, multiple and particularly single pituitary deficits occur fairly often. These data clearly indicate the need for routine monitoring of pituitary function in all at-risk patients after brain injury.

Several groups of researchers have characterised the prevalence of TBI-induced hypopituitarism. These studies evaluated endocrine function in patients with TBI with no overt symptoms of hypopituitarism or pre-existing history of endocrine disease and whose clinical features at presentation were attributed entirely to TBI.[2,3,43,54] Overall, alterations of the hypothalamic-pituitary axis occurred in 33–50% of the patients studied, with severe GHD reported in 15–20% of adult patients.

Bondanelli et al.[13] studied pituitary dysfunction in 50 patients with TBI over a 5-year period. Basal pituitary hormone assessments conducted between 1 year and 5 years after TBI revealed a total of 27 patients (54%) with pituitary dysfunction: seven (14%) with hypogonadotrophic hypogonadism; five (10%) with central hypothyroidism; four (8%) with low prolactin levels and four (8%) with high prolactin levels. Seven (14%) patients had low insulin-like growth factor-1 (IGF-1) levels for age and sex. Provocative testing with GHRH plus arginine revealed 10 patients with partial GHD and four with severe GHD. In this study, pituitary dysfunction was not correlated with the type, outcome or number of years since TBI.

The neurobehavioural, cognitive and psychosocial profiles of patients with moderate or moderate-to-severe TBI are similar in many ways to the signs and symptoms of hypopituitarism. For instance, in a study of 96 patients with moderate or severe TBI Hellawell et al.[39] reported that, 1 year after injury, 40–60% of patients experienced clinical signs and symptoms that are similar to those of individuals with hypopituitarism from other causes. Léon-Carrión et al.[52] reported that 50% of patients with severe TBI (n = 39) experienced depression—a common manifestation seen in individuals with hypopituitarism from other causes—more than 18 months after injury. However, neither of these studies specifically addressed the issue of TBI-induced hypopituitarism.

SCREENING FOR TRAUMATIC BRAIN INJURY-INDUCED HYPOPITUITARISM

Who Should Screen Patients?

TBI patients are typically first seen and treated by trauma surgeons and neurosurgeons, and by psychiatrists and neurologists if appropriate, with subsequent treatment provided by rehabilitation physicians. These front-line specialists must be able to determine which patients are candidates for screening TBI-induced hypopituitarism and be able to identify the signs and symptoms. It is important to note, however, that because pituitary deficits may not be diagnosed for many years after the TBI itself, rehabilitation physicians must continuously monitor their patients for signs and symptoms indicative of hypothalamic-pituitary impairment.

Although endocrinologists and internists are generally not among the first physicians called to attend patients with TBI, they must be educated about and encouraged to actively share their expertise—eliminating the need for rehabilitation doctors to seek them out about patients with possible endocrinopathies. Appropriate replacement therapy is necessary for patients with hypopituitarism to prevent increased mortality and reduced quality of life. Since evidence shows that pituitary function is impaired in at least 20–30% of patients following TBI, all patients with moderate-to-severe TBI and clinical signs or symptoms associated with hypopituitarism should be screened for their pituitary function.

Screening

The first step in diagnosing hypopituitarism is recording of a detailed patient and family history. In cases of presumed idiopathic hypopituitarism, the family as well as the patient should rigorously be questioned about any history of head injury because the patient's memory of the event may be compromised. A patient history can also reveal possible risk factors for hypopituitarism [age, sex, acute diabetes insipidus (DI)]. Additional risk factors may include abnormal pupillary reactivity, presence of hypotension or hypoxia within 24 hours after injury, presence of major pathological findings and/or diffuse brain swelling on the first two CT scans obtained.[43] However, it should be stressed that results of other studies indicate no relationship between the severity of an injury and the incidence of TBI-induced hypopituitarism.[55] From the perspective of the endocrinologist, patients with proved vital endocrinological deficits (namely DI, secondary adrenal insufficiency and thyroid insufficiency) should immediately be treated for their deficiency. In the context of multiple hypopituitary deficits, other pituitary deficits such as secondary gonadal insufficiency and severe GHD will probably require appropriate replacement, provided these diagnoses are reconfirmed after correction of other deficits. On the other hand, hormonal replacement for patients with proved isolated gonadal deficit or severe GHD could be reconsidered after retesting and in the appropriate clinical context.

Although the incidence of TBI-induced hypopituitarism is likely to be under-diagnosed, not all patients will have deficits and not all of those with deficits will benefit from therapy. For instance, the ramifications of a permanent vegetative state are so profound that it is highly unlikely that such patients would actually benefit from replacement therapy for conditions such as a gonadal deficit or GHD. In general, patients in a permanent vegetative state should be evaluated for DI, inappropriate ADH syndrome, hypoadrenalism and thyroid deficits if indicated, but excluded from further endocrinological testing. Furthermore, because these consensus guidelines are primarily targeted for outpatients,

typically patients who function at a very low level and consequently who are institutionalised as a result of a TBI should also be excluded from replacement therapy beyond hydrocortisone, vasopressin and T4, along with any other patients who, in the opinion of the physician, would not benefit from therapy. With these exceptions, all patients with moderate and severe TBI should routinely undergo baseline hormonal evaluation for pituitary deficiencies, particularly if they were hospitalised for at least 1 day following injury.

Notably, it has been hypothesised that there may be a difference between patients with TBI-induced GHD and those with GHD that is not related to a TBI, and that the group with TBI-induced hypopituitarism might benefit slightly more from therapy with GH. If this is true, the slight advantage offered by GH replacement would likely be of particular interest to the rehabilitation physicians since there are so few therapeutic options currently approved specifically for management of the persistent signs and symptoms after TBI.

WHO SHOULD UNDERGO IMMEDIATE HORMONAL REPLACEMENT?

There is considerable controversy within the medical community over the potential ramifications of HRT. Class I studies have yet to be conducted on hormone replacement in the treatment of patients with TBI-induced hypopituitarism, and such studies are necessary to determine the degree to which these patients will benefit from replacement in terms of either rehabilitation or endocrinological function. This controversy underscores the need for physicians to be able to accurately identify that sub-population of patients with TBI who could benefit from HRT. Even then, the advantages and disadvantages of hormone therapy must carefully be weighed before the decision is taken to initiate therapy.

Physicians who manage patients with TBI should carefully examine the natural history of each individual patient's endocrinological abnormalities and try to determine if the disorder is permanent or transient. To date, there are no study data regarding the transient or late-onset nature of hypopituitarism following TBI, and it is necessary to determine whether it is possible for early-onset hypopituitarism (particularly isolated deficits) following the occurrence of a TBI to be transient or, conversely, for late onset of impaired hypothalamic-pituitary function following a TBI. To conduct such a study, it is essential that baseline values be clearly defined and that the criteria for measuring improvement be clearly delineated. Prospective studies would also increase one's understanding of how and why patients improve and what factors are responsible for triggering improvement. Specifically, because pituitary abnormalities appear to occur very early following TBI, a prospective study is needed comparing the endocrinological status of patients shortly after TBI with that of patients 1 year after brain insult to determine whether abnormalities are transient or chronic.

Nevertheless, it is clear from present knowledge that immediate HRT should be instituted for patients with isolated hypopituitarism in the cases of:

- diabetes insipidus (DI),
- secondary adrenal insufficiency and
- secondary thyroid insufficiency (just after adrenal replacement has been started).

Patients with panhypopituitarism or multiple pituitary deficits should also undergo immediate replacement therapy of all pituitary deficiencies, with the notable exception of GHD. It has been demonstrated that replacement of other hormonal deficits can restore normal GH response to provocative testing; thus, it is mandatory that appropriate replacement therapy be provided for other hormonal deficits to avoid unnecessary replacement therapy in patients with transient GHD that simply reflects other pituitary impairment. Replacement hormone therapy should be reserved for patients who are truly GHD, so GH replacement should only be provided once the diagnosis of GHD is confirmed following optimised replacement of other deficits.

In a somewhat similar fashion, replacement therapy for a gonadal deficit is always recommended in the context of panhypopituitarism or multiple deficits including a gonadal deficit. However, as with GHD, transient impairment in the gonadal axis may occur as a result of concurrent stressful conditions but can recover over time. Thus, when an isolated gonadal deficit is indicated or suspected, the patient should be retested before hormonal replacement is initiated.

After GHD has been demonstrated and replacement therapy is about to be initiated, the endocrinologist and rehabilitation physician must collaborate to tailor the precise dose and modality of therapy for each patient. For instance, recombinant human growth hormone (rhGH) doses must be individualised and titrated based on circulating IGF-1 levels and desired therapeutic outcome. Initial dose should not exceed 0.3 mg kg^{-1} per week, with older patients usually requiring lower doses of human GH. Approximately 4–8 weeks after initiating GH therapy, the dose should be titrated according to age-adjusted IGF-1 levels or symptom tolerance.

For patients with permanent disabilities, therapy for symptoms of hypopituitarism will result in a substantial improvement in the quality of life. Furthermore, HRT for management of TBI-induced hypopituitarism would be a targeted intervention that directly addresses the underlying cause for many of the symptoms of a TBI.

For instance, treatment with GH may increase energy level, degree of socialisation, emotional stability and psychological well-being and it may enhance the physical condition by increasing lean body and muscle mass, decreasing atherogenic lipids and reducing carotid intima-media thickness.[34]

WHO SHOULD UNDERGO FURTHER FOLLOW-UP BEFORE HORMONE REPLACEMENT?

All patients with proved TBI-induced hypopituitarism who are already receiving HRT should undergo periodic

follow-up testing by an endocrinologist to monitor their overall health and endocrinologic status, not simply the status of their GH replacement therapy.

According to the Consensus Guidelines for Diagnosis and Treatment of GHD, for patients with total hypopituitarism or multiple deficits including severe GHD, rhGH therapy must be delayed until the diagnosis of severe GHD is confirmed, which can only occur after appropriate (optimal) replacement of other pituitary deficits, e.g. hypothyroid or hypoadrenal states, has been instituted for at least 3–6 months. For patients with an isolated pituitary deficit of severe GHD, it is proposed that initiation of rhGH replacement therapy also be delayed until retesting 12 months following the TBI to determine persistence.

For patients with isolated, secondary hypogonadism, hormonal replacement should be evaluated on a case-by-case basis. For instance, replacement therapy may be helpful in men to take advantage of the anabolic action of testosterone. In contrast, a better approach for women with secondary amenorrhoea may be to forestall hormone therapy and monitor menses over time, since post-menopausal women do not need oestradiol replacement therapy. As in the case of immediate replacement therapy, the modalities and doses of delayed replacement therapy should be determined by the endocrinologist in collaboration with the rehabilitation physician.

PATHOGENESIS OF ENDOCRINAL ABNORMALITIES

The endocrinal problem following TBI could result either due to damage to the pituitary or hypothalamus. The pituitary is highly vulnerable due to its location in the sella turcica, its vulnerable blood supply and delicate infundibular hypothalamic structures. In contrast to the low incidence of clinical dysfunction, autopsy reports indicate a higher incidence of pituitary lesions (30–33%) in fatal cases of head injury.[16] Daniel et al. reported hypopituitarism in 40% of patients with moderate and severe head injury. Kornblum and Fischer[48] demonstrated pathological lesions secondary to trauma in 62% of pituitary glands. Capsular haemorrhage was the most common finding on histopathology, being detected in up to 50–59% cases.[2,3,10,13,19,21,24,30,34,39,43,47,48,50,52,54,55,65,73,75] Anterior lobe infarcts have been reported to occur in about 13–22% of cases.[2,3,10,13,19,21,24,30,34,39,43,47,48,50,52,54,55,65,73,75] No report of posterior pituitary infarct is available. The confinement of the pituitary gland in the sella turcica by the diaphragma sellae makes the stalk as well as the infundibulum vulnerable to the shearing strain. Subsequent swelling of the gland is limited by the diaphragma sellae, which has only a small circular opening serving as a passage for the pituitary stalk. As it swells, the fragile long hypophyseal vessels get compressed, resulting in anterior pituitary infarction.[48] Hormone abnormalities may exist even in the absence of pituitary lesions, suggesting the active involvement of other areas of the brain in regulating the hormonal milieu of the body. It is generally believed that pituitary dysfunction following head injury is by and large due to diffuse brain swelling, hypotension or hypoxic insult.[1,29] However, primary pituitary damage is well described.[16] Prior to CT scans, most of the evidence was autopsy based. In autopsy studies pituitary abnormality is recorded in almost 75%.[48] The significant primary abnormalities include capsular haemorrhage in over 50%, followed by posterior lobe and stalk haemorrhage in 30% and 20% cases approximately. Necrosis is another important finding. The common site of necrosis is the anterior lobe followed by the pituitary stalk (Table 1). In an autopsy study, Kornblum and Fisher in 1969[48] had reported anterior pituitary necrosis in 35% of patients with a fatal head injury who had survived longer than 12 hours. Necrosis patterns always correspond to the blood supply of the long hypophyseal portal veins. Long portal veins pass through the diaphragma sella, where they are vulnerable to mechanical compression from swollen brain and a swollen pituitary gland.[16,23,48] Long hypophyseal portal veins contribute 70% of the blood supply to the anterior pituitary. The somatotrophs and gonadotrophs are laterally placed, hence more frequently involved.[28] This anatomical arrangement very well explains the long-term hormonal insufficiency. Direct stalk injury in the form of stalk transection and stalk haemorrhage also leads to immediate and long-term hypopituitarism.[1,7,11,41] This can result due to fracture of the sella turcica.[11] With the advent of CT and MRI, it is possible to demonstrate rupture of the pituitary stalk.[7,37,41]

Table 1: Pathology in pituitary gland following head injury

Primary	Haemorrhage	Capsular	50–55%
		Posterior lobe	30
		Stalk	15
	Necrosis	Anterior pituitary	20%
		Posterior pituitary	0%
		Stalk	3%
Secondary	–	– Hypoxia	
		– Oedema	
Direct stalk injury		Rupture of stalk	
		Transection of stalk	
		Stalk haemorrhage	

Hypothalamic injury can also lead to hypopituitarism following severe head injury. By and large these patients do not survive long enough to have long-term hypothalamic problems. Massol et al.[58] described hypothalamic lesions in closed head injury patients. Recently, with improved imaging, such lesions are more frequently diagnosed radiologically.[29,41,44] Traumatic SAH with or without vasospasm also contributes to hypothalamic and pituitary dysfunction.

Trauma causes the T3 to fall, but T4 usually remains normal or is marginally elevated (euthyroid sick syndrome/non-thyroid illness/low T3 and normal

T4 syndrome).[82,86] TSH values are found to be higher amongst survivors as compared to those who succumb to their injuries. According to Chiolero et al.[17] significant lower serum TSH values are present amongst non-survivors. TSH has been shown to reduce biological activity due to impaired receptor binding in cases of severe TBI.[9,84]

Severe catabolic response with marked tissue wasting seen in head injury patients is attributed to higher ACTH levels.[46] Abnormally elevated levels of cortisol have been seen as late as four months after head injury.[46] Stimuli from the injured area traverse the peripheral nerves, ascend through the spinal cord and brainstem to integrating centres in the reticular formation and limbic areas, where these impulses may or may not be modified by stimuli descending from the cerebral cortex. Impulses are then transmitted to the median eminence where corticotrophin releasing factor is liberated. This traverses to the anterior pituitary through hypothalamic hypophyseal portal vessels and in turn releases ACTH that is then transmitted into the systemic circulation to the adrenal gland and stimulates secretion of cortisol.[40] Rinne,[66] in a series of head-injured patients who did not present with clinical evidence of endocrine dysfunction or abnormal basal excretion of urinary 17-hydroxysteroids showed that about one-third of patients in his group demonstrated limited ACTH reserve as measured by response to metyrapone.[66] The author found that those with limited ACTH reserve had been unconscious for a longer time than those who had a normal response to metyrapone. Patients who succumb to injury demonstrate a poor rise in cortisol levels as compared to survivors.

A paradoxical growth hormone response is seen in traumatised patients (GH increases post glucose in severe head injury with normal GH response in less severely injured patients).[45] Studies of CSF of comatose patients following head injury indicate increased turnover of nonadrenaline, serotonin and dopamine.[57] All these transmitters exert a positive effect on GH secretion and could favour a paradoxical response.[56] According to a recent report by Bondanelli et al.[12] GH levels were found to be normal in severe head injury patients evaluated at least one month after leaving the intensive care unit (ICU), when their nutritional status had improved.

Basal prolactin increases following head injury and suggests hypothalamic damage.[5,56,59,86] Edwards and Clark[28] in their review on post-traumatic hypopituitarism reported elevated prolactin (4 out of 12 female patients developed galactorrhoea). As the lactotrophes which secrete prolactin are located in the periphery of the gland, anterior pituitary necrosis could occur with destruction of other pituicytes but leaving the lactotrophes relatively intact.[74] Few authors have reported low basal prolactin levels with an absence of response to TRH, indicating damage to lactotrophes with extensive anterior pituitary necrosis.[17,28]

Hypogonadism associated with transient increase in LH concentration falling to subnormal levels with an exaggerated response to exogenous GnRH stimulation is seen in TBI.[18,86] Hypogonadism after trauma could be due to primary gonadal dysfunction with increased levels of catecholamines, and cortisol having a direct suppressive effect on Leydig cells.[20,85] In a series of 99 patients of severe head injury seen at our institute (of which 59 survived and were evaluated for hormonal abnormalities subsequently), elevation of cortisol followed by prolactin was the most common hormonal derangement followed by elevation of GH, TSH, LH and FSH and suppression of T3. There was a statistically significant temporal trend (over 6 months) in T4, cortisol and GH ($p < 0.05$). Fatal outcome was directly related to LH and gonadotrophin elevation and inversely related to TSH elevation ($p > 0.05$) (Table 2).

CLINICAL SIGNS AND SYMPTOMS OF HYPOPITUITARISM

Hypopituitarism is associated with a number of non-specific signs and symptoms. Fatigue is a major symptom[15,49,51,54,62] and it is also a major symptom of TBI. Examples of other signs, symptoms and laboratory abnormalities indicating hypothalamic-pituitary impairment include decreased lean body mass with increased body fat and dyslipidaemia; reduced exercise tolerance and muscle strength;[15,54] DI; decreased TSH and FT_4 levels and adrenal insufficiency;[10,15,54] amenorrhoea/infertility, erectile dysfunction and hyperprolactinaemia;[10,22] diminished cardiovascular function; impaired cognitive function, memory loss, decreased concentration, mood disturbances, increased anxiety and depression, irritability, insomnia[25,39,52] and a greater sense of social isolation.[15,68] A deficiency of GH produces metabolic effects in essentially all organs and is manifested both physically and emotionally. Ultimately, hypopituitarism can compromise a patient's sense of well-being and overall the quality of life.

These signs and symptoms of hypopituitarism have the same potential for presentation among hypopituitaric patients after TBI. Clinical manifestations of TBI widely vary depending on the type, location and severity of the injury. Pituitary gland dysfunction as a result of a TBI is particularly problematic due to the critical role the pituitary gland plays in regulation of essential hormone production from the thyroid, gonads and adrenals—hormones that regulate many processes with profound physiological and/or psychological consequences. Furthermore, as noted by many authors, the signs and symptoms associated with hypopituitarism often mimic the sequelae of TBI. Consequently, pituitary hormone deficiencies could result in sub-optimal rehabilitation for patients with TBI-induced hypopituitarism.

Table 2: Trends of hormone abnormality seen in severe head injury patients*

Hormone	*Post-trauma days*	*No of patients*	*Minimum level*	*Maximum level*	*Mean*	*Std deviation*	*P value*
T3	D-0	59	0.75	1.64	1.126	.1972	NS
	D-15	54	0.85	2.00	1.205	.2149	
	D-90	51	0.50	1.70	1.165	.2266	
	D-180	48	0.53	8.40	1.289	1.0731	
T4	D-0	59	4.5	14.0	8.017	1.983	P<0.05
	D-15	54	4.0	13.0	7.417	1.868	
	D-90	51	4.7	12.0	7.713	1.356	
	D-180	48	3.2	11.0	7.368	1.447	
TSH	D-0	59	0.4	16.0	3.390	3.271	NS
	D-15	54	0.5	12.5	3.211	2.607	
	D-90	51	0.5	12.0	3.073	2.370	
	D-180	48	0.8	11.0	3.141	2.076	
PRL	D-0	59	5	76	18.47	11.56	NS
	D-15	54	2.3	76	19.80	12.35	
	D-90	51	3	66	19.13	14.00	
	D-180	48	4	35	16.25	8.64	
Cortisol	D-0	59	60	472	275.6	88.18	P<0.01
	D-15	54	50	476	260.6	96.76	
	D-90	51	18	440	224.2	93.37	
	D-180	48	40	395	165.3	97.59	
GH	D-0	59	0.1	18	3.273	3.537	P<0.01
	D-15	54	0.3	14	3.496	3.251	
	D-90	51	0.3	12	2.248	2.513	
	D-180	48	0.2	12	1.622	1.937	
LH	D-0	59	2	125	8.81	16.38	NS
	D-15	54	2	20	6.4	3.912	
	D-90	51	2	22	5.559	3.371	
	D-180	48	2	14	5.238	2.596	
FSH	D-0	59	2	35	5.558	5.897	NS
	D-15	54	2	13	5.14	2.28	
	D-90	51	2	13	4.39	1.54	
	D-180	48	3	14	5.03	1.90	

*Data of head injury patients seen at AIIMS (New Delhi): 59/99 surviving patients (17–60 year age group) admitted within 24 hours of severe head injury (GCS ≤ 8). Those patients with history of endocrine abnormalities suffering from pulmonary/metabolic disorders have been excluded.[56]

Endocrinological Symptoms of Hypopituitarism in Traumatic Brain Injury

Traditionally, the onset of DI was considered a good indicator of hypopituitarism because it is routinely attributed to pituitary insult. However, reports of the incidence of DI following brain injury vary widely, with Benvenga et al.[10] reporting it in as many as 30% of cases compared with Aimaretti et al.[3] who reported an incidence of 5.5%. Likewise, reports of the incidence of hyperprolactinaemia, another marker of hypothalamus-pituitary derangement, following brain injury vary even more dramatically.[3,10,55] While these findings provide evidence that TBI is associated with derangement of the hypothalamus-pituitary unit, it underscores the fact that a full endocrinologic assessment is necessary to determine the extent of the hormonal effects of TBI and the need for a global endocrine evaluation should be considered.

The clinical problem in head injury varies from the acute stage to chronic problems. In the acute stage, there is likely to be cortisol and ADH deficiency which can manifest with persistent hypotension in the absence of any obvious cause as patients cannot withstand stress in the presence of acute pituitary failure. DI is not uncommon in severe head injury. Failure of the posterior pituitary leads to fall of plasma ADH resulting in DI. This can be diagnosed as patients pass a large volume of urine, which is of low specific gravity, of high serum osmolality and low urinary osmolality.[7,58] The syndrome of inappropriate ADH (SIADH) in severe head injury is not rare and can be diagnosed on the basis of biochemical parameters of serum and

urine. Pituitary dysfuctions are also reported following minor or moderate head injury.[28] Ziaber et al.[87] reported plasma cortisol and beta-endorphin abnormality following minor head injury.

DI is an important clinical problem in severe head injury.[7,58,79] In addition to DI, SIADH is not uncommon.[76] These clinical problems are also to be differentiated from patients with cerebral salt wasting (CSW). In these patients, serum sodium is low and 24-hour urinary sodium excretion is very high. For the above reasons electrolyte balance should be monitored in severe head injury patients up to 2 weeks.[76] Electrolyte and plasma osmolality abnormalities are more frequent in patients with diabetes mellitus and chronic alcoholism.

Clinically, significant hypogonadism is not uncommon in major head injury.[18,36,85] The hypogonadism could be transient[85] or long term. Clark et al.[18] in 1988 reported 33 male patients with major head injury in whom total free testosterone was significantly lower on the 3rd day. However, persistent hypogonadism was only reported in 5 of these 21 patients in whom the tests were performed between 3 months and 6 months after injury. They suggested repeated endocrinal assessment in patients with severe head injury. Woolf et al.[85] in 1986 reported transient hypogonadism following head injury. They included both severe and moderate head injury patients. They studied 31 male patients in whom testosterone and other hormonal assessments were performed shortly after injury and on the 4th day. They observed good correlation between severity of head injury and sex hormone abnormalities. Precocious puberty is another rare problem following severe head injury.[36] The precise mechanism is still not clear. Some authors have hypothesised extrahypothalamic involvement.

The neurobehavioural impact of hypopituitarism is significant. Chronic behavioural problems have been recorded in a significant number of patients with brain injury.[27,53,69,71] Both behavioural and cognitive defects have been seen 1 year following injury.[27,53] Saatman et al.[69] in 1997 demonstrated cognitive abnormality in experimental brain injury. It is generally believed that the deficiency of growth hormone or IGF-1 deficiency results in neurobehavioural and cognitive deficit.[67,69] Saatman et al.[69] reported improvement in cognitive functions by supplementing insulin-like growth factor. Loss of memory, higher anxiety level, impaired motor skill and lower quality of life are also attributed to GHD.[8,14,67,69] Sex hormone deficiency leads to mood disturbances and behavioural problems.

INVESTIGATIONS

Routine Baseline Screening Tests

- Both anterior and posterior pituitary functions are tested, when there is a high degree of suspicion of hypopituitarism.[61]
- Insulin tolerance test (ITT) is a simple test to find out corticotrophin and somatotroph secretion by measuring GH and cortisol level.
- TRH stimulation test is important to assess the level of TSH and prolactin. GnRH stimulation test is necessary to assess gonadotroph function (Table 3).

Derangement of posterior pituitary function is not less important, as it may lead to fluid and electrolyte imbalance, DI and SIADH. Hence, measurement of serum sodium, blood urea nitrogen, creatinine and osmolatity of plasma and urine are important. In addition, a regular check of urinary specific gravity and 24-hour urinary sodium excretion is also carried out to differentiate one from the other. Assessment of serum ADH level is also important.[44]

Basal hormonal evaluations are an essential means of demonstrating hypopituitarism—including deficits of the adrenal, thyroid and gonadal axis—without the need for provocative testing. Regarding the diagnosis of GHD, there is a growing body of evidence indicating that IGF-1 levels are the best markers of GH status as these levels provide an integrated measure of GH secretion.[31,35,63,77]

However, total IGF-1 levels do not distinguish between normal subjects and patients with severe GHD due to considerable overlap between the two populations (GHRS Consensus). Moreover, at present, it is not possible to set reliable, internationally acceptable cut-off points for assessing IGF-1 levels because IGF-1 assays vary from laboratory to laboratory. As a general rule of thumb, patients should be considered to have a substantially abnormal value if their IGF-1 levels are more than 2 SD below the norm for their age group as defined in each laboratory. These patients should be referred to an endocrinologist because such low IGF-1 levels are strongly predictive of GHD. However, it must be noted that because normal IGF-1 levels do not rule out the possibility of severe GHD, when GHD is suspected,

Table 3: Hormonal assessment in pituitary dysfunction diagnosis

Hormone	*Test*	*Method*	*Adult hormone levels*
GH	Insulin tolerance test	RIA	0–5 ng/ml
ACTH	Insulin tolerance test	RIA	9–50 ng/ml
TSH	TRH stimulation	Immnochemoluminescence assay	0.4–4.2 mu/l
Free thyroxin		RIA	5.5–11.5 µ/dl
FSH	GnRH stimulation test	Fluroimmunometric assay	FHS-20–250 pg/dl
Testosterone	GnRH stimulation test	RIA	298–1043 ng/dl

further investigation by means of provocative testing is required.[4,38]

Routine basal hormonal testing should be performed on any patient who has been hospitalised with a TBI and who has symptoms such as hyponatraemia and hypotension. Prospectively, all patients who had a TBI—regardless of its severity—should undergo a baseline hormonal evaluation 3–12 months after the primary brain insult or discharge from the hospital or ICU. Patients with adrenal insufficiency, DI or other clinical symptoms of hypopituitarism should undergo immediate testing of the rest of the pituitary axis without waiting for 3 months. Patients with clinical signs or symptoms suggestive of impaired hypothalamic-pituitary function (e.g. polyuria) should be investigated whenever medically warranted (e.g. a decrease in ability that cannot otherwise be accounted for by changes in CT scan or changes in medication).

Retrospectively, all patients with any signs or symptoms of hypopituitarism who experienced a moderate or severe TBI more than 12 months before their onset should undergo immediate hormonal testing. Given the 12-month passage of time, it is unlikely that any hormonal deficit is transient, so for these patients the screening can be done in a single session.

Provocative Testing

Abnormal or questionable results from basal hormonal testing should always be reviewed by an endocrinologist. Patients should be referred to an endocrinologist for provocative testing if results of their basal evaluations are unclear. For instance, a low IGF-1 level in the absence of malnutrition is highly suggestive of severe GHD and calls for provocative testing. However, since a normal IGF-1 level does not rule out the possibility of GHD, provocative testing is recommended regardless of IGF-1 level when other pituitary deficits are present or if there is a high index of clinical suspicion of GHD.

The ITT is considered the gold standard for the diagnosis of GHD as well as for ACTH deficiency. In fact, hypoglycaemia represents a potent stimulus of both somatotrophic and corticotrophic function. However, the ITT is generally contraindicated in patients who have central nervous system pathologies and hypoglycaemia-induced side effects are known to be potentially hazardous. Among classical provocative tests, glucagon is considered a good alternative to ITT for investigation of either GH or ACTH and cortisol secretion.[70] However, GHRH in combination with arginine[33] as well as in combination with GH secretagogues (synthetic GHS such as GHRP-6 or hexarelin or the natural GHS ghrelin)[33,64] has been shown to represent the best alternative test for the diagnosis of GHD.

Other available provocative tests used to further investigate the existence of deficiencies of other anterior pituitary hormones include GnRH, TRH, CRH, ACTH and metyrapone tests. Specific provocation tests to be performed for each patient should be determined by the endocrinologist in collaboration with the rehabilitation clinicians.

TREATMENT OF HYPOPITUITARISM

Endocrinal abnormality, be it in the acute phase of head injury or chronic state requires careful evaluation and replacement therapy. In the acute stage, patients with DI, or SIADH or CSW, need treatment to correct the deficiency. The treatment may be long-term or short-term depending on the need of an individual patient. DDAVP nasal spray, arginine vasopressin and pitressin injections are widely used.[7,44,58] Several studies dealing with GH deficient patients showed the beneficial role of GH replacement, which included improved memory, attention, comprehension and vocabulary. Improvement also included general well-being of mood and reduction in depression and anxiety state[26,61] GH also helps in increasing muscle mass. Some authors have used IGF-1 and shown improvement in various cognitive functions.[67,69]

Other important replacement therapy includes the deficiency of testosterone. Testosterone replacement in men helps in normalisation of libido and sexual function, helps in bone formation and increases the muscle mass.[80,81] Sex hormone deficiency in women is adequately treated with oestrogen therapy, which improves their neurobehavioural and cognitive functions.

CSW occurs due to unregulated release of natriuretic peptide.[6,32,42,72,78,83] Patients present with persistent hyponatraemia, hypernatriuresis with hyperosmolar urine. In CSW, volume is depleted, hence volume is replaced with Na-containing fluids and deranged haematocrit should be restored. Infusion of saline, plasma and blood is necessary depending on the need. Fludrocortisone acetate is the specific treatment for CSW,[6,32,42,72,78,83] which helps in sodium retention with fluid and corrects hyponatraemia.

CONCLUSIONS

Endocrinal abnormality related problems in head injury are a neglected aspect of comprehensive management of such patients. Overall, 40% of severe head injury patients develop either short-term or long-term endocrinal problems. Basic reasons may be hypothalamic or pituitary damage, which may be primary or even secondary to hypoxia or hypotension. The anterior and posterior pituitary may be involved. Pituitary stalk necrosis or avulsion can also occur. Elevation of cortisol followed by prolactin is the most common hormonal derangement followed by elevation of GH, TSH, LH, FSH, ADH and suppression of T3. GH and gonadotrophin deficiency is also to some extent responsible for long-term behavioural and cognitive problems. Diabetes insipidus, SIADH and CSW are quite frequent. The entire endocrinal problem needs proper evaluation and adequate short-term or long-term hormonal replacement to improve the overall outcome in patients with both severe and minor head injuries. Results of recent and ongoing studies have made it clear that TBI poses substantial risk to pituitary function, perhaps even greater risk than previously believed.

It is essential that patients with TBI be screened both prospectively and retrospectively for pituitary deficits—both isolated and multiple. Patients with demonstrable TBI-induced hypopituitarism should initially receive critical replacement therapy such as with antidiuretic hormone (ADH), glucocorticoid and thyroid hormones. Gonadal and growth HRT should also be introduced if there are persistent demonstrated deficiencies. It has been suggested that patients with signs and symptoms of hypopituitarism following a TBI may benefit in particular if the hormonal replacement alleviated those signs and symptoms masked by sequelae of the TBI itself.

By increasing awareness among physicians of the risks of TBI-induced endocrinopathies and the need for appropriate endocrinological testing, it may be possible to improve the quality of life and enhance the rehabilitation prospects for these patients.

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46 Optic Nerve Injury

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INTRODUCTION

Optic nerve injury is a rare condition; nevertheless, it is important as it can cause significant visual loss and even blindness after blunt or penetrating injury. While projectiles or other sharp objects injure the optic nerve directly, the most common form of traumatic optic neuropathy (TON) is indirect, as a result of a concussive force to the head, particularly the forehead. This impact is thought to transmit a shock wave to the optic canal, damaging the optic nerve. In some cases a relatively mild concussive impact can result in indirect TON. Visual abnormalities are uncommon findings following closed head injury. The exact incidence of optic nerve injury is difficult to determine, as many unconscious patients with this pathology may die undiagnosed when autopsy is not carried out. Mahapatra et al.[28,41,55,91] reported a 1.5% incidence of optic nerve injury in head injury cases. Jennette et al. noted a 13% incidence of optic nerve injuries in severe head injuries, while Crompton[17] noted a 4.4% incidence of optic nerve injuries with 24% of them being bilateral.

The pathogenesis of optic nerve injuries till date is unclear and, while the diagnosis of indirect TON can usually be made with the aid of a careful history and examination, its optimal management is far less well defined. There is endorsement in the literature for corticosteroids (dosages ranging from 60 mg to 7 g per day), surgical decompression of the optic canal (via intracranial, transethmoidal, endonasal, sublabial or other approaches) (Table 1) and observation alone. Evidence for the relative benefits of these approaches has mainly been based on small retrospective and anecdotal studies and, therefore, a convincing rationale for treatment is lacking. This chapter highlights a few of these issues.

ANATOMICAL AND PATHOLOGICAL CONSIDERATIONS

The visual pathway is divided into anterior and posterior parts. The anterior visual pathway includes the optic nerves and chiasma. The posterior visual pathway includes the rest of the visual system distal to the chiasma. Barring occipital infarction due to herniation, involvement of the posterior visual pathway in head injury is rather rare. The most important pathology in optic pathway injury is optic nerve involvement.[20,22,23,28,58,70,91,93] The optic nerve extends from the globe to the chiasma and is approximately 5 cm long. The optic nerve is divided into four parts: (1) Intraocular part; (2) Intraorbital part, which is the longest measuring 25–30 mm in length; (3) Intracanalicular part, 4–10 mm long and lies in the optic canal, where the nerve is fixed to the periosteum, and (4) Intracranial part, 10–15 mm long. The intracanalicular part, located in the

Table 1: Literature on optic nerve decompression surgery for optic nerve injuries [26,49,50,54,70]

First author (Year)	*Design*	*n*	*Initial vision*	*Pre-operative steroids*	*Timing of surgery*	*Length of follow-up*	*Losses to follow-up*	*Definition of visual improvement*	*n (%) improved*
Luxenberger (1998)[25]	Retrospective	14	No formal measurement	Megadose for all patients	Within 48 hrs in 67%	Not stated	Not stated	Not stated	7 (50%)
Chou (1996)[18]	Retrospective	25	NLP 36% LP-20/200 56% >20/200 8%	All treated: dose varied	2-54 days Median 15 days	Not stated	Not stated	≥1 line	15 (60%)
Levin (1994)[26]	Retrospective	31	NLP 48% LP-20/300 32% ≥20/200 19%	Megadose for all patients	≤24hrs 32% 25-72 hrs 29% 73-144 hrs 39%	Not stated	Not stated	Not stated	22 (71%)
Fujitani (1986)[23]	Retrospective	70	NLP 40% LP-20/200 44% >20/200 16%	Not stated	Within 3 wks in most cases	3 mon-2 yrs	Not stated	Varied depending on intial vision	34 (48%)
Matsuzaki (1982)[24]	Retrospective	11	NLP 27% LP-20/200 64% >20/200 9%	Not stated	Within 1 wk in 55%	6-12 mon Median 12 Median 12	Not stated	≥1 line	3 (27%)

optic canal, and the intraorbital portions of the optic nerve are surrounded by dura and arachnoid. The subarachnoid space surrounding the intracranial part of the nerve extends forwards and communicates with the subarachnoid space around the intracanalicular and intraorbital portions of the nerve. The optic nerve passes through the medial part of the annular tendon and below the levator and superior rectus muscles. The dural sheath around the optic nerve blends smoothly into the periorbita at the anterior end of the optic canal. After passing through the optic canal, which forms a prominence in the upper part of the sphenoid sinus immediately in front of the sella turcica and along the medial aspect of the anterior clinoid process, the intracranial portion of the nerve is directed posteriorly, superiorly and medially towards the optic chiasm. The intraocular portion of the optic nerve, which includes the optic disc, lies within the sclera. The intraorbital portion of the optic nerve is surrounded by orbital fat and follows a slightly tortuous course. The ciliary nerves and arteries pierce the sclera in the area around the optic nerve. The ophthalmic artery enters the orbit on the lateral side of the nerve and passes above the nerve to reach the medial side of the orbit. The superior ophthalmic vein arises in the anteromedial part of the orbit and crosses above the nerve to reach the orbital apex. Both the artery and the vein course between the superior rectus muscle and the optic nerve. The branch of the inferior division of the oculomotor nerve to the medial rectus muscle passes below the optic nerve at about the same level that the ophthalmic artery and nasociliary nerve passes above the optic nerve. Near the intracranial opening to the optic canal there is a strong and sharp dural edge. There is a potential risk of damage of the optic nerve against this sharp edge. The blood supply to this part to the optic nerve is important. The intracanalicular part is relatively avascular and derives blood supply from the centripetal branch of the pial vessels. The intracranial optic nerve is supplied by the small pial vessels of the anterior cerebral and anterior communicating arteries. These small vessels play an important role in optic nerve injury and lead to ischaemic neuropathy.

PATHOLOGY

Visual problems following head injury can involve (a) anterior, or (b) posterior visual pathways. According to the site of injury, the lesion can be at various places.

Introduction

The optic nerve is the most frequent site of visual pathway injury in head injury. Hippocrates first described it. Probably the first case of optic nerve injury was described by Dutonchel in 1822. However, in 1879, Berlin[57] described the optic nerve lesion at autopsy. Battle,[7] in 1890, had distinguished direct optic nerve injury from indirect optic nerve injury. Callon,[11] in 1892, had postulated the mechanism of optic canal fracture leading to optic nerve injury and reviewed 80 cases of optic nerve injury reported in the literature.

Optic Nerve Injury

Optic nerve injury is reported to occur in 0.6–3% of all head injuries.[17,28,41,55,91] The most frequent site of the injury is the optic canal. Hughes, in 1962, described the various types of optic nerve injuries, depending on the site: (a) anterior marginal tear; (b) anterior optic nerve injury, and (c) posterior optic nerve injury, which can be intraorbital, intracanalicular and intracranial[41] (Table 2).

Anterior Marginal Tear

It occurs at the optic nerve head in the retina. It was first described by Lowenstein in 1943.[53] Hughes reported an incidence of 13.3% of anterior marginal tear in his patients with optic nerve injury. This type is also associated with retinal and choroidal injury. Ophthalmoscopy reveals haemorrhage and irregular disc margins.

Anterior Optic Nerve Injury

It involves the optic nerve behind the globe till the entry of the central artery of the retina. Hughes[41] observed it in 12.3% of cases in his series. Retinal vessel spasm occurs in 30–35% of cases.

Posterior Optic Nerve Injury

It is more frequently seen. Traumatic orbital apex syndrome is a rare condition, occurring in the muscle cone. In this situation the optic nerve is involved and there is associated proptosis and III, IV and VI cranial nerve palsy. Intracranial optic nerve injury occurs in the optic canal, where the nerve is relatively fixed and the nerve sheath is firmly adherent to the periosteum. This type of injury can occur in anterior cranial fossa fracture. Hughes reported bilateral optic nerve injury in patients with LeFort type III fractures.[41]

PATHOPHYSIOLOGY OF OPTIC NERVE INJURY

The exact mechanism of optic nerve damage is not understood. However, a large number of hypotheses have been put forward. Walsh and Lindenberg,[92] in 1963, classified optic nerve injury into primary and

Table 2: Hughes classification of optic nerve injury based on site of injury[41]

Anterior visual pathway injury	*Posterior visual pathway injury*
Optic nerve injury • Anterior marginal tear • Intraorbital optic nerve injury • Intracanalicular injury • Intracranial optic nerve injury	Optic tract and geniculate lesion Optic radiation and calcarine lesion
Chiasmal injury	

Table 3: Walsh and Lindenberg classification of optic nerve injury based on pathology[92]

Primary pathology	*Secondary pathology*
Concussion	Oedema
Avulsion or tear: partial/complete	Ischaemia
Contusion	Microvascular thrombosis
Haemorrhage: intraneural/ extraneural	Infarction of the nerve

secondary type depending on the nature of the pathology as observed at autopsy (Table 3).

Concussion of the optic nerve was first described by Walsh in 1979.[93] Secondary involvement of the optic nerve is due to oedema and ischaemia, leading to infarction of the nerve, as a result of microvascular thrombosis.[36,41,92] Microvascular thrombosis is probably due to shearing strain on the nerve as a result of acceleration and deceleration injury to the orbit. It is also likely that midline forehead injury can produce bilateral optic nerve injury while a blow over the supraorbital/temporal area produces unilateral optic nerve injury. The shearing and stretching forces can lead to rupture of optic nerve axons.

One of the most favoured mechanisms of optic nerve damage in head injury is vascular insufficiency.[28,41,91] The vascular injury is generally to the pial vessels, which could be immediate. Delayed onset of visual involvement is due to oedema and ischaemia. In patients with irreversible visual loss, the most important cause is probably optic nerve infarction.[8,28,91] In two cases of Hughes, the histology of the intracranial optic nerve revealed infarction.[41] Infarction was also reported by Ramsey,[79] in both the intracanalicular and the intracranial portion of the optic nerve.

Fracture of the anterior cranial fossa, orbital roof, anterior clinoid process and the optic canal can produce optic nerve injury. These fractures can produce tear or compression of the nerve. Contusion of the nerve is a form of primary injury, which results from a shearing force to the nerve. Hooper, in 1951, had reported contusion of the intracranial optic nerve in a patient with anterior clinoid fracture.[40] Rarely, an optic sheath haematoma has also been reported.[29,42,78,87] Intraneural haemorrhage occurs due to the rupture of small veins or capillaries, resulting in a perivascular haematoma. Imachi et al.[42] have reported a few cases of intraneural haematoma. Tandon et al.[87] observed one case of optic nerve haematoma among 100 patients. Mahapatra et al.[65] observed a single case among 27 patients subjected to optic nerve decompression (OND).

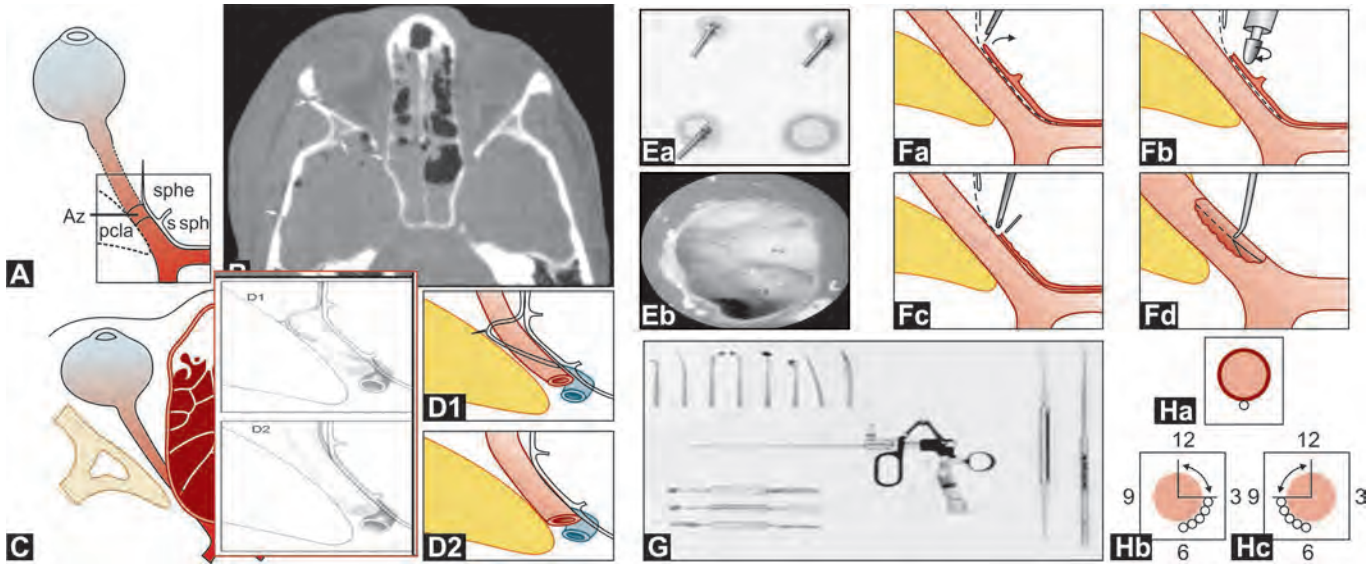
In spite of a normal looking nerve at surgery or at autopsy, histopathological abnormalities are consistently reported.[40,41,87,91] Pathological entities, such as degeneration of myelin, loss of axons and chronic inflammation with phagocytosis, are found at microscopic examination. Vascular involvement in the form of thrombosis, ischaemia and infarction are also seen.

PATHOLOGICAL ANATOMY

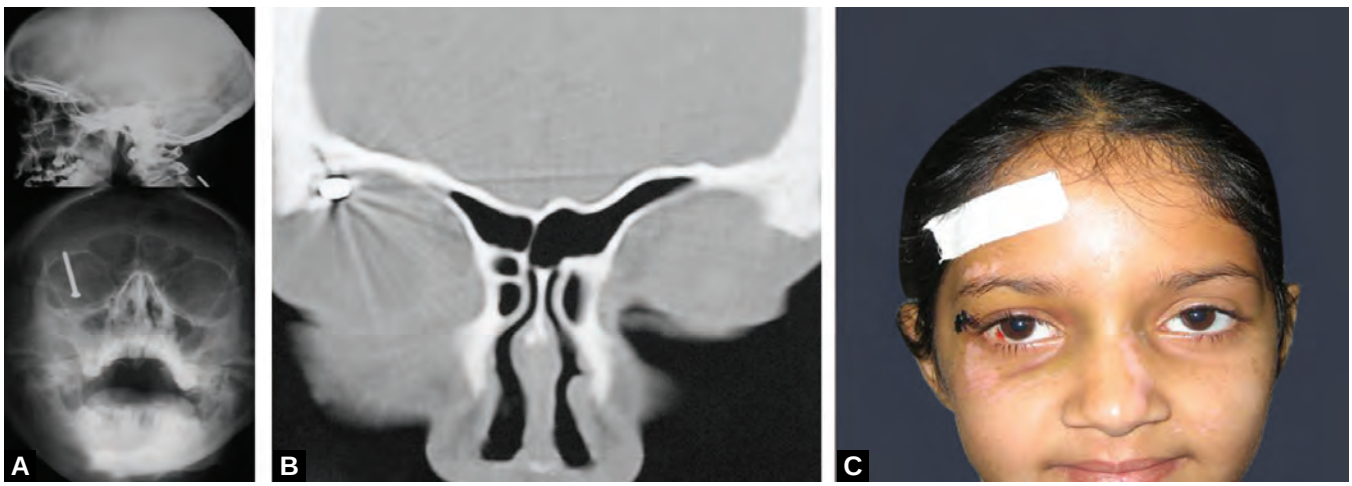
The optic canal is formed by the two struts of the lesser wing of the sphenoid and carries the optic nerve and the ophthalmic artery. The optic nerve, in contrast to a peripheral nerve, is a direct continuation of the brain and has all three of the meningeal layers—pia, arachnoid and dura—covering it (fasciculus opticus). Different mechanisms of injury are implicated with damage to the various segments of the optic nerve. The intraocular and intraorbital portions are typically damaged by direct ocular injuries; however, occasionally, indirect trauma may result in either an intrasheath or orbital haematoma. These haematomas may compromise the blood supply to the optic nerve via compression and subsequently result in a loss of vision. The intracranial portion of the optic nerve is most frequently injured by blunt trauma, and tears of the optic nerve itself or of the optic chiasm are occasionally seen. If at all indicated, OND in these cases is a neurosurgical approach via craniotomy. The intracanalicular portion of the optic nerve is the site most frequently involved in indirect lesions, such as blunt trauma, and it is with an injury to this segment that OND may be most beneficial (Figs 1A to H). The dural covering of the optic nerve consists of two layers, the outer layer arising at the orbital apex where the central nervous system dura splits to form the periorbita and the optic nerve sheath, and the arachnoid attached to the inner portion of the dural sheath. This anatomical structure has clinical implications, because theoretically it should be possible to incise only the outer layer of the dural sheath and not enter the subarachnoid space, thus, avoiding a potential cerebrospinal fluid leak during OND. Although theoretically possible, it is unlikely that an incision will incise only the superficial layer of the dural sheath because the layers are intimately related. Thus, precautions to avoid a cerebrospinal fluid leak should be taken if the nerve sheath is to be incised.

CLINICAL FEATURES

In conscious patients diagnosis is not difficult. A history of unilateral visual loss or, rarely, bilateral visual loss is the main complaint. The visual loss could be immediate or delayed.[28,55,64,70,91] In 90% of cases, patients do have a history of loss of consciousness. Typically, the retina and optic disc initially appear normal, and the only objective finding is the presence of a relative afferent pupillary defect. Optic atrophy does not become apparent for 3–4 weeks. In severe head injury, when a patient is unconscious, unilateral fixed dilated pupil with retained consensual light reflex should raise the possibility of unilateral optic nerve injury (Marcus Gunn Pupil). In unconscious patients it is difficult to determine the timing of onset of visual deterioration. In 15–20% of patients, visual loss may be partial and patients may also have visual field cuts. In patients with optic nerve concussion, there will be a transient visual loss. Hence,



Figs 1A to H: (A) Line diagram showing the relations of the intracanalicular portion of the optic nerve. (B) CT scan, bone windows of the brain showing multiple fractures of the orbit along with injury of the intracanalicular portion of the optic nerve. (C) Diagram showing pneumatisation of the posterior ethmoidal cells resulting in prominence of the optic canal in its lateral wall. (D1) Normal course of the ophthalmic artery entering the optic canal from the inferolateral aspect. (D2) Variant anatomy of the ophthalmic artery. It is entering on the medial side of the orbital aperture of the optic canal. (Ea) Diagram showing the method of enlarging the sphenoid ostium. (Eb) Endoscopic picture showing the bulge of the optic nerve and the internal carotid artery seen after entering the sphenoid sinus. (Fa to Fd) Diagrammatic representation showing the thinning and removal of the bony canal. (G) Set of neuroendoscopic instruments for performing OND with sickle knife to open the optic nerve sheath and annulus of Zinn. (Ha) Direction and axis of removal of the bony canal to give 1800 decompression on the (Hb) right and (Hc) left side



Figs 2A to C: (A and B) CT scan showing injury to the right orbit. (C) Clinical picture of a child having bilateral optic nerve injury, patient showed full recovery in vision after 2 months

it may be possible to have some visual recovery by the time patients reach the neurosurgeon[8,20,29,65] [Figs 2 (A to C) and Table 4].

Examination usually reveals a normal cornea, lens and vitreous. In anterior marginal tear, ophthalmoscopy may show retinal haemorrhage.[28,40,91] In the vast majority of cases the fundus reveals no abnormality. Rarely, congestion of the disc may be observed.

Table 4: Results of 800 patients with optic nerve injury at AIIMS (1983-2002)[67]

Visual recovery	*% of recovery*
Complete recovery	10
Partial recovery	48
No recovery	42

Fundus Finding

Fundus findings vary according to the site of the injury and the degree of damage to the nerve. Except anterior marginal tear, immediate or early examination may not show any abnormality. In anterior marginal tear, fundus examination a few hours later usually shows oedema and haemorrhage. In anterior optic

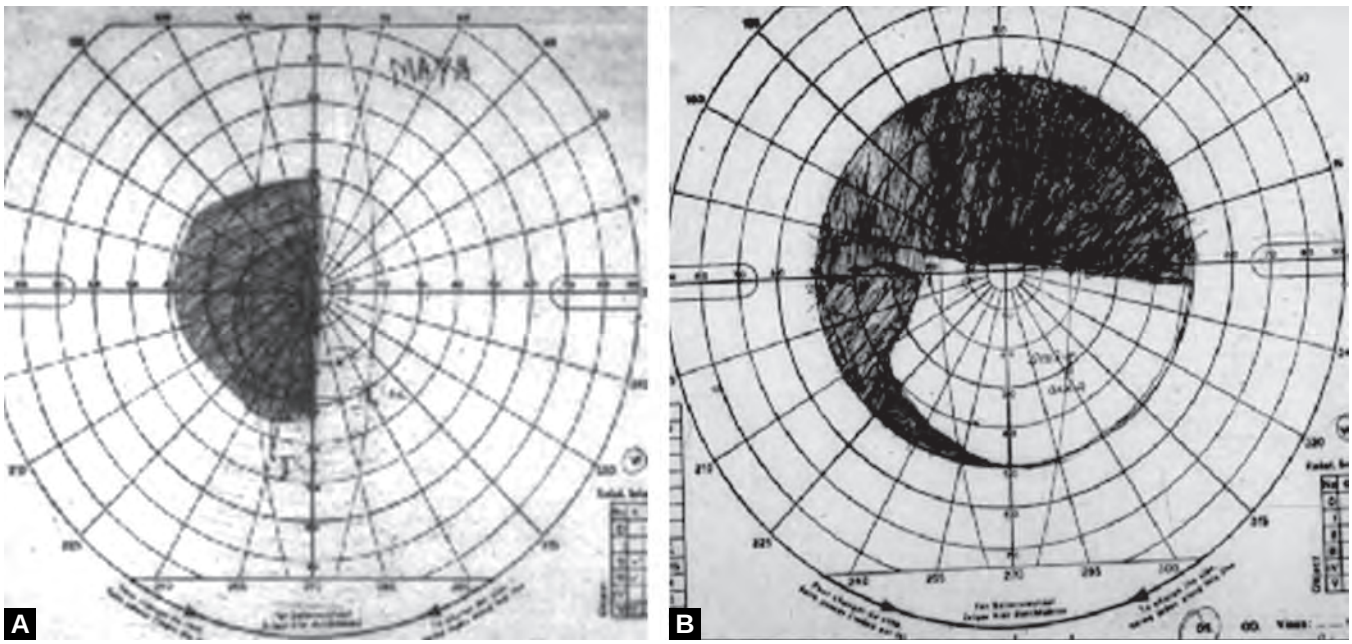
nerve injury, when the site of damage is nearer to the eyeball, fundus changes occur earlier than distal optic nerve injury. Generally, optic atrophy sets in 3–6 weeks time.[1,19,28,41,89]

Field Defects in Optic Nerve Injury

Various types of field defects have been reported in patients with optic nerve injury (Figs 3A and B).[1,19,28,41,60,70,89] Traquir et al.[89] had reported central or paracentral scotoma and altitudinal field cut. Hughes,[41] in 1962, had reported inferior field cuts only in their observation. Mahapatra et al.[56] noted all possible field defects including nasal field. However, the temporal field was most frequently involved possibly resulting from selective involvement of nasal fibres as the bone in the medial side of the orbit is thin and is likely to fracture more frequently.

INVESTIGATIONS

X-rays of skull paranasal sinus view and optic canal view are important radiological investigations. Skull fractures are reported in 50–80% of patients.[19,28,70,91] A wide variation in incidence of optic canal fractures (0–90%) has been reported.[22,23,57,64] This is basically due to differences in surgical, radiological and autopsy findings. With the advent of CT scan, demonstration of optic canal fracture has become easy. CT cuts with bone window helps in establishing the fracture. CT scanning is regularly used in suspected cases of optic nerve injury (Fig. 4).[5,31,44,55,64,68,70] High resolution CT is the procedure of choice. Manfredi et al.[68] reported sphenoid and ethmoid haemorrhages in PNS view and among them five had CT scan evidence of optic canal fracture. Grove[31] had pointed out the role of soft tissue injury. Mahapatra



Figs 3A and B: Perimetry showing visual field deficits in a case of optic nerve injury

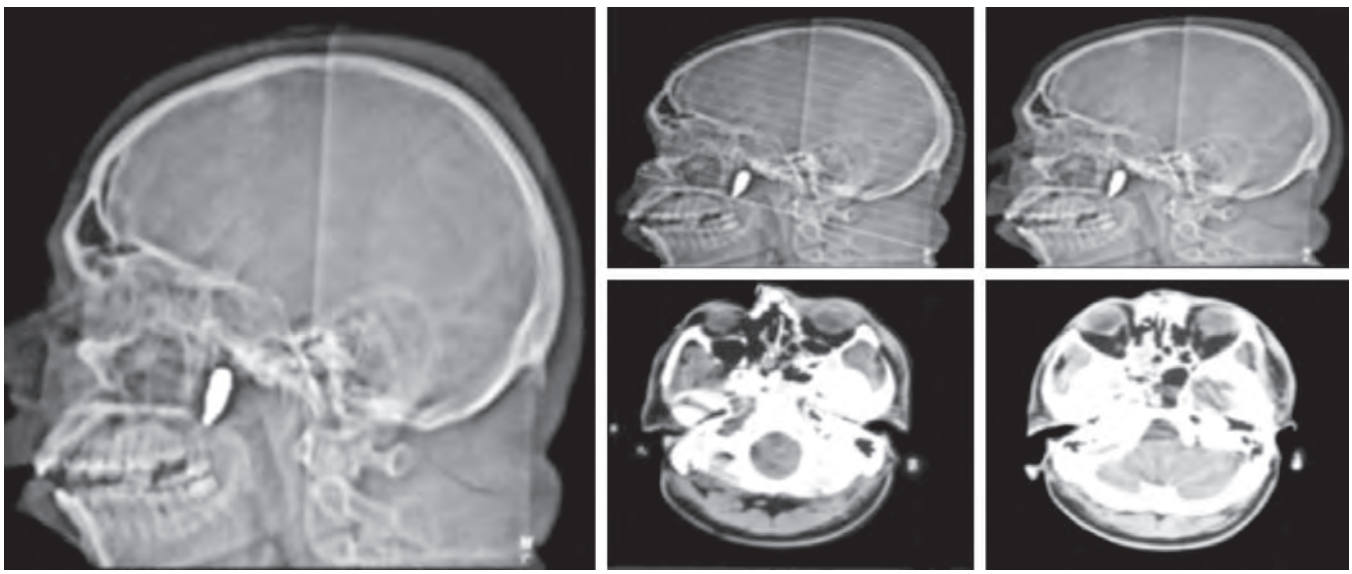


Fig. 4: CT scan of the head in a case of bullet injury in the right eye with optic nerve injury

et al. noted optic canal fracture in 8–10% of their cases in CT scan.[55–57,64] CT frequently shows a fracture in the anterior cranial fossa and opacity in the ethmoid and sphenoid sinuses. Rarely, CT scan may show optic sheath haematoma. Mahapatra et al. reported a single case of optic sheath haematoma among 100 patients.[56] MRI scans show nerve swelling and contusions very well.[56,64,70] Orbital ultrasound is also useful; it can show thickening of the nerve, orbital haematoma or a bony fragment.[15] Mahapatra et al.[56] carried out orbital ultrasound in 20 cases and noticed early optic nerve thickening in their series, which resolved in 3–4 weeks time (Table 5).

Role of Visual Evoked Potentials

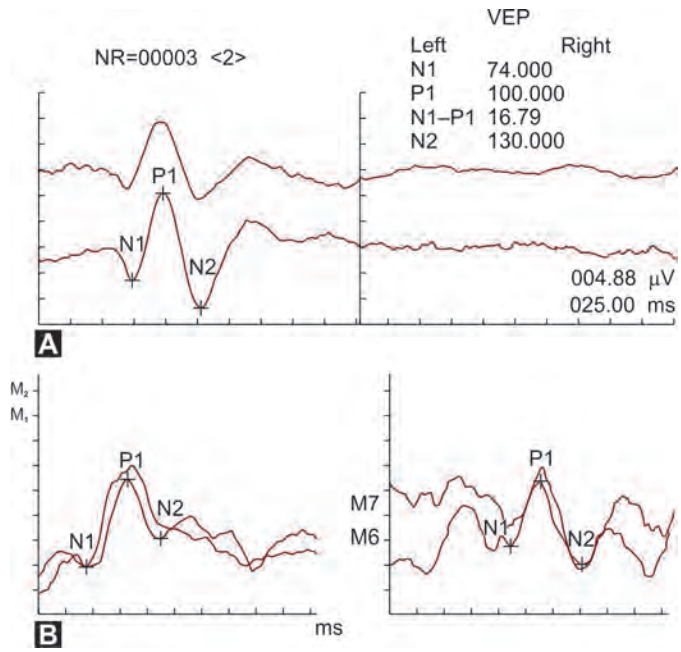
Visual evoked potentials (VEPs) provide a good indication of the integrity of the visual pathway.[16,18,43] VEPs must be recorded in every case to assess the integrity of the anterior visual pathways. However, not much literature is available on the role of VEP in the management of optic nerve injury. Till the late 1980s, this test was not frequently used in optic nerve injury. Feinsod and Auerbach,[21] in 1973, and Shaked et al.[81] in 1982, looked at the role of VEP and electroretinography in their series. Nau et al.[74] in 1987, observed poor outcome in patients having no VEP tracings, however, they didn't comment on the value of normal VEP tracings in predicting good outcome. Mahapatra and Tandon showed that there was 85–90% visual improvement in patients who had repeated normal VEPs.[55–57] In their experience, none of the patients with repeatedly absent VEP had shown visual recovery. VEP also helps in diagnosis of visual loss in unconscious patients. Light emitting diodes (LEDs) are used for recording VEP in unconscious patients. In our department, VEPs are routinely performed by using the Nicolet 1170 model or Nicolet Compact four model. VEPs are recorded either by using the pattern reversal method or by LEDs. LED is used in unconscious or uncooperative patients and helps in establishing the diagnosis in those in whom visual loss is suspected. VEPs are routinely performed within 48 hours of initial evaluation and the test is repeated within 7–10 days to assess the electrophysiological improvement. VEPs are categorised as normal, abnormal or absent depending upon their wave formation and latencies. Latencies longer than 2 SD of the control value are considered as abnormal. In a series of 78 cases published by Mahapatra,[66] overall improvement occurred in 29 (56%) patients. All the 10 patients with normal VEP recovered. Among 29 patients with abnormal VEP, 26 (86.6%) showed visual improvement. Thus 36 out of 39 patients (92.2%) with a positive VEP wave had visual improvement ultimately. Among 39 patients with initial absent VEPs 31, who had repeated absent VEP waves, had no subsequent improvement. Mahapatra and Bhatia[55] in a recent study of 45 patients with optic nerve injury established the predictive value of VEPs in patients with traumatic unilateral blindness. They reported improvement in 90% of patients with positive P 100 waves. Mahapatra[39,59,66] in his study established the role of both positive and negative VEPs in the diagnosis and in predicting the outcome and also noted that in unconscious patients VEPs did help in establishing the diagnosis of optic nerve injury.

Table 5: Investigations in patients with optic nerve injury

Investigations in patients with optic nerve injury:
• X-ray skull
• Visual evoked potential (VEP)
• Field charting
• CT scan with orbital cut
• MRI scan
• Orbital ultrasound

Flash Visual Evoked Potential

Flash visual evoked potential [(FVEP) Figs 5A and B] recordings are routinely done as per the technical guidelines developed by the American Clinical Neurophysiology Society.[2,3,39] Visual flashes are delivered by means of light-emitting diode goggles placed over the eyes. These goggles are covered by a clear plastic bandage. Electrodes are placed in the following locations: midoccipital (MO, 5 cm above inion), left occipital (LO, 5 cm left of MO), right occipital (RO, 5 cm right of MO), Cz (midline vertex position, based on standard 10–20 EEG location[2] left or right earlobe (A1/2) and ground (any scalp location). Referential recordings are obtained with monocular stimulation; MO, LO, RO, and Cz are all



Figs 5A and B: (A) Visual evoked potential in a patient with right optic nerve injury showing normal VEP tracing on left side with no waveform seen on the right side. (B) Visual evoked potential in a patient with right optic nerve injury showing normal tracing in the left eye and delay in P1 latency on the right side

referred to A1/2. Filter settings include low frequency at 1 Hz, high frequency at 250 Hz and notch filter (60 Hz) on "off". Sensitivities range up to 100 μV. The protocol calls for 200 flashes for each eye, with stimulus duration of 250 ms and rate of 1.9 Hz. Grand averages are displayed for each of the four channels of each recording. If present, waves labelled I through VI are then identified in each channel within the first 250 ms after stimulation. Latencies and amplitudes of each wave are then calculated. FVEP waveforms are identified in the grand averages of MO-A1/2, RO-A1/2 or LO-A1/2 in the eye with TON and in the normal (control) eye. At approximately 100 ms after the stimulus, the greatest amplitude was exhibited in one of these three channels in the TON eye (corresponding to the "P100" in pattern-reversal VEPs studies). This is typically the second wave, with surface positive polarity, in the MO-A1/2 channel. The corresponding waveform in the same channel on the control side is then identified. The amplitudes of these waves are manually measured peak to peak, with the aid of electronic calipers. An amplitude ratio is then calculated by dividing the FVEP amplitude obtained in the TON eye by the FVEP amplitude obtained in the control eye.

The presence of FVEPs has been considered to reflect at least some functional integrity of visual pathways. However, the information that these studies convey has generally been perceived to be qualitative only, an "all or nothing" phenomenon that provides little if any information on the degree of damage to the optic nerve or visual radiations.[2,3] Until now, in the unconscious head-injured patient, one could only state whether or not optic nerve injury was present. Homes et al.[39] showed that careful assessment of the FVEP ratio in unilateral TON may allow one to grade the severity of optic nerve injury before the patient regains consciousness. This knowledge in turn may help direct therapy and counsel the family regarding prognosis. Whereas VEPs, including FVEPs, have been of value in predicting visual outcome after direct ocular injury, such studies are of more limited value in anticipating neurological outcome after head trauma.[32,37,38,45] However, applying FVEPs to evaluate visual outcome when the optic nerve has been damaged in the setting of head injury may prove to be highly useful.[74] Given that subject co-operation is often problematic in head-injured patients, FVEP is the most practical laboratory method to investigate the visual system in TON. When TON is unilateral, the unaffected eye may serve as the normal eye when FVEP amplitudes are measured (Fig. 6).

Patients with TON fall in two distinct groups: (1) those who eventually have good-to-excellent visual outcome and (2) those who have very poor to no visual recovery.[39] Ultimately, the determining factor for permanent visual loss must be the degree of damage to the optic nerve. The FVEP simply reflects whatever degree of optic nerve injury has taken place, and the FVEP ratio is a method to avoid systemic bias, such as drugs or level of consciousness. The amplitudes alone are not meaningful. When the FVEP ratio, a measure of relative optic nerve functional integrity, is at least 50%, a favourable visual outcome may be anticipated in unilateral TON (Fig. 7).[39]

TREATMENT OF OPTIC NERVE INJURY

Although traumatic optic neuropathy (TON) has been known for long, the best treatment methods remain controversial. No treatments, like megadose corticosteroids, surgical optic canal decompression or a combination, are the present management options. The main controversy,

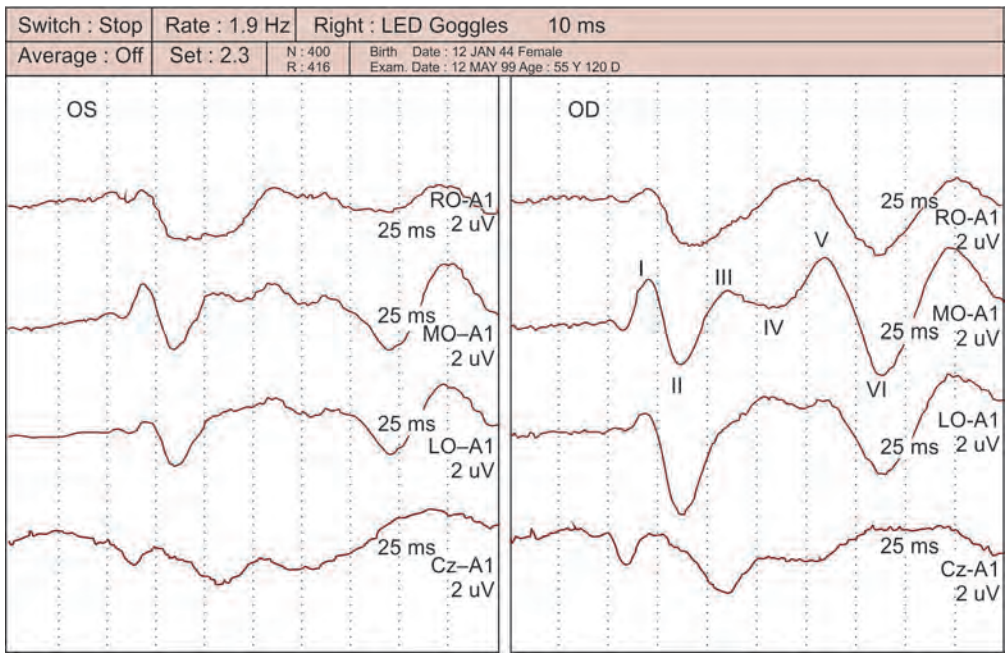


Fig. 6: Amplitude ratio of the eye with traumatic optic neuropathy, (OS)/normal (OD), was greater than 0.5 for this subject. Visual acuity OS was 20/25. Ratios were based on amplitudes of the second wave (wave II) in the mid-occipital–A1/2 channel on either side, occurring 100 ms after stimulation

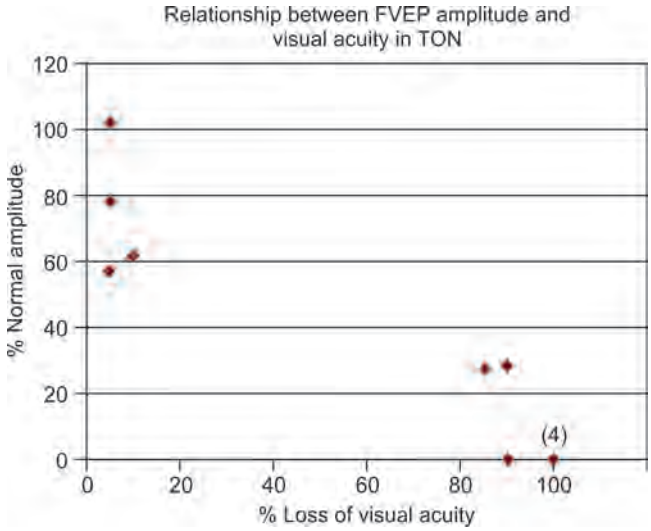


Fig. 7: Comparison of percentage of normal amplitude of flash visual evoked potentials response in traumatic optic neuropathy against percentage loss of visual acuity

however, centres on the indications for surgery. A large number of studies reported in the world literature show similar results in medically managed and surgically treated groups.[23,28,29,55,58,61,70,87,91,93] While many authors from different countries have favoured medical management; the Japanese authors have popularised and favoured surgical treatment[23,26,58,76] (Tables 6A and B).

Various prospective series on optic nerve injury management and evaluating the role of early surgery versus medical management have been published by Mahapatra et al.[57,63,64,67,88] Spontaneous visual improvement has been noted with a frequency of 20–38% in short reports or in small case series.[41,49,66,67,80,94] The treatment of TON with megadose corticosteroids evolved since it was first proposed in 1982, based on the salutary effects of corticosteroids in treating experimental central nervous system injury.[6,80] No effective surgical approaches for decompressing the optic nerve were identified until 1961, when Niho et al. developed a technique based on an extracranial transethmoidal approach.[75,76] Subsequently, other authors published their own surgical techniques and results.[27,44,70,76] However, these subsequent works reported the results of combined medical and surgical treatment, making it difficult to ascertain the therapeutic value of individual treatments. Therefore, the indications for surgical OND alone remain uncertain. Possible prognostic factors include not only the therapeutic intervention implemented but also the patient's age, initial visual acuity (IVA), the presence of optic canal fracture and the timing of treatment.

Medical Management

There is scanty literature on the medical treatment of optic nerve injury.[40,65,67,70] The use of megadose intravenous corticosteroids is based on laboratory studies demonstrating that timely use of corticosteroids can reduce the oedema and tissue damage resulting from ischaemic and traumatic injuries.[34] Notably, the National Acute Spinal Cord Injury Study on the use of megadose methylprednisolone appeared to confirm clinically the laboratory results.[4,10] Moreover, Seiff[80] reported the results of a non-consecutive and non-randomised retrospective series of 36 patients with TON who were either not treated (15 patients) or treated with dexamethasone (21 patients). Seiff found that visual improvement occurred in 62% of treated patients and in 33% of untreated patients, although the difference was not significant. Spoor et al.[84] reported the results of an uncontrolled, non-consecutive, retrospective investigation of 21 patients (22 eyes) with TON studied at two centres. Eight patients at one centre received dexamethasone, whereas 13 patients at the second centre received methylprednisolone. Vision improved in 7 of 9 patients in the dexamethasone group and in 12 of 13 patients in the methylprednisolone group. Although Spoor's study[84] is too small to draw any meaningful conclusions about the efficacy of corticosteroid treatment, it is interesting that patients treated with dexamethasone appeared to do as well as patients treated with methylprednisolone. Methylprednisolone was used in this study, and 44.4% (8/18) of patients treated with it alone gained visual improvement (Table 7).

Many authors, who did not believe in surgical management, offered no treatment. Walsh stated that "cortisone and mannitol may be helpful in patients in whom optic nerve swelling is a feature". However, establishing swelling of the optic nerve is difficult. With the advent of ultrasound and MRI scan optic nerve swelling can be diagnosed. Delayed onset of visual deterioration also suggests swelling or oedema of the optic nerve. Matsuzaki et al.[93] treated 22 patients with a combination of prednisolone, 20% mannitol, urokinase and Vit B_{12} and reported 58.5% recovery in this group. Anderson et al.[19] used high dose steroid in 6 patients and 3 patients showed good recovery. Mahapatra et al.[55–57,61,74,87] observed overall improvements in 53–58% patients and recommended steroid treatment (dexamethasone or methylprednisolone) for 3–4 weeks duration.

Indications for Surgery

Earlier, conservative management was the treatment option followed in the majority with surgery being indicated in only a few subsets of patients. Mahapatra laid down criteria for surgery in optic nerve injuries. Every patient is offered 3 weeks corticosteroid treatment initially. VEPs are monitored and patients are closely followed. Patients progressively improving or not showing any improvement are not subjected to surgery. A group of patients who show minimal improvement and then remain static are subjected to surgery. This situation only suggests that the optic nerve is not completely damaged and given a chance, further improvement may occur. Following this criterion patients are operated. As the group subjected to surgery is highly selective, chances of improvement are also high.[87] Thus, the role of surgery in optic nerve injury is limited.

Table 6A: Literature on course of optic nerve injuries without treatment

First author (Year)	*Design*	*n*	*Initial vision*	*Timing of initial examination*	*Length of follow-up*	*Losses to follow-up*	*Definition of visual improvement*	*n (%) Improved*
Chou (1996)[18]	Retrospective	10	NLP 40% LP-20/200 30% ≥20/200 30%	3-54 days Median 10 days	Not stated	Not stated	≥1 line	0 (0%)
Seiff (1990)[19]	Retrospective	15	NLP 47% LP-20/200 27% ≥20/200 27%	Not stated	2-810 days Median 25 days	Not stated	≥1 line	5 (33%) 2 of 7 baseline NLP 3 of 8 baseline ≥LP
Lessell (1989)[3]	Retrospective	25	Not stated	Not stated	1 mon–3 yrs Mean 8.75 mon	Not stated	Not stated	5 (20%)
Edmund (1963)[20]	Retrospective	16	Not stated	Not stated	Not stated	Not stated	Not stated	4 (25%)
Hughes (1962)[2]	Retrospective	56	NLP 64%	Most during hospital admission from injury	Not stated	Not stated	Improvement/useful vision	27 (48%) improved 16 of 36 baseline NLP improved: 6 recovered useful vision 7 of 20 baseline ≥LP improved
Hooper (1951)[12]	Retrospective	21	NLP 67%	Not stated	Not stated	Not stated	Useful vision	5 (24%) 2 of 14 baseline NLP 3 of 7 baseline >NLP

Table 6B: Literature on corticosteroid treatment of optic nerve injuries[13,19,40,41,49,70,71,76,80]

First author (Year)	*Design*	*n*	*Initial vision*	*Timing of steroids*	*Dose of steroids*	*Length of follow-up*	*Losses to follow-up*	*Definition of visual Improvement*	*n (%) Improved*
Chou (1996)[18]	Retrospective	23	NLP 35% LP-20/200 65%	1-60 days Median 13 days	Oral prednisone 60-80 mg QD in 6 Dexamethasone 1.3 mg/kg/d IV in 17	Not stated	Not stated	≥1 line	13 (57%) 2 of 8 baseline NLP 11 of 15 baseline ≥LP
Mauriello (1992)[21]	Retrospective	16	NLP 38% LP-20/200 56% >20/200 6%	≤48 hrs of injury	Methylprednisolone 1g IV bolus then 250 mg q 6 hrs × 3 d	Not stated	Not stated	Significant improvement	9 (56%)
Spoor (1990)[22]	Retrospective	22	NLP 36% LP-20/200 55% >20/200 9%	2 hrs–15 days Median 22 yrs	Megadose in 12 High dose in 9	1 wk-3 yrs Median 2.5 mon	Not stated	Significant improvement	18 (82%) Megadose 11 of 13 High dose 7 of 9
Seiff (1990)[19]	Retrospective	21 eyes	NLP 52% LP-20/200 48%	≤48 hrs of injury	Dexamethasone 1 mg/kg/d IV × ≥3 days	3-1095 days Median 24 days	Not stated	≥1 line	13 (57%) 2 of 8 baseline NLP 11 of 15 baseline ≥LP
Fujitani (1986)[23]	Retrospective	43	NLP 21% LP-20/200 40% >20/200 40%	≤7 days 28% 8-30 days 44% >30 days 28%	Oral prednisone 60 mg/day	3 mon-2 yrs	Not stated	Varied depending on intial vision	19 (44%) 0 of 9 baseline NLP 19 of 34 baseline ≥LP
Matsuzaki (1982)[24]	Retrospective	22	NLP 27% LP-20/200 45% >20/200 27%	1 day-11 mon Median 1 mon	Oral prednisone 40-100 mg ×5-7 days	6-12 mon Median 6 mon	Not stated	≥1 line	10 (45%) 0 of 6 baseline NLP 10 of 16 baseline ≥LP

Table 7: Results of conservative treatment in various series

Authors	*Year*	*No. of cases*	*% of recovery*
Hooper[20]	1951	17	29
Matsuzaki et al[10]	1982	33	33
Mahapatra et al[25]	1992	100	57
Mahapatra[53]	2002	800	58

Optic Nerve Decompression

Although surgical optic nerve decompression (OND) made its debut early in the 1900s, little research was done in this area until Niho et al.[76] developed the extracranial transethmoidal approach. Surgical intervention for TON is empirical due to the lack of a large body of evidence supporting its effectiveness, as well as outlining the potential risks associated with the procedure. Notably, the potential risks associated with surgical OND include further vision loss, cerebrospinal fluid leakage, ascending meningitis and injury to the internal carotid artery.[44] The rationale for OND is that it will reduce bone fragments impinging on the optic nerve and open the canal to reduce compression of a swollen optic nerve and its vascular supply within the optic canal. About 30 series of OND have been published, but they are difficult to compare because they each use different techniques, selection criteria and definition of improvement. The frequency of visual improvement after treatment in these series ranges from 12 to 79%.[44,50,77] Besides treatment modalities, some clinical factors also influence the prognosis of TON, including IVA, optic canal fracture, age and time from injury to treatment. In the literature, the treatment of those patients who have immediate vision loss is especially controversial. Matsuzaki et al. echoing Walsh,[70,90] said that recovery was exceptional in such patients. However, visual improvement was reported in these patients treated with steroid alone, with an improvement rate ranging from 12.5 to 62.5%.[72,80,84] Some authors found improvement with steroids and surgical intervention, with a rate of 16.7–57.1%.[27,72] To compare and identify which is superior to other treatment modalities in these retrospective reports is difficult because of selection bias and small patient numbers. In some large series, the incidence of optic canal fracture in TON varied from 21 to 55%.[27,49,70,72] The finding of optic canal fractures has been considered to be an indication for surgical decompression, which is often the source of selection bias. The effect of optic canal fracture on visual improvement is controversial.[27,34,76] Seiff[80] reported that 63% of patients with canal fractures initially had no light perception (NLP) vision, compared with only 40% of those with no fractures or fractures of other orbital bones. Sometimes, optic canal fractures radiologically not detectable are discovered during surgery. In fact, radiologically diagnosed optic canal fracture is not a dependable indicator of OND.[27,63]

Patients with TON are mostly in the 20–40 years age group and represent the major trauma population. Levin et al. reported the relationship between age and the outcome of TON after surgical decompression and drew the conclusion that younger patients (< 40 years) had a better visual outcome from undergoing surgical decompression than did older ones (≥ 40 years).[50] Although it is reasonable to hypothesise that the younger have more potential for recovery, and there is insufficient data in this study to confirm it. Motor vehicle accidents were the most frequent mechanism of injury in this study. Associated head injury and multiple traumas existed in such patients, precluding precise visual examination and often delaying treatment. Joseph et al. described a series of 14 patients with TON operated by transethmoidal/trans-sphenoidal optic canal decompression.[44] They do not recommend surgery if more than 7 days have elapsed since the injury.[44] Analysis of results of this study demonstrated that regardless of the therapeutic intervention employed, patients receiving treatment within 7 days improved more than those treated more than 7 days later. Although the appropriate treatment of patients with TON remains controversial, the benefits of early detection and treatment are universally recognised, making early detection and treatment mandatory.

Decompression of the optic nerve following injury has been tried for many years[23,28,41,46,49,58,73,75,77,83,87,91] (Table 8). Prior to the introduction of transethmoidal surgery by Niho et al.[76] the transcranial route was used for decompression. There is a great deal of controversy regarding the need for surgery and timing of OND. Gjerris,[28] in 1976, stated "Comparison between two groups of patients treated with and without operation reveals that the prognosis is the same in both groups, that there is no clear cut guidelines for one or the other". Walsh and Hoyt[91] considered immediate visual loss at the time of impact as a contraindication for surgery, as visual recovery is unlikely. Other authors have considered optic canal fracture as one of the indications for surgery.[58,75] Gjerris[28] was against surgery in patients with immediate visual loss and showing no signs of visual recovery in the next few days. He also suggested conservative management when optic nerve injury is diagnosed in unconscious patients. Fuzitani et al.[26] suggested a trial of steroid therapy for 3 weeks; patients not improving on steroid were unlikely to benefit from surgery either. Lessell,[49] in 1989, observed that the eyes with total loss of vision at the end of 3 weeks on steroid are unlikely to respond. However, Mahapatra,[62] in 1992, reported delayed

Table 8: Results of surgical decompression in optic nerve injury

Authors	*Year*	*No. of cases*	*% of recovery*
Nicho et al.[52]	1961	7	66
Impachi et al.[22]	1968	61	70
Fukado[7]	1981	700	42
Matsukzak et al.[10]	1982	11	42
Karnik[71]	1986	37	20
Tandon et al. (Selected cases)[76]	1994	39	74

recovery from optic nerve injury. Thakar et al.[88] in 2003, reported the results of delayed OND for optic nerve injury. Determination of potential benefit from OND depends on the cause of injury. Cases with complete disruption of the optic nerve will not recover regardless of whether OND is performed, because the optic nerve is a direct continuation of the brain (fasciculus opticus). In contrast, insults from oedema, haematoma or moderate bony compression may respond favourably to OND. Traumatic injuries of the optic nerve are not the only indications for OND.

Endoscopic Optic Nerve Decompression

Traditional surgical approaches to OND are a neurosurgical or craniotomy approach, extranasal transethmoidal approach, transorbital approach, transantral approach and intranasal microscopic approach. Recent advances in instrumentation and surgical techniques have made an endoscopic approach to OND possible. The endoscopic method offers many advantages over the traditional approaches. Decreased morbidity, preservation of olfaction, rapid recovery time, more acceptable cosmetic results with no external scars, no risk of injury to developing teeth in children and less operative stress in a patient who may have multi-system trauma are some of the benefits associated with endoscopic OND.

In the endoscopic technique of OND, the optic nerve is approached from its medial aspect and several anatomical features should be considered.[77] One typically expects to encounter the optic nerve just superior to where the internal carotid artery creates a bulge in the lateral wall of the sphenoid sinus. In 12% or more of cases the optic nerve will be travelling through a posterior ethmoid cell (Onodi cell).[47] Posterior ethmoid cells are called Onodi cells (or sphenoethmoidal cells) when they have pneumatised considerably laterally to and/or superiorly to the sphenoid sinus and the optic nerve tubercle or even the canal itself is prominent in its lateral wall (Fig. 1C), thus leaving the nerve vulnerable to injury or possible transection if appropriate attention is not given to identify the nerve before entering the sphenoid sinus. Another potential problem with catastrophic results could be surgical transection of the ophthalmic artery. Either way, packing or coagulation would result in a counterproductive effect regarding optic nerve function in such a case. The ophthalmic artery typically enters the nerve sheath from an inferolateral direction and thus is not in the surgical field of an endoscopic endonasal approach. However, 15.5% of patients may have the ophthalmic artery entering on the medial side of the orbital aperture of the optic canal and be susceptible to injury by the medial approach[47,82] (Figs 1D1 and D2).

The orbital apex is the fibrous annulus of Zinn. This is the area where the pia and arachnoid fuse and is a very likely site for compression of the optic nerve, as it is usually located at the entrance to the most narrow portion of the optic canal. It may be identified as a thickened area of fibrous tissue in the region of the orbital apex.[47] Care must be taken to be certain this annulus is incised during slitting of the optic nerve sheath in order to achieve adequate decompression, as this is the least expandable portion of fibrous tissue around the optic nerve.

Surgical Technique for Optic Nerve Decompression

An endoscopic sphenoethmoidectomy is performed using the Messerklinger and Stammberger technique with preservation of the middle turbinate. Care is taken not to violate the lamina papyracea or periorbita at this point. The sphenoid sinus is entered and a circular cutting sphenoid punch is used to enlarge the opening into the sphenoid sinus (Fig. 1Ea). The bulge of the internal carotid artery and optic nerve is identified as they course through the lateral wall and/or roof of the sphenoid sinus (Fig. 1Eb). As mentioned before, it is possible to encounter the optic nerve in an Onodi cell, so care must be taken to avoid an iatrogenic injury to the optic nerve. At a distance of 7–10 mm anterior to the optic tubercle, the lamina papyracea is then removed with extreme care to avoid injury to the periorbita (Figs 1Fa to Fd). Violating the periorbita at this time could result in herniation of the orbital fat into the operative field, obstructing the surgeon's vision. A specially modified diamond drill ideal for endoscopic usage has been developed for thinning out the bony optic canal. This drill is designed so that the rotating burr can be retracted into a protective sheath until it is in the right position for drilling, thus preventing entanglement of the soft tissues in the drill bit. An irrigation system is built into the drill. The drill is now used to thin the bony covering of the optic canal from the orbital apex proceeding posteriorly as it courses towards the optic chiasm. A dissector/elevator modified from the Fisch ear instruments is used to elevate the thinned bony canal from over the optic nerve. Extreme care must be taken not to exert pressure on the optic nerve with the elevators. This completes the bony decompression, resulting in a 180° liberation of the optic nerve on its medial and inferior aspects.

In addition to the bony optic canal, the optic nerve sheath and the annulus of Zinn potentially contribute to pressure on the optic nerve. The opening of the optic nerve sheath and the annulus of Zinn is accomplished with a sickle knife (Figs 1G and H). However, slitting the optic nerve sheath is a controversial procedure for which there are no studies to indicate proper patient selection. In certain cases we routinely open the nerve sheath: these cases include patients with an intrasheath haematoma, fracture of the intracanalicular portion of the optic nerve canal or lateral displacement of the bony optic canal with impingement on the optic nerve as well as cases with papillary oedema and/or bleeding. Also in cases where, upon removal of the bony optic canal, the impression of a bulging optic nerve is obtained, the sheath is decompressed. Avoidance of a potential cerebrospinal fluid fistula with opening of the optic nerve sheath is obtained by placing fibrin glue over the incision site.[85] OND can easily be combined with an orbital decompression at the same sitting if indicated.

As with any surgical procedure, this technique has potential disadvantages and limitations. The lateral and superior aspect of the optic canal cannot be reached by this approach, so decompression is limited to the medial and inferior portions of the bony optic canal. With the opening of the optic nerve sheath, the subarachnoidal space is opened and a cerebrospinal fluid fistula could possibly be created, although clinical experience has not shown this to be a significant problem. Fibrin glue is routinely applied to the region of the optic nerve if the optic nerve sheath is opened to avoid a cerebrospinal fluid fistula.

An iatrogenic injury to the nerve fascicle itself or the ophthalmic artery could occur, resulting in additional damage. Thus, this procedure should only be undertaken by experienced endoscopists. The surgeon must utilise extreme care when incising the optic nerve sheath to be certain that no medially arising ophthalmic artery prevails. A risk of infection, transmitted from the contaminated nasal cavity and paranasal sinus system exists, although we have not encountered any in our cases.[57,64,87,88]

Contraindications to OND exist and these apply not only to the endoscopic approach but to the other surgical approaches as well. Contraindications include complete disruption of the optic nerve or optic chiasm, complete atrophy of the optic nerve, carotid cavernous sinus fistulae and other life-threatening problems making any surgical procedure hazardous.

One should not completely rule out approaches other than the endoscopic approach to OND and each case should individually be evaluated. In patients with large lacerations of the scalp, a transfrontal approach may be the best. If the patient is to undergo a craniotomy for other indications, then the OND should be performed through the craniotomy at the same sitting. An inexperienced endoscopist or a surgeon who has more experience with an external ethmoidectomy approach to OND should proceed with the technique most familiar to him or her.

In the technique described by Yang[95] for endoscopic assisted transorbital decompression, a 0°, 2.7 mm endoscope is placed through a 1 cm medial transconjunctival incision. The subperiosteal dissection is continued posteriorly (Fig. 8A). The anterior and posterior ethmoidal vessels are coagulated to reduce intra-operative blood loss. The bony defect is created in the posterior one half of the orbital medial wall just anterior to the annulus of Zinn to gain access to the medial optic canal ring (Fig. 8B). As the orbital contents are retracted laterally, the thick optic canal ring is thinned by a 3 mm diamond burr and removed with the endoscopic punch forceps gradually (Fig. 8C). After this, decompression of the medial wall and partial roof of the entire optic canal is achieved with a microcurette alone or combined with a small diamond burr in the posterior and superior direction (Fig. 8D). By this technique, the optic canal can be decompressed up to at least 180° medially.

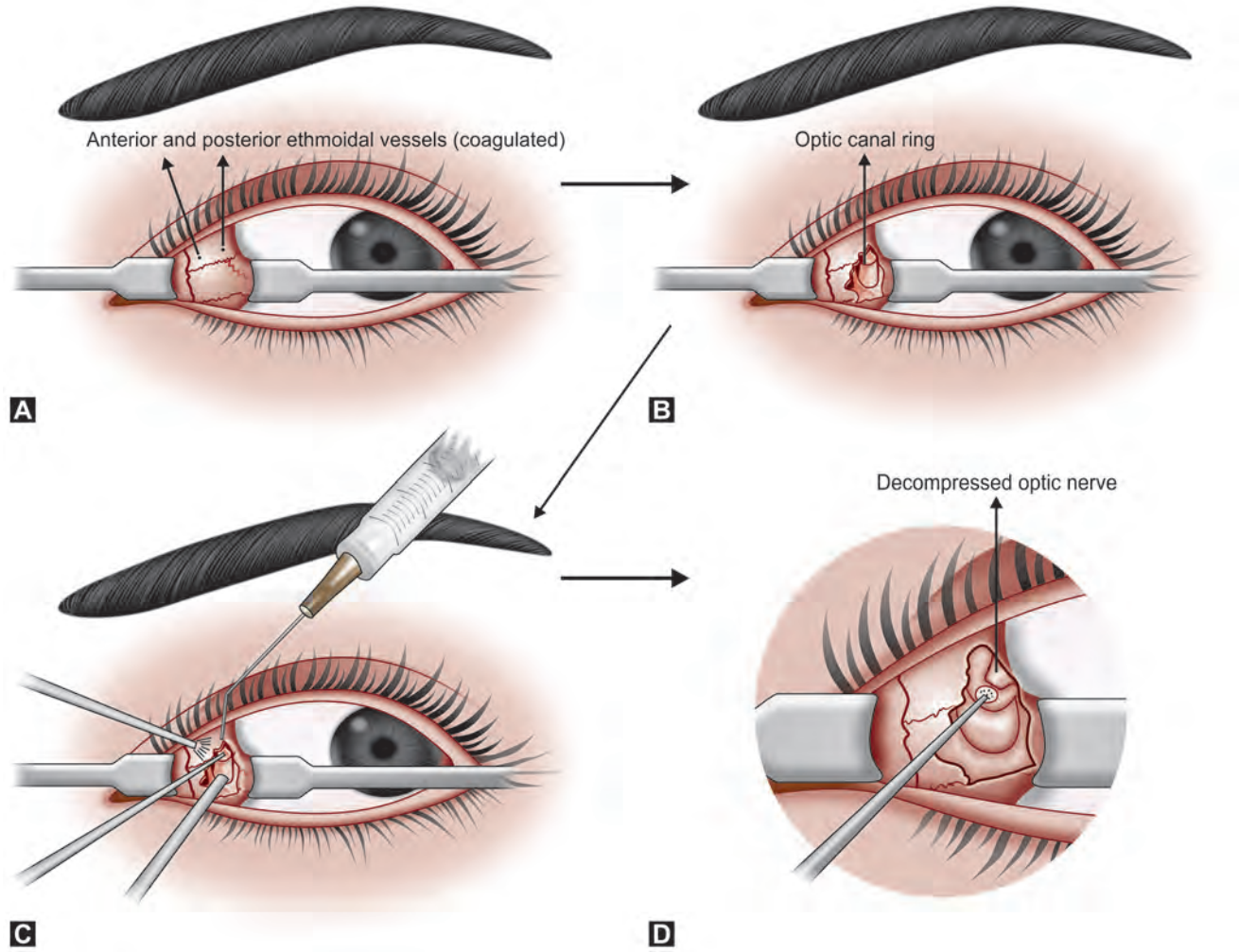
INTERNATIONAL OPTIC NERVE TRAUMA STUDY

The study of International Optic Nerve Trauma Study (IONTS)[9,33] was organised to investigate the optimal treatment of indirect TON (Table 9). It was initially conducted as a randomised controlled pilot study to assess feasibility, one arm being extracranial optic canal decompression combined with very high-dose ("megadose") corticosteroids and the other arm being corticosteroids alone. However, after 2 years of patient recruitment, it became clear that the enrolment of eligible patients would be insufficient to provide statistical validity, even if the study were to continue for several more years. Therefore, the IONTS was transformed into an observational study, with the goal of evaluating which of several treatment paradigms best improved the visual function of patients with indirect TON. Mahapatra contributed the largest number of cases to the IONTS.[67]

A total of 133 patients with TON (127 unilateral and 6 bilateral) who had an initial visual assessment within 3 days of injury were studied. At least 1 month of follow-up was required for inclusion in the primary analysis. On the basis of treatment received within 7 days of injury, patients with unilateral injuries were categorised as being in one of three treatment groups: (1) untreated (n = 9); (2) corticosteroid (n = 85) or (3) optic canal decompression surgery (n = 33). Visual acuity increased by ≥ 3 lines in 32% of the surgery group, 57% of the untreated group and 52% of the steroid group (P = 0.22). The surgery group had more patients whose initial vision was NLP. After adjustment for the baseline visual acuity, there were no significant differences between any of the treatment groups. There was no indication that the dosage or timing of corticosteroid treatment or the timing of surgery was associated with an increased probability of visual improvement. No clear benefit was found for either corticosteroid therapy or optic canal decompression surgery. The number of patients studied was sufficient to rule out major effects in the treatment groups, although clinically relevant effects in specific subgroups could have been missed. These results and the existing literature provided sufficient evidence to conclude that neither corticosteroids nor optic canal surgery should be considered the standard of care for patients with TON. The authors concluded therefore, clinically, it is reasonable to decide to treat or not to treat on an individual patient basis as described in Table 10.[51,72]

OUTCOME AND FACTORS INFLUENCING OUTCOME

Visual outcome in patients with optic nerve injury depends on several factors. In visual recovery, age, mode of injury, unilateral or bilateral involvement, presence or absence of VEP and presence or absence of vision play an important role (Table 11).[28,39,50,55,56,64,70,87,91] In two of our studies in the paediatric age group we reported a recovery which was worse than in the adult. Similarly,



Figs 8A to D: Figure showing steps of endoscopic optic nerve decompression: (A) The medial orbital wall. The anterior and posterior ethmoidal vessels were coagulated. The lamina papyracea will be removed to expose ethmoid sinuses. (B) The lamina papyracea overlying the posterior ethmoid air cells was removed to gain access to the sphenoid sinuses and expose the optic canal ring. (C) A 3-mm diamond burr was used to thin the thick optic canal ring. A straight suction was placed intranasally into the sphenoid sinuses. (D) The decompressed optic nerve. The optic canal ring, medial wall and roof were removed with a microcurette alone or combined with a small diamond burr. The optic canal could be decompressed at least 180° medially

the presence or absence of VEP wave is of great importance.[55,64,70,81,94] Normal VEP indicates a good chance of recovery in all the patients. We find the time interval between injury and surgery and the presence or absence of optic canal fracture is of very little significance. Mahapatra also observed better outcome in patients with bilateral optic nerve injury[17,64] and they also noted only 10% of patients had normal visual recovery and 40–50% had partial visual recovery after optic nerve injury.[56,64,70] Rarely, visual recovery may start 8–12 weeks after injury. Agarwal and Mahapatra reported 23% recovery rate in 100 patients with PL negative vision following optic nerve injury.

Although the degree of visual loss after indirect TON may be quite variable, approximately 50% of patients are left with "light perception" or "no light perception" vision, making TON a significant cause of permanent visual loss.[13,49,86] At present, there is no proven form of treatment for this condition and there is controversy over its optimal management. Cook et al. in a meta-analysis,[14] reported that recovery of vision in patients treated with megadosage steroids or surgical decompression of the optic canal was significantly better than recovery in patients receiving no treatment. As there are no controlled guidelines for correct management, patients affected by TON remain a clinical dilemma. A recent uncontrolled case series reported that visual recovery occurring shortly after trauma may not be permanent at long-term follow-up, with progressive deterioration of visual function.[24,69]

The identification of prognostic signs during the hospital admission of such patients has important implications, as such signs may be used to justify medical or surgical treatment depending on the expected outcome.[14,73] Furthermore, the IONTS group has found that selected cases with initially negative prognostic signs may show clear benefit from treatment versus observation alone. Carta et al.[12] investigated, in their series of 35 cases of TON, for a possible correlation between final

Table 9: Demographic profile of patients included in IONTS[51]

Characteristic	*Total (n-127)*	*No. Treatment (n = 9)*	*Steroids (n = 85)*	*Surgery (n = 33)*	*3 – Group P*	*2 – Group P (Surgery vs all others)*
Age, mean (SD)	34 (18)	40 (26)	33 (17)	38 (18)	0.21	0.06
Male, n (%)	108 (85)	6 (67)	72 (85)	30 (91)	0.42	0.40
Injury type, n (%)					0.05	0.01
Vehicle/bicycle accident	58 (46)	3 (33)	43 (51)	12 (36)		
Assault	18 (14)	1 (11)	11 (13)	6 (18)		
Fall	27 (21)	3 (33)	13 (15)	11 (33)		
Other/unknown	24 (19)	2 (22)	18 (21)	4 (12)		
Loss of consciousness, n (%)					0.04	0.06
Yes	57 (45)	4 (44)	44 (52)	9 (27)		
No	49 (39)	5 (56)	28 (33)	16 (49)		
Unknown/missing	21 (17)	0	13 (15)	8 (24)		
Visual loss immediate, n (%)					1.0	1.0
Yes	85 (67)	6 (67)	57 (67)	22 (67)		
No	13 (10)	1 (11)	9 (11)	3 (9)		
Unknown/missing	29 (23)	2 (21)	19 (23)	8 (24)		
Baseline visual acuity					0.002	<0.001
Unable to test	3 (2)	0	3 (4)	0		
NLP	51 (40)	3 (33)	26 (31)	22 (67)		
LP	13 (10)	0	8 (9)	5 (15)		
HM	17 (13)	1 (11)	14 (16)	2 (6)		
<20/200 to CF	20 (16)	2 (22)	16 (19)	2 (6)		
<20/40 to ≥20/200	11 (9)	2 (22)	8 (9)	1 (3)		
≥20/40	12 (10)	1 (11)	10 (12)	1 (3)		

Table 10: Author's criterion for optic nerve injury management[67]

1. All the patients are put on corticosteroids
2. VEP and clinical examination repeated every 2-3 days for the first 3 weeks
3. Patients showing good visual recovery do not need surgery
4. Patients in whom visual acuity remains PL negative in spite of corticosteroid at the end of 3 weeks do not need surgery
5. Surgery is beneficial in those patients in whom visual improvement is marginal and then remains static
6. One emergency indication for surgery is delayed onset optic nerve injury, when vision rapidly deteriorates in spite of corticosteroids

Table 11: Factors influencing outcome in patients with optic nerve injury as reported by Mahapatra et al.[67]

Factors	*Good prognostic* factors	*Bad prognostic* factors
Age	Adults	Children
Mode of injury	Blunt	Missile/blast injury
Unilateral/bilateral	Bilateral	Unilateral
Positive or negative VEP	VEP +ve	VEP –ve
Vision	PL +ve	PL –ve

visual acuity and the presence at baseline of various systemic and local (orbital/ocular) signs. The authors noted that four variables showed a significantly increased risk for no recovery of visual acuity: (1) presence of blood within the posterior ethmoidal cells (RR = 2.25, 95% CI 1.25– 4.04); (2) age over 40 years (RR = 1.79, 1.07–2.99); (3) loss of consciousness associated with TON (RR = 2.21, 1.17–4.16) and (4) absence of recovery after 48 hours of steroid treatment ($p < 0.01$, Fisher's exact test). Recovery documented at the first follow-up visit after treatment was significantly associated with recovery at the last follow-up visit ($p < 0.01$, Fisher's exact test). Carta[12] concluded that the above four prognostic signs in patients affected by TON may be useful in predicting the visual outcome in patients developing visual loss after head trauma and in deciding on the need for surgical treatment.

Previous laser interferometer studies have shown that forces applied to the frontal bone are transferred and concentrated in the optic canal region.[30] Histopathological studies of patients with indirect injury to the optic nerve have been consistent with localisation of the lesion to this area.[17] Bleeding within the posterior ethmoidal cells presumably reflects a greater amount of energy applied to this region and it should therefore make sense that this sign is associated with a worse visual prognosis. Similarly, as ethmoidal bleeding reflects the local severity of trauma, it could also account for the fact that loss of consciousness is associated with a reduced likelihood of visual recovery. Zapala[97] in their study of 100 patients with unilateral post-traumatic optic nerve neuropathy tried to establish new clinical guidelines for patients suffering from post-traumatic optic nerve neuropathy; 76 were blind and 24 with progressive weakening of visual acuity from the time of injury. 56 patients received conservative treatment only, among them 48 underwent steroid therapy. In 23 patients a decompression of the optic nerve in its canal and in 21 in the intraorbital section was performed. Improvement in vision was obtained in 44 patients, 52 did not improve

and in 4 cases their vision deteriorated.[97] Zapala[97] concluded that post-traumatic optic nerve neuropathy is an indication for immediate steroid therapy and progressive visual loss in an optic nerve canal fracture is an indication for its decompression. Cochrane data base review in 2005 was carried out with the aim to examine the effects and safety of surgical interventions in the management of TON analysing only randomised controlled trials of TON in which any form of surgical intervention either on its own or in combination with steroids was compared to steroids alone or no treatment. The conclusions derived were that the current body of evidence consists mostly of small, retrospective case series. Given the wide range of surgical interventions used in TON, it is very difficult to compare these studies, even qualitatively. However, there is a relatively high rate of spontaneous visual recovery and no evidence that surgical decompression of the optic nerve provides any additional benefit. On the other hand surgery carries a definite risk of complications such as post-operative cerebrospinal fluid leak and meningitis. The decision to proceed with surgery in TON therefore remains controversial and each case needs to be assessed on its own merits. Although there is an urgent need for an adequately powered, randomised controlled trial of surgical intervention in TON, this will prove a difficult endeavour.[96]

Yang et al.[95] retrospectively analysed 42 cases of TON to identify factors that can affect the final outcome and to recognise the proper management for patients with TON after maxillofacial trauma (Megadose methylprednisolone was administered to all patients during the first 3 days after diagnosis. Twenty-four patients received treatment with megadose steroids combined with OND and the remaining 18 with megadose methylprednisolone alone). IVA was the statistically significant factor affecting the outcome of TON (P = 0.006 for improvement rate). Patients treated within 7 days after injury had a better improvement degree, P = 0.056. Patients in a surgical group with an IVA of NLP had a better improvement rate and degree (31.3%; 59.34% ± 22.18%) than those in non-surgical group (0%, 0%; P = 0.272). Yang et al.[95] concluded that IVA is the critical factor that affects the outcome of TON and surgical OND is considerable in maxillofacial trauma patients with an IVA of NLP.

CHIASMAL INJURY

Chiasmal injury is a rare condition. Hughes,[41] in 1962, noted 4.4% chiasmal injury and 7.8% opticochiasmal injury in their series. Only over 100 cases have been reported in the literature so far with the largest series being reported by Mahapatra et al.[48]

Pathological Types of Chiasmal Injuries

Primary:
- Sagittal split or tear
- Transverse split
- Contusion
- Laceration.

Secondary:
- Oedema
- Ischaemia
- Necrosis (infarction).

Pathogenesis

The pathogenesis of chiasmal injury is not clear. However, chiasmal injury can be primary or secondary as observed at operation or at autopsy. Primary involvement could be in form of a tear, laceration or contusion.[1,17,28,40,91] In most of these patients, there is evidence of fracture in the anterior cranial fossa. In closed head injury, due to forehead impact, there is anterior-posterior distortion of the skull, which leads to midline chiasmal tear.[40,78] The usual site of the chiasmal necrosis is at the site of decussation. Contusion and chiasmal necrosis of the central part is seen most commonly in primary chiasmal injuries. The chiasm can also get involved secondary to oedema and ischaemia leading to infarction.

Clinical Findings

Patients are usually adult vehicular accident victims.[48] History of unconsciousness is available in over 90% of cases and the head injury is usually severe in such cases.[22,28,40,41] Chiasmal injury is also described as traumatic bitemporal hemianopia, indirect chiasmal injury or post-traumatic chiasmal syndrome. Bleeding from the nose and CSF rhinorrhoea are commonly seen in these patients.[22,41,48]

Bitemporal hemianopia is the most common field defect seen.[48] Temporal field cut in one eye and no PL in the other eye suggest optochiasmal injury. Rarely, patients may present with visual deterioration due to basal meningitis and arachnoiditis. Other unusual symptoms associated with chiasmal injury are anosmia, pituitary insufficiency and diabetes insipidus.[28,41,91] Rarely, there may be cranial nerve deficit, traumatic aneurysm of ICA and carotid-cavernous fistula (CCF).

Diagnosis

Clinical diagnosis is difficult in unconscious patients. However, when a patient is conscious, diagnosis is made by the history of bilateral temporal defect, confirmed by field charting. CT and MRI have made the diagnosis easy.

Treatment

There is no specific treatment for chiasmal injury. As secondary involvement of the chiasma can occur due to oedema, it is probably rational to prescribe corticosteroids.[35] The role of surgery in chiasmal injury remains unproven.[40,41,52]

Visual Outcome in Chiasmal Injury

Almost all patients develop varying grades of optic atrophy over a period of time. As the central field is retained, daily activities of the patient are mostly unaffected. Recovery occurs over several weeks and depth perception is regained.[69]

Injury to Posterior Visual Pathway

Posterior visual pathway is the portion distal to the optic chiasma. Direct injury to these structures could result due to penetrating injury, either due to bullet or by splinters. However, rarely these structures can get involved in closed injury. Injury to the posterior visual pathway occurs in patients with severe head injury.[22,28,91] Injury to the optic tract, optic radiation and calcarine area has been studied well in war injured patients. In closed head injury the optic tract and optic radiation can get involved in contusion or intracerebral haematoma involving the temporal or parietal lobes. Patients with compression of the posterior cerebral artery due transtentorial herniation may not survive.

Damage to the optic tract, optic radiation or geniculate body is difficult to diagnose in unconscious patients. Cortical blindness does occur with head injury and the outcome is unpredictable.

CONCLUSION

The issue of medical, surgical, combination therapy or expectant management for traumatic injuries of the optic nerve remains unresolved. OND has been reported to have a favourable outcome by many surgeons. Various approaches for OND have been advocated, each with its own advantages and disadvantages. The endoscopic approach to OND, owing to its low morbidity and rapid post-operative recovery merits consideration by the surgeon. Endoscopic OND may allow operative intervention and return of visual function in patients whose medical condition would otherwise contraindicate surgical intervention.

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SECTION

5

Spinal Injuries

Ravi Ramamurthi

47 Assessment and Emergency Management of Acute Spinal Injuries

Anil Pande, Pradeep Kumar Jain N

INTRODUCTION

Spinal injuries are common and their economic and social implications are a problem of great magnitude.[135] The patient is often the only earning member of the family and the consequences of these injuries can be devastating. The annual incidence of spinal cord injuries (SCI) in developed countries varies from 11.5–53.4 per million and the incidence has two peaks, one in the second and third decades of the male population and another in the elderly.[149] Most of the Western studies have shown road traffic accidents as the leading cause of spinal trauma followed by falls, diving into shallow water and sports injuries. Males are more prone to spinal cord injury. Indian epidemiological studies in the rural regions also have shown a high preponderance of spinal trauma involving males, with the ratio of male to female ranging from 9:1–13.5:1.[2,3,9,42,125] In an agricultural country like India, injuries due to fall from trees, unprotected terraces and fall into uncovered wells and specific injuries caused by fall of a coconut on the head are common.

Chacko et al.,[32] Shanmugasundaram[137,138] and Roop Singh et al.[125] found the most common cause for spinal injuries was fall from a height followed by road traffic accidents compared to the West. Gunshot wounds to the spine are comparatively rare in India.[14] About 60% of spinal injuries involve the cervical spine with the maximal incidence at C5-6 level. Bhatoe and Singh reported 22 cases with missile injuries of the spine and the authors emphasised that these can be associated with injuries to other organs. The initial management of these injuries is similar to injuries sustained by other mechanisms. Incomplete injuries and injuries to the cauda equina are definite indications for surgery. Retained fragments rarely lead to infection or delayed neurological deficits and prophylactic removal is not warranted except in cauda equina injury.[16]

In the elderly, the incidence of fractures of C1 and C2 is more frequent due to the relatively high occurrence of odontoid fractures,[94] whereas the incidence of injuries to the subaxial spine is less. The incidence of spinal injuries increased from 1 in 300 to 1 in 14 when seat belts are not used. The use of helmets has not been associated with an increase of spine injuries as was once thought. The absence of national level programmes to educate the public on trauma like "THINK FIRST" is one of the reasons why the actual burden and the large economic cost of spinal injuries continue to escalate in India. The absence of city and town planning leads to a very high incidence of these injuries.

Neurosurgeons must educate the public and policy makers and push for reforms in transportation and civic infrastructure to reduce the incidence of this devastating condition. The setting up of spinal injuries centres in all regions of the country is a priority that has to be met on an emergency basis.

INITIAL TRAUMA EVALUATION

Suspicion of Injury to the Spine

It is mandatory to assume spinal injury in all patients who have significant trauma, with loss of consciousness, altered mental status, evidence of intoxication, spine pain, tenderness or deformity, neurological signs and symptoms of radiculopathy/myelopathy or instability and suspected extremity fractures. Spinal cord injury occurs due to primary and secondary events and surprisingly 3–25% of spinal cord damage occurs after the initial trauma, due to faulty and delayed transportation and inadequate initial management (the golden hour). In addition the primary injury sets off a cascade of cellular molecular events that cause further cell injury and death. Secondary spinal cord injury can also occur due to factors like hypoxia, hypothermia, hyperthermia, hypotension and cardiovascular and respiratory instability.[72,74,78,89] About 20% of spinal injuries involve multiple, non-contiguous vertebral levels and therefore the whole spine must be assessed completely in all such patients.

Clearing the spine[3] is a very important neurosurgical responsibility and must follow stringent criteria. Patients with spinal injuries usually die due to shock and aspiration. The advanced trauma life support (ATLS) protocol specifies; first take care of the airway, followed by assessment of breathing effort, followed by circulation and haemorrhage control ("ABC"s) and thereafter an urgent transfer to a regional spine injury centre.

The patients are seen and evaluated as they are found (as they lie) and the mechanism of injury can be understood from a well taken history and studying the scene of trauma.

PREADMISSION SPINE IMMOBILISATION

All patients suspected to have spinal injury should be managed with spinal column immobilisation till an injury has been definitely ruled out and appropriate treatment has been initiated. Spine immobilisation can reduce the possibility of secondary neurological injury and pain in patients with an unstable spine.[154]

Spine immobilisation consists of a cervical collar, supports on both sides of the head and long and short backboards with associated straps to attach and immobilise the body (Fig. 1). The earlier practice of spine immobilisation using sandbags and tape alone is insufficient. A vacuum splint device, particularly when used with a cervical collar is an effective and comfortable alternative to a rigid board.[31] Kendrick extrication device, extrication plus-one device and Russel extrication device have also been used.[58]

Any limb fracture is also strapped and immobilised. Thoracic elevation or an occipital recess to prevent flexion of the head and neck when restrained supine on an otherwise flat backboard may allow for better neutral alignment and immobilisation of the cervical spine in children younger than 8 years due to the relatively large head in these younger children, and is recommended.[31,61,107]

TRANSPORT OF SPINAL INJURED PATIENT

Definitive assessment, resuscitation and care of patients with an acute spine injury cannot be given at the site of injury and optimal care includes initial resuscitation, immobilisation and early and proper transport to a spinal injuries centre. The transport vehicle should be equipped with respiratory and vascular support measures and the most rapid mode of transport is chosen.[150] Rural areas account for 70% of serious accidents and the mortality rates are 4–5 times higher. The distance to the spinal injury centre and extent of the patients' injuries are the best determinants of the mode of transportation. An ideal situation demands an on-board anaesthetist who can provide respiratory, cardiac and haemodynamic monitoring, resuscitation and intubation if necessary, thereby reducing morbidity and mortality.[150] Survival and outcome for patients with SCI are determined by rapid medically supervised transfer to a specialised centre and initial management in the intensive care unit (ICU).[105,150]

All developed countries possess an effective trauma-care and transport system, which transports the victims, within the first 12–24 hours, to the spine injuries centres in well-equipped ambulances or helicopters. The lack of any such effective transport system in India is a very sad reality. In a study Upendra et al.[152] found that only 59.1% of the victims reached the treating centre within the first 48 hours and only 47.7% of the patients with spinal trauma were transported in an ambulance. Most of the victims were shifted 2–4 times between various health-care centres before reaching the definitive spinal-care centre. Only 7.27% of the patients were transferred directly to the centre, and the average number of transfers was 3.4 per patient. Chacko et al.[32] highlighted that an ambulance is used to transfer only 34% of spine injured patients in rural India. Most of the victims are transferred by relatives of the patient in cars, rickshaws, jeeps, etc., with little knowledge of the importance of spinal immobilisation. Pandey et al.[114] reported that there was an average of 45 days (range 0–188 days) of delay in presentation to a specialised spinal unit and most of the time the cause for the delay was unawareness on the part of patients and doctors regarding specialised spinal units. Early presentation of spinal injured patients to a spinal unit enables early surgery, which is beneficial in terms of reducing complications, length of stay and hospital cost.[150]

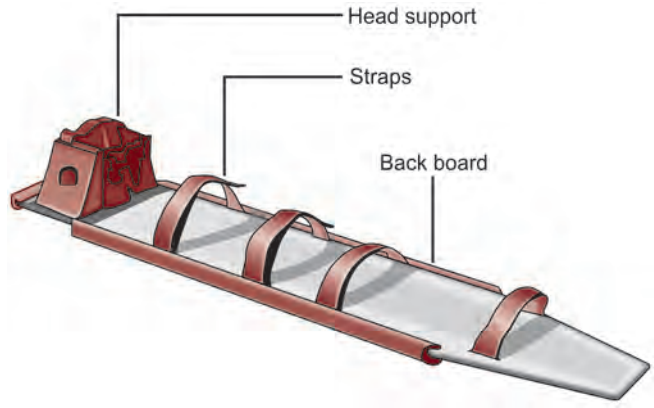

Fig. 1: Spine board

EVALUATION AND TRIAGE

Once the patient reaches the centre, the initial evaluation and triage of the patient is done by the anaesthetist, neurosurgeon, general or trauma surgeon, orthopaedic surgeon and if necessary a vascular surgeon. An urgent initial general evaluation is done to decide on what is to be done first.

CLINICAL EVALUATION

Evaluation of suspected cervical spine injury includes taking a careful and detailed history with attention to mechanism of injury and whether the patient had any neurological symptoms immediately after the event and loss of consciousness, seizures and ENT bleed should alert the neurosurgeon about an associated cranial injury.[4] The clinical examination and radiographic evaluation follows and is used to ascertain the presence of instability, identify neurological deficits, guide management and predict the outcome. During the course of initial assessment, patients are kept in the supine position with rigid collar immobilisation while standard ATLS protocols are followed.

Clinical examination of spinal injury patients is very important and should be very thorough, but has been found to have a sensitivity of only 77% in blunt trauma patients.[50] For a complete assessment the patient must be awake, alert, non-intoxicated and without any serious systemic injuries. Patients with high risk for spine injury include those with facial fractures, polytrauma, closed head injury and those with blunt and penetrating neck injuries. The attending neurosurgeon must get a very careful history about the injury mechanism and its injury severity score (ISS)[4] is calculated (Tables 1A and B). Clinical protocols for determining the need for radiography have been developed, such as the NEXUS low risk criteria [(NLC) Table 2] and the Canadian C-spine (CCS) rule (Fig. 2), which are used to aid in emergency room triage. Stiell et al.[146] found that the CCS is superior to NLC in sensitivity and specificity.

The clinical examination[38] includes inspection and palpation of the spine, and a complete neurological examination, and a general examination is mandatory to rule out polytrauma. Systemic examination to look for bruises, ecchymosis and abrasions will point towards the possible region of spinal injury.

Table 2: The NEXUS low-risk criteria

Cervical-spine radiography is indicated for patients with trauma unless they meet all of the following criteria:
1. No posterior midline cervical-spine tenderness
2. No evidence of intoxication
3. A normal level of alertness
4. No focal neurologic deficit
5. No painful distracting injuries

Beevor's sign: The patient is asked to lift the head with the examiner gently pressing on the forehead and, if the lower abdominal muscles are weaker (below T-9), the umbilicus moves upwards. Priapism indicates a loss of sympathetic tone and is an indicator of poor prognosis in spinal injuries.

Bulbocavernosus reflex is elicited by gently squeezing the glans penis or tugging an indwelling Foley's catheter. A normal response in the form of contraction of the anal sphincter is noted. This reflex is lost if there is injury to the conus medullaris or cauda equina. A negative response in the absence of injury to the conus or cauda equina is suggestive of spinal shock. This is the first reflex to return after spinal shock.

Table 1A: Injury severity score

Region	*Injury description*	*AIS*	*Square only the top three*
Head and neck			
Face			
Chest			
Abdomen			
Extremity			
External			

The injury severity score (ISS) is an anatomical scoring system that provides an overall score for patients with multiple injuries. Each injury is assigned an abbreviated injury score [(AIS) Table 1B] and is allocated to one of six body regions [head, face, chest, abdomen, extremities (including pelvis), external]. Only the highest AIS score in each body region is used. The three most severely injured body regions have their score squared and added together to produce the ISS score. The ISS score takes values from 0–75. If an injury is assigned an AIS of 6 (unsurvivable injury), the ISS score is automatically assigned to 75

Table 1B: Abbreviated injury score (AIS)

AIS score	*Injury*
1	Mild
2	Moderate
3	Serious
4	Severe
5	Critical
6	Unsurvivable

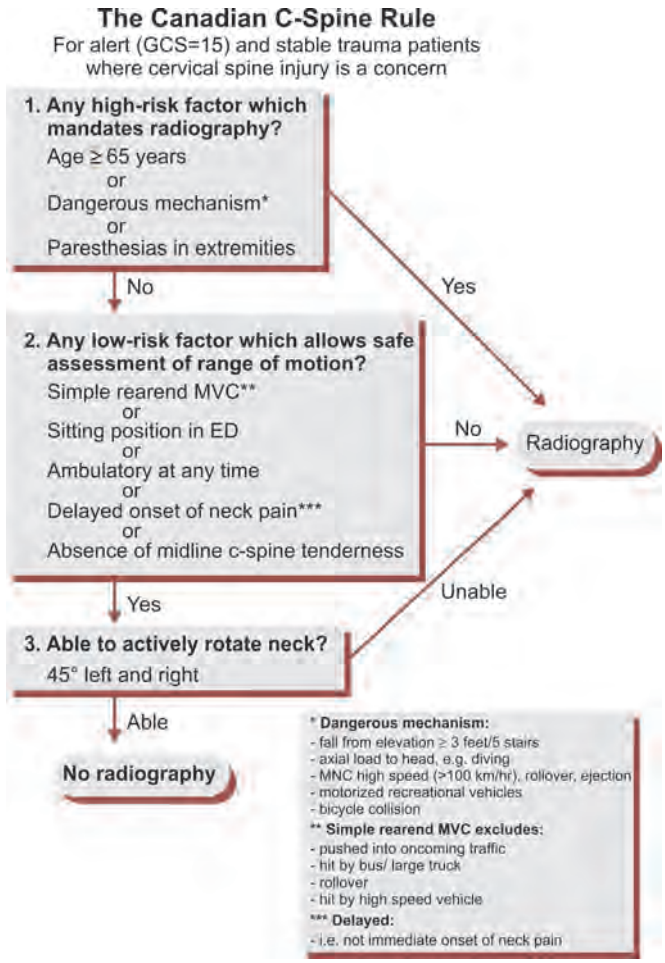

Fig. 2: Canadian C-spine rule

The motor, sensory and autonomic nervous system is rapidly assessed using the American Spinal Injury Association (ASIA) score.[63] Cranial nerve (CN) involvement (VI, VII, IX, X, XI and XII) can occur in association with upper cervical spine injuries or these may be due to associated cranial trauma. Missing other systemic injuries is very common since patients with spinal injury can have concurrent injuries to one or more organ systems.

SPINAL INJURY GRADING SYSTEMS

After the initial general and neurological examination, grading systems, like Frankel's and the currently used ASIA score, are used to standardise the clinical evaluation.

Frankel Grading System

Frankel divided spinal injuries into five gradations with decreasing neurological deficits:

Grade A: Complete loss of motor and sensory function below the level of lesion.

Grade B: Complete motor paralysis with some sensory preservation (e.g. sacral sparing)

Grade C: Retained motor function but useless

Grade D: Useful motor function

Grade E: Free from neurological symptoms

ASIA Score

The ASIA score for neurological and functional classification of spinal cord injury is recommended as the preferred neurological examination tool for clinicians involved in the assessment and care of patients with acute SCI.[63] This is a point score and is used in the initial evaluation and the assessment includes motor and sensory neurological level, completeness of the injury and zone of partial preservation. The motor and sensory levels are the most caudal segment of the spinal cord with normal function on both sides of the body. The most caudal muscle must have grade III power. The assessment of sacral sensations is very important because it may be the only evidence of neurologic function distal to the injury. It is important to distinguish between complete and incomplete injuries as complete injury has a poor prognosis (Figs 3A and B).

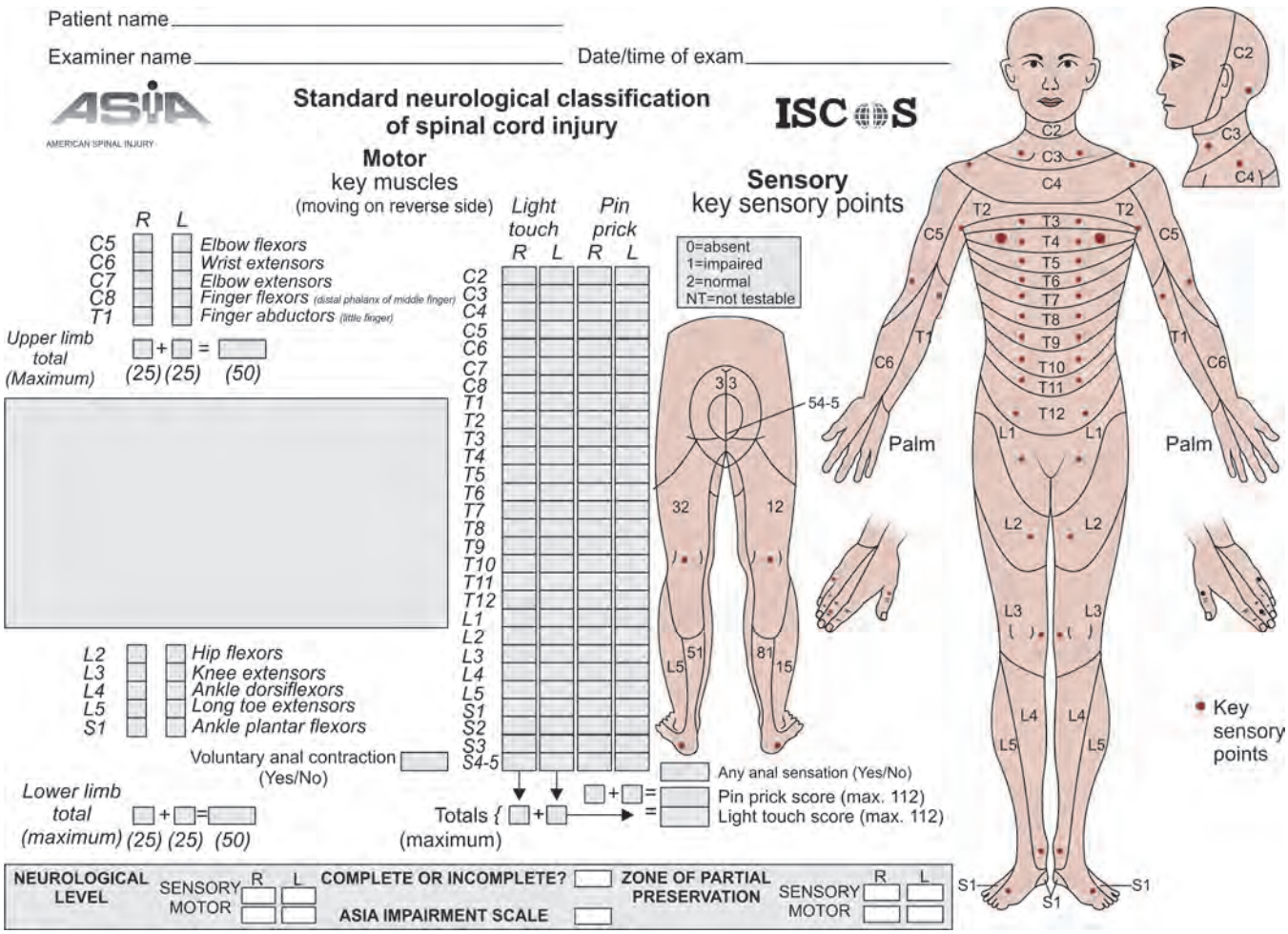

Fig. 3A: ASIA impairment chart

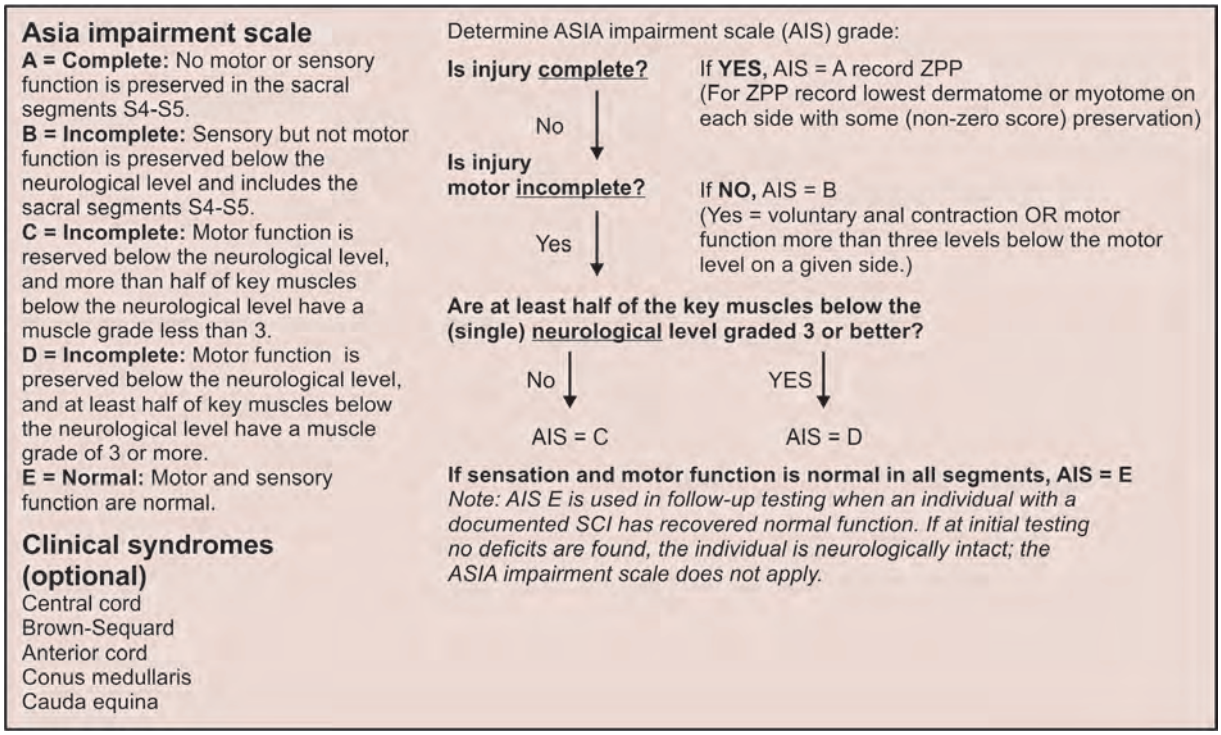

Fig. 3B: ASIA impairment score

SPINAL SHOCK

It is the transient loss of all neurologic functions including segmental and polysynaptic reflex activity and autonomic function which causes flaccid paralysis and areflexia; which can be of variable duration (1–2 weeks) rarely months and sometimes can be permanent below the level of injury.[12] Complete and incomplete injuries can be discriminated only after the spinal shock has elapsed.

SPINAL CORD NEUROPRAXIA

Torg et al.[148] have analysed this transient neurological deterioration that occurs during sport activity and found that the narrowing of the sagittal diameter of the cervical canal in the adult spine was the main causative factor. Cervical cord neuropraxia was not associated with permanent neurological injury and no permanent morbidity occurred in patients who returned to contact activities. But of the patients returning to contact activities, 35 (56%) experienced a recurrent episode.

WHIPLASH INJURIES

An injury caused to the muscles, ligaments, discs and facet joints of the neck by hyperextension, hyperflexion or rotational excessive forces, with no fracture, fracture dislocation or disc herniation is called a whiplash injury. Occipital neuralgia, headaches, cognitive impairment and lumbago are commonly associated symptoms.

Incomplete Injury

It implies the presence of motor and sensory function more than three segments below the injury. The term "sacral sparing" is used to indicate preserved perianal sensation, voluntary rectal sphincter contraction or voluntary toe flexion.

Complete Injury

Complete injury of the spinal cord is the loss of all motor, sensory and autonomic function more than three segments below the level of injury.

SPINAL INJURY SYNDROMES

Spinal trauma can manifest clinically in differing ways. The common presenting syndromes are the Bell's cruciate paralysis, anterior cord syndrome, posterior cord syndrome, Brown-Sequard syndrome, central cord syndrome, conus medullaris syndrome, cauda equina syndrome and cord transection.

BELL'S CRUCIATE PARALYSIS SYNDROME

This syndrome is characterised by weakness and paralysis of the hands and arms and relative sparing of the lower limbs. It is seen usually in patients with cervicomedullary injuries; most common are C2 fractures. The upper limb fibres of the corticospinal tract decussate at a higher and more central level and thereby the lower limb weakness is less.

ANTERIOR CORD SYNDROME

This is characterised as a syndrome involving the anterior and lateral motor corticospinal tracts (motor level) and spinothalamic tracts (pain and temperature) and the sparing of posterior column function (two point discrimination, position sense and deep pressure sense). In trauma, this can result due to injury of the anterior spinal artery or anterior cord pressure by a prolapsed disc, dislocated bone or osteophytes.[133]

POSTERIOR CORD SYNDROME

Injury to the posterior part of the spinal cord by a depressed laminar fracture or contusion has minimal motor signs but is characterised by pain and burning paraesthesias.

BROWN SEQUARD SYNDROME[29]

This syndrome is not frequent[126] and is seen in only 2–4% of traumatic injuries and consists of unilateral involvement of the corticospinal tracts, and posterior column tracts. On the contralateral side of the lesion, the spinothalamic tract is involved causing dissociated sensory loss, i.e. loss of pain and temperature (lateral spinothalamic tract) and preserved light or crude touch (anterior spinothalamic tract).

CONUS MEDULLARIS SYNDROME

The conus medullaris is located between D11-L1,2 and thoracolumbar fractures can cause injury to the conus and this is characterised by symmetrical weakness of the lower limbs, flaccid rectal tone and bladder involvement.

CAUDA EQUINA SYNDROME

Cauda equina syndrome occurs as a result of a traumatic lesion below L2 that occurs at the level of the cauda equina roots presenting as asymmetric pain, sensory loss and bowel and bladder disturbances.

CENTRAL CORD SYNDROME

Central cord syndrome, described by Schneider et al. In the 1950s,[129,132,134] is the most common type of incomplete spinal cord injury.[23,65] This usually occurs in a patient who has a primary or secondary canal stenosis and when an extension injury occurs in the presence of large osteophytes. There is greater motor involvement of the upper limbs with relative sparing of the lower limbs with bladder dysfunction and variable sensory disturbance ("man in a barrel" syndrome, burning hands syndrome). Spinal cord injury here is due to compression between the disc-osteophyte complex and an in-buckling ligamentum flavum.[134] The long tract fibres of the upper limb are located in the central region of the cord, hence, when an injury is more in the centre, the upper limbs are more involved. The treatment protocol for these injuries as proposed by Hardop et al.[81] includes:

- Patients less than 50 years of age with a traumatic injury and instability warrant operative intervention.
- Patients less than 50 years of age with an acute disc herniation may benefit from an anterior decompression.
- The benefit of surgical intervention in "classic" central cord syndrome in elderly spondylotic patients is uncertain.[25,35,51,56,73,103]

SPINAL INSTABILITY

Stability of the spine has been defined by White and Panjabi as "the ability of the spine under physiologic loads to maintain an association between vertebral segments in such a way that there is neither damage nor subsequent irritation of the spinal cord or nerve roots and, in addition, there is no development of incapacitating deformity or pain due to structural changes". White and Panjabi have provided a scoring system that has been widely adopted in predicting the presence of instability on cervical radiographs that have segmental kyphosis greater than 11 degrees and anterolisthesis greater than 3.5 mm of one vertebral body on another. Guidelines for determining instability are published and at times instability must be assumed on clinical and radiological clues. When there is involvement of anterior elements the injury is unstable in extension. A posterior column injury is unstable during flexion. Delayed instability is that which is recognised only 20 days after injury after initial pain and muscle spasm have subsided.[45]

Degrees of Instability

- First degree is mechanical.
- Second degree is neurological.
- Third degree instability is a combination of both.

RADIOLOGICAL ASSESSMENT

For optimal examination of patients with suspected cervical spine injuries, it is recommended that specific diagnostic algorithms including complete sets of proper radiographs with functional flexion/extension views, secondary evaluation of the radiographs by experienced staff, and further imaging like computed tomography (CT), magnetic resonance imaging (MRI) has to be done. Guidelines for symptomatic and asymptomatic patients have been published.[122,123] Bono et al.[24] emphasised that analysing radiographic findings should be only done using a standardised and uniform set of measurement techniques. Only through prospective studies can the clinical significance of these imaging characteristics be fully appreciated.

X-Rays

Plain X-rays are still the initial investigation and are used in the initial evaluation of spine injuries,[36] and doing a

cross table lateral, AP and open mouth odontoid views are standard.[122] The threshold for getting an X-ray of the suspected region should be very low when a possible spine injury is suspected.

Cross Table Lateral View

The radiographic features which are looked for in a lateral view are the presence of soft tissue swelling anterior to the vertebral bodies; a loss of the normal smooth cervical lordosis with special attention to the normal lordotic lines; disc space narrowing; segmental kyphosis; antero or retrolisthesis of one vertebral body relative to another and spreading apart of the spinous processes, chip and tear drop fractures and opening of the anterior disc space.[22] In elderly people and in patients with DISH and ankylosing spondylosis careful evaluation of the fracture of the anterior osteophyte may help to localise the injury.

Anteroposterior view X-ray is studied for alignment, canal encroachment, and pedicle morphology. Foreign bodies, like nails and bullets, are also visualised well on these X-rays. False positive X-rays are not infrequent and may require re-evaluation by CT and MRI.[97]

Oblique view X-rays demonstrate the uncinate process, pedicles, superior and inferior facets and the laminae, and will show the neural foramina which may be blocked by a unilateral locked facet. The articular facets and laminar alignment can also be studied.[15]

The swimmers view is also called the "twining view" and while taking this view the X-ray tube is positioned above the opposite shoulder and the film is placed centred on the axilla with the arm raised above the head, the tube angled 10–25 degrees towards the head and this is used to visualise the cervicothoracic junction.

Oblique pillar view of the dens is used to visualise the articular masses and C2 fractures. The head is rotated to one side and the X-ray tube is off centred 2 cm from the midline in the opposite direction and the beam is angled 25 degrees caudally centred at the superior margin of the thyroid cartilage.

Synchondroses of the atlas can be mistaken for odontoid fracture, but a fracture can pass through the synchondroses and this can be difficult to interpret and may require dynamic imaging on MRI.

Pseudospread of the atlas is due to a normal but disproportionate growth of the atlas on the axis and can be misdiagnosed as a Jefferson's fracture. More than 2 mm of total overlap of the C1 lateral masses on C2 on the AP view is common in children aged 2–5 years.

Pseudosubluxation is seen in children in the presence of spasm and when the X-ray is not taken in a true neutral position. This is usually seen at C2-3, C4-5 and C5-6 in children older than 10 years.

Missed diagnosis of a spinal injury is usually attributed to:

- Not taking an X-ray.
- Radiological misinterpretation.
- Incomplete sets of radiographs.
- Inadequate poorly taken radiographs (which do not show the level of the injury) and, finally, failure of the treating surgeon to see and properly interpret the X-rays.

Computerised Tomography

The CT remains the most valuable modality to assess cranial trauma, visualising bone, blood and contusions very well. It is very often used to screen the whole spine and specially the cervicothoracic junction, which is usually not visualised well on routine X-rays even with the shoulders pulled down. Sharma et al.[140] reported that cervical spine radiographs were false negative in 29% of patients, who were found to have SCI on spine CT. Spine CT had 98% sensitivity and detected 45% additional injuries in cervical spine X-ray positive patients. The advantages of CT are its easy availability, rapidity of the latest generation scans and the "One Stop"[28] ability to rule out polytrauma, thus making it a good screening tool. Brandt et al.[28] have suggested that data collected from CT scans obtained for workup of chest or abdominal injuries can provide data that is sufficient to screen for spinal fractures and this can decrease the cost and time of spine evaluation after trauma. The CT can miss ligamental and soft tissue injuries. Studies have suggested that CT alone is sufficient for spine injury clearance in unreliable patients based on follow-up MRI. But newer generation CT continues to miss injuries in patients. The MR changed the management in 7.9% of patients having had an admission CT with no acute injury.[110,117]

The CT based spine clearance protocols have been published.[128] Thin cuts (1.5–3 mm) CT followed by 2D, 3D sagittal reconstruction is done in regions where an injury is suspected. The body, posterior arch fractures, facet fractures, dislocations of facets, C1-C2 injuries and intracanal fragments are best seen on a CT. Spiral CT is widely available and has largely replaced traditional plain radiography in many institutions.[10] Spiral CT has been found to have a sensitivity of 99% and specificity of 100% and the risk of missed spine injury is 0.04%.[8,109,117,118,142] The CT scan of the chest and abdomen should be done immediately if blunt visceral trauma is suspected and chest X-ray or ultrasound abdomen show signs of injury.

CT Myelogram

CT myelogram is done where MRI is not available or is contraindicated in patients with a pacemaker or metallic implants.

CT Angiogram

The CT angiogram may be required for studying vertebral artery injuries or to rule out an anomalous vertebral artery course, especially when planning transarticular screw fixations.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is currently the investigation of choice for imaging the traumatic spine. The MRI visualises ligamentous injuries, disc injuries and herniations, compression of the neural elements, cord oedema, contusion, haematomas (EDH, SDH, SAH) and haematomyelia, and provides information which helps in neurological prognostication. Signal intensity changes in the cord may be due to repetitive cord trauma as seen in chronic segmental instability of cervical spondylotic myelopathy. In patients on traction and on ventilator support, precautions have to be taken, e.g. MRI compatible traction sets and ventilators with long circuits are used. Central cord injury is well characterised by MRI.[51] Ligamentous injury is seen as increased signal on T2-weighted images due to oedema and disrupted ligaments demonstrate a discontinuity in the normal low signal intensity of the ligament. This is very useful in studying craniovertebral junction injuries where a disrupted ligament may be the only sign of instability. Vertebral artery injuries can be visualised on the MRI and MR angiography will give more details.

Dynamic Imaging

Dynamic X-rays, dynamic fluoroscopy, dynamic CT[55] and MRI flexion and extension are useful to assess instability.[79] These should be done very cautiously and in patients who are conscious and oriented. They are avoided if instability is apparent or is clinically obvious.

SPINAL SCREENING

A new tool total imaging modality (TIM) is very useful in picking up a second noncontiguous injury. If this is not available CT screening or X-ray screening of the whole spine is mandatory in high-risk cases, e.g. fall from significant height or polytrauma. A suspicion of noncontiguous spinal injury must be maintained in all patients with known spinal injuries as they have an incidence of 15–20%.[140] Sharma et al.[140] recommend that assessment of the entire spinal column should be done in patients with spinal column injuries.

CLASSIFICATION AND A BRIEF OVERVEIW OF SPINAL TRAUMA

Spinal trauma is a problem with a wide spectrum from spinal cord neuropraxia and minor ligamentous injury to severe osteoligamentous rupture with spinal cord transection.

Classification systems of spine injuries have been developed to predict instability, standardise injury types and guide standardised management protocols. These systems are specifically designed for each region of the spine. Nicoll, in 1949, identified stable and unstable spinal injuries.[19] Holdsworth recognised the importance of the mechanism of injury and classified injuries into five types. Whitesides proposed a two column crane hypothesis with the anterior body and disc being the weight bearing structures and the posterior elements acting as the guy ropes. Louis pioneered the 3 column concept and differentiated between osseous and temporary instability and chronic instability due to discoligamental injury. Lob, Bohler and Roy-Camille further modified these concepts and Denis[46] added the middle column (the posterior part of the anterior column) which had to be injured to create acute instability. McAfee combined the Denis model with the White and Panjabi classification and, using CT, simplified the classification according to the type of failure of the middle column.

OCCIPITOCERVICAL DISLOCATION

Occipitocervical dislocation is uncommon and has high mortality.[6,45] These injuries are more common in children and may be asymptomatic or with CN involvement and cord injury. Classification of these injuries is based upon the displacement of the occiput:[80]

- Type I injuries are anterior subluxations and are the most common.
- Type II injuries have vertical distraction greater than 2 mm of the atlanto-occipital joint.
- Type III injuries are posterior dislocations and are rarely reported.

Traction is contraindicated. Treatment options are immobilisation, but an occiput to C2 fusion is usually required to provide long-term stability.

OCCIPITAL CONDYLE FRACTURES

Occipital condyle fractures[8,21,112] have been reported to occur in 3–15% of trauma patients. These present with lower CN deficits and cord injury. Anderson and Montesano[8] have classified them into different types. Type I fracture, which is a result of axial loading and lateral bending and there is no instability. Type II is a skull base fracture that extends into the occipital condyle. This is also a stable injury, because the alar ligaments and the tectorial membrane are not injured. Type III is an avulsion injury of the occipital condyle. If there is disruption of the alar ligaments and tectorial membrane, then potential for instability exists. Traction should be avoided as it is associated with a risk of neurological deterioration. Type I and II fractures are typically treated conservatively with immobilisation in a rigid cervical collar for 6–8 weeks. Type III may require occiput to C2 fusion.

ATLAS FRACTURES

Atlas fractures comprise 1–3% of all spinal injuries and 3–13% of cervical spine fractures.[75,86,91,95,99] The common mechanism of injury is axial loading. Type-I fractures involving a single arch. Type-II burst fracture of C1 (Jefferson's fracture),[83] Type-III Lateral mass fractures. Fractures without injury of the transverse ligament or

associated with bony avulsion of the transverse ligament can be treated with halo-brace immobilisation and instability may be excluded with flexion-extension imaging. Surgical fixation is recommended for injury of the transverse ligament with instability. Posterior arch fractures are the most common and are typically bilateral, and these are stable. Lateral mass fractures are usually unilateral and may be unstable if there is associated ligamentous injury.[30,58]

AXIS (C-2) FRACTURES[70,90]

The fractures of C-2 are: (1) Odontoid fracture; (2) Hangman's fracture and (3) Miscellaneous C-2 fractures.

Odontoid Fractures

Odontoid fractures are common cervical spine fractures, representing up to 10–20% of all cervical spine fractures and are often missed.[1,54] They have a bimodal incidence, with the first peak in young patients in association with high-velocity trauma; and the second peak occurring in elderly patients.[94,98] The Anderson and D'Alonzo classification[7] is based upon the location of the fracture line.

Type I fracture is the least common. The fracture line occurs at the tip of the odontoid. These are usually stable injuries and have a high union rate, and are treated conservatively.

Type II fractures are the most common. The fracture line is at the odontoid base and these have a high incidence of nonunion.[1]

Type II(a) are comminuted fractures involving the base of the dens with associated free fracture fragments and these form 5% of type II fracture. These are very unstable and managed by posterior fusion of C1 and C2.

Type III fractures are fractures of the odontoid which extend into the body of C2. These have a much higher union rate, with only 8% going on to nonunion. Factors associated with higher rates of nonunion are age greater than 65 years, smoking[11] and displacement greater than 5 mm or angulation greater than 10 degrees. Anterior odontoid screw fixation or a posterior fusion may be necessary.

Traumatic Spondylolisthesis of the Axis

Traumatic spondylolisthesis[41,53,66,76] of the axis called, "Hangman's fracture" by Schneider,[131] is a bilateral pars interarticularis fracture of C-2 with a C2-3 subluxation. The Effendi classification[57] modified by Levine is in current use. Type I is a bilateral pars fracture with a vertical fracture line, less than 3 mm of displacement and no angulation. Type 1(a) has an "atypical" fracture pattern[101,145] and the fracture runs through the posterior body of C2. Type II injuries have a vertical fracture line with displacement of greater than 3 mm and significant angulation and with associated fracture of the anterior and superior endplate of C3. Type II(a) fractures, representing 10% of "Hangman's" fractures differ from Type II fractures and have an un-displaced oblique fracture of the pars, but with angulation which is greater than 15 degrees. They are associated with severe disc and posterior longitudinal ligament (PLL) injury caused by a flexion-distraction injury force. A Type III fracture is a Type I fracture with bilateral C2-3 facet dislocation.

Miscellaneous C-2 Fractures

These include fractures of C-2 lamina, spinous process facets and lateral mass, and these may require external immobilisation or Halo immobilisation, if unstable.

ATLANTOAXIAL DISLOCATION

It occurs due to ligamental injury involving C-1, C-2 and rarely due to Os Odontoidium.[47,48]

Atlantoaxial Rotatory Instability

It is an uncommon injury in the adult patient population and may be associated with other upper cervical spine fractures. Fielding and Hawkins classification: Type I—Rotatory fixation without anterior displacement of the atlas. Type II—Rotatory fixation with anterior displacement of the atlas of 3–5 mm. Type III—Rotatory fixation with anterior displacement greater than 5 mm. Type IV—Rotatory fixation with posterior displacement.

Atlanto-Dens Instability

Atlanto-dens instability is usually a result of injury of the transverse ligament and occasionally the alar ligaments and tectorial membrane. It is usually due to a flexion injury and is assessed by a measurement of the anterior atlanto-dens interval. In adults up to 3 mm is considered normal.

OS ODONTOIDEUM

It is an ossicle with smooth circumferential cortical margins representing the odontoid process that is separate from the body of C2.[37,113,143] It is of two types: (1) Orthotopic type—an ossicle that moves with the anterior arch of C1 and (2) Dystopic type—an ossicle that is fused functionally with the basion and can sublux anterior to the arch of the atlas. Patients who develop instability and have neurological deficits are surgically fused. Transoral decompression may be considered in patients with os odontoideum who have irreducible ventral cervicomedullary compression.

COMBINATION FRACTURES OF C1-C2

Treatment of atlas-axis combination fractures is based on the specific characteristics of the axis fracture. External immobilisation of most C1-C2 combination fractures is recommended. C1-Type II odontoid combination fractures with an atlanto-dens interval of 5 mm or more and C1—Hangman's combination fractures with C2-C3

angulation of 11 degrees or more should be considered for surgical stabilisation and fusion. In some cases, the surgical technique must be modified as a result of loss of integrity of the ring of the atlas.[106]

SUBAXIAL CERVICAL SPINE TRAUMA (C3-T1)[100,151]

Subaxial spine traumatic lesions are classified according to Allen and Ferguson's[5] classification into six groups based on the initial force of injury and the position of the spine at the time of injury.

Flexion Injuries

These are caused by vehicular accidents, falls and diving into shallow water and constitute 15% of all cervical trauma.

A. Flexion-compression injuries: Posterior element fractures occur in 50% of compression flexion injuries.
B. Flexion-distraction injuries: These types of injuries are the most common injury patterns in Allen and Ferguson's classification and range from mild posterior ligamentous sprains, subluxations and severe bilateral facet dislocations.[15,24,52,77,130]
C. Vertical compression injuries:[13] These types of injuries result in examples of cervical burst fractures and are the most severe injury. The C6 and C7 bodies are exposed to greater axial compression and flexion loads and are prone to develop burst fractures.

Extension Injuries

A stage I lesion is manifested by abnormal widening of the disc space due to disruption of the ALL and disc. In the stage II lesion, the posterior ligaments are also disrupted and the upper vertebrae retropulse into the canal.

Thoracolumbar Injuries

These are common and are usually associated with severe abdominal and vascular injuries. The McAfee classification based on CT scans describes six types and uses the Denis three column model of stability:[26,46,84,102,109]

1. Wedge compression fractures are failures of the anterior column.
2. Burst fracture is a combined anterior and middle column injury. Surgery is indicated when there is neurological deficit, an angular deformity of more than 20 degrees, 50% canal compromise and reduction of anterior body height by 50%.[34]
3. Seat belt fractures are severe injuries and involve flexion compression of the anterior column associated with distraction and failure of the middle and posterior columns.
4. Fracture dislocation is a three column injury.

Sacral Injuries

Sacral fractures[68,127] are caused by fall from a height and seen in association with pelvic fractures. The neurologic deficits in pelvic fracture are due to associated sacral fractures. These have been classified into three zones.

Zone I: Fracture involving the ala and sparing the central canal.

Zone II: Fracture involves the sacral foramina on one side causing L5, S1 and S2 involvement with sciatic pain.

Zone III: These fractures involve the canal and cause sphincter disturbance and saddle anaesthesia. Zone III fractures are divided into vertical and transverse types; vertical associated with pelvic fractures while transverse are associated with severe deficits.

Intensive Care Management of Spinal Injuries

In the emergency department the "Trauma Team" comprises of an anaesthetist, intensivist, general surgeon, orthopaedic surgeon and the neurosurgeon. Simultaneously and quickly they evaluate the patient.

Potentially life threatening cardiac and respiratory events occur within the first 2 weeks after the injury and patients with severe injuries (ASIA grades A, B) benefit the most when initially they are kept in the ICU for 7–14 days after injury.[105]

Management of patients with acute spinal cord injury, particularly patients with severe cervical level injuries, in an ICU or similar monitored setting is recommended.[103,105] Use of cardiac, haemodynamic and respiratory monitoring devices to detect cardiovascular dysfunction and respiratory insufficiency in patients after acute cervical spinal cord injury is routine.

Cardiovascular

This intensive care management[104,105] is critical to prevent life threatening cardiovascular instability and respiratory insufficiency and to maintain mean arterial pressure at 85–90 mm Hg for the first 7 days after injury, which may improve spinal cord perfusion and neurological function.[20] Guha et al.[74] recommend that normotension should be attempted, irrespective of the severity of spinal cord injury. Induced hypertension after severe spinal cord injury was not found to be beneficial in improving spinal cord blood flow at the injury site while potentially increasing the risk of haemorrhage and oedema. Measures are taken to control bleeding. Intravenous (IV) access and fluid resuscitation must be started with 0.9% saline or ringer lactate solution. Fluids are replaced with colloids, crystalloids and, if required, with blood. If a pressor is necessary, dopamine is the drug of choice and phenylephrine is avoided. Concomitant low dose dopamine should be used with phenylephrine as a precaution against renal ischaemia. Atropine and vagolytics, like glycopyrolate, are used for preventing bradycardia associated with hypotension.

RESPIRATION

Respiratory complications are common after traumatic injuries to the spine, especially if the injury is cervical. There is decreased vital and inspiratory capacity due to diaphragm paralysis and intercostal muscle dysfunction. After assessing the respiratory effort, oxygen supplementation via mask/prongs is given. Prophylactic intubation in conscious patients is not done. When there is need for respiratory support "chin lift" instead of "jaw thrust" is used, with great care taken not to extend the neck. Endotracheal intubation should be performed with inline traction of the spine. Awake blind nasal intubation is another option, but the safest option is awake fibreoptic intubation. Cricothyroidectomy and tracheostomy are the other options to secure airway and should be done early when indicated. Neurogenic pulmonary oedema is rare and can lead to adult respiratory distress syndrome if not recognised and treated. It is managed pharmacologically and by ventilation.

AUTONOMIC SYSTEM MANAGEMENT

Spinal shock is the complete loss of motor, sensory and autonomic function of the spinal cord and may last for a few hours to weeks. This can cause haemodynamic instability due to loss of vasomotor tone attributable to injury of the spinal cord.[12] Spinal shock has to be differentiated from vascular shock which may coexist. Ryle's tube insertion is required to prevent vomiting and aspiration as paralytic ileus is common. Decreased sweating can cause hyperthermia in tropical countries like India. Prevention of decubitus ulcers is very important and can be done by frequent turning of the patients, proper skin care and nursing the patient on air or water beds. Bladder and bowel care are of great importance and most patients with spinal injuries may have retention and should be catheterised with proper precautions.

NUTRITION IN SPINAL INJURY PATIENTS

The hypermetabolic, catabolic injury cascade occurs immediately after both traumatic brain and SCI leading to depletion of whole body energy store, loss of lean muscle mass, reduced protein synthesis and finally loss of gastrointestinal mucosal integrity and compromise of immune competence. This prolonged nitrogen loss and severe malnourishment occurs within 2–3 weeks of injury; therefore, nutritional support of patients with SCI is done expeditiously. Energy expenditure is best determined by indirect calorimetry in these patients, because equation estimates of energy expenditure and subsequent caloric need tend to be inaccurate.[111] Due to poor nutrition spinal injury patients have poor wound healing and increased susceptibility to infections.

MEDICAL AND PHARMACOLOGIC

Injury to the spinal cord involves mechanical forces like compression, penetration, laceration, shear and distraction. The secondary mechanisms include reduced blood flow, loss of autoregulation, loss of microcirculation, vasospasm, thrombosis and haemorrhage. Other events are electrolyte shifts, permeability changes, loss of cellular membranous integrity, oedema and loss of energy metabolism. The pathological cascade also includes neurotransmitter accumulation, arachidonic acid release, free radicals and prostaglandin production and lipid peroxidation. All these lead to axonal disruption and cell death.[63,135,141] Pharmacotherapy has been very ineffective in the management of these cascades and research into compounds, like tirilazad mesylate, nalaxone, methylprednisolone, GM-1, is still ongoing and results are awaited.[116]

METHYLPREDNISOLONE

Giving methylprednisolone after spinal injury is an option that can be undertaken with the knowledge that side effects are very common.[85,116,121] The benefits of methylprednisolone[27] are only seen when the drug is given within 8 hours of the injury and when given later the outcomes are worse. The initial bolus is given as 30 mg/kg/IV over 15 minutes and the maintenance infusion is started 45 minutes after the bolus and is at a rate of 5.4 mg/kg/hr for 23 hours if therapy was started within 3 hours of injury and 47 hours if begun 3–8 hours after injury.

Sharma et al.[139] suggested that methylprednisolone sodium succinate was effective in promoting post-traumatic clinical and histological recovery and to a greater extent when given 1 hour after trauma. Methylprednisolone sodium succinate is more effective than dexamethasone in reducing oedema.

TRACTION

Traction, which earlier was the only modality of treatment of spinal injuries has a limited stand alone application in the modern era of spinal surgery.[93] Traction is used for initial closed reduction of cervical fracture dislocation injuries.[88] It is absolutely contraindicated in the management of atlanto-occipital dislocation, Type II(A) and III Hangman's fractures, in children below 3 years, in patients with a distraction injury and in any patient who develops severe local pain, radiculopathy, myelopathy or autonomic dysfunction.[59] It should not be used in patients with impaired sensorium. In patients with a locked facet, it is a safe option to get an MRI and exclude a sequestered disc which can cause neurological deterioration when traction is applied. Today, most neurosurgeons practicing spine surgery would put in a 3 pin fixator and reduce a dislocation with controlled

traction under fluoroscopic control and maintain reduction with different anterior or posterior instrumentation. Most fracture dislocations can be easily reduced by careful positioning of the neck in extension. Over-distraction may occur due to excessive weight, nature of injury and poor muscle tone, and due to the use of muscle relaxants during anaesthesia.

Applying Traction

The Gardner-Wells tongs are the ones in current use and many Indian variations of the same are available. The site of application is usually 1.5–3 cm above the pinna and below the equator of the skull. Placement of pins is avoided beyond 1 cm anterior to the meatal line as risk of pin perforation in the thinner squamous temporal bone increases and temporalis muscle injury can cause pain.

Extension Traction

The pins are placed 3 cm above and 2–3 cm in front of the external auditory meatus. This is rarely used because retroluxations are very rare.

Neutral Traction

The pins are placed 3 cm above and in line with the external acoustic meatus.

Flexion Traction

The pins are placed 3 cm above the pinna and 3 cm behind the external auditory meatus and above the mastoid process. This is the position used for reduction of locked facets.

ORTHOTIC DEVICES IN SPINE TRAUMA

Halo

The 4 pin halo can also be used for immediate immobilisation for acute subaxial spine injuries[33,39] and Indian versions are also available. Traction can be applied using the halo and after the fixation, if necessary, the halo can be continued for immobilisation. The halo provides relative immobilisation of the upper cervical spine, but the lower cervical spine is not immobilised well.[69,82]

Minerva Jacket

This is still used occasionally and new thermoplastic Minerva jackets limit cervical "snaking" better than the Halo.

Soft Cervical Collar

This is used only in the treatment of pain caused by muscle spasm and provides very little immobilisation and should not be used in patients with bony and discoligamental injuries.

Philadelphia Collar

It is used postoperatively to limit flexion and extension.

Yale Brace

It is characterised by extended support to the sternum and upper thoracic spine and is better at immobilisation than the Philadelphia collar.

SURGERY

Surgery is usually indicated in incomplete cord lesions, unstable injuries and in patients with a radiculopathy or myelopathy due to pressure on the spinal cord or roots. Surgery in complete injuries may be necessary to optimise recovery, prevent deformity and allow for early mobilisation.[40]

Early surgery: Timing of surgery in trauma is controversial and many surgeons prefer earlier cord and root compression.[62,147,154]

PAEDIATRIC SPINE INJURIES

These are infrequent and most paediatric spine injuries can be treated by immobilising in Halo and rarely Minerva jackets. Anatomical reduction of deformity, stabilisation of unstable injuries and decompression of the spinal cord, and isolated ligamental injuries associated with deformity are indications for surgical management.[107]

Spinal Cord Injury without Radiographic Abnormality[120]

Pang and Wilberger[115] described spinal cord injury without radiographic abnormality (SCIWORA) in 1982. Patients are usually children and this is seen rarely in adults. Patients present with signs of myelopathy as a result of trauma and no evidence of fracture or ligamental instability on plain X-rays and CT. This can appear as late as 4 days after injury.

The spinal column in children is more flexible and elastic and in the absence of bony or ligamental injury, the MR images can show a spectrum of injuries including cord contusion, vascular injury, traumatic disc prolapse, traction injuries, meningeal rupture and even cord transection. SCIWORA is more common in patients with asymptomatic Chiari 1 malformation.[23] Patients with SCIWORA,[119] have a 20% rate of repeat injury within 10 weeks of the original injury and so patients are recommended immobilisation for 3 weeks to 3 months. Contact and non-contact sports are prohibited for 3 months before allowing these children to go back to their normal routine. Dynamic imaging is done to rule out occult asymptomatic instability.[144]

Geriatric Spine Injuries

The elderly population is at a higher risk of spine injuries after even minor falls due to the loss of the normal spine biomechanics and flexibility, osteoporosis, cervical

spondylotic myelopathy, cord ischaemia and secondary canal stenosis. Abnormal ossification, ossification of posterior longitudinal ligament (OPLL), diffuse idiopathic skeletal hyperostosis (DISH), flurosis and ankylosing spondylitis are other factors that complicate spine injury in the elderly. Patients with ankylosing spondylotis[71,96] are highly susceptible to extensive neurological injury and spinal deformity after sustaining cervical fractures from even minor traumatic forces.

Deep Vein Thrombosis[44]

Thromboembolism leading to complications is very high in spinal injured patients and the incidence of a thromboembolic event ranges 7–100%. This is diagnosed clinically by observing signs of inflammation and confirmed by duplex Doppler, ultrasound, impedance plethysmography and venography. The prophylactic measures advocated are low molecular weight heparin and rotating beds. Heparin is given as a titrating dose to achieve a PTT of 1.5 times the control. Low dose heparin with pneumatic compression stockings or electrical stimulation is another option. Vena cava filters are used for patients who do not respond to anticoagulation and in those in whom anticoagulants are contraindicated. The prophylaxis therapy is given for 6–12 weeks.[44]

Vertebral Artery Injury

About 0.5% of all trauma patients can have a vertebral artery injury, and the pathology can be arterial dissection, occlusion, transection or pseudoaneurysm formation. This can cause cerebral, brainstem and spinal cord strokes.[17,60,87] Cervical spine translation injuries and transverse foramen fractures are the most common injuries associated with vertebral artery injuries. Most patients remain asymptomatic, but sudden unexpected deterioration is possible. The incidence of neurologic deficits ranges 0–24%. Wallenberg's syndrome, which is characterised by V, IX, X and XI CN deficits, Horner's syndrome, ataxia, dysmetria and contralateral pain and temperature loss is a frequent clinical presentation. Digital subtraction angiography is the most sensitive imaging study. CT angiography has sensitivity and specificity close to that of catheter angiography. Anticoagulation is recommended in patients with evidence of posterior circulation stroke, either observation or anticoagulation in patients with evidence of posterior circulation ischaemia, and observation of patients with no evidence of posterior circulation ischaemia.[18,108]

Double Noncontiguous Spinal Injuries

The incidence of noncontiguous injuries approaches 15% in patients with multiple injuries. Vaccaro et al.[153] found that 15 fractures in 12 patients were missed on admission and 25% of these patients had a progressive neurologic deficit as a result of improper initial immobilisation. The locations of missed fractures were found to be primarily at the extremes or junctions of the spine (i.e. cervicothoracic, thoracolumbar). Double noncontiguous cervical injuries have an incidence of 3.2%.[86] The reason for the second lesion in the same trauma event can be due to a pre-existing benign spinal lesion or because of a biomechanical event due to spinal column position at the time of injury. The second lesion in double noncontiguous cervical lesions can appear through a single great impact in pre-existing lesions, double impacts at the same time with injuries at two levels or repeated impacts in very quick succession in the same trauma.[153]

Neglected Spinal Injuries

Sengupta[136] found that spinal injuries are most often missed in unconscious or intoxicated patients and in patients with polytrauma. These were 4.5 times more frequent in the cervical spine compared with the thoracolumbar spine. The most common cause was the failure to obtain radiographs.[43,67,92,136] Use of CT and MRI scans as screening tests may be good ways to diagnose these injuries. The most serious consequence of overlooked spinal injuries is progressive neurological deficits.[124] Deformity and persistent pain require surgical intervention. Untreated or inadequately treated spinal injuries with late presentation are more often seen in the developing countries like India.

The reported frequency of missed injuries in the cervical spine varies from 4–30%.[124] Characteristic injury patterns which are commonly missed include odontoid, teardrop, facet and Hangman's fractures.[64] No radiological imaging modality can be 100% accurate and X-rays, CT and MRI have missed injuries, and even in the absence of fractures, clinically significant instability can exist. Spinal cord injury without radiographic abnormality has been found to occur in 0.08% of adults with blunt cervical spine trauma. When injuries are missed on initial assessment, a delay in diagnosis occurs that puts the patient at risk for progressive instability and neurologic deterioration. In one series by Davis et al.,[43] 29% of patients with missed injuries developed permanent neurologic sequelae.

OUTCOME SCORES

The standardisation of studying outcomes is very important as otherwise analysis of surgical and management protocols will not be possible.[49,152]

The functional independence measure and the modified Barthel index are recommended as the functional outcome assessment tool for clinicians involved in the assessment and care of patients with acute SCI.[38]

FUTURE GOALS

The main target is preventive neurosurgery and the prevention of spinal trauma. Educating the attendants of the patients regarding precautions to be taken while transporting and shifting spinal cord injured patients, creating awareness amongst the Indian population for

identifying spinal trauma and its initial management and providing tertiary level hospitals with specialised spinal trauma units.[114,120,152] Implementation of guidelines as published by the Congress of Neurological Surgeons in 2002 will decrease time for spine clearance and incidence of missed injuries. Rehabilitation is a greater responsibility of the treating neurosurgeon and requires dedicated facilities, physical medicine specialists, physiotherapists and psychologists.[120] The establishment of spine injury centres have been associated with better standard of care all over the world and these centres must be created all over India also.

RECOMMENDED READING

Neurosurgery supplement, guidelines for the management of acute cervical spine and SCI. Section on disorders of the spine and peripheral nerves of the American Association of Neurological Surgeons and the Congress of Neurological Surgeons. 2002;50(3).

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48 Biomechanics of the Spine

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INTRODUCTION

Biomechanics is the study of the functional anatomy of the spinal column. This includes the study of its normal structure, curves, attachments of ligaments and muscles and intrinsic biological tissue characteristics. The dynamic character of the vertebral column, intervertebral disc and a large number of variables makes this subject difficult and forbidding. Yet not knowing the subject makes the treatment of patients with spinal disorders inappropriate, incomplete and, sometimes, the treatment worse than the disease. Traumatic, neoplastic, infectious and other diseases of the spine and spinal cord are difficult problems, combining issues of biomechanical instability and neural injury. These two problems are often inseparable. Spinal surgery often involves the handling of the spine to a degree that may affect its stability and the neurosurgeon must be capable of managing instability and reconstructing the functional anatomy of spinal column. Modern biomechanics involves the application of engineering and computational principles to biological problems and has been aptly described by Benzel[150] to be the root of spine surgery.

HISTORICAL BACKGROUND

Sannan and Rengachary,[150] in their comprehensive review of the development of biomechanics, detail concepts which have lead to modern spinal surgery. Ancient Indian, Sumerian, Chinese and Egyptian among other sources, point to a long tradition of knowledge of spinal ailments.[62,83,102,103] In the Srimad Bhagawat Mahapuranam (3500–1500 BC) we find the oldest documentation of spinal traction.[80] Giovanni Alfonso Borelli 'Father of spinal biomechanics' proposed the term "Iatromechanics", i.e. application of mechanics to physiology in "De Motu Animalium" in 1680, the first comprehensive text devoted to biomechanics.[141]

Most of the experimental models for biomechanics are based on work done by the neurologist Alfred Reginald Allen[152] who, in 1911, developed a research model using graded weights. 'Allen's Weight drop technique' remains the basis on which experimental spinal lesions are created, even today.[152]

Walter Jones, in the 1930's, classified spinal injuries to be mostly of the flexion type. Junghans, in 1932, proposed the concept of "Motion Segment", which is the functional unit of the spine formed by the intervertebral disc and two adjacent vertebrae. In 1945 Nicoll,[106] on analysing 166 thoracolumbar fractures in coal miners, brought an early classification which bracketed these injuries into, anterior wedge fractures, lateral wedge fractures, fracture dislocations and neural arch fractures. He also tried to define the concept of stability and felt that the interspinous ligament was an important component.

Penning, in 1962, described biomechanical aspects of plain radiography of the cervical spine in chronic myelopathy[136,137] and, in 1971, published the normal movement of the cervical spine and postulated "the Pincer mechanism of Penning", an important biomechanical cause of myelopathy.

Frank W Holdsworth introduced the first modern classification on the basis of the "Two column theory" of spinal injuries.[60,61] This classification helped to better treat thoracolumbar injuries.[150,155] In the 1980s, Denis proposed the "Three column theory" based on a study of more than 400 radiographs of spinal fractures.[33,34] White and Panjabi's classic work on the biomechanics of the spine has been seminal[118–127,129,130] Benzel,[6–10] Yoganandan and his colleagues,[87,90,91,178–184] Pintar et al.[138] and Goel,[47–50] have been among others who have contributed to the understanding of the complexity of the biomechanics of the spine.

Currently, complex computer software programmes are used to study and understand normal and applied biomechanics. The "Finite element method" is a mathematical model using "elements" and "nodes".[46,48,77,82,94]

BIOMECHANICAL TERMINOLOGY

Voltaire once aptly said "Before you converse define your terms" and nowhere it seems more so than in the field of biomechanics, which is an amalgam of the biological and mechanical and also new properties that arise which are characteristic of living systems.

Scalar

This is a quantity defined by only its magnitude and has no direction. An action that changes the state of rest of the body to which it is applied can be defined as a force, because force has no direction, it is a scalar.

Vector

Forces applied to the spine can be broken down into component vectors. A vector is force oriented in a fixed and well-defined direction in 3-dimensional space. It is a quantity that possesses both magnitude and direction.

Force Vector or Load Vector

This is a force applied in a particular direction. In the laboratory, pure vector forces such as flexion, extension, vertical compression (axial loading, vertical distraction, lateral flexion or bending, rotation, shear or a combination of these) produce bony and ligamental injuries of the spine. The injuries are classified according to the vector forces causing them.[22]

Cartesian Co-ordinate System

This consists of X, Y and Z axis. These can have both rotational and translation movements along these axes, which can be positive or negative. The right handed cartesian system is used in biomechanics (Fig. 1).

Deformation

Deformation results when force is applied to a non-rigid body. The forces that can act can be rotational or translational and deformation results in strain.

Strain

This is the change in unit length or angle in a body subject to a force.

- Shear strain is the change in the right angle.
- Normal strain is the change in the length divided by the original length.

Stiffness

It is the ratio of force to the deformation.

Biomechanical Load Deflection Response

This curve has three components (Fig. 2):

- Physiological loading phase
- Traumatic loading phase
- Failure or post-traumatic loading phase.

During the physiological loading phase, the stiffness offered gradually increases and this is a mechanically efficient phase with no structural damage.

During the traumatic loading phase, micro failures start occurring and stiffness starts to decrease. In the post-traumatic loading phase, the structure has an increase in the deformation that results in the decrease in the load.

Coupling

The spine is a three-dimensional structure and coupling is a unique characteristic of the spine, where every primary motion can have associated obligatory movements like translation or rotation. Principal motion is the motion associated with the direction of the external force.

Instantaneous Axis of Rotation

This is the axis perpendicular to the plane of motion of the body and this passes through a point within the confines of the body. It is also the central point about which the vertebra rotates (Fig. 3). This is not a static point but is dynamic and changes with position, posture and direction of movement.[170] Each segment has a unique instantaneous axis of rotation (IAR) for every movement and is influenced by spine alignment, anatomy, muscles and loads exerted. According to White and Punjabi,[173] the IAR is located in the ventral portion of the vertebral body. The human body's centre of gravity is located approximately 4 cm ventral to the sacrum.[71]

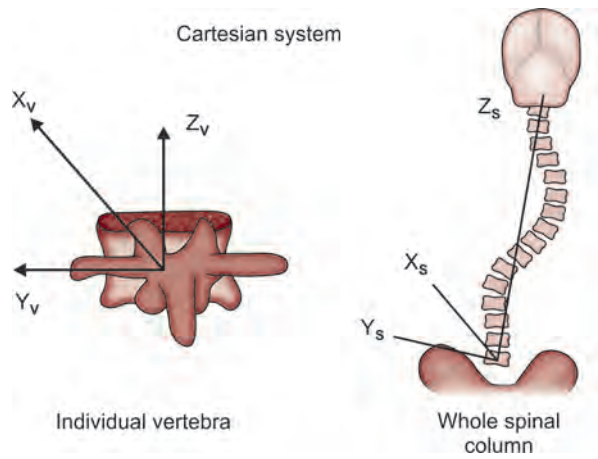

Fig. 1: Diagrammatic representation of cartesian co-ordinates of individual vertebrae and the whole spine

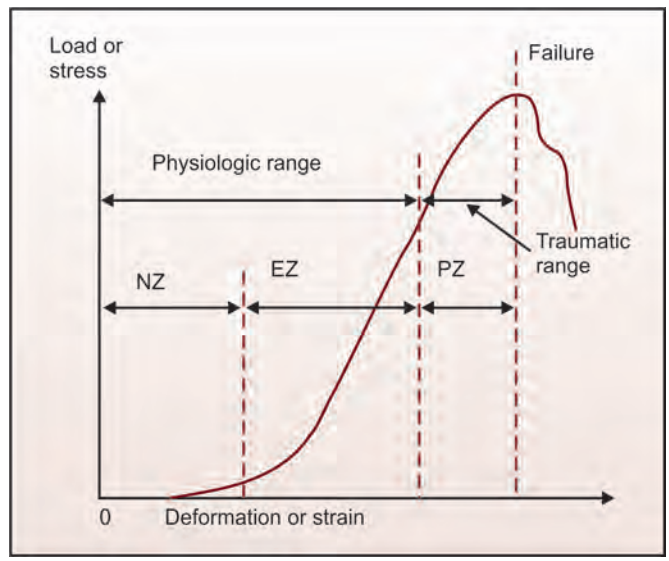

Fig. 2: Load deflection response curve showing physiological range, traumatic range and failure

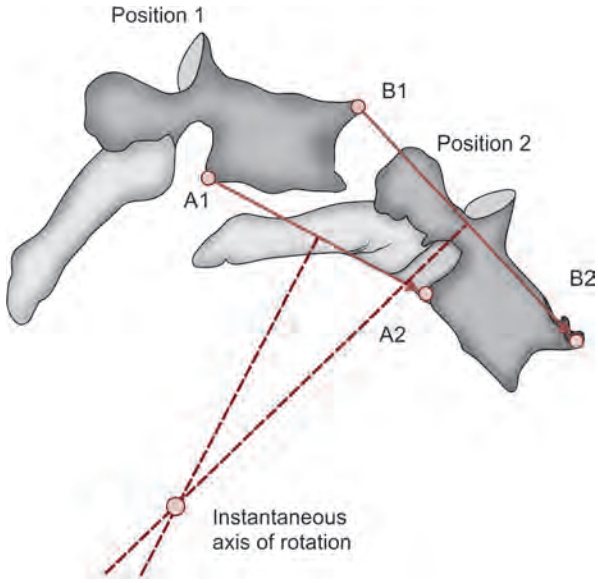

Fig. 3: Instantaneous axis of rotation

Range of Movement

They are the limits of rotational and linear motion. The spinal cord has six degree of freedom with three angles and three displacements of a chosen point along a coordinate axis.

- Extension is a backward bending moment
- Flexion is a forward bending moment
- Subluxation is an anteroposterior or postero-anterior shear
- Rotation is an axial turning or torsion
- Distraction is stretch or tension.

Relaxation

The return or adjustment of a system to equilibrium following displacement or abrupt change is relaxation.

Creep

A rheologic effect of metals and other solid materials (disc) that may become elongated or deformed as a result of a load being applied for a long period.

A constant applied load causes a deformation over time or creep response.

Elastic Modulus of Young The constant or scale factor which defines quantitatively the relationship between the deformation of any elastic medium and the deforming force.

Elastic Deformation

It is the reversible deformation of tissue: The change in shape of an object under an applied load from which the object can recover or return to its original unloaded state when the load is removed.

Plastic Deformation

Any irreversible deformation of tissues is plastic deformation.

Break Point

This is a point of discontinuity, change or cessation beyond which the strength of a structure fails.

Hysteresis

This is a lagging or retardation of one of two associated phenomena or a failure to act in unison of different parts of a body.

Kyphosis

This is an excessive sagittal angular deformity that is beyond the established normal range. Thoracic spine curvature is 25–40 degree with a transitional zone of 40–55 degree. Kyphosis greater than 60 degree in the thoracic spine is abnormal. In the thoracolumbar junction, the normal kyphosis is 0 degree and the lumbar spine is normally lordotic. A post-traumatic deformity of greater than 30 degree at the thoracolumbar junction and a kyphosis of greater than 5 degree in the lumbar spine are considered abnormal.

Junghans Motion Segment

Junghans defined the basic functional unit of the spine. This consists of two vertebral bodies and an intervening disc with the ligaments and joints (Fig. 4). The basic structure of a spine functional segment is an anterior column, mechanically supported by a hydraulic cushion and posterior secondary joints, resulting in a strong load-bearing and flexible structure. Thus, the motion segment is the smallest structure for performing biomechanical tests of the human spinal column. The human spine has 24 motion segments.

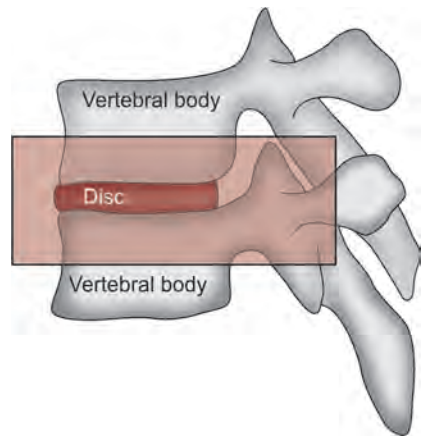

Fig. 4: Diagrammatic representation of Junghans motion segment

Bending Movement

The bending moment (M) is the product of the force (F) applied to the lever arm and length of the lever arm (D).

$$M = F \times D.$$

BIOMECHANICAL TESTING METHODS

The study of spine biomechanics includes the use of mechanics and mathematical principles. The validation and application of theories have been accompanied by *in vitro* tests of both animal and human spines, to determine stiffness, strength, strain and failure loads of spinal segments and surgical implants.[4,36,89,145,172,173] *In vivo* instrumentation has been used to measure strains and pressures in the spine during daily activities.[128]

In vivo Testing

These may be *in vivo*, in animals[164] and rarely in human beings where intradiscal pressure measurements or instrumentation that has sensors has been used to give information about biomechanics.[8]

In vitro Testing

This is usually of complete or part preparations of human cadavers[172] and animal specimens, (e.g. sheep, porcine spine functional unit).

Mathematical Model Testing (Finite Element Analysis)

Computational mechanic techniques, in particular the finite element method, have been widely applied to the analysis of spinal problems. This testing involves the breaking down of the structure to be studied into a finite number of geometric shapes or elements which are interconnected by nodes.[46-48]

The geometric information is obtained from CT study of human spines and the material properties of various components, such as the modulus of elasticity, the shear modulus, density and Poisson's ratio and these are based on predetermined values. These are then studied with complex computer programmes and are easily reproduced.[51] Kumaresan et al.[81] have described the physiological mechanics of the growing spine specific to 1, 3 and 6-year-old and compared them with mature spines. Such data will assist mathematical models of the spine to improve validation and lead to better design of stabilising systems.

Biomechanical Tests can be Dynamic and Static

- *Strength test:* This is a static test where load is applied till failure occurs.
- *Stability test:* The load is applied, avoiding permanent deformation and the specimen is only tested on the elastic segment of the stress versus strain curve. It studies stiffness, creep and viscoelastic properties of the material.
- *Fatigue or cyclic load tests:* These tests involve cyclical loading with subfailure loads till failure occurs and a fatigue curve is plotted out.

ROLE OF IMAGING IN BIOMECHANICS

The precise quantification of spine motion behaviour in the clinical setting remains difficult and imaging the spine is critical to evaluating instability in the clinical sense.

Radiography

Plain dynamic radiography should be used with great caution in evaluating trauma but it is indispensable. It is useful in diagnosing instability, classifying injuries and fractures, evaluating surgical results and follow-up. Digital X-rays have better resolution and clarity. The cost effectiveness, utility and pre-operative uses make these the best resource to study applied biomechanics. 3D radiography is useful in studying axial rotation and lateral bending.[135] Dynamic radiographs have been used to study the characteristics of sagittal vertebral alignment.[84]

Computed Tomography

It has been used to study the bony anatomy, especially in the craniovertebral junction and can give great information about various anomalies and abnormal biomechanics and guide surgical restoration of the column.[21] McAfee et al.[93] have emphasised the value of the CT scan in studying and classifying spinal column injuries, specifically the thoracolumbar spine. Where MRI is unavailable or contraindicated, CT myelography can be a valuable tool to study dynamic canal stenosis, abnormal disc response and CT angiography can give an idea about safety of the instrumentation. CT studies are also used to study structural dimensions and morphology of the spine and this data is then used for the computer models and finite analysis. Computer assisted anatomic study to evaluate canal size was done by Ebraheim et al.[38]

Magnetic Resonance Imaging

It has allowed three-dimensional imaging of the spine for accurate assessment of anatomy, sagittal balance, pathology, deformity and kinematics.[167] Pathology of the ligaments at the craniovertebral junction is very well visualised. In trauma, the role of MRI is invaluable and when combined with whole neuraxis screening is very comprehensive. Soft tissue and ligament injuries, including tears of the ligaments of the craniovertebral junction are well seen.[79,96,97,99] The area of signal intensity change in the cord can help in localising segmental instability.[72] Dynamic MRI and MRI that can image while a patient is standing have been in clinical use.

BRIEF NORMAL ANATOMY OF THE SPINE

It is customary to sub-classify the spinal column as each of the regions has specific anatomic and biomechanical characteristics. The spinal column must be also considered holistically because the normal curves, shape and structure correspond to other biomechanical properties which cannot be understood by studying the subdivisions alone. In fact, the spine cannot be studied in isolation to all the tissues that surround it and that mutually support one another.[74,75] Studying the motion segment in a preparation is informative but the normal *in vivo* spine mechanics and anatomy is absolutely essential for neurosurgical planning and management of complex spinal pathologies.

Curvatures of the Vertebral Column

The spinal column *in utero* has a thoracic and lumbosacral kyphosis and when the child starts raising the head post-natally, the cervical and lumbar curvatures begin to form. The adult vertebral column has a cervical and lumbar lordosis and a thoracic and lumbosacral kyphosis (Fig. 5). The thoracic and lumbosacral kyphosis are called primary curves. The lumbar lordosis develops after the upright position of the trunk is attained during growth. The shape and size of the intervertebral disc, the vertebrae and muscles contribute to the curves. The centre of gravity of the spinal column passes from the dens of C2 through the body of the vertebrae to the promontory of the sacrum. Abnormal curves may be congenital or acquired.[5,98] Iatrogenic flat back syndrome[174] is a well recognised condition where the loss of the normal curve causes severe symptoms. The altered biomechanics of spinal deformity have been elaborated on by Schlenk et al.[151] Kyphosis[92,158] is a frequent result of injury.

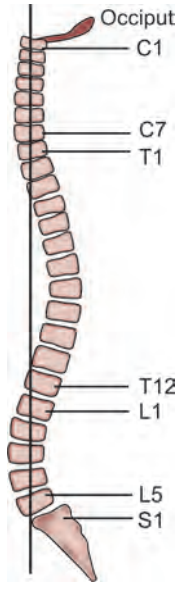

Fig. 5: Diagram showing normal curvatures of the spine

Vertebral Body

The vertebral body is a box-like structure with a central spongy and cancellous core, surrounded by a hard cortical shell and the upper and lower endplates. The endplates support the nucleus pulposus and provide points of attachment for the annulus fibrosus.[24] The cortical bone has vertical lamellae to resist axial loads.[53,126] The trabeculae of the cancellous bone also resist loads. The superior and inferior vertebral body surfaces are concave and interspersed with the fibrocartilaginous discs. Dorsally, there is an arch formed by the facet joint, pedicles, laminae and the spinous processes. The thoracic and lumbar vertebrae have transverse processes. The cervical vertebrae are smaller and cylindrical and their spinous processes are short and bifid. The transverse processes have a foramen for the vertebral artery. The pars interarticularis is also called the lateral mass. The facets from C2 to C7 are oriented at 45 degree and aligned in a coronal orientation.[119,120] Thoracic vertebrae are heart shaped and have special costal facets on the body and transverse processes and these articulate with the ribs. T1 to T4 have cervical features and T9 to T12 have lumbar features. The lumbar vertebrae are large and wider in the transverse diameter and their facets are aligned in a sagittal plane.[12,45,78] The atlas is a bony ring with two lateral masses and anterior and posterior arches. The axis has a body unlike the atlas and odontoid process at its superior anterior surface. It has two superior facets on the lateral aspects. The sacrum is a fused triangular structure. The coccyx is a terminal part of the column. The vertebral bodies and the intervertebral discs support 80% of the spinal loading and 20% is by the facet joints and the posterior elements.

Facet Joints

The cervical facet joints have a coronal orientation, the thoracic ones are of intermediate orientation and the lumbar have a sagittal orientation. The orientation of the facet joints in the lumbar area makes the lumbar spine weak to flexion and translational forces but is able to resist rotational forces.[171] The cervical spine facets do not resist flexion, extension, lateral bending and rotation and thus, the cervical spine is very mobile.[140]

Pedicles

The morphology of the cervical, dorsal and lumbar pedicles has been studied[70,78,188] because it allows for a single trajectory to stabilise all three columns via a posterior approach, using pedicular screws.[66]

Intervertebral Discs

The human vertebral column has 33 vertebrae and 23 intervertebral discs. The discs vary in size and constitute 1/3rd to 1/5th of the total height of the column. The lumbar disc is the largest avascular structure in the body and the disc consists of three zones; the outer annulus

fibrosus, the central nucleus pulposus and the intermediate transition zone. Three types of macromolecules, collagen, proteoglycans and glycoproteins constitute the disc parts.[32,44]

Annulus Fibrosus

This is a concentrically arranged outer layer of collagen fibres, fibrocartilagenous area and a transitional area. The fibres of the annulus pass obliquely from the vertebral body and are arranged in a helicoid manner. The orientation of the fibres in the adjacent layers defers by 40–70 degree and each band is oriented to the opposite direction, leading to a 120 degree difference in orientation. The inner layer of the annulus is attached to the cartilaginous end plates and the outer layer is attached directly to the vertebral bodies by Sharpey's fibres.

Nucleus Pulposus

This consists of a soft pulpy elastic mucoprotein gel. The elastin fibres are loosely and irregularly arranged. It occupies 30–50% of the cross sectional area and in the lumbar region the nucleus is located in the dorsal aspect of the disc.

Because of the complex structure of the disc, there is three-dimensional deformation which allows the disc to resist great loads.[101] The first component to fail in the functional spinal unit is the end plate. The disc also resists compression, tension, shear, bending and torsion forces. These qualities reduce significantly in an ageing and degenerated disc.[104]

The weakest component of the functional spinal unit is at the end plate and not the disc itself. The disc loses its strength as it degenerates and the effects of discectomy on the kinematics of the lumbar spine have been described by Goel et al.[49] The intervertebral disc contributes significantly to the stability of the spine.[165] Repeated micro-trauma cause intervertebral disc pressure changes and these lead to low back ache.[180,183]

Spinal Canal

The spinal canal varies in size from the craniovertebral junction to the sacrum and the dorsal canal has the smallest diameter. Congenital canal stenosis and acquired types have been described. The canal size may be reduced due to osteophytes, disc, ligamental hypertrophy or OPLL.[55] The sagittal diameter of the canal has long been recognised as an important cofactor in varied spinal cord pathologies.[176] Dynamic canal stenosis has been characterised by the Penning effect in cervical spondylotic myelopathy. Lumbar canal stenosis is the most common congenital stenosis followed by congenital cervical canal stenosis.

Ligaments

These are composed of elastin and collagen and connect the vertebrae. They may be short, connecting adjacent segments or long. They are the anterior longitudinal ligament (ALL), posterior longitudinal ligament (PLL), ligamentum flavum, interspinous ligament, intertransverse ligament, capsular ligament and supraspinous ligament (Fig. 6). The upper cervical spine and CV junction ligaments include the atlanto-occipital capsule, cruciate ligament, tectorial membrane, atlanto-axial capsule, ligamentum flavum, apical ligament, alar ligament and posterior atlanto-occipital membrane. These ligaments respond to tensile forces and their effectiveness depends on the morphology and movement arm through which it acts.

A weak ligament which has a long lever arm may provide more stability and ligaments that are away from the IAR demonstrate greater strength. Each ligament resists physiological loads differently, because of the orientation and location in relationship to the IAR of each vertebral segment.[50,100,121,138,177,178,182]

The effectiveness of each ligament is related to the strength of the ligament and also the movement arm through which the ligament acts. A weak ligament with a long lever arm provides more support to the spine than a very strong ligament with a short movement arm.

The incompetence of ligaments, either primary, due to collagen disorders or secondary, due to trauma and rarely degeneration, infection and neoplastic disorders leads to instability and may require surgical management. Spinal instrumentation and fixation changes the biomechanics and histology of the ligaments.[58,75,110,149] Conditions like Forestier's disease,[42] which cause loss of normal elasticity of the ligaments, reduce the capacity of the spine to bear physiologic loads.

Anterior Longitudinal Ligament

This begins as the anterior occipito-atlantal membrane at the occiput and ends at the sacrum. It is multilayered, with the deep layer binding to the adjacent intervertebral discs. The middle layer binds to the discs and vertebral bodies over three levels. The superficial layer extends to 4 to 5 vertebral bodies. ALL maximally resists extension loads. ALL disruption allows hyperextension.[56]

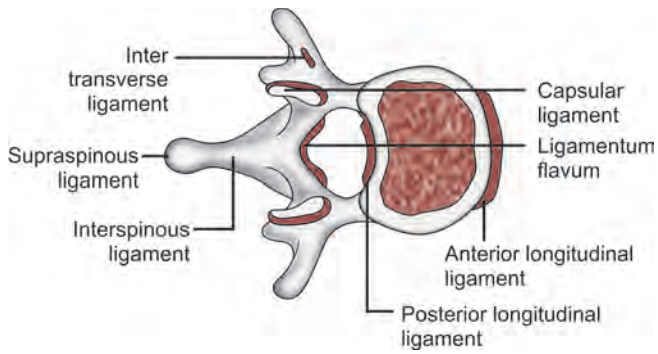

Fig. 6: Diagrammatic representation showing attachment of various ligaments to the spine

Posterior Longitudinal Ligament

This begins as the tectorial membrane and extends down to the sacrum, the fibres being spread out at the disc level and narrowing at the body level. It has several layers with the deep layers attached to adjacent bodies and superficial layer spanning several levels. PLL prevents mainly flexion and lateral bending. PLL disruption allows hyperflexion.[56]

Ligamentum Flavum

Extending from C1-C2 level to L5-S1 level, these have very high elastin content and are the most elastic tissues in the human body and are distinctively yellow. These begin from the ventral surface of the lower lamina and attach to the dorsal surface of the upper border of the superior lamina. They are absent in the mid vertebral region and have a gap at the midline. Laterally, they blend with the ligament of the joint capsule.

Capsular Ligaments

These ligaments surround the facet joints and are attached to the bone outside the synovial joint with the fibres running perpendicular to the plane of the joint. They resist lateral bending, axial rotation and flexion.

Interspinous and Supraspinous Ligaments

These attach from the base to the tip of each spinous process and begin at C2-3 and end at L5-S1 levels. The supraspinous ligaments connect the spinous processes at the tips.[25]

SPECIAL REGIONAL ANATOMY

Craniovertebral Junction

The craniovertebral junction (CVJ) is an exceedingly mobile region, especially in children. It is uniquely adapted for both stability and motion. Menezes'[95] classification of CV junction pathology into reducible and non-reducible is very useful in the management of patients. The CV junction is less stable in children, as the plane of articulation between the cranium and atlas is almost horizontal and the occipital condyles of children are not deeply seated into the fossa of the superior facet of the atlas. Hyperflexion is prevented by the contact of the basion with the anterior arch of atlas. Hyperextension and ventral translation is checked by the tectorial membrane. Lateral flexion is limited by the alar ligaments. The occipito-atlantal joints allow 15–20 degree of flexion and extension and 5–10 degree of lateral bending. The atlanto axial joint allows 47–50 degree of axial rotation, 15–20 degree of flexion and extension and 15–20 degree of lateral bending coupled with axial rotation. Head nodding occurs at the occipito-atlantal joint. Knowledge of the bony configuration, ligamentous attachments, joint articulations, vascular supply, muscle function and lymphatic drainage, as well as the kinetic anatomy of the craniocervical junction is necessary to understand the aetiology of abnormalities in this area and their treatment.[39,68,95,142,148]

Sub-Axial Cervical Spine

The cervical spine is very mobile and there are eight motion segments related to this region and all of these are coupled multi-planar movements described as range of movements (ROMs). The cervical IAR is located ventral to the vertebral bodies. The biomechanical analysis of the extensors of the cervical spine showed that the semispinalis muscle acted as a dynamic stabiliser and removal of its attachment resulted in loss of cervical lordosis.[15] Cervical spine muscles and ligaments[182] maintain the lordotic curve and without muscle support the cervical spine buckles and fails at 1/5th of the weight of the human head.

The cervical lordotic curve is important as the axial loads are dispersed dorsally into the facet joints and large articular pillars, rather than the vertebral body.[30] The greatest motion in the subaxial cervical spine occurs at C4-5 and C5-6 and the least at C2-3. The total range of motion (ROM) from C2-7 is 50 degree to greater than 90 degree with a normal Gaussian distribution and a mean of 67 degree. This decreases with age.[183] White and Panjabi[127] proposed a working classification for acute instability in which greater than 3.5 mm of anterolisthesis or more than 11 degree of angulation constitutes instability in the lower cervical spine. Disc arthroplasty retains the normal range of motion at the treated and adjacent levels.[41] Cervical axial and coronal segment specific non-linear moment angulation corridors have been evaluated by Yoganandan et al.[184] and may be used to evaluate dysfunction and instability.

Cervicodorsal Junction

This area is subject to complex biomechanics because it is between the highly mobile cervical spine and the relatively immobile thoracic spine. The spinal canal is narrow in the thoracic region and this leads to a high incidence of severe neural injuries. Surgical access can be difficult and the morphology of the dorsal pedicles and the narrow canal makes management of pathologies in this region difficult.

Thoracic Spine

The thoracic spine is well protected by the musculature and the rib cage. However, as explained above, the narrow canal in this area predisposes the spinal cord to injuries. The normal curve of the thoracic spine is kyphotic and the normal sagittal curvature of the thoracic spine is between 20 degree and 45 degree. Females have a greater degree of kyphosis. The apex of the thoracic kyphosis is at the 7th thoracic vertebra and there is a mild right sided lateral curvature. Biomechanics of the ribcage and sternum, which have a significant stiffening

effect on the thoracic spine are indispensible in studying this region.[2,88,122,123,126,165] Table 1 shows the ROMs in degrees in the thoracic spine.

Thoracolumbar Junction

The thoracolumbar junction again is a borderland between the rigid thoracic spine and the relatively mobile lumbar region and there is a change of the shape from the dorsal vertebra to the lumbar vertebra, which is large for weight bearing. The thoracolumbar epidural space was measured between T7-L4 by Reynolds et al. and they found the ventral epidural space to be 1 mm and 2 mm laterally.[144] The thoracolumbar region is commonly involved in severe spine trauma, due to its biomechanical characteristics and location.[23] The transition zone is a change from the stiff thoracic spine to a mobile lumbar spine. This zone of transition across T10 to L2 is related to the absence of the stabilising effect of the rib cage and also the change in the orientation of the facet joints.

Lumbar Spine

The lumbar spine has five vertebrae (L1-L5) and five intervertebral discs and the lumbar vertebrae have a large body and a wide canal with sagittally oriented facet joints. Lumbar facet dislocations are very rare due to the orientation of the facets and very strong ligamentous attachments.[1,138] The normal lordotic curve is 20 degree at L4-L5 and 28 degree at L5-S1. The pedicle size and morphology permits a comparatively easy placement of pedicle screws which are biomechanically superior as they are able to stabilise all three columns.[43,54,64,168] Appropriate surgical corridors and short segment fusions can be used to manage biomechanical problems in the thoracic and lumbar region.[9,10] Table 2 shows the ROMs in degrees in the lumbar spine.

Lumbosacral Junction

The integrity of the pelvic ring is dependent upon the sacroiliac, sacrotuberous and sacrospinous ligaments

Table 1: Limits and representative values of ranges of rotation of the thoracic spine

	Limits of range in degrees		
Level	*Combined Flexion and extension*	*One side Lateral bending*	*One side Axial rotation*
T1-2	3–5	5	14
T2-3	3–5	5–7	4–12
T3-4	2–5	3–7	5–11
T4-5	2–5	5–6	5–11
T5-6	3–5	5–6	5–11
T6-7	2–7	6	4–11
T7-8	3–8	3–8	4–11
T8-9	3–8	4–7	6–7
T9-10	3–8	4–7	3–5
T10-11	4–14	3–10	2–3
T11-12	6–20	4–13	2–3
T12-L1	6–20	5–10	2–3

Adapted from: Clinical Biomechanics of the Spine. White and Panjabi, Philadelphia: Lippincott.

Table 2: Limits and representative values of ranges of rotation of the lumbar spine

	Limits of range in degrees		
Level	*Combined Flexion and extension*	*One side Lateral bending*	*One side Axial rotation*
L1-2	5–16	3–8	1–3
L2-3	8–18	3–10	1–3
L3-4	6–17	4–12	1–3
L4-5	9–21	3–9	1–3
L5-S1	10–24	2–6	0–2

Adapted from: Clinical Biomechanics of the Spine. White and Panjabi, Philadelphia: Lippincott.

and the sacroiliac joints. Resection through the mid body of S1 retaining one-third of the sacroiliac joint is still compatible with clinical stability. Amputation of the sacrum higher than this and involvement of the sacroiliac joint require lumbopelvic stabilisation. Understanding the anatomy and biomechanics of the spinopelvic apparatus and the lumbosacral junction, as well as having a familiarity with the various techniques available for carrying out sacrectomy and pelvic ring reconstruction, will enable the neurosurgeon to effectively manage sacral tumours.[105]

SPINAL STABILITY AND INSTABILITY

Instability in an engineering sense refers to a loss in the mechanical stiffness of a structure, such that small applied loads may result in unusually large or catastrophic displacements. Another definition of instability of the vertebral column is excessive motion beyond physiological limits of one vertebra upon another in at least one of the three motion planes; X axis (flexion-extension), Y axis (rotation) and Z axis (lateral bending). The most common cause of instability is trauma. The other causes are degenerative, metabolic, neoplastic, congenital and iatrogenic.[116,131,156,163,164]

The central nervous system, an osteoligamentous system and a muscle system combine to maintain spine stability.

NEURAL CONTROL

The fine tuned multiple spinal segmental loops involving the alpha and gamma motor neurons and the proprioception system are responsible for the normal muscle tone which maintains the axial and transverse stability. Axial stability is maintained along a vertical column: this consists of two columns at the C1–C2 level and three columns from C2 to the sacrum. Transverse stability at the motion segment levels is produced by a coupling of joints and ligaments.

ROLE OF THE MUSCULATURE

Spinal column instability and injury is caused by overload. This can be due to macro-trauma or repetitive micro-trauma. Motor control is a key component in injury prevention, and muscles and their role in spinal stability are being recognised. An unexpected sudden load is likely to cause spinal column failure and, in patients with muscle and ligamental incompetence spinal instability is much more frequent.[52,139]

DEFINITION OF CLINICAL INSTABILITY OF WHITE AND PANJABI

"The loss of the ability of the spine under physiologic loads to maintain its pattern of displacement, so that there is no initial or additional neurological deficit, no major deformity, and no incapacitating pain".[127,129]

Benzel has categorised four subcategories of instability of the spine.

Acute

a. Overt acute instability
b. Limited acute instability.

Chronic

a. Glacial instability
   For example, Spondylolisthesis, trauma, tumour and infections
b. Dysfunctional segmental motion associated instability.

Current quantification of instability of the sub-axial cervical, thoracic and lumbar region based on a point system suggested previously by White and Panjabi, was modified by Benzel, so that the point system could be applied uniformly to the complete spine (Table 3). Instability also can vary in magnitude: first degree (mechanical), second degree (neurological) and third degree (mechanical and neurological).

Table 3: Benzel point system for quantification of acute instability in the sub-axial, cervical, thoracic and lumbar spine

Loss of integrity of anterior (and middle) column	2
Loss of integrity of posterior column(s)	2
Acute resting translational deformity	2
Acute resting angulation deformity	2
Acute dynamic translation deformity exaggeration	2
Acute dynamic angulation deformity exaggeration	2
Neural element injury	3
Acute disc narrowing at level of suspected pathology	1
Dangerous loading anticipated	1

A score of 5 points or more implies the presence of instability.
A score of 2 to 4 implies the presence of limited instability.
From clinical or radiographic evaluation; one point if incomplete evidence exists.
Three points for cauda equina injuries, 2 points for cord injuries and 1 for isolated root injuries

Adapted from: Edward CB. Biomechanics of Spine Stabilization. Philadelphia: Lippincott.

THEORY OF LOUIS

The spine bears weight principally by sustaining axial loads along the vertebral body, intervertebral disc and two facet joint complexes at each segmental level.[85]

TWO COLUMN THEORY OF HOLDSWORTH

Holdsworth[60,61] on the basis of clinical experience along with that of Nicoll[106] and the experimental work of Roaf[146] and Louis,[85] began describing stability in terms of columns.[156] In the 'two column theory', he defined the anterior column as consisting of the anterior vertebral bodies, the anterior longitudinal ligament, the disc and the posterior longitudinal ligament (Fig. 7). The posterior column consists of everything posterior to the posterior longitudinal ligament, including the capsular ligaments, the facet joints, ligamentum flavum and the interspinous and supraspinous ligaments. Holdsworth believed that the stability of the spine depended on the integrity of the dorsal ligament complex.

THREE COLUMN THEORY OF DENIS

Denis,[34,35] in 1983, described the three column theory in relation to thoracolumbar fractures and this is currently applied to the complete spine. Posterior column disruption did not lead to instability and Denis then divided the anterior column into the anterior and middle column, the anterior part of the disc, annulus and anterior longitudinal ligament, forming the middle column and the posterior disc, annulus and the posterior longitudinal ligament forming the posterior column (Fig. 8). This theory helps in evaluating bony collapse associated with axial loading and the effects of distraction, flexion and extension injuries. This was based on experimental studies that showed that when the PLL and dorsal part of the disc were transected, instability occurred and, thus, instability requires injury to at least two columns with an emphasis on preservation of the middle column for the maintenance of stability.

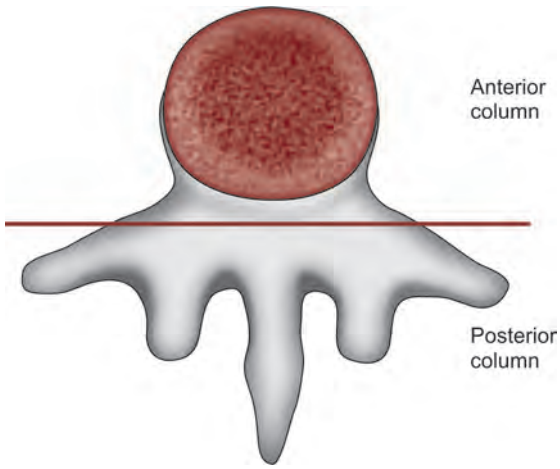

Fig. 7: Two column theory of Holdsworth

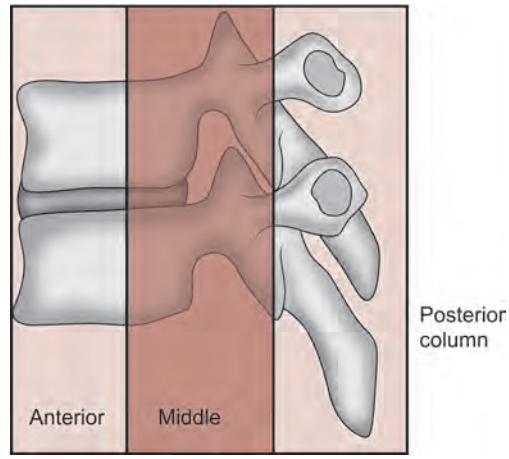

Fig. 8: Three column theory of Denis

Of the three columns, the anterior and posterior columns are the principle support structures. The anterior column resists compression and axial loading and the posterior column maintains the tension. To maintain the correct posture, all forces and movements must be balanced about the IAR. The IAR is located dorsal to the annulus fibrosis in the intact spine.

EVANS FLAGPOLE CONCEPT

The stability of the spine is not dependent solely on the integrity of the spinal column but also on the functional capabilities of the paraspinal muscles and the ligaments of the spine, which participate in the "Flagpole" concept of spinal stability (Fig. 9). Evans uses the Flagpole model to describe the biomechanical advantages of PLIF. The central graft placement represents the flag pole, with the facets, remaining annulus anteriorly and posterior ligamentous restraints representing the surrounding guy wires. This construct, according to Evans, balances both compressional and torsional forces.[40]

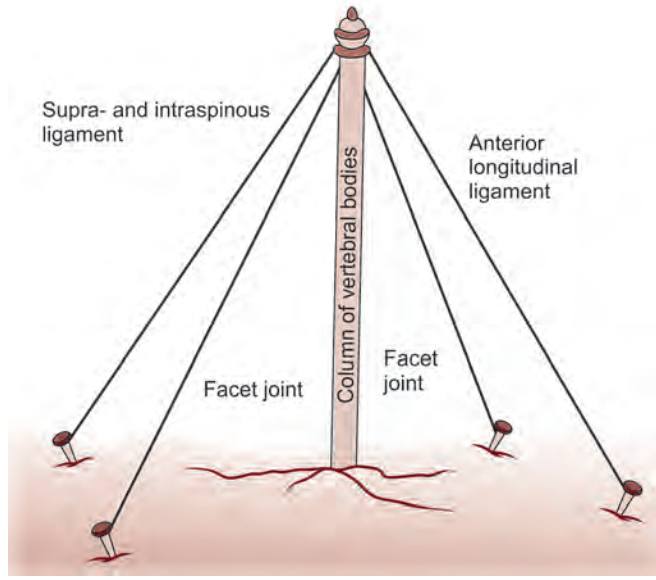

Fig. 9: Evans Fagpole concept

WHITESIDE'S CONSTRUCTION CRANE ANALOG OF THE SPINE

Kelly Whiteside,[174] in 1968, proposed that the anterior column resisted compressive forces and the posterior column resisted distraction. The equilibrium is maintained by anterior compression vectors against the posterior tension vectors. The dorsal ligamentous complex and paraspinal muscles act as a dorsal tension band. The gravitational forces exert an axial load leading to a ventral angular vector. Whiteside used the analogy of the construction crane to illustrate this mechanical principle.

BIOMECHANICS AND AXIAL TRACTION

Currently, MRI should be performed to exclude the presence of a traumatic disc before traction is applied and closed reduction is attempted. Traction is contraindicated in Hangman's type 2A fractures, where traction can worsen the translation and cause stretch injury to the spinal cord. The major liability of axial traction is the inability of being able to directly measure the distraction force in order to make sure that this force does not exceed the compliance of normal body tissue and cause traction injury. The neutral zone (NZ) is a region of intervertebral motion around the neutral posture where little resistance is offered by the passive spinal column.[26,130] The NZ appears to be a clinically important measure of spinal stability function.[187] Its size may increase with injury to the spinal column, which in turn may result in spinal instability or low-back pain.

BIOMECHANICS OF TRAUMA

Modern vehicular transport and high rise buildings have increased the incidence of severe spinal trauma. The adoption of safety features such as seat belts, airbags and helmets have been biomechanically tested and are indispensable in reducing the incidence of grievous injuries.[63,90] In the AO classification, the 'A' type injuries are axial injuries (compression and burst fractures). The 'B' injuries are the distraction injuries (flexion, distraction and chance injuries). The 'C' injuries are rotational injuries (fracture dislocation, shear injuries). The key factor is the integrity of the ligaments. The knowledge about the causative mechanism of injury may hold a key to its treatment, as exemplified by the management of locked facets by ventral reduction and fusion.[11,76,115] Bhatoe,[14] in an analysis of 89 patients, found that degenerative changes and developmental narrowing were important pre-existing factors related to the extent of the injury. Pang and Wilberger[117] reported on spinal cord injury in children without radiographic abnormalities and SCIWORA is much more common in children.

APPLIED BIOMECHANICS

Soft tissue injury, the whiplash trauma was studied by Cusik et al.[29] who found ligamentous and facet joint injuries in whole body post-mortem on human subjects, secondary to single rear impact acceleration and they were able to explain the mechanisms of headache and neck pain. These findings were also indicative that females were more susceptible to soft tissue spinal injuries. Yilmez et al.[177] in a study, found that instability increased with the number of levels of discectomy and that the excision of the PLL did not increase instability.[154]

BIOMECHANICS OF SPINE DEFORMITY

The normal curves of the spine are a major factor in maintaining the normal biomechanics of the spine. Pathological spinal deformation is usually a result of one unstable motion segment. The goals of spinal deformity surgery are reasonable correction of deformity, prevention of further deformity, restoration of sagittal and coronal balance, cosmetic optimisation and improved neurological function.[20] Scoliosis is a complex deformation that is nearly always associated with the phenomenon of coupling.[65,151,157] There is no generally accepted, scientific theory for the aetiology of idiopathic scoliosis, which is a developmental abnormality in the central nervous system creating a rib vertebra angle asymmetry.

The flat back syndrome[175] results from iatrogenic loss of lumbar lordosis with forward inclination of the trunk, inability to stand upright and back pain. The other causes are post-traumatic, neuromuscular, degenerative or infectious. The management options for spinal deformity include bracing and dorsal, ventral and combined surgical procedures.[28,57,107,175]

Biomechanically ventral reconstruction and instrumentation provides superior mechanical stability over an equal number of spinal segments to compressive loads than the dorsal instrumentation techniques.[111,112] The removal of the dorsal tension band after trauma with ventral compression leads to further neurological compromise caused by the tethering of the neural elements (bow string effect) over ventral bony components.

BIOMECHANICS OF CORD INJURY

Tator[166] described spinal cord injury and the various resulting syndromes were described by Schneider.[153]

The presence of cervical spine mobility, instability and kyphosis is strongly predictive of clinical progression in patients with cervical spondylotic myelopathy.[185,186] Deformation of the spinal cord by the presence of spondylotic transverse bars and tethering of the cord by local stenosis appear to be major factors leading to stretching of the deformed and tethered cord.[16–19,31,59,109] This shear and strain theory is supported by the concept of dynamic stenosis which was earlier studied by Penning.[137] There is a decreased cross sectional area of the spinal canal due to the dorsal bulging of the annulus as well as the infolding of the ligamentum flavum and the scaffolding of the lamina, leading to a pincer like action on the cord. Irreversible damage occurs when compression exceeds more than 30% of the initial cord diameter.[113] In 1966,

Penning, on the basis of 20 myelograms in cadavers found that in compressive spondylotic myelopathy, the cord was becoming pinched between the anterior and posterior walls of the canal. Especially in extension, the available canal diameter became smaller and the cord was getting pinched, a finding confirmed in the era of the MRI. In flexion, the cord had 1–2 mm more space but there was functional stenosis between C4-T1.[96,114]

BIOMECHANICS OF BONE GRAFTS

Sir William Macewen[86] introduced bone grafting to replace missing bone and induce new bone formation. Enhancing spinal fusion[6] has biomechanical and other components. The Wolf law postulates that the form and function of bone is a result of changes in the internal architecture, according to self ordered mathematical rules and the remodelling of bone is influenced by level and distribution of functional strain, thereby bone heals optimally under compression.[108] Dynamic implants are implants that prevent stress shielding and allow a limited and controlled type of deformation. As per White and Panjabi, the placement of a fusion mass at the maximum distance from the IAR will be more effective in preventing movement around those axes. Instrumentation without structural bone grafts generally fails and a strong structural graft is required to resist axial loading and flexion. Tricorticate illium, fibular graft and titanium cages packed with autogenous graft provide good anterior column support. Single rib graft may not provide adequate structural support, but multiple rib grafts stacked together and tied, provide excellent support and osteoinduction. The instrumentation causes stress shielding, but generally rigid fixations result in better fusion rates.

BIOMECHANICS OF SPINAL IMPLANTS

It is a rapidly expanding field and the biomechanical properties of screws, plates, wires, cages and newer disc arthroplasty and dynamic implants are tested along with the associated vertebral column. Dynamic systems, semi-rigid countoured plates and implants that are lighter and stronger and more similar to biological tissues (Titanium, carbon fibre, PEEK, ceramic and bioabsorbable implants)[147] are undergoing biomechanical testing.

Instrumentation also adds to the stability of fusion by load sharing and preventing graft extrusion and mal-alignment. Osteoporotic bone[35,53,132,160] presents unique biomechanical problems during instrumentation. Ventral cervical plating loads the graft in extension and may lead to graft pistoning and failure in multilevel constructs. The dynamic plates share loads more effectively than static plates. The lower end of the construct is more likely to fail, due to the longer moment arm and increased forces on caudal end of the construct. Comparison between anterior and posterior implants provides clinical guidelines.[27,68,133] The application of locking screws[161] to plates has greatly reduced the incidence of screw pullout. Ventral approaches to thoracic and lumbar spine have advanced because of better understanding of biomechanics and sagittal balance and permit short segment fixation. Circumferential fixation provides more stability than anterior instrumentation alone after cervical corpectomy. After corpectomy or spondylectomy, long circumferential instrumentation provides better stability than short circumferential fixation, except during axial rotation. Circumferential fixation more effectively prevents axial rotation after corpectomy than after spondylectomy.[37,134,159] In comparison to a tricortical iliac crest bone graft and a non-expandable cage, expandable cages have no biomechanical advantages. Due to the low extension and rotational stiffness, none of the implants can be recommended as a stand-alone device. Additional anterior plating increased biomechanical stability adequately.[69,73,162] Therefore, additional posterior stabilisation should only be considered in cases of severe rotational instability of the cervical spine. Threaded cages are comparable with 360 degree fusion.[143] The screw angle was the most important parameter that affected the final stiffness and the coupling behaviour. The initial stiffness was mainly afforded by the bone grip of the screw. Betz et al.[13] recommend that the anterior instrumentation should be put in place with the axis of the screws aligned as close as possible with the coronal plane and bi-cortical purchase is preferable. Biomechanical comparison of pedicular screws[63] has demonstrated that they are biomechanically more stable. A conservative construct utilising a single screw per vertebral body and a one-holed plate system appears to be strong enough to afford stability in both traumatic and non-traumatic lesions of the sub-axial cervical spine, comparable to others.[169,172]

FUTURE OF BIOMECHANICS

Fernstrom, in the 60s, implanted stainless steel spheres and began the modern era of applied biomechanics. This was followed by the AcroFlex artificial disc, the Charite artificial disc, disc nucleus replacement, posterior dynamic stabilisation systems, interspinous devices and facet joint arthroplasty.[3]

Non-fusion surgery using artificial ligament stabilisation,[67] dynamic stabilisation and the use of image guidance and dynamic imaging has become routine. Finite element method has been used in spine biomechanics research for nearly a quarter of a century and is being used to study spinal loading movements. It is also used to analyse load distributions and study mechanisms of injury.[186] These are then used to develop therapeutic interventions.[187] The micro-electro-mechanical system (MEMS) technology uses nano machines and integrates them on a chip. These are then used to measure, transmit and modify biomechanical properties and functions.[8] The combination of minimally invasive and image guided neurosurgery and restoration of normal biomechanics will lead to better outcomes in spine surgery.

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49 Injuries of the Craniovertebral Junction and Upper Cervical Spine

Sarat Chandra P, Vamsi Yerramani

INTRODUCTION

The region of the craniovertebral junction includes the occipital bone and condyles, the atlas and the axis. It is different from the remainder of the cervical spine with regard to its bony anatomy, joint shape and orientation. The craniovertebral junction has a complex bony anatomy designed to protect the vital neurological structures while offering the mobility required for head movements. Given the extent of mobility in different axis, this area is very much susceptible to injuries, especially in high-velocity automobile accidents. As the injuries at this level affect the cervical cord and the brainstem, it is imperative to maintain high index of suspicion and investigate this region thoroughly. Compounding the problems is the fact that most of the injuries in this region cannot be detected on routine cervical X-rays. In general, injuries of this region can be categorised as an isolated ligamentous or bony injury or as mixed ligamentous and bony injury. The bony injuries heal well with immobilisation when the fractured segments are well apposed. In contrast, ligamentous injuries heal poorly with immobilisation alone. In this chapter we deal with the fractures involving the individual bones forming the craniovetebral junction.

SURGICAL ANATOMY

The craniocervical ligamentous structures may be divided into intrinsic and extrinsic ligaments. The extrinsic ligaments include the ligamentum nuchae, which extends from the external occipital protuberance to the posterior aspect of the atlas and all the cervical spinous processes. Fibroelastic membranes replace the anterior longitudinal ligament, intervertebral disks, and ligamentum flavum between the occiput and atlas and between the atlas and axis. The atlanto-occipital and atlantoaxial joint capsules also contribute to the extrinsic stability.

The intrinsic ligaments, located within the spinal canal, provide most of the stability for the spine. These ligaments form three layers anterior to the dura (Fig. 1). From dorsal to ventral, they include the tectorial membrane, the cruciate ligament and the odontoid ligaments. The tectorial membrane connects the posterior body of the axis to the anterior foramen magnum and is the cephalad continuation of the posterior longitudinal ligament. The cruciate ligament lies anterior to the tectorial membrane, behind the odontoid process. The transverse atlantal ligament is the strongest component, connecting the posterior odontoid to the anterior atlas arch, inserting laterally on bony tubercles. Vertical bands extend from the transverse ligament to the foramen magnum and body of the axis. The odontoid ligaments (alar and apical ligaments) are the most ventral ligamentous structures. The paired alar ligaments connect the odontoid to the occipital condyles. They measure 5–6 mm in diameter and are relatively strong, in contrast with the small apical ligament that runs vertically between the odontoid and foramen magnum.

The range of motion between the occiput and atlas is 25 degree in flexion-extension, 5 degree to each side in lateral bending, and 5 degree to each side in rotation. The range of motion between the atlas and axis is 20 degree in flexion-extension, 5 degree in lateral bending, and 40 degree in rotation. The major stabilising structures between the occiput and upper cervical spine are

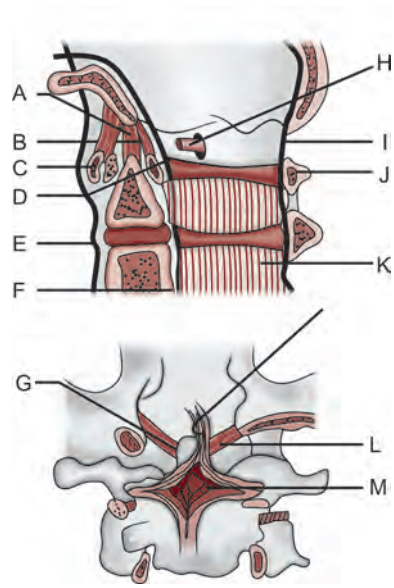


Fig. 1: Schematic diagram of the anatomical structures constituting the craniovertebral junction: (A) Apical ligament of dens. (B) Superior longitudinal band of cruciate ligament. (C) Anterior arch of C1. (D) Transverse ligament. (E) Anterior longitudinal ligament. (F) Posterior longitudinal ligament. (G) Odontoid process. (H) Vertebral artery. (I) Tectorial membrane. (J) Posterior C1 arch. (K) Ligamentum flavum. (L) Alar ligament. (M) Transverse ligament

the tectorial membrane and alar ligaments. Flexion is limited by the bony anatomy, while extension is limited by the tectorial membrane. Rotation and lateral bending are restricted by the contralateral alar ligaments. Distraction greater than 2 mm is prevented by the tectorial membrane and alar ligaments. Translation should not exceed 1 mm and is limited by the facet joints, when there are an intact tectorial membrane and alar ligaments.[11,44,46]

CLINICAL FEATURES

Craniovertebral junction and upper cervical spine injuries can result from various traumatic events. Motor vehicle accidents are the most frequent cause; however, falls, diving accidents and gunshot wounds are also common mechanisms. In addition, individuals may be predisposed to severe spine injury due to underlying congenital or developmental abnormalities, arthritic conditions or tumours.

Patients with an upper cervical injury may have an associated head injury, which can alter their level of consciousness and complicate obtaining an accurate history and physical examination. Consequently, all patients who sustain significant polytrauma and/or head trauma should be thoroughly screened for cervical spine injuries.

In history, it is important to find out the mechanism of injury (including potential forces imparted by the injury), whether the patient was restrained, and whether transient motor or sensory deficits occurred at the scene of the accident. Awake patients will often complain of neck pain or headache. Advanced Trauma Life Support procedures to maintain the airway, breathing and resuscitation should be the first priority. A careful, complete physical examination of the entire spine should follow—inspection, palpation and neurologic evaluation while the head and neck are stabilised in neutral alignment. Neurologic examination should include testing of the cranial nerves as well as motor function, sensory perception and reflexes in the extremities. Results of neurologic examination may range from normal sensorimotor functions to variable sensorimotor impairment, including incomplete to complete spinal cord injury. Cranial nerve injury—including of nerves VI, VII, IX, XI and XII—may result from upper cervical injuries and should not be overlooked.

The screening radiography should include anteroposterior (AP), lateral and open-mouth views. If detailed radiography is not possible, then even a good quality lateral view is sufficient in a patient without suspected injury, yet the examination should include an open-mouth view whenever upper cervical spine injury is suspected. The lateral radiograph should visualise the entire cervical spine from the base of the skull to T1.

With a normal atlanto-occipital relationship, the clivus on lateral radiograph should point towards the tip of the odontoid, and the basion (tip of the clivus) should be within 5 mm of the odontoid vertically. Retropharyngeal soft-tissue swelling greater than 5 mm at C3 is abnormal and should raise suspicion for the presence of an anterior arch fracture of the atlas. A diastasis greater than 2 mm between the occiput and atlas is also abnormal. Harris et al.[27] described the rule of 12, which is superior to the Powers ratio for identifying occipitocervical dissociation. The rule of 12 uses three landmarks:

- The basion
- The rostral tip of the odontoid
- The rostral extension of the posterior cortical margin of the axis (posterior axial line)

The basion-axial interval is the distance between the basion and the posterior axial line; the basion-dental interval is the distance between the basion and the tip of the odontoid. The method is applicable to adults and to children older than 13 years. Both intervals should be less than 12 mm in normal individuals (Fig. 2).

An open-mouth radiograph allows visualisation of the atlas, odontoid process and lateral masses of the axis. Although the lateral masses of the atlas normally articulate symmetrically with the axis, asymmetry between the dens and the lateral masses of the atlas is not always indicative of injury.

Careful follow-up is necessary in patients with initial cervical muscle spasm because the spasm may mask instability in the acute setting. Computerised tomography (CT) is a very sensitive method for evaluating craniocervical relationships and is the preferred method of investigation for evaluating most suspected injuries in the upper cervical spine. Properly oriented thin slices are necessary in the CT scan for proper visualisation of fractures. Magnetic resonance tomography (MRI) is

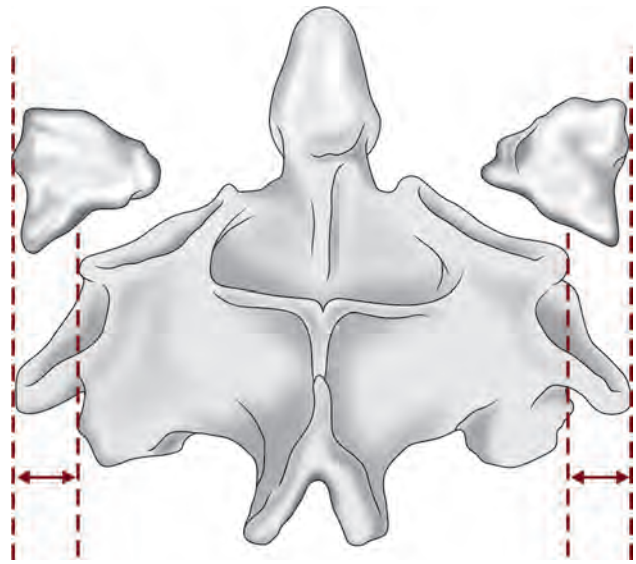


Fig. 2: Occipitocervical dissociation. The upper cross shows the basion and the lower cross the odontoid process. The distance between them is the basion-dental interval. The thick line represents the posterior axial line drawn posterior to the odontoid process and C2 body. The distance between it and the basion (upper cross) is the basion-axial interval. Both distances are >12 mm and clearly abnormal

useful in patients with neural deficit or with suspected ligamentous injury (especially the transverse atlantal ligament).[31]

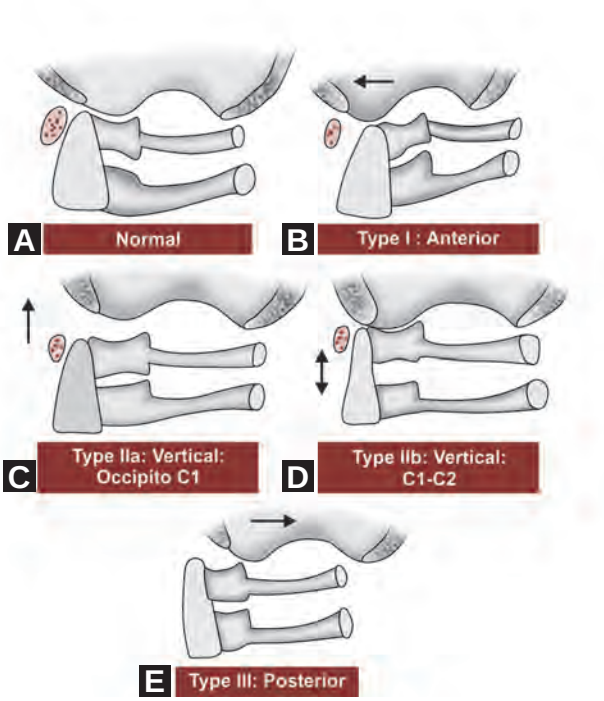
OCCIPITOCERVICAL DISSOCIATION

Occipitocervical ligamentous injuries have a high mortality rate and often do not reach the hospital. In autopsy studies, they represent 5–12% of identified cervical injuries; the most common mechanism is pedestrians struck by motor vehicles.[5,7,10] Prompt recognition, high index of suspicion and immobilisation are essential. Children are predisposed to these injuries because of their inherent ligamentous laxity; immature occipitocervical joints; and larger ratio of head to body size than in adults.

OCCIPITOCERVICAL INSTABILITY

This injury may occur due to several different mechanisms and can be classified according to the direction of occipital displacement[20] (Figs 3A to E):

1. Type I injuries are most common and have anterior occipital displacement
2. Type II injuries have vertical displacement greater than 2 mm between the occiput and C1 (Type IIA). Vertical instability also can occur at C1-2 (Type IIB) because the same ligamentous structures, the tectorial membrane and alar ligaments, resist distractive forces at both levels
3. Type III injuries are rare and have posterior occipital displacement.



Figs 3A to E: Schematic diagram showing various types of occipitocervical instabilities. (A) Normal relationship of occiput, C1 and C2 bodies. (B) Type I: anterior—the occiput has translated anteriorly. (C) Type IIa: vertical—vertical occipito C1 distraction. (D) Type IIb: vertical—vertical C1-C2 distraction. (E) Type III: posterior—posterior dislocation of occiput in relation to the C1

Early diagnosis and treatment are critical because patients are at high risk for neurologic injury or even sudden death. Once occipitocervical instability has been diagnosed, reduction of displacement should be performed carefully under fluoroscopic guidance by carefully positioning the head with a bolster behind the thorax (for anterior displacement) or the occiput (for posterior displacement). "Traction and collar immobilisation can precipitate axial displacement, precipitating neurologic injury and accordingly should be avoided". For vertical displacement, reduction can be performed by providing gentle downward pressure or by elevating the head of the bed. A halo vest can provide temporary immobilisation, but surgical stabilisation is necessary. Occipitocervical fixation and arthrodesis, using plates with C2 fixation obtained with C1-2 transarticular screws or C2 pedicle screws is preferable to wire and graft techniques. Fixation with plates and screws removes the need for a post-operative halo vest and more accurately maintains reduction.

CONDYLAR FRACTURES

Occipital condyle fractures are commonly caused by an axial compression mechanism and are frequently diagnosed as a concurrent finding on head CT scan done for trauma. The classification system described by Anderson and Montesano[1,3,6] was based on CT pattern and evaluates the potential for instability.

A type I injury is a comminuted (impaction) fracture of the condyle and is generally stable. A type II fracture is a condyle fracture with associated basilar skull fracture. This injury is stable except when the entire condyle is separated from the occiput. A type III injury is an avulsion fracture of the attachment of the alar ligaments. This injury can be bilateral and occurs in 30–50% of patients with atlanto-occipital dislocations. Stable type I and II fractures should be treated in a collar for 6–8 weeks. Displaced type II injuries should be treated in a halo vest for 8–12 weeks. Type III injuries are treated based on stability; stable undisplaced injuries are treated using a collar with a chin support, and minimally displaced injuries are treated in a halo vest. Any evidence of AP displacement, joint incongruity, or abnormal diastasis makes the injury unstable, necessitating an occiput-C2 fusion.

ATLAS FRACTURES

The atlas acts as a transitional structure between the occiput and cervical spine. In various adult series, fractures of the C1 vertebra have accounted for 25% of craniocervical injuries, 3–13% of cervical spine injuries, and 1.3–2% of all spinal injuries.[11,27,44,46] The most common causes are motor vehicle accidents and falls. The most common mechanism is axial loading. Atlas fractures are commonly associated with other injuries of the cervical

spine. Axis fractures are associated with 40–44% of atlas fractures.[21,24,25,30,41] Isolated fractures of the anterior or posterior arches are the commonest with isolated burst fractures next in line. Other associated injuries include subluxation, rupture of the transverse ligament, non-contiguous cervical spine fractures and closed head injuries.

Classification of Atlas Fractures

Sir Geoffrey Jefferson, a British neurosurgeon, presented a series of 42 patients with atlas fractures in addition to four of his own patients with the injury[28] (Fig. 4).

Type I fractures involve the posterior arch alone.

Type II fractures involve the anterior arch alone.

Type III fractures are bilateral posterior arch fractures associated with a unilateral or bilateral anterior arch fracture.

Type IV fractures involve the lateral mass.

Type V fractures are transverse fractures of the anterior arch.

The classic Jefferson fracture is the burst type III fracture associated with lateral displacement of the lateral masses. Based on Jefferson's classification, the most common fracture types seen in various clinical series are type I followed by type III.

The transverse ligament plays a crucial role in determining atlantoaxial stability.[15] Atlas fractures have often been defined as stable or unstable based on the inferred integrity of the transverse ligament. According to the Spence[43] rule, if the sum of the displacement of lateral masses exceeds 6.9 mm after an atlas burst fracture, the transverse ligament is probably torn (Fig. 5).

Clinical Presentation

Patients with upper cervical spine fractures frequently present with neck pain, spasms of the cervical muscles and limited neck motion.[44] Neuralgia and paraesthesias related to compression of or injury to the C2 nerve are common. Retropharyngeal swelling may cause difficulty in swallowing. Dissecting injuries of the vertebral artery and neuropathies of the lower cranial nerves are some of the uncommon presentations. Isolated burst fractures of the atlas usually are not associated with neurological deficits as they cause the spinal canal to expand.

Diagnosis

To evaluate atlas fractures using plain X-rays, it is essential to obtain open-mouth odontoid, lateral and

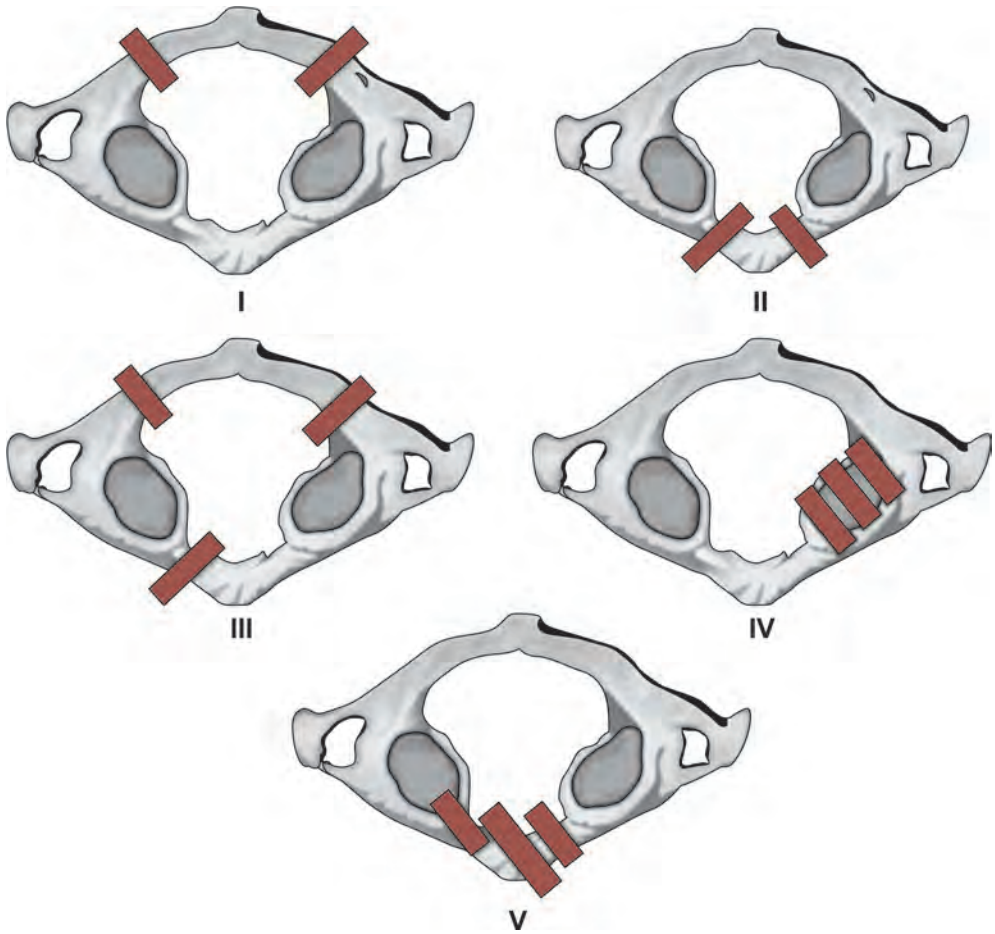


Fig. 4: Jefferson's classification for atlas

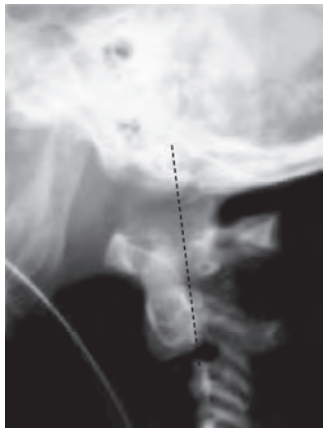


Fig. 5: Assessing for transverse atlantal ligament injury on an open-mouth view of C1-2. The sum total of lateral displacement equals a + b. When the total displacement is >6.9 mm, rupture of the transverse ligament is confirmed. (Adapted from Anderson PA. Injuries to the occipital cervical articulation. In: Clark CR, Dvorak J, Ducker TB (Eds). The Cervical Spine, 3rd edition. Philadelphia, PA: Lippincott-Raven; 1998. p. 411.)

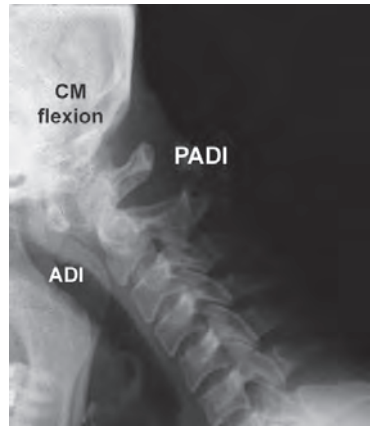


Fig. 6: The following roentgenogram shows the criteria for atlanto-axial instability: (1) Atlantodental interval (ADI) >3 mm (5 mm in children). (2) Posterior atlantodental interval (PADI) <13 mm (measured as the distance between posterior border of the dens and the C1 arch. (3) Unilateral axial rotation >45 degrees. (4) Lateral mass overhang >7 mm. Criteria 3 and 4 are better made out on anteroposterior views

flexion-extension views. An open-mouth odontoid view will show overlapping of the C1 and C2 facets. Any displacement of the C1 lateral mass over C2 facets is suggestive of an atlas burst fracture. In a normal variant (pseudo-spread of the atlas) in children younger than 7 years old, the ossified lateral masses of the atlas may project beyond the ossified articular processes of C2, giving a false sign of a Jefferson fracture in children.

In lateral views, an atlantodental interval (ADI) greater than 3 mm in adults and greater than 5 mm in children is highly suggestive of a ruptured transverse ligament. The MRI is the modality of choice for assessing the transverse ligament integrity.[12] Posterior atlanto dental interval (PADI) is measured from the posterior border of the dens to the anterior border of the posterior tubercle. This index may be more important because it more directly assesses the space available to the spinal cord. The degree of neurologic deficits has been demonstrated to correlate with the PADI. A PADI of less than 13 mm is considered significant (Fig. 6). Posterior arch fractures can be assessed on lateral or 60 degrees oblique X-rays. Anterior arch fractures are often difficult to diagnose from plain X-rays. To rule out pseudo-spread of the atlas, thin-slice CT with cuts parallel to the C1 arch is the optimal imaging modality and is recommended for all children suspected of harbouring a Jefferson fracture.

Treatment and Results

Treatment of atlas fractures depends on whether they occur in isolation or in conjunction with other cervical spine fractures. Treatment recommendations are based on several case series (class III evidence), which are summarised below:

- Isolated atlas fractures can be treated by external immobilisation of the craniocervical junction for 8–12 weeks
- Late instability must be ruled out by using dynamic imaging studies such as flexion-extension X-rays
- Instability persisting after external immobilisation should be treated by an occiput–C2 fusion or a C1-C2 fusion, whatever suits the given case
- There are no established standards or guidelines for the treatment of combined C1-C2 fractures. The treatment strategy is based on the nature of the C2 fracture and the integrity of the transverse ligament.
- Presence of an occipitoatlantal dislocation warrants occipitocervical fusion.

RUPTURE OF TRANSVERSE LIGAMENT

Rupture of the transverse atlantal ligament is generally caused by a flexion force and often affects not only the transverse ligament but also the alar and apical ligaments. With an intact ligament, the maximal ADI is 3 mm in an adult and 5 mm in a child. Experimentally produced transverse ligament insufficiency with intact alar and apical ligaments results in a maximal translation of 5 mm, as shown by Fielding et al.[16] Displacement greater than 7 mm was associated with loss of integrity of the alar ligament and tectorial membrane. Complete ligamentous disruption can be accompanied by a significant incidence of neurologic injury. In addition, headache, nausea, visual abnormalities and sensorimotor deficits may result from vertebral artery compression.

Disruption may occur in isolation or in association with other upper cervical injuries. Using thin-section CT or MRI Dickman et al.[12] classified disruptions of the mid substance of the ligament as type I injuries and avulsions of the ligament from the C1 lateral mass as type II injuries.

Treatment depends on the degree of initial displacement and identification of any coexistent fractures. If the ADI is less than or equal to 5 mm in a neurologically

intact patient, collar immobilisation is sufficient initially. For an ADI greater than 5 mm, non-surgical treatment including halo immobilisation has generally yielded poor results except in selected cases when a bony avulsion can be documented on CT. The method used for C1-C2 arthrodesis in patients with this injury needs to be carefully selected; some wire techniques, even with halo immobilisation can result in post-operative displacement. C1-C2 transarticular screw fixation for arthrodesis may be indicated.

ODONTOID FRACTURES

The first description of the surgical management of an odontoid fracture was in 1910 and is credited to Mixter and Osgood.[36] Odontoid fractures constitute 8–18% of all cervical fractures, with neurologic deficits occurring in 10–20% of cases.[13,37,38] They represent 75% of childhood cervical spine fractures as a result of the large ratio of head to body size. High-velocity trauma, such as motor vehicle accidents, accounts for most of these injuries in young adults, while low-velocity injuries, such as falls, account for the majority of injuries in the elderly and children.

The classification system of Anderson and D'Alonzo[2] is based on the anatomic level of the fracture, which has been shown to have a correlation to prognosis for fracture healing (Fig. 7).

Type I fractures occur at the tip of the odontoid process cephalad to the transverse atlantal ligament. They are the least common odontoid injury and generally are stable. They may also represent an avulsion of the alar ligaments, which can occur in atlanto-occipital distraction injuries.

Type II fractures occur at the junction of the base of the odontoid and body of the axis. They are the most common fracture type and are least likely to heal with non-surgical treatment and are unstable. These fractures were subdivided into three types by Hadley et al:[23]

- Type IIA: The fracture line is transverse and with less than 1.0 mm of displacement. Both surgery and external immobilisation have good success rates. The treatment strategy has to be decided based on the individual merits of the case
- Type IIB: The fracture line is from antero-superior to postero-inferior or a transverse fracture with displacement greater than 1.0 mm. Surgical fixation is the treatment of choice
- Type IIC: The fracture line passes from antero-inferior to postero-superior or a fracture with significant comminuted segments of the dens. This subtype is best treated with posterior atlantoaxial fixation. The fractured odontoid process may be displaced anteriorly or posteriorly relative to the body of C2. Odontoid screw placement in these fractures is technically difficult and also the non-union rates are high. Posterior fixation is a good option in this group of patients

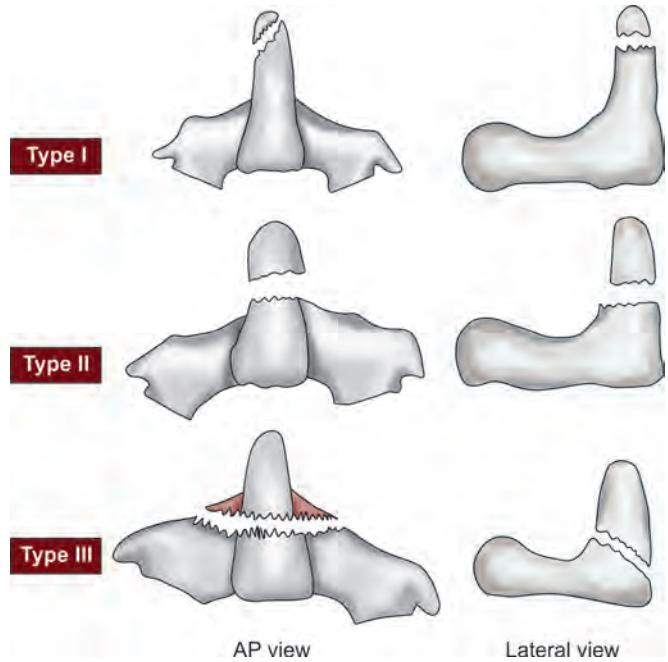


Fig. 7: Classification of dens fractures

Type III fractures extend into the body of the axis. They may be more stable than type II fractures and have a higher union rate with non-surgical treatment.

Treatment

There have been many treatment strategies proposed for odontoid fractures. These strategies are based on fracture type, the degree of initial dens displacement, the angle of the fracture line with respect to the body of the axis, the integrity of the transverse ligament and the age of the patient. Treatment options include both non-operative and surgical strategies. There are several external immobilisation orthoses available for non-operative management of odontoid fractures, each with variable results. Surgical options include both anterior and posterior approaches. Anterior approaches include odontoid screw fixation and a rarely used salvage technique of anterior transarticular screw fixation. Posterior arthrodesis approaches include the use of wiring techniques, Halifax clamps, screw and rod constructs, and posterior transarticular screw fixation.

Julien et al.[29] performed an evidence-based analysis of the literature to evaluate the management of odontoid fractures. Halo/Minerva fixation or cervical traction followed by immobilisation in a rigid cervical collar resulted in fusion of all type I odontoid fractures and 84–88% of type III fractures. Cervical traction followed by immobilisation is not the most effective treatment of type II odontoid fractures. They reported that treatment of type II fractures with cervical traction/cervical collar resulted in a fusion rate of only 57%. Management with a halo-type orthosis has a variable non-union rate from

7% to 100%. Hence, it is clear from this study that while type I fracture may be treated conservatively, type II has to be always treated surgically. Both surgery and medical treatment have been shown to be effective for type III fractures, hence either option is suitable.

TRAUMATIC SPONDYLOLISTHESIS (HANGMAN'S FRACTURE)

Traumatic spondylolisthesis of the axis most often occurs as a result of either motor vehicle accidents or falls and represents approximately 15% of all cervical spine fractures. Although the fracture pattern may resemble that resulting from judicial hanging, the injuries are quite different. A properly accomplished judicial hanging results in a violent hyperextension injury to the spine with distraction, severing the spinal cord. Traumatic spondylolisthesis, however, results from hyperextension with axial load. Neurologic injury is uncommon because the fracture fragments separate, decompressing the spinal canal.[32]

The hyperextension and axial load mechanisms result in fractures of the pars interarticularis. With increasing severity of injury, the rebound flexion or flexion/distraction mechanism results in disruption of the C2-3 disc and posterior longitudinal ligament. Additionally, the anterior longitudinal ligament may be stripped from its bony attachment. The most severe and complex injuries most likely occur as a result of flexion, causing dislocation of the C2-3 facets, followed by hyperextension with axial load, producing the pars fractures secondarily.

The classification system for this injury was first described by Effendi et al.[17,32,33,40] in 1981 and was later expanded by Levine and Edwards,[32] who described four fracture patterns. Others have added a fifth type[17] (Fig. 8). The classification is based on translation and angulation between C2 and C3. Type I injuries are bilateral pars fractures with translation less than 3 mm and no angulation. The C2-3 disc and ligamentous structures remain intact because the major injury is bony.

Type IA is an atypical fracture and the most recently recognised. There is minimal translation and little or no angulation. Elongation of the C2 body is often seen radiographically. The CT will reveal extension of one fracture line into the body and often through the foramen transversarium. As a result, injury of the vertebral artery may occur.

In Type II fractures, the C2-3 disc and posterior longitudinal ligament are disrupted, resulting in translation greater than 3 mm and marked angulation. The anterior longitudinal ligament generally remains intact, but is stripped from its bony attachment.

Type IIA fractures are less common. In contrast with type II, the fracture line is more oblique than vertical. There is little or no translation, but there is significant angulation. Traction will cause further fracture displacement and should be avoided.

Type III injuries are a combination of pars fracture with dislocation of the C2-3 facet joints. This injury is very unstable with free-floating inferior articular processes. This is the most common injury to be associated with neurologic deficit and requires surgery; it is irreducible by closed means.

Type I and IA fractures can be treated by collar immobilisation, both initially and definitively. Type II and IIA fractures require gentle reduction. Type II fractures require light traction and extension by placing a bolster behind the shoulders to achieve reduction. Type IIA fractures require extension and gentle axial load to achieve reduction. Type III fractures are irreducible because the dislocated inferior facets of C2 are not connected to any other bony structure as a result of the bipedicular fracture lying just anterior to them. Closed traction is, therefore, unable to provide reduction and open reduction is required.

Once reduction is verified radiographically, type II fractures are immobilised in a halo vest for 6–8 weeks. Adjustment of the halo may be performed as necessary while monitoring fracture alignment. For type II fractures with displacement greater than 5 mm and/or angulation greater than 10 degree, traction is performed to reduce the displacement, followed by halo immobilisation for an additional 6–8 weeks. Alternatively, surgical stabilisation with transpedicular lags crews may be considered if anatomic alignment can be achieved. Because spontaneous anterior fusion is common, non-surgical

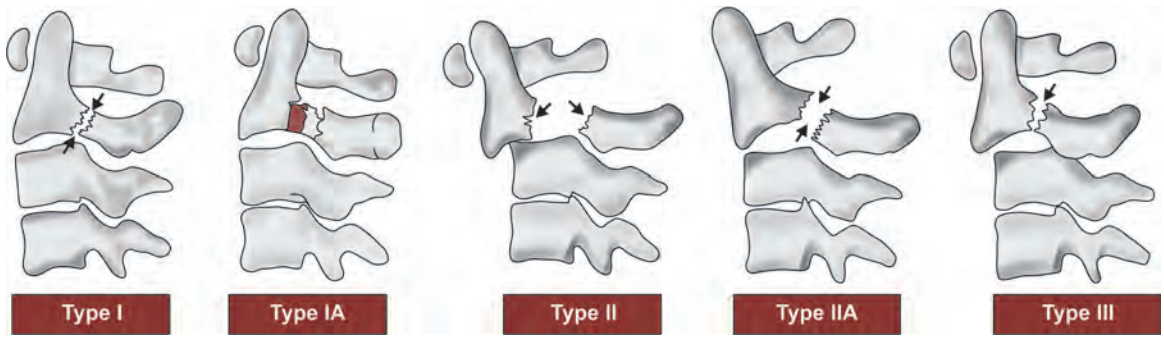


Fig. 8: Classification of traumatic spondylolisthesis (Adapted from Levine AM, Edwards CC. The management of traumatic spondylolisthesis of the axis. J Bone Joint Surg Am. 1985;67:217–26)

management is favoured with type II injuries. Type III fractures require open reduction followed by internal fixation with a wiring or plating technique, based on the integrity of the facets and/or lamina. Anterior C2-C3 plating also has been used.

Although no long-term studies exist, Levine and Edwards[32] reported on 52 patients with a 4.5-year follow-up. Ninety percent of type I fractures healed; 10% had symptomatic degenerative changes; 70% of type II fractures developed spontaneous anterior fusion. Type III fractures generally had a poor prognosis related to the resultant neurologic deficit. Francis et al.[17] reported on 123 patients with traumatic spondylolisthesis of the axis, who had a 94.5% union rate regardless of initial displacement or angulation. Seventy two percent were treated with traction and halo immobilisation, with a 5% non-union rate. Duration of traction did not influence fracture healing because 47% were treated with less than 2 weeks of traction, with only one non-union. Alternatively, more recently, surgical treatment is the preferred option[8,9,14] as it has a low-risk and up to 98% fusion rates with transpedicular screw fixation.

OPTIONS OF SURGICAL PROCEDURES FOR CRANIOVERTEBRAL JUNCTION TRAUMA

Posterior Fusion Techniques

Historically, posterior cervical fusion (Figs 9A to L) was the primary operative alternative when external immobilisation failed or was considered unsuitable.

Wiring Techniques

Over time, wiring techniques have evolved to the use of braided cables instead of monofilament wire. Braided cables have the advantage of being flexible, strong, and resistant to distortion and fatigue. Braided cables also are not susceptible to over twisting because a crimping mechanism is used to securely lock and fix the construct. Braided cables, however, can cut through bone via a Gigli saw-type action. Therefore, it is recommended that crimping not exceed a torque of 8–12 in-lb of force for normal healthy lamina and 6–8 in-lb for osteoporotic bone (Fig. 9A).

Gallie's Technique

Gallie[18] described his method of C1-C2 arthrodesis in 1939. A superior notch in the spinous process of C2 holds the H-shaped on-lay graft more securely in place, and the graft is secured with a wire that is only sublaminar at C1. The drawback of his technique is that it is a solitary, midline fixation and fusion construct susceptible to rotational forces.

Brooks' and Jenkin's Technique

It involves two wedge bone grafts secured between C1 and C2 with sublaminar wiring. They designed it to overcome the rotational deficiencies of the Gallie method.

Dickman and Sonntag

Dickman and Sonntag described an atlantoaxial arthrodesis secured with a sublaminar wire at C1 that incorporated an iliac crest strut-graft between the posterior arches of C1 and C2 secured with wire around the base of the spinous process of the axis.

Interlaminar Clamps

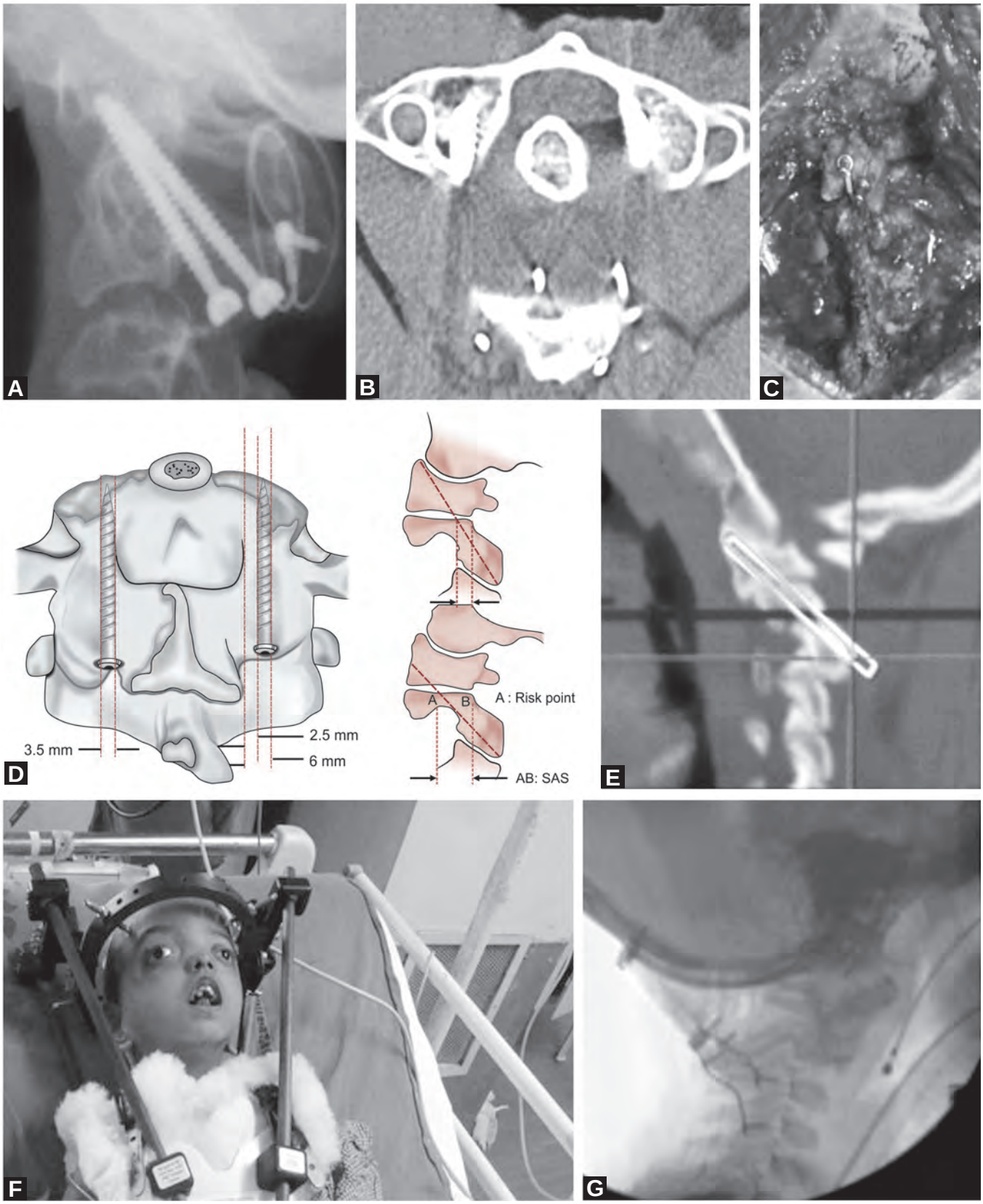
Halifax clamps were initially described by Tucker[45] in 1975. Several problems were observed with these clamps, and they ultimately fell out of favour. One problem was that in tightening the clamps, the odontoid could be angulated dorsally, causing ventral encroachment upon the spinal cord. There were several other problems reported. The superior clamp sometimes did not mate well with the C1 lamina. The screws and, therefore, clamps became loose with time. A large C2 spinous process makes vertical alignment of the clamps difficult, causing suboptimal interface of the clamp with the C1 lamina. Any one of these problems could cause the clamps to disengage.

Jeanneret and Magerl Transarticular Screw Technique

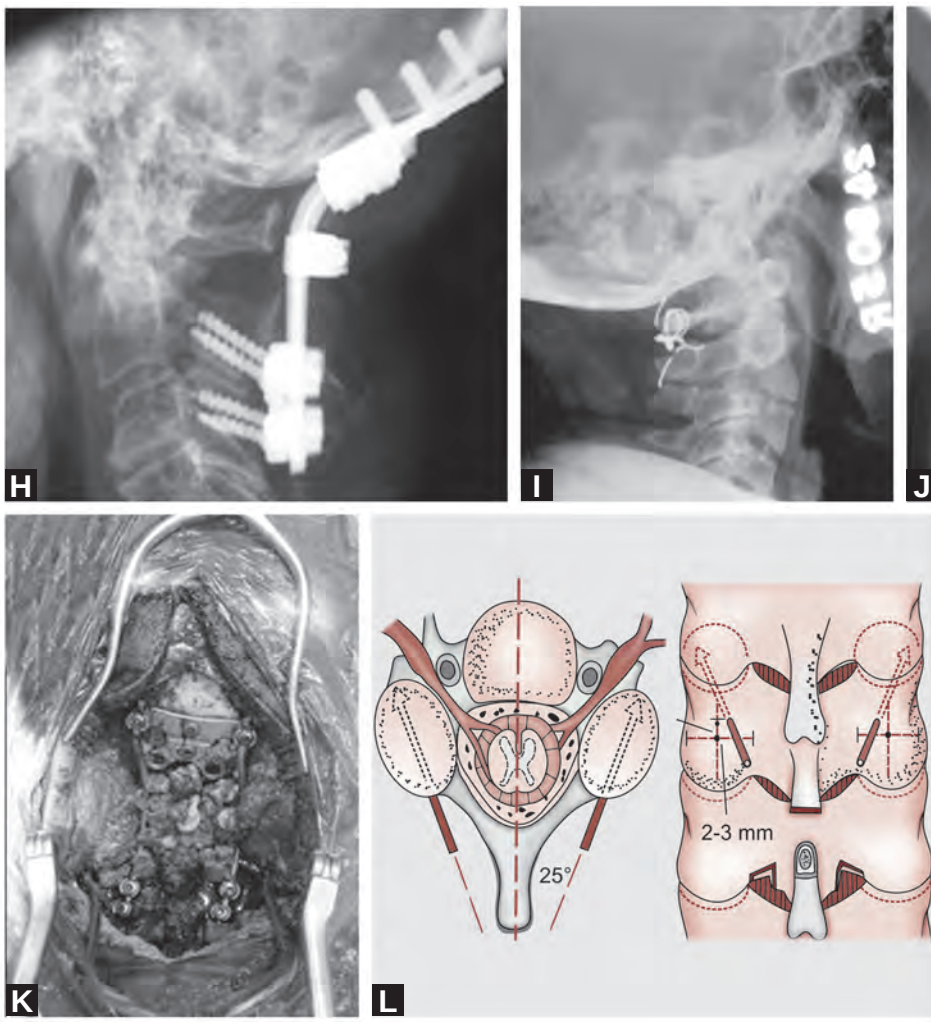
Transarticular screw fixation of C1 and C2 was first described by Magerl and Seeman.[34] The entry point on C2 is 2 mm lateral from the medial edge of the facet and 3 mm superior to the caudal edge. The trajectory is straight up across the C1 and C2 articular surfaces and into the lateral mass of C1. The drill is aimed at the superior portion of the C1 anterior arch. Transarticular screws offer good biomechanical stability in all directions of motion compared to the wiring techniques. Bone fusion rates range between 98% and 100%. When the anatomy is favourable, this is the preferred method of posterior fixation. Transarticular screws combined with C1-C2 wiring techniques have achieved 100% fusion rates. Posterior fusion may be preferred in patients who have a comminuted type II or III fracture or an associated unstable Jefferson fracture. C1-2 joint fusion eliminates 50% of the rotation of the head, a significant loss of motion. Consequently, a technique for treating odontoid fractures, anterior odontoid screw fixation, has been developed to preserve the normal motion of the C1-2 joint.

Goel and Laheri/Harms and Melcher Fixation

The use of lateral mass screws in C1 and pedicle screws in C2 with plate fixation was first described by Goel and Laheri[19] in 1994 and later with polyaxial screws and rods in 2001 by Harms and Melcher.[26] A point of difference between the two methods is that Goel and Laheri described distraction of the C1-C2 joint space with spacers. Resnick and Benzel[39] described a C1-C2 fixation method similar to the Harms and Melcher method using C1 and C2 pedicle screws. This method of atlantoaxial fixation is the procedure of choice for



Figs 9A to G: Posterior procedures for craniovertebral complex. (A) C2-C1 transarticular screws (Magrel's) with braided titanium wiring. (B) Computerised tomography (CT) axial section showing position of screws shown in 8. (C) Operative view of 9A and B. (D) Entry point for C1-C2 Magrel's technique. (E) Using C2-C1 transarticular screw using image guidance. (F) Halo immobilisation is useful especially for paediatric age group especially when instrumentation cannot be used due to (G) Immature bone



Figs 9H to L: (H) Shows use of translaminar screws. (I) Single stranded stainless steel wire though cheap has the disadvantage of breaking. (J) C1 and C2 transpedicular screws (Goel's technique). (K) Occipitocervical poly axial lateral mass screw fixation. Note that presence of a midline occipital plate provides the maximum strength for occipital screws. (L) Schematic diagram showing the entry point for cervical (C3-C6) lateral mass screws

patients with C1-C2 fixed (irreducible) subluxation or an aberrant vertebral artery that may make transarticular screws difficult and/or dangerous.

Crossed C2 Intralaminar Screws

In 2004 Wright[47] described the most recent technique for screw fixation of the axis. This technique involves the use of polyaxial screws inserted into the lamina of C2 in a bilateral crossing fashion.

Occipitocervical Lateral Mass Polyaxial Rod and Screw Placement

This technique has become very widely accepted due to rigid long segment immobilisation and distraction forces provided, along with the ease, safety and strength of the lateral mass screws. Lateral mass screws are available as 12, 14 and 16 mm polyaxial screws of diameter 3.5 mm. They are placed about 1 mm medial to the centre of the lateral mass (C3-C6) and directed lateral and superiorly at an angle of 25 degree. However, before performing the procedure, it is essential that the adequacy of the lateral mass of the cervical vertebrae is confirmed on CT scan bone windows.[4,35,42]

If all the techniques are compared, Magrel's (C2-C1 transarticular) provides maximum strength against axial rotation, followed by Brook's, Halifax, the least being Gallie's technique.[22] Likewise, if other movements like flexion, extension and lateral bending are assessed, Brooks has the most stability followed by Magrel's, Halifax and again least by Gallie's procedure. Not surprisingly, bone fusion is least for Gallie's (60–80%) and Magrel's has the highest incidence of bone fusion (95–100%).

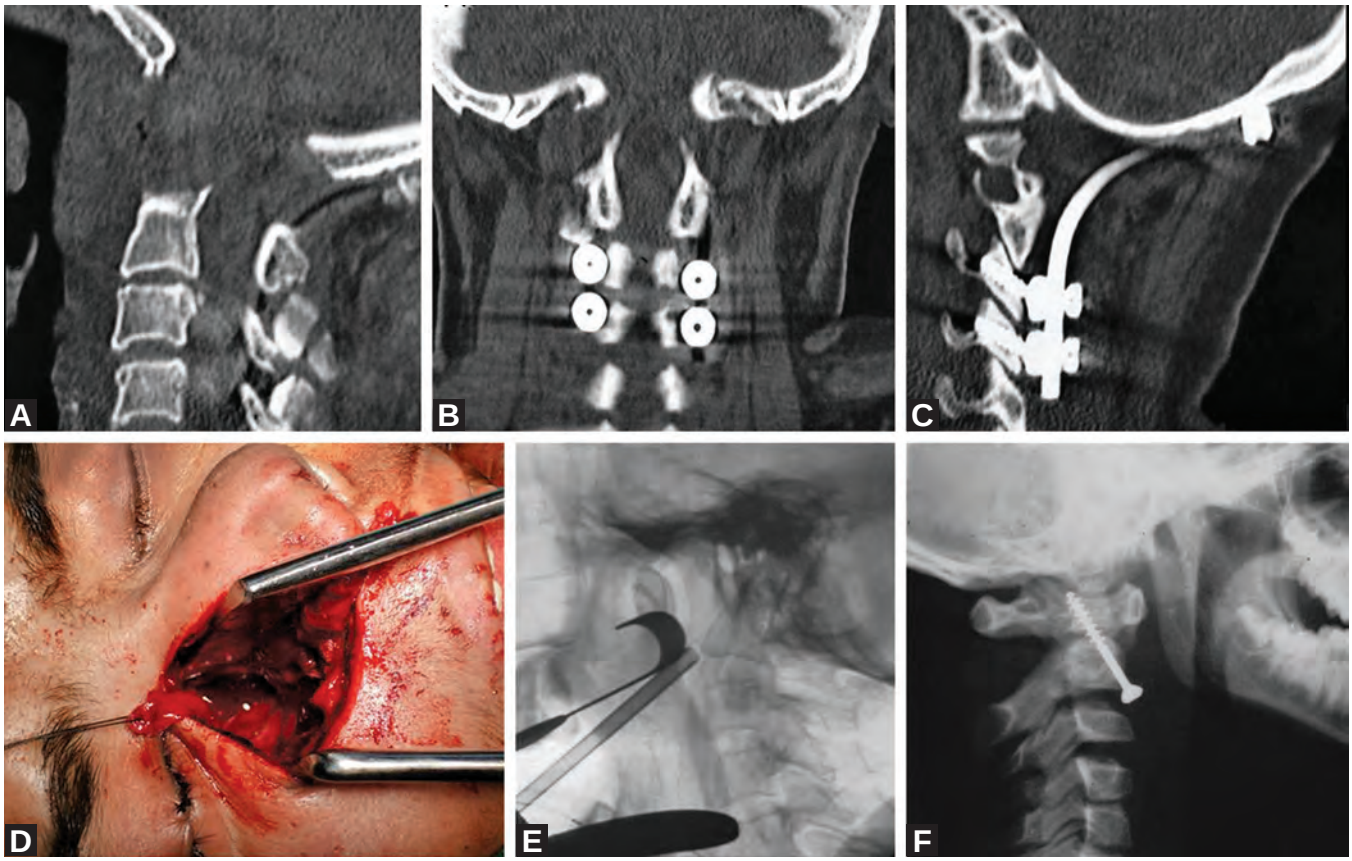
Anterior Fusion Techniques

Anterior fusion can be performed by techniques (Figs 10A to F) as mentioned below.

Odontoid Screw Fixation

There occurs a reduction of 47 degree of axial rotation and a reduction of 10 degree of flexion and extension after posterior atlantoaxial internal fixation and fusion. Odontoid screw fixation allows the surgeon to directly reduce and fixate the fracture itself, while maintaining atlantoaxial rotational mobility. Disruption of the transverse ligament is an absolute contraindication to odontoid screw fixation. Displacement more than 6 mm, age greater than 50 years, fractures more than 6 months old and poor patient habits are associated with high rates of non-union.

The issue of whether to place one or two odontoid screws is controversial. Two-screw constructs have been



Figs 10A to F: Anterior procedures for the craniovertebral junction. (A) Transoral odontoid excision indicated for old odontoid fractures type III fractures with impingement on the cord. (B and C) Transoral odontoid excision should be followed by a long segment posterior fixation, e.g. occipitocervical lateral mass fixation. (D and E) Extended approaches for transoral odontoid excision are rarely required unless the dens is placed quite high up, e.g. in fracture clivus. (F) Odontoid screw fixation is indicated in type II and some type III fractures

advocated to prevent an axis of rotation around a single screw. In some patients, however, the odontoid process is not large enough to accommodate two screws.

Anterior Atlantoaxial Facet Screw Fixation

This is a rarely used technique described by Feiz-Erfan et al.[14] for failed posterior atlantoaxial fusion or for C1-C2 instability with destruction of the posterior elements of C1 and C2. The approach for this procedure is the same as that for odontoid screw fixation. The C1-C2 joint is identified bilaterally, and screws are placed in the anterior cortex of C2 and through the C1-C2 joint space at a 90-degree angle.

SUMMARY

Injuries of the upper cervical spine are a major cause of morbidity and mortality. Although survival is increasing secondary to improved traffic safety measures and advances in spinal stabilisation techniques, the injury patterns are numerous and the neurologic sequelae many. Careful emergency management, a high index of suspicion and complete evaluation minimise delays in diagnosis. The possibility of concomitant injuries should always be suspected because the incidence is high. The goals of treatment are to protect the neural structures, reduce and stabilise the injured segment, and provide long-term stability. Non-surgical treatment often can be instituted with a satisfactory outcome.

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50 Injuries of the Subaxial Cervical Spine

Anil Pande, Ravindranath Kapu

INTRODUCTION

The subaxial cervical spine, also called the middle and lower cervical spine, includes the cervical spine from C3 to C7 and the craniovertebral junction is excluded, as the anatomy and biomechanics of these two regions are quite different. The cervical region is the most vulnerable part of the spinal column due to increased mobility, small vertebral bodies, oblique articular facets and the mobility of the heavy skull on the cervical spine. Cervical spine injury occurs in 2–3% of patients with blunt trauma who undergo imaging and is the most frequently injured spinal region following trauma.[3] An incidence of 14,000 injuries/year in North America has been reported with most of these being cervical.[22] Accidents are the most common cause of injury. Subaxial spine injuries include musculoligamentous sprains, whiplash injuries, traumatic disc prolapse, fracture dislocations, burst fractures, locked facets, posterior element fractures, cord contusions and, rarely, extradural haematoma and subdural haematoma. The paediatric and geriatric age groups present differently.[71,105] Spinal cord injury without radiological abnormality (SCIWORA) is seen in children who have a more elastic spine. Patients with congenitally narrow canals (<13 mm) are more predisposed to neural injury. Patients who have connective tissue abnormalities, e.g. Down's syndrome, collagen disorders, diffuse idiopathic skeletal hyperostosis (DISH) and fluorosis, have more serious injuries.[117,118]

HISTORICAL BACKGROUND

The ancient Indian surgical classic "*Sushruta Samhita*" has a chapter on the management of recent traumatic wounds, followed by a chapter on the management of fractures and dislocations. Twelve types of fractures and six types of dislocations are mentioned along with four methods of reduction, i.e. traction, pressure, apposition and bandaging with bark splints. Sushruta describes the reduction of a cervical fracture by manual traction followed by splinting and bandaging.[104] For the next 2,700–2,900 years, the treatment guidelines did not change significantly.[63,64,79]

Most technical advances in cervical spinal surgery have been made in the last 50 years.[79] Before the era of spinal instrumentation and routine use of the operating microscope, most of these injuries were managed with traction, postural reduction and external immobilisation.[63,79] Surgical corridors were then developed to approach the subaxial cervical spine according to the site of pathology.[116] The experimental work of Roaf[90] was based on many earlier contributors to the study of spinal instability and the understanding of the biomechanics was essential for the evolution of surgery of subaxial spine injuries.[5,11,25,79,119] In 1968, Kelly and Whitesides proposed the evaluation of thoracolumbar spinal injuries in terms of anterior and posterior columns[79] which was adopted by Holdsworth for the cervical spine, and he suggested several mechanisms of cervical spinal injury.[45] The work of the American neurosurgeon Schneider[95–99] has been seminal in the understanding and management of spinal cord syndromes.

Posterior Era

The results of spine trauma surgery were poor with no microscope and modern imaging and surgical approaches that were essentially posterior. Although, most spinal injuries involve the anterior and middle column, approaching the spine from the posterior side was detrimental, as the only undamaged column was injured during surgery. Berthold Hadra[42] described his technique of spinous process wiring in 1891 and pioneered the spinal instrumentation era and, in 1942, Rogers suggested his interspinous wiring method for cervical trauma. This was modified by Bohlman as quoted by Omers et al.[79] as "Triple Wiring Technique". Scoville and Whitcomb in 1966 introduced the posterior approach to the cervical disc. Roy-Camille[92] introduced screws into the lateral masses of the cervical spine to stabilise the unstable spine in 1964. Luque rods with sublaminar wires were introduced in the 1970s[79] and this technique has been used of late with less frequency in the subaxial cervical spine. Facet wiring was modified in 1977 by Callahan to stabilise the spine in the absence of laminae. Posterior wiring techniques have been modified by Benzel[10] and others[19] for use in middle and lower cervical spine injuries. Thereafter, interspinous wiring, facet wiring and sublaminar wiring techniques evolved to the current lateral mass screws and pedicle screws with plates and rods.

Anterior Era

The anterior approach to the cervical spine was introduced in 1955 by Robinson and Smith.[91] Verbiest[116] reported on 47 cases of subaxial spine injuries and their surgical management. In the presence of multiple column injury and resultant instability, anterior fusion, when attempted using bone graft alone, was followed by graft extrusion and retropulsion, causing neurological deterioration and deformities. The need to provide immediate stability and allow for bone fusion led to the development of anterior plate systems. Bohler,[13] in 1967, first reported the use of anterior cervical plate and screw fixation in a patient with cervical spinal trauma. Cloward[23] popularised the anterior approach and introduced dedicated instrumentation for this procedure. An early plating system for anterior stabilisation was designed by Orozco.[80] He described the use of a one-third tubular plate in the 1970s, and subsequently designed custom "H" and "HH" plates, which were adopted by the Arbeitsgemeinschaft fur Osteosynthesefragen (AO) for use throughout Europe in anterior cervical spine surgery.[79] Caspar[20] developed a "trapezoidal" rigid plate with bicortical screws in 1980 for use in the cervical spine. Morscher devised unicortical locking screws in the 1980s.[79] In 1994, Abumi et al.[2] were the first to report the successful use of cervical pedicle screws in managing subaxial traumatic instability. Dynamic load-sharing plates with variable angle screws were introduced in 2000.[15,79]

The use of the surgical microscope, high-speed drills, intra-operative fluoroscopy and somatosensory, and motor evoked potential monitoring have become common in surgery of the subaxial cervical spine. The availability of neuronavigation allows for precise cervical screw placement and, recently, there has been resurgence in the use of posterior approaches and instrumentation in subaxial spine surgery.

ANATOMICAL CORRELATES OF THE SUBAXIAL CERVICAL SPINE

Knowledge of the surgical anatomy of the subaxial cervical vertebrae, spinal cord and the arterial and venous relations is essential to effectively manage traumatic lesions of the subaxial cervical spine.[32,66,78,81,82] The subaxial cervical spine includes the vertebral bodies, upper and lower articular processes, pedicles, lamina, a bifid spinous process, transverse process and uncinate process which forms the uncovertebral joint (Fig. 1). The vertebral body height increases from C3 to C7 with a slight reversal of this relationship at C6. Each body has an uncus; laterally is the ventral ramus of the transverse process and dorsolaterally the pedicle. Computer-assisted anatomic images of cadaver cervical spines were obtained for measurements of the disc spaces and vertebral bodies by Lu et al.[66] and this data from cadavers may be helpful during the anterior approach for discectomy, vertebrectomy and anterior screw-plate placement. The anteroposterior (AP) depth gradually increases from 16.56±2.21 mm at C3 to 19.32±2.30 mm at C7. Greater values of AP depth at the inferior endplate were found at C5 (20.75±2.87 mm) and C6 (20.56±2.31 mm) compared with the values at C3 (18.26±1.82 mm), C4 (19.27±2.88 mm) and C7 (19.21±3.22 mm). The AP depth at the superior endplate was greater than that at the inferior endplate. The height of the disc space was found to be lowest at the posterior disc space from C2-3 to C7-T1 (2.95±0.86 mm at C2-3, 2.78±0.93 mm at C3-4, 2.45±0.79 mm at C4-5, 2.92±0.64 mm at C5-6, 2.46±0.59 mm at C6-7, 2.93±1.05 mm at C7-T1), when compared to the height of the disc space at the anterior disc space from C2-3 to C7-T1 (4.07±0.85 mm at C2–3, 4.34±1.18 mm at C3-4, 3.95±1.37 mm at C4-5, 3.55±1.37 mm at C5-6, 3.55±0.76 mm at C6–7, 3.67±1.17 mm at C7-T1). The mid-axis of the disc space was situated at approximately 3 mm above the anterior midpoint of the annulus fibrosus at the level of the lower cervical spine. To reach the posterior portion of the disc space from the anterior midpoint of the annulus fibrosus, a 5 degree cephalad angulation of the drill relative to the mid-axis of the disc space was considered necessary by Lu et al.[66] The uncovertebral joints prevent excess lateral translation and allow for coupled lateral bending and rotation of the cervical spine. The lateral surface of the pedicle, the dorsal surface of the anterior tubercle and the ventral surface of the posterior tubercle form the foramen transversarium, which transmits the vertebral artery. Oh et al.[78] found that the vertebral artery migrates from posterior to anterior, from C3 to C6 and posteriorly again at C7; and these variations were relevant while decompressing the neural foramen. Subaxial spine pedicles connect the vertebral bodies with the lateral masses. The lateral mass consists of the facet joint, which is a coronally oriented (average angle being 45 degree) synovial joint. The Inter-Luschka distance increases from C3 to C7, which should be known in detail for adequate lateral decompression in anterior cervical spinal surgery.[78] The pedicle to the

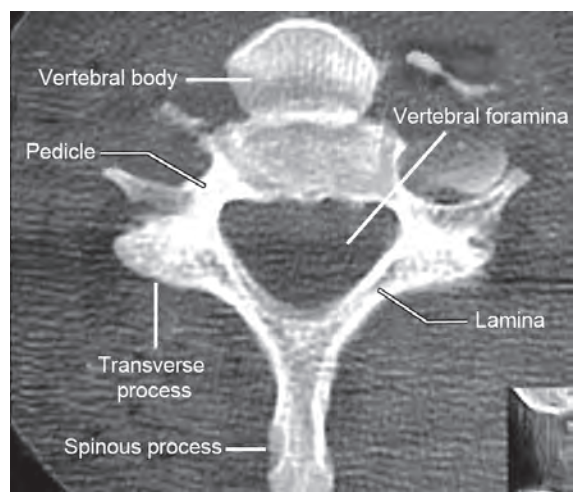


Fig. 1: Subaxial cervical vertebra-parts

Luschka joint distance has been measured by Oh et al.[78] at different levels and they found that the pedicle is lateral to the Luschka joint from C3 to C6 and medial to the joint at C7. This variation explains the lack of root decompression at some cervical levels, even when decompression extends to the Luschka joint bilaterally. The distance between the medial borders of the longus colli muscles increases in a rostral to caudal direction.[81] The lower subaxial spine, especially the C6-7 vertebrae, is exposed to great axial compression and flexion loads due to its location, and the transition between a very mobile cervical and a rigid thoracic spine. Ebraheim et al.[31] found that the sympathetic trunk may be more vulnerable to damage during anterior lower cervical spine procedures because it is situated closer to the medial border of the longus colli muscle at C6 than at C3. The longus colli muscles diverge laterally, whereas the sympathetic trunks converge medially at C6. As the transverse foramen or uncovertebral joint is exposed with dissection or transverse severance of the longus colli muscle at the lower cervical levels, the sympathetic trunk should be identified and protected.

Sherekar et al.[103] have studied the standard values for normal alignment of the upper and lower cervical spine in healthy individuals of the Indian population and the normal ranges of values of the cervical spine was established. It was found that the mean C1-C2 angle was significantly larger in females. The mean C2-C7 angle was significantly larger in males. The mean Oc-C2 angle had a weak negative correlation with the C2-C7 angle and the authors found that the alignment of the occiput and upper cervical spine and occiput and lower cervical spine are inter-related. If lordosis of the occiput and upper cervical spine increases (the Oc-C2 angle increases), the alignment of the lower cervical spine becomes kyphotic and vice versa.

The intervertebral foramen contains the exiting nerve root and is related anteriorly to the lateral portion of the intervertebral disc and the uncovertebral joints, superiorly and inferiorly to the pedicles and posteriorly to the lateral masses. The exiting root corresponds to the lower vertebra (C6 root exits the C5-6) foramen. Pait et al.[82] described the anatomy of the cervical articular pillar (lateral mass) and defined key bony landmarks and their relationship to critical neurovascular structures. They divided the articular pillar into four quadrants and, the superior lateral quadrant, under which there are no neurovascular structures, was considered the "safe quadrant" for placement of posterior screws and plates.

Ebraheim et al.[32] evaluated the anatomic relationship between the vertebral artery foramen and the posterior midpoint of the cervical lateral mass using cervical spine specimens and found that there was no risk of damaging the vertebral artery, if a screw is directed perpendicular to the posterior aspect of the lateral mass at C3-C5 and 10 degrees lateral to the sagittal plane at C6 starting at the midpoint of the lateral mass.

The ligamentum nuchae is attached to the external occipital protuberance and ends at the spinous process of C7; it limits excessive flexion of the cervical spine. The flexion extension movements have a range of 65–75 degree and translation is restricted to 2–3 mm. The cervical disc has an average height of 4 mm anteriorly and this reduces to 2.5–3 mm posteriorly. The anatomy in the Indian population has yet to be studied, but the average morphology is smaller, and this has to be taken into consideration, e.g. the longus colli muscles are very small and may not hold the self-retaining Cloward's retractors safely.

MECHANISMS AND TYPES OF INJURY

Subaxial cervical spine injuries are common and range in severity from minor ligamentous strain to complete fracture dislocation with osseous and ligament injury, and severe spinal cord injury (SCI). Multiple contiguous and non-contiguous cervical injuries can occur due to a single or multiple impact forces.[46,61] Pre-existing lesions, like haemangiomas of the bone, osteoporotic or sclerotic spine due to ageing, spondylotic myelopathy, DISH, ossification of the posterior longitudinal ligament (OPLL) and ankylosing spondylosis (AS), cause a spectrum of injuries. A whiplash injury is commonly seen in motor vehicle accidents and presents with nagging neck pain, radiculopathy and, rarely, myelopathy, and also a non-specific post-traumatic concussional syndrome is often associated.

AS, DISH, OPLL and fluorosis are disorders characterised by abnormal ossification of the spinal column, which predisposes these patients to spinal injuries with potentially devastating consequences.[117,118] Patients with AS are much more prone to serious neurological injury and spinal deformity after sustaining cervical fractures from even minor trauma forces and are more likely to require surgical management.[51]

Maiman et al.[67] tested the hypothesis that initial alignment of the head-neck complex affects cervical spine injury mechanism, trauma rating, injury classification based on stability and fracture pattern, and confirmed that spinal alignment is a strong determinant of the biomechanics of impact-induced cervical spine injury.

Subaxial cervical spine injuries are divided into stable or unstable injures. Instability exists, if there is greater than 3.5 mm of translation or greater than 11 degree of angulation changes as compared to other segments. The degree of ligamentous injury on magnetic resonance imaging (MRI) correlates with instability in patients with lateral mass facet fractures, with rupture of multiple ligaments including the anterior longitudinal ligament, posterior longitudinal ligament, interspinous ligament, or facet capsule. Patients with congenitally narrow canals and those with less than 13 mm length of the sagittal canal are predisposed to neurological injury. Conversely, patients with a wide canal may escape injury of the spinal cord.[74] Vertical compression injuries can also cause canal occlusion and vertebral column shortening.

CLASSIFICATION OF SUBAXIAL CERVICAL SPINE INJURIES

Allen, et al.[5] in 1982, put forward a mechanistic classification of middle and lower cervical spine injuries and subdivided them into eight groups based on a force vector (initial dominant force) and resultant injury based on the three-dimensional position of the spine at the instance of failure. Each of these is further graded according to severity. The failure of the anterior column results in more instability in extension and posterior element failure predisposes to instability in flexion. Patel et al.[83] reviewed the subaxial injury classification (SLIC) and severity score SLIC system, which identify three major injury characteristics to describe subaxial cervical injuries:

1. Injury morphology
2. Discoligamentous complex integrity
3. Neurological status.

Minor injury characteristics include injury level and osseous fractures. Each major characteristic is assigned a numerical score based upon injury severity. The sum of these scores constitutes the injury severity score. This system addressing both discoligamentous integrity and neurological status, overcomes the major limitations of earlier classification systems. Vaccaro et al.[113] reiterate that the SLIC and severity scale provide a comprehensive classification system for subaxial cervical trauma.

The common injuries of the subaxial spine are compression flexion, compression extension and distraction flexion injuries. Vertical compressions are of intermediate frequency and lateral flexions are the least frequent.

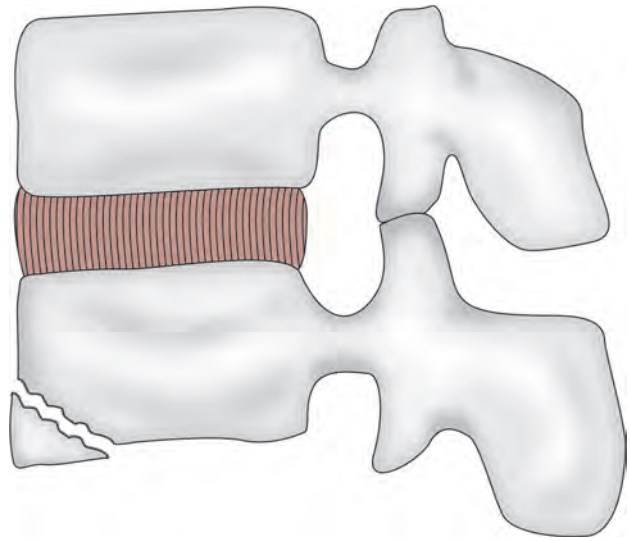


Fig. 2: Tear drop fractures

Compression injuries	I. Anterior compression	II. Comminuted fracture	III. Tear drop fracture
Flexion-extension-distraction injuries	I. Moderate sprain dislocation	II. Severe sprain	III. Bilateral fracture
Rotation injuries	I. Unifacet fracture (UFF)	II. Fracture separation of the articular pillar (FSAP)	III. Unilateral dislocation (UD)

Fig. 3: Allen and Ferguson subaxial cervical spine classification

Flexion Injuries

These form about 15% of injuries of the subaxial cervical spine and usually result due to fall from a height, diving into shallow water or empty pools and road traffic accidents.

Flexion-Compression Injuries

These represent a spectrum of spinal injuries with simple vertebral body compression fractures and injuries that result in the triangular "teardrop" fracture (Fig. 2) of Schneider and Kahn[97] or a "quadrangular" fracture with posterior ligamentous disruption. The most severe injury is posterior subluxation of the posterior vertebral body into the canal, causing acute kyphosis and disruption of the ALL, PLL and posterior ligaments. The SCI in these compressive flexion injuries ranges from 0 to 91% in the most severe cases. Posterior element fractures occur in up to 50% of these cases and pure ligamental injury is usually rare.

Tear drop fractures are serious injuries and patients are seen with complete spinal injury or central cord syndrome.[95–99] There is a fracture of the vertebral body in the sagittal plane and retrolisthesis of the vertebrae and these require to be differentiated from simple avulsion fractures. These have associated facet joint and discoligamental injuries.

Quadrangular fractures are characterised by oblique vertebral body fracture, subluxation, angular kyphosis and discoligamental injury, and are unstable.

Flexion-Distraction Injuries

These injuries represent a spectrum of pathologies from mild posterior ligamentous sprains to bilateral facet dislocations (locked or jumped facets).[106] These are the most common injury patterns in Allen and Ferguson's classification (Fig. 3).[5] They include subluxation injuries and dislocation injuries. The mildest form of injury in this class is facet subluxation which can present as instability, due to the poor healing of posterior ligamentous injuries. Horizontal subluxation of more than 3.5 mm of one body over another or more than 11 degree of angulation of one vertebral body relative to the next indicates instability. Jumped facets or sprung facets may be unilateral or bilateral. The normal facets have a shingled relationship (inferior facet of level above is

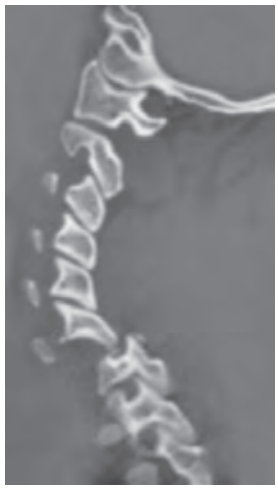


Fig. 4: Unilateral facet dislocation—computed tomography scan

Fig. 5: Bilateral facet dislocation—computed tomography scan

posterior to superior facet of level below). Mild injury of the facet capsule leads to ligament laxity, resulting "perched facets".

Beatson[8] classified facet dislocation injuries into four stages of progression:

1. Posterior ligament strain with facet subluxation and interspinous widening and rounding of the anterior-superior aspect of the caudal vertebral body
2. Unilateral facet dislocation, with varying degrees of posterior ligamentous injury
3. Bilateral facet dislocations
4. Complete anterior subluxation of the rostral vertebral body.

Dislocation injuries: These include unilateral and bilateral facet dislocations.

Unilateral facet dislocations: These are caused when there is flexion and a rotational vector acting together and facet fracture dislocations represent the next pattern seen in the spectrum of injury (Fig. 4). They typically present with translation of 25% of one vertebral body on another and have a pathognomonic "sail" or "bow tie" sign on lateral X-rays. The C6-7 is the level most commonly involved, and patients present with radiculopathy and SCI.

Bilateral facet dislocations: These dislocations have a higher incidence of neurological injury (Fig. 5). These injuries require reduction with traction or internal reduction and may have associated large anterior disc prolapse.

Vertical Compression Injuries

Vertical compression injury to the subaxial cervical spine results in the cervical burst fracture. These burst fractures are subdivided into three categories of severity. They are classified as the most severe pattern in the Allen and Ferguson vertical compression phylogeny and are classified as A3 lesions in the AO classification; they represent about 10% of all subaxial cervical spine fractures. Roaf[90] found that the vertical compression injured the vertebral end plate rather than the intervertebral disc. The cervical spine has a lordotic curve and a small spinal canal. Axial loading of the cervical spine causes compression of the vertebral body and the posterior wall retropulses into the canal causing neural injury. These can be associated with posterior ligamentous injury when there is an associated flexion component of the injury force.

Extension Injuries

These were described by Taylor and Blackwood.[109] These represent approximately 8% of all subaxial cervical spine injuries and two stages have been described:

1. Stage I injury is disruption of the anterior longitudinal ligament without posterior displacement and is seen on imaging as abnormal widening of the disc space due to the ALL and disc injury.
2. Stage II injury is when both the posterior ligaments and the anterior ligaments are injured and the superior vertebra is retropulsed into the spinal canal. Extension injuries without bony injuries lead to the central cord syndrome in adults and SCHIWORA in children. These are more commonly seen in the elderly and in patients with pre-existing cervical spondylotic disease or other conditions like DISH, AS and OPLL.

MANAGEMENT

Intensive Care and Initial Management

Management of spinal injuries is begun by taking an accurate clinical history, and doing a complete general and neurological examination including motor, sensory and autonomic systems using the American Spinal Injury Association (ASIA) score. The clinical evaluation then guides an appropriate radiological evaluation protocol.[22]

All trauma patients with a cervical spinal column injury or with a mechanism of injury having the potential

to cause cervical spine injury should be immobilised at the scene of accident and during transport with a combination of a rigid cervical collar and supportive blocks on a backboard with straps. This is effective in limiting the motion of the cervical spine. The long-standing practice of attempted cervical spine immobilisation using sandbags and tape alone is not recommended.[21] Evaluation of cervical spine injuries should begin in the emergency department.[70] Management of patients with acute SCI, particularly patients with several cervical level injuries, in an intensive care unit or similar monitored setting is recommended.[70] Use of cardiac, haemodynamic and respiratory monitoring devices, to detect cardiovascular dysfunction and respiratory insufficiency in patients after acute cervical SCI, is routine. Hypotension (systolic blood pressure <90 mmHg) should be avoided, if possible or corrected as soon as possible after acute SCI. Maintenance of mean arterial blood pressure at 85–90 mmHg for the first 7 days after acute SCI is required to improve spinal cord perfusion.[12] Use of protocols and management algorithms reduce the possibilities of error and arbitrary treatment.[7]

Steroids

Treatment with methylprednisolone for either 24 hours or 48 hours immediate post-trauma is recommended as an option in the treatment of patients with acute spinal cord injuries that should be undertaken only with the knowledge that the evidence suggesting harmful side effects is more consistent than any suggestion of clinical benefit.[86]

Venous Thromboprophylaxis

Steps to prevent venous thromboembolism are guided by clinical acumen and protocols. Ploumis et al.[88] on the basis of a literature review, concluded that the prevalence of deep-vein thrombosis following a spine injury is higher among patients who have a SCI than among those who do not, and the consensus was that thromboprophylaxis should start as early as possible once it is deemed safe in terms of potential bleeding complications. Within this population, low-molecular-weight heparin was more effective in the prevention of deep-vein thrombosis, with fewer bleeding complications, than un-fractionated heparin. The use of vitamin K antagonists appeared to be effective for the prevention of pulmonary embolism.

EXAMINATION

The instability of the cervical spine is picked up by the clinical signs of radiculopathy, neck pain or myelopathy. In clinical practice, the presence of instability can be inferred from an abnormal position of the neck, injury signs, like bruises and rope marks, and spinal deformity and tenderness are obvious pointers to an occult injury to the subaxial cervical spine. The nature of the accident should be inquired into.[49] The ASIA international standards for neurological and functional classification of SCI are recommended as the preferred neurological examination tool for clinicians involved in the assessment and care of patients with acute spinal cord injuries.[22] All precautions to rule out polytrauma and, especially concurrent carotid and vertebral artery, injuries should be undertaken.[34,47]

INVESTIGATIONS (IMAGING OF THE SUBAXIAL CERVICAL SPINE IN TRAUMA)

In light of clinical signs and symptoms and even in asymptomatic patients who have had significant trauma[74] including inebriated patients, imaging must be very carefully ordered and studied.[16] Usually static X-rays, computed tomography (CT) scans, MRI scans or, very rarely, a myelogram is done. In patients with cervical pain and those who do not have any radiculopathy or myelopathy, instability can be confirmed by dynamic imaging (flexion and extension views).[11,35,89,119] Bono et al.[14] have attempted consensus in techniques of measurement of kyphosis (Cobb angle and posterior vertebral body tangent methods); vertebral body translation; vertebral body height loss; maximal spinal canal compromise and spinal cord compression; facet fracture fragment size and percentage of facet subluxation.

Agarwal,[3] in a recent review of cervical spine injuries and cervical spine clearance protocols, emphasises the importance of early recognition of high-risk patients, and three-view cervical spine X-rays (AP, lateral and odontoid views) are usually done in radiographic evaluation of the cervical spine in patients who are symptomatic after traumatic injury. Digital X-rays are taken with the shoulders pulled down to visualise up to C7. A swimmers view may be necessary, if there is suspicion of injury to the C7-T1 region, clinical signs of progression or development of radiculopathy or myelopathy. This is followed, if necessary, with CT to define areas that are suspicious or not well-visualised on the plain cervical X-rays. Immobilisation in awake/conscious patients can be discontinued after either (a) normal X-ray or adequate dynamic flexion/extension radiographs with no evidence of movement or (b) a normal MRI study which is obtained within 48 hours of injury. Cervical spine immobilisation in obtunded patients may be discontinued if there is:

- Normal cervical spine X-rays (including supple mental CT as necessary)
- Normal dynamic flexion/extension studies performed under fluoroscopic guidance
- After a normal MRI study is obtained within 48 hours of injury
- At the discretion of the treating physicians.[44,89]

Delfini et al.[27] caution that patients with even mild cervical trauma must be scrupulously evaluated during the acute phase and that, in some cases, it may be advisable to perform a more detailed neurological investigation.

In children who have experienced trauma and are alert, conversant, have no neurological deficit, no midline cervical tenderness, and no painful distracting injury, and are not intoxicated, cervical spine X-rays are not necessary to exclude cervical spine injury. In children who have experienced trauma and who are either not alert, non-conversant, have neurological deficit, midline cervical tenderness, or painful distracting injury, or are intoxicated, it is recommended that AP and lateral cervical spine X-rays be obtained. In children younger than age 9 years, who have experienced trauma, and who are non-conversant or have an altered mental status, a neurological deficit, neck pain, a painful distracting injury, are intoxicated, have unexplained hypotension, AP and lateral cervical spine X-rays should be obtained. In children aged 9 years or older who have experienced trauma, and who are non-conversant or have an altered mental status, a neurological deficit, neck pain, or a painful distracting injury, are intoxicated, or have unexplained hypotension, AP, lateral and open-mouth cervical spine X-rays should be done.[71,89]

Static X-Rays

Proper interpretation of lateral cervical spine X-rays is very important and it remains an essential radiological tool.[120] Patients with potential neck injury must be identified rapidly and handled carefully.

Williams et al.[120] stress the urgency in obtaining a good, readable lateral C-spine film and advice a systemic "ABCS" approach to reading this film. This approach includes specific, sequential attention to alignment, bony integrity, cartilaginous structures, and the surrounding soft-tissue spaces. Kim et al.[55] discussing the pitfalls in plain film diagnosis of cervical spine injuries, found that 14% of patients referred as having cervical injury on X-rays were subsequently found to have no fracture or dislocation when re-evaluated.

Dynamic X-Rays: Flexion Extension Views

Flexion/extension cervical X-rays or fluoroscopy may be considered to exclude gross ligamentous instability when there is a suspicion of cervical spine instability after static X-rays are obtained, but flexion extension X-rays must be ordered with caution, and neurosurgeons must supervise personally them being taken in high-risk cases in patients with significant ligamental instability. These may require to be repeated as the immediate post-injury painful muscle spasm can mask the instability. Criteria for demonstrating instability of the cervical spine have been published, but require clinical judgement and experience.[11,25,119]

Computerised Tomography

Cervical CT scan is a very efficient imaging modality in picking up bony injuries, having a sensitivity of 100%. A single cross-table lateral view X-ray appeared to be insufficient, as a sensitivity of only 63% was found, but functional radiography or MRI is also necessary, as plain radiographs and CT scan may fail to detect significant ligamentous injuries in 6% of the patients.

Tan et al.[108] reported that CT of the inadequately visualised C7-T1 level on plain radiography is cost-effective, especially given the relatively young age of the trauma population and, therefore, the high-associated morbidity of the sequelae of these injuries overtime.

CT scans are useful in studying and measuring kyphosis (Cobb angle and posterior vertebral body tangent methods), vertebral body translation, vertebral body height loss, maximal spinal canal compromise and spinal cord compression, facet fracture fragment size and percentage of facet subluxation.

Clearing the cervical spine[87] in polytrauma patients still presents a challenge to the trauma team. The risk of an overlooked cervical spine injury is substantial, since these patients have multiple injuries and clinical examination may not be possible. Poor-quality X-rays, poor technical quality or incomplete visualisation of the cervical spine may not show the extent of the injury as dynamic imaging does usually. Ligamentous injuries are missed despite complete sets of standard radiographs and cervical CT scans.[35] Factors which point towards a discoligamental injury include severe head injury, higher energy of trauma and focal neurological deficits. Stassen et al.[107] feel that in the obtunded patient, expeditious cervical spine evaluation is important as missed injuries and prolonged unnecessary immobilisation can result in adverse outcomes. They confirmed that cervical spine CT, when used in combination with MRI, provides a safe and efficient method for cervical spine clearance in this patient population and CT alone misses a statistically significant number of cervical spine injuries.

Magnetic Resonance Imaging

Benzel et al.[9] have emphasised the importance of MRI in evaluation of patients with occult spinal injury. D' Alise et al.[26] confirmed that sagittal T1-weighted and T2-weighted MRI appears to be a safe, reliable method for evaluating the cervical spine for non-apparent injury in comatose or obtunded trauma patients. In the early post-injury period, nursing and medical care are thereby facilitated for patients in whom occult injury to the spine is ruled out and for whom those attendant precautions are unnecessary.

Menaker et al.[73] found that newer generation CT continues to miss cervical spine injuries in unreliable patients and magnetic resonance (MR) changed the management in 7.9% of patients having had an admission CT with no acute injury. They recommend continued use of MRI for cervical spine clearance in the unreliable patient and ongoing evaluation as the quality of CT imaging continues to evolve.

Neurosurgeons prefer to do the MRI study before attempting closed reduction.[14,38] Grauer et al.[39] found

that timing of MRI and its influence on management of patients with cervical facet dislocation remains highly variable.

MRI of the cervical spine may also be considered to exclude cord or nerve root compression, evaluate ligamentous integrity, or provide information regarding neurological prognosis. The presence of injury to at least three ligaments, like those of the facet capsule, interspinous ligament and either of the longitudinal ligaments may be related to instability in unilateral facet fractures.[43]

Keiper et al.[53] reported posterior soft-tissue injury or ligamentous injury to be the most common finding in 10 paediatric patients with mild-to-moderate trauma, and acute disc bulges and longitudinal ligament disruption were uncommon. The MRI was superior to CT for assessment of the extent of soft-tissue injury and for identification of spinal cord injuries and intracanalicular haemorrhage in six patients with more severe trauma. The MRI specifically influenced the management of all four patients requiring surgery by extending the level of posterior stabilisation. Traumatic cervical facet dislocations are very serious three column injuries. These are associated significantly with disruption to the posterior and anterior longitudinal ligaments and facet capsules. The MRI is an excellent means of assessing ligamentous disruption, disc herniation and compression of the neural elements.

A study by Vaccaro et al.[115] showed that MRI allows visualisation of disruptions and damage of the posterior longitudinal ligament, which was less frequent in unilateral facet dislocations than bilateral facet dislocations.

Disc injury is defined on MRI as the presence of herniation or disruption. Herniation is described as deformation of the thecal sac or nerve roots, and disruption is defined as a disc with high T2-weighted signal characteristics in a widened disc space.

Yagi et al.[125] stated that cervical instability was a risk factor for the post-operative expansion of the high-signal intensity and indicated that this high-signal intensity area occurred not only from necrosis secondary to ischaemia of the anterior spinal artery, but also from the repeated minor trauma inflicted on the spinal cord from an unstable cervical spine. The long-term neurological outcome found in the preliminary study of patients with compressive cervical myelopathy who had cervical instability and intramedullary signal intensity changes on MR images suggested that surgical treatment should include posterior fixation along with cervical laminoplasty or anterior spinal fusion. These findings can be extrapolated to signal intensity changes seen on MRI scans of patients with post-traumatic discs.

The vertebral arteries are seen as regions of signal voids, and MR angiography and CT angiography may aid in picking up vertebral artery injuries and carotid injuries.

TREATMENT

The management of patients with subaxial cervical injuries lacks consensus, particularly with regard to decisions like which surgical approach or combination of what approaches to use and which approach yields the best clinical outcome in the distinct injury and is highly dependent on the nature of injury, its severity, the experience and competence of the surgeon and the availability of resources.[111] Management is also guided by the issue of instability and as per White and Panjabi[119] loss of function of all anterior or posterior bony or ligamental elements cause spinal instability. Generally, an operating microscope and good bipolar and monopolar electrocautery are essential, along with anterior and posterior spinal instrumentation. Fluoroscopy and neuronavigation are also very useful.

CONSERVATIVE

Many injuries of the subaxial cervical spine without significant discoligamental injury, fracture or dislocation can be managed conservatively using orthoses like the soft cervical collar, Philadelphia collar, Guilford brace, sternal occipital mandibular immobiliser (SOMI) brace and the Yale brace. But these patients must be followed up with great caution, and patients with SCIWORA and sports related injuries, like spinal concussion, spinal cord neuropraxia and burning hands syndrome, may be advised avoidance of high-risk activities for up to 6 months after the injury event.

Lemon et al.[60] identified the following risk factors in association with failure of conservative management in subaxial cervical spine injuries: patients with more than 40% of compression of a cervical vertebra, more than 15 degree of kyphotic angulation or more than 20% of subluxation of one vertebra over another. Persisting pain, progressing myelopathy, radiculopathy or deformity are the indications for surgery as per the modified recommendations of Schneider.[96] Acute central cord syndrome[95–99] is usually managed conservatively.

Axial Controlled Traction

Traction has been used for a very long time in subaxial spine trauma.[63] Traction can be used with caution to re-align and maintain the alignment, usually following an MRI prior to this, as nearly 80% of bilateral locked facets will have an associated post-traumatic disc. Early closed reduction of cervical spine fracture dislocation injuries with craniocervical traction is recommended to restore anatomic alignment of the cervical spine in conscious/awake patients. Closed reduction in patients with an additional rostral injury is not recommended. Patients with cervical spine fracture/dislocation injuries, who cannot be examined during attempted closed reduction, or before open posterior reduction, should

undergo MRI before attempted reduction. The presence of a significant disc herniation in this setting is a relative indication for a ventral decompression before reduction. MRI study of patients who fail attempts at closed reduction is also recommended. Pre-reduction MRI performed in patients with cervical fracture dislocation injury will demonstrate disrupted or herniated intervertebral discs in one-third to one-half of patients with facet subluxation. Vaccaro et al.[112] reported that the process of closed traction reduction appears to increase the incidence of intervertebral disc herniations.

Halo

Halos which have been used since 1959 were regarded as a standard for external stabilisation of the injured cervical spine. The use of the halo has been increasingly questioned as an immobilisation technique in cervical trauma due to reports of high complication rates and unacceptable treatment results. Treatment with halo was successful in 85% of patients and 74% of survivors completed their intended treatment period. Their use is associated with several complications like infection, pin loosening, dysphasia, skull and dural penetration, and pressure ulcers.[17] A pin less non-invasive halo has been introduced with the goal of providing cervical spine stabilisation and control approaching that of the conventional halos in a less invasive fashion.[94]

Surgery

There is lack of consensus in the management of subaxial cervical spine trauma,[30,59,77,113] due to the lack of a clinically relevant system for classifying these injuries.[14,83,113] The aim of surgery is to maintain alignment, correct deformity to restore the sagittal balance, and prevent radiculopathy, myelopathy and instability. Vaccaro et al.[113] presented an algorithm to guide the choice of surgical approach in cervical subaxial burst fractures, distraction injuries, and translation or rotation injuries. Burst or compression injuries and distraction injuries are more likely to be treated with a single anterior approach, whereas the more severe translation or rotation injuries may more commonly be approached posteriorly or with combined anterior and posterior surgery. This algorithm, derived from the SLIC scoring system, may assist surgeons in answering the two most common questions they face when managing subaxial cervical spine trauma: "Should I operate?" and "Which surgical approach should I select?"[113]

GUIDELINES

Subaxial Cervical Facet Dislocation Injuries

Closed or open reduction of subaxial cervical facet dislocation injuries is recommended.[48] Treatment of subaxial cervical facet dislocation injuries with rigid external immobilisation, anterior arthrodesis with plate fixation, or posterior arthrodesis with plate or rod or interlaminar clamp fixation is recommended.[41,76,77] Treatment of subaxial cervical facet dislocation injuries with prolonged bed rest in traction is recommended, if more contemporary treatment options are not available.[48,69]

Subaxial Cervical Injuries Excluding Facet Dislocation Injuries

Treatment of subaxial cervical spinal injuries with external immobilisation, anterior arthrodesis with plate fixation, or posterior arthrodesis with plate or rod fixation is recommended for patients with fracture dislocation without facet dislocation.[101]

Closed reduction is successful for most patients with subaxial cervical spine fracture dislocations injuries. Closed reduction is usually not successful with facet dislocation injuries[48] and may be injurious when there is a large disc.[29]

Immediate open anterior reduction of bilateral cervical locked facets and combined AP fixation/fusion is safe and reliable.[84,85,106] This treatment strategy avoids time loss and patient discomfort from attempted closed reduction by traction and results in excellent stability.

Unilateral Locked Facets

Unilateral facet injuries were earlier treated with halo immobilisation. Currently they are surgically decompressed, reduced and fixed.[36] Shapiro et al.[102] suggested that a reduction procedure in which internal fixation and bone fusion are performed will be the most successful treatment for this injury and this reduces the incidence of malalignment, glacial instability and pseudoarthrosis.

LATERAL MASS FRACTURES

Lateral mass fractures are divided into the following four subtypes by Kotani et al:[57]

1. Separation
2. Comminution
3. Split
4. Traumatic spondylolysis.

The subtype analyses of lateral mass fractures demonstrated; high rates of anterior translation in separation, split, and traumatic spondylolisthesis, as well as significant coronal malalignment in comminution and split types. Cervical pedicle screw fixation of these fractures provided superior deformity correction without pseudoarthrosis, as well as excellent neurological recovery.

Spondyloptosis

An unusual case of traumatic C6-7 total spondyloptosis with neurological intactness at the time of injury was reported in a 35-year-old man by Menku et al.[74] The patient was treated with a single-stage combined anterior-posterior and anterior operation to restore the

cervical spondyloptosis, and creation of a three-column stabilisation of the spine without neurological deficits.

Burst Fractures

Burst fractures of the subaxial cervical spine are common as described earlier and usually involve the C6-7 vertebrae depending upon the amount of canal compromise and reduction in vertebral body height. These are usually operated upon by an anterior cervical approach and median vertebrectomy is done to decompress the cord followed by iliac crest graft and anterior plate fusion. These may be associated with injury to the vertebral arteries.

Laminar Fractures

Laminar fractures are rare and, unless causing cord pressure, are managed conservatively. These may also be associated with posterior ligamental injury and, if there is evidence of instability posterior single stage decompression, and lateral mass screw and rod fixation can be done.

Management

There are four general indications for spinal stabilisation as outlined by White and Panjabi:[119]

1. To restore clinical stability to a spine in which the structural integrity has been compromised
2. To maintain alignment after correction of a deformity
3. To prevent progression of a deformity
4. To alleviate pain.

A patient was considered to have an unstable injury, if he had five points or more in the White and Panjabi instability checklist.

Anterior Instrumentation

The choice of surgical approach in the treatment of traumatic cervical dislocations is highly variable and may be influenced by a variety of factors. There are a variety of ventral subaxial fixation techniques.[68] Khosla et al.[54] reviewed the advantages of the anterior approach to the subaxial cervical spine and described a number of technical modifications of the procedure. Neurosurgeons commonly use anterior approaches either alone[72] or as the first stage in a combined approach when a disc herniation is present regardless of the neurological status of the patient. When a patient is neurologically intact, an anterior approach is more commonly used than a posterior approach even when a disc herniation is not present. Combined approaches were preferred for the treatment of bilateral facet dislocations. Woodsworth et al.[123] reported that anterior cervical discectomy and fusion performed using interbody structural allograft and plate fixation is highly effective in the treatment of unstable posterior cervical lateral mass, facet and ligamentous injuries. This treatment option results in low intra-operative blood loss, short operating time, and a brief length of hospital stay. Radiographic outcome with respect to segmental stability are excellent, and fusion rates with the use of structural allograft alone were high. Outcomes with respect to pain, function and patient satisfaction were high, and complications were acceptably low. The anterior approach has a disadvantage as it causes destruction of the anterior elements in the presence of posterior instability. There has been growing evidence ever since, that anterior decompression and instrumented fusion (Fig. 6) alone is an adequate form of treatment for unstable cervical spine injuries. Lambris et al.[58] opined that many such injuries, including the dislocations, can be managed with anterior instrumented fusion alone. Hacker et al.[40] found that interbody cages were safe and effective in the treatment of degenerative cervical disc disorders, but these are avoided in traumatic lesions. Vaccaro et al.[114] stated that anterior reconstruction of the cervical spine with an anterior cervical graft and plate acting as a tension band is the ideal treatment method for stabilisation of acute distraction extension injuries involving primarily the soft tissue structures (anterior longitudinal ligament and intervertebral disc). Type 2 injuries, depending on the degree of displacement and the adequacy of closed reduction, may need to be approached initially posteriorly to obtain adequate alignment, followed by an anterior reconstructive procedure. Great care should be taken during anterior graft placement to avoid over-distraction of the spine.

Posterior Instrumentation

Posterior fusion of the subaxial cervical spine has become common. Liu and Das[62] have reviewed the indications and techniques of posterior fusion of the subaxial cervical spine. Three major modifications of the original description by Roy-Camille[92] are commonly used in managing cervical instability: (1) Magerl; (2) Anderson and (3) An et al.[6] The screw is generally, directed superiorly and laterally to avoid the nerve root and the technique by An et al.[6] demonstrated the lowest risk of nerve root damage due to over-penetration in drilling or insertion of too

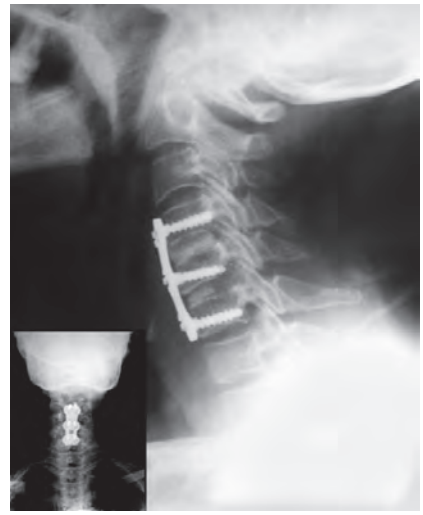


Fig. 6: Anterior cervical fixation

long screw. When screws 15 mm or shorter are used, the chances of injury to the vertebral artery or nerve root were low in all three techniques. Yukawa et al.[126] using posterior instrumentation in 144 unstable cervical spines concluded that the placement of cervical pedicle screws using a fluoroscopy-assisted pedicle axis view technique provided good clinical results and few complications for unstable cervical injuries. Solid posterior bony fusion without secondary dislodgement was accomplished in 96% of all cases, but a careful surgical procedure was needed to safely insert the screws and improvement in imaging and navigation systems are expected. Cervical pedicle screws are alternative fixation devices for posterior cervical plating. In biomechanical studies conducted in animal models and human cadavers, investigators have demonstrated that this technique offers superior stability, fixation and resistance to screw pullout forces compared with lateral mass plating. Abumi et al.[2] have demonstrated in clinical studies that cervical pedicle screws can be effectively used in the reconstruction of the cervical spine after decompressive laminectomy, correcting kyphosis from a posterior approach, and reducing trauma-induced disc herniations.

Wu et al.[124] proposed a modified technique with a universal method of screw placement suitable for stabilisation of every level of the subaxial cervical spine, from C3 to C7. The technique of lateral mass screw placement yielded good fusion rates with very few complications. Cervical pedicle screw fixation is also an effective procedure for stabilising an unstable motion segment; however, it is generally, considered unsafe due to the potential for injury to neurovascular structures, such as the spinal cord, nerve roots or vertebral arteries. A careful surgical procedure is needed to safely insert the screws and more improvement in imaging and with the use of navigation systems is expected to reduce the rate of complications. Roy Camille et al.[92] reported on 221 cases of lower cervical spine injuries, in which posterior stabilisation was done in 89%. They reported no secondary displacement in 85% of cases.

Halifax clamps: The interlaminar clamps[4] are used in managing a subluxation where the injury is mainly due to the posterior ligaments with no bony injury, especially to the facets and lamina. Most neurosurgeons would prefer posterior plating options. Posterior stabilisation procedures may be performed with wires and cables, with or without rods. The plates and screws are biomechanically superior to wiring and avoid canal penetration. They are ideal when there is loss of the posterior elements. Pedicle fixation should be considered when operating on the C2 or C7 level. Posterior wiring techniques of various authors[10,19,33] can be very useful when posterior screws cannot be placed.

POST-TRAUMATIC DISC

The incidence of traumatic disc herniation in one series was 32%.[2] They occur frequently in association with injury of the cervical spine and are usually associated with instability and, being a discoligamental injury, they tend to heal poorly. Conventionally they are approached anteriorly using standard microsurgical techniques and, after discectomy, fusion is done using iliac crest bone graft and anterior plating systems.[37] Many local Indian cervical plating options are available that are affordable and of good quality. Posterior approaches are less commonly used for these injuries. The cervical pedicle screw system has been described as an alternative treatment option for the cervical spine injury-related traumatic disc herniation.[1] Abumi et al.[2] in their experience found that the cervical pedicle screw system allowed three-dimensional reduction of the injured cervical segment and reduction or reversal of a disc herniation. After surgery, compression of the thecal sac and/or spinal cord had disappeared. The cervical pedicle screw system provides effective and safe fixation of the cervical spine injury-related traumatic disc herniation, and the surgery can be performed safely in a single posterior-approach procedure without need of additional anterior decompressive interventions.

Combined Anterior and Posterior Approaches

McAfee et al.[72] on the basis of experience with 100 cases of which there were 31 cases of traumatic injury, used a one-stage anterior decompression followed by posterior stabilisation and stated that the development of more biomechanically rigid cervical instrumentation did not obviate the need for a combined approach. Liu P et al.[63] published a retrospective study of nine patients who underwent operations as treatment of old distractive flexion injuries (Stages 2 and 3) of the subaxial cervical spine. They did a posterior procedure first which comprised of soft tissue release, facetectomy and interspinous wiring, followed by an anterior procedure including soft tissue release, discectomy, reduction, intervertebral grafting and anterior plating, with good outcomes.

Circumferential Fusion

These patients can be treated with a single-stage combined anterior-posterior or anterior operation alone[100] to restore the cervical spondyloptosis, and creation of a three-column stabilisation of the spine without neurological deficits.

Instrumentation

Abraham et al.[1] reported on the indications and increasing trends for anterior cervical fusions. However, good the instrumentation system is, it does not replace the need for bone graft and good fusion techniques, as repetitive loading will cause implant failure unless fusion occurs. Anterior cervical plate fixation has gained widespread acceptance for the treatment of various cervical spine pathologies as, theoretically, it enhances the rate

of arthrodesis (fusion). Kaiser et al.[50] reported that the fusion rates for one and two level anterior cervical discectomy and fusion (ACDF) with anterior fixation were 96% and 91% respectively, compared with 90% and 72% for one and two level ACDF without anterior fixation. Similarly, in their series of 59 patients who underwent three level discectomy with and without plate fixation, Wang et al.[118] found that the pseudoarthrosis rate was 18% for patients with plating and 37% for patients with no plating. Lowery et al.[65] emphasised the significance of hardware failure in anterior cervical plate fixation. Strategies that can minimise screw pull out include triangulation, providing additional points of fixation, minimising the length of the construct and normalising the geometry of the cervical spine.

OUTCOME

Functional and clinical outcome data of subaxial cervical spine injuries using validated measures is vague. Using validated outcome scores the relation between radiographic, functional and clinical outcome parameters can be studied with statistically significant correlations. Miyanji et al.[75] on correlating neurological outcome with MRI findings, found that maximum spinal cord compression (MSCC), spinal cord haemorrhage and cord swelling are associated with a poor prognosis for neurologic recovery. Extent of MSCC is more reliable than presence of canal stenosis for predicting the neurologic outcome after SCI.

Radiographic outcomes include fusion scores and sagittal alignment measurements. Outcome scores with respect to neck pain, satisfaction with surgery and function are recorded for each patient (Fig. 7) according to analog pain and satisfaction scales and the neck disability index (Fig. 8). Koller et al.[56] on reviewing mid to long-term outcome of instrumented anterior cervical fusion for subaxial spine injuries, found that patients were more likely to maintain a high satisfaction level, if they succeeded to maintain segmental lordosis (< 0 degree), had a solid fusion, an increased plate-to-disc distance, and if they were judged to have a successful surgical outcome that included the absence of construct failure and reconstruction of lordosis within +/-1 SD of normalcy.

- Excellent: All preoperative symptoms relieved; abnormal finding improved
- Good: Minimal persistence of preoperative symptoms; abnormal findings unchanged or improved
- Fair: Definite relief of some preoperative symptoms; other symptoms unchanged or slightly improved
- Poor: Symptoms and signs unchanged or exacerbated

Fig. 7: Odom's criteria

Functional Outcome Assessment

The functional independence measure and modified Barthel index (Fig. 9) are recommended as the functional outcome assessment tool for clinicians involved in the assessment and care of patients with acute spinal cord injuries.

COMPLICATIONS

Complications in subaxial cervical spine trauma can be classified as both intra-operative and post-operative,[52] and both the patient and surgeon can be the variables involved. Failure to maintain anatomic reduction of subaxial cervical fracture-dislocation injuries even after operative management ranges from 1 to 18%.[110,111] Anterior procedures were better in maintaining normal alignment. Around 9% of patients had recurrent angulation or subluxation despite surgical management.[111] Other complications commonly encountered are implant failure like screw back-out, poor purchase due to the screws being in the disc space rather than the body and, rarely, screw breakage. Post-operative haematoma, misplaced implant and retraction injury can cause dysphagia and, rarely, respiratory distress.[24,52] Graft extrusion in anterior cervical surgery was seen in as many as 10% of patients.[111] Graft displacement was seen in 4% of patients and in none of the patients who had an anterior cervical plate.[52] Posterior instrumentation was also associated with complications and radiculopathy was reported in 25% of cases in one series. Prolonged bed rest and traction alone for 12–16 weeks has been associated with high mortality and morbidity, especially in patients with facet dislocation.[111]

Carotid Artery Injury

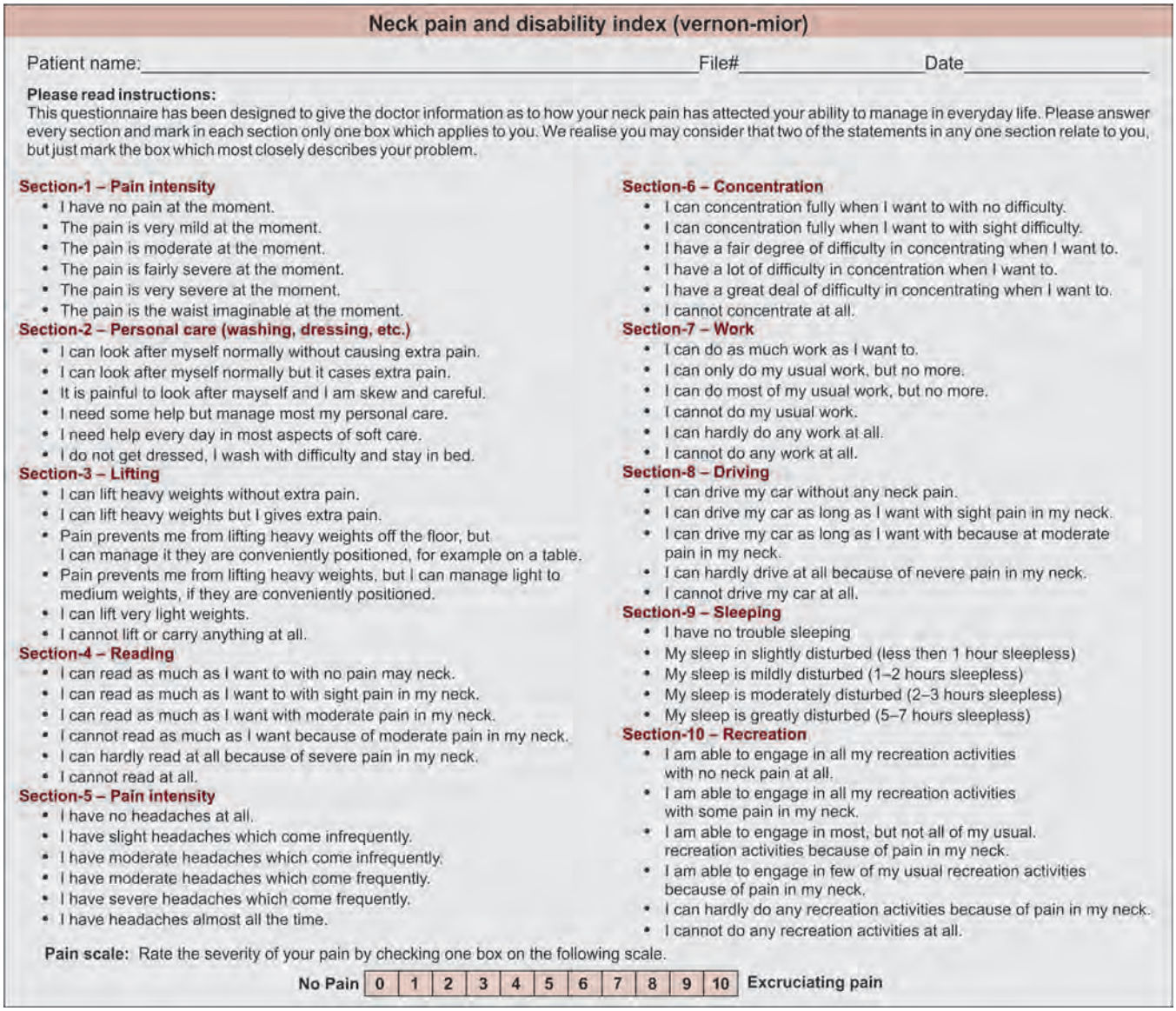
The carotid artery can be injured during anterior cervical exposure and the artery can be occluded due to excessive retraction, which may cause dislodgement of a plaque with subsequent intracranial embolus.

Vertebral Artery Injury

The reported incidence ranges from 0.3 to 0.5%. It is commonly caused by direct injury by instruments and high-speed drills during the lateral decompression.[121] Vertebral artery injuries can be associated primarily with cervical spine injuries.[34,47]

Injury to the Spinal Cord and Roots

The incidence of nerve root injury has been reported to be 0.17%. In anterior procedures the reported rates of C5-C6 radiculopathy range from 2 to 15%. The susceptibility of the C5 rootlet to injury is due to short length and angle of exit from the cord. Saunders[93] identified risk factors associated with the occurrence of post-operative radiculopathy and they include: age greater than 60 years, severity of the pre-operative myelopathy,



Neck pain and disability index (vernon-mior)

Patient name:_____ File#_____ Date_____

Please read instructions:
This questionnaire has been designed to give the doctor information as to how your neck pain has attected your ability to manage in everyday life. Please answer every section and mark in each section only one box which applies to you. We realise you may consider that two of the statements in any one section relate to you, but just mark the box which most closely describes your problem.

Section-1 – Pain intensity
- I have no pain at the moment.
- The pain is very mild at the moment.
- The pain is moderate at the moment.
- The pain is fairly severe at the moment.
- The pain is very severe at the moment.
- The pain is the waist imaginable at the moment.

Section-2 – Personal care (washing, dressing, etc.)
- I can look after myself normally without causing extra pain.
- I can look after myself normally but it cases extra pain.
- It is painful to look after mayself and I am skew and careful.
- I need some help but manage most my personal care.
- I need help every day in most aspects of soft care.
- I do not get dressed, I wash with difficulty and stay in bed.

Section-3 – Lifting
- I can lift heavy weights without extra pain.
- I can lift heavy weights but I gives extra pain.
- Pain prevents me from lifting heavy weights off the floor, but I can manage it they are conveniently positioned, for example on a table.
- Pain prevents me from lifting heavy weights, but I can manage light to medium weights, if they are conveniently positioned.
- I can lift very light weights.
- I cannot lift or carry anything at all.

Section-4 – Reading
- I can read as much as I want to with no pain may neck.
- I can read as much as I want to with sight pain in my neck.
- I can read as much as I want with moderate pain in my neck.
- I cannot read as much as I want because of moderate pain in my neck.
- I can hardly read at all because of severe pain in my neck.
- I cannot read at all.

Section-5 – Pain intensity
- I have no headaches at all.
- I have slight headaches which come infrequently.
- I have moderate headaches which come infrequently.
- I have moderate headaches which come frequently.
- I have severe headaches which come frequently.
- I have headaches almost all the time.

Section-6 – Concentration
- I can concentration fully when I want to with no difficulty.
- I can concentration fully when I want to with sight difficulty.
- I have a fair degree of difficulty in concentrating when I want to.
- I have a lot of difficulty in concentration when I want to.
- I have a great deal of difficulty in concentrating when I want to.
- I cannot concentrate at all.

Section-7 – Work
- I can do as much work as I want to.
- I can only do my usual work, but no more.
- I can do most of my usual work, but no more.
- I cannot do my usual work.
- I can hardly do any work at all.
- I cannot do any work at all.

Section-8 – Driving
- I can drive my car without any neck pain.
- I can drive my car as long as I want with sight pain in my neck.
- I can drive my car as long as I want with because at moderate pain in my neck.
- I can hardly drive at all because of nevere pain in my neck.
- I cannot drive my car at all.

Section-9 – Sleeping
- I have no trouble sleeping
- My sleep in slightly disturbed (less then 1 hour sleepless)
- My sleep is mildly disturbed (1–2 hours sleepless)
- My sleep is moderately disturbed (2–3 hours sleepless)
- My sleep is greatly disturbed (5–7 hours sleepless)

Section-10 – Recreation
- I am able to engage in all my recreation activities with no neck pain at all.
- I am able to engage in all my recreation activities with some pain in my neck.
- I am able to engage in most, but not all of my usual. recreation activities because of pain in my neck.
- I am able to engage in few of my usual recreation activities because of pain in my neck.
- I can hardly do any recreation activities because of pain in my neck.
- I cannot do any recreation activities at all.

Pain scale: Rate the severity of your pain by checking one box on the following scale.

No Pain	0	1	2	3	4	5	6	7	8	9	10	Excruciating pain

Fig. 8: Neck pain disability index

increased number of levels decompressed and the degree of cervical kyphosis. He also found that decreasing the width of the corpectomy defect from 20 to 15 mm led to a decrease in the occurrence of radiculopathy. Injury to the cord may be due to inadvertent slippage of instruments or the high-speed drills and are rare. Graft impingement or implant mis-alignment are other causes.

Injury to the Recurrent Laryngeal Nerve

This is considered the most common neurological complication after anterior cervical spine surgery. The incidence varies between 0.2 and 11%.[18,122] Clinical signs may range from hoarseness and loss of effective cough mechanism, to upper pharyngeal dysphagia with aspiration, to life-threatening airway obstruction from bilateral recurrent laryngeal nerve injury. Bulger et al.[18] suggest considerations for the prevention and treatment. Self-retaining retractors or hand-held retractors, exerting pressure on the trachea and tracheoesophageal groove can result in injury. This is reported to be more common on the right side where the recurrent laryngeal nerve course is more variable. The injury is much more common in redo surgeries. Usually it is better to approach an already operated upon patient from the same side of the earlier surgery to avoid damaging the nerves on both sides. Most commonly the injury to the nerve is transient lasting several weeks, but it may also be permanent. Monitoring of the endotracheal cuff pressure and temporarily deflating the cuff after retractor placement may minimise injury to the nerve. Intermittent relaxation of the retractors may also prevent injury.

Injury to the Sympathetic Trunk

Ebraheim et al.[31] point out the vulnerability of the sympathetic trunk during the anterior approach to the lower cervical spine.

Patient name	*Rater name*	*Date*	
ACTIVITY			**SCORE**
Feeding			
0 = unable			
5 = needs cutting, spreading butter, etc. or requires modified diet			
10 = independent			_____
Bathing			
0 = dependent			
5 = independent (or in shower)			_____
Grooming			
0 = needs help with personal care			
5 = independent face/hair/teeth/shaving (implements provided)			_____
Dressing			
0 = dependent			
5 = needs help but can do about half unaided			
10 = independent (including buttons, zips, laces, etc.)			_____
Bowels			
0 = incontinent (or needs to be given enemas)			
5 = occasional accident			
10 = continent			_____
Bladder			
0 = incontinent, or cathetorised and unable to manage alone			
5 = occasional accident			
10 = continent			_____
Toilet use			
0 = dependent			
5 = needs some help, but can do something alone			
10 = independent (on and off, dressing, wiping)			_____
Transfers (bed to chair and back)			
0 = unable, no sitting balance			
5 = major help (one or two people, physical) can sit			
10 = minor help (verbal or physical)			
15 = independent			_____
Mobility (on level surfaces)			
0 = immobile or <50 yards			
5 = wheelchair independent, including corners, >50 yards			
10 = walks with help of one person (verbal or physical) >50 yards			
15 = independent (but may use any aid, e.g. stick) >50 yards			_____
Stairs			
0 = unable			
5 = needs help (verbal, physical, carring aid)			
10 = independent			_____
		Total (0–100)	

Fig. 9: Modified Barthel index

Distraction Injury

Axial traction has been used to reduce the dislocation caused by injury to the subaxial cervical spine, but the current practice option involves controlled traction using a three-pin fixation and pre-operative fluoroscopy followed by maintenance of alignment using instrumentation. Various techniques using contoured plates and screws and sequential screw tightening causing controlled reduction and deformity correction are in current

practice. There are instances of surgically related neurological deterioration as a result of over-distraction of the anterior column inter-space at the time of graft placement.

PAEDIATRIC SUBAXIAL SPINE INJURIES

Dogan et al.[28] found subaxial cervical spine injuries were common in children of 9–16 years of age, and occurred mainly between C5 and C7. Multilevel injury was more common in children of 8 years of age and older, than in younger children and infants. Most patients with subaxial cervical spine injuries can be treated conservatively. Keiper et al.[53] found that posterior soft-tissue or ligamentous injury was the most common finding in the 10 paediatric patients with mild-to-moderate trauma, while acute disc bulges and longitudinal ligament disruption were uncommon. Both anterior and posterior approaches are safe and effective.[28,71] Instrumentation in children can be difficult due to the size and the bone quality of the vertebral column. There is also concern about the instrumentation hindering normal growth patterns. Bioabsorbable plates may be an option. In children who have a SCIWORA injury, the parents must be cautioned to avoid any high-risk activity for the next 6 weeks.

GERIATRIC SUBAXIAL SPINE INJURIES

Elderly patients commonly have cervical spine injuries after trivial falls, due to altered biomechanics as the soft tissues, i.e. ligaments and discs degenerate or calcify and there is a high incidence of pre-existing cervical spondylotic myelopathy. Whang et al.[118] found that most of these injuries involved the subaxial cervical spine between C5 and C7. In all, 41.2% of AS patients were considered to be ASIA A, whereas 44.4% of DISH patients were classified as ASIA E. The rate of neurologic injury was high for both groups. The AS patients were more likely to exhibit neurologic deficits and undergo operative management. Although the majority of these spinal injuries were treated surgically, stable fractures without any associated neurologic deficits were often successfully managed with immobilisation. Sokolowski et al.[105] in a large series of elderly patients with cervical spine injuries, found that survival rates were comparable regardless of anatomic level of injury and the operative treatment of subaxial injuries was associated with an improved acute survival rate versus non-operative management.

DELAYED SUBAXIAL SPINE INSTABILITY

Old subaxial cervical spine injuries missed on the primary trauma survey present to the neurosurgeon with progressing signs of radiculopathy and myelopathy, and deformity due to glacial instability. Cervical instability that is not recognised until beyond 20 days after injury is called delayed instability. These injuries may require gradual axial traction, but most can be managed by an anterior approach and a fusion with bone graft and contoured plates using the techniques to correct deformity.

FUTURE TRENDS AND PREVENTIVE NEUROSURGERY

Schneider[95–99] was a pioneer in recognising the mechanisms of spinal trauma and his research paved the way for many modifications of rules in sports to prevent the incidence of subaxial cervical spine injuries. Further research into the biomechanics and classification of subaxial spine injuries will lead to the development of better spinal implant systems which will allow for less invasive surgical corridors and better outcomes. In India there is an urgent need to develop spine injury centres that are located in all parts of the country and deal exclusively with trauma and spine injury.

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51 Whiplash Injury

Harjinder S Bhatoe

Acceleration injury or whiplash injury of the neck refers to the cluster of symptoms following application of a propulsive force to the head and neck complex. This has to be distinguished from contact injury in which there is impact to the head and/or neck (as by a hit to the forehead by a beam or bottom of a swimming pool) resulting in a spectrum of fractures and dislocations. Acceleration injury on the other hand is called neck sprain, whiplash or soft tissue neck injury. The clinical presentation presents diagnostic and therapeutic challenges. The mechanism is universally similar—rear-end impact to the body in motion as the neck is unsupported. Although the typical example is the injury suffered by a car occupant with a rear-end collision, there is a variable set of clinical circumstances with an equally variable symptom complex.

MECHANISM AND PATHOLOGY

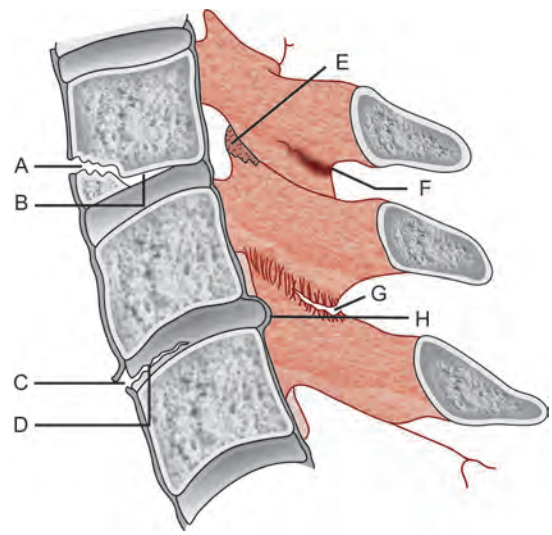
While it is universally agreed that cervical acceleration injury occurs due to rear-end impact to occupants in a stationary vehicle, the exact biomechanics has been a subject of research. Whiplash injury has been simulated in several experimental studies. McNab suspended anesthetised monkeys with their head and neck unsupported and dropped them from a height; the drop was arrested short of ground impact, simulating neck hyperextension.[7] In a similar study, Clemens and Burrows, studied the mechanics using embalmed cadavers subjected to rear-end impacts producing 13–16 G forces.[3] Both these studies reported minor injuries to the sternocleidomastoid, partial avulsion of the longus colli and retropharyngeal haematomas. The most common finding was intervertebral disc failure and tears of the anterior longitudinal ligament, found in nearly 90% of cases. These findings have been confirmed on autopsy studies. Taylor et al.[9] identified three patterns of injury to the intervertebral disc:

1. Anterior rim lesion—there are linear clefts in the peripheral cartilage plate in the region where this cartilage is continuous with the fibrous annulus. The anterior longitudinal ligament is intact and cervical spine alignment is normal on radiographs.
2. Posterior contusions and herniation of intervertebral discs.
3. Partial or complete avulsion along the disc-vertebral interface—usually seen in children. MRI shows high signal intensity on T2-weighted images. It is important to recognise ligamentous injury since there is potential for segmental instability.

According to a study conducted by Grauer and his coworkers, there is a kinematic biphasic response of the unsupported cervical spine when it is rear impacted.[5] Initially the upper cervical spine as well as the lower cervical spine hyperextends converting the cervical spine to an 'S'. Milliseconds later, this is followed by hyperextension of the entire cervical spine. Injury is sustained in the first phase (Figs 1A to H).

CLINICAL PROFILE

The clinical picture of acceleration injury is dominated by neck pain, which is accentuated on movement. This is accompanied by other symptoms (Table 1), many of which are poorly explained. The symptom complex may be aggravated by various psychosocial factors like anger, anxiety, depression and pending litigation. Clinical examination reveals restriction of neck movements, spasm of paraspinal neck muscles and tenderness over the



Figs 1A to H: Diagrammatic representation of pathology of cervical spine acceleration injury. (A) Fracture involving the epiphyseal surface. (B) Avulsion of epiphyseal plate. (C) Anterior annular tear. (D) Transverse rupture of intervertebral disc. (E) Fracture of apophyseal joint. (F) Articular pillar fracture. (G) Zygapophyseal joint capsule injury and (H) Posterior disc herniation

Table 1: Symptom complex in whiplash injury

• Neck and shoulder pain
• Occipital headache
• Arm pain/dysaesthesiae
• Vertigo
• Tinnitus
• Temporomandibular joint pain
• Depression
• Anxiety

posterior neck muscles. Nearly 70% of the patients are females, often with occupations requiring low physical demands.[6] Neurological examination is normal. Cervical spine radiographs are usually normal, except for loss of physiological lordosis. The symptoms persist for more than 1 year in about 88%, and more than 2 years in 64% of patients.[1] A severe injury in the elderly may rarely be complicated by oesophageal rupture and mediastinitis.[6]

Cognitive dysfunctions are the least understood aspect of cervical spine acceleration injury. Broadly, these dysfunctions fall in two categories: (1) cervicocephalic and (2) lower cervical spine syndrome.[8] In cervicocephalic syndrome, there is demonstrable abnormality of auditory and visual information processing, mood changes, sleep disturbances, psychoneurotic reaction, depression and "litigation neurosis". In lower cervical spine type of presentation, in addition to painful symptoms pertaining to the cervical spine, there is disturbance in visual information processing.

IMAGING

Cervical Spine Radiographs

Dynamic radiographs of the cervical spine show restriction of motion at one level, and loss of the normal lordotic curve (Fig. 2). Prevertebral swelling is variable. Degenerative changes pre-existing at the time of initial presentation are likely to be associated with persistence of symptoms.

Magnetic Resonance Imaging

Many of the changes produced by acceleration injury can only be revealed by MRI. These changes affect the anterior column, and are seen as disruption of the anterior longitudinal ligament, anterior annular tears, occult vertebral end-plate fractures, acute cervical disc herniation, zygoapophyseal joint injury, etc. (Figs 3 and 4).[4]

MANAGEMENT

Management depends upon the severity of the problem, and patients with intense symptoms may require hospitalisation. Usual treatment consists of analgesics, cervical collar, rest, muscle relaxant and anti-inflammatory medication. Narcotic analgesics may be required to interrupt the "pain-spasm" cycle. Trigger point injections

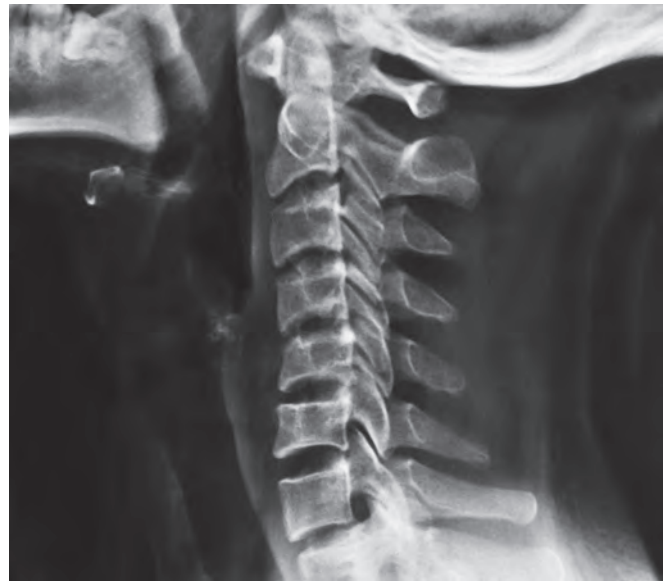


Fig. 2: Cervical spine radiograph (lateral view) showing straightening of the cervical spine from C1 to C4 in a patient with cervical acceleration injury

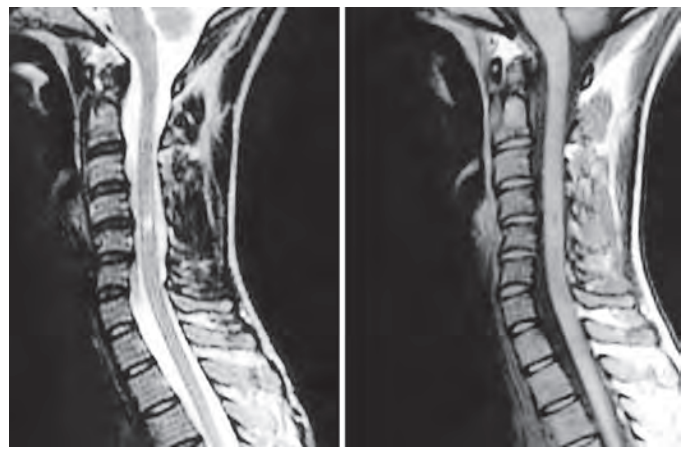


Fig. 3: MRI (T2-weighted images) showing straightening of the cervical spine from C1 to C4

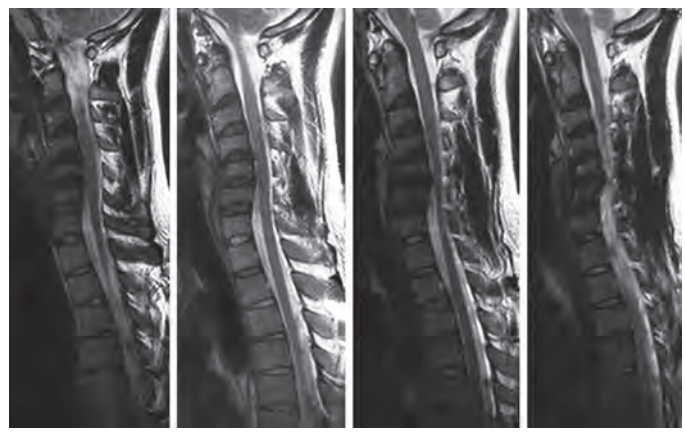


Fig. 4: MRI (T2-weighted images) showing posterior annular bulge at C4/C5 with straightening of cervical spine from C1 to C4

and epidural blocks may be required in refractory cases. Local infiltration with corticosteroids advocated by some is not beneficial.[2] Surgery is reserved for those with disc avulsion, especially with pre-existing degenerative disc disease. These patients require discectomy with fusion. A psychiatric consultation may be required for patients with chronic persistent pain.

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52 Thoracic and Thoracolumbar Injuries

Ramakrishna Easwaran

INTRODUCTION

The human spinal cord in most areas measures less than 10 mm in diameter. A permanent traumatic damage to this tiny region leaves a person paralysed for life. Loss of earning is a lesser catastrophe than the loss of self-esteem after traumatic paraplegia. The picture becomes more poignant because of the propensity of polytrauma to pick persons in their prime. The incidence of spinal injury is increasing every decade. A study from Norway shows that the annual population incidence of spinal cord injury (SCI) has risen from 5.9 per million in the 1950s to 21.2 per million in the 1990s.[35] The pathophysiology and management of SCI is dealt with elsewhere in this textbook. About 20% of patients with thoracolumbar spine injury have neurological deficits.[26] This chapter deals with thoracic and lumbar spine injuries. Sacral injuries are dealt with in the next chapter. It is essential to clarify the nomenclature of the various segments of the spine at the outset and this is summarised in Table 1.

EPIDEMIOLOGY AND AETIOLOGY

The population incidence of SCI varies in different countries from 15 to 40 per million per year.[88] Thoracic and lumbar injuries accounted for 75% of all spine injuries in a study from Jammu.[91] The most commonly fractured level in the whole spine is L1, followed by T12. The vulnerability of the T12-L1 region is ascribed to the change from a kyphotic curve of the relatively immobile thoracic spine to a lordotic one in the mobile lumbar spine. Spinal trauma is, world over, commoner in males and the gender bias is more pronounced in India. The male-female ratio of incidence of spinal injury was 3:1 in a report from Haryana,[92] but an earlier rural study showed a ratio of 13:1.[16] The mean age of occurrence is 35 years and the median age group 20–29 years.[92] A second peak is seen in the elderly due to osteoporotic vertebral fracture.[80] A rare case of neonatal SCI has been reported from Vellore.[96]

Table 1: Nomenclature of levels of spinal lesions

Level	*Name*
Occiput to C2	Craniovertebral junction
C1, C2	Upper cervical spine
C2–C7 or T1	Subaxial cervical spine
C7-T2	Cervicothoracic junction
T1–T6	Upper thoracic spine
T6–T12	Lower thoracic spine
T11-L2	Thoracolumbar junction, lumbodorsal junction
L2–L4	Midlumbar spine
L5, S1	Lumbosacral spine
S1–S5	Sacral

Fall from heights are commoner causes than road traffic accidents in most Indian series. Falling from trees, electric poles, staircases, ladder, upper storeys of houses and construction sites account for about 50% of all spine injuries.[91] Falling off camels is common in Rajasthan and the Middle East! When a person falls into a well that is being dug, the caving mud crushes the spine and adds to the injury caused by the fall. Osteoporotic thoracolumbar wedge compression fractures occur after trivial domestic falls and this is the only type of fracture that is commoner in women. Load carriers are prone to spine injury when the load slips from the head or shoulder. Another common mechanism of injury is the 'last seat fracture'—a compression fracture in the dorsolumbar junction sustained by a person travelling in the rear seat of a long bus that hits a big pothole.

Sporting activities associated with spine injury in India include wrestling and bull fighting (known as jallikattu in Tamilnadu). Diving, horse riding, skiing, pole vaulting, gymnastics, motor sports and altitude sports are common causes in other nations. Road traffic accidents cause more than 50% of spinal injuries in Western societies. In a British study, spinal injuries occurred in about 11% of 1,121 motorcyclists and 14% of 2,718 car occupants involved in road accidents.[79] About a third of these patients had isolated spinal injuries. The thoracic spine was injured in over 50% of the motorcyclists in this study. Rollovers and ejection from the vehicle are usually implicated. Seat belt fractures notwithstanding, there is proof that the combination of air bags and seat belts reduce the severity (if not the incidence) of spine injury in motor vehicle accidents.[102]

We live in an increasingly violent society. Missile injuries of the spine, once the sole preserve of Armed Services hospitals,[9] have become commonplace in triage departments of big city hospitals. Non-missile penetrating injuries of the spine accounted for 7% of all spinal injuries in Chandigarh.[95]

CLASSIFICATION

Classification schemes of thoracic and lumbar injuries continue to evolve with our imaging technology and understanding of biomechanics. The major classification systems are presented in Table 2. Holdsworth's scheme of 1953 was based on radiographic findings.[41] In the absence of axial CT, burst fracture could not be well made out in those days and though recognised by Holdsworth, it was not described as a separate entity. He described the slice fracture near the upper part of the lower body with dislocation of the inferior articular process of the upper body in flexion-dislocation injuries. Kelly and Whitesides introduced the two-column model in 1968 (Fig. 1).[47] The concept of stable and unstable fracture was better defined. Wedging fractures are those with an intact posterior vertebral body margin while burst fractures are those with a disruption of the same. They also showed that the surgical approach could be decided from the type of fracture. Those who have anterior column damage need anterior strut grafting. Most importantly, their model showed the danger of performing laminectomy in patients with anterior column injury.

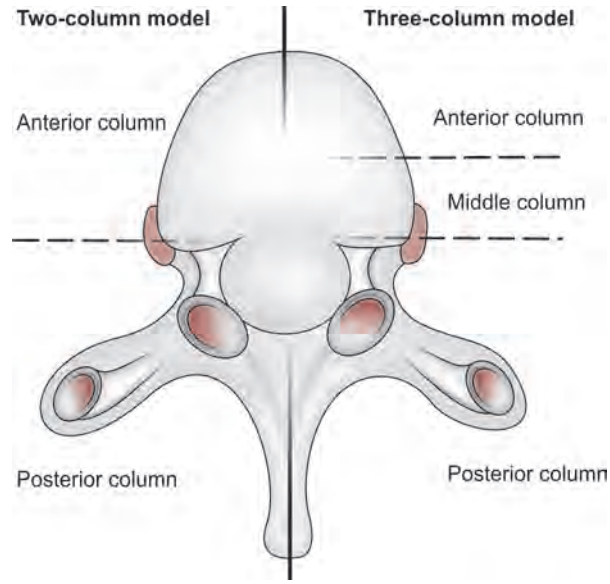


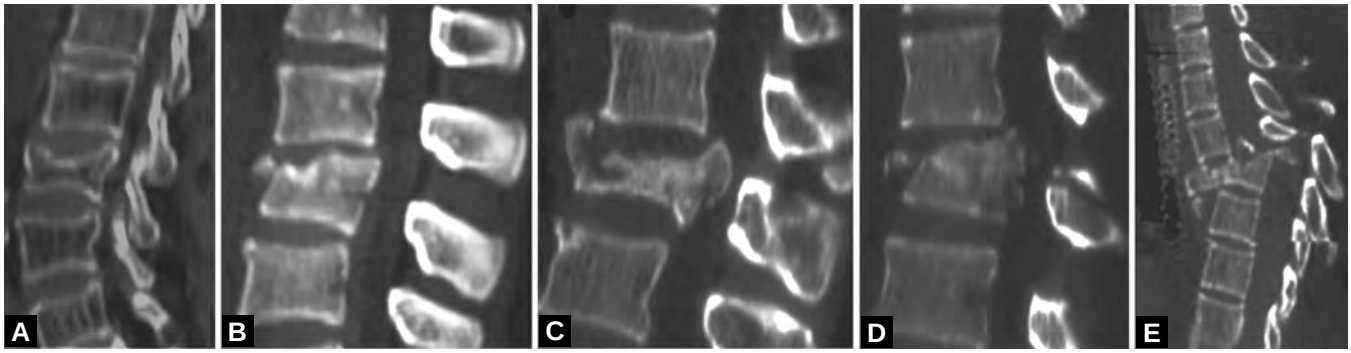
Fig. 1: Diagram showing the Kelly & Whitesides two-column model on the left and the Denis three-column model on the right[26,47]

The introduction of axial CT made it possible to see burst fractures and sagittal body fractures. Denis brought out the importance of the osteoligamentous middle column made up of the posterior wall of the vertebral body, the posterior longitudinal ligament and posterior annulus fibrosus (Fig. 1).[26] He classified wedge compression fractures into anterior and lateral types. The burst fractures are divided into five subtypes in the Denis system, based on the additional force involved, apart from the axial load that is common to all burst fractures. Type A—involves both endplates (pure axial load), type B—only the superior endplate, type C—only the inferior endplate (axial load plus flexion in B and C), type D—additional rotation and type E—additional lateral flexion. Seat belt injury (Chance fracture) is given a separate category. There are three subtypes under the fracture-dislocation category (flexion-rotation, shear and flexion-distraction). It must be remembered that the

Table 2: Classification schemes of thoracic and lumbar spine injuries

Holdsworth 1953[41]	*Kelly & Whitesides 1968*[47]	*Denis 1983*[26]	*McAfee 1983*[59]	*Magerl 1994*[58]	*TLICS 2005*[99*]
Flexion-compression	Two column concept	Three column concept	Wedge compression	Type A-Compression	Morphology
Flexion-dislocation	Stable fractures	Minor injuries	AC flexion	A1	compression
(disc and posterior	Wedging fractures	(isolated fractures of the	Stable burst fracture	A2	translation-rotation
ligaments ruptured)	Anterior wedging	transverse process,	AC & MC compression	A3	distraction
Flexion-torsion	(flexion injuries)	spinous process, facets,	Unstable burst fracture	Type B-Distraction	Integrity of PLC***
(fracture-	Lateral wedging	pars interarticularis, lamina)	AC & MC compression	B1	intact
dislocation)	Stable burst injuries	Major injuries	PC compression, lateral	B2	disrupted
	Unstable injuries	Compression: AC**	flexion and rotation	B3	indeterminate
	Flexion dislocation	Burst fractures: AC, MC	Chance fracture	Type C-Rotation	Neurological state
	(Fracture usually	Seat belt injury: MC, PC	All 3 columns flexion	C1	intact
	present)	Fracture dislocations:	but axis anterior to AC	C2	nerve root injury
	Flexion-rotation	(all 3 columns)	Flexion-distraction injury	C3	cauda equina injury
	(Fracture-	See text for details of	AC compression,	(see Fig. 3 for	incomplete cord
	dislocation/	subtypes	MC & PC flexion	details)	injury
	"Slice" injuries)		Translational injury		complete cord injury
	Unstable burst?		All 3 columns and lateral		
			displacement		
			(see Fig. 2 for examples)		

Note:
*TLICS = Thoracolumbar Injury Classification System of Spine Trauma Study Group[71]
** AC = Anterior Column, MC = Middle Column, PC = Posterior Column
***PLC = Posterior Ligament Complex



Figs 2A to E: Sagittal reconstructed CT images of: (A) Compression fracture; note the intact posterior vertebral margin. (B) Stable burst fracture; posterior border is broken but there is only minimal displacement of fractured fragments. (C) Unstable burst fracture; loss of height of body by > 50% and retropulsed fragment in canal. (D) Flexion-distraction injury: note the horizontal fracture through the upper part of the spinous process with a compression fracture of the body. (E) Fracture-dislocation (all three plane translational injury)

force causing the injury is a matter of guesswork. The depiction of the bony injury became more accurate with multiplanar CT reconstruction. The patterns of injury are illustrated with reconstructed CT images in Figures 2A to E, following McAfee's nomenclathure.[59]

The Magerl scheme follows the general principles of Arbeitsgemeinschaft für Osteosynthesefragen (AO) nomenclature.[58] There are three basic types of injuries: (A) vertebral body compression; (B) anterior or posterior element distraction and (C) rotation plus type A injury (C1), rotation plus type B injury (C2) and rotation with shear (C3). These three basic types are further divided into three groups each and some into further subgroups. The severity of the injury and the degree of instability increases between and within each group. They are illustrated in Figure 3. Magerl's system is widely used in Europe. The extensive number of subgroups makes it difficult to be used in daily practice. We must remember that all these schemes apply mostly to the thoracolumbar junction. The Denis scheme had a lower inter-observer and intra-observer reliability than the AO system, but both the systems had only moderate reliability in a comparative study.[105]

A recent development is the thoracolumbar injury classification system (TLICS) designed by the Spine Trauma Study Group.[99] This system makes a departure from the traditional method of using the putative mechanism of injury, which is a matter of conjecture. Instead, this system uses a description of the injury morphology, which is directly observable on imaging. In addition, the TLICS assesses the integrity of the posterior ligament complex (PLC). The PLC is made up by the facet capsules, ligament flavum and interspinous and supraspinous ligaments which contribute to spinal stability, serving as the "posterior tension band" of the spinal column. Due to its poor healing capability, disruption of the PLC alone may necessitate surgical stabilisation. This system also addresses the neurological state. The number of subgroups is not unwieldy as in the AO system. Based on points assigned, a TLICS severity score is calculated (Table 3). If the total score is 3 or less, the patient is managed conservatively. If the score is 5 or more, the patient is offered early surgical stabilisation. The decision has to be individualised for those with a score of 4. The inter-observer reliability and validity of predictions from TLICS has now been well proved.[37,71,78] The McCormack load sharing classification of burst fractures is of great relevance in deciding about surgery and it is described later in this chapter.[60]

ASSOCIATED INJURIES

Thoracic and lumbar spinal injuries may be associated with another spinal injury such as an upper cervical spine injury. Rib fractures, haemothorax and lung contusions are common with severe thoracic spine injuries and they may be missed or picked up only after a delay in a paraplegic patient (Fig. 4).[83] Splenic, hepatic and renal injuries associated with spine fracture are commoner with motor vehicle accidents than with falls. Their incidence is also higher with multiple levels of spine fracture than with single level fracture.[74] Fracture of the lumbar transverse processes may indicate renal or ureteric injury. Seat belt injuries are associated with abdominal hollow or solid viscus injury, especially in children.[86] Chance fracture is associated with mesenteric or bowel injury in 40% of cases.[8] It is equally important to realise that a significant thoracic or lumbar spinal injury may be missed in the unconscious head-injured patient or in patients who have major abdominal or thoracic trauma.[6] A painful calcaneal or femur fracture might overshadow a dorsolumbar junction wedge fracture.

PREDISPOSING FACTORS

Conditions that weaken the bone increase the fracture risk. The most important predisposing factor for thoracic and lumbar fractures is osteoporosis. This is dealt with in detail in another chapter of this textbook. Pathological

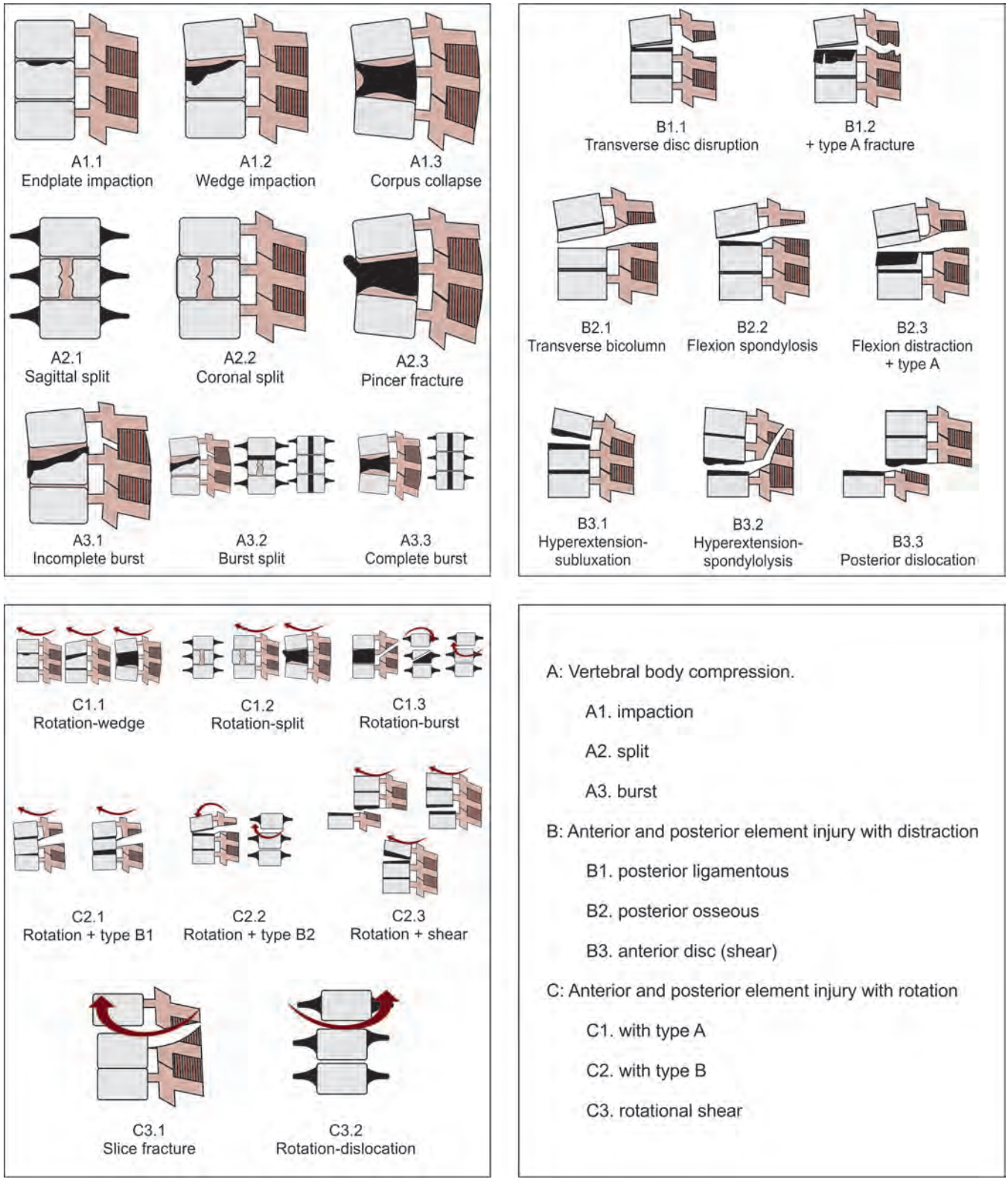


Fig. 3: Magerl's AO classification of thoracolumbar fractures (modified from Cassar-Pullicino & Imhof[14])

fractures are also seen with myeloma,[54] metastasis[72] or tuberculosis.[24] These patients may present with sudden paraplegia after trivial trauma. Conditions that cause narrowing of the spinal canal do not make the spine more prone to fracture, but they render the cord more vulnerable to damage. These conditions include congenital or degenerative thoracic canal stenosis,[46] achondroplasia,[65] ossification of the posterior longitudinal ligament and ossification of the ligamentum flavum.[40] Calcium pyrophosphate dihydrate deposition disease

Table 3: Assignment of point values in the TLICS system[99]

Factors considered	*Assessed by*	*Point value*
Morphology*	Imaging	
Compression fracture	Lateral radiograph, sagittal CT reconstruction	1
Burst component	Axial CT, sagittal CT reconstruction	2
Rotation or	AP radiograph, axial CT	
Anteroposterior translation or	Lateral radiograph, sagittal CT reconstruction	
Side-to-side translation	AP radiograph, coronal CT reconstruction	3
Distraction	Lateral radiograph, multiplanar CT reconstruction	4
PLC integrity	Fat suppressed T2 sagittal MRI	
Intact		0
Indeterminate		2
Disrupted	Splaying of spinous process, facet joint distraction on lateral radiographs and sagittal CT reconstruction are also suggestive	3
Neurological status	Clinical examination	
Intact		0
Nerve root injury		2
Complete		2
Incomplete (cord or cauda equine)**		3

Note:

*For calculating 'morphology score', the most severe component alone is taken. Hence the minimum total score can be 1 and the maximum score 10.

**Incomplete neurological lesions merit a higher score, as they are likely to deteriorate further if not stabilised

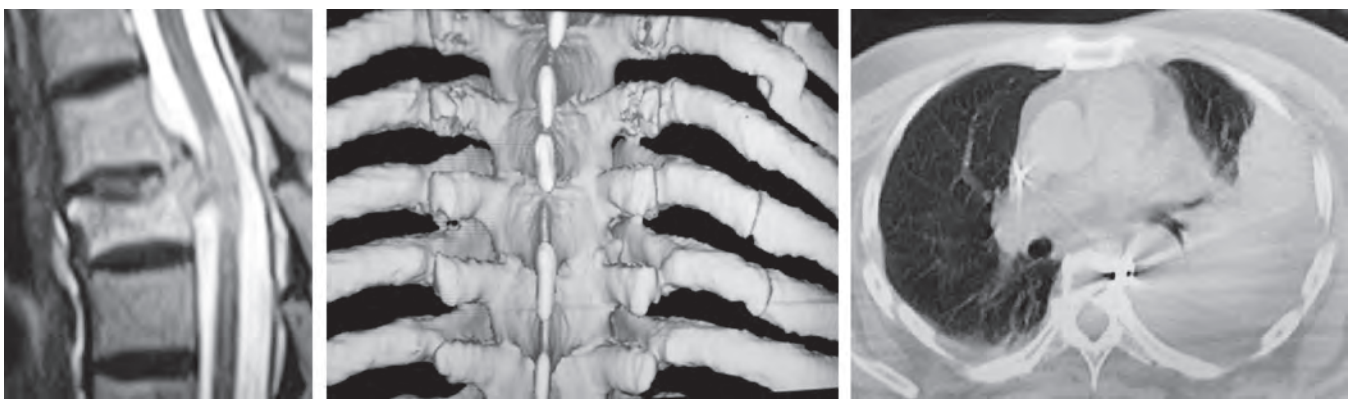


Fig. 4: Thoracic spine fracture (MRI) associated with multiple rib fractures (3D CT) and haemothorax (axial CT)

(pseudogout) may rarely present with paraplegia following minor trauma.[68] There is also a set of conditions that may not show fractures on radiographs but require CT and MRI for demonstrating it, such as ankylosing spondylitis,[98] diffuse idiopathic skeletal hyperostosis[39] and skeletal fluorosis. Extension injuries and shear are commonly seen even with low-energy impacts and the neurological deficit is severe in these ankylosed spines.

CLINICAL FEATURES AND ASSESSMENT

Pain is the commonest presenting symptom of thoracic or lumbar spine injury. Young children, patients with obtundation due to head trauma or ethanol effect and those with minor fractures may not complain of spinal pain in the casualty department. A bruise over the back, a fluctuant haematoma or a tender gibbus may be palpable, but only on turning the patient over—a manoeuvre that is often sadly missed by doctors in the emergency room. Lack of posterior midline tenderness has occasionally been noted with fractures even in sober, alert patients who do not have another painful distracting injury.[25] On the other hand, a minor fracture or ligament injury may present with severe pain and muscle spasm causing total immobility. Priapism is sometimes picked up only when one tries to catheterise the bladder. Conus and cauda injuries might present with isolated inability to void urine in a patient who comes walking

in. A patient who was being treated for a scalp avulsion developing progressive paraparesis 18 hours later due to a total dislocation at T1-T2 level has been reported from Chennai.[93]

Neurogenic shock, manifested by the triad of hypotension, bradycardia and hypothermia may be seen in injuries above T6. It is due to disruption of the thoracolumbar sympathetic outflow and unopposed vagal action.

Neurological syndromes seen are root injury, cauda equina syndrome, incomplete cord lesion and complete cord injury. Note that the American Spinal Injury Association (ASIA) guidelines (International Standards for Neurological Classification of Spinal Cord Injury—ISNCSCI) define complete cord injury as absence of sensory and motor functions in the lowest sacral segments.[5] The completeness of the cord injury can be confirmed only after spinal shock passes off. Spinal shock can be taken to have passed when the anal or bulbocavernosus reflexes reappear. Anterior and central cord syndromes, seen commonly with cervical spinal trauma, are not generally seen in thoracic trauma. Brown-Sequard like syndrome might be seen in non-missile penetrating trauma. It is well to remember that the spinal fracture may be anywhere above the highest neurological level of involvement in incomplete cord injury. With complete injury the rule of minus 2 in the upper thoracic and minus 3 in the lower thoracic spine holds. For example, if the patient has the highest neurological level of impairment at T6, the vertebral lesion is likely to be at T4; neurological impairment at T12 indicates T9 vertebral injury. Though the modified Frankel scale (Table 4) is the most widely used one for assessment because of its simplicity, it has its demerits. The groups are too broad and so one cannot pick up the smaller but useful increments of function. The ASIA Impairment Scale is too detailed for daily clinical use but is useful for research. It can be calculated through a Macromedia Flash based program available for free download at http://www.medicine.usask.ca/pmr/asia.exe.[57] Neurological improvement in paraparesis is best assessed by the WISCI (Walking Index for SCI).[28]

IMAGING

Plain Radiography

Radiographs of the spine are quick and cheap, but the quality of emergency room radiographs is often below par. Patient restlessness, inability to position the patient appropriately and lower output of portable machines may lead to failure in detecting spinal fractures. The cervicothoracic and lumbosacral junction are notoriously difficult areas to depict on radiographs in the triage. Digital radiographs are better than plain film radiographs, but the hard copy should not be in a very small format. Any positive radiographic finding must be backed up by further studies. A normal looking radiograph does not exclude spinal injury and so further studies are warranted, if there is clinical suspicion of spinal injury.

Table 4: Modified Frankel scale

A	No neurological function, complete paralysis
B	Preservation of sensory function below injury level
C	Inadequate motor function below injury level
Da	Allowing ambulation with assistance
Db	Self ambulation with minor difficulty
E	Normal neurological status

Spinal cord injury without radiographic abnormality (SCIWORA) in the thoracic region is mainly seen in the paediatric spine that bends but does not break. Thoracic SCIWORA may be due to high-speed direct impact, distraction from seat belts and run-over when the child is in the prone position.[69] Conversely, one occasionally sees a patient with a gross thoracic fracture dislocation without any neurological impairment.[42] Such a phenomenon has been ascribed to the decompressive laminar fractures, but a congenitally roomy canal and absorption of the impact energy by bone and ligaments might also protect the cord. The situation may be analogous to a vehicle crash, where the front of the car is badly crushed but the occupants escape unhurt.

The finding of one level of spinal injury must lead to a radiographic search for another spinal injury, whether symptomatic or not. Standard antero-posterior and lateral radiographs suffice. Unlike in the cervical spine, there is little role for flexion-extension study in thoracic or lumbar spine injury.

Computerised Tomography Scanning

The wide availability of CT, especially multi-detector CT, has made it possible to image the deformation of the neural canal accurately. Even the 2.5 mm slices of chest and abdomen helical CT done for trauma screening can be reconstructed to obtain good spine images.[81] Table 3 brings out the role of multiplanar CT reconstruction in the TLICS classification.[78] Figure 2 shows some examples of CT in thoracic and lumbar spine trauma. Pneumorachis is associated with skull-base fracture or pneumothorax but may be a primary event in blunt thoracic spine trauma.[17] A "dissolving pedicle" sign has been reported in axial CT of Chance fracture.[8] CT is the best method of identifying canal compromise. The axial transverse canal area might correlate better with neurological state than the mid-sagittal diameter or percentage patency in thoracolumbar burst fractures.[77] The Spine Trauma Study Group suggests measuring the sagittal-to-transverse canal diameter ratio, canal total cross-sectional area and the per cent canal occlusion, to assess canal dimensions.[48] Generally, less than 30% canal narrowing is not associated with neurological deficit but more than 50% is almost invariably accompanied by deficit, at least at the L1 level. Variations between levels and individuals abound.

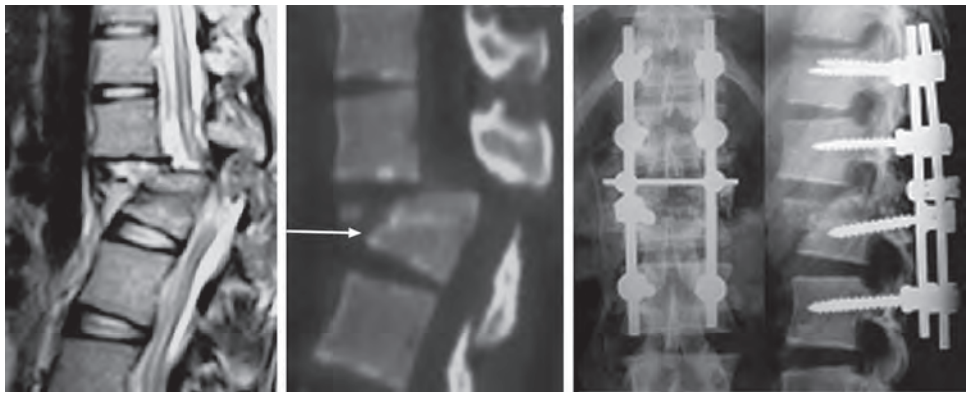


Fig. 5: Sagittal T2 MR imaging of what looks like cord transaction (left). Note the severe canal compromise on CT (middle). This patient has improved from Frankel A immediately after injury to Frankel C in 4 months after extended short segment posterior instrumentation (right- post-operative radiographs), proving that he did not have a true transaction

Magnetic Resonance Imaging

The prevertebral and paravertebral soft tissues, discs, ligaments and spinal cord are best assessed by MRI. Minor fractures missed on radiographs may be suspected from MR by the associated marrow oedema and 'bone bruise'. Acute Schmorl's nodes form due to endplate fracture that allows the disc material to herniate into the vertebral body. These are common in the T8-L1 region and are well imaged by MR.[30] Fat suppressed sagittal T2 imaging best identifies the integrity of the PLC.[56] Rupture of the anterior and posterior longitudinal ligaments, disc disruption and shearing of the subepiphyseal growth zone of the vertebral endplates are demonstrable by MRI in paediatric patients with SCIWORA. These are markers for occult instability and indicate the need for spinal bracing.[70] The 'sandwich sign' of linear haemorrhage in the posterior neural arch framed by marrow oedema has been observed in Chance fractures. These flexion-distraction injuries are also associated with a severe soft tissue injury.[34]

The spinal cord abnormalities seen in MRI are complete transaction (Fig. 5), major or minor haematomyelia and oedema. MRI and somatosensory evoked potentials are also normal in up to 15% of SCIWORA children with persistent myelopathy.[70] The traumatic cord oedema might extend beyond the level of the injury, usually upwards. Figure 6 shows a patient with T12 fracture who had clinical ascent of deficit *pari passu* with the oedema ascending over days to the cervical level. A vascular aetiology has been proposed to explain the delayed ascending myelopathy.[87] Post-traumatic syringomyelia is seen months or years after trauma. T2 hyperintense signal around the cranial border of the post-traumatic syrinx indicates progression.[45] Traumatic extradural haematoma is rarer than the spontaneous variety, unlike in the cranium. Two cases have recently been reported from AIIMS, New Delhi.[49] Gadolinium enhancement is not needed unless there is a suspicion of a tumour or inflammatory disease resulting in pathological fracture.

CONCEPT OF INSTABILITY

At the end of clinical and imaging evaluation, the neurosurgeon should be able to decide if the spine is already rendered unstable by the trauma or if there is a risk of potential instability in the future. While this should be quite straightforward, say, in an isolated spinous process fracture (= stable) or in a fracture dislocation (= unstable), there are grey areas in between. Instability is defined as the inability to limit excessive spinal displacement.[7] Acute instability that results from trauma may be overt or limited. Overt instability is the circumferential loss of spinal integrity resulting in the inability

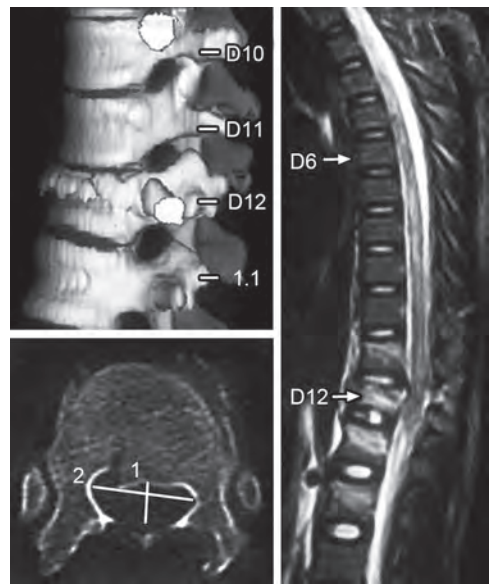


Fig. 6: Ascending cord oedema (right-sagittal T2-weighted MR) up to cervical region 5 days after stable burst fracture of T12 (left-CT). The patient presented with paraplegia that had ascended from L1 level to T6 level at presentation on the 3rd day, following postural reduction at another hospital. Over the next 2 days he had sensorimotor symptoms and signs up to C8 level. He was treated conservatively and the neurological level descended to T3 in a week

Table 5: Quantifying thoracolumbar instability. If the score is > 5, overt instability and if it is 2–4, limited instability exists (modified from White & Panjabi[103])

Factors taken into account	*Points*
Loss of integrity of the anterior (and middle) column	2
Loss of integrity of the posterior column	2
Resting sagittal or coronal plane translation	2
Resting sagittal plane rotation (angulation)	2
Cauda equina (3), spinal cord (2) or root (1) injury	3
Dangerous loading anticipated	1

to support the torso during all normal activities. Limited instability is the loss of either ventral or dorsal integrity with the preservation of the other. Thus the spine with limited instability can support the torso during some activities but not during some others. Denis described three degrees of instability:[26]

1. Mechanical (first degree) instability that results in progressive kyphotic deformity
2. Neurological (second degree) instability that carries the risk of neurological compression
3. Combined (third degree) instability that has both the above components

Table 5 gives a simple method of quantifying the instability, so as to clarify the situation in the grey areas mentioned above.[103] The Spine Trauma Study group advocates the measurement of the Cobb angle (to assess sagittal alignment), vertebral body translation percentage (to assess traumatic anterolisthesis) and anterior vertebral body compression percentage as indicators of instability.[48] Loss of vertebral body height by more than 50% and kyphotic deformity of 20° or more are considered signs of instability.[85] Assigning the Magerl nomenclature, TLICS score or the load sharing score helps decide if an injury is unstable or not. It must be made clear that instability is a clinical concept and not merely a matter of mensuration on images.

MANAGEMENT

Triage Care

The initial goals of resuscitating polytrauma patients must vigorously be pursued in the spine-injured patient. It is necessary to have appropriate oxygenation and perfusion pressures to prevent a secondary damage to the injured cord. Nursing personnel must be instructed to avoid unnecessary movement of patients from beds to trolleys and to take spine precautions when moving. A major chest or abdominal injury takes precedence over spine injury. Methylprednisolone use is recommended by the NASCIS 3 guidelines[11] as a standard of care but niggling doubts remain over the study.[18,43]

A review of pharmacological neuroprotection measures in SCI is available for free download at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC534914/?tool=pubmed.[36]

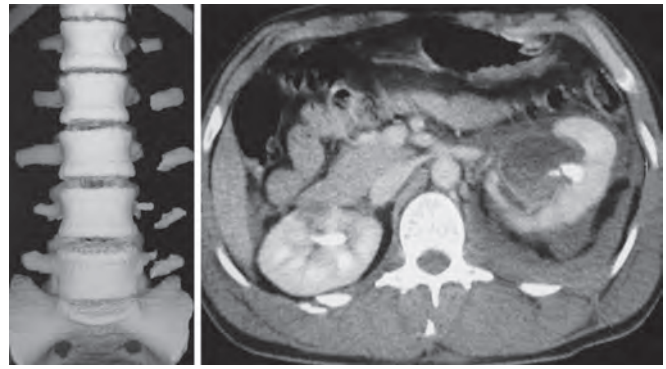


Fig. 7: Multiple lumbar transverse process avulsion fractures on 3D CT reconstruction (left). Since it is a stable injury, this patient was treated with rest and analgesics, followed by lumbar corset use. Renal injuries are common with L1 transverse process fracture as seen in contrast CT of another patient (right)

Non-Surgical Management

Most minor fractures require nothing more than rest and analgesics (Fig. 7). The duration of bed rest has come down over the decades, from months to days. Spinal bracing is popular but its utility remains unproved.[32] Anterior (hyperextension) braces are preferred for thoracolumbar junction fractures. Isolated fractures of the transverse process or spinous process and most stable wedge compression fractures can be treated thus.

Sir Ludwig Guttman established the National Spinal Injuries Centre at Stoke Mandeville near London during the Second World War to treat spinal injuries. He laid down the principles of institutionalised non-surgical management of spinal injuries. Extension of the spine over rolls effected postural reduction in flexion injuries. When the spine is maintained in this position he showed that spontaneous healing by fusion can occur. We must remember that this was at a time when nothing other than laminectomy was available as a surgical option. The rigorous attention to transportation, postural care, pressure sore prevention/treatment and bladder management helped reduce the mortality of paraplegic patients greatly. His work showed the importance of team approach in specialised spine injury centres. These principles are no less relevant today, even in the era of early mobilisation through stabilisation surgery.[29] Guttman's emphasis on rehabilitation extended to wheelchair sports of the Stoke Mandeville Games, the forerunner of the modern paralympics.

Non-operative treatment of burst fractures can be attempted only if the patient is neurologically well preserved, the alignment is acceptable (initial or after postural reduction) and there is no PLC disruption. Conservative treatment is also done for those in whom spine surgery is contraindicated (haemodynamic instability, severe head injury, sepsis or medical comorbidities). The reduction of spinal fractures in frames with head halter and pelvic traction and body slings, followed by application of body casts is out-of-fashion these days

in most centres. One can visit at http://www.maitrise-orthop.com/corpusmaitri/orthopaedic/mo58_spine_fracture/mo58_spine_fractures.shtml to know the details of such techniques. Rotating beds are rarely available in developing nations. Patients find it difficult to accept a body cast or tight-fitting brace in tropical weather. The long-term results of non-operative treatment of selected thoracolumbar burst fractures indicate about 15% incidence of deformity, causing pain and impairment of function and often requiring late surgery.[21]

Surgical Management

Controversy abounds in every area of surgery for spinal injuries. Which patients should be operated, what is the optimal timing of surgery, which route is to be employed and what kind of stabilisation is to be done are all subjects of debate. Spinal surgeons have performed only a handful of prospective trials (and even less randomised ones) to examine these vital issues. It is sobering to note that these studies in general do not show striking differences in clinical or radiological outcome in the different treatment arms. These studies are alluded to in the relevant sections below. Since most of the other studies and reports belong only to level 4 or 5, the recommendations emerging from them can only be given grade C or D status in the language of evidence based medicine (see http://www.cebm.net/index.aspx?o=1025 for the definition of these levels and grades).

Goals of Surgery

The twin goals of surgery in thoracolumbar fractures are neural decompression and restoration/maintenance of spinal alignment. Instrumented fixation and bone fusion are the techniques used to achieve the latter aim. Logically, achieving these twin goals should lead to greater neurological recovery, prevent neural damage, permit earlier ambulation with a painless spine and should prevent delayed deformity. Do the facts justify this logic? Ask any spine surgeon and the answer is a resounding 'yes', but search the literature and the answer is 'may be'.

Controversy over Decompression and Timing of Surgery in Patients with Neurological Deficits

Decompression of the cord can be done directly (removing the bone pieces in the canal) or indirectly through ligamentotaxis (by reducing the fracture, the intact posterior longitudinal ligament pushes the fragments away from the canal). Table 6 presents the routes of decompression of the neural canal. The proponents of decompression argue that continuing compression adds to the cord damage. They hold that faster and greater neural recovery results when the cord is decompressed. They also contend that decompression reduces the incidence of delayed pain. They base their argument on personal anecdotal experience and evidence from experimental situations. In a dog experiment, the longer the compression, the greater was the deficit and lesser its tendency to recover; early decompression resulted in greater return of evoked potentials and lesser motor deficit.[13] Similar findings have been reported in a study on rats.[76] Some studies of the degree of canal compromise (CC) on CT and incidence of neurological deficit indicate a direct and strong correlation (but this relation does not hold for the severity of deficit).[31] More CC is needed lower down the spine to produce deficit. Burst fractures causing ≥ 35% CC at T11–12 had a significant risk of neurological involvement but it required ≥ 45% CC at L1 and ≥ 55% CC at L2 and below.[38]

Non-randomised studies have shown the benefit of decompression. A systematic review of the literature from 1966 to 2000 showed that early decompression (within 24 hours) resulted in better outcome compared with both conservative management ($P < 0.001$) and late surgery ($P < 0.001$).[52] The effect was more pronounced for incomplete SCI than complete SCI. The time limit for decompression has varied from 8 to 72 hours in various reports, making the comparison of results invidious. Early fixation was associated with a lower incidence of pneumonia, a shorter intensive care unit stay, fewer ventilator days and lower charges in a study that retrospectively compared thoracic fracture fixation within or after 3 days of injury.[19] Early fixation was found to result in fewer complications and shorten hospital days in a systematic review.[82] A Turkish study reported in 2008 showed that surgery within 8 hours was associated with not only these benefits but also better neurological outcome.[15] Delayed decompression, months or years after the injury, has also been reported to improve the neurological deficit and reduce the incidence of pain.[97]

The main argument against decompression has been that there is no large prospective randomised trial showing the benefit of decompression in general and early decompression in particular. Those against decompression feel that paralysis occurs at the moment of injury and is not related to the position of the fragments of the fracture on subsequent imaging. A recent Indian study found no correlation between CC and the severity of neurological deficit in thoracolumbar burst fractures, though the authors did mention that this holds for L1 level but not T11 or T12 level.[64] The same group had earlier shown that there was no correlation between the recovery from the neurological deficit and the extent of CC.[63] A review in the year 2000 of 275 publications on burst fractures, of which 60 met minimal inclusion criteria (only 3 prospective studies), failed to establish a significant advantage of surgical over non-surgical treatment as regards neurological improvement. The reviewers concluded that surgical treatment for burst fracture in the belief that neurological improvement can be achieved is not justified, although surgery may still be indicated for structural reasons.[10] There have been more recent retrospective case series that show no benefit of decompression in relation to neurological

Table 6: Methods of decompression and fusion for thoracolumbar injuries

Method	*Rationale and technique*	*Comments*
Indirect	Using ligamentotaxis to force the fragments out of the canal, on reducing the fracture by postural methods or by long or short segment posterior fixation	Fails with large trapezoidal fragment. Requires intact posterior longitudinal ligament. Must be done early, say, within 3 days of the injury. Usually accompanied by posterolateral fusion
Direct	Entails surgical removal of the bone pieces in the canal	Surgeon must ensure that the removal of the bone piece does not add trauma. Must be prepared to tackle CSF leak that often occurs on removing the bone piece
Anterior	This approach is anterior to the cord and exposes the anterolateral part of the vertebral body. Safest for the cord. See routes in Table 9. Best for reconstruction of anterior column	Usually accompanied by anterior fusion with autogenous iliac/fibular bone graft or replacement with titanium spacers/femoral ring allografts. Can be combined with anterior or posterior instrumented fixation
Extended costo-transversectomy or lateral extracavitary approach	Same as 'anterolateral decompression' popular for spinal TB. Done through arched paramedian incision, 7 cm of the rib and entire transverse process removed. Through extrapleural space, the posterolateral part of the body is exposed	Disadvantage of being a unilateral approach. Exposure across the midline makes it possible to do long segment posterior fixation but not contralateral decompression or short segment fixation. Block grafts or cages can be placed but they support only one side of the anterior column
Transpedicular	Aims at creating a cavity in the mid-portion of the vertebral body through bipedicular route, into which the retropulsed fragments in the canal anterior to the cord can be pushed with angled probes from either side and retrieved	Large pieces are risky to manipulate and remove. Only morselised bone grafts can be placed in the interbody interval and not bone blocks resulting in poorer fusion. Must be combined with short segment posterior fixation
Laminectomy	Not to be used as a stand-alone procedure in trauma, especially if there is anterior column injury	Must be combined with long or short segment posterior fixation and posterolateral fusion

outcome.[61] Motor improvements were noted in the non-surgery group, though this was ascribed to there being a greater number of incomplete injuries in this group. This fact must be tempered with the knowledge that greater improvement is seen in incomplete SCI even in the operated group. Injudicious surgery may result in complications. Surgery might reduce hospital stay,[61] but it is innately more expensive. The canal tends to remodel itself over years even if not surgically decompressed or grafted.[3,67]

A prospective single-blinded randomised clinical trial has now been started to assess the efficacy of early and delayed decompression surgery for thoracolumbar injuries. The study plans to recruit about 330 cases, a number that is needed to be able to detect a statistically significant difference in motor recovery.[75] Until the results are available and are found to be reproducible, we have to make decisions based on personal experience and tailor-make the treatment process to each patient. The only consensus now is that patients who are progressively worsening in their deficit must be offered emergency surgery.

Controversy over the Treatment of Burst Fractures without Neurological Deficit

Burst fractures without neurological deficits pose three problems: (1) pain at the fracture site that might continue unabated for months or years; (2) delayed kyphosis and (3) delayed neurological deficits due to stretch of the cord over an internal gibbus. Hence, several surgeons have advocated anterior and/or posterior surgery for such lesions. This matter has been tested in some trials but these trials have been of poor design or of small sample size. A prospective non-randomised study of 80 patients reported in 2001 showed that posterior instrumentation provided early pain relief and immediate correction of kyphosis as compared to non-surgical treatment. However, the advantages of surgery had evaporated by 2 years of follow-up.[89] A study reported in 2003, randomised 47 patients with stable thoracolumbar burst fracture (24 operated) and found no significant difference in pain, kyphosis, canal diameter improvement or work capacity between the operated and the unoperated groups over a minimum follow-up of 2 years.[104]

This was also the conclusion of a Cochrane Database Review in 2006.[106] Another recent study that focussed on functional outcome at 5 years showed no difference between those treated conservatively and those operated upon for type A3 fractures without deficit, but there were more severe fractures (A3.2 and A3.3) in the operated group.[73]

Available Options for Surgery

The types of available procedures for surgical stabilisation of thoracic and lumbar fractures can broadly be categorised into long segment posterior fixations, short segment posterior fixations or anterior fixations. These are summarised in Table 7.

Posterior procedures: It is likely that reducing the kyphosis by posterior instrumentation causes the intact posterior longitudinal ligament to stretch and push the retropulsed fragments into the body, thereby effecting canal decompression without direct surgical handling of the fragments. CT has proved that this phenomenon of ligamentotaxis increases the narrowed canal diameter in the short as well as the long term.[66] However, large trapezoidal fragments resist ligamentotaxis. Such fragments might require direct surgical removal, especially in those with incomplete neurological deficit. The extent of clearance of the canal can be checked during posterior surgery with intra-operative ultrasonography.[55]

Generally, the posterior procedures are most effective in the acute stage (within 72 hours) after trauma (Figs 8A to D). Though multiple segments are incorporated in long segment instrumentation, the fusion is performed only at the level of the fracture. This has been succinctly described as 'rod long but fuse short'.[2] Long segment instrumentation ultimately fails when bony union (by spontaneous or surgical fusion) does not occur. Short segment procedures are based on pedicle screw systems that can theoretically provide three-column support to the spine. Short segment instrumentation immobilises fewer segments and hence causes less interference with whole spinal motion (Fig. 9). Adding a horizontal cross connection increases the strength of the construct (Figs 10A to C).[27] The pedicle screw used must be of the largest diameter that the pedicle can take. This is not a matter of guesswork or slavish application of statistics. The pedicle diameter, the pedicle inclination to the vertical and the screw path length must be measured on the preoperative CT at every required level. Convergent pedicle screws have greater resistance to pullout (Figs 10A to C). Pedicle screw placement is a more demanding surgical technique but involves less blood loss and shorter operating time than long segment or anterior procedures.

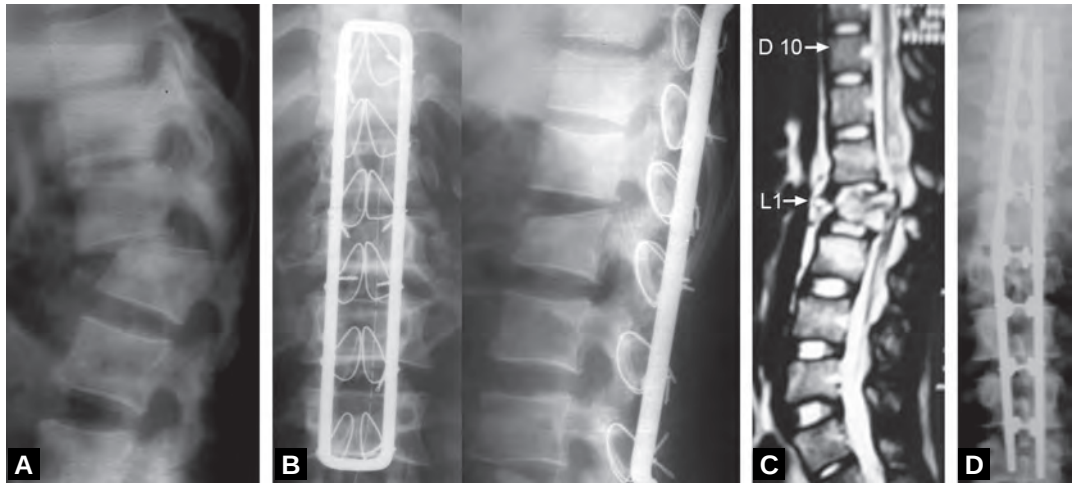
The canal clearance was a shade better with Harrington rods than pedicle devices but both systems produced good enough clearance if surgery was done within 4 days of trauma in a prospective randomised study.[100] Another small prospective randomised study showed better sagittal plane deformity correction with long segment as compared to short segment fixation.[94] Loss of correction in the sagittal plane is seen on follow-up in both conservatively treated and operated patients. Figure 11 shows an example of loss of correction with short segment fixation after 5 years, though the patient was asymptomatic. Passing pedicle screws 2 levels above and 2 levels below the injury site, instead of the customary 1 level above and below is a via media, instead of resorting to long segment (3 levels above and below) instrumentation (Fig. 5).[4] A recent paper suggests that short segment fixation using pedicle screws 2 levels above and 1 below the thoracolumbar junction injury prevents re-kyphosis and hardware failure while retaining the lumbar mobility.[62] The significant complications of pedicle screw placement in the thoracic spine and techniques for minimising these have been pointed out in a review article in Neurology India.[107] In women and persons of small frame the pedicles (especially D11 and D12) may be too narrow to take a screw of adequate diameter. Such persons may need long segment posterior fixation or an anterior approach. A recent trend is to use neuronavigation for placing the difficult pedicle screws.[53]

In order to decide between long or short posterior spinal fixation, a load sharing classification has been developed[60] (Table 8). Those burst fractures that are highly comminuted have wider spread of fragments and that need greater kyphotic correction will experience implant failure after short segment posterior instrumentation.[4] Hardware failure occurred in 40% of 50 cases of unstable thoracolumbar fractures treated by Steffee variable screw-plate device in a recent Indian series, even though there was good kyphosis correction and only a little loss of correction over time.[12] Hardware failure rate was lesser (only 20% of 50) in another Indian series using Moss Miami type of pedicle screw-rod construct and so the type of device also seems to matter.[85] A recent multicentre prospective randomised study (of 34 patients) has shown that Magerl Type A3 fractures without neurological deficits fared significantly better in the kyphotic angle, pain/function scores and ability to work after short segment fixation as compared to non-operative treatment.[90]

The importance of fusion with bone grafts in posterior surgery has recently been questioned. Transpedicular intracorporeal grafting in the treatment of burst fractures did not have a detectable effect on the rate of reconstruction of the canal area or on remodelling in a prospective, randomised, controlled study of 21 patients.[3] However, morselised transpedicular grafts could achieve and maintain kyphosis correction, and provide better anterior vertebral height in a randomised study of 70 thoracolumbar burst fractures from China.[101] On the other hand, a retrospective study of transpedicular grafts found graft incorporation and fusion only in 34% of 29 patients.[50] In a recently reported prospective,

Table 7: Instrumented fixation for thoracic and lumbar fractures

Procedure	*Comments*	*Complications*
Long segment posterior fixation	3 or more levels above and 3 or more levels below the injury. 'Fix long, fuse short' principle	Loss of normal thoracic kyphosis and lumbar lordosis, back stiffness due to greater number of segments being fixed
Hook-rod systems	Hooks on facet-lamina better than transverse process hooks	Hook pull out, rod breakage
Harrington distraction	Anterior longitudinal ligament must be intact. Used for wedge/burst fractures, fracture dislocation, translational injuries, typically in the early phase	Overdistraction. Poor resistance to rotational deformation
Harrington compression	Used for flexion distraction injury/Chance fracture. Uses thoracic transverse process and lumbar laminar hooks. Not to be combined with sublaminar wires	Need to remove long rods after fusion is solid (in 1–2 years)
Wires-rod (Luque 'L'/Hartshill rectangle) systems	Resists rotational deformation better than hook-rod systems	Wire breakage, usually the inferior most. Rods may slip or break but rectangles do not
Sublaminar wires	Flavotomy needed. Wire passes between ligamentum flavum and dura, from below upwards. A titanium rectangle designed by Dr. R. R. Ravi, Neurosurgeon, Kochi, is lighter; wires tightened through holes in the rectangle instead of around the stem; notched external border prevents slippage or cutting	Cord injury and dural tear during wire passage. Generally reserved for complete cord injury
Spinous process wires—Drummond (Wisconsin)	Easy procedure. Less deformity correction in sagittal plane. Less canal restoration. Useful for facet dislocation and coronal plane translational injury	Avulsion of base of spinous process more likely than wire breakage
Combined systems		
Harrington distraction with sublaminar wires	Improves resistance to rotational deformation	
Cotrel-Dubousset (CD) system	Uses multiple hooks, pedicle screws coupled to rods that can be horizontally cross linked. Type 1 provides distraction, Type 2 gives compression and Type 3 maintains lumbar lordosis	Complicated instrumentation
Texas-Scottish Rite Hospital (TSRH) system		Not available in the author's practice
Short segment posterior fixation	1 level above and 1 level below the injury (rarely 2 levels above and below). Only devices to provide all 3-column support. Avoids unnecessary loss of movements at multiple segments. Though compression and distraction can be applied to correct sagittal plane deformation, are less effective in correcting severe deformity or dislocation. Cross linking needed if > 2 levels	Pedicle violation leads to cord or root injury and weakening of construct. Higher rate of pedicle screw breakage and loss of correction over time than in degenerative disease
Pedicle screw-plate systems	E.g. Roy Camille, Steffee, Luque	Difficult to contour plates, screw break at junction
Pedicle screw-rod systems	Mono/polyaxial screws, single/double lock, reduction screws	More versatile
Anterior fixation		Complications due to thoracotomy
Screw-plate systems	E.g. Zdeblick plate	Screw penetration into canal
Screw-rod systems	E.g. Kaneda. Pedicle screws can be used as body screws instead. Above T9, 1 screw per body. T10 and below, 2 per body	Use of staples needed to prevent screw erosion into body
Combined anterior and posterior fixation	Combinations of above	



Figs 8A to D: (A) Lateral radiograph of D12-L1 dislocation with Frankel A complete cord injury. Posterior operative reduction and long segment fixation done in 48 hours using stainless steel sublaminar wires and Hartshill rectangle. (B) Note the correction of deformity and canal restoration in AP and lateral radiographs. (C) MRI of L1 unstable burst fracture operated 14 years ago, before pedicle screw systems were available. (D) AP radiograph after long segment posterior fixation with spinous process Drummond wires. Note the buttons in wires to prevent the wire from cutting through the bone

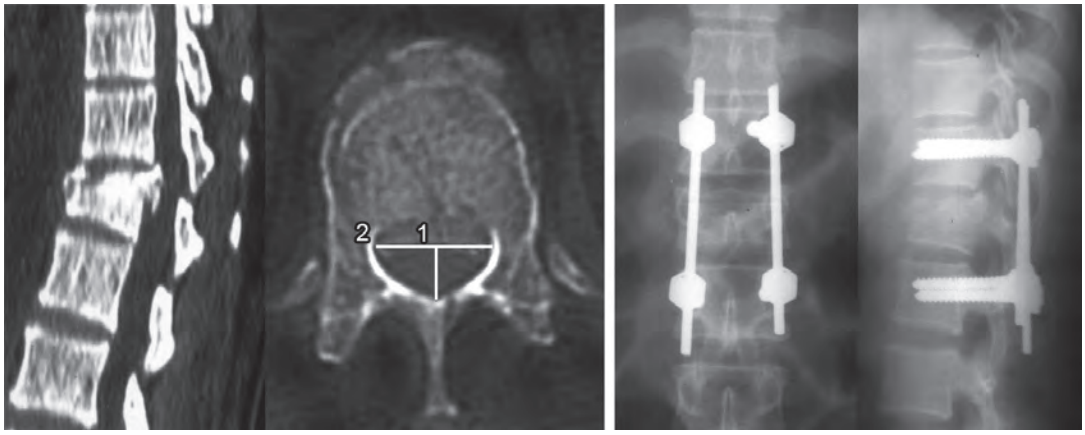
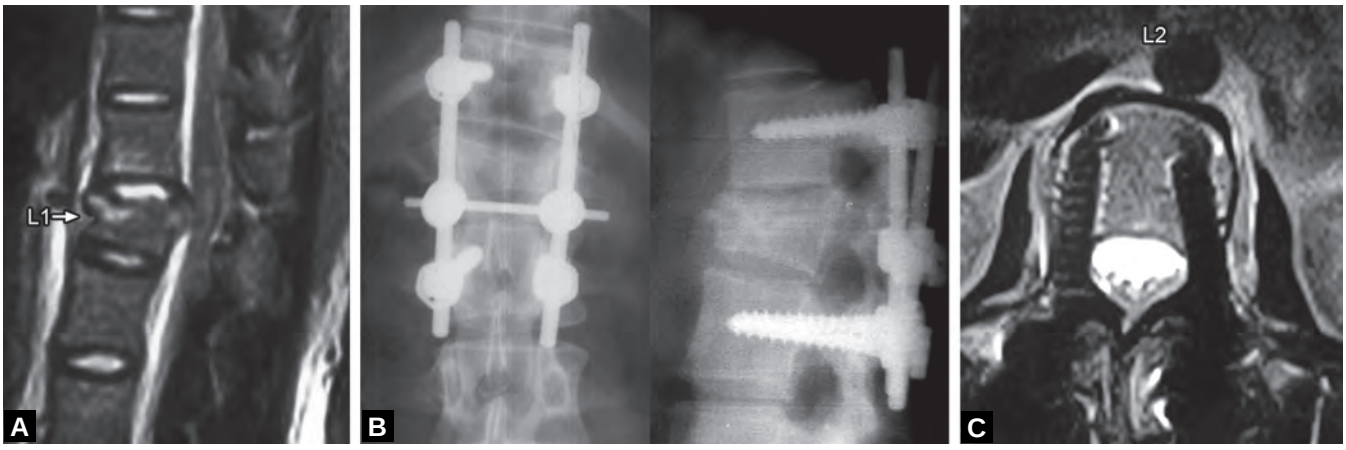


Fig. 9: Sagittal and axial CT of L1 unstable burst fracture with retropulsed fragment (left), treated by short segment pedicle screw (Moss Miami type) system. Note the correction of kyphosis in the post-operative radiographs (right)



Figs 10A to C: L1 burst fracture in a woman with neurogenic bladder dysfunction alone. Since the canal was preserved and as there is not much comminution of body in pre-operative imaging. (A) Only short segment posterior fixation was done. The use of cross-connector augments short segment posterior fixation. (B) Note artefact-free axial MR imaging with titanium pedicle screws and the correct screw trajectory. (C) The patient made full recovery and had a baby 18 months later

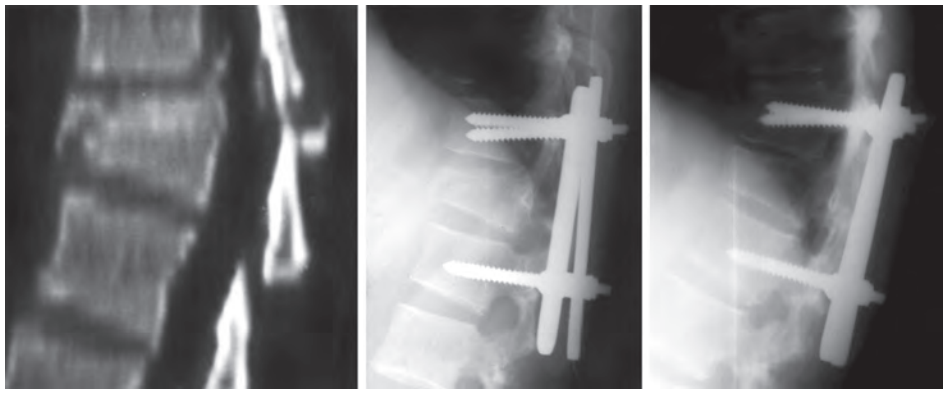


Fig. 11: Sagittal reconstructed CT of unstable burst fracture of T12 body treated by short segment Steffee variable screw plate instrumentation (left). Radiograph immediately after surgery (middle) showed moderate correction of kyphosis, which was partially lost in the follow-up film after 5 years (right), even though the patient was asymptomatic

Table 8: McCormack load sharing classification for surgical decision making in thoracolumbar burst fracture.[60] Patients with score of < 7 can be managed by short segment posterior fixation. Those with score ≥7 will need anterior column support or long segment posterior fixation

Factors considered	*Assessed by*	*Points*
Comminution	Sagittal and axial CT	
Less (< 30%)		1
More (30–60%)		2
Most (> 60%)		3
Apposition of fragments	Axial CT	
Minimal (hardly any displacement of fragments)		1
Spread (2 mm displacement < of 50% of cross section of body)		2
Wide (2 mm displacement > of 50% of cross section of body)		3
Required kyphotic correction	Lateral radiograph	
3°or less		1
4°–9°		2
10° or more		3

randomised, controlled study of 73 patients of burst fracture and a load sharing score of ≤ 6 and followed up for 5 years, no significant difference in radiographic or clinical outcomes was noted between the fusion and the non-fusion groups after short segment posterior fixation.[22] Operative time and blood loss were significantly less in the non-fusion group. Donor site pain was reported by 67% of the fusion group even at the last examination.[22] Posterior bone fusion/long segment fixation/anterior column reconstruction is advisable in fractures with load sharing scores of ≥ 7.

Anterior procedures: Anterior procedures offer the advantage of reconstructing and instrumenting the anterior and middle columns. They also offer the advantage of clearing the retropulsed fragments of bone and disc without stressing the cord (Fig. 12). The flip side is that the procedure is more major, involves more blood loss/operating time and often needs the help of a thoracic or abdominal surgeon. The complications of lung collapse/consolidation, pleural collection, ileus due to retroperitoneal dissection, wound dehiscence and wound pain are significant.[44] The routes of anterior approach preferred by the author are outlined in Table 9.

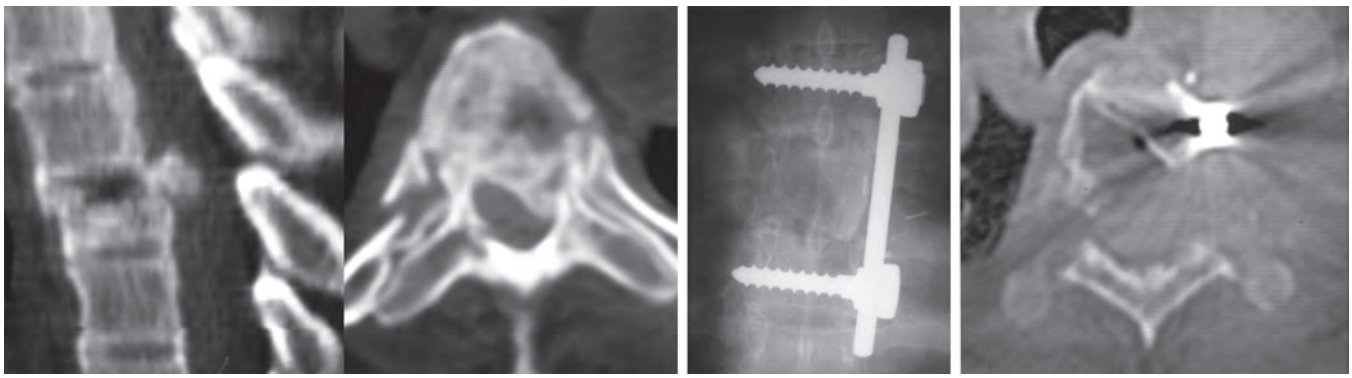


Fig. 12: Sagittal and axial CT of the same patient as in Fig. 4 with T5 burst fracture (left). Transthoracic corpectomy, anterior stabilisation and iliac autograft placement were done (middle). The smaller size of the thoracic body permits only one screw placement in each body but this proves sufficient. The vertical rod also serves to prevent lateral graft extrusion. The graft is impacted with the screws in distraction for restoration of height. Once seated, the graft is placed under compression. Note the canal decompression in the postoperative axial CT (right)

Table 9: Routes of anterior approach to thoracic and lumbar spine injuries

Level of injury	*Approach of choice*	*Comments*
C7 toT2	Low anterior cervical for patients of asthenic build	Left side approach avoids recurrent laryngeal nerve injury,
	Transmanubrioclavicular for corpulent patients	but carries risk of thoracic duct injury
T2 to T3 or T4	Right third intercostal space thoracotomy	Right side approach avoids the arch of aorta and its branches that hinder left side approach
T4 or T5 to T10	Left thoracotomy	Approach through the intercostal space that is in line with the targeted vertebra at the midaxillary line
T11 to L1	Left thoracotomy, transdiaphragmatic retroperitoneal	Retroperitoneal space can be opened by either splitting the costal cartilage or by sweeping off the peritoneum from the under surface of the diaphragm after thoracotomy. Diaphragm is cut and repaired circumferentially
L2 to L4	Left flank incision, retroperitoneal	The lower the level the more anterior the incision extends
L5, S1	Midline transperitoneal	ALIF retractors are very useful to keep the abdominal
	Paramedian retroperitoneal (mini-ALIF approach)	contents away and to increase space between iliac vessels

Anterior reconstruction began with strut bone grafts and went on to incorporate anterior instrumentation. Cages are substituting grafts in some centres (Fig. 13). In a retrospective Indian series of 60 patients, the anterior procedure was chosen for thoracolumbar junction injury with incomplete or complete neurological deficit with a large retropulsed fragment in the spinal canal, when canal compromise was 67%, when the anterior column was comminuted and kyphosis was ≥ 30° and when the patients were operated beyond 4 days from the time of injury.[84] In a Chinese prospective randomised study of 65 patients undergoing anterior plating for a thoracolumbar burst fracture with a load-sharing score ≥ 7 and followed up for a minimum of 4 years, the autograft and titanium spacer groups had similar fusion rates and clinical/radiological results.[20] The details of operative techniques and various instrumentation devices are beyond the scope of this chapter, but the salient points are mentioned in Tables 6, 7 and 9.

Combined procedures: Anterior and posterior procedures are considered for three-column injuries so as to affect 360° fusion/stabilisation. The usual combination is short segment posterior fixation and anterior decompression with strut grafting (Figs 14A to C); which procedure should be done first will depend on the situation. For example, in a vertebral body fracture with severe kyphosis and facet dislocation, the posterior procedure can be done first followed by the anterior. It is vice versa for a comminuted fracture with severe canal compromise and lesser kyphosis (Fig. 15). Anterior surgery can also be combined with posterior long segment fixation (Figs 16A to C). The two procedures can be done in a single session in a fit patient, but it is prudent to stage

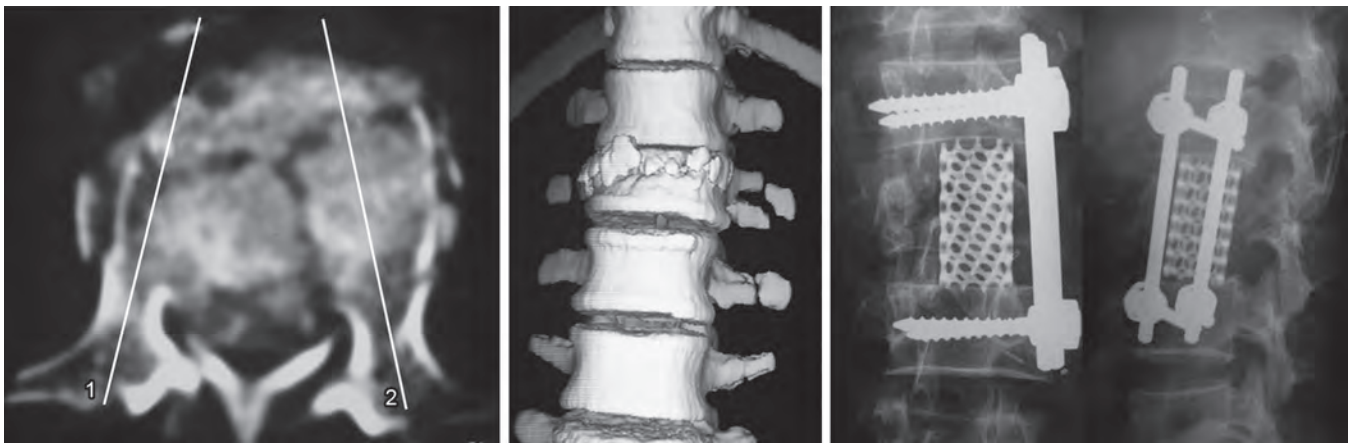
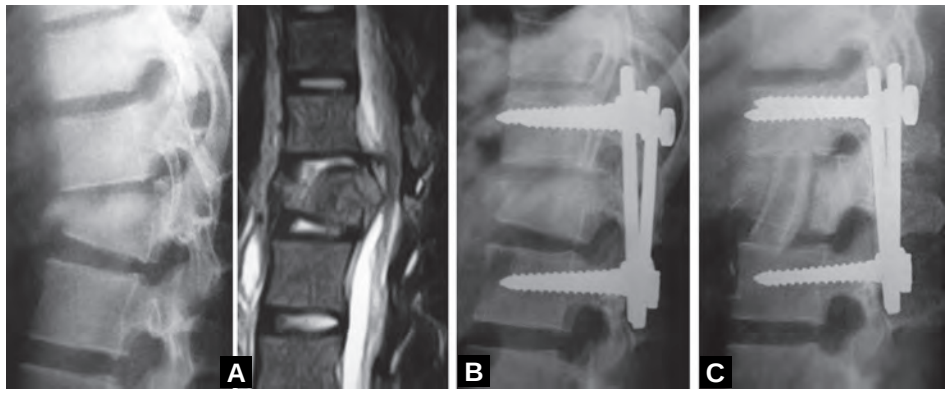


Fig. 13: Axial and 3-D CT of unstable burst fracture of L2 with laminar fracture (left). Anterior corpectomy, placement of titanium spacer and stabilisation with two screws each in L1 and L3 bodies. Note the canal restoration and deformity correction in the post-operative radiographs (right)



Figs 14A to C: Lateral radiograph and MRI of L1 burst fracture with unilateral motor deficit and sparing of bladder function. (A) The patient underwent short segment pedicle screw instrumentation first. (B) followed by anterior corpectomy and iliac strut grafting after 4 days. (C) Patient made rapid neurological improvement and is asymptomatic

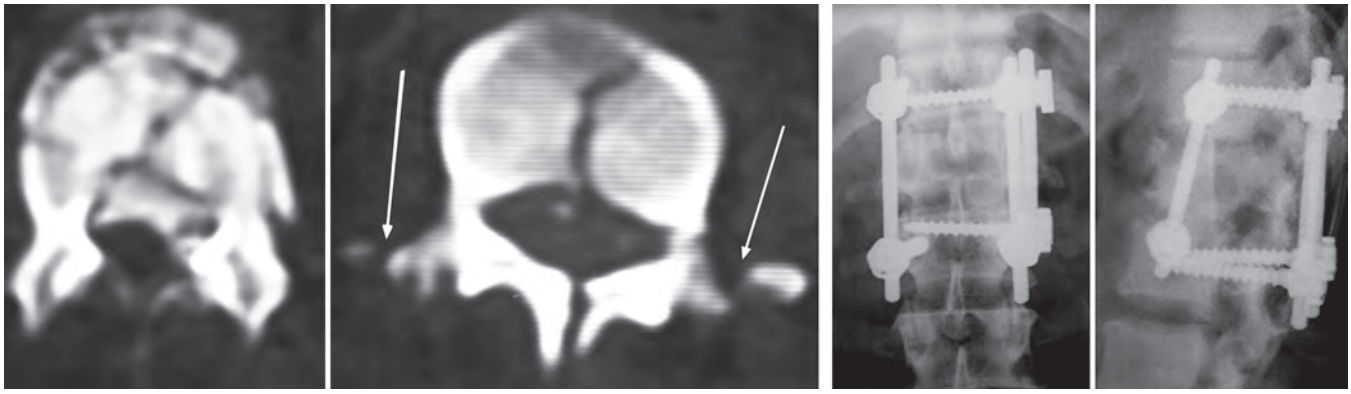
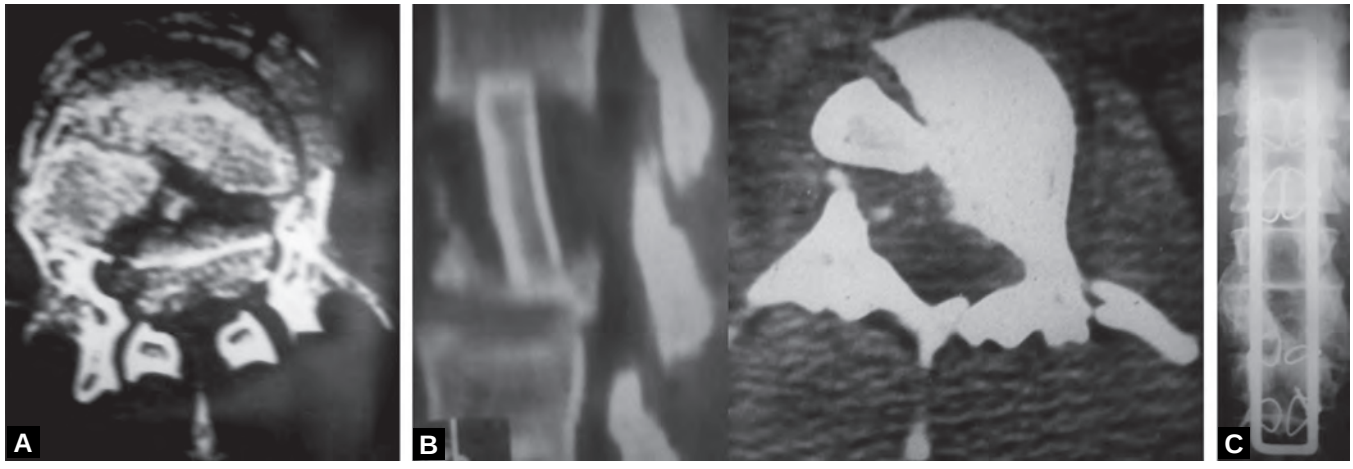


Fig. 15: Axial CT of L1 burst-split fracture with 50% canal compromise and no neurological deficit (left). The patient underwent anterior corpectomy, iliac strut grafting and anterior instrumentation (single body screw per level) followed by short segment pedicle screw instrumentation after 4 days. AP and lateral radiographs after both the procedures (right). Patient remains neurologically normal and is pain-free, back at his job



Figs 16A to C: Axial CT of L1 burst fracture in Frankel A with canal compromise: (A) The patient underwent transthoraco-phreno-retroperitoneal corpectomy and strut grafting. Note height restoration and canal clearance in the post-operative sagittal and axial CT. (B) This was followed after 5 days by long segment posterior fixation with sublaminar wires and rectangle seen in AP radiograph. (C) The patient recovered to Frankel D

the procedures 3–7 days apart. Anterior augmentation with polymethylmethacrylate vertebroplasty after short segment posterior fixation has recently been reported to be successful for non-osteoporotic burst fractures.[1] Vertebroplasty and kyphoplasty for osteoporotic fractures has been dealt with in another chapter of this textbook. Laparoscopic or thoracoscopic procedures also reduce the morbidity of anterior procedures, although endoscopic exposures have been used for less complicated cases.[44]

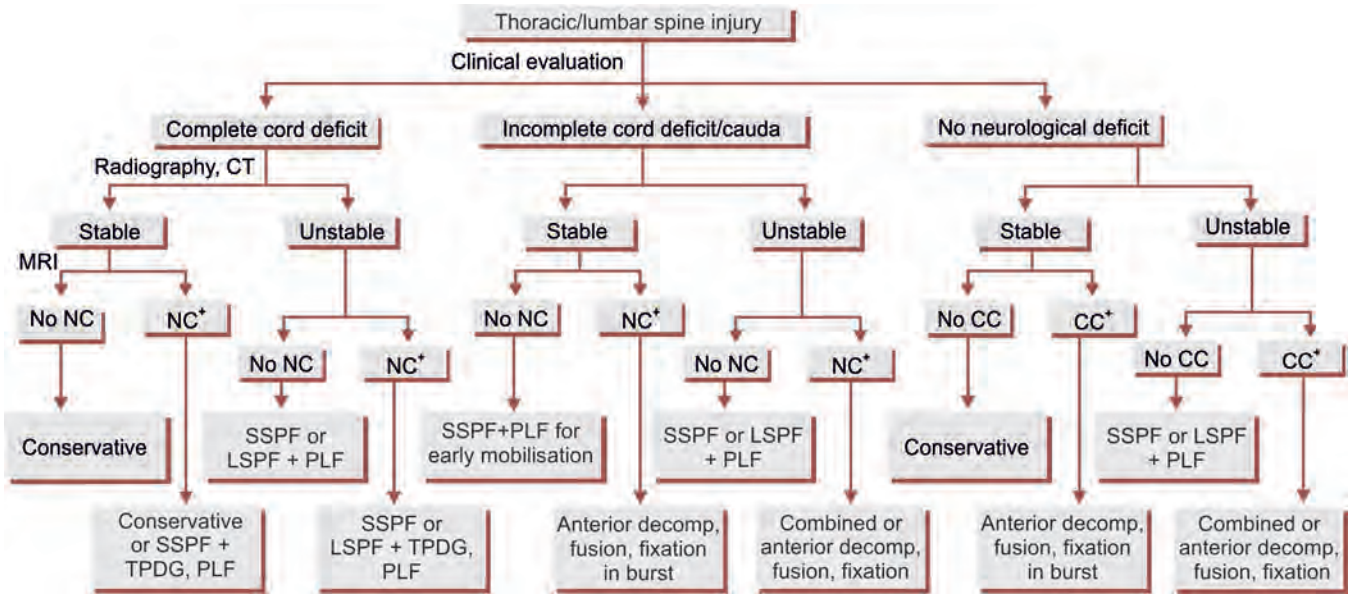


Fig. 17: Algorithm for management of thoracolumbar injuries. NC – neural compression, CC – canal compromise, SSPF – short segment posterior fixation, LSPF – long segment posterior fixation, PLF – posterolateral fusion, TPDG – transpedicular decompression and grafting

The cost and availability of branded titanium spinal implants are limiting factors in developing nations. Stainless steel implants are definitely stronger than comparable sized titanium ones. Stainless steel implants are lower in cost but interfere significantly with CT and MR imaging. The higher torsional resistance of stainless steel implants makes them useful for long segment instrumentation.[51]

Decision Making

The questions to be answered while treating a thoracolumbar fracture are: (1) whether to operate or not; (2) when to operate (emergency/early/delayed) and (3) how to operate (route/level/decompression/fusion/instrumentation).[23] In order to answer these questions, the surgeon must take into account several factors. Age, general medical status, body weight and time since injury must be factored in. Associated injuries might impact the treatment plan. The extent and evolution of neurological deficit matter much. The level of the injury, the classification of injury, the TLICS score and the load sharing score profoundly influence the operative approach. Finally, the experience of the surgeon and the availability/affordability of instrumentation are germane issues. Demonstrable neural compression with progressing deficit is the strongest indication for decompression. Canal compromise with incomplete cord injury, cauda equina syndrome or severe pain is the next best indication. In the face of complete SCI, issues of stability decide the surgery rather than the canal compromise. Since decompression procedures add to the instability, they are almost invariably done along with an instrumentation/fusion procedure. The algorithm currently employed by the author is given in Figure 17, granting that this is oversimplification of a complex issue. It must be emphasised that the decision has to be tailor-made to the individual patient and type of injury.

OPEN SPINE INJURIES

Missile injuries can be either of high-velocity, such as those due to military weapons, or of low-velocity, such as those due to country-made firearms. If a bullet grazes the spine but does not go through it, the cord injury is due to the associated shock wave and this has some potential for recovery; not so with a direct cord laceration, transection or root avulsion.[9] Bullet removal is recommended for cauda equina injuries. Surgical exploration is warranted in most patients with a stable general condition to decompress the cord and to avoid external CSF leak or meningitis, even though the septic complications are less frequent than with non-missile injuries.

Non-missile injuries are common in the thoracic spine when the standing victim is attacked from the back. The sharp object enters the interlaminar space and lacerates the dura. CSF leak from a stab wound in the back is a telltale sign. Brown-Sequard syndrome from stab injury has already been mentioned. The blade of the knife may be retained and one should resist the urge to yank it out in the emergency room. It should be removed after a formal surgical exploration of the tip.[33] CT myelography was needed in one of our cases to locate the site of leak, which might not be necessarily at the site of the entry wound (Fig. 18). Surgical exploration is mandatory for removing retained foreign bodies and for repairing the

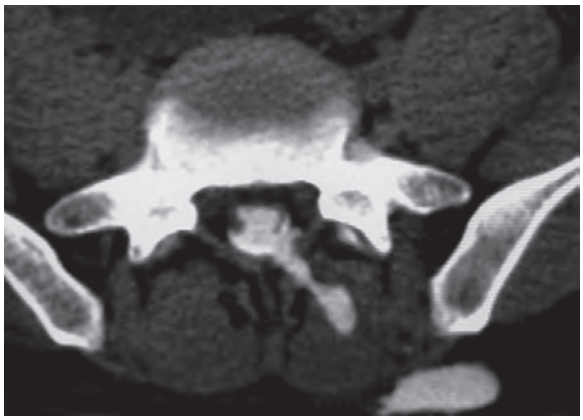


Fig. 18: A young man was knifed in the buttock. There was no neurological impairment. The entry wound in the upper gluteal region was sutured elsewhere. CSF leaked out of the wound 4 days later. CT myelography showed the dural fistula at L5-S1 level with a subcutaneous collection. He made uneventful recovery after dural repair through laminotomy

dura. There is usually no need for stabilisation. Infective complications cause significant mortality and morbidity.

CONCLUSION

Thoracolumbar spine injuries are common in neurosurgical and orthopaedic practice. A thorough clinical and imaging evaluation helps in understanding the mechanism of injury and selecting the correct treatment approach. We are now able to correct the orthopaedic part of the injury well, but recovery of lost cord function remains an unfulfilled goal.

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53 Lumbar and Lumbosacral Injuries

Ramakrishna Easwaran

Sacral fractures are rare, accounting only for 1% of all spinal traumas. In pedestrians struck by motor vehicles, spinal injuries are seen in 8%. These spinal injuries are more or less evenly distributed in the spinal column and 27% of these injuries affect the sacrum.[18] The sacrum completes the pelvic ring and sacral fractures are present in about 45% of pelvic fractures.[8] In such cases, the sacral fracture is the least conspicuous of all the fractures. Only 5–10% of all sacral fractures are isolated fractures.[8]

CLASSIFICATION

The sacral fracture classification scheme of Schmidek, the sacral zones of Denis and a morphological classification of transverse fractures are given in Table 1.[3,14] A direct blow to the coccyx causes the low transverse fracture at S3 or below, whereas the high transverse fracture at S1-2 level is due to indirect trauma, transmitted through the pelvis. Since most sacral fractures are vertically oriented and as the line of the sacral foramina form a weak area, it is logical to divide the sacrum into vertical zones: (1) Zone 1 fractures that are lateral to the foramina are caused by lateral compression of the pelvis; (2) Zone 2 fractures in the foramina by vertical shear and (3) Zone 3 fractures affect the sacral canal and are the least common, and have the highest incidence of neurological damage. The transverse fractures (5–15% of all sacral fractures) may affect all the three zones. Based on sagittal CT and lateral radiographs, the transverse fractures have been classified into four types by Roy-Camille (Table 1).[10] Lumbosacral fracture dislocation follows one of the five types described by Aihara.[2] The type 4 lumbosacral dislocation in the scheme (Table 1) has previously been described as 'acute traumatic spondylolisthesis', but the former name is more apt, considering the amount of anterior and posterior ligament damage in this unstable injury.

CLINICAL FEATURES

Sacral fractures are missed or only detected after a delay in 30% of patients.[8] This is especially true for sacral insufficiency fracture that occurs in the osteoporotic elderly patient after a trivial fall. Sacral stress fractures also occur in athletes[15] and after labour.[16] Suicide jumpers may have an isolated transverse sacral

Table 1: Schemes of classification of sacral fractures

Schmidek (1984)[14] classification	*Denis (1988)[3] classification*	*Root damage*
Direct trauma	Zone 1 (alar zone)	L5 partial in 6%
Penetrating	Zone 2 (foraminal zone)	Sciatica in 28%
Comminuted	Zone 3 (sacral canal zone)	Saddle anaesthesia and sphincter dysfunction in 57%
Low transverse		
Indirect trauma		
High transverse		
Type I		
Type II	*Morphological classification of transverse fractures*	
Type III	H shaped	
Vertical	U shaped	
Lateral mass	T shaped	
Juxta-articular	λ shaped	
Cleaving		
Avulsion		

Roy Camille (1985) classification of sacral transverse fractures[10]
1. kyphotic angulation
2. partial anterior translation
3. complete anterior translation
4. burst fracture

Aihara (1998) classification of lumbosacral dislocation[2]
Type 1: Unilateral L5-S1 facet dislocation with or without facet fracture
Type 2: Bilateral L5-S1 facet dislocation with or without facet fracture
Type 3: Unilateral L5-S1 facet dislocation with contralateral facet fracture
Type 4: Bilateral L5 pars interarticularis fracture with dislocation of L5 body
Type 5: Fracture of L5 body or pedicle with dislocation of L5 body

fracture.[13] Patients without neurological deficit present with pain in the low back, buttock or perianal region, which increases on sitting or defecating. Isolated urinary retention has been reported.[12] Neurological deficits may be unilateral or bilateral. It is important to assess the S2–S5 roots by checking rectal sphincter tone and action, saddle and perianal pinprick sensation and reflexes (anal and bulbocavernosus). Digital rectal examination (and vaginal examination) may reveal an open fracture. The sacral root injury can range from neurapraxia to neurotmesis. The neurological deficit might be obvious only after a delay.[7] Sacral alar fractures cause L5 root injury. Transverse fractures across zone 3 are more prone to produce neurological deficits and even transection of roots.[13] Sexual dysfunction is a common sequel.

DIAGNOSTIC TESTS

Nearly 60% of sacral fractures are missed in the initial plain film radiography.[5] Sacral fractures are difficult to visualise on an anteroposterior (AP) radiograph because of the tilt of the sacrum. The lateral views are obscured by soft tissue of the buttocks. Tracing the arcuate lines in the sacrum may detect an inobvious fracture.[5] The outlet view of the pelvis provides a good AP view of the sacrum and the inlet view displays the sacral spinal canal. Lateral view of the sacrum can be supplemented by sagittal CT reconstruction. The transverse fractures are best made out in coronal or three-dimensional CT reconstruction. H (or U) shaped fracture is often seen in osteoporosis. It is vital to study the entire bony pelvis in a case of sacral fracture. CT can also display anatomical variants due to sacral dysmorphism. MRI is sensitive to the marrow oedema that accompanies a sacral insufficiency fracture. Oblique coronal MRI of the sacrum can show the whole length of sacral nerves and depicts root compression by fracture fragments. A complete urodynamic evaluation with cystometrography and sphincter electromyography is needed for proper bladder management.[12] Sphincter electromyography is useful for monitoring the sacral roots during surgery.

MANAGEMENT

Most sacral fractures can be treated non-surgically. These include stable, undisplaced sacral fractures without pelvic ring disruption, fractures that spare the lumbosacral junction and fractures without neurological injury. Bed rest and analgesics suffice. Transverse fractures with minimal displacement or angulation can also be managed conservatively, if the patient has only minimal deficits.[9] Painful insufficiency fractures can be treated by percutaneous polymethylmethacrylate sacroplasty.[6] Sacral fractures that are a part of an unstable pelvic fracture require external or internal pelvic fixation. The reduction of the pelvic fracture might lead to sacral root entrapment. Delayed entrapment neuropathy can occur due to stretch over a deformity or callus. Surgery is recommended for those with neurological deficits and imaging documented root compression. Delayed pain is a common problem and often calls for surgical exploration. The nerve roots must be exposed by sacral laminectomy/foraminotomy and freed from compression by fracture fragment or entrapment within the fracture.

After operative reduction, internal fixation of sacral fractures is done with iliosacral screws, posterior sacral plating or posterior iliosacroilial bars.[17] Iliolumbar (lumbopelvic) fixation can be done to avoid hardware prominence or skin ulceration associated with iliosacral screws. It can also be done when the sacral screws are precluded by a comminuted fracture. The technique has been described from Amrita Institute of Medical Sciences, Kochi.[1] Triangular osteosynthesis fixation entails placement of L4, L5 pedicle screws, posterior ilial and iliosacral screws. This allows early full weight bearing at 6 weeks while preventing loss of reduction in comminuted vertical shear transforaminal sacral fractures.[11] Lumbosacral dislocation is managed with pedicle screw stabilisation. L4 often needs to be included. Sacral alar or S2 screws may be used to augment the inferior part of the construct. In Aihara type 5 injuries, L5 pedicle screw cannot be placed. Hence, additional anterior fusion is needed. Circumferential fusion is often needed in type 4 and 5 injuries.[2] The improvement in sphincteric and sexual dysfunction is poor compared to the recovery from pain after sacral fracture management. Severe angulation, displacement of fracture and neurotmesis indicate a poor prognosis.[4]

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54 Penetrating Injuries of the Spine

Harjinder S Bhatoe

Missile Injuries

INTRODUCTION

Missile injuries of the spine (MIS) are the third most common cause of spinal cord injury after motor vehicle accidents and falls.[1] The poor outcome associated with these has been recognised since the Battle of Trafalgar, when Admiral Nelson was shot through his spine, and died shortly thereafter.[50] Management of MIS has evolved through the various wars; nevertheless, the debate on the aim and scope of surgical management of these injuries is far from settled. Till the early part of the twentieth century, mortality was high due to accompanying injury to visceral structures, and to the inadequate nursing care. Cushing reported a mortality of 71.8% during World War I, with only patients with incomplete injury surviving. The review of War Surgery and Medicine prepared by Harvey Cushing and published in 1918 advised that a transected cord should never be operated upon unless the lesion was below L1.[46] Hanson[14] echoed the contemporary opinion on the management of MIS when he said, "War wounds of the spine are particularly distressing…one scarcely knew where to begin, if to begin at all".

During World War II, advances in resuscitation, antibiotics and prompt evacuation to a hospital saw more of these patients being operated upon early, although pessimism persisted. Some surgeons though started exploration and decompression and, by the time of the Korean conflict, operative exploration was universally advocated.[51] Improvement in resuscitation, helicopter evacuation, early surgery and improved nursing care during the Vietnam conflict, however, failed to show any improvement in neurological outcome in complete injuries. Thus, with multidisciplinary trauma teams and helicopter evacuation, there is improvement in survival of polytrauma victims of missile injuries; however, the prognosis for neurological recovery remains uncertain and the goals of surgery have been redefined.

LOCATION OF WOUND

Spinal injury at more than one site is highly unusual in civilian MIS, while these may be seen more often in military practise. Most of these injuries are located in the thoracic spine (54%), followed by lumbosacral (33%) and cervical (13%) spine.[19] In a report from the Croatian War involving 96 cases, however, the lumbar spine was injured in 55% of cases.[20] Most of the patients are shot from the back.

APPLIED BALLISTICS

The Missiles

Projectiles travelling at less than 2,000 feet/sec fall into the category of low velocity missiles, while those travelling above this speed are high velocity missiles. There is a distinct difference in the pattern of injury and outcome of low velocity missile injuries (LVMIs) and high velocity missile injuries (HVMIs). Most handguns and revolvers use heavy bullets weighing about 0.5 oz and have muzzle velocities ranging from 550 ft/sec to 900 ft/sec. In contrast, most rifles and small arms (rifles, stenguns, machine guns, etc) used in war use light bullets having muzzle velocities averaging 3,000 ft/sec. High velocity missiles, as they reach the limit of their range, become low velocity (spent bullet) and may inflict less severe wounds as compared to that within their effective range. Handgun ammunition can achieve effective muzzle velocity of 1,200 ft/sec over a short distance. Pieces of shrapnel from exploding devices may have a velocity of 600 ft/sec; unlike rifled bullets, however, they rapidly lose energy due to their irregular shape and non-aerodynamic nature. The commonly observed CNS missile injuries are inflicted by one of the following missiles:

- The 7.62 mm bullet can be fired by AK-47 assault rifle (Kalashnikov), self loading rifle (SLR), light machine gun or medium machine gun (LMG/MMG). The bullet weighs 150 gm and has a muzzle velocity of more than 2,000 ft/sec.

- The 5.56 mm bullet fired from Indian Small Arms System (INSAS) and M-16 rifle. The bullet weighs 55 gm and has a muzzle velocity of more than 3,000 ft/sec.
- Low velocity missiles fired from a variety of firearms, viz. revolvers, shotguns, handguns, 12 bore single/double barrel guns and country made weapons (katta, tamancha, etc. as prevalent in parts of Bihar and Uttar Pradesh).
- Fragments of exploding devices: The variety of exploding devices reflects the ingenuity of the minds that assemble them, often in innocuous looking forms. They may be made to look like toys, transistors, cassette players, etc. which are often detonated by handling or by remote access. A domestic LPG cylinder placed on its top often makes an innocuous looking but deadly combination for explosion. Other familiar sources of missiles are the HE 36 mm grenade, rockets and exploding artillery/mortar shells. Fragments of exploding devices initially travel at high speeds of over 3,000 ft/sec, and then rapidly lose speed because of their volume, weight and irregular shape and become low velocity at distances of 10 metres or more.
- Glass fragments, nails, etc. may rarely act as missiles.[38,55]

Energy Transfer

A bullet is stable in its flight through the atmosphere, but becomes less stable on entering the tissues, when it tends to yaw, deform and tumble due to resistance offered by the tissues and thus, releasing kinetic energy (KE). Injury to the tissues by a missile is a function of energy released over time, and of the volume and location of tissue disruption. The amount of KE contained in the missile is defined by the formula $E = -1/2\ mv^2$, where m is the mass of the missile and v its velocity. Since energy contained in the missile directly varies with the square of its velocity, the latter is relatively more important in determining the energy transfer by the missile than the mass. The amount of tissue damage caused by a missile may be correlated with the amount of energy deposited within the tissues by the missile. The energy transferred can be expressed by the equation:

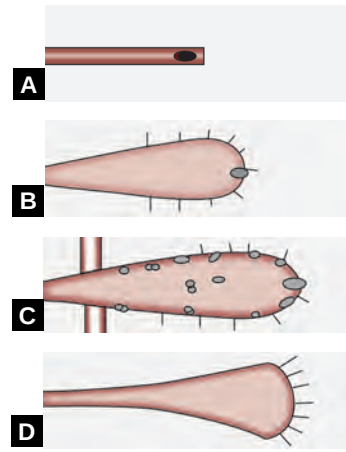
$$E_t = E_{en} - E_{ex}$$

where E_t = Missile energy transferred, E_{en} = Energy of entry at the time of impact and E_{ex} = Energy contained in the missile at the time of its exit from the tissues. If the missile exits, only part of its KE will be deposited within the tissues. The same amount of energy may be deposited by a missile of a smaller mass with a high velocity, or a greater mass missile with low velocity. The amount of energy transfer to the brain is the difference of the energies of the missiles at entry into and exit from the skull. If the missile does not exit from the skull, the energy transferred is the energy contained in the missile at the moment of impact. Thus, lower the residual velocity, greater the energy liberated.[17]

The extent and degree of damage in wounds are proportional to the amount of KE of the missile dissipated in the wound (Figs 1A to D). The injury produced by the missile is increased by factors causing it to give up more of its energy in the tissues. A missile that yaws will give up more of its energy. Similarly, a hollow point bullet that shatters upon impact will tend to give up more KE to the brain and is more destructive than bullets that do not shatter. Likewise, shotgun injuries caused by multiple pellets at close range, each with a relatively small amount of KE are extremely destructive; each of these pellets acts as an independent missile invested with KE according to its mass and velocity. Other factors that determine KE transfer by a missile are the resistance offered by the tissues and the tendency of the bullet to deform and increase the area with which it impacts the spine with a consequent increase in energy transfer to the tissues. Bullets with a flat front and expansion on impact (*dumdum bullets*) present a large surface area to the tissues to transfer energy. A rifled bullet fired at low velocity, spinning with its long axis parallel to the trajectory may pass cleanly through the tissue and exit, retaining much of its KE it had on impact. A high velocity rifle bullet of the same calibre will more likely strike with its long axis at a slight angle to its trajectory[3] and, as a consequence of this and its great velocity, deform and may even disintegrate in the tissues. The much greater tissue resistance to this high velocity deformed and 'tilted' missile and its fragments leads to release of an enormous amount of KE. The tissue damage is proportionately greater. Transfer of energy is greatest in dense tissues with high water content. Thus, wounds of neural tissue (and those of liver, kidney, muscle and bone) are more destructive than wounds of less dense tissue such as lung or fat.

Physical Effects of Missile Wounding

Missile wounding can be understood in terms of physical interactions between the missile and the tissues



Figs 1A to D: Passage of high- and low-velocity missiles through animal tissues: (A) Low velocity, small entrance and exit, no cavitation. (B) High velocity, with cavitation and tissue compression. (C) High velocity with secondary missiles from bone and cavitation. (D) High velocity trough thin tissue and large, ragged exit

through which it passes. The primary destructive effects of a missile interacting with tissues are caused by two mechanisms:

1. *Crushing action of the missile*: There is fracture of the skull, laceration and fragmentation of brain tissue and injury to vascular structures.
2. *Pressure waves and cavitation*: Besides the direct crushing action, a missile moving in water or tissue medium generates distinctive types of pressure waves within the medium it transits:
   a. *Juxta-missile pressure*: Extremely high pressures (thousands of atmospheres) are generated immediately in front of and at right angles to a moving missile, owing to flow of medium (through which the missile is travelling) around the missile.
   b. *Longitudinal shock wave*: When a missile strikes animal tissues, a high pressure compression front or shock wave is formed which spherically moves away from the point of impact. It is doubtful whether these shock waves result in any energy transfer to cause tissue damage.[16]
   c. *Pressure waves from KE transfer (cavitation)*: Cavitation was first recognised as a pathological phenomenon in missile injuries by Woodruff.[13,54] At the same time, Sir Victor Horsley[18] experimentally demonstrated the cavitation in missile injuries of the brain by firing into clay models of the brain. When a high velocity missile passes through tissues, KE is transferred to adjacent tissue elements, which are radially propelled, creating a large subatmospheric temporary cavity directly behind the missile. When the elastic limit of this outwardly displaced tissue is reached, it falls inwards whence it was displaced. This cycle may be repeated several times before the deranged tissue comes to rest around the permanent track created by the missile. The oscillatory, outwards and inwards rush of tissue creates a long lasting (milliseconds) lower amplitude (20–30 atmospheres) pressure wave which propagates throughout the medium. It has been considered that these lower amplitude and longer lasting pressure waves are the causes of damage to the tissues at a distance from the site of actual missile injury. KE deposited by a missile is partitioned between that which directly crushes tissues in its path and that which displaces tissues adjacent to the missile track. The latter is less destructive than the former owing to the elastic properties of the displaced tissue, which may be deformed without being irrevocably destroyed.[6]

Missiles and Mechanism of Injury

In military practise, the missiles are generally bullets or shrapnel, while in civilian practise the injury is sustained due to shotgun pellets and pistol/handguns/improvised explosive devices. The latter are generally LVMIs without significant accompanying visceral or soft tissue injury, especially if fired upon from the back or lateral aspect, since the thick paraspinal musculature and bony spine dissipates much of the KE of the missile. There may, however, be extensive soft tissue damage due to dispersal of pellets. In military combat, the large calibre HVMs usually cause extensive multi-organ damage in addition to spinal injury. The injury is produced by the following mechanisms:

- *Direct crush injury*: The missile crushes the tissue in its path, producing cord and nerve root laceration over more than one segment and an external communicating wound. The cord may be damaged by bone or disc fragments, even though the bullet does not come in contact with the spinal cord.
- *Cavitation*: Cavitation may stretch the neural tissue as the energy is transferred to the wound track producing damage. The temporary cavity collapses, leaving behind a smaller, permanent track.[6]
- *Concussive wave*: Myelopathy may be seen even if there has been no damage to the discoligamentous or disco-corporeal components of the spine in HVMIs. This occurs due to a concussive wave, which traverses the cord as the missile passes close to it, producing cord concussion and oedema. The severity of myelopathy is usually mild.
- *Intramedullary haematoma*: Injury to brachial nerve rootlets may lead to their avulsion at their origin from the cord and an intramedullary haematoma. The patient will have features of brachial plexus injury, with myelopathy; the latter is usually mild and resolves in due course.

Illustrative Cases

a. A 23-year-old soldier sustained a gunshot wound to the left supraclavicular region. The bullet exited through the back of the neck. He was admitted with pain over the left forearm and weakness of the left hand. Clinically, he had weakness of small muscles of the left hand and numbness over C7/T1 distribution. Tendon reflexes were brisk in both lower limbs with extensor plantars and grade 4+/5 power. While cervical spine radiographs and CT did not reveal any bony injury or malalignment, MRI after 7 days demonstrated intramedullary T2 hyperintensity at the periphery of the cord in the region of the ventral root. Nerve conduction studies were normal. He showed complete recovery of myelopathy over the next 3 months.
b. A 20-year-old soldier sustained gunshot wound to his left supraclavicular region and was admitted with weakness of all four limbs. The bullet had exited through the back of the neck. Clinically, he had grade 4/5 power in the triceps, both hands and both lower limbs, with brisk tendon reflexes and hypertonia in all four limbs. There was patchy sensory impairment over the trunk. Cervical spine radiograph was unremarkable. MRI revealed intramedullary

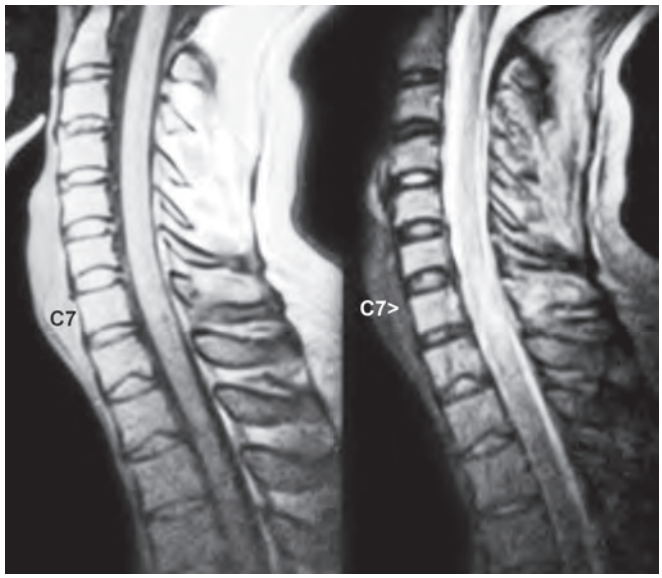


Fig. 2: MRI showing intramedullary T2 hyperintensity in a patient with gunshot wound to the soft tissues of the neck

hyperintensity at C6/C7 (Fig. 2). He was managed conservatively and showed complete neurological recovery over the next 6 months.

APPROACH TO A PATIENT WITH MISSILE INJURIES OF THE SPINE

MIS should never be approached in isolation; the initial principles are resuscitation, securing airway and haemodynamic stabilisation, so as to preserve perfusion to vital organs. Hypotension may be due to neurogenic or hypovolaemic shock, and the distinction may not immediately be apparent; nevertheless, accompanying bradycardia is more often a feature of neurogenic shock. A judicious combination of intravascular volume replacement, vagolytics and vasopressors may be required for resuscitation.

Once haemodynamic stabilisation has been achieved, careful survey of the level of injury together with anatomical structures damaged is carried out. Polytrauma may be sustained due to multiple missiles or by a single missile traversing multiple anatomical levels and structures. Cervical spine injury may be accompanied by vascular, pharyngeal, tracheo-oesophageal or pulmonary injury, while dorsal spine injury may be accompanied by haemopneumothorax or cardiac tamponade. Dorsolumbar injuries may be complicated by retroperitoneal or intraperitoneal injuries, colonic injuries being of immediate concern for their potential for contamination. The attending surgeon should also be able to suspect spinal injury in the presence of these non-neurogenic injuries, especially if the patient's sensorium is altered, or if he is hypotensive. Wounds of entrance and exit are carefully examined for cerebrospinal fluid (CSF) leakage and the extent of tissue damage is assessed.

Table 1: Neurological grading system (Benzel & Larson, 1987)

Grade I: Complete functional neuronal transection. No motor or sensory function below the level of injury.
Grade II: Motor complete. No voluntary motor function below the level of injury, with preservation of some sensation.
Grade III: Motor incomplete—non-functional. Minimal non-functional voluntary motor function below the level of injury.
Grade IV: Motor incomplete functional. Unable to walk; some functional motor control below the level of injury.
Grade V: Motor incomplete—functional. Limited walking, lack of endurance or fear of falling.
Grade VI: Motor incomplete—functional. Unlimited walking, difficulties with micturition and slightly discoordinated gait.
Grade VII: Normal.

Baseline neurological assessment is extremely important. In an unconscious patient, the attitude of the limbs and presence of spontaneous movements is noted as is the response to pain, and the muscle tone. Some idea of sensory level may be possible by noting response to pinprick. In a conscious patient, motor-sensory evaluation is carried out, and an appropriate neurological grade is assigned. Frankel grade is easy to apply and useful to stratify the patients with MIS, and can be used to prognosticate the outcome. Benzel and Larson[2] devised a more comprehensive scale which utilises seven grades instead of five of Frankel grading (Table 1).

Imaging

Missile injuries of the dorsolumbar spine are biomechanically stable injuries, and instability is rare,[36] except in children.[8] The biomechanical vectors that are in force in closed injuries as that seen in flexion, distraction, rotation, axial loading, etc. that result in instability are not operative in MIS; instead, the energy transfer due to missile injury takes place in a sharply focused region of the spinal column, resulting in localised damage without causing major biomechanical disruption of the functional spinal unit. However, in the cervical spine, due to smaller volume of the target organ, these disruptions can cause instability.

Plain Radiography

Multiplanar spinal radiographs should be obtained to detect metallic fragments, and their craniocaudal as well as anteroposterior distribution. Fractures and dislocations are readily detected by plain radiographs. Presence of metallic or bone fragments should be noted within the spinal canal or in the neural foramina (Figs 3 to 5). Plain radiographs will also detect subcutaneous emphysema, haemopneumothorax or pneumoperitoneum in the presence of associated injuries.

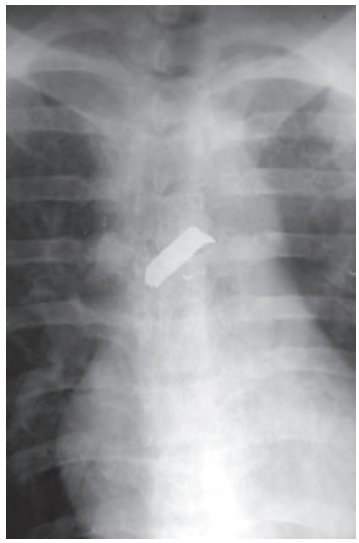


Fig. 3: Dorsal spine radiograph showing bullet embedded in the spine

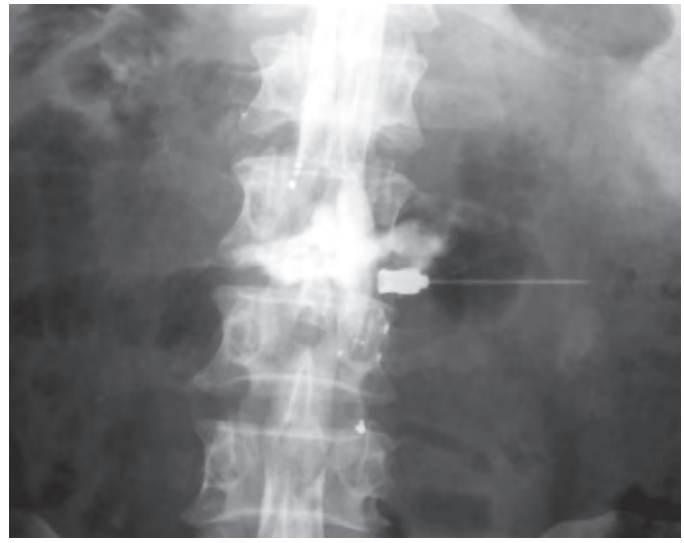


Fig. 6: Iohexol myelogram showing extravasation of the contrast

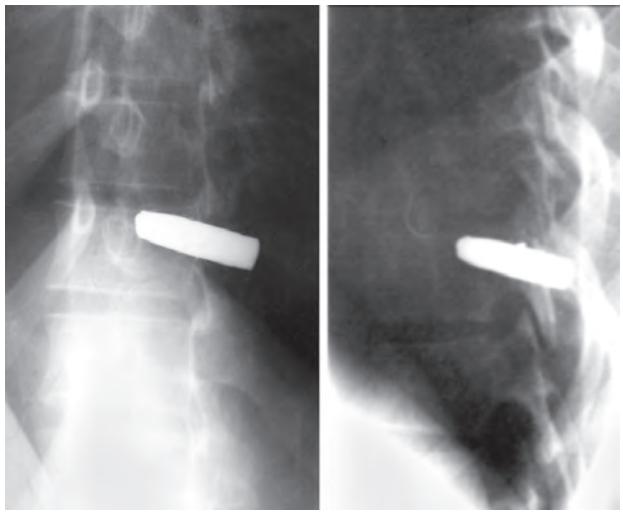


Fig. 4: Dorsolumbar spine radiograph showing bullet embedded in the spine

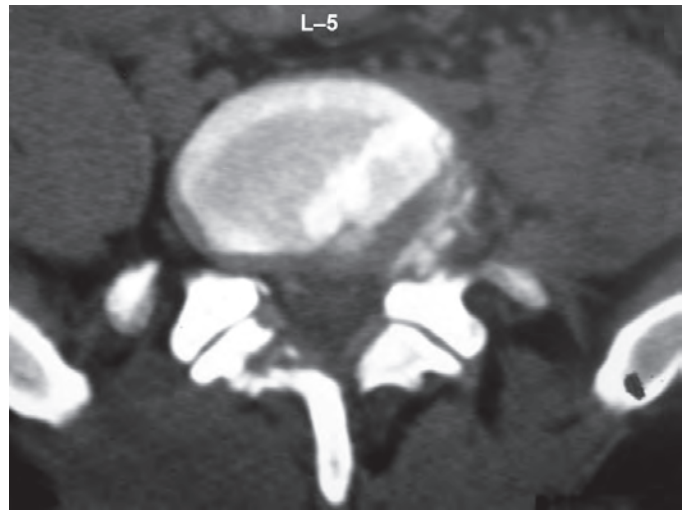


Fig. 7: CT showing missile track in the vertebral body

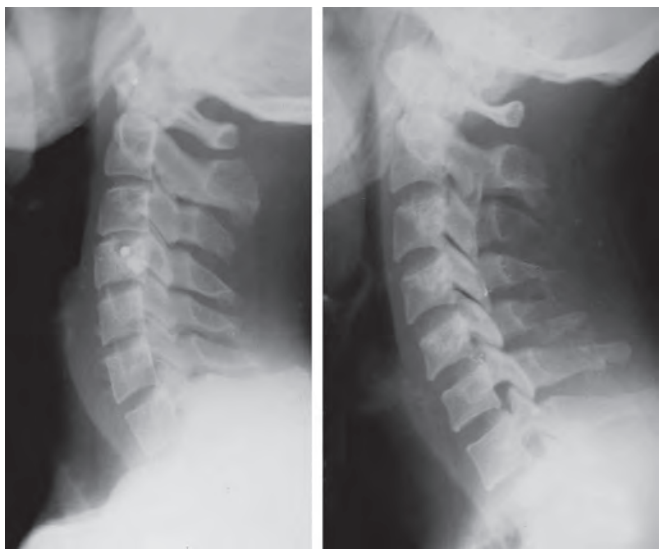


Fig. 5: Cervical spine radiograph (lateral view) showing multiple splinters in the soft tissues

Myelography

In the absence of computed tomogaphy, myelography is a good substitute to detect dural injury as evidenced by extravasation of intrathecal contrast (Fig. 6). A myelographic block may be an indication for surgery, and complications like arachnoiditis are rarely seen with water soluble contrast media like iopamidol or iohexol.

Computed Tomography

Computed Tomography (CT) is the diagnostic modality of choice in the evaluation of MIS. Precise delineation of the fracture can be made, and intraspinal fragments and soft tissue foreign bodies can be visualised. CT myelography (Figs 7 to 13) can be useful to detect the extravasation of contrast and CSF fistula.[8]

Magnetic Resonance Imaging

Magnetic Resonance Imaging (MRI) is the imaging modality of choice for assessing the extent of spinal cord

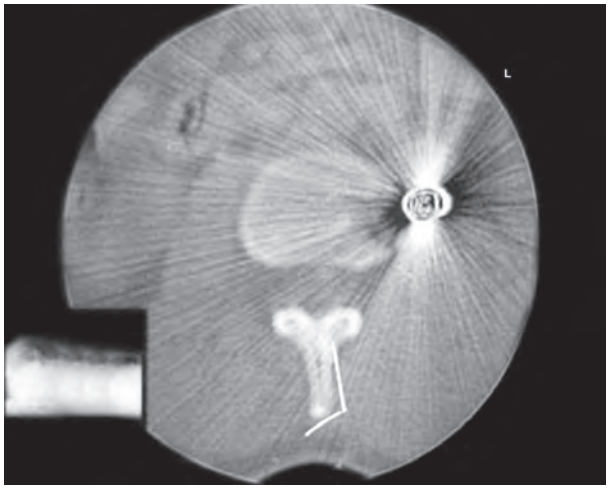


Fig. 8: CT showing missile lodgement near the vertebral body

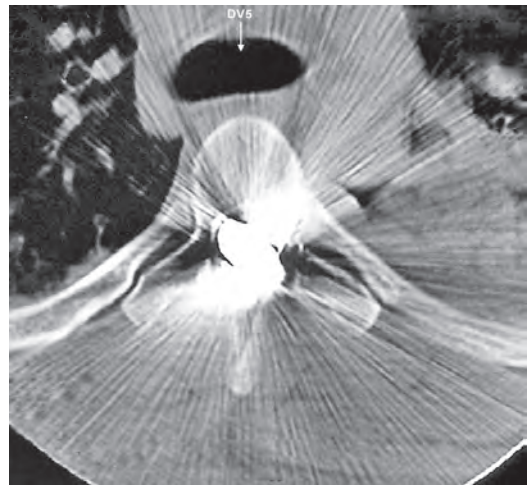


Fig. 11A: CT showing intraspinal lodgement of bullet

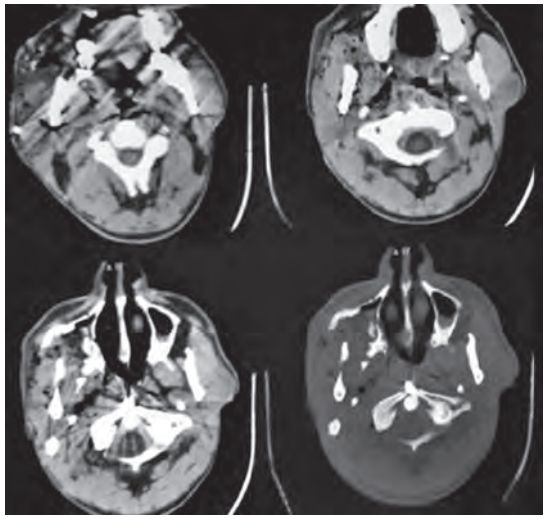


Fig. 9: CT showing splinter lodged at the anterior tubercle of atlas

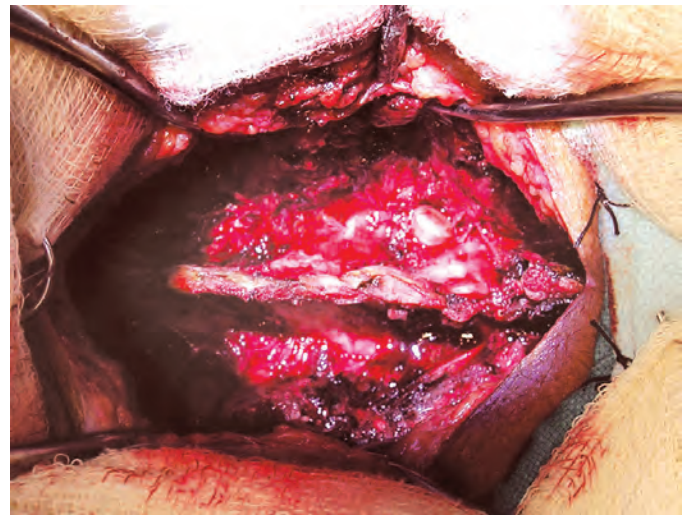


Fig. 11B: Operative appearance of bullet lodged in the lamina

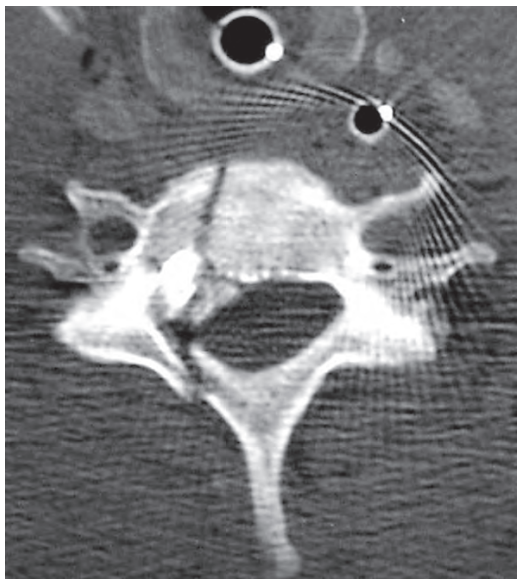


Fig. 10: CT showing three column injury with bullet lodged in the spine

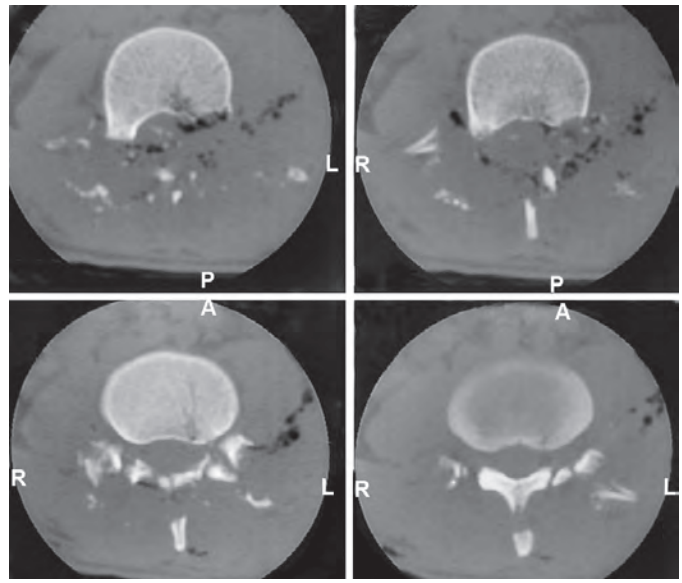


Fig. 12: CT showing injury to posterior elements

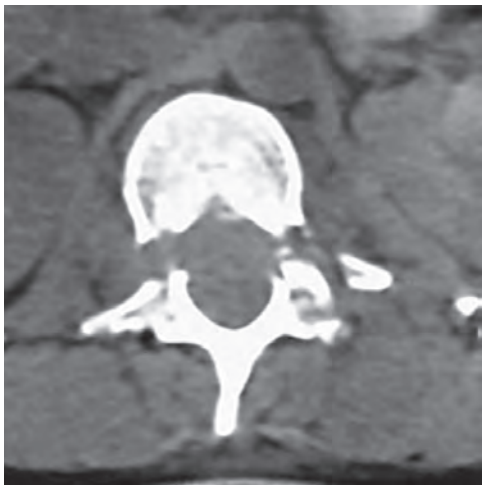


Fig.13: CT showing fracture of both pedicles due to bullet injury

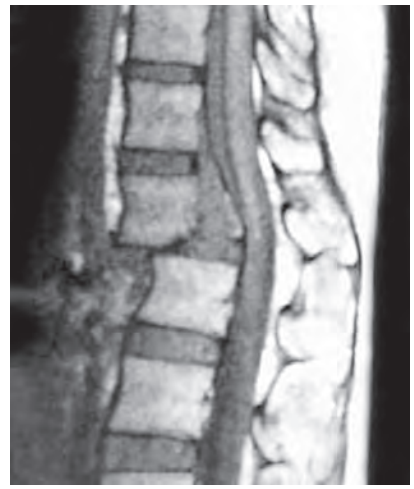


Fig. 14: MRI showing dislocation of D12/LV1 due to missile injury

injury, yet its use in MIS is restricted due to the possibility of movement of the ferromagnetic missile fragments. In addition, movement artefacts can create difficulties in interpretation. MRI is especially useful in the diagnosis of spinal injury if the missile has exited (Fig. 14), provided there has been no associated injury to the disco-corporeal components of the spine (Fig. 2). MRI is also useful in the follow-up of such patients to detect the possible formation of post-traumatic syrinx, in the setting of delayed neurological deterioration (Fig. 15).

Controversies and Evolution of Treatment Philosophy

Surgical versus Conservative Management

Surgery for missile injury of the spine has been a matter for debate, with most of the early military studies uniformly advocating surgical intervention,[35] while the civilian studies have adopted a more selective approach. Proponents of surgical intervention cite prevention of infection, CSF leakage, lead toxicity, pain and late deterioration as the goals, and the possibility of neurological improvement following surgery. Reports of civilian penetrating injuries do not generally advocate surgical intervention unless there is delayed deterioration. The disparity between military and civilian reports of seemingly better neurological outcome following exploration may be due to higher incidence of spinal cord concussion from HVMs in military injuries, which in turn may lead to a higher false incidence of improvement after routine surgical exploration.[57] Moreover, increased incidence of wound infection and CNS infections is reported in patients who have undergone surgical exploration.[21] Differences in the regional anatomy of the spinal cord and the greater potential for recovery in injuries involving the nerve roots account for the differences in the effects of surgery in the thoracic, thoracolumbar and

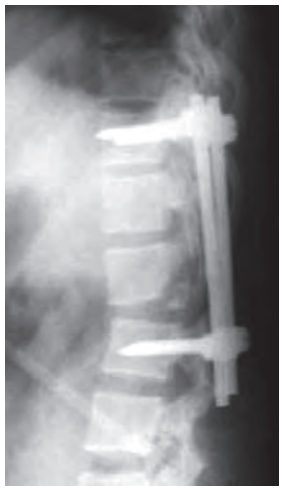


Fig. 15: Post-operative radiograph showing reduction and stabilisation

lumbar regions. In injuries up to the D12 level, the cell bodies as well as axons in the spinal cord are damaged and the resulting glial scar forms an impenetrable barrier to regenerating axons. A peripheral nerve or root injury leaves the cell bodies intact, and there is relative abundance of myelin surrounding the axon. Disintegration of a motor axon within a peripheral nerve due to local injury progresses proximally to the next node of Ranvier. In the region of axonal degeneration, the Schwann cells proliferate and form neurolemmal tubules. Growth from the central end of the damaged axon can be guided across the sites of trauma, allowing motor reinnervation over-time. These factors contribute to the favourable outcome in cauda equina injury. Based upon a review of various studies in the preceding decades, coupled with their own wartime experience, Bhatoe and Singh[4] formulated indications for surgery in MIS as follows:

- Incomplete neurological deficit
- Cauda equina injuries

- Cervical cord injuries
- Presence of external CSF fistula
- Worsening of existing neurological deficit.

Doubts have been raised about the tenability of the phenomenon of worsening of existing neurological deficit. The role of surgery in the presence of complete deficit is still not settled. However, the presence of a compressive lesion would be an indication for exploration in such cases.

Intraspinal Fragment

The main question to be answered is whether to remove the bullet or not? Removal of a bullet has been advocated for improving the neurological outcome, prevention of infection, prevention of delayed neurological deterioration,[24,56] lead toxicity[12] and prevention or treatment of pain syndromes. Waters and Adkins[52] observed neurological improvement after removal of bullets from the thoracolumbar region, but not after removal of bullets from the thoracic region. However, no increased incidence of infection was seen if broad spectrum antibiotics were administered early.[44] The consensus of opinion at present seems to be to remove intraspinal fragments located in the cauda equina and in the cervical spine. Cauda equina injuries carry the potential for better recovery, and prevention or treatment of radicular pain can be achieved, while the cervical spine fragments are removed to obviate or treat radicular pain as well as with the hope of effecting recovery even of a single root, which can influence the rehabilitation process.

Associated Injuries and Spinal Cord Decompression

A high percentage of MIS are associated with non-neurological injuries, especially to the chest and gastrointestinal tract. Some authors have advocated primary debridement of the spine and paravertebral tissues through the operative incision of the primary procedure, obviating the need for a second procedure.[5,22] However, primary neurosurgical intervention has been implicated in causation of spinal osteomyelitis.[31] After analysing one of the largest series of associated injuries with MIS, Venger et al.[49] came to the conclusion that neurosurgical intervention can safely be deferred till the general condition of the patient improves, and there was no difference in the neurological outcome between operated and non-operated cases. Thus, it can be recommended that neurosurgical intervention in the presence of associated visceral or vascular injury takes second priority, and can safely be deferred till the patient is stable after abdominal/thoracic surgical intervention.

Cauda Equina Injury

Patients with cauda equina injury form a distinct subset of patients with MIS in whom the deficit is usually incomplete, neurological recovery can be expected, and the role of surgery is more definite. During the Korean War, out of 254 servicemen with HVMs of the lumbosacral spine, neurological recovery occurred in 52.22% after surgery.[51] Improvement following surgical exploration has been reported in civilian cauda equina injuries as well.[1] The mechanism of injury may be neuropraxia, traction or concussive wave.[45] Moreover, compression may occur due to fracture fragments, foreign bodies or intraspinal haematoma. Herniated nucleus pulposus has been reported to cause nerve root compression in a case of MIS.[33] Debridement can be accomplished with a low degree of morbidity. Intraspinal fragments deserve special consideration in cauda equina injuries, especially in incomplete injuries and in the presence of radicular pain. The better prognosis in these patients is due to sparing of the nerve roots, first noticed by Matson;[34] recovery may be expected as with peripheral nerve injuries.[30,49] While some patients may achieve recovery without surgery,[44] there are no clinical, radiological or electrodiagnostic predictors for recovery.[7] The nerve roots have a potential both for recovery and to produce pain; doing laminectomy and decompression will provide an optimal environment for recovery of the damaged nerves. Hence, it is recommended that cauda equina injuries should surgically be explored, fragments excised and decompression affected.

Spine Stabilisation

It is generally presumed that most MIS are stable injuries. Meyer et al.[36] reported no instance of instability in 1300 patients with MIS. If, however, the bullet passes transversely fracturing both the pedicles and the facets, the injury is likely to be unstable.[52] The flight path of the bullet must be considered and, if instability is suspected, appropriate imaging is done under supervision, and stabilisation planned. Cervical spine injuries are considered inherently unstable and need to be stabilised after decompression.

CURRENT MANAGEMENT

Broad spectrum antibiotics, preferably ones that cross into the CSF, are administered on admission. There is no reported benefit of administering methylprednisolone in patients with MIS.

Wound Debridement

Debridement of wounds of entry and exit is carried out at the time of initial admission. Devitalised tissue, foreign bodies and debris are excised, and haemostasis is achieved. Extensive soft tissue injuries as those sustained with HVMs or by multiple pellets sprayed over a wide surface area may require assistance from a reconstructive surgeon.

Operative Management for Missile Injuries of the Spine

The injured spinal cord is approached by a standard laminectomy. A longitudinal incision is made centred

over the involved region. Muscles are separated from the laminae by sharp dissection and an assessment is made of the bony injury. Use of electrocautery should be avoided to expose the involved lamina if there is an impacted bullet or shrapnel in the lamina, lest there be further damage to the cord due to electric current (Fig. 11B). The spinous process of the cephalad and caudad vertebrae and that of the injured vertebra are excised and the laminae are nibbled carefully on both sides, so as to avoid compression on the dura, and to avoid dislodgement of the intraspinal fragment at this stage. Once adequate dura has been exposed, the injured site is carefully defined, utilising copious saline irrigation. Comminuted fragments are carefully dislodged and the dural tear is defined. The dura is then opened between stay sutures and normal looking cord is exposed. Devitalised tissue, haematoma and loose fragments are removed. A judicious decision is made whether or not to remove an embedded intramedullary fragment. Obviously compressed roots are decompressed, especially in the cauda equina region. Weak suction is employed so as to prevent nerve roots getting pulled into the suction. One should avoid excising the dura and even free patches can be sutured back. One must make an endeavour to achieve a water-tight yet tension free dural closure. If the dura appears intact, and there is no evidence of intradural haematoma or any other compressive lesion, dural opening is unnecessary. The wound is thereafter closed in layers.

Post-Operative Management

Care of paraplegic and quadriplegic patients demands the highest levels of dedication and care from the nursing staff. Kinetic therapy table provides ease of turning the patient to prevent pressure ulceration. Two hourly change of posture, care of the skin, prevention of contractures, urinary infection, chest infection and deep vein thrombosis form the mainstay of post-operative care of these patients. Antibiotics are administered for a period of 14 days. Rapid mobilisation is essential and a multidisciplinary rehabilitation programme is commenced early. A cheerful, optimistic attitude goes a long way in encouraging early mobilisation and facilitates rehabilitation. Functional recovery (improvement in sensory level, improvement of motor power, return of continence) has to be assessed periodically.

Prevention of Deep Vein Thrombosis

Deep vein thrombosis and thromboembolic disease in adult patients with cervical spinal cord injury are the major cause of morbidity and mortality in the first 2–3 months after injury. The risk decreases with passage of time. Low molecular weight heparin, adjusted dose heparin, pneumatic compression devices and electrical stimulation are effective in prevention. Oral anticoagulation alone does not seem to be as effective as other prophylactic measures.[13]

SEQUELAE

Pain and delayed neurological deterioration constitute two broad groups of sequelae of MIS.

Pain

There are three distinct variants of pain syndrome following initial recovery from MIS. These are:

a. *Central pain of spinal deafferentation:* This type of pain is dysaesthetic in nature. This is poorly localised and quite intractable to medical treatment.[11] Carbamazepine and amitryptyline have been tried with varying success. In thoracic cord injuries, dorsal root entry zone lesioning and spinal cord stimulation have shown promising results.[8]
b. *Radicular pain:* This type of pain is seen more often with cervical cord and cauda injuries, and is characterised by burning sensation over the extremities with a dermatomal localisation. If secondary to a retained intraspinal splinter, this type of pain is most amenable to treatment by removal of the offending foreign body. Relief may be seen even in patients who have been symptomatic for years after the initial injury.[23]
c. *Vertebral pain:* Pain arising from disco-corporeal elements is fairly localised over the region of injury. There may be local tenderness. Imaging may reveal infective sequelae, and treatment would consist of debridement with the possibility of stabilisation.

Delayed Neurological Deterioration

Deterioration may occur due to infective sequelae, especially osteomyelitis.[22,32] Cord compression can also occur due to exaggerated granulomatous response, especially in injury due to steel and glass.[21,56] Other causes of deterioration are formation of post-traumatic spinal cysts (post-traumatic syringomyelia) and intraspinal migration of missile fragments. Post-traumatic cystic myelopathy follows tethering of the contused cord and localised arachnoiditis with alteration in CSF flow; these lead to rostral and caudal cystic degeneration and cord cavitation.[8] Migration of bullets in the subrachnoid space can lead to new deficits.

All patients with delayed neurological deterioration should be investigated by CT myelography or by MRI, subsequent to which further treatment can be planned. Extradural cord compression may require debridement with or without instrumentation. Post-traumatic cystic myelopathy is improved by shunting,[9] and excision of migrating bullets is curative.

Lead Toxicity

Retained bullets and shrapnel tend to get sealed off by fibrosis and lead is not absorbed to cause lead toxicity. However, symptoms of lead poisoning (abdominal pain, anaemia, headaches, memory loss, muscle weakness) may occur if the lead object is in communication with

synovial fluid such as a joint or pseudocyst.[27,39,56] Treatment consists of chelation therapy with ethylenediamine tetra-acetic acid (EDTA), d-penicillamine or dimercaprol (BAL).

It is likely that neurosurgeons will be seeing more patients with missile injury to the spine, and it is important that certain facts are borne in mind when treating such patients. As a general rule, the decision about initial neurosurgical intervention is made after correlating the clinical profile to the imaging findings. Complete neurological deficits generally do not warrant surgical exploration. Incomplete neurological deficits with evidence of cord compression, cauda equina injuries and those injuries with external CSF fistula need neurosurgical intervention. Broad spectrum antibiotics should be administered early and associated visceral injuries should be tackled first. These patients demand the highest standards of post-operative and nursing management in the acute phase, and subsequent watch has to be kept for early diagnosis of neurological deterioration. Rehabilitation should be commenced early in specialised centres so that these patients can once again find their rightful place in society.

Non-Missile Penetrating Spinal Injury (Stab Injury)

Compared to missile injuries, non-MIS are rare. While there have been few reports from India,[43,47] reports from South Africa account for most of the large series reported.[28,29,37]

Mode of Injury

The majority of these injuries are due to assault with knives (stabbing). Penetrating injuries, however, can occur due to fall on sharp objects, and stabbing with screwdriver, bicycle spokes, scissors, garden forks, sickles, etc. have been reported.[37] In general, the penetrating object or weapon is withdrawn after stabbing; rarely, the attacker breaks the blade at the handle. Most of the victims are young males, although such injuries are being often seen in women also.[53] Usually the wound of entry is posterior thoracic (54–63%) or cervical (27–30%).[37,47] In the latter instance, there may be injury to the brachial plexus and carotid vessels.

APPROACH

Careful transportation to a trauma centre is essential for optimum evaluation and assessment of the damage. A complete assessment is made to detect injury to major vascular structures, bronchi, aorta and other visceral organs. Volume replacement is made and chest tube insertion is carried out, if indicated. No attempt should be made to remove an externally visible retained weapon in the emergency room and by the paramedics.

Neurological Presentation

Spinal cord or root injury may occur immediately after the stabbing indicating physical damage by the weapon, and delayed deficit may manifest months later due to the retained weapon and formation of post-traumatic syrinx. Infection causing meningitis or intraspinal suppuration too can result in delayed neurological deterioration.[10,26] Immediate neurological deficit is in the form of Brown-Séquard syndrome in most of the cases, which may be typical or incomplete; nearly 21% of cases have complete spinal cord injury.[37,42,47] On the other hand, nearly a third of the patients may not have any neurological deficit.[47] The injury can remain extradural and may cause deficits months after the injury.[15] Inflammatory reactions in the nervous tissue to retained metallic fragments can also result in delayed neurological deficits. Copper is associated with severe scarring and fibrosis, while nickel and lead excite a less severe response.[41] Oxidation of metallic fragments can result in deposition of rust particles on the nervous tissue.

Imaging

Plain radiography is the initial investigation in all cases. A retained metallic object will be revealed along with other injuries like haemopneumothorax and emphysema. Computerised tomography shows injury to the disco-corporeal components, presence of haematomas and the track of the injuring weapon. Streak artefact can be used to determine the location of the tip of the blade.[25] MR imaging can be employed in those cases with no retained metallic fragment/weapon. Integrity of the spinal cord, presence of haematoma, disc herniation, etc. can be seen with great accuracy.

Surgical Approach

An externally visible stuck weapon has to be removed in the operation theatre after preparing the operation theatre for thoracotomy/laparotomy/neck exploration. The externally visible portion of the weapon or its handle can be grasped and gently pulled in its long axis. The external wound is extended if required, debrided, irrigated with saline, hydrogen peroxide and antibiotic solution, and closed in layers. No definite guidelines exist for the management of stab injuries of the

spine. Only 20 patients out of 450 managed by Peacock et al. underwent laminectomy.[37] While Velmahos et al. reported surgical exploration in 22 out of 143 patients.[48] Thakur et al. explored 9 of their 11 patients.[47] In another review of 16 patients with non-missile penetrating injuries, it was brought out that surgical intervention made no difference to the final outcome.[42] The consensus is that surgical exploration should be carried out for those patients with incomplete neurological deficits, persistent CSF leak, retained intraspinal foreign body or bone fragment and persistent pain.[40] Although CSF leak may stop spontaneously, the patient may develop meningitis and there may be formation of pseudomeningocoeles as these CSF fistulae heal. Hence, presence of CSF leak beyond 96 hours should be an indication for surgical intervention. Surgical intervention is also indicated in cases with delayed neurological deterioration, especially in the presence of a retained intraspinal foreign body.[15] The surgical procedure involves laminectomy, defining the normal dura cranial and caudal to the site of stab, and opening the dura with stay sutures. Conservative debridement is carried out and only the detached, non-viable neural tissue is debrided. The haematoma is evacuated and the dura is closed with a dural substitute if necessary. A lumbar subarachnoid CSF drain is inserted for 5–10 days and antibiotics in antimeningitic dosage are administered. Spinal stabilisation is generally not required, since these injuries are stable.

All patients are closely monitored for delayed neurological deterioration and deafferentation pain. Overall neurological recovery is better than that observed with missile injuries.

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SECTION

6

Peripheral Nerve

VS Mehta

55 Anatomy and Physiology of the Peripheral Nerve

Sharma M, Gupta A, VS Mehta

The central nervous system is one of the major control centres of the human body. The central nervous system is unique in the vast complexity of thought processes and linked actions it can perform. It receives and processes large amounts of information from the various organs of the body.

It contains about 100 billion neurons and 1,000 to 50,000 billions of glial cells (also called supporting cells). The neurons are the structural and functional units of the nervous system.

The peripheral nerve is a special living conduit that transmits impulses in both directions, with a special structure, so as to maintain its function, vascularity and vitality in the face of adverse mechanical forces, such as those across joints and in different limb positions.

As the peripheral nerve is composed of parts of axons arranged in a special manner, it is appropriate to start with basic details about the neuron.

NEURON

Classification

On the Basis of Processes

- *Unipolar neurons:* Only one process leaves the cell body. They are sensory in function and located in the craniosacral ganglia.
- *Bipolar neurons:* A single dendrite and a single axon leave the body. They are purely sensory in function and located in the cochlear and vestibular ganglia of the VIII nerve, in the olfactory nerve and in the retina.
- *Multipolar neurons:* Most common type of cells. Have numerous branched dendrites projecting from the cell body and on the opposite side there is a single process called the axon. They are the largest population of nerve cells and form motor neurons, interneurons, pyramidal cells, Purkinje cells and neurons of the autonomic nervous system.

On the Basis of Function

- Central cell body
  - Cortical neurons: Impulses from the cerebrum, cerebellum and optic lobes to the affector organs.
  - Interneurons: Connector neurons.
  - Central effector neurons: They include motor neurons, autonomic neurons and hypophyseal neurons.
- Peripheral cell body
  - Peripheral effector neurons: From the autonomic and invertebrate ganglia.
  - Bipolar neurons: Those of the optic, vestibulocochlear, olfactory and cutaneous neurons.

Structure

Cell Body

It is also called the perikaryon. It contains a large, central nucleus with a prominent nucleolus and it gives rise to the axons and the dendrites (Fig. 1). It is located at the dendritic zone end of the axon but it can be within the axon or attached to the side of the axon. It also contains Nissl substance which contains rosettes of polysomes and rough endoplasmic reticulum and hence has a role in protein synthesis. Nissl substance is also present in the dendrites but is not present in the axon hillock or the axon.

Dendrites

The cell body gives rise to 5–6 processes that extend outwards and branch extensively. The small, knobby

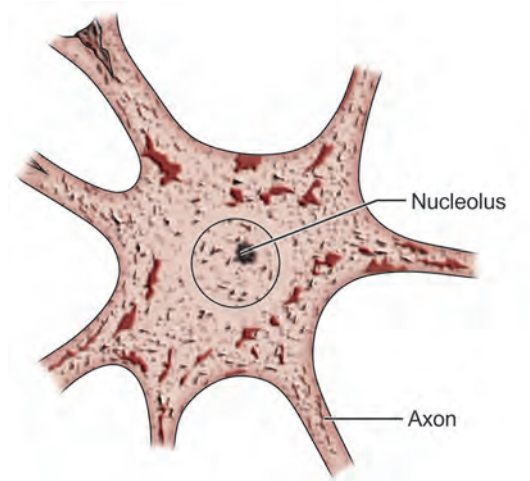


Fig. 1: Diagrammatic representation of a multipolar neuron

projections of the dendrites are called dendritic spines. The dendrites conduct impulses towards the cell body.

Axons

An axon is a neuron process that originates from a thickened area of the cell body called the axon hillock. The first portion of the axon is called the initial segment. The axon divides into terminal branches, each ending in a synaptic knob also called terminal buttons or axon telodendria. The cytoplasm present inside the axon is called axoplasm and the outer membrane is called the neurilemma.

Schwann Cells

They are also called neurolemmocytes. They extend along the axon from its origin to its termination. They form the myelin sheath around the larger axons. Smaller axons are surrounded only by the Schwann cell cytoplasm. Along the length of the myelinated axon are small gaps in the myelin sheath between individual Schwann cells called the node of Ranvier. Such of the axons that do not have a myelin sheath are called unmyelinated.

NERVES

A *nerve* is an enclosed, cable-like bundle of *nerve fibres* or axons, which includes the glia that ensheath the axons in myelin. Neurons are sometimes called nerve cells, although this term is technically imprecise, since many neurons do not form nerves.

Nerves are part of the peripheral nervous system. Afferent nerves convey sensory signals to the central nervous system, for example, from skin or organs, while efferent nerves conduct stimulatory signals from the central nervous system to the muscles and glands. Afferent and efferent fibres are often arranged together, forming mixed nerves.

Most nerves connect to the central nervous system through the spinal cord. The twelve cranial nerves, however, connect directly to parts of the brain. Spinal nerves are given letter-number combinations, according to the vertebra through which they connect to the spinal column. Cranial nerves are assigned numbers, usually expressed as Roman numerals from I to XII. In addition, most nerves and major branches of nerves have descriptive names. Inside the central nervous system, bundles of axons are termed tracts rather than nerves.

Nerves carry action potentials which begin typically in the cell body of a neuron and propagate rapidly down the axon to its tip or "terminus". The signals cross over from the terminus to the adjacent neurotransmitter receptor through the synapse.

Histology of a Nerve Fibre

Endoneurium

It is a connective tissue layer surrounding each nerve fibre.

Perineurium

It is a connective tissue layer which surrounds each fascicle (a bundle of nerve fibres).

Epineurium

It is the connective tissue layer surrounding each nerve (Fig. 2).

Basic Nerve Physiology

Tables 1 and 2 show nerve fibres types, function and the numerical classification.

Excitation and Conduction

Nerve cells have a low threshold for excitation and they respond to mechanical, electrical or chemical stimuli (Figs 3A and B).

Two types of physio-chemical disturbances are produced:

- Electrotonic potentials which are non-tonic propagated potentials.
- Action potentials are the propagated disturbances.

Conduction is an active, self-propagating process and the impulse moves along the nerve at a constant amplitude and velocity. The electrical events in neurons are rapid, being measured in milliseconds and the potential changes are small being measured in millivolts.

Resting Membrane Potential

It is the negative potential inside the cell membrane when the cell is at rest. In neurons it is -70 mV.

Latent Period

If the axon is stimulated and a conducted impulse occurs, a characteristic series of potential changes known as the action potential is observed. When a stimulus is applied there is a brief, irregular deflection of the baseline called the stimulus artefact. The stimulus artefact is followed by an isopotential interval called the latent

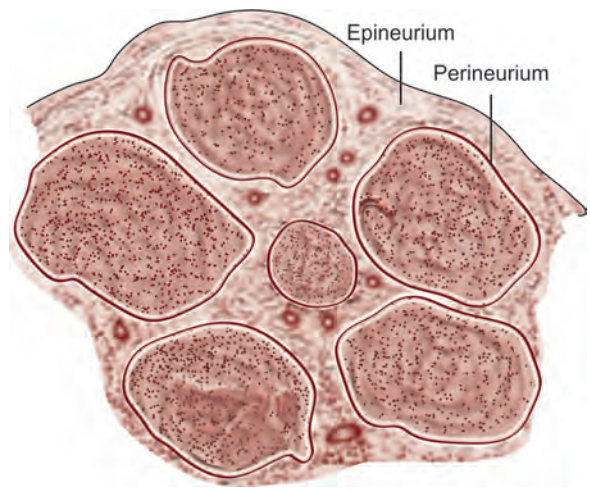


Fig. 2: Cross-sectional anatomy of the human tibial nerve

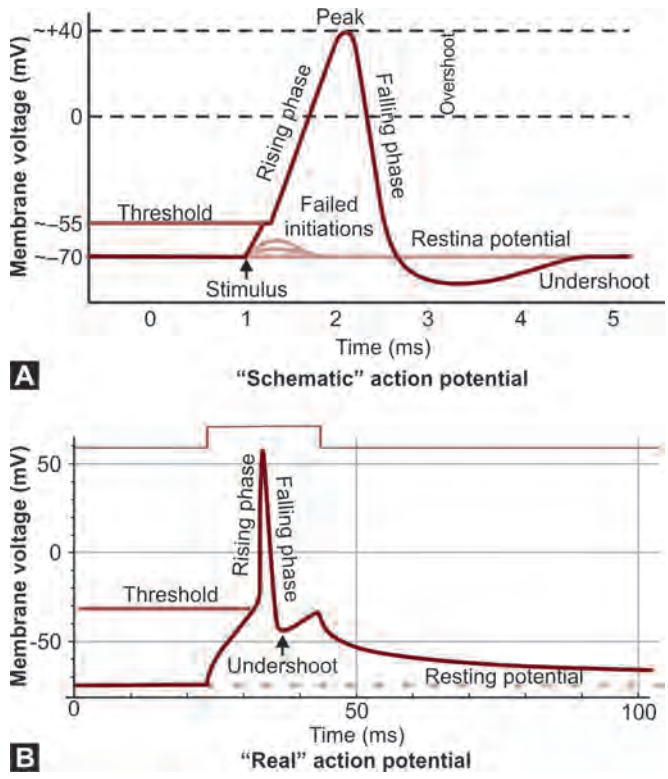
Table 1: Nerve fibre types and functions

Fibre type	*Function*	*Fibre diameter*	*Conduction velocity*	*Spike duration*	*Absolute refractory period*
A alpha	Proprioception and somatic motor	12–20	70–120		
beta	Touch and pressure	5–12	30–70	0.4–0.5	0.4–1
gamma	Motor to muscle spindles	3–6	15–30		
delta	Pain, cold, touch	2–5	12–30		
B	Pre-ganglionic autonomic	<3	3–15	1.2	1.2
C dorsal root	Pain, temperature, mechanoreception, reflex response	0.4–1.2	0.5–2	2	2
sympathetic	Post-ganglionic sympathetic	0.3–1.3	0.7–2.3	2	2

A and B fibres are myelinated, C fibres are unmyelinated.

Table 2: Numerical classification

Number	*Origin*	*Fibre type*
I a	Muscle spindle, annulospiral ending	A alpha
I b	Golgi tendon organs	
II	Muscle spindle, flower-spray endings, touch, pressure	A beta
III	Pain and cold receptors, some touch receptors	A delta
IV	Pain, temperature, and other receptor	Dorsal root C



Figs 3A and B: (A) A schematic view of an idealised action potential illustrates its various phases, as the action potential passes a point on a cell membrane. (B) Actual recordings of action potentials are often distorted compared to the schematic view, because of variations in electrophysiological techniques used to make the recording

period that ends with the start of the action potential and corresponds to the time it takes for the impulse to travel along the axon from the site of stimulation to the recording electrodes.

Action Potential

The first manifestation of the approaching action potential is an initial depolarisation of the membrane. After an initial 15 mV of depolarisation, the rate of depolarisation increases. The point at which this change occurs is called firing level or threshold. Thereafter, depolarisation reaches and overshoots the isopotential line to approximately + 35 mV. It then reverses and falls rapidly to the resting level. When repolarisation is about 70% completed, the rate of repolarisation decreases and the tracing approaches the resting level more slowly. The sharp rise and rapid fall are the spike potential of the axon and the slow fall is called the after depolarisation. After reaching the previous resting level, the tracing overshoots slightly in the hyperpolarising direction to form the small but prolonged after hyperpolarisation.

All or None Law

Threshold intensity: It is the minimal intensity of stimulating current that acting for a given duration will just produce an action potential. The threshold intensity varies with the duration—with weak stimuli it is long and with strong stimuli it is short.

The relation between strength and duration of the stimulus is called the strength-duration curve. Once the threshold intensity is reached, a full-fledged action potential is produced. Further increases in the intensity of the stimulus produce no increment or other change in the action potential as long as the other experimental conditions remain constant.

The action potential fails to occur, if the stimulus is sub-threshold in magnitude and it occurs with a constant amplitude and form, regardless of strength or form, if it is at or above threshold intensity. The action potential is thus all-or-none in character and is said to obey the all-or-none law.

Ionic Basis of Excitation and Conduction

The cell membranes of nerves contain different types of ion channels, some are passive, some are voltage-gated, while others are ligand gated. It is the behaviour of these channels and particularly sodium and potassium channels that explains the electrical events in the nerves.

Ionic Basis of the Resting Membrane Potential

Due to the difference between the permeability of membranes to different ions, there is a greater efflux of K compared to the influx of Na which results in a negative potential inside the cell membrane which is termed as the resting membrane potential.

Ionic Fluxes During Action Potential

This is due to the changes in membrane conductance of sodium and potassium as detailed in Figure 3.

Neuromuscular Junction

The neuromuscular junction is the connection between an efferent nerve and muscle fibres controlled by this nerve. Transmission is universally mediated by acetylcholine released from the presynaptic terminal by the arrival of an action potential. The release of this neurotransmitter is mediated by fusion proteins on the membrane and appears to be dependent on an influx of calcium ions. Once the acetylcholine is released into the synaptic cleft, it rapidly diffuses to the postsynaptic membrane, where it binds to acetylcholine receptors. These, in turn, trigger a rapid influx of calcium into the muscle cells, triggering muscle contraction. The remaining acetylcholine in the synaptic cleft is rapidly degraded by acetylcholinesterase to prevent desensitisation of the synapse.

If, after peripheral nerve injury or transection, the neuromuscular junction does not undergo excitation at all, over a period of time the density of acetylcholine receptors gradually declines. In fact, it has been shown that after 18–24 months of loss of nerve continuity, the neuromuscular junction undergoes irreversible loss of excitability, resulting in no clinical motor improvement, if surgery is delayed up to this time.

Peripheral Nerve Transection

Once a peripheral nerve has been transected, Wallerian degeneration of the distal axons begins and macrophages enter the area to remove the myelin and axonal debris. During this process, the basement membrane which surrounds the axon and Schwann cell remain intact. Schwann cells line up in the basement membrane tube and synthesise growth factors, which attract axonal sprouts, formed at the terminal of the proximal segment of the severed axon. The basement membrane tubes provide pathways for the regenerating axons to follow to the muscles and skin. The Schwann cells then remyelinate the newly formed axons; however, the newly formed myelin is thinner than normal and the newly formed internodes are shorter than normal.

Nerve injury is most commonly classified in one of two ways.

Seddon's Classification of Nerve Injury

This is the earliest and the most well-known classification system. Prior to World War II, no precise classification existed for peripheral nerve injuries. The description by Seddon, in 1943, therefore constituted a major advance in the clinical evaluation and management of these cases. He described three grades of severity:

Neuropraxia: An injury to the nerve covering (called the myelin sheath), but not the nerve, by trauma or compression, which causes blockage of the nerve signals. Larger nerves covered by greater amounts of myelin are most susceptible to this injury. Reflexes, muscle function, vibratory and two-point discrimination are typically lost, while pain, temperature and autonomic function (sweating and circulatory regulation controlled by nerves) is typically preserved. Repair may take days to months and healing is usually perfect as only the sheath needs be repaired. This corresponds to Sunderland's 1st degree injury.

Axonotmesis: Involves disruption of the nerve itself, but the surrounding and supportive nerve myelin sheath is not affected. Causes include long or severe periods of compression, pulling or loss of blood flow to the nerve. All nerve types may be affected. Nerve fibre healing occurs at a rate of 1 mm per day from the point of injury. Recovery is usually good, although the further from the spine the injury occurs, the better the prognosis. This corresponds to a 2nd or 3rd degree injury in Sunderland's system.

Neurotmesis: A disruption of both the nerve fibre and the supportive myelin sheath. This injury may be seen with severe trauma, such as lacerations, gunshot wounds, open bone fractures, punctures, and exposure to toxins. Healing is usually poor without surgical repair. This corresponds to a 4th or 5th degree injury in Sunderland's system.

Sunderland Classification of Nerve Injury

After Seddon's description, Sunderland, in 1978, proposed his own system of grading nerve injuries into five increasing grades. However, clinical distinctions do not accompany various grades as described by him, but the grading itself remains a very useful tool.

First degree: Injury with only local changes to the nerve sheath (myelin).

Second degree: Incomplete injury to the nerve axons (the functional unit of the nerve). Nerve itself is still intact.

Third degree: Severe axonal injury with scar tissue. Nerve itself may be injured, but is still intact.

Fourth degree: Complete disruption of axon. Nerve itself may be severely injured, but is still intact.

Fifth degree: Complete transection of the nerve.

Neurotrophic Factors

Neurotrophins are a family of molecules that encourage survival of nervous tissue. Neurotrophic factors are secreted by cells in a neuron's target field and act by prohibiting the neuron from apoptosis. In this way, target neurons are not removed.

The neurotrophin family includes the nerve growth factors, nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin 3 (NT-3) and neurotrophin 4 (NT-4). There are two classes of receptors, p75 and the "Trk" family of tyrosine kinases receptors. p75 is a low affinity neurotrophin receptor, to which all neurotrophins bind. The Trk family includes TrkA, TrkB and TrkC and will only bind with specific neurotrophins, but with a much higher affinity. The Trks mediate the functional signals of the neurotrophins.

Nerve growth factor is the prototype for the neurotrophin family of polypeptides which are essential for the development and survival of certain sympathetic and sensory neurons, in both the central and peripheral nervous systems. NGF was discovered when mouse sarcoma tissue transplants in chicken embryos caused an increase in the size of spinal ganglia. In the course of attempting to characterise the agent responsible for this action, snake venom, employed as a phosphodiesterase, was found to be a rich source of NGF. A homologous tissue, the submaxillary gland of adult male mice, has become the preferred source of NGF; other unusually large concentrations are found in the guinea pig prostate gland and in bovine seminal plasma. The physiological relevance of these sources is not established. NGF is critical for the survival and maintenance of sympathetic and sensory neurons. NGF is released from the target cells, binds to and activates its high affinity receptor (TrkA) and is internalised into the responsive neuron. The NGF/TrkA complex is subsequently trafficked back to the cell body. This movement of NGF from axon tip to soma is thought to be involved in the long-distance signalling of neurons.

There is recent interest in the role of these neurotrophic factors in assisting and guiding the process of nerve and axonal regeneration, which is being tried using synthetic tubes and scaffolds for neuronal and glial cells, in nerve injuries and root avulsions.

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56 General Principles of Management of Peripheral Nerve Injuries

David A Omahen, Hazem Eltahawy, Abhit Guha

INTRODUCTION

The goal of peripheral nerve injury management is to maximise functional outcome. This is dependent on a thorough clinical and neurophysiological assessment, proper surgical technique and above all sound decision-making.[16] Given time, many peripheral nerve injuries recover spontaneously, with knowledge of the anatomy, natural history and pathophysiology of peripheral nerve injuries helping to guide if and when neurosurgical intervention may be required. This chapter will endeavour to provide the clinician with a solid background in the basic management principles for peripheral nerve injuries.

ANATOMY

The neuronal axon and its surrounding Schwann cells can be viewed as the functional unit of a peripheral nerve. A collection of connective tissue, known as endoneurium, surrounds each individual nerve fibre. A nerve is composed of several fascicles, or groups of axons, surrounded by a sheath of compact connective tissue called the perineurium. This thin layer is the anatomical substrate of the "blood-nerve barrier" akin to the "blood-brain barrier", to provide a proper external environment for axonal conduction. The tensile strength of a nerve is from the mesodermal derived epineurium, which can be subdivided into the looser internal epineurium separating the individual fascicles and the stronger external epineurium which envelops the entire nerve and provides the main tensile strength. It is this external epineurium that is most often used to insert sutures during nerve grafting (Fig. 1).

Interspersed between these layers of the nerve, there are numerous longitudinally oriented blood vessels to provide a rich vascular plexus to the nerve. However, the microcirculation can be compromised to a significant extent and lead to nerve dysfunction and pain by systemic diseases such as diabetes and local therapies such as radiation. Along the course of the nerve the axonal-fascicular relationships are constantly changing, with axons switching between individual fascicles. However, as the end organs are neared, motor and sensory fascicular differentiation becomes better demarcated. Functional outcome can be maximised when appropriate fascicles are put in the correct spatial juxtaposition.[25]

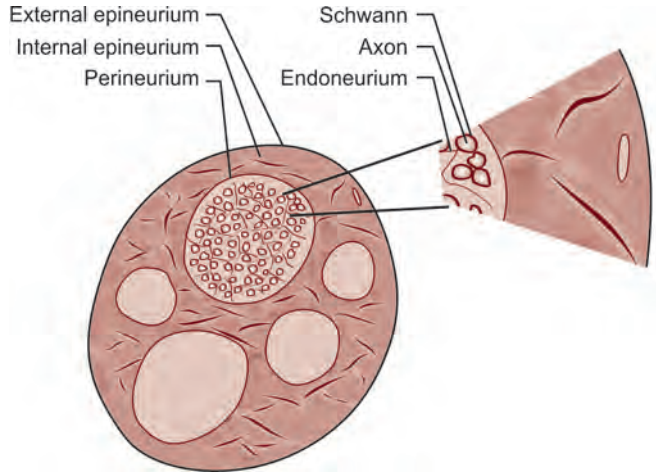


Fig. 1: The internal microarchitecture of a peripheral nerve

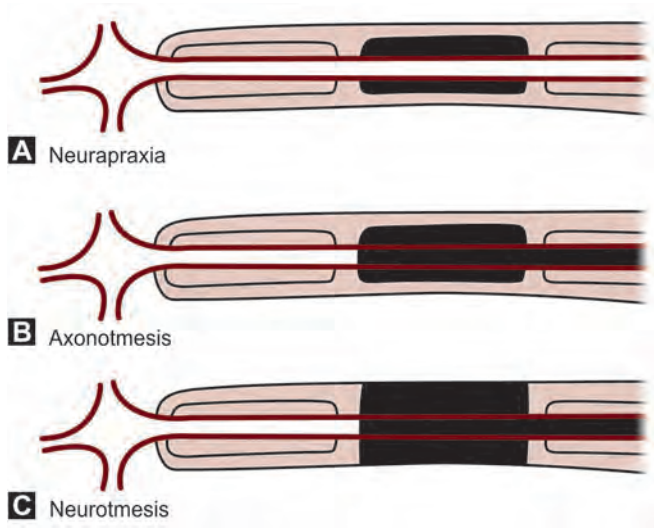
PATHOPHYSIOLOGY OF NERVE INJURY

In cases of nerve entrapment or other forms of compressive nerve injuries, early changes include endoneurial oedema secondary to impaired venous flow and breakdown of the blood-nerve barrier at the level of the perineurium.[18] Morphological studies have revealed relative sparing of smaller and unmyelinated fibres, with greater damage to large myelinated fibres.[6] This process leads to paranodal or segmental demyelination within a few days, resulting in blockage of axonal conduction.[23] This form of injury, if the nerve is caught, leads to a neuropraxic injury, not accompanied by axonal severance and usually full recovery within a few weeks, once the nerve microcirculation is stabilised with restoration of the segmental foci of demyelination.

In cases of more severe nerve injury with interruption of the axon (axonotmesis or neurotmesis), characteristic pathological changes occur.[5,25] Within 24 hours distal Wallerian degeneration begins,[2] with associated fragmentation of cellular components, breakdown of the axon and myelin sheath, and phagocytosis by invading macrophages and Schwann cells. Subsequent failure of conduction at the neuromuscular junction also occurs. Proximal to the site of injury, the process of chromatolysis[2] takes place with swelling of the cell body and clumping of chromatin.

NERVE REGENERATION

Recovery from axonotmesis or neurotmesis involves axonal regeneration.[2] First, there is a reversal in the visible changes of chromatolysis, with an increase in neuronal metabolism leading the cell body to produce axoplasm, which in turn forms the regenerating axon tips called "growth cones". Axonal outgrowth can commence as early as one day after injury and this regenerative response can continue for 12–18 months.[2] The ability of the growth cones to reach their target organs depends upon the distance they need to travel, the presence of residual endoneurial tubes to guide them, and the degree of scarring present at the site of injury. If an axon reaches the correct end target, which is approximated to be at a rate of 1 mm/day or 1 inch/month, effective though often sub-maximal reinnervation can occur up to 12–18 months post-injury.[2] During this time physiotherapy and occupational therapy are of paramount importance to maximise recovery and prevent secondary problems such as contractures. Exercise has the capacity to further improve function resulting from the reinnervation by promoting muscle-fibre hypertrophy and increased size of the motor-units or number of muscle-fibres supplied by a nerve ending by sprouting.



Figs 2A to C: The Seddon classification of peripheral nerve injury. (A) Neurapraxia refers to temporary loss of conduction along a nerve without axonal degeneration. (B) Axonotmesis involves degeneration of the axon with preservation of the surrounding supporting soft tissue sheath. Spontaneous recovery can occur since sprouting growth cones are guided to their appropriate targets along these sheaths. (C) Neurotmesis involves gross interruption of nerve continuity, and requires operative repair to restore continuity

CLASSIFICATION SYSTEMS FOR PERIPHERAL NERVE INJURY

There have been several attempts to classify peripheral nerve injury based on anatomical and clinical criteria. Broadly, nerve injuries may be classified as open or closed. Open injuries can further be subdivided into sharp (knife, glass wound, etc.) or blunt (compound fractures, gunshot wounds, etc.). Closed injuries (brachial plexus stretch injury, etc.) are often injuries in continuity, with mechanical distortion, intraneural and extraneural scarring and ischaemia all playing a role in the pathophysiology.

At a pathological-clinical level, two systems of classification have gained widespread use in clinical practise (Figs 2A to C). The first is the Seddon system,[24] which introduced the terms neurapraxia, axonotmesis and neurotmesis. Neurapraxia is a temporary dysfunction of a nerve with maintenance of anatomic continuity of the axons and connective tissue structures. It has variably been attributed to focal demyelination, haemorrhage or local metabolic or electrolyte imbalances.[25] The prognosis for complete recovery within 6 months is excellent.[29] Physical interruption of the axons with sparing of Schwann cell tubes, endoneurium, perineurium and epineurium is defined as axonotmesis. Since the fascicular structure of the connective tissue elements is still intact, axonal regeneration is possible. Schwann cells form tubules, which guide the regenerating axons to their targets. The time to recovery depends upon the site of the nerve injury. Axonal regeneration occurs at a rate of about 1 mm/day or 1 inch/month.[20,21,29] Both neuropraxic and axonotmetic injuries will eventually result in regeneration, so surgery is generally not needed. Neurotmesis refers to total nerve dysfunction secondary to complete interruption of the entire nerve. Though described later in more detail, neurapraxia may be distinguished from axonal interruption several weeks after injury with the use of electrophysiologic studies. In the setting of a closed injury, the only way to distinguish between neurotmesis and axonotmesis is to surgically explore and inspect the nerve. Figure 2 illustrates the injury patterns described in the Seddon system.

Building on the scheme put forth by Seddon, Sunderland introduced a five grade classification system.[26] Simple neurapraxia was called a Grade 1 injury. Axonotmesis (axonal interruption with an intact endoneurium) was defined as a Grade 2 injury. Neurotmesis was subdivided into three grades. Grade 3 injuries involve loss of endoneurial and axonal continuity with preservation of the perineurium. Grade 4 injuries have in addition interruption of the perineurium with preservation of epineurial integrity. Grade 5 injuries involve division of the entire nerve trunk. Other classification systems based on function, such as LSUMC grading, have merits but of limited wide-spread use.[11,12] Of course, many acute nerve injuries are a mixture of the above subtypes, a situation sometimes referred to as a grade 6 lesion.[19] They often demonstrate a biphasic recovery, with rapid resolution of neurapraxic dysfunction followed by slower or limited recovery of axons undergoing Wallerian degeneration.[24] Table 1 outlines the differences between the Seddon and the Sunderland classification systems.

Table 1: The Seddon and Sunderland classifications of nerve injury

Seddon classification	*Sunderland classification*	*Structures involved in injury*				
		Myelin	*Axon*	*Endoneurium*	*Perineurium*	*Epineurium*
Neurapraxia	1	+/–				
Axonotmesis	2	Yes	Yes	No	No	No
	3	Yes	Yes	Yes	No	No
	4	Yes	Yes	Yes	Yes	No
Neurotmesis	5	Yes	Yes	Yes	Yes	Yes
	6					
	(Mackinnon/Dellon)	Mixed pattern of injury				

PATHOGENESIS OF PERIPHERAL NERVE INJURIES

Open Injuries

Laceration Injuries

Of all the mechanisms of peripheral nerve injury, this is the one most likely to lead to transection.[12] Even with near or complete functional loss, approximately 20% of nerves are left in at least partial continuity.[12,14] Generally these injuries fall into two major categories: sharp and blunt. Sharp laceration, as caused by glass, knives or razors, is usually dealt with via exploration and primary repair if a major nerve injury is accompanied by severe loss of function. Blunt injury, such as that inflicted by chainsaws or commercial machinery, is usually dealt with in a delayed manner, as there is usually a variable and unpredictable amount of non-viable tissue proximal and distal to the site of injury. The injured nerve stumps can be sutured to nearby soft tissue planes to avoid retraction if they are identified during repair of other soft tissue injuries.[12,14] At a later time, non-viable tissue will become more clearly demarcated, allowing trimming of the stumps back to viable tissue prior to repair.[4,16]

Gunshot Wounds

With gunshot wounds, a variety of injuries can occur depending on the nature and velocity of the missile, as well as the trajectory. Even with clinical evidence of nerve injury, the incidence of transection is only 15–20%.[14,18] Progressive loss of function and pain, audible bruits or palpable thrills, or evidence of distal ischaemia may indicate a major vascular injury.[12,14] Entities such as pseudoaneurysm formation, compressive haematoma, major vessel transection or arteriovenous fistulae may necessitate acute exploration. Otherwise, serial clinical and EMG examination to document the course of any spontaneous recovery during the first 2–3 months is usually advised.

Iatrogenic Injuries

Direct injection injuries occur most commonly to the sciatic nerve at the buttock and the radial nerve in the upper arm,[12,14] and may be associated with development of chronic pain. The lesion should be explored if no evidence of improvement occurs during 3 months of serial evaluation. Intra-operative nerve action potentials (NAPs) are invaluable in deciding how to deal with such injuries. Kline et al. report poor results with repair of sciatic injection injuries involving only the peroneal division.[12,14,15,20] Intrafascicular injection seems to be associated with a greater degree of damage.[7,21] Acute repair of sharp injuries (such as scalpel-induced lacerations) is usually indicated. Blunt or traction injury is usually best dealt with in a delayed manner as described below.[12,14]

Closed Injuries

Stretch Injuries

Stretch injuries occur when traction on a nerve exceeds the elastic limit of the nerve.[17] They are often associated with spinal injury or joint dislocation. This often results in formation of a neuroma-in-continuity with a high likelihood of neurotmesis and obliteration of fascicular anatomy.[12,14] Widespread and varying injury occurs along the length of the nerve.[12,14] As with other lesions in continuity, they are best dealt with by careful longitudinal evaluation and delayed surgical intervention when indicated.

Crush Injuries

Crush injuries involve variable combinations of stretch, contusion, ischaemia and blunt transaction.[2,7] They are usually dealt with in a delayed manner, as described for stretch injuries.

Ischaemic/Compressive Injuries

With ischaemia, damage may occur not only to the nerves themselves but also to their supportive environment. Painful paresthesias followed by progressive loss of function, swelling of an extremity, skin discolouration and signs of distal peripheral vascular compromise may signal an evolving compartment syndrome which requires urgent treatment with fasciotomies.[12,14]

Electrical/Thermal Injuries

Severe scar formation and potential extensive necrotic soft tissue loss often accompany these injuries.[3,19] Graft

and/or flap reconstruction is often required. The accompanying nerve injury is usually extensive, non-focal and difficult to treat.[12,14]

CLINICAL AND ELECTROPHYSIOLOGICAL EVALUATION

Symptoms of peripheral nerve injury include pain, dysesthesias and partial or complete loss of motor and sensory function.[2,25] Evaluation involves a thorough history and physical examination, relevant radiological studies and electrodiagnostic evaluation. Answers to the following important questions should be sought out: what was the exact timing and mechanism of injury? Is there concomitant injury to bone, blood vessels or other soft tissue structures? Is the injury open or closed? If an open injury exists, is the nerve lacerated cleanly, or does a blunt injury exist? What is the extent and grade of the injury? Has there been evidence of progression or recovery? Power is tested in individual muscles or muscle groups and graded according to the MRC grading system.[10,22] Examination of sensory function involves assessment of light touch, two-point discrimination, pinprick, vibration and proprioception.[22,23] Tinel's sign refers to paresthesias elicited by regenerating axonal growth cones when tapping along the course of a nerve, and is useful in the localisation of a nerve injury.[9,24] The course of regenerating sensory axons can be mapped by progressive distal advancement of Tinel's sign. Reflex changes should also be evaluated.

Electrophysiological studies involve those undertaken serially pre-operatively to determine if and what degree of spontaneous recovery is occurring to augment the clinical examination. In an effort to identify injuries that will not require surgical intervention, an early study is performed 2 weeks post-injury followed by studies at 2–3 months. These usually include EMG, nerve conduction and specific wave forms such as the "F" wave to determine the status of the proximal spinal nerve roots and dorsal root ganglion. If both clinical and electrophysiological improvement is demonstrated, then further nerve surgery is unlikely. Neurapraxic injuries are characterised by interruption of nerve conduction across the site of injury with preserved distal conduction, without evidence of denervation on EMG evaluation. The situation is different with axonotmesis and neurotmesis. The distal axons will conduct nerve impulses for the first few days, but then cease to do so as Wallerian degeneration ensues.[2,25] After 2–3 weeks the EMG shows clear-cut signs of denervation including denervation potentials, positive waves and spontaneous activity. Differentiation between axonotmesis and neurotmesis requires delayed nerve conduction studies. In the case of axonotmetic injury, regenerating axons will cross the site of injury and grow distally. Regeneration potentials are seen as denervation potentials which decrease and usually precede clinical evidence of motor improvement.[2,25] The absence of advancing conduction on serial testing means spontaneous regeneration is unlikely to occur and a surgical solution is required. Intra-operative electrophysiological examination, comprising direct nerve stimulation, sensory evoked potentials (SEPs) and NAPs are important adjuncts to the microscopic and macroscopic status of the nerve, enabling the neurosurgeon to undertake optimal surgical decisions. Post-operative serial electrophysiological examination, which usually commences after 2–4 months after nerve surgery, are also utilised to augment the clinical follow-up for determining the extent of neural reinnervation.

RADIOLOGICAL EVALUATION

Currently, radiological examination plays little role in the management decisions for nerve injuries. However, emerging improvements in MRI neurography techniques may provide clues about peripheral nerve injuries. Experimental studies in animal models[1,25] have demonstrated the ability to non-invasively distinguish between axonotmetic and neurotmetic injuries based on changes in nerve and muscle. Correlation with histological and clinical evidence of axonal degeneration and regeneration has been good. One day this modality may reduce the need for exploratory surgery.

MANAGEMENT OF PERIPHERAL NERVE INJURIES

Sharp open nerve transections should primarily be repaired with end-to-end nerve suturing of the epineurium at the time of injury. A small amount of the cut surface may be cut to freshen up the cross-sections. Blunt open nerve injuries in which the transected nerve ends are ragged and contused is better repaired after a 3–4 week delay, allowing for a reduction in tissue oedema and more importantly scar formation at the edges of the transected segment. Scarring allows for discrimination between healthy proximal and distal nerve ends and the fibrosed nerve segments. Fibrosed segments can then be resected back to normal fascicular structure at both ends and then a repair with or without nerve grafts can be performed.[8,26]

Closed injuries often require more complex management decisions. The nerve remains in continuity in most such injuries. Stretch or compression injury causes injury of varying severity. Given enough time, spontaneous recovery occurs in 80% of closed nerve injuries.[10] The surgeon's task is early identification of the cases in which there is lack of clinical or electrophysiological recovery. Most surgeons believe that, if no signs of regeneration are seen after 3–4 months, operative intervention is the best course of action. The location of the injury is another important consideration. In proximal lesions, such as in the supraclavicular brachial plexus, waiting too long for recovery to manifest may miss the window of opportunity for useful outcome from nerve repair.[13,27] However, age is an important factor as the regenerative capacity of

infants or young adults is much more than older adults, hence, we tend to be more aggressive in this age group, even after a prolonged delay. However, in general, if recovery of useful motor function is to occur, muscles must be reinnervated within 2 years,[10,24] since after this time period denervated muscles undergo irreversible atrophy and replacement with fatty tissue. In proximal brachial plexus injuries with documented nerve root avulsion, consideration should be given to direct neurotisation. This involves providing viable motor axons from a donor nerve, whose function is redundant or less important, to a denervated distal muscle group.

Early operation is associated with the following advantages:[12,26] (1) less scarring which simplifies dissection of peripheral nerve elements; (2) direct evaluation of anatomic and electrophysiological continuity which dictates the necessity of a surgical repair and (3) earlier repair may result in better outcome with faster reinnervation of denervated muscle. Potential improvements in outcome following early surgical repair must be balanced against the risk of operating on a proportion of patients who would have recovered on their own without surgical intervention.

PRINCIPLES OF SURGICAL NERVE REPAIR

Surgical intervention for peripheral nerve injuries has two goals. The first is diagnostic, whereby one determines the site(s) of nerve injury by macroscopic, microscopic and intra-operative electrophysiological evaluation. Most often this can be predicted by the pre-operative clinical and electrophysiological evaluation, but confirmation with the exposed nerves is required. Multiple sites of injuries along the course of a nerve pathway are common, especially in stretch injuries, hence exposure of the full length of the nerve (i.e. supra-clavicular, retroclavicular and infra-clavicular brachial plexus exposure) is advised. The second surgical goal is therapeutic intervention to optimise nerve regeneration. This depends not only on the extent of the injury, but also the pre-operative goals, knowledge of what reinnervation is realistic given the patient characteristics, etc. Multiple types of interventions may be warranted depending on the specific evaluation of the nerve injury in the same patient. This may include a simple external neurolysis if physical and electrical continuity is present, excision of the neuroma in continuity and direct end-to-end repair if the gap is minimal, interpositional nerve grafts from donor sites such as the sural nerve or direct or indirect neurotisation procedures if endogenous proximal nerve fibres cannot be obtained. Basic principles of surgery include the following:

Exposure of the Healthy Nerve Proximal and Distal to the Site of Injury

A generous skin incision is based on the surface anatomy of the nerve and centred on the site of injury. Careful proximal and distal exposure of the suspected lesioned area is performed. Working towards the injury from both directions, sharp dissection is used to expose the lesion. The deep subperineurial longitudinal blood supply[12,26] to the nerve should be preserved, but most collaterals can be sacrificed to gain a full circumferential exposure of the nerve.[12,14] The lesion in continuity can then be inspected and palpated with certain operative findings helping to predict internal pathology. A hard or firm consistency suggests a greater degree of internal scarring with the degree of internal scarring almost always worse than it appears on external examination. Although, in most cases, a fusiform neuroma is seen, a lateral neuroma suggests partial nerve transection, especially in a setting of partially spared pre-operative function in the distal distribution of the nerve. The size of the neuroma is also important as swelling more than twice the diameter of the nerve is suggestive of a neurotmetic lesion rather than an axonotmesis.[12,26]

Intra-operative Electrophysiological Evaluation

Intra-operative electrophysiological evaluation includes the recording of SEPs, NAPs and electromyography (EMG) (Figs 3A and B). During patient positioning, electrodes are placed in relevant muscles as well as adjacent to relevant peripheral nerves, either superficially on the skin surface or percutaneously. If SEP recordings are used, electrodes are placed over the scalp in the parietal region and percutaneously adjacent the cervical spine. Use of regional or local anaesthetic blocks or a tourniquet is avoided along with long-acting muscle paralytics to prevent compromise of intra-operative electrophysiological testing. Direct electrical stimulation of nerves is performed using bipolar electrodes with a biphasic square wave pulse with a duration of 0.05–0.10 milliseconds. We generally start with a stimulus intensity of 0.5 mA and increase the amplitude up to 5 mA using a frequency of 1 per second. The stimulus is delivered to the nerve segment distal to the site of injury to record SEPs or proximal to the lesion to observe an EMG response, with the functional integrity of motor nerve fibres assessed by either visual observation or electromyographic documentation of muscle contraction. Alternatively, sensory conduction across the lesion in continuity can be measured through recording of SEPs. Both the velocity and amplitude of a nerve conduction response can be measured, with the velocity of the response influenced by the degree of myelination, whereas the amplitude of the response is determined by the number of conducting nerve fibres.[27,28] NAPs are very useful in aiding intra-operative decision-making, especially when evaluating a neuroma in continuity. The presence or absence of a NAP across the lesion helps to determine the need for resection of a damaged nerve segment.[27,28] As early as 6–10 weeks after injury, a recordable response across a traumatic lesion in continuity indicates the presence of at least several thousand functioning nerve fibres.[10,12,24,26,28,29] Such conducting lesions imply an axonotmetic lesion and, therefore, require no

further surgical repair because of the high probability of clinical recovery of function through regeneration. In contrast, lesions in continuity without a NAP should surgically be resected and the nerve ends approximated using grafts as indicated.

Intra-operative Microscopic Examination by Quick (Frozen) Section

Under the magnification of the surgical microscope, the centre of the neuroma is incised using an 11-blade knife and the ends are carefully inspected for fascicular patterning. The neuroma is then serially sliced distally and proximally (Fig. 4). After each slice, the fresh ends are re-examined under the microscope and the cut slice is submitted for quick pathological examination by frozen section to look for a normal fascicular pattern.

Fascicular Microsuture Technique

The nerve ends are carefully inspected under the surgical microscope to determine the fascicular topography. A useful method is to sketch diagrams of the fascicular patterns of the proximal and distal stumps. The sketches are matched and from this an approximate estimate of the corresponding fascicle groups in the proximal and distal stumps is made.[28,29] Another technique is to utilise surface vessels to aid in the correct alignment (Fig. 5) of proximal and distal stumps.[12,14] The nerve stumps are handled with fine tipped 'jeweler's forceps' to minimise trauma to nerve tissue. We use 9-0 nylon epineurial stitches to approximate the fascicles in a tension-free manner.

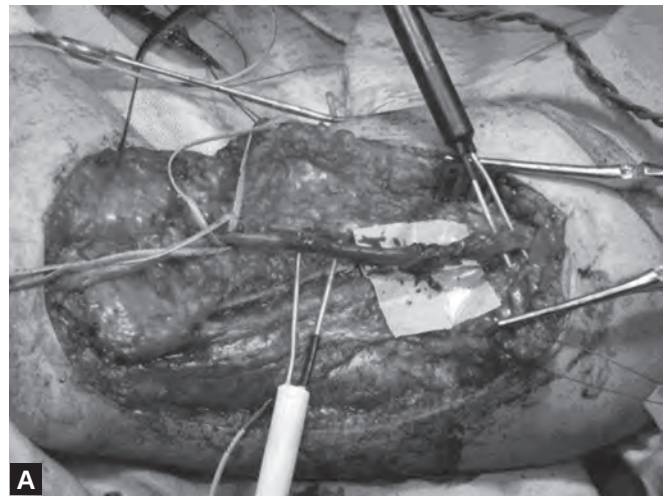
Technical Pearls

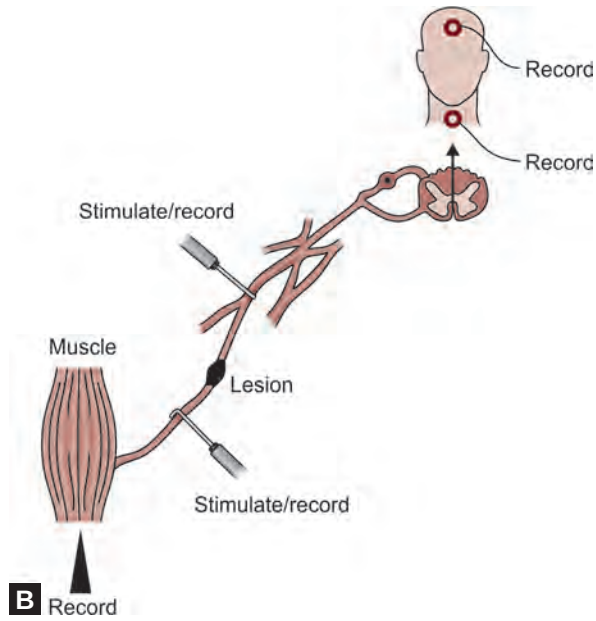
Avoidance of Tension

Tension is highly detrimental and should be avoided in nerve repair surgery.[29] If the gap between the nerve stumps is small and the two ends can be approximated without tension then a primary end-to-end repair is performed. The nerve proximal and distal to the point of injury can be mobilised to reduce the intervening nerve gap. Care should be taken to assess the maximum possible gap created when the appropriate joints are put through their full range of motion. If suturing cannot be achieved without tension, then the two ends should be approximated using interposition nerve grafts. Common donor nerves for grafting are harvested from superficial sensory nerves such as the sural nerve in the lower extremities and the medial brachial and antebrachial cutaneous nerves and superficial branch of the radial nerve in the upper extremities.[12,14] The grafts must be long enough to allow the proximal and distal ends to lie free from tension with the extremity in full extension.

Using a Minimal Number of Sutures

The aim of microsuturing is to effect full coaptation between the cross-sectional area of the nerve fascicle group and the donor graft or distal stump fascicle. If





Figs 3A and B: Intra-operative electrophysiological evaluation of a neuroma-in-continuity: (A) The presence or absence of intra-operative NAPs across a lesion-in-continuity help the surgeon decide whether excision of the lesioned nerve segment is required. In this example, a lesion-in-continuity of the right ulnar nerve has been dissected out, and NAPs are being recorded across the site of injury. (B) To assess sensory conduction, stimuli are delivered to the nerve segment distal to the injury site and SEPs are recorded over the scalp or at the level of the cervical spine. Motor conduction is assessed with stimulation proximal to the lesion to observe an EMG response in the distal musculature

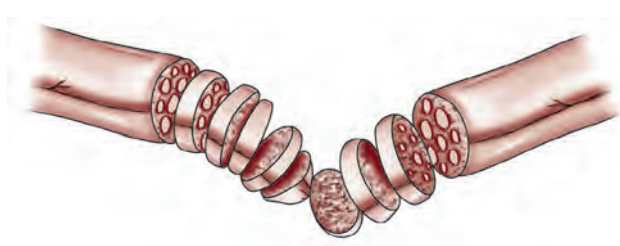


Fig. 4: Intra-operative frozen section evaluation of a neuroma-in-continuity: serial proximal and distal cross-sectional slices at the site of the neuroma-in-continuity are sent for frozen section evaluation until a normal fascicular pattern is identified

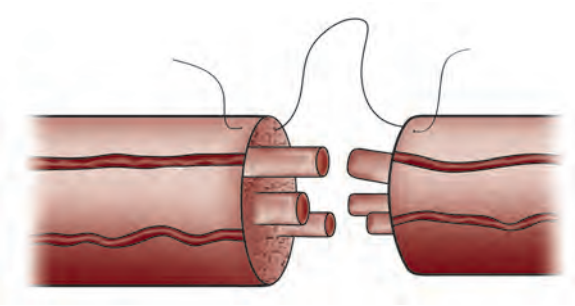


Fig. 5: Matching fascicular anatomy during nerve microsuturing: proper realignment of two segments of the cut nerve can be established by matching both the internal fascicular pattern and the superficial vascular structures

no tension is present, this can be achieved with a single suture for each fascicle group (Figs 6A to C). Fibrin glue and argon beam lasers have been used to approximate fascicles in the hope of reducing scar tissue formation. Improved functional results using these techniques have not yet been definitively demonstrated.[11,28,29]

Maximising the Number of Motor Fibres Available for Repair

Identification of motor fascicles is possible by dissecting the motor branch of the nerve up to the graft site and anastomosing into it. Histochemical methods, such as the use of choline esterase techniques, used during the intra-operative quick section of the cut nerve slices are also sometimes useful to identify the motor fascicles. However, obtaining the results can take several hours, which is usually impractical during surgery.

Matching the Graft to Recipient Nerve Fascicles

The graft should connect corresponding motor fascicles in the proximal and distal nerve stumps. Additionally, the number of grafts should be sufficient to cover the cross-sectional area of the recipient fascicles (Fig. 7).

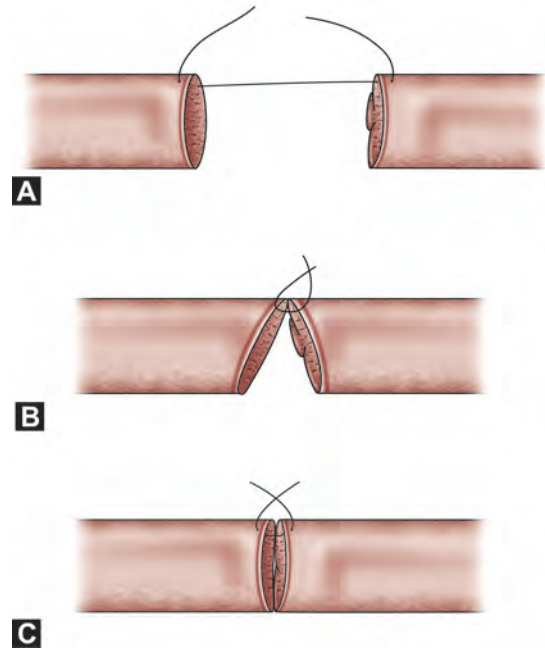
POST-OPERATIVE MANAGEMENT

Immobilisation

The extremity is immobilised in the exact position in which it was placed during the operation. We usually leave a compression bandage on for 24 hours and the limb is put in a splint for 3 weeks. After that gradual mobilisation is encouraged. An active physiotherapy program is crucial to maintain muscle bulk and prevent frozen joints.

Follow-up Electrodiagnostic Studies

Serial electrophysiological studies can be very useful in detecting early signs of muscle reinnervation several months before muscle contraction is clinically evident. The results of these studies, when positive, can provide



Figs 6A to C: Microsuture fascicular re-approximation: when a tension-free repair is performed, a single suture for each fascicular bundle is sufficient

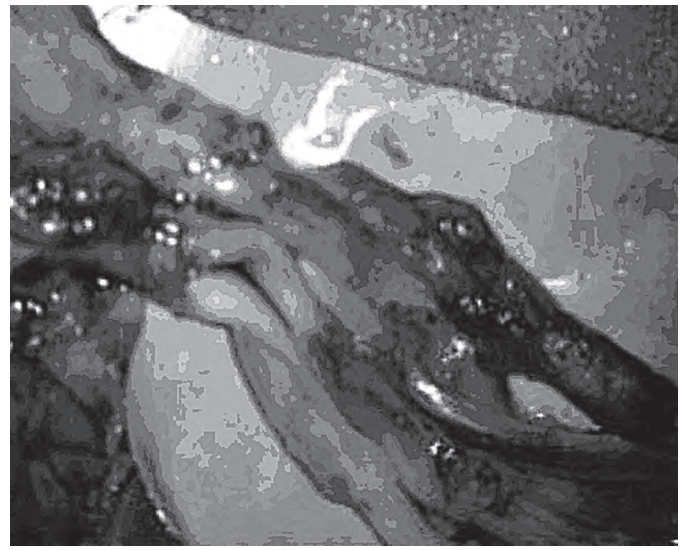


Fig. 7: Matching nerve grafts with motor fascicles: Ideally, nerve grafts should connect corresponding motor fascicles in the proximal and distal stumps. The size and number of grafts should be sufficient to cover the entire cross-sectional area of the fascicles being grafted. In this example, several sural nerve cable grafts were required to repair a common peroneal nerve injury

hope to the patient and can also be helpful in predicting clinical outcome. Nerve conduction studies will hopefully show an advancing conduction response across the graft or repair site. Realistic expectations should be given to the patient regarding the time for regeneration, which can take many months depending on the distance

that needs to be travelled by the regenerating axons at the rate of 1 mm/day.

Prognosis and Reasons for Failure

Many factors influence the quality of nerve regeneration. Advanced age and a long interval between the injury and doing the repair are unfavourable factors.[28,29] Other causes of poor results include delayed wound healing, infection and presence of scar tissue crossing the nerve graft site. Scarring at the repair site may be due to rupture of one of the suture anastomoses or due to scarring at the distal site of the graft. This is characterised by a failure of the advancing Tinel's sign or nerve conduction response to cross the distal anastomosis site after successfully progressing along the graft. If this persists for more than 2–3 months, then reoperation is indicated for the resection of 'distal coaptation scar'.

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57 Surgical Anatomy and Management of Brachial Plexus Injuries

Venkataswami R, Purushothaman V

INTRODUCTION

One of the most challenging problems in neurotrauma is the management of brachial plexus injuries. With the advent of microneural surgery and the better understanding of nerve grafting under the microscope, the results have improved, thanks to pioneers like Narakas, Seddon, Millesi, Mackinnon, Julia Terzis, Gu, Chang, Oberlin, Bertelli and Mehta (who pioneered brachial plexus surgery in India). The difficulties in locating the level of the lesion, various pathologies existing in the same individual, the prolonged operative sessions and above all the unpredictable results due to several variables, add to the challenges.

SURGICAL ANATOMY

It is very essential to know the detailed anatomy of the brachial plexus (Fig. 1).[6]

The brachial plexus is constituted by the ventral rami of C5 to T1 nerve roots. They can have a contribution either from C4 wherein it is called prefixed or contribution from T2 when it is called post-fixed. As the roots emerge from the intervertebral foramina, they lie on the scalenus medius muscle behind the scalenus anterior. In a large percentage of brachial plexus injuries, there is tremendous scarring involving these muscles. This is as a result of the injury to the area. It becomes very difficult to locate the roots, unless the scarred muscles are released by multiple cuts along their lateral border. The phrenic nerve travelling on the surface of the scalenus anterior must be identified, dissected and neurolised, if necessary and kept out of harm's way, while dividing the scarred muscles. The phrenic nerve, when traced upwards, leads to the C4 root and, sometimes, this will be an important guide to locate the C5 and proceed downwards.

The roots and trunks lie in the posterior triangle, the divisions lying behind the clavicle, the cords behind the pectoralis major and the nerves below the pectoralis minor. This is the tentative arrangement. In avulsions and severe traction injuries, the whole plexus may migrate downwards and this has to be kept in mind while dissecting to identify the various structures. The C8 and T1 lie on the first rib in close relation with the subclavian vessels. While dissecting them from the scar, one has to be very careful to identify and keep the vessels away.

The suprascapular, axillary and musculocutaneous nerves are important as they control shoulder and elbow function. Most of the nerve crossings involve these branches. The suprascapular nerve is the first branch from the upper trunk. The axillary nerve is the smaller of the two main divisions of the posterior cord. The other one is the large radial nerve. The musculocutaneous nerve is the lateral branch from the lateral cord.

From the clinical examination and functional point of view, the C5 and C6 roots are for shoulder and elbow functions and C8 and T1 for hand and forearm functions. C7 contributes to shoulder, elbow and hand functions. In other words, C7 has considerable cross-innervations with C5, C6 and C8. Because of this cross-innervation, no single muscle is innervated by C7 alone. Therefore, C7 transection will cause minimal muscle dysfunction which is compensated very quickly.

CLASSIFICATIONS

A classification is necessary to evaluate and plan the line of management. The pathological classification of Sunderland [15] into various degrees is well-known. Third and fourth degree injuries have to be differentiated carefully on exploration. When the fascicular pattern is preserved only neurolysis is required, otherwise, resection and grafting will be required.

It can be classified on functional and clinical basis under various headings:

Anatomical

- Upper plexus
- Lower plexus
- Total

All this can be either complete or incomplete.

Depending on the nature of violence, it can be compression, traction, division, rupture or avulsion.

Division is usually seen in direct penetrating injury like stab or gunshot injuries. Based on the level of lesion in relation to the clavicle, they can be supraclavicular or infraclavicular lesions. Infraclavicular lesions can be associated with vessel injury and skeletal injuries, including fractures of the humerus and scapula (Figs 2A and B). In relation to the sensory ganglion in the dorsal rami, it can be pre-ganglionic or post-ganglionic. The pathological classification of Sunderland helps in

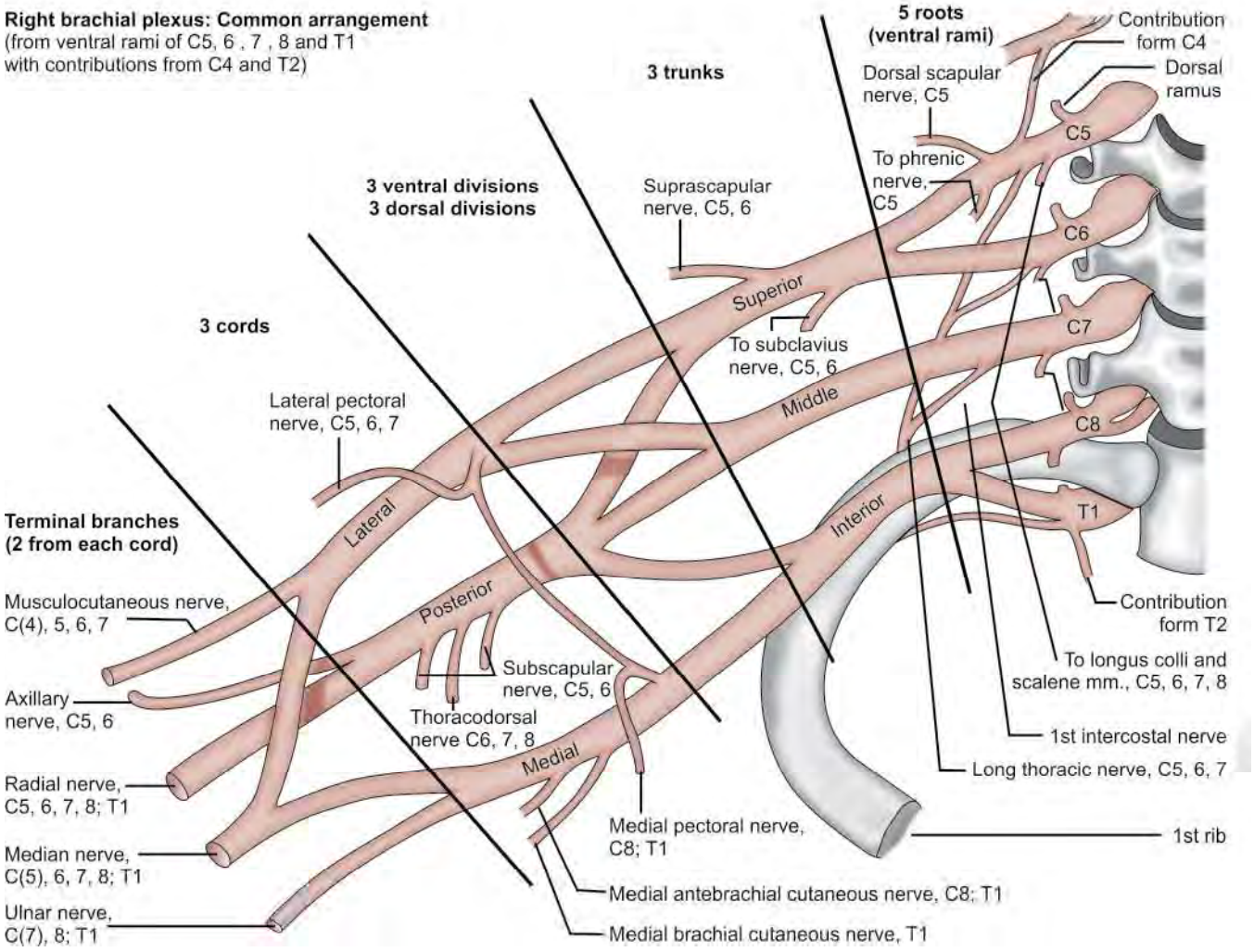


Fig. 1: Normal arrangement of right brachial plexus

Fig. 2A: Left lower plexus palsy

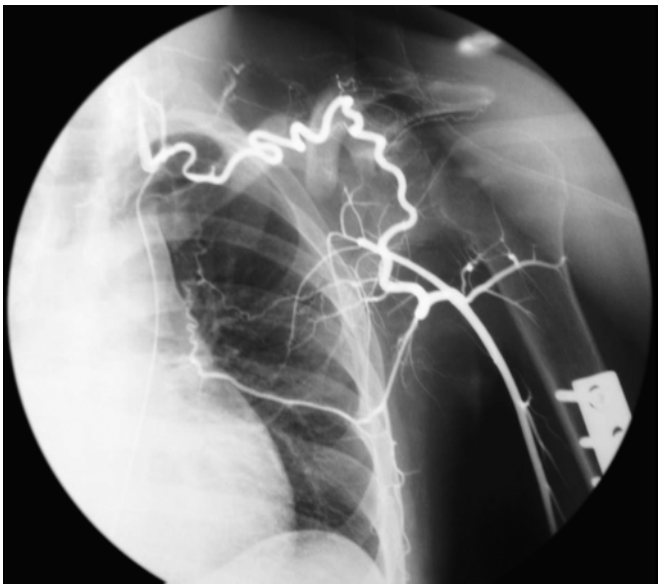


Fig. 2B: Same patient with fracture clavicle with subclavian artery injury with well formed collateral

deciding on the type of repair required in each instance. It is interesting to note that all the types can exist in a single patient. This makes the diagnosis of locating the level of lesion more difficult. It also adds to the problem of choosing the line of management.

CLINICAL EXAMINATION

In spite of the availability of a spate of sophisticated invasive and non-invasive investigations, a systematic clinical examination is the sheet anchor in the diagnosis of brachial plexus injuries. Routine examination of motor and sensory functions in the territory of the brachial plexus is essential. A chart of this nature (Fig. 3A) will help immensely. At a glance, you can find out each muscle and its corresponding roots.

One should be familiar with areas of absolute sensory loss and their corresponding roots. This will help in sharpening the clinical localisation of the lesion. Absence of sensation over the palmar aspect of the index and little fingers indicate lesions of the median and ulnar nerve, respectively. Anaesthesia in the dorsum of the metacarpophalangeal joint of the thumb indicates a radial nerve lesion (Fig. 3B).

It is essential to differentiate a pre-ganglionic from a post-ganglionic lesion. Horner's syndrome (Fig. 4) is characteristic of root avulsion of C8 and T1. Diaphragmatic paralysis is seen in a C4 lesion. Tinel's

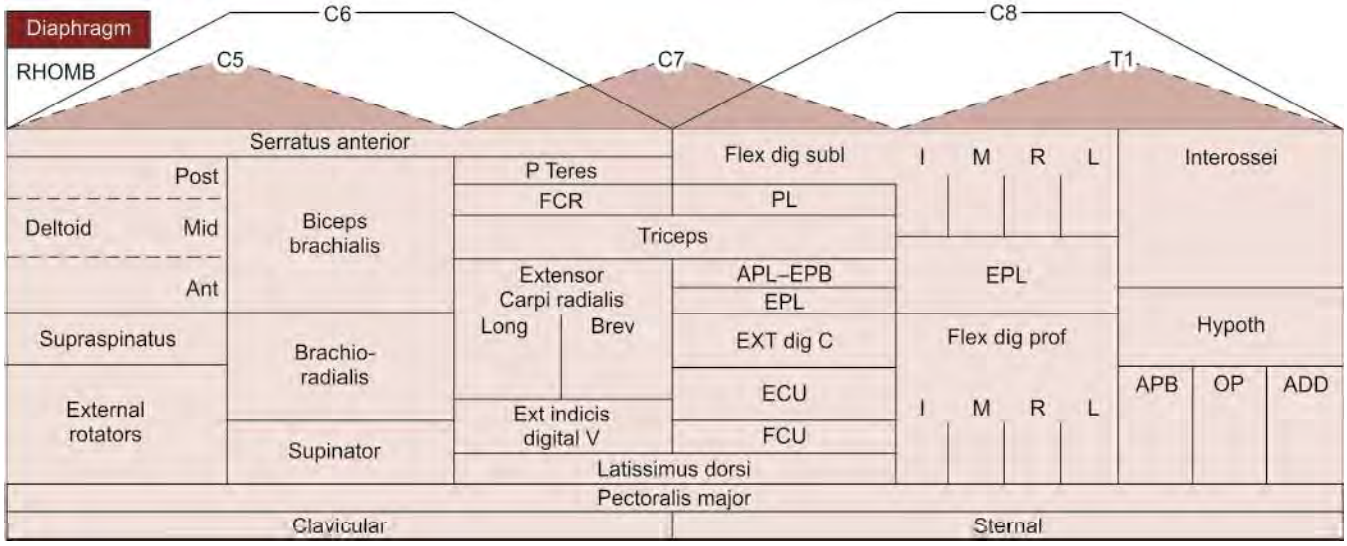


Fig. 3A: Muscle chart

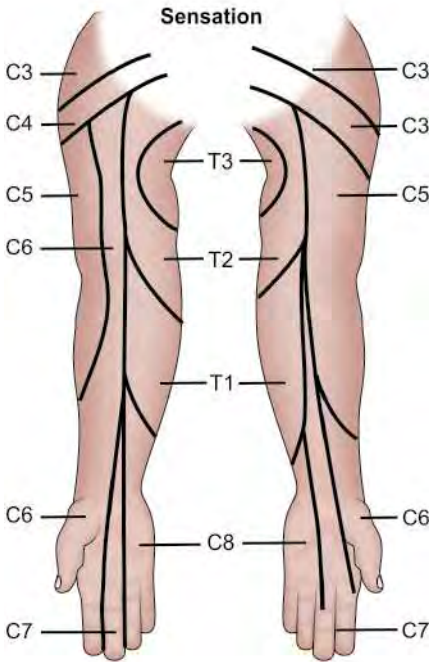


Fig. 3B: Sensory chart

Fig. 4: Left Horner's sign in a case of birth palsy

sign is absent in pre-ganglionic lesions. The presence of Tinel's sign is quite useful, as it indicates that some roots are regenerating and it is a post-ganglionic lesion. The paravertebral muscles are paralysed in pre-ganglionic lesions. A classical example is winging of the scapula (Fig. 5). Paravertebral anaesthesia and sweating in the anaesthetic area are pathognomonic of a pre-ganglionic lesion. Sensory nerve action potential (SNAP) is positive in the anaesthetic areas and there will be a positive axonal reflex. Somato sensory evoked potential (SSEP) will be absent.

The roots can be damaged at five possible sites:

- Immediately proximal to the trunks. In this case the serratus anterior and rhomboids may be intact.
- Proximal to white rami communicans—C8. Horner's syndrome will be present.
- Proximal to grey rami communicans. Sweating in anaesthetic areas will be seen.
- Proximal to dorsal root—Paravertebral muscles are paralysed.
- Proximal to posterior root. Here axonal reflex will be present.

The presence of deep pressure pain is an indication of continuity of that nerve and its roots. This is performed by applying full pinch pressure across the patient's finger tip at the base of the nail. Then, with the pressure maintained, the patient's finger is pulled sharply out from between the examiner's thumb and index finger. This is painful in a normal finger and the pain is carried by the smallest sensory fibres in the nerve. In an apparently anaesthetic finger, if any burning sensation is appreciated in the limb after this manoeuvre, there must be some continuity of the nerve supplying the finger (Thumb tip—C6, tip of middle finger C7, tip of little finger C8). These small fibres seem to be the least affected by compression of a nerve trunk following injury and swelling and they continue to function when all other nerve fibres have stopped functioning. This finding does not help in any way in assessing the value of the intact nerve root. In summary, although clinical examination can easily identify unambiguous physical signs, interpretation may be difficult when multiple lesions are present that involve the various roots or when an extensive lesion leaves a few informative findings.

DIAGNOSTIC STUDIES

They can be broadly classified into imaging studies and neurophysiological investigations. The understanding of the accuracy and reliability is crucial in planning the treatment.

Imaging Studies

Plain radiographs of the cervical region, upper chest and upper arm are essential. Fracture of the transverse process of the cervical spine strongly indicates avulsion of the roots at C4, C5 and C6 levels from the spinal cord, as these roots are intimately related to the transverse processes. C7, C8 and T1 roots are not attached well to the transverse processes. One should suspect damage to C8 and T1 roots and, the subclavian vessels when there is an associated fracture of the first rib and clavicle. X-ray chest is essential. Elevation of the diaphragm indicates damage to the phrenic nerve (Fig. 6).

CT myelography is sensitive in identifying small meningocoeles at the site of root avulsion. Water soluble contrast material is very useful, according to some authors, in assessing the damage to nerve roots. Nagano et al.[11] have done detailed analysis on the role of myelography. Normal rootlets are shown as thin linear filling defects that arise from the cord and converge as they enter the nerve root sheath. The origin of the roots is seen as fine streaks. They cause the filling defect in a normal myelogram.

They have classified the picture into six types including the normal (N, A1, A2, A3, D and M) (Fig. 7). It varies from a slight irregularity to a full fledged meningocoele. By definition, N is a normal shadow; A1 is a

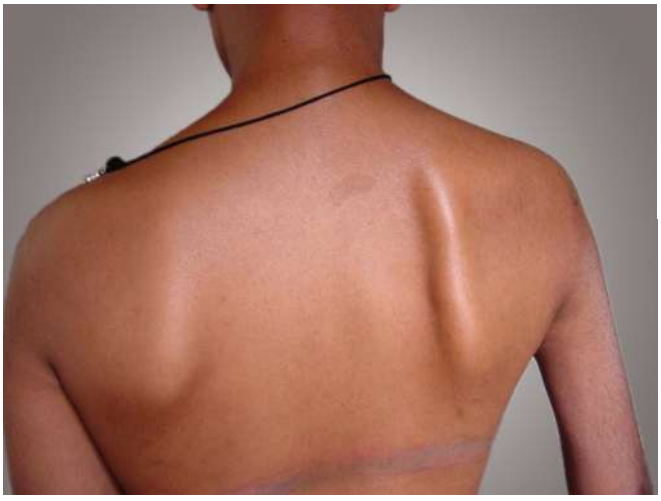


Fig. 5: Winging of the scapula

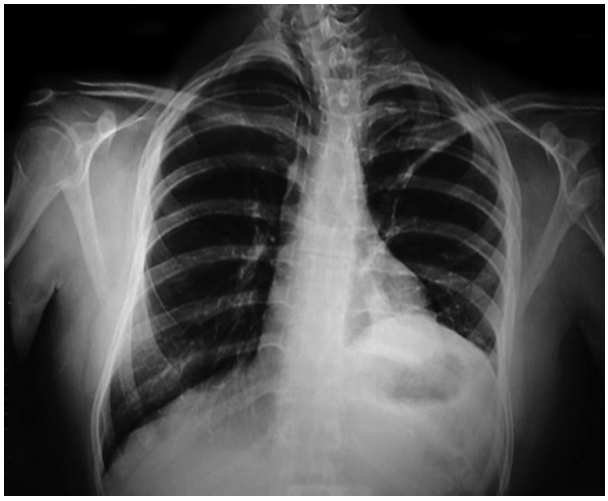
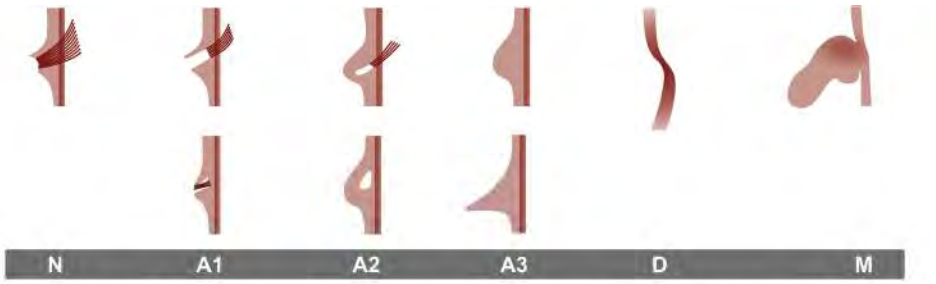


Fig. 6: Elevation of the left dome of the diaphragm



N: Normal, A1: slightly abnormal root sleeve shadow, A2: obliteration of the root tip of the root sleeve with shadow of root or rootlets showing, A3: obliteration of the tip of the root sleeve with no root and rootlets shadow visible, D: defect instead of root sleeve shadow, M: traumatic meningocoele

Fig. 7: Classification of myelographic findings

slightly abnormal root sleeve shadow in which shadows of roots and rootlets can be recognised but appear different from those on the unaffected side; A2 is obliteration of the tip of the root sleeve with the shadows of roots or rootlets visible; A3 is obliteration of the tip of the root sleeve with no shadows of roots or rootlets visible; D is a defect instead of a root sleeve shadow; and M is a traumatic meningocoele. They claim 96% correct diagnosis with this method. Four percent false positive and 12% false negative have been reported by others. Yet, it is an important adjuvant in the diagnosis of pre-ganglionic lesions.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) has advanced considerably and plays an increasing role in peripheral nerve pathology diagnosis and treatment. MRI is helpful in identifying root avulsion. A good MRI can show an intact root, a pseudomeningocoele, the continuity of the plexus, the scarring in the scalene muscles, etc. Being non-invasive, MRI has literally taken the place of CT myelogram. The recent 3 T MRI is even more valuable in assessing the integrity of the brachial plexus (Figs 8 to 10).

Neurophysiological Examination

In recent years, neurophysiological examination has been used in locating the level of the lesion in brachial plexus injuries, but it has its own limitations and clearly defined areas.

Electromyography

Electromyography (EMG) is not useful in the first 10–14 days, when axonal degeneration changes do not appear, but the presence of voluntary motor unit action potentials excludes complete transaction of a nerve root. Absence of signs of denervation in a paralysed muscle after 2–3 weeks indicates a neuropraxic lesion. Paraspinal EMG can differentiate pre-ganglionic and post-ganglionic lesions.

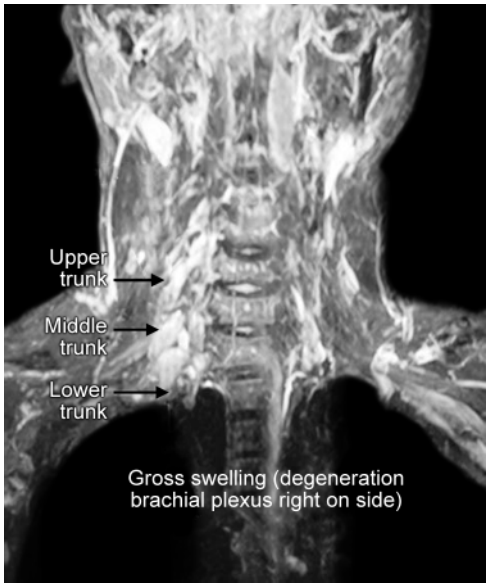


Fig. 8: MRI showing right brachial plexus and its derangement

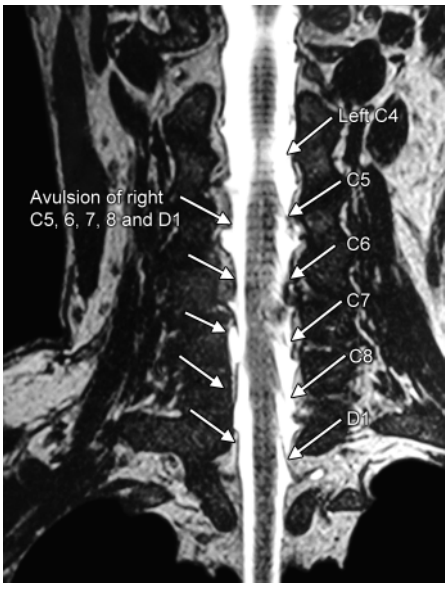


Fig. 9: MRI showing root avulsion on the right side

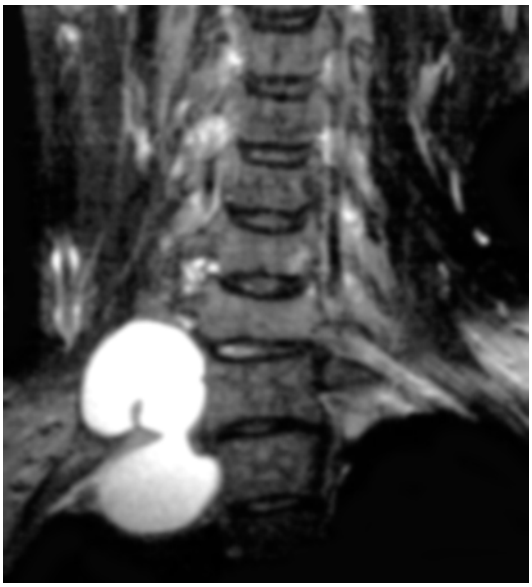


Fig. 10: Pseudomeningocoele C8, T1

Sensory Nerve Action Potentials

The cell bodies of the sensory axons are located in the dorsal root ganglion. When the lesion is proximal to the dorsal root ganglion, the peripheral sensory axons retain continuity with their cell bodies and do not undergo Wallerian degeneration. Therefore, demonstration of SNAP in nerves whose cutaneous territories are anaesthetic is evidence of a pre-ganglionic lesion.

SNAP can be elicited in the superficial radial (C6), median and ulnar nerves (C6, 7, 8). C5 cannot be studied, as it has no significant representation in these peripheral nerves. In this situation, histamine test of the axonal reflex may be useful in examining the C5 root. In a combined pre-ganglionic and post-ganglionic lesion, SNAP is not reliable.

Somatosensory Evoked Potentials

SSEP is essentially an intra-operative test to establish the continuity of the root with the cord and to the brain in cases of post-ganglionic lesions where the root stumps are seen in the region of the intervertebral foramen. In essence, absent SSEP means root avulsion.

In summary, all the investigations narrated above have their specific roles in coming to a conclusion. All of them have to be correlated with the clinical findings. Tinel's sign indicates a post-ganglionic lesion, but it cannot rule out root avulsion in another root. Operative exploration is imperative to establish the diagnosis and to decide on the further course of management.

MANAGEMENT

When to intervene surgically is the most debatable point. Whether we operate or not, from day one the following have to be ensured:

- Mobilise all the joints
- Splint the shoulder in abduction
- Electrical stimulation of the muscles to keep up the nutrition.

Electrical stimulation is advised in all patients even while they are at home. In the pre-operative period, all groups of muscles are targeted, whereas in the post-operative period, only the repaired nerves and their target muscles are stimulated. Stimulation of the repaired nerves and target muscles is done with a frequency of 2 Hz, pulse width of 200 microseconds and output current of 5–10 mA. This is done twice daily for 15 minutes per nerve muscle unit.

There are two schools which have divergent views. Nagano et al.[12] in a series of 50 cases came to the conclusion that all post-ganglionic lesions should be treated conservatively with the expectation of spontaneous recovery leaving behind ultimately some residual defects. In their study of these cases, they had 44% useful recovery in total paralysis, 38% recovery in upper plexus lesions and 18% did not show any recovery. After a period of 15–18 months, further reconstructions are advocated.

The other school, which forms the majority all over the world, is in favour of early exploration and nerve reconstruction. In early exploration, some are in favour of operating on day one or after 3–4 weeks; the period required for neuropraxia lesions to recover. Some wait for 3–4 months.

All agree that surgical intervention is necessary, if the lesions are pre-ganglionic. During the last 15 years, a policy has evolved from a conservative approach to a more aggressive approach. Nowadays, surgeons prefer to operate, if the patient has no signs of any recovery in 4–6 weeks time—the time for the neuropraxic lesion to recover. In direct injury to the plexus as in stab injury or gunshot injury early elective exploration is ideal.

Early exploration has many advantages. It is easy to dissect. Diagnosis of various lesions is made early. Before the muscles start wasting, one must pave the way for their re-innervation. Immediately after the accident, other major associated injuries take precedence. If the general condition is good, early exploration can be done.

If and when the patient shows signs of recovery, the patient is watched carefully over the coming weeks and months. Both in these cases and following nerve reconstruction, the limb is splinted in such a way that the muscles are not overstretched and at the same time permit mobilisation of all joints. When the improvement comes to a halt, the residual deficits have to be made good by suitable muscle and tendon reconstruction.

Surgical Exploration

The aim of exploration is to do a nerve reconstitution which may be by decompression, neurolysis, direct repair, nerve grafting, nerve crossing or direct neurotisation.

Techniques

The classical incision as shown in Figure 11 aims to expose the entire posterior triangle of the neck. If extension is needed, it is extended into the axilla and arm as shown. Tumescence solution is used to have a bloodless field. (Tumescence solution contains 500 ml of Ringer lactate with 1 vial of hylase with 20 ml of sodium bicarbonate and 1 ampoule of adrenaline without xylocaine).

After raising the skin and platysma as a flap, the fibro-fatty layer is reflected based laterally. This layer is incised along the sternomastoid and elevated by sharp dissection.

Once it is raised anteriorly, with dry gauze dissection, this fatty layer can be elevated as a superolateral based flap and this vascular layer can be placed on the scarred bed for the nerve grafting or crossing. Sometimes, one is amazed to see the severe scarring surrounding the plexus. In such instances, it is better to dissect the unaffected plexus distally or more proximally and proceed towards the scar. The scalenes form an important landmark as the plexus emerges in between them, but in some cases they too are badly scarred and the roots cannot be located. In such a situation, it is better to identify the phrenic nerve on the sclaneus anterior and start dissecting upwards. If the nerve is ensheathed in the scar, it has to be carefully neurolysed. On following this proximally, one reaches the C4 roots. The other method to identify C4 is to follow the supraclavicular sensory nerves. Once the C4 is identified, one can come down separating the scalenes, to locate the nerve roots. If the scalenus anterior is badly scarred, it has to be resected carefully avoiding injury to the phrenic nerve and the roots. The roots tend to bulge out after resection of the scarred muscles.

While dissecting C8 and T1, one should positively identify the subclavian artery and keep it out of the field of dissection. If the T1 is badly tethered, it is better not to continue but instead choose the other option of going down to locate its branches. When dissecting on the left side, one has to be careful about the thoracic duct. In case it is divided or damaged, the cut ends are identified and ligated with non-absorbable sutures.

Division of the clavicle is a debatable point. In an occasional case, where the scarring extends down to the cords and their branches, the clavicle may be divided. This increases the exposure and helps in dissection of the major vessels from the plexus. Division of the clavicle does not cause any morbidity or disability. Actually, in a case of a compression neuropathy following a fracture clavicle, the patient (Figs 12A to D) had a large callus pressing on the nerves causing progressive paralysis. Exploration and complete excision of the fracture clavicle and neurolysis resulted in complete recovery of all the nerves and he did not have any disability in movements of the upper limb due to removal of the whole clavicle.

Various possible scenarios might present themselves. There may be division, avulsion, traction or loss of segments of the various constituents of the plexus. As mentioned earlier, combination of a variety of lesions may exist. The aim is nerve reconstruction, which may be by direct repair, neurolysis, nerve grafting or nerve crossing.

Direct Nerve Repair

It is not indicated commonly. Only in sharp penetrating injuries it is possible, especially when the exploration is immediately after injury. It will be a rewarding experience as the recovery is good. Figures 13A to C show an example of direct repair done for a C 5–6 injury after excising the neuroma. But, even here, by the time the axons reach the hand, the muscles are wasted. When the gap is not suitable for direct repair, interfascicular nerve grafting is the procedure of choice.

Neurolysis

It is indicated in the presence of scarring involving the plexus. It is common in compression and traction lesions.

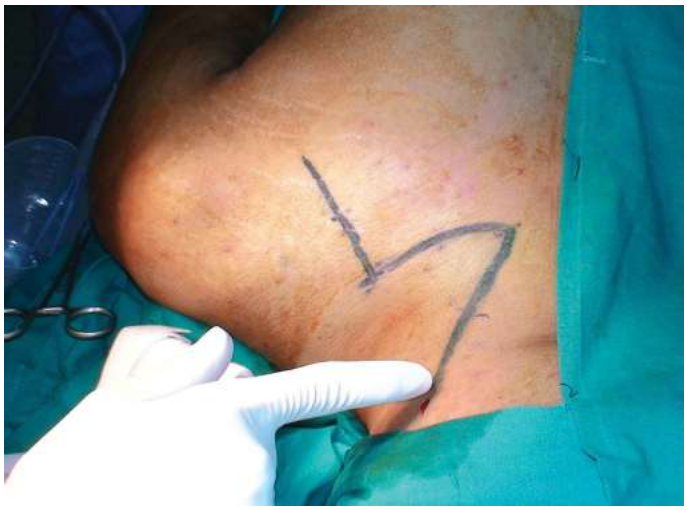


Fig. 11: Classical incision

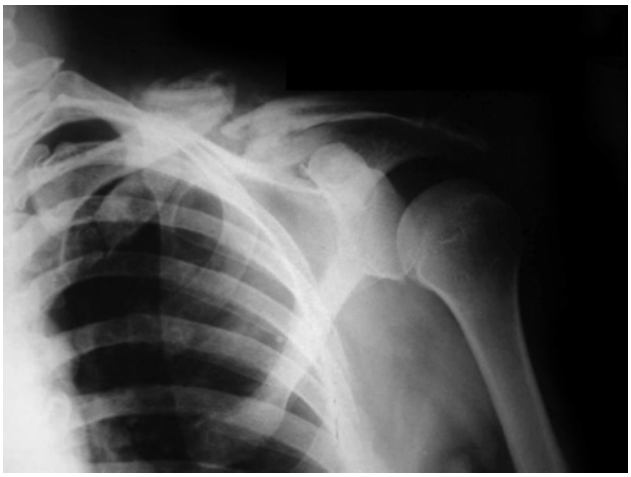


Fig. 12A: Fracture clavicle with a large callus pressing on the plexus

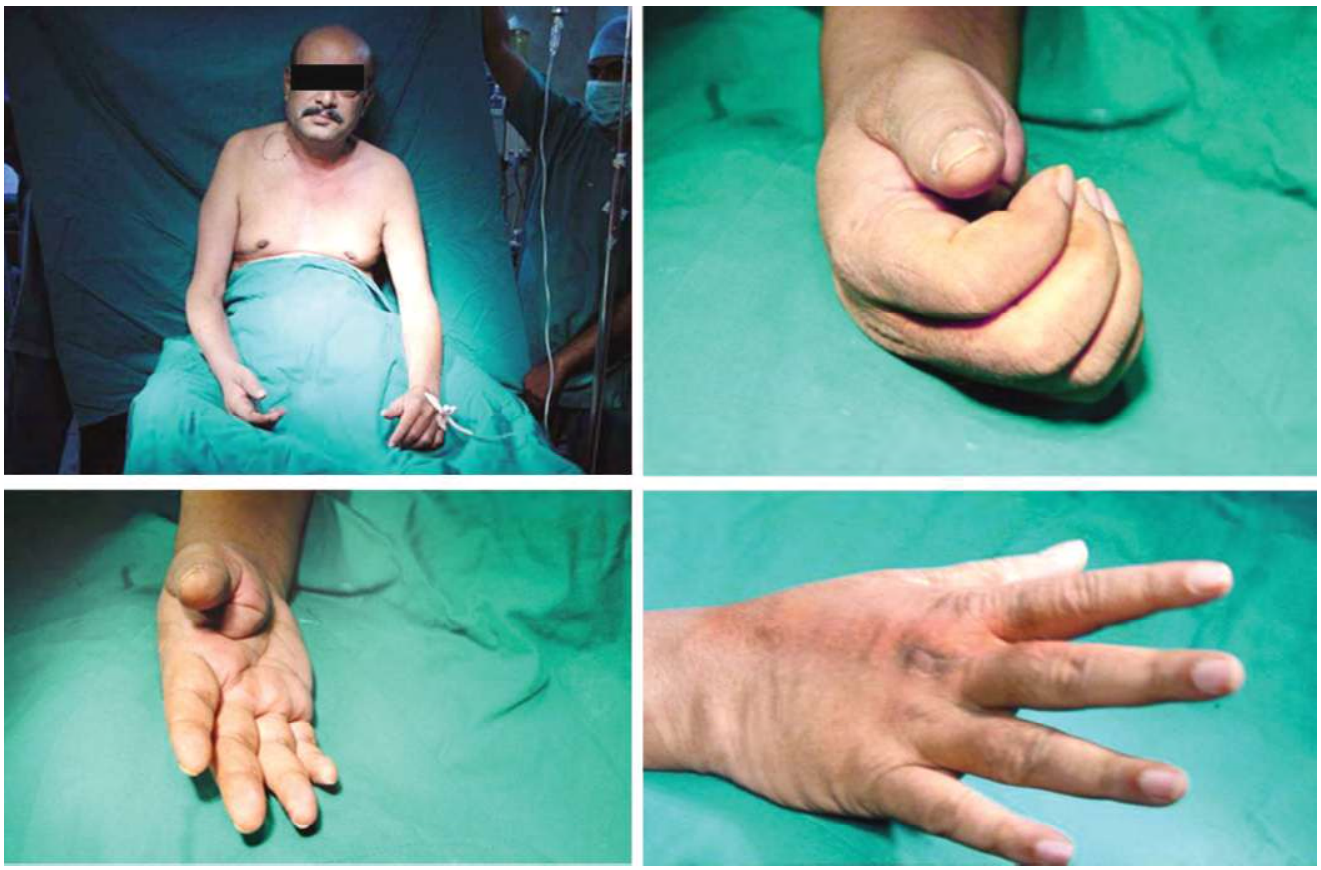
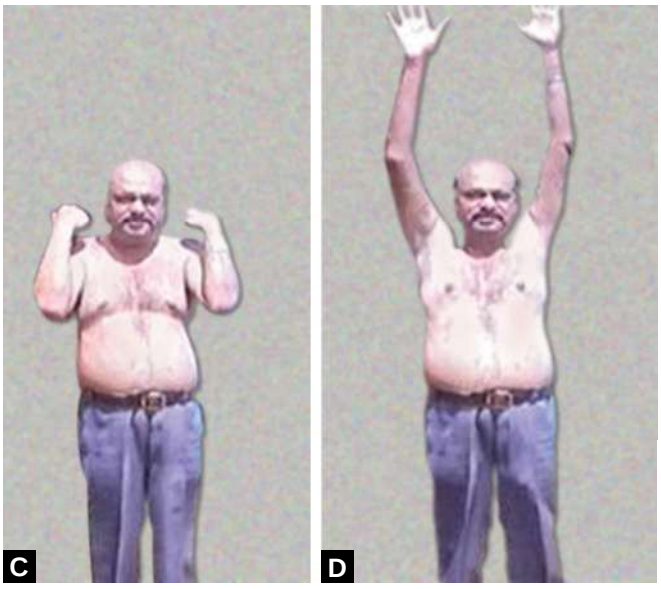


Fig. 12B: Upper plexus paralysis



Figs 12C and D: Complete recovery

This scarring is classified into three types.

Type A: Scarring outside the plexus
Type B: Interfascicular scarring
Type C: Scarring involving the perineurium and endoneurium.

Neurolysis is done under magnification. If the fascicular pattern is preserved, simple neurolysis will suffice (Fig. 14). Otherwise, resection of the affected segment and nerve grafting will be necessary.

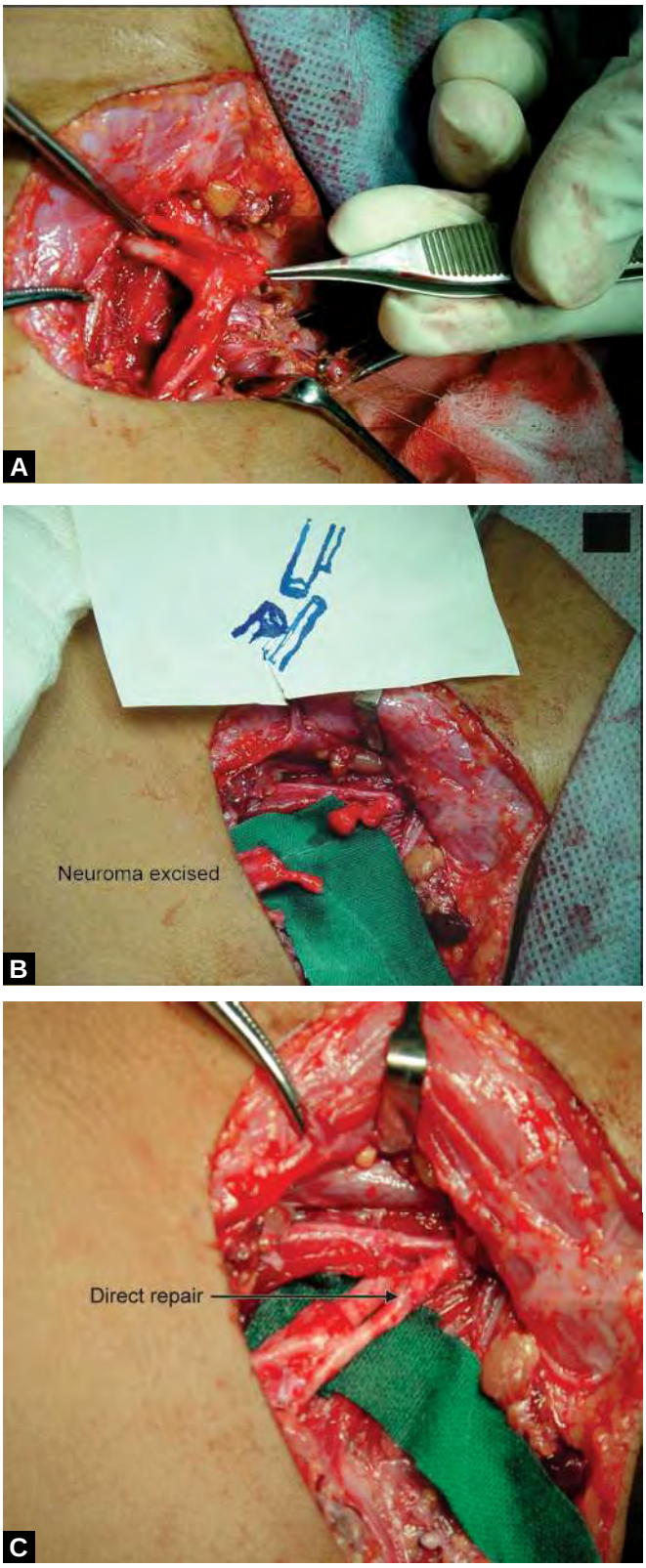
Nerve Grafting

In cases of post-ganglionic rupture and in 4th degree damage, it is essential to resect the scarred areas and connect the cut ends with a nerve graft. If the rupture is just outside the intervertebral foramina, one has to assess the viability of the proximal roots. Root cross-section should show the fascicles, and positive SSEP and muscle contraction on stimulation of proximal motor branches confirm the viability.

It is well known that shorter grafts give better results. When the gap is more than 7–8 cm, it is better to connect the roots to the selected individual nerves rather than to the main roots, trunks, divisions or the cords. This will obviate the wastage of axons to the important branches. This concept of targeting the individual nerves is gaining ground in several centres across the globe in severe traction and avulsion injuries.

As discussed earlier, restoration of shoulder and elbow functions are more important. Hence, the suprascapular nerve, axillary nerve and musculocutaneous nerve are connected to the appropriate roots with grafts. The median nerve can be connected for sensory re-innervation of the hand.

It is always better to spread the grafts, so that there is space between them. This will facilitate vascularisation. It is better to abduct the shoulder before laying the grafts so that there is no tension at the site of coaptation after surgery.



Figs 13A to C: (A and B) C5, 6 neuroma excised. (C) Primary repair

The vascular fatty layer elevated during exposure is useful for giving a scar free bed to the graft. It provides both vascular supply and a good bed for the nerves to glide.

In penetrating injuries, one should anticipate injury to nearby major vessels.

A young man (Figs 15A to D) had a penetrating injury dividing the C5 and C6. He came 10 days after the injury and exploration was undertaken. There was a haematoma under the fat—fascial flap. When this was sucked out, there was a gush of fresh blood from behind the clavicle. There was a rent in the subclavian vein junction with the internal jugular. This had to be repaired. The 10-day interval made it impossible for a direct repair and nerve grafting had to be done.

Nerve Crossing

In pre-ganglionic and in severe post-ganglionic root avulsions where the proximal nerve is not available, the only option is to neurotise the distal nerves. It is not possible to get donor nerves to neurotise the entire brachial plexus if there is total avulsion. The aim should be to restore shoulder, elbow and hand functions by neurotising the suprascapular, axillary, musculocutaneous, nerve to triceps and median nerve, utilising nearby healthy nerves. The motor branches of the deep cervical plexus (C4) have a good number of myelinated fibres. The branches to the levator and rhomboid can also be used.

There are several donor nerves available. It is better to have nerves that have more number of myelinated fibres. The spinal accessory, phrenic, muscular branch of C4, ipsilateral C7 and intercostals are the commonly used donor nerves. If the nerve can be transferred directly without a graft in between, two suture lines can be avoided and the results are better.

Once it is ascertained that the nerve lesion is severe and spontaneous recovery is next to impossible, one must decide quickly to restore nerve continuity, because nerve regeneration is a race against time. Every nerve repair is a nerve crossing, unless otherwise proved. Only the connective tissue can be joined and the growing axons have to find their own way. Predictable good results can be achieved by nerve crossing, wherever possible, in nerve reconstruction. Nerve crossing is like nerve rerouting or nerve bypass. Nerves destined to do certain functions are diverted to do some other function. This is not a new concept, way back in 1913 itself, Tuttle[17] has done multiple nerve crossings both intraplexal and extraplexal.

Shoulder stability and abduction is essential to provide greater range of motion for the arm and forearm. Shoulder abduction is a very complex mechanism, requiring synchronous movements of the scapula and humerus. There are several muscles involved. The scapula thoracic group to move the scapula forward, the depressors to keep the humeral head in the glenoid and finally the abductors to abduct. It is impossible to get them all back. In practice, the supraspinatus and deltoid can achieve 80–150 degrees of abduction. Next is elbow function; the biceps to flex and the triceps to extend. Finally, the hand function will recover.

One has to follow certain rules in nerve crossing. First and foremost is the timing of surgery. When can

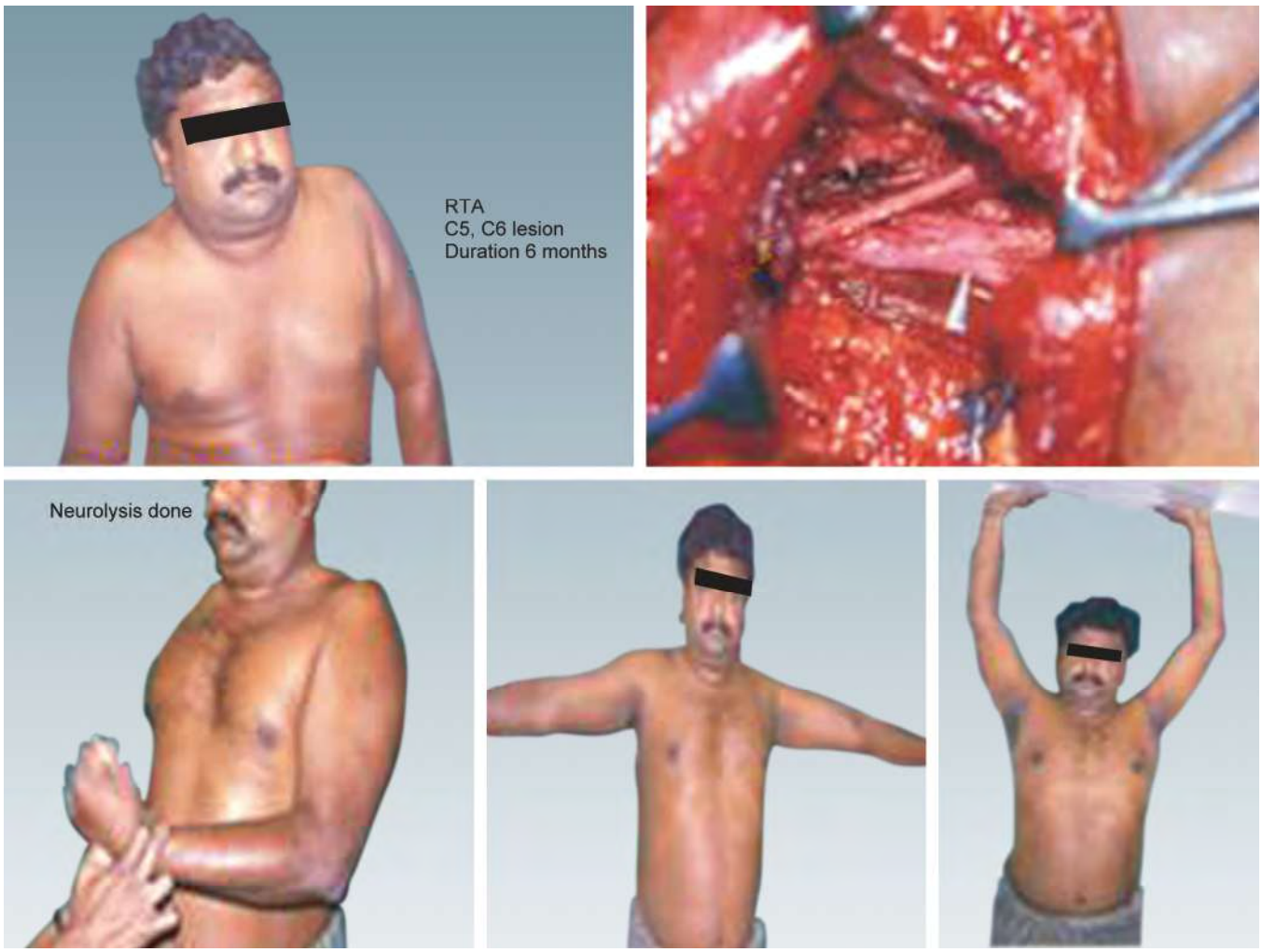


Fig. 14: C5, 6 palsy—after neurolysis complete recovery

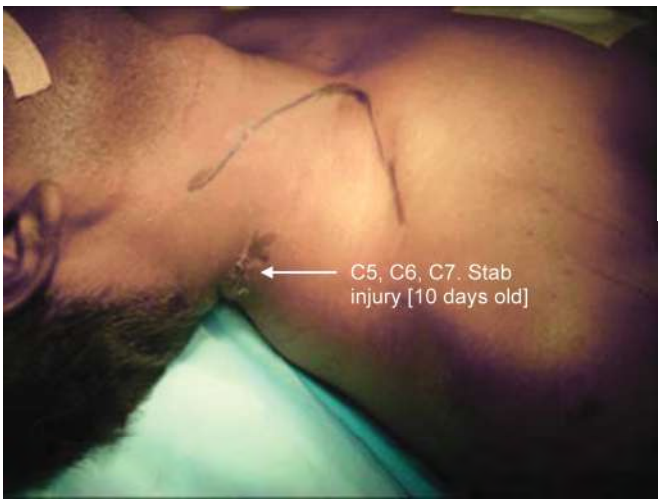


Fig. 15A: 10 days old stab injury with C5, C6, C7 palsy

you do this? How far you can stretch the time limit? It is well known the earlier it is done the better, but sometimes the patient comes after about 6–8 months resulting in a dilemma, whether to do a nerve reconstruction or not. If the nerve has to grow only 4–6 cm, then nerve reconstruction can be done even after 1 year.

The ideal donor nerve must have synergistic function, it must be from a nearby cortical representation and it must have adequate quantity of neurons. It is better to avoid nerves like the phrenic, intercostals and the hypoglossal. Finally, it must be dispensable either partially or totally. Shoulder elevation is synergistic with shoulder abduction. So, one can use nerves supplying shoulder elevation for shoulder abductors.

One of the most important factors for success in nerve crossing is the neuronal quantum. It must have adequate axons to achieve good functions. The density of the axons of each nerve has been worked out and it is mandatory that at least 30% of axonal density is recruited to achieve good results.

The neuronal density of some of the common donor nerves:

Spinal accessory – 1700,
Phrenic – 800,
Intercostal – 1300,
C4 – motor branches (4) – 3400 – 4000,
C7 – 16,000 – 40,000.

Nerve crossing is always better, if it is done more peripherally, because the recovery can be quick. Sensory motor mismatching can be avoided, co-contractions can

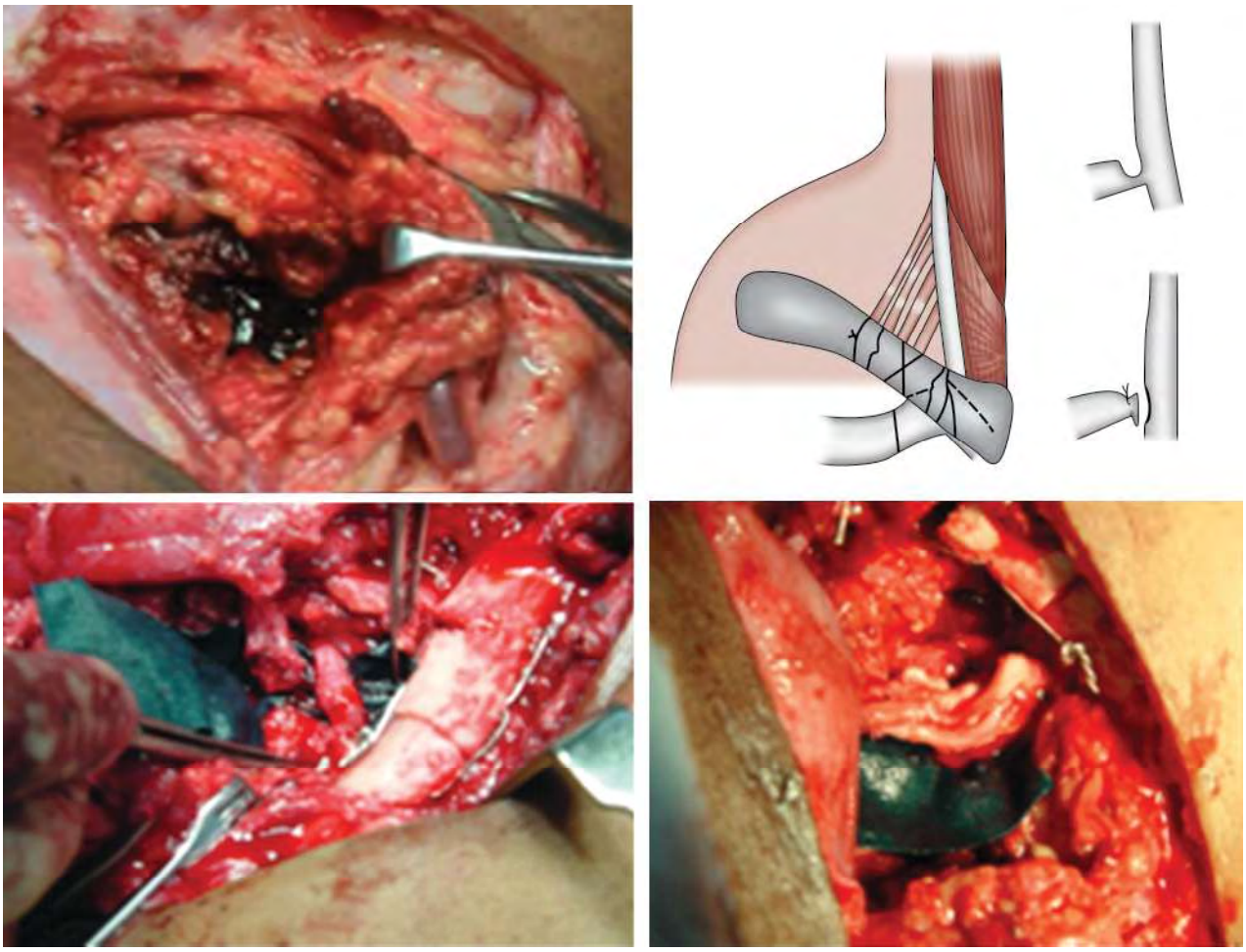
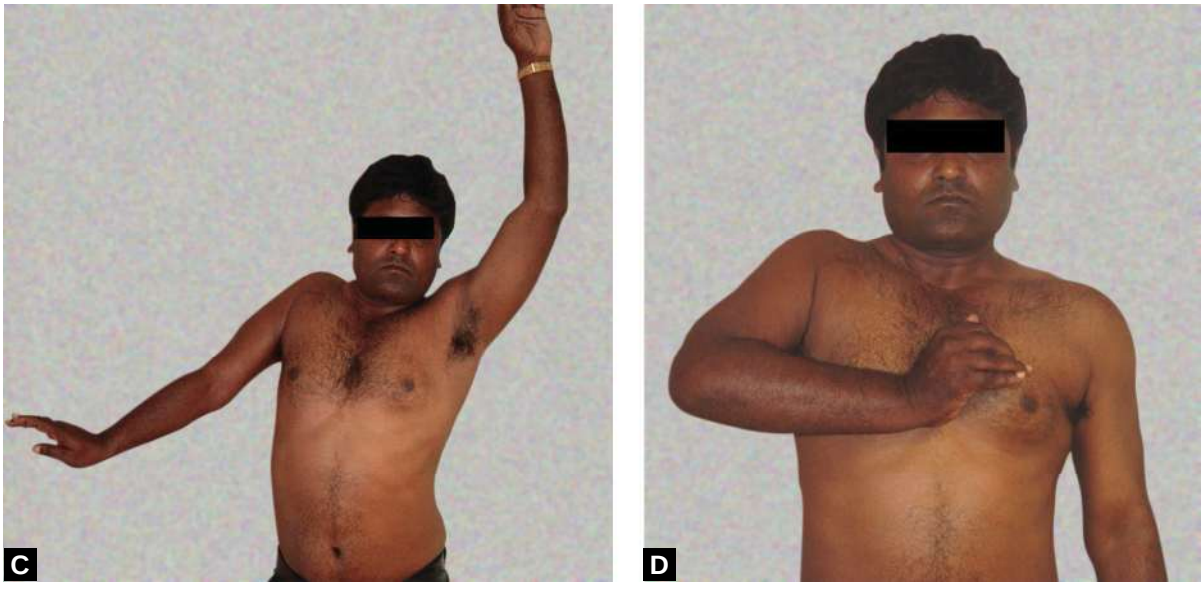


Fig. 15B: On exploration after haematoma evacuation a rent in the subclavian-jugular junction, repaired and nerve grafting done



Figs 15C and D: One year follow-up. (C) Shoulder. (D) Elbow recovering

be avoided and double level lesions can be skipped which are common in the suprascapular and axillary nerves.

Ideal recipient nerves are pure motor nerves like the suprascapular, nerve to biceps, nerve to brachialis, nerves to triceps, anterior and posterior interosseus nerves and the axillary nerve, where the sensory branch can be isolated and left behind. These nerves are dissected close to the hilum. They must supply a single muscle, but if they supply multiple muscles, all of them must have a synergistic function. Nerve crossing can be done for sensory nerves also.

Spinal accessory to suprascapular: The spinal accessory nerve supplies the trapezius and this is synergistic with the shoulder abductors and, being in the same territory, it is easy to dissect and transfer without the need for a nerve graft. Since both are pure motor nerves having a similar density of axons, the results are predictable (Fig. 16).

The spinal accessory can be located one finger breadth above the emergence point of the great auricular nerve. Stimulation of the nerve confirms it. This is dissected and followed to the trapezius. The branches to the sternomastoid and the first branch to the trapezius can be spared and the remaining two terminal branches can be taken and divided. These are taken to the suprascapular nerve. The great advantage of the spinal accessory is that it is a pure motor nerve and all its fibres are useful in re-innervating the motor end plates. Since its function is related to shoulder elevation, rehabilitation after transfer to the suprascapular is easy. The nerve can be identified lower down also. It lies just one finger breadth below the anterior border of the trapezius.

The suprascapular nerve is found regularly along the upper margin of the upper trunk and this is the first branch of the upper trunk. Unless shifted downwards, it is usually located in the supraclavicular fossa.

Intact ulnar nerve as donor: The next commonly done nerve transfers for elbow flexion are Oberlin 1 and 2 procedures. Oberlin 1 procedure was suggested by Christophe Oberlin[14] in 1994. In Oberlin 1 (Fig. 17), one fascicle is dissected from the ulnar nerve and sutured to the motor branch to the biceps. It is a simple, safe procedure which leads to recovery in a high percentage—M3 in 6 months. If the power of elbow flexion has to be increased, the brachialis also has to be neurotised and this can be achieved by taking one fascicle from the intact median nerve to the brachialis and this is called Oberlin 2 procedure[10,13] (Fig. 18).

Triceps nerve branches to axillary nerve: Motor branches supplying either the long head or the lateral head of triceps can be transferred to the entire axillary nerve[1] or only to the anterior branch of the deltoid[9] (Fig. 19) and the results are very promising (Fig. 20 and Figs 21A to C). If the C7 is also paralysed another donor nerve, either the phrenic, intercostals or C4 motor branches have to be used to neurotise the axillary nerve.

Intercostal nerves: Ever since Yeomen and Seddon[19] used these nerves for neurotisation, intercostal nerves were used to neurotise the axillary, musculocutaneous,

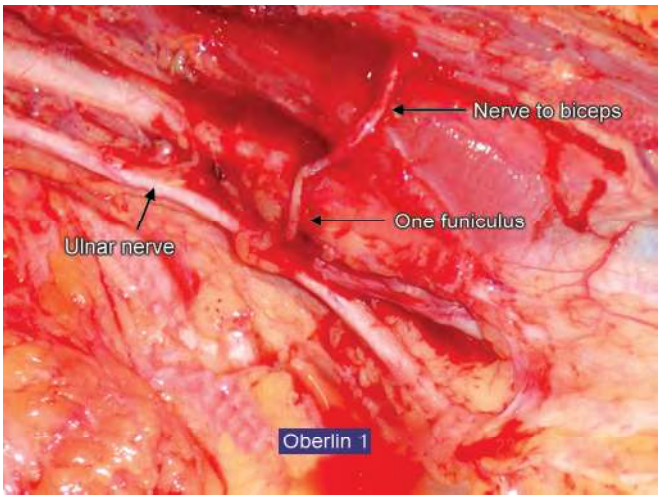


Fig. 17: Oberlin 1 procedure

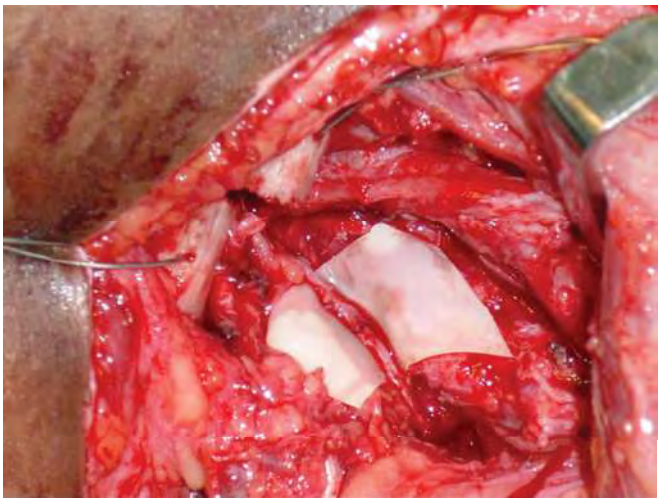


Fig. 16: Spinal accessory to suprascapular transfer

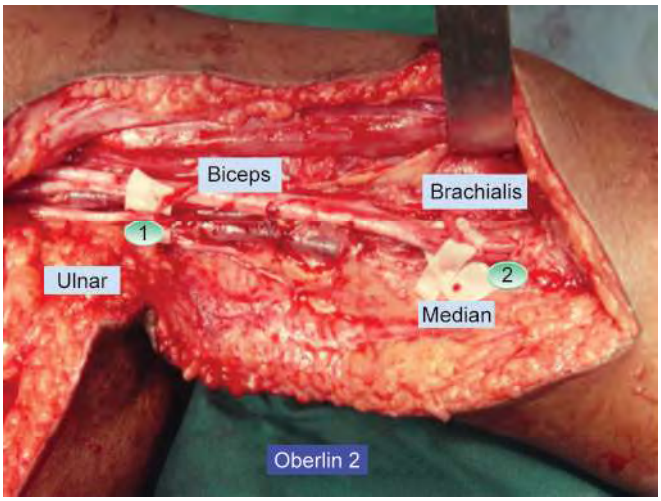


Fig. 18: Oberlin 2 procedure

median and radial nerves (Fig. 22). They are mainly used for restoration of elbow function by the majority of surgeons and for neurotising the free muscle transfer. The 3rd, 4th and 5th intercostals are commonly used. Up to five nerves can be used without problems.

Meticulous technique has to be used to dissect the intercostal nerves. The periosteum is stripped off the rib from the posterior axillary line to the nipple region. The rib is lifted up and the central motor branch is identified by incising the periosteum and hooked with a curved artery forceps or a hook. The nerve is then lifted and dissected both medially and laterally, as far as possible, collecting all the motor branches. On proceeding laterally, one can locate the sensory branch which passes inferiorly and laterally. This is also developed to the same length as the central motor branch. All the three intercostal nerves can be coapted together and anastomosed to the musculocutaneous nerve. One way of preventing axonal wastage is to separate the muscular branch of the musculocutaneous nerve near its entry into the muscle and anastamosing it to the intercostal nerves. This may need a sural graft.

Another technique adapted by Chang et al.[3] is to dissect the musculocutaneous nerve up to its origin from the posterior cord and turning it down to reach the

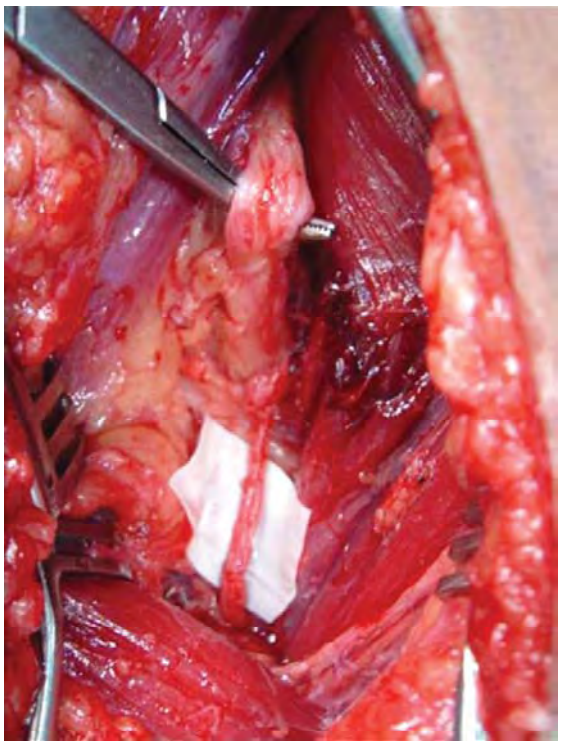


Fig. 19: Triceps branches from radial nerve transferred to anterior branch of axillary nerve

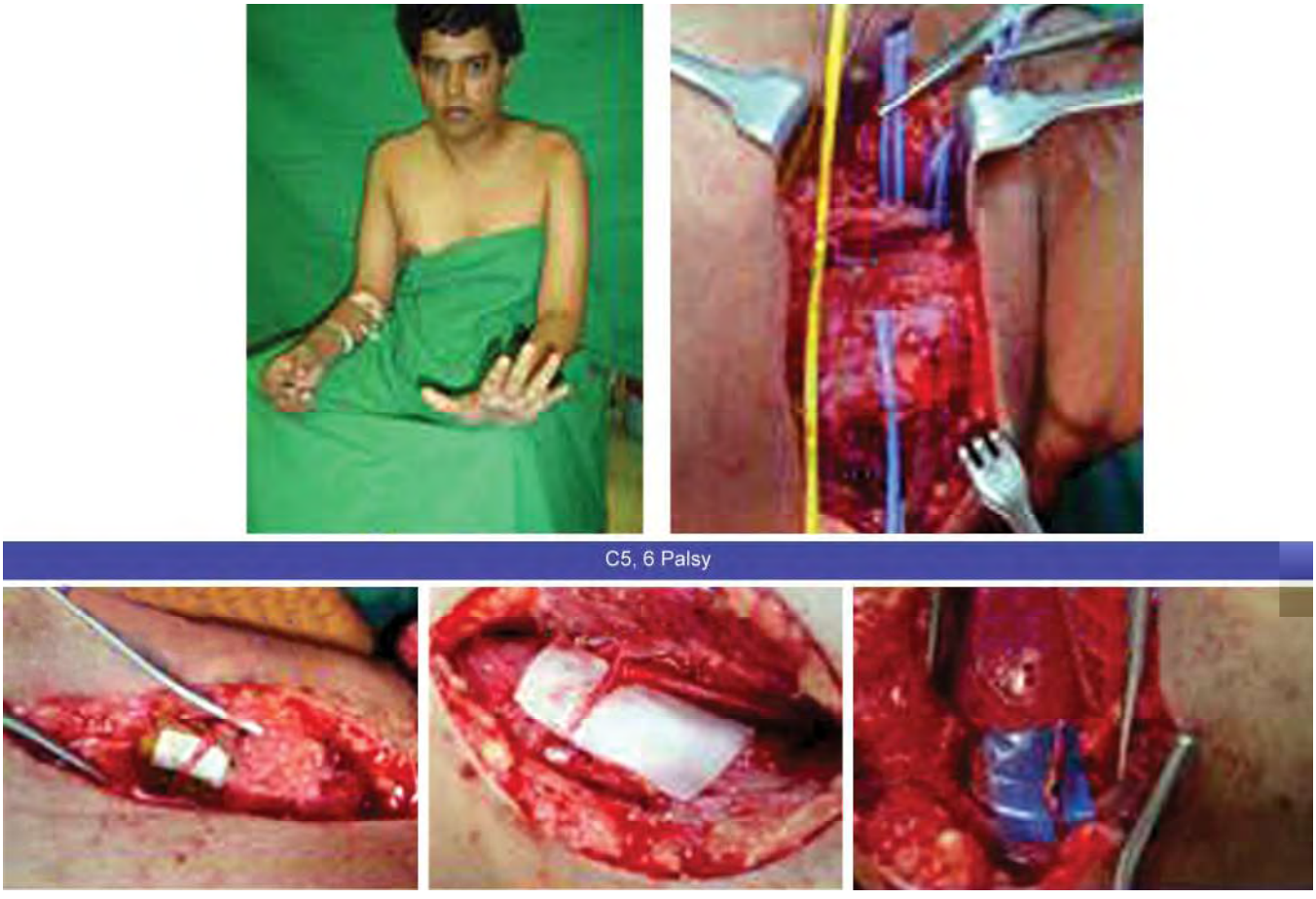
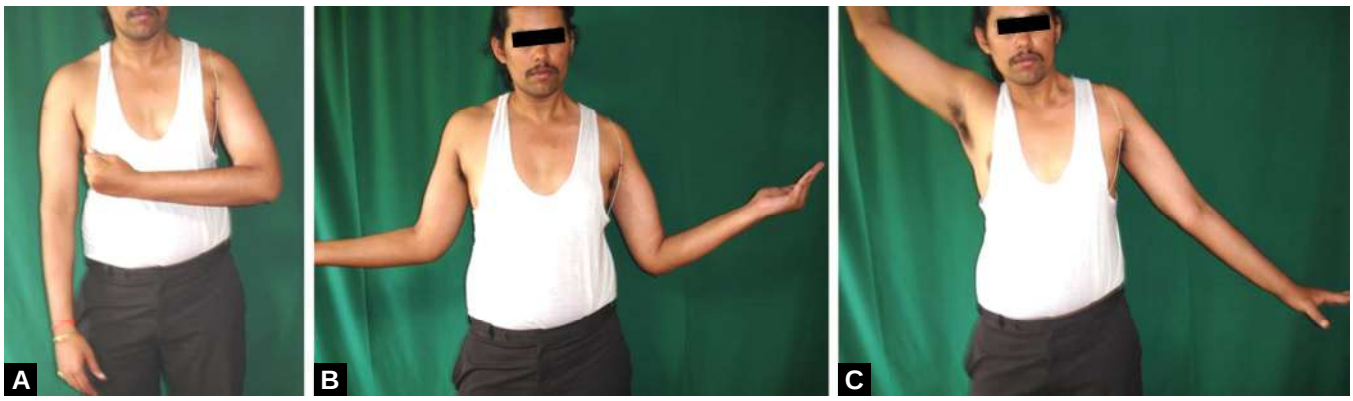


Fig. 20: A case of C5, 6 palsy – after neurolysis nerve crossing done; 1- Spinal accessory → Suprascapular 2- Oberlin 1 procedure, 3- Somsak's procedure



Figs 21A to C: Result after 1½ years showing. (A) M4 elbow flexion. (B) Good external rotation. (C) 70°–80° of shoulder abduction

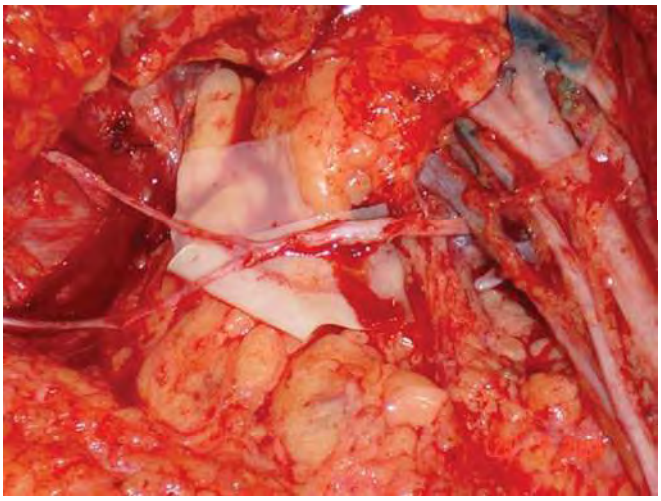


Fig. 22: 3rd and 4th intercostal nerves transferred to axillary nerve

interocostals without an interpositional graft. They have found the motor fibres mainly concentrated in the middle third of the musculocutaneous nerve. The upper pole has mainly the sensory nerves and the lower has a mixture of motor fibres meant for the brachialis and sensory fibres. The cut surface of the musculocutaneous nerve is monofascicular but it can be separated into three parts. By coapting the central motor branches of the intercostals to the central area, one can achieve maximum use of motor fibres. The sensory branches are anastomosed to the upper and lower poles. Biceps neurotisation with the intercostals leads to consistently good results.

It is generally observed that EMG changes of reinnervation in the biceps, following intercostal neurotisation, appear 4–8 months after surgery. Clinically, muscle contraction appears with deep inspiration. Patients learn to flex the elbow with respiration. It takes 1–1½ years for them to flex the elbow without relating to the respiratory rhythm, but EMG changes persist with respiration for nearly 2–2½ years before they disappear finally. Similarly, sensation returns in the musculocutaneous nerve area, but there is cortical misrepresentation. In some reported series, it takes 6 years to disappear. The intercostals can be used for neurotising the triceps and axillary also.

Phrenic nerve: The phrenic nerve is the other possible donor nerve. It is easily identified over the surface of the scalenus anterior. It is not advisable to use this nerve in children, as the diaphragm is not fixed to the vertebral bodies unlike in adults. If it is sacrificed in infants, the diaphragm will elevate and occupy half the hemithorax causing severe respiratory distress. In adults it rarely causes any problem. Some may develop mild dyspnoea on the 1st day. The phrenic nerve is dissected down to the level of the jugular fossa and shifted to the axillary nerve. Endoscopic harvest[18] of the intrathoracic portion of the phrenic nerve also has been reported in order to avoid a nerve graft.

Direct Neurotisation[8]

Re-innervation of the denervated muscle can be done by implanting into it a new nerve or grafts connected with the proximal stump of the proper nerve and divided into several artificial branches.

When new nerve fibres are inserted into a denervated muscle, they are accepted and form a new motor end plate. These motor end plates are two or three times bigger than normal as has been proved by electron microscopy and EMG study. It has been postulated that a regenerated axon is probably able to adopt muscle fibres belonging to three or four non-regenerated axons.

The proximal nerve should be healthy and if it does not reach the muscle it can be extended by a graft. The distal end of the graft is divided into as many slips as possible. A normal looking area in the denervated muscle is chosen and nerve slips are buried into that as atraumatically as possible. Bleeding is avoided, to limit the scarring. The epineurium is sutured to the muscle fascia with 6 '0' and 8 '0' ethilon. The anastomosis has to be protected by immobilisation for at least 3 weeks (Fig. 23).

Contralateral C7:[7] As discussed earlier, the C7 can be transected without much noticeable deficiency. Several series from China, Taiwan and Thailand have reported using the contralateral C7 (C-C7). The entire C7 can be used or its anterior or posterior division. Since the anterior division has more sensory fibres it is co-opted to the median nerve. The posterior division has more motor fibres and, hence, it is used to neurotise the radial nerve. As mentioned earlier, there is no significant damage to the donor side. Even this can be prevented by selective transection.

The vascularised ulnar graft:[16] The vascularised ulnar nerve graft can be taken as a pedicled nerve graft based on the superior ulnar collateral vessels and the nerve can be flipped to reach the same side neck or the C-C7 (Fig. 24). In case the superior ulnar collateral vessel is damaged, then one has to harvest the vascularised ulnar nerve graft as a free flap based on the ulnar artery and transferred as a free tissue transfer. The distal end of the ulnar nerve is divided at the wrist level and dissected proximally with the ulnar artery and its veins. The dissection is continued up to the origin of the ulnar nerve from the medial cord and divided. The vascularised nerve is tunneled under the skin to the C-C7 and anastomosed to the main trunk. The ulnar vessels are anastomosed to the transverse cervical vessels. In the opinion of the authors, the results are better where the ulnar vessels are revascularised. Here again, the spinal accessory is transferred to the suprascapular and the

Fig. 23: A case of radial nerve palsy, distal nerve ends could not be identified. Nerve grafts buried into extensor muscle mass. Good recovery after 1 year

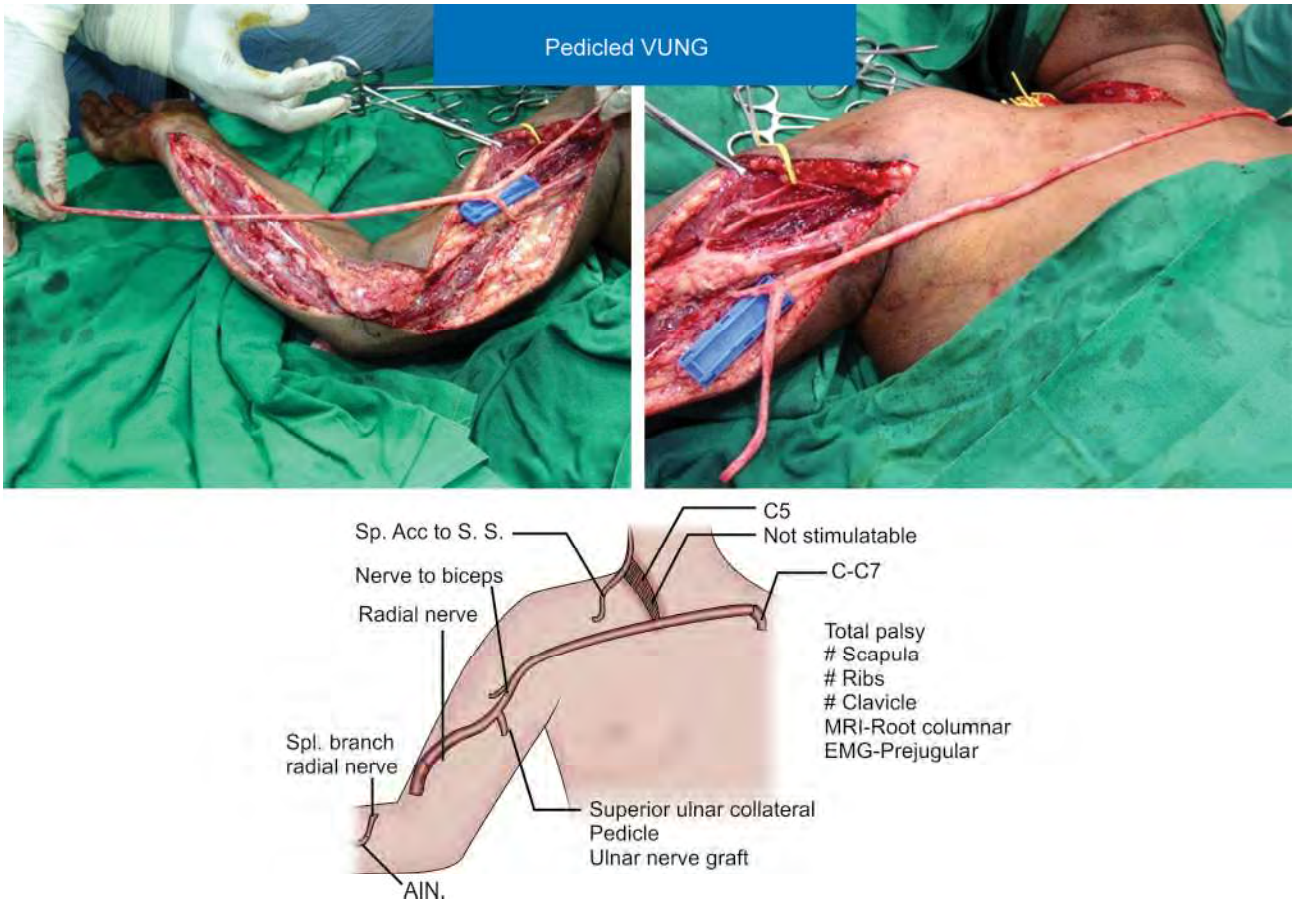


Fig. 24: Vascularised ulnar nerve graft: operative pictures and diagrammatic respresentation

remaining recipient nerves namely, the axillary, nerve to biceps and anterior and posterior interosseus nerves are connected sequentially (Figs 25A to C). The authors have done seven cases of vascularised ulnar nerve graft and seen good shoulder stability, elbow flexion and later on a flicker of flexion in the fingers. Some do it in two stages. In the first stage the distal end of the ulnar nerve is anastomosed to C7. After the appearance of Tinel's sign in the axilla (usually within 10 months), the proximal end of the ulnar nerve is divided for neurotising the nerves or for neurotising the free vascularised muscle that is transferred. Too long a delay between the two stages gives rise to poor results.

FUNCTIONAL FREE MUSCLE TRANSFER

Doi Procedures[4,5]

The original technique of double functional muscle transfer consisted of five established reconstructive procedures done in two stages. This technique yielded the most reliable prehensile function after irreparable injuries according to Doi.

First Stage

1. Surgical exploration of the brachial plexus, intraoperative diagnosis using electrophysiologic testing and repair of the disrupted cervical roots when possible.
2. The first "first functional muscle transfer" (FFMT) supplied by the spinal accessory nerve transfer to restore elbow flexion and finger extension.

Second Stage

3. The second FFMT supplied by the fifth and sixth intercostal nerves to restore finger flexion.
4. Transfer of the third and fourth intercostal nerves to the motor branch of the triceps brachii muscle (done concomitantly with the second FFMT) to restore elbow extension.
5. Transfer of the supraclavicular sensory nerves or the intercostal sensory rami to the median nerve or the ulnar nerve component of the medial cord of the brachial plexus (done concomitantly with the second FFMT), to restore hand sensibility.

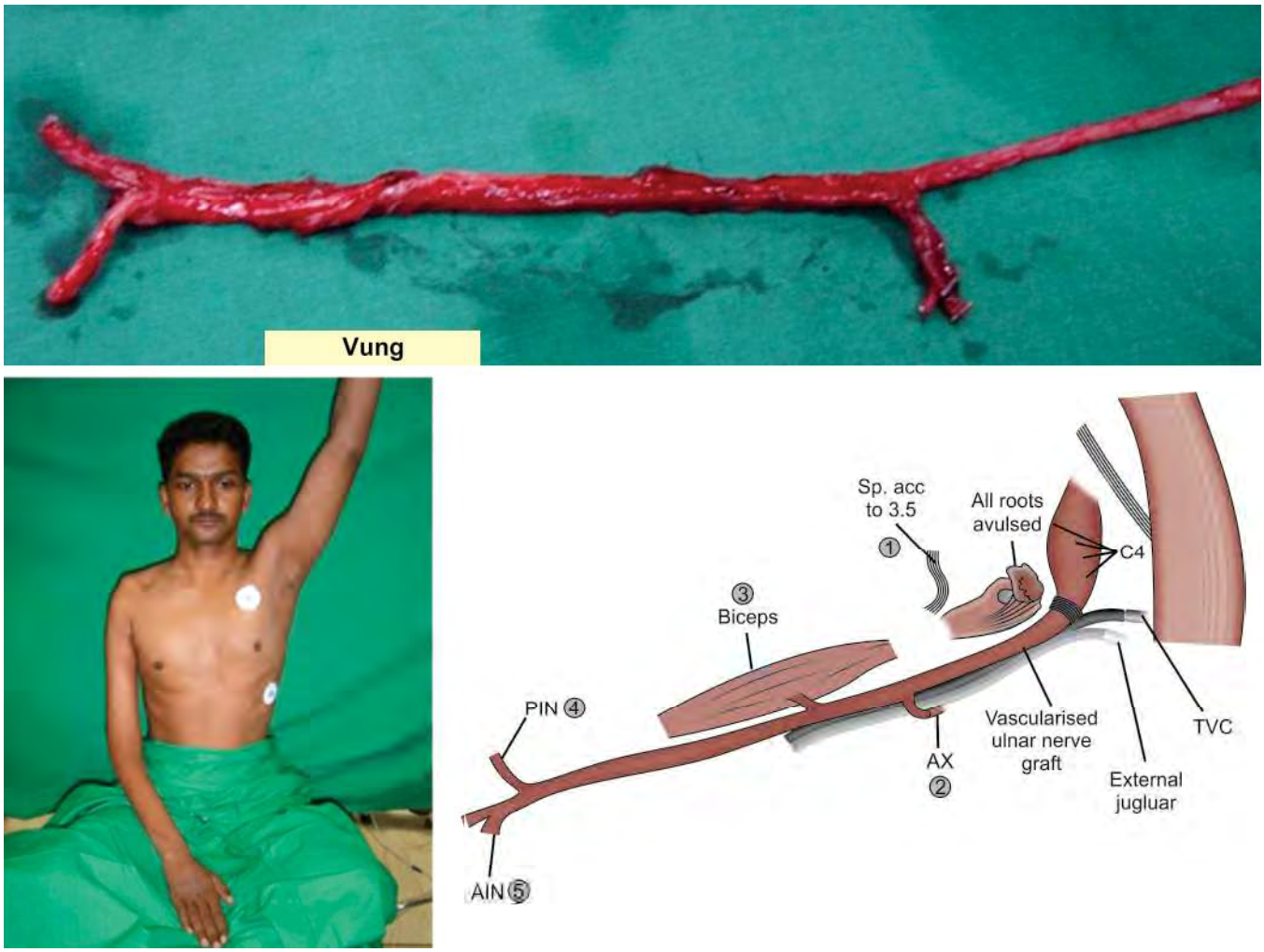


Fig. 25A: Intraoperative picture of Vung, pre-operative of a patient who underwent Vung and diagrammatic representation of the branches in Vung

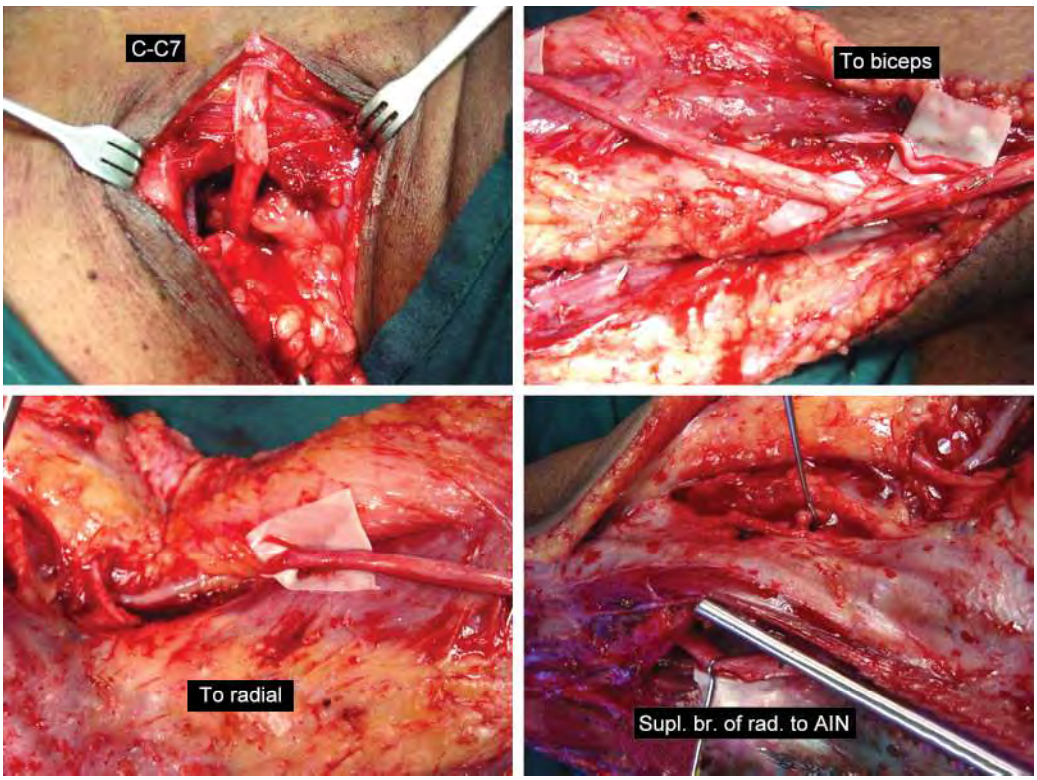
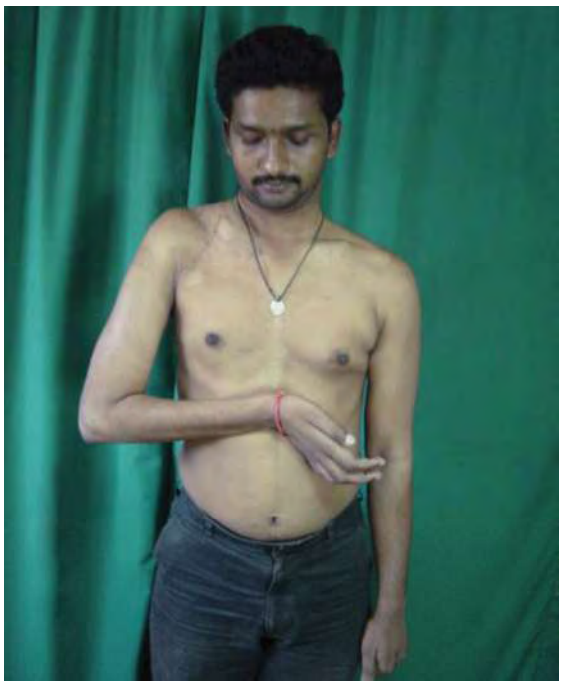


Fig. 25B: Intraoperative pictures of vascularised ulnar nerve graft surgery



Figs 25A and B: Post-operative picture of the patient who underwent Vung showing good shoulder stability and biceps motor power (M3)

The gracilis muscle is the choice for free muscle transfer. Two of them are transferred in two stages. The first transfer is for flexion of the fingers. The gracilis is anchored to the 2nd and 3rd ribs. The donor vessels are the thoracodorsal and the 4th and 5th intercostals for innervation of the muscle. The muscle is routed to the forearm by taking it along the medial side of the arm and forearm to the flexor digitorum sublimis tendons. It is taken underneath the pronator teres which acts as a pulley and sutured to the flexor digitorum profundus tendons. At the same time the 2nd and 3rd intercostals are sutured to the nerve to triceps to get elbow extension. The stability of the elbow in extension is very essential for finger flexion and extension. Hence, the functioning of the triceps should be ensured by intercostals neurotisation.

The second muscle should be transferred after 6 months for finger extension. It is attached to the coracoid process and taken along the anterolateral aspect of the arm and under the brachioradialis at the elbow, which acts as a pulley and attached to the common extensors. The vessels are the pectoral vessels as donors and the spinal accessory to neurotise the muscle.

The literature claims a range of 40–110 degrees finger flexion with power ranging from M2 to M5. The clawing is overcome by splinting or by correction by static procedures like Zancolli's. The wrist can be stabilised by arthrodesis.

In summing up, as it stands today, the prognosis of brachial plexus injuries is good as far as the restoration of shoulder and elbow function. The restoration of hand function in total palsy or lower plexus palsy is not possible following primary reconstruction, as the hand muscles degenerate by the time the growing nerves reach their destination. As an alternative, free functional

muscle transfer is available for restoration of hand function.

OBSTETRICAL BRACHIAL PLEXUS PALSY

For a long time, these were being treated conservatively. This resulted in severe disabilities and deformities. With growing interest, the modalities of treatment have been crystallised. If there are no signs of recovery of deltoid and biceps by the 2nd month, the prognosis is poor and so, surgical intervention is favoured for the following indications:

Biceps power Mo after 3 months

Insufficient recovery of extensors of elbow, wrist and fingers.

Once exploration is undertaken, the nerve and muscle reconstruction are similar to adults (Figs 26A and B). Phrenic nerve crossing is to be avoided in children for the fear of respiratory compromise.

PROGNOSIS

The collective opinion based on the experience of the last few decades is that there are clear prognostic pointers as shown here. Early exploration in younger age group gives better results. So also early recovery signs point to ultimate better results.

FUTURE

The greatest breakthrough in this field is the attempt to re-attach the avulsed root to the spinal cord. Animal and human experiments have yielded encouraging results. Carlstedt[2] is the pioneer in clinical replantation of avulsed nerves. He published two cases in 1995. The unsolved problems and surgical difficulties are many. It is expected that these will be solved one day and this will become a routine procedure.

The major challenge in any peripheral nerve surgery is to make the growing axons in their full quantum to reach their original destination, crossing the suture lines without getting arrested. In the meantime muscle nutrition should be kept going without wasting of muscle fibres and disappearance of motor end plates. Today there are many questions unanswered. Why some cases show recovery even after 1–1½ years of injury? Why a recovering muscle does not gain more power beyond a

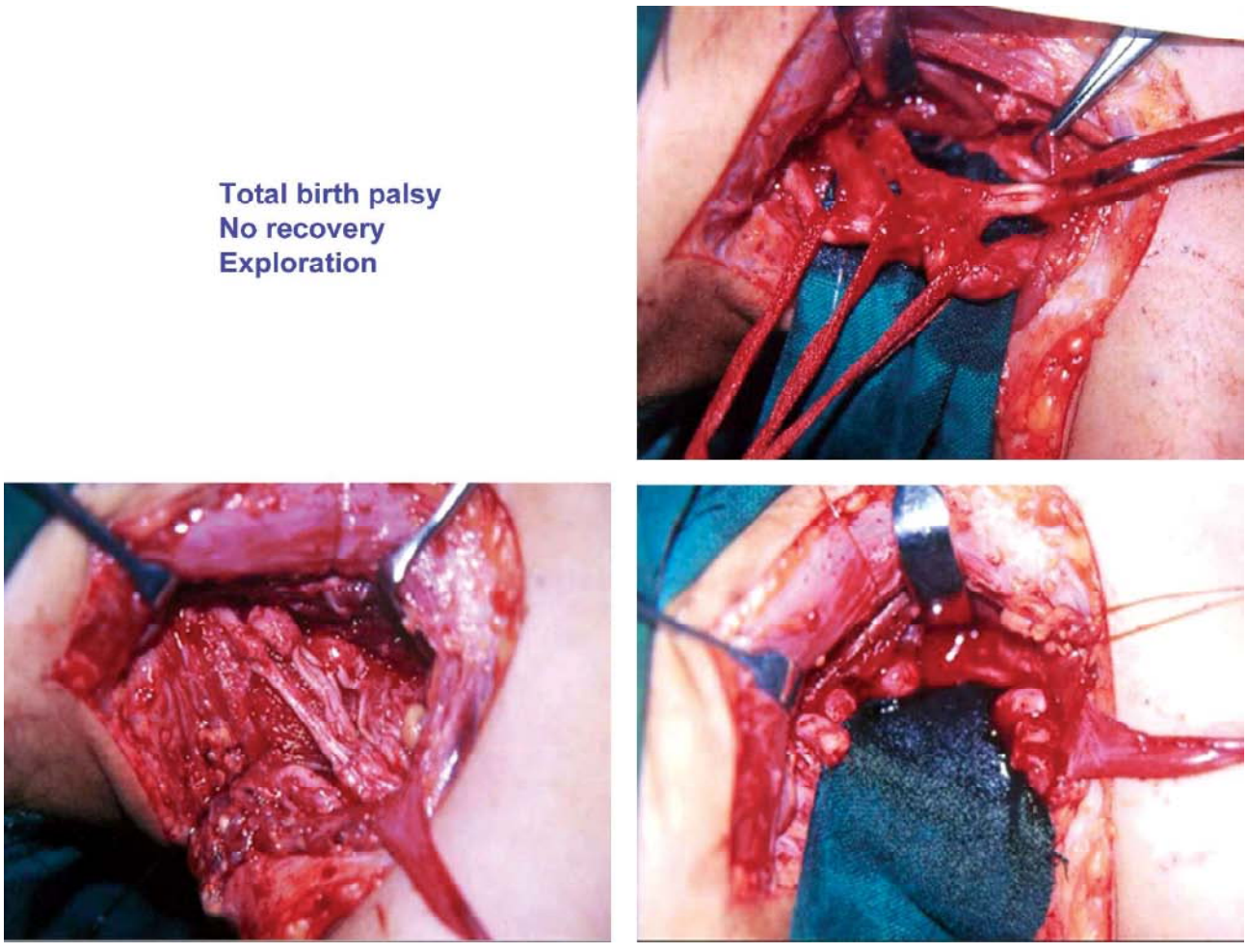


Fig. 26A: A young boy, 2 years of age, with no biceps function had his brachial plexus explored and was found to have a post-ganglionic injury. (A) The scar was resected and nerve grafting done

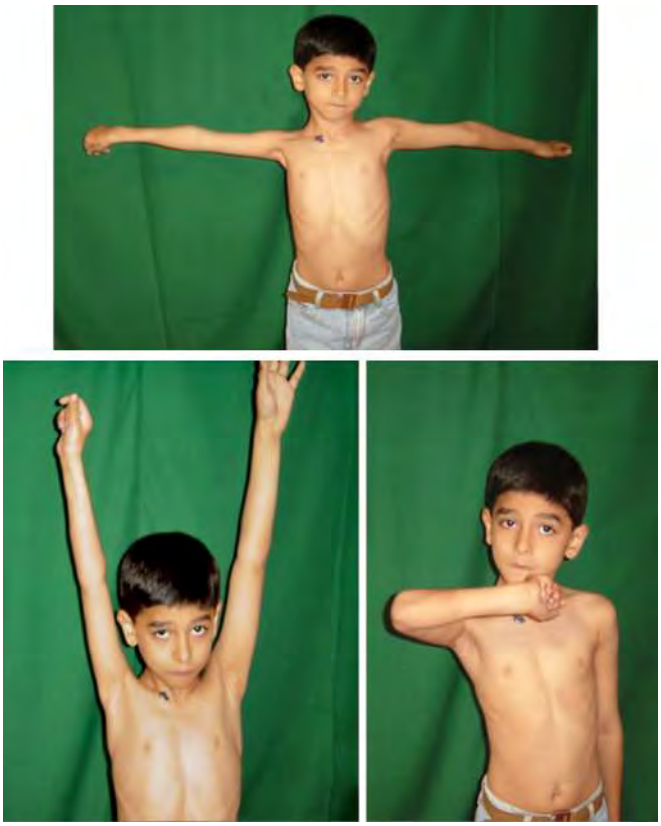


Fig. 26B: Six years post-operative good recovery of shoulder and elbow, but only partial recovery of the hand

point, in spite of best techniques of microneural repair? How to pin point the diagnosis pre-operatively with all the investigations at our command? Future research should directed towards answering these questions.

In countries like India, this problem should be taken up as a national problem to obviate and ameliorate the disastrous consequences of this palsy, affecting the most productive age group of the country.

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58 Management of Injuries to Specific Peripheral Nerve

Gupta A, Ahmad FU, VS Mehta

GENERAL CONSIDERATIONS

Introduction

Neurosurgeons often encounter patients who suffer from peripheral nerve injuries, either in isolation or with other vascular or systemic injuries. A thorough understanding of the anatomy of the nerves, physiology of nerve repair and pathology helps in deciding the need for surgery, timing of surgery and the correct procedure to be adopted. Proper management of these injuries is vital to regain maximum possible function of limbs. The other coexistent injuries also need to be managed appropriately, calling for a team approach, as is required for any patient with polytrauma.

It must be stressed that peripheral nerve injuries may also occur during surgical procedures, undertaken by general surgeons, orthopaedic surgeons or others. It is, therefore, preferable, that all surgical specialists have some degree of familiarity with this topic, so as to take appropriate steps to safeguard against iatrogenic injury, or to manage/refer such injuries in a timely fashion when they are detected.

Anatomy

Peripheral nerves comprise of three components: 1) conducting axons, 2) insulating Schwann cells and 3) a surrounding connective tissue matrix that can support axonal regeneration. The axons are bounded within a semi-permeable membrane called the axolemma, which is surrounded by a myelin sheath of Schwann cells. The entire axons are embedded within a connective tissue compartment called the endoneurium. The endoneurium, in turn, is encircled by a compact layer called the perineurium, which is composed of concentrically arranged elongated perineural cells.[32] The axon bundles inside a perineurial sheath constitute a 'fascicle' and they are the smallest structural element of a nerve which is visible under the operating microscope (Refer to Fig. 2 of chapter 55 on Peripheral Nerve: Basic Anatomy and Physiology).

The perineurium is a thin but important physiological layer forming the structural basis of the blood-nerve barrier. These nerve fascicles are embedded within a connective tissue compartment called the internal epineurium, which is encircled by external epineurium. Both the internal and external epineurium contains fibroblasts, macrophages, mast cells, blood vessels and fat.[34,35,38] The external epineurium provides the main tensile strength to the nerve.

The axons inside each fascicle are repeatedly branching and follow an undulating course. Similarly, fascicles repeatedly branch and reunite to form a complex fascicular structure within the nerve. These features of the nerves ensure protection against traction forces generated by the movement of joints. It is only in the distal parts of the nerves that motor and sensory fascicles form separate groups.

An important feature of the peripheral nervous system, in comparison with the central nervous system, is its remarkable capacity for recovery through both remyelination and regeneration of axons and this physiologic capacity is the key resource utilised for successful nerve repair after trauma.

Mechanisms of Nerve Injuries

Open Injuries

They can be sharply incised wounds like those caused by knives, glass, etc. They can be repaired primarily unless any contraindication exists (see later). Injuries associated with extensive laceration, contusion or tearing of nerve fibres, as caused by a chainsaw or missiles are associated with ragged nerve edges and a great deal of tissue injury and are thus unfit for primary repair.

Closed Injuries

Most of these are caused by stretch or traction. They are usually associated with anatomical continuity of nerves and are more difficult to treat, because of the following reasons:[24]

a. Extensive intrafascicular damage and fibrosis is a significant impediment to regenerating fibres.
b. Injury is often concealed inside the fascicles and the complete extent of the injury cannot be appreciated on inspection or palpation.

c. Associated rupture of blood vessels may lead to extensive haemorrhage and post-traumatic scarring.

Miscellaneous Injuries

They include injection injuries, thermal/electrical injuries, pressure injuries, iatrogenic damage during surgery, fracture reduction, tight casts and splints, etc. Bullet injuries deserve special mention because they cause damage, not only by direct injury but also by cavitation effect. The injury is often more severe than what appears from the wound and such injuries should always be repaired after an interval of 3–4 weeks.

Grading of Nerve Injuries

In 1943, Seddon[31] defined three grades of nerve injury (neuropraxia, axonotmesis and neurotmesis) based on the extent of injury to the three structural components of the peripheral nerve described above. While he admitted that these three grades were only a rough approximation, these terms have been retained in literature. The beauty of the three-grade classification scheme lies in its simplicity and clinical relevance in predicting functional outcome and formulating an appropriate treatment plan.

Neuropraxia, the mildest grade of nerve injury, is characterised by disruption of the myelin sheath with conduction block across a segment of nerve. Axonal continuity is maintained. The key feature is its reversibility within hours to weeks of injury.[40] After complete nerve palsies, neuropraxia can be distinguished from other forms of injury only in retrospect, after recovery has taken place sooner than would be expected from Wallerian degeneration. In incomplete injuries, the motor component is often affected more than sensory and autonomic functions. Tinel's sign is absent due to preservation of axons.

Axonotmesis represents a more severe grade of nerve injury and is characterised by disruption of the axons with preservation of the fascicles. Distal Wallerian degeneration of the axons occurs over several days.[8,11,15] Recovery can occur through axonal regeneration because of the preservation of the connective tissue 'tubes', which consists of Schwann cells and their extracellular matrix.[30] Regeneration can be followed by an advancing Tinel's sign or by electrophysiological evaluation. Since one cannot reliably predict whether the injury is purely axonotmic in nature or the fascicles are also disrupted, the degree of recovery in such lesions cannot be predicted with certainty. Even if the lesion is purely axonotmic, many proximal motor neurons may enter sensory tubules and vice-versa, thus decreasing the effectiveness of regeneration.

Neurotmesis is the most severe grade of peripheral nerve injury. Neurotmesis is characterised by disruption of the axons, myelin and connective tissue components of the nerve, with various grades of internal disruption of the endoneurium, perineurium and epineurium and/or complete disruption of nerve ends. These injuries generally require surgical correction.[15,42]

To better distinguish between different grades of neurotmesis injuries, Sir Sydney Sunderland[33] categorised nerve injuries into five grades. Grades I and II correspond to neuropraxic and axonotmetic grades of injury. In Sunderland Grade III injuries, the continuity of the endoneurium is disrupted, while preserving the continuity of the perineurium. In Grade IV injuries, there is additional disruption of the perineurium also, while in Grade V injuries epineurial continuity is also disrupted, which corresponds to a neurotmesis lesion in discontinuity. An additional level of complexity is introduced, in that peripheral nerve injuries can represent combinations of these different grades of nerve injury, such as Grade VI presented by Mackinnon and Dellon.[21]

However, we should remember that neural injury is a continuum and clear differentiation into these grades is not always possible. Also, different grades of injuries may coexist in a particular patient with nerve injury.

Evaluation of Nerve Injury

Clinical history should include the mode of injury, time since injury, extent of functional impairment, associated injuries (vascular, bony, visceral, etc.) and recovery of functions. Examination should include the degree and distribution of muscle wasting, grade of power in different muscles, range of movements and extent of sensory impairment. Local examination for the presence of neuroma, Tinel's sign, associated bony or vascular injury, external wounds and deformities is important.

The presence of Tinel's sign is useful to localise a nerve injury. Tinel's sign refers to paraesthesias elicited by tapping along the course of a nerve. Progressive distal advancement of Tinel's sign over time can be useful clinically to follow the course of regenerating sensory axons.[10,15] Serial electrodiagnostic studies can also detect a distally advancing nerve conduction response representing the regenerating front of axons.

Electrodiagnostic tests are useful adjuncts to clinical examination. Two to three weeks after an axonotmetic or neurotmesis grade of injury, the results of electromyography (EMG) become abnormal.[4,12,20,36,39] Spontaneous activity, including fibrillations, fasciculations and positive sharp waves, develops in the affected muscles.[20] The results of EMG performed after a neuropraxic injury, usually remain normal and can be used to distinguish a neuropraxic grade of injury from the more severe axonotmetic and neurotmesis grades of injury. Radiology is not of much use in surgical decision making, except for demonstration of associated fractures and callus formation.

Philosophy of Management

Both neuropraxic and axonotmetic grades of traumatic injury do not require surgical intervention. Patients with such injuries should be followed-up with serial clinical and electrodiagnostic examinations, to document recovery and confirm the diagnosis. Complete nerve injuries may represent either an axonotmetic or neurotmesis

grade of injury. It is important to distinguish between these two, as the latter requires surgery for recovery to occur.[32]

As mentioned earlier, traumatic peripheral nerve injuries can be classified into open and closed injuries. Decision making for open injuries is relatively straightforward.[15,21–23,35] Immediate repair of acute sharp lacerating injuries should be undertaken, with the aim of performing a primary end-to-end suture repair. Contraindications to primary repair are extensive bruising, destruction of tissues, contamination of the wound, ragged nerve ends or loss of length of nerve.[24] Under these circumstances, the nerve ends should then be tagged together to prevent further retraction and for identification later. The surgery should then be performed 3–4 weeks later when the associated wound has healed. This delay will allow for demarcation of the healthy proximal and distal nerve ends from the intervening scarred segment. Lesions in continuity cannot be accurately assessed during the acute period, when seen during tendon repairs or open reduction of a fracture.

Closed Injuries

In the majority of closed traumatic injuries, however, the nerves are not actually transected. Instead, a "lesion in continuity" representing the damaged segment of nerve may be produced, which results in either a neurapraxic, axonotmetic or neurotmesis grade of injury.[19,25]

These injuries should be explored:[24]

a. When nerve function is steadily deteriorating.
b. When recovery stops before reaching any useful degree.
c. When spontaneous recovery is overdue: if there is no clinical or electrophysiological evidence of recovery, even after the time it was expected to occur (3–4 months in brachial plexus injury but different in different nerve injuries), the patient should be explored.
d. When there is a painful traumatic neuroma.

It is necessary to time the surgical exploration, so that a successful nerve repair results in muscle re-innervation within 1–2 years of the injury. If there is no clinical or electrodiagnostic evidence of muscle re-innervation after 3–4 months of injury, then a surgical exploration using intra-operative electrophysiological monitoring should be performed.[9]

Another philosophy of management, not practiced by the authors, is to operate as soon as feasible, as there is less scarring in the beginning and earlier repair may result in a better outcome. However, many patients recover on their own without surgical intervention and this approach risks exposing those patients to unnecessary surgery.

Treatment Options

The surgical techniques applicable to peripheral nerve surgery include both external and internal neurolysis. External neurolysis involves freeing the nerve from its bed, by removing constrictive adhesions attaching it to the surrounding tissues. Although controversial, it has been hypothesised that scar tissue around nerves can produce pain, as well as sensory and motor deficits through tethering and/or compression.[33,41] Surgical resection of the scar may promote recovery of nerve function.

Before suture or graft repair can be performed, any epineural scarring must be resected using fine dissecting scissors, micro-scissors or a scalpel and regions of bleeding at the epineural or subepineural level must be coagulated, using an irrigating bipolar forceps. It should always be done with the aid of the operating microscope and healthy fascicles should be isolated both proximal and distal to the scar tissue before intra-operative neural action potentials (NAPs) are recorded. Careful observation and palpation are important at this stage.

Kim et al.[13] suggest that, while performing intra-operative recordings of the NAP on a lesion in continuity, stimulating and recording electrodes should be placed on the nerve proximal to the lesion to assess the NAP. The recording electrodes should then be moved distally from the lesion and changes in the evoked NAP observed. If the NAP is present, external neurolysis, with or without internal neurolysis, is sufficient to achieve a favourable outcome. If NAP is absent across a lesion in continuity, resection and repair of the injured nerve is necessary.[14,17] The velocity and amplitude of the nerve conduction response can be measured.

Tiel[41] and Kline[14] and their colleagues showed that intra-operative NAP recording is a reliable indicator of useful electrophysiological recovery in the assessment of nerve injury. It can assist with more precise localisation of pathological findings and aids the decision concerning whether or not to resect the nerve lesion.

Internal neurolysis is indicated in cases in which an injury is more severe at one portion of the nerve than another, in the presence of an NAP transmitted across the lesion. Split or partial graft repairs may be necessary, when individual fascicles or bundles of fascicles do not transmit NAPs.[9,15,34] Conducting fascicles are spared and non-functioning elements are repaired, either end to end or with an interposition nerve graft. However, there is a risk that if it is done in a clumsy manner, it can lead to further neurological deficit.[21] Intra-operative frozen section of the cut nerve ends can be used to determine if normal fascicular anatomy is present.[6]

Kim et al.[13] suggest that in cases of transected nerves or those in which a nerve segment is unable to transmit an NAP, resection is required, and end-to-end epineural repair can sometimes be achieved with the aid of magnification. Sharp dissection is necessary before suture or graft repair to mobilise the proximal and distal stumps, with adequate resection of the stump to healthy epineurium and fascicular structure. We prefer approximating the two ends of the nerves with 9-0 or 10-0 nylon sutures. Meticulous attention should be paid to the surgical technique to ensure good coaptation of the nerve

ends. It is well known that tension can impair recovery of nerve function.[27] If mobilisation of the nerve is inadequate for a tensionless repair, the two ends should be approximated using interposition nerve grafts to avoid tension.

The nerve ends should carefully be looked at to determine the fascicular topography before approximating them. Another method is to utilise surface vessels for alignment. A minimum number of sutures should be used to decrease scarring.

Two leading causes of regenerative failure across the suture repair site are inadequate preparation of the nerve stumps and persistent tension. Both of these factors can lead to the formation of an intraneural scar, which interferes with regenerating nerve fibers.[2,16,18,19,26,27,28,35,38]

Sutureless Repair

Laser welding, cuff union or fibrin adhesives of axon conduits have been used to approximate fascicles in the hope of reducing scar tissue formation. Improved functional results using these techniques have not yet been demonstrated definitively.[1,3,5,7,29,37]

Nerve Grafts

Several types of nerve autografts have been described which include:[24]

Cable nerve graft: Many parallel grafts of donor peripheral nerves are used to match the thickness of the recipient nerve.

Group interfascicular nerve graft: The fascicles at the proximal and distal ends are appropriately grouped and matched with cable grafts.

Free neurovascular nerve grafts: A nerve is transferred along with its vascular pedicle.

Pedicle nerve graft: A full thickness nerve graft is transferred in a two-stage procedure.

Tubal graft: Using a vein, artery or other mesothelial tubes.

Post-Operative Management

The management of peripheral nerve injury does not end with surgery. It is extremely important that patients undergo regular physical therapy, both supervised and on their own, to maintain range of movement and to optimise the recovery of motor function as re-innervation of muscles occurs.

When suture-repairing a nerve with or without grafts every effort is made to minimise nerve tension, by either mobilising or transposing the nerve or by using nerve grafts of adequate length, so that the repair site is not disrupted. Despite these precautions, overzealous post-operative mobilisation can result in disruption of the suture repair site(s) and therefore should be avoided.

Follow-up electrodiagnostic studies can be very useful in detecting early signs of muscle re-innervation, 3–6 weeks before clinically evident muscle contraction. The results of these studies, when positive, can provide hope to the patient and can also be helpful in predicting clinical outcome.

Along with physiotherapy, occupational therapy, orthosis, limb reconstruction, and wherever required, psychotherapy should be used in the post-operative period.

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Injuries to Specific Nerves

Radial Nerve

Most of the serious radial nerve (RN) injuries result from fractures, lacerations, contusions or gunshot wounds. Seventy percent of RN injuries related to fractures occur at the level of the arm. In particular, fractures involving the junction of the middle and distal third of the humerus and the midpoint of the humerus at the level of the spiral groove were associated with RN injuries. The RN supplies branches to the long and medial heads of the triceps (elbow extension) before the radial groove, while braches to the brachioradialis and extensor carpi radialis longus are supplied after the radial groove, before crossing the elbow. All extensor muscles of the hand and forearm are innervated after the RN pierces the supinator muscle. Loss of wrist extension significantly reduces the ability to grasp, due to a reduction in the mechanical advantage of flexion at the distal interphalangeal joints by the flexor digitorum profundus muscle. This adds to the functional disability, which is present already due to loss of elbow and wrist extension. In spite of the generally poor outcome seen in recovery of wrist extension after brachial plexus injuries, outcome after repair of RN is surprisingly fair. Taha and Taha[29] have highlighted several factors contributing to this: 1) the predominance of motor fibres that reduce the possibility of cross motor-sensory re-innervation; 2) muscles innervated by the RN receive their input relatively proximally within the limb and are not involved in delicate movements that require complex coordinated muscle contraction and 3) even though the initial loss of the extensor carpi radialis longus muscle results in significant disability, the muscle recovers well.

A period of observation is recommended for fracture-related RN injuries because spontaneous recovery rates as high as 76% have been reported in the literature.[3,21,23,24,30] In their series of patients, Bostman et al.[2] observed that it was more common for the distal third of the humerus to sustain a longitudinal spiral fracture. The nerve often gets trapped in the fracture line after attempted closed reduction of the humeral fracture.[3,28,30] However, if the fracture is to be reduced openly and internally instrumented or if vascular repair is necessary, the injured nerve should be explored.[13,17,20,21,23] Further management depends upon several factors, including the time elapsed after injury and the status of the nerves. Kim et al.[13] observed motor function recovery to Grade 3 or better in 10 (91%) of 11 patients who underwent primary suture repair, 25 (83%) of 30 who underwent secondary suture repair, 43 (80%) of 54 who received graft repair and 63 (98%) of 64 in whom neurolysis was performed after RN injury.

Median Nerve

The median nerve (MN) does not give any branches in the arm. It supplies all the forearm flexor muscles (except the flexor carpi ulnaris and medial part of the flexor digitorum profundus) in the proximal part of the forearm and three thenar muscles and two lumbricals in the hand, resulting in impairment of important functions of pinch and grasp after its injury. The mechanisms of injury include lacerations, gunshot wounds, stretch injury or contusion, fracture-related contusion, iatrogenic injury, compression and electrical injury.

Surgical intervention for MN injuries with complete or severe deficits achieves a favourable outcome. The most common mechanism of injury seen at all levels by Kim et al.[13] was laceration. They observed that for lesions in continuity, a functional recovery of Grade 3 or better was seen in 72 (95%) of 76 patients who underwent neurolysis, 18 (86%) of 21 who received suture repair and 21 (75%) of 28 who received graft repair. In lesions not in continuity, favourable results (Grade 3) were seen in 10 (91%) of 11 patients who underwent primary suture repair, seven (78%) of nine who had secondary suture repair and 15 (68%) of 22 who underwent graft repair.

However, several factors determine the outcome after these nerve injuries. Surgical timing is vitally important for patients who have severe or poorly recovering MN injuries that show little spontaneous improvement.[3,12,13]

In their study of 132 delayed repairs of sharp and blunt MN injuries, Kallio and Vastamaki[8] observed that injuries farther than 56 cm from the fingertip, delays in surgery longer than 24 months and graft repairs more than 7 cm long were associated with relatively poor outcome.

Ulnar Nerve

This nerve arises from the medial cord of the brachial plexus and lies on the medial side of the axillary artery. Like the MN, it also does not give any branches in the arm. It supplies the flexor carpi ulnaris and medial part of the flexor digitorum profundus in the proximal forearm. The ulnar nerve has its greatest importance at the hand level, where it innervates most of the intrinsic muscles. It has been reported that recovery of small muscles of the hand is poor after repair of the ulnar nerve and the results are much worse when compared to outcome after radial or MN repairs.[1,22,25] This is in spite of the fact that an additional 2.5–3.5 cm of length of the ulnar nerve can be gained by transposing it anterior to the elbow, thereby avoiding the need for a nerve graft in many cases. However, we normally do not recommend anterior transposition of the ulnar nerve at the elbow, as it may cause vascular damage to the nerve and, if not performed adequately, it may cause acute angulation of the nerve.

The most common mechanism of injury observed by Kim et al. was laceration.[11] Stretch, fractures and firearm injuries were other common mechanisms. They observed that functional recoveries of Grade 3 or better were seen in 81 (92%) of 88 patients who underwent neurolysis, 42 (72%) of 58 patients who received suture repair and 24 (67%) of 36 patients who received graft repair. Nevertheless, fewer Grade 4 or 5 recoveries were achieved than those seen in patients with RN or MN injuries. [11–13]

Axillary Nerve

The axillary nerve is the most commonly damaged by stretch/contusion injuries, with or without associated other nerve injuries, like posterior cord/suprascapular nerve or brachial plexus injuries. Kline and Kim[19] observed that these injuries usually began in the posterior cord. In their analysis of 99 patients with axillary nerve repair, they found better recovery after neurolysis of intact nerves (to mean grade 4), as compared to suture repairs or graft repairs (mean grade 3.7). They concluded that operative intervention is worthwhile in carefully selected cases.

Sciatic Nerve

The sciatic nerve is the biggest peripheral nerve of the whole body, far from the target organs and with a complicated structure. The tibial nerve (TN) and the common peroneal nerve (CPN) keep relatively independent from the early part of their course. Injuries of the CPN are the most frequent and lesions of the sciatic and TNs are rather rare.[4,5,7,9,18] Injury at the thigh level can produce complete injury of both divisions of the sciatic nerve, complete injury in one and incomplete in the other, incomplete in both divisions or complete/incomplete in one and none in the other. Lesions of the femoral and obturator nerve are uncommon.[5,7] The mechanism of injury of the lower extremity nerves includes laceration, compression, traction and focal ischaemia. Penetrating trauma, bone fractures, joint dislocations, injection injuries and operative iatrogenic lesions are relatively more common causes of lower limb nerve injuries, as compared to upper limb injuries. Nerve injuries in the lower limbs are also said to have a worse prognosis than those in the upper limbs.[26,27,31]

Kline et al.[18] in their review of 380 cases of sciatic nerve injury managed over 24 years, observed that surgical exploration was not warranted in one fourth of injuries at the thigh level and almost half of hip level injuries. They found good to excellent outcome in only 36% of cases after suture repair/nerve graft of the peroneal nerve. However, they found that outcome after TN repair was more favourable, regardless of the level or mechanism of injury.

Kim et al.[15] analysed 353 surgically treated cases over 32 years and observed that sciatic nerve divisions in which positive intra-operative nerve action potentials were found and who underwent neurolysis, attained at least Grade 3 functional outcomes in 108 (87%) of 124 and in 91 (96%) of 95 buttock and thigh-level tibial divisions, respectively, compared with 84 (71%) of 119 and 75 (79%) of 95, respectively, in the peroneal divisions. For suture repair, recovery to at least Grade 3, occurred in eight (73%) of 11 buttock-level and in 27 (93%) of 29 thigh-level tibial division injuries and in three (30%) of 10 buttock-level and 20 (69%) of 29 thigh-level peroneal division lesions. These observations support the findings of Kline et al.[18] that outcome after TN lesions is more favourable.

In their analysis of 270 cases with lower extremity injuries Gosk et al.[6] found CPN injuries to be most common (125 cases), followed by those of the sciatic nerve (93 cases). This is because of the more susceptible location of the CPN and also its increased sensitivity to trauma. They observed that the efficacy of surgical intervention (very good and good results) in these groups was 68.5% after neurolysis, 48% after reconstruction—sural nerve grafting and 50% after reconstruction—direct suture.

Results of surgery are consistently better for TN lesions, as compared to those of CPN, regardless of the local factors and aetiology of the injury. Of 75 patients with thigh level TN lesions, 69 (92%) improved to grade 3 or better after surgery. Of patients with CPN lesions at the thigh, only 50 patients out of 77 improved after surgery. Similarly, for buttock level injuries, 48 out of 53 patients with TN injuries improved to grade 3 or better, as compared to 29 out of 48 operated for CPN injuries at the same level.[10]

Femoral Nerve

The femoral nerve (FN) originates from the anterior divisions of the L2, L3 and L4 roots. After a long retroperitoneal course over the iliopsoas muscle, it travels under the inguinal ligament, medial to the femoral artery and FN. It divides in the upper thigh (around 4 cm distal to the inguinal ligament) into muscular and sensory branches. FN is a major flexor of the hip joint (iliopsoas) and extensor of the knee (quadriceps). Sensory branches supply the medial part of the thigh and knee.[10,16]

Results of FN surgery are encouraging.[14,16] Of the 54 cases of FN injuries operated upon by Kim and Kline,[14] 42 patients (77%) improved to grade 3 or better power (average follow-up 26.1 months). Iatrogenic injury was the most common mode of injury seen by them (arterial bypass/angiography/hernia repair/gynaecologic surgery) followed by hip/pelvic fracture[19] and laceration.[30] Of the 24 cases managed conservatively, 12 improved to grade 3 or better after an average follow-up of 20 months.

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59 Entrapment Syndromes

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INTRODUCTION

Entrapment neuropathy is defined as a condition in which a nerve is continuously irritated by compression created by encroachment or impingement of a nearby anatomical structure.

There may be a number of conditions and even a larger number of situations, including trauma, where this may occur. The most common ones are listed below. The most common entrapment neuropathy is carpal tunnel syndrome followed by ulnar nerve entrapment at the elbow.

TRAUMATIC AND ENTRAPMENT NEUROPATHIES[18]

- Carpal tunnel syndrome
- Ulnar nerve at elbow or wrist
- Cervical or lumbosacral radiculopathies (includes thoracic outlet syndromes)
- Median nerve at elbow
- Anterior interosseous syndrome
- Radial nerve in upper arm
- Sciatic nerve
- Common peroneal nerve at knee
- Tibial nerve at knee
- Lateral cutaneous femoral nerve (meralgia paraesthetica)
- Spinal accessory nerve in posterior cervical triangle
- Subscapular neuropathy.

The clinical manifestations of neuropathy depend on the type and distribution of the affected nerve modalities, the degree of nerve or myelin damage, and the course of the disease. Demyelinating neuropathies primarily affect the myelin sheaths whereas, axonal neuropathies target the peripheral nerve axons. When motor nerves are damaged, weakness and muscle atrophy occur. Damage to sensory nerves can cause loss of sensation, paraesthesia and dysaesthesia, pain and sensory ataxia. Autonomic dysfunction can result in postural hypotension, impotence, gastrointestinal and genitourinary dysfunction, abnormal sweating and hair loss. Involvement of small myelinated and unmyelinated sensory fibres typically results in impaired pin prick and temperature sensation, numbness, and painful burning, cold, stinging, or tingling paraesthesia. Large diameter sensory fibre involvement manifests as loss of vibration and position sensation, sensory ataxia and numbness or tingling paraesthesia. Deep tendon reflexes are frequently diminished or absent, particularly in the demyelinating neuropathies. Since most nerve trunks have a mixture of fibre types, damage to the peripheral nerves often affects more than one of these functions.

Carpal Tunnel Syndrome

Synonym: Median nerve entrapment at the wrist.

This is the commonest kind of entrapment seen in clinical practice. The first description of a chronic median nerve entrapment at the wrist was by Paget[42] concerning a patient with a previous distal radius fracture.[48] This was a severe entrapment accompanied by ulceration in the fingers 1 to 3. The first surgery for carpal tunnel syndrome was done in 1933 at the Mayo Clinic. Carpal tunnel syndrome received increasing attention in the 1940s and 1950s from both neurologists and surgeons. The clinical importance of carpal tunnel syndrome is illustrated by the more than 2,000 papers published in the last 10 years by neurologists, neurosurgeons, orthopaedic, plastic and hand surgeons, as well as physicians specialised in occupational medicine and physiatry.

Aetiology

The aetiology of carpal tunnel syndrome is compression of the median nerve in the carpal tunnel. The carpal bones form the floor and walls of the carpal tunnel, and the roof is created by the transverse carpal ligament (Fig. 1). Nine flexor tendons with their sheaths accompany the median nerve in the carpal tunnel. Just before entering the carpal tunnel, the median nerve gives off the palmar cutaneous branch that carries sensory fibres from the thenar eminence. After the median nerve exits from the carpal tunnel, it gives off the thenar motor branch innervating the abductor pollicis brevis, the opponens pollicis and the first and second lumbrical muscles. It, sometimes, also supplies the flexor pollicis brevis. The other branches are sensory digital branches that supply the thumb, index finger, middle finger and the lateral half of the ring finger.

Carpal tunnel syndrome occurs in conditions that either reduce the space in the tunnel or cause increased susceptibility of the nerve.

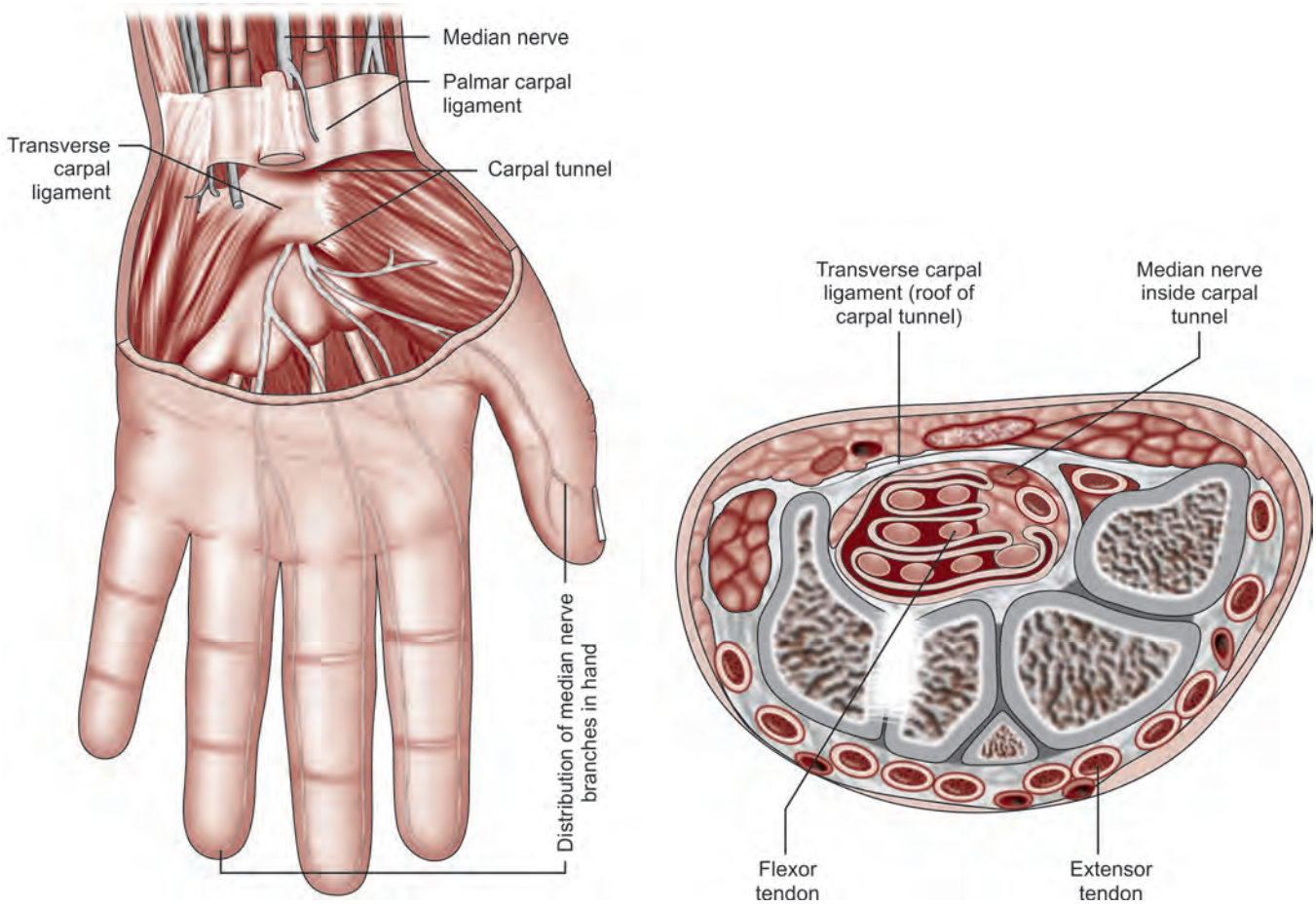

Fig. 1: Anatomy of carpal tunnel in the wrist

Reduced space may be caused by tenosynovitis, rheumatoid arthritis, ganglia, osteophytes, osteosis, anomalous muscles or tumours. Fluid retention is thought to be responsible in pregnancy, during lactation or during the use of oestrogens. Conditions which increase the susceptibility of the nerve are diabetes, hypothyroidism, hereditary neuropathy with pressure palsies, acromegaly, focal amyloid deposition that can be idiopathic or secondary to a genetic defect, systemic amyloidosis or dialysis. Work-related carpal tunnel syndrome occurs with repetitive hand and wrist movement and is seen with a variety of activities and occupations. Increased pressure within the carpal tunnel due to certain positions of the hand and wrist and oedema of the flexor tendons are thought to contribute to occupational carpal tunnel syndrome.

Although the vast majority of carpal tunnel syndrome occurs sporadically, genetic factors may play a role. There is reportedly an autosomal dominant form of carpal tunnel syndrome.[38] Rare, inherited connective tissue diseases, such as mucopolysaccharidosis, can cause severe carpal tunnel syndrome.

Acute carpal tunnel syndrome is mostly seen in the setting of traumatic injury to the hand or wrist and, occasionally, the forearm. It can be caused by the common Colles' fracture of the distal radius. Furthermore, bleeding into the carpal canal due to coagulation disorders seen in cases of leukaemia, haemophilia or anticoagulant therapy can provoke acute carpal tunnel syndrome. Urgent surgical release is indicated for acute severe carpal tunnel syndrome.

Subacute carpal tunnel syndrome, with symptoms usually presenting within 1 week, may occur after rear or front end automobile collisions, presumably through hyperextension of the wrist against the steering wheel.[14] Manifestations of carpal tunnel syndrome can also be seen in a much more delayed fashion after traumatic injury and have been described after a variety of fractures, lacerations and burns.

Pregnancy: During pregnancy there is an increased incidence of carpal tunnel syndrome, presumably due to fluid retention. Treatment is usually conservative as spontaneous recovery occurs after delivery in about 50% of patients.[44] If symptoms persist, steroid injection or surgical carpal tunnel release should be considered.

Associated Disorders

- Amyloid neuropathy
- Amyloidosis
- Colles' fracture
- Diabetes mellitus
- Dialysis
- Hereditary neuropathy with pressure palsies

- Hypothyroidism
- I-cell disease and pseudo-Hurler polydystrophy
- Median neuropathy
- Mucopolysaccharidoses
- Repetitive strain injury
- Rheumatoid arthritis

Epidemiology

Epidemiological studies are not available from India. However, the incidence, as quoted in the literature, is 2–3% of the population.[5] In general, a higher incidence of carpal tunnel syndrome is associated with activities where repetitive hand movements are frequent.

Clinical Manifestations

The incidence of carpal tunnel syndrome is highest among middle-aged women. There is also an association with pregnancy. The clinical manifestations of carpal tunnel syndrome consist of intermittent pain, numbness and tingling in the fingers that is dependent on the position of the hand and wrist and commonly associated with subjective weakness of grip. The symptoms occur initially at night only and may wake the patient from sleep. In more severe cases, the symptoms occur also during the day. They are often provoked by hyperextension or hyperflexion of the wrist during activities such as driving, or during work-related repeated hand movements. The pain can radiate up into the forearm or even up to the shoulder. There frequently is subjective hand swelling and stiffness. The patient will often shake the hand and fingers in an effort to obtain relief from the discomfort (flick sign).

On clinical examination, there can be a discrete sensory disturbance in the lateral three fingers and weakness or atrophy of the thenar muscles with a positive Tinel's sign over the carpal tunnel. Phalen's test, where the patient is asked to hyperflex the wrist for one minute, may provoke the symptoms.[43] Hyperextension of the wrist for one minute may have the same effect. Phalen's test is more specific for carpal tunnel syndrome than Tinel's sign, but both can be present in normal individuals.[24] It is, more often, the clinical history than the physical examination that is highly suggestive of carpal tunnel syndrome.

Prevention

Ergonomic intervention may be helpful in preventing carpal tunnel syndrome by focussing on tool design, improvement of workstations, the avoidance of repetitive pinching, wringing and grasping motions as well as other measures.

Differential Diagnosis

Carpal tunnel syndrome should be differentiated from other neurologic disorders that can cause pain, numbness, tingling and weakness in the hand, such as cervical radiculopathy, polyneuropathy, other entrapment of the median nerve, ulnar neuropathy, and brachial plexopathy. Non-neurologic causes of wrist and hand pain include de Quervain tenosynovitis of the abductor pollicis longus and extensor pollicis brevis tendons, trigger finger, non-specific tenosynovitis, osteoarthritis of the basal joints of the thumb, and Raynaud's disease.

A thorough clinical examination in combination with electrodiagnostic testing usually leads to the correct diagnosis. Occasionally, radiological investigation is necessary, especially when cervical radiculopathy is suspected.

Diagnostic Workup

Electrophysiological testing has an important role in the diagnostic workup for carpal tunnel syndrome. It can document a median nerve entrapment at the wrist and, thereby, support the diagnosis of carpal tunnel syndrome in the presence of appropriate symptoms. Since the first description,[5] increasingly refined nerve conduction techniques have demonstrated slowing of conduction in the median nerve across the carpal tunnel.

Electrodiagnostic testing usually includes motor and sensory nerve conduction studies of both median nerves and at least one ulnar nerve. Needle examination of the abductor pollicis brevis muscles is routinely performed to look for denervation. Needle examination of several other upper extremity muscles and the cervical paraspinal muscles is often necessary to exclude other entrapment neuropathies, plexopathy or radiculopathy.

Sensory nerve conduction studies are the most sensitive in confirming the diagnosis. The most common finding is an increase in distal latency due to focal slowing of conduction across the carpal tunnel. Special adaptations may be necessary to demonstrate milder carpal tunnel syndromes.[26,52]

The next most sensitive feature is a decrease in amplitude of the sensory response. Increased distal motor latency is seen less frequently, and reduced amplitude of the median motor response is even less common. In severe carpal tunnel syndrome there is acute or chronic denervation on needle examination of the abductor pollicis brevis, suggesting axon loss of median motor nerve axons. The severity of clinical weakness and sensory loss, but not of the complaints of tingling and pain, correspond in general with the severity of electrodiagnostic findings.

Median and sensory nerve conduction studies provide accurate and reproducible measurements that can confirm a clinical diagnosis of carpal tunnel syndrome with a high degree of sensitivity (66–82%) and specificity (82–97%).[26]

The MRI of the wrist can document abnormalities in the median nerve that are compatible with carpal tunnel syndrome.[27] The MRI may be helpful if tumours or other structural abnormalities are suspected. A routine wrist X-ray is not useful unless it is to demonstrate a fracture of the wrist.

Management

Carpal tunnel syndrome, unless accompanied by a severe clinical deficit, is usually first treated conservatively with the use of a resting wrist splint and advice to reduce provoking activities. This is successful in about 50% of patients and gives permanent relief only in 50% of these patients. Steroid injections into the carpal tunnel can provide immediate relief, but this is usually not sustained and local complications may occur. If conservative treatment is not effective, surgical carpal tunnel release is performed. This results in an improvement rate of 80–90%.[15] Patients can usually return to work in 2–3 weeks. It should be kept in mind that this rate of success comes down significantly in patients who would be seeking compensation. Endoscopic carpal tunnel release supposedly produces less scarring than open surgery, but precludes visualisation of the median nerve properly. Controversy remains regarding which procedure is the best.[13,17,39,45,50,54,57] However, certain advantages of endoscopic treatment are earlier return to work, less immediate post-operative pain and avoidance of post-operative splinting. More recent innovations like the use of single portal endoscopic technique has made the procedure much less invasive. At the All India Institute of Medical Sciences, New Delhi, both the authors developed an endoscopic carpal tunnel system, which is compatible with most of the endoscopic systems. Since 2000, about 127 patients were operated upon using a patented disposable endoscopic carpal tunnel instrument (patent no. 306/DEL/2009). Using this instrument, the procedure requires just two small sutures (wrist and palm) and the procedure takes about 5–10 minutes. In the majority of patients the symptoms were severe (87%). Post-operative relief was obtained in more than 90% of cases over a follow-up period of 6–56 months.

Prognosis and Complications

The prognosis for recovery is good with either conservative or surgical treatment. The complications include persistent weakness and sensory loss in the distal median nerve distribution. The most dramatic complication is complex regional pain syndrome, a condition which is characterised by severe pain, hyperalgesia, dysaesthesia and trophic disturbances.

Median Nerve Entrapment at Other Sites

Entrapment of the median nerve at other regions of the upper limb is much less common (Fig. 2).

After carpal tunnel syndrome, the most common median nerve entrapment is the pronator teres syndrome.[4] Other less common entrapment sites include the ligament of Struthers, lacertus fibrosus and the tendinous origin of the flexor digitorum superficialis. In 1848, Struthers depicted in fine detail the supracondylar process 5 cm above the medial epicondyle and its ligament. Struthers' ligament can compress the median nerve.[36] Anterior interosseous neuropathy was originally described in two patients who had spontaneous recovery.[30] Median nerve entrapment under the bicipital aponeurosis was described over three decades ago.[33]

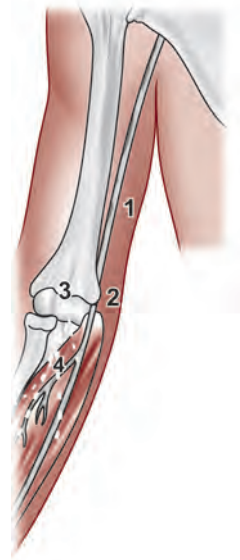

Fig. 2: Median nerve entrapment at other regions of the upper limb (apart from carpal tunnel): (1 and 2) Paralysis des amants; (3) Ligament of Struthers compression 1–2%; (4) Lesion in the pronator teres space (most common cause of median nerve entrapment after carpal tunnel)

Ulnar Entrapment at the Elbow

Ulnar neuropathy is the second most common entrapment neuropathy. In contrast to carpal tunnel syndrome, in which sensory impairment is generally the most significant disability, motor loss is usually the most important problem in ulnar nerve entrapment, most notably in the intrinsic muscles of the hand.[8,11]

Aetiology

There are at least four potential sites of compression of the ulnar nerve in the region of the elbow:

1. At the medial intermuscular septum (arcade of Struthers) just above the elbow.
2. In the retroepicondylar (ulnar) groove.
3. At the humeroulnar aponeurotic arcade ("cubital tunnel").
4. At the nerves' point of exit from the flexor carpi ulnaris.

Lesions in the ulnar groove account for most cases, but humeroulnar aponeurotic arcade compression is also common.[11] The exit compression syndrome is infrequent, but does turn up regularly if one is sensitive to its existence. Compression at the medial intermuscular septum is rare.

In the majority of patients with ulnar neuropathy at the elbow, the initial symptoms are intermittent ulnar distribution numbness and tingling, often associated with elbow flexion. Similar to carpal tunnel syndrome, these symptoms are most noticeable at night. With mild

involvement, such intermittent symptoms may persist for months or years. Patients may not seek medical care until significant intrinsic hand muscle atrophy develops. The ulnar sensory distribution typically includes the palmar surface of the little finger and the ulnar half of the ring finger. The ulnar aspect of the palm is innervated by the palmar cutaneous branch that arises proximal to the wrist. The dorsal cutaneous branch supplies the dorsal ulnar aspect of the hand and fingers. Sensory loss is usually easiest to detect over the tip of the little finger, and diminution of sensibility is usually more pronounced for light touch and two-point discrimination as opposed to pinprick and temperature. The ulnar nerve provides fine motor control, co-ordination, and dexterity to the hand, in contrast to the median nerve that provides more in the way of raw power. The median nerve has been called the "workman's nerve" and the ulnar nerve the "musician's nerve". A frequent early manifestation of ulnar neuropathy is a tendency of the small finger to get "hung up", as when placing the hand in a pocket, and an abducted posture of the small finger on examination (Wartenberg sign). Observing the patient's ability to touch the index to the small finger is a good test of interosseous function. Another useful manoeuvre is to have the patient press their first dorsal interosseous or abductor digiti minimis together to see if one side overpowers the other.

Froment sign results from substituting the flexor pollicis longus to adduct the thumb and provide a pincer function. The ulnar griffe, or claw deformity, is due to weakness of the third and the fourth lumbricals. The lumbricals flex the metacarpophalangeal joints and extend the proximal interphalangeal joints. In ulnar lesions, unopposed extensor tone at the metacarpophalangeal joints and unopposed flexor tone at the proximal interphalangeal joints draw the ring and small fingers into a position with extension at the metacarpophalangeal joints and flexion at the proximal interphalangeal joints. Clawing varies depending on the amount of muscle weakness, the laxity of the metacarpophalangeal joints and the level of the lesion. A "low" (distal) ulnar lesion with preserved function of the flexor digitorum profundus induces more clawing than a "high" (proximal) ulnar lesion, where the accompanying long finger flexor weakness creates less of the unopposed flexor pull deforming the ring and small fingers. Conditions other than ulnar neuropathy can produce a hand deformity mimicking ulnar clawing.[10]

Evaluation of a patient with suspected ulnar neuropathy at the elbow should include examination of the elbow both for range of motion and for deformity. Impaired range of motion, flexion contracture, valgus deformity, or other bony or joint abnormality suggests an elbow level lesion. Reproduction of symptoms with elbow flexion and ulnar groove pressure can be informative. Worsening of the hypaesthesia or pain with sustained elbow flexion, especially if combined with digital pressure over the nerve, suggests ulnar nerve compression near the elbow (the "elbow flexion" test). Eliciting Tinel's sign can be useful, but many normal individuals "Tinel" over all their nerves; only the presence of a disproportionately active Tinel's sign over the clinically suspect ulnar nerve has any localising value. Palpation of the nerve itself may disclose an area of thickening or point tenderness. Each of these tests should be compared with the opposite extremity.

A nerve conduction study is also a useful diagnostic test, with conduction delays of at least 10 m/s in the affected arm relative to the unaffected arm. When significant atrophy is noted, differences of at least 15 m/s are typically found.[4] Pronounced ulnar nerve thickening at the time of the diagnosis is associated with poor outcome at follow-up, especially in conservatively treated cases, whereas electrodiagnostic signs of demyelination on testing indicate a favourable outcome.[8]

Prevention

The symptoms, when they occur due to external pressure and excessive elbow motion, can be prevented by avoiding the precipitating factors.

Differential Diagnosis

Weakness of non-ulnar C8 muscles is the usual clue to disease involving the lower brachial plexus, C8 root or cervical spinal cord. This finding should, in turn, prompt further examination of the cervical spine and a check for Horner's syndrome. Elderly patients, particularly those with dementia, Parkinson's disease and other debilitating illnesses, may have non-specific atrophy of the hand muscles that should not be mistaken for ulnar neuropathy. An ulnar nerve lesion at the wrist can usually be identified by more significant slowing of nerve conduction across the wrist than across the elbow, a normal dorsal ulnar cutaneous sensory potential, and by lack of denervation in the forearm. A lesion of the deep palmar branch produces a characteristic, but complicated electrodiagnostic picture. True neurogenic thoracic outlet syndrome (TOS) classically produces ulnar distribution paraesthesias and sensory loss accompanied by median distribution weakness and atrophy. Possible diagnoses of amyotrophic lateral sclerosis and syringomyelia can be excluded by identification of sensory nerve abnormality and the finding of denervation restricted to ulnar-innervated muscles. A polyneuropathy presenting as an ulnar nerve lesion can be recognised by identifying generalised abnormalities of nerve conduction. Several neurologic and non-neurologic conditions can produce an abnormal hand posture (pseudoulnar claw) that could be confused with an ulnar griffe.[11]

Dupuytren contracture is a painless thickening characterised by fibroblastic proliferation and disorderly collagen deposition of tissue beneath the skin on the palm of the hand and fingers. Subsequently, nodules will form due to contraction of fibroblasts in the superficial palmar fascia.

Management

The treatment of ulnar neuropathy at the elbow is generally considered surgical, but many patients, especially those with mild involvement, may recover spontaneously or with conservative treatment (Table 1).[16] Conversely, the best surgical outcomes occur in patients with the least severe neuropathies and the shortest duration of symptoms; patients with end-stage neuropathies do poorly. Ulnar nerve surgery, however, does not have the excellent success record of carpal tunnel release; studies generally report a good outcome rate of approximately 70%.

Anterior transposition is the most common ulnar nerve operation. It is done by mobilising the nerve, freeing any attachments at the humeroulnar aponeurotic arcade or medial intermuscular septum and then moving the nerve anterior to the medial epicondyle. The two types of transposition methods now commonly employed are: (1) the subcutaneous, or superficial, and (2) the submuscular, or deep. The nerve is placed superficial to the flexor pronator muscle mass for subcutaneous transposition, and deep to it for submuscular transposition. Complications from any of these procedures include persistent or recurrent symptoms due to inadequate surgery or to recurrent scarring of the nerve. Patients are occasionally left with painful paraesthesias and significant disability due to chronic pain. Submuscular transposition is often used as a salvage procedure following failed anterior subcutaneous transposition.[1] Recently, there has been renewed interest in the old surgical concept of reconstruction of the ulnar groove.

The main advantage of decompression and medial epicondylectomy over transposition is preservation of the ulnar nerve blood supply, as extensive dissection with the possibility of devascularisation of the ulnar nerve is unnecessary. More recently, an endoscopic release has also been described but the results are too early to derive any conclusions.[41]

Table 1: Conservative treatment of ulnar neuropathy at the elbow

Minimisation of elbow flexion
Elbow pads
Arms never crossed
Forearm supinated and resting on thigh while sitting
Telephone in asymptomatic hand only
Book stand for reading
Avoidance of external pressure
Elbow pads or night splints
Elbow resting on pillow during desk work
Nonsteroidal anti-inflammatory drugs when repetitive motion is involved

(Source: Modified from Dellon et al. 1993)[21]

Ulnar Entrapment at Other Regions

This is much less common (Fig. 3).

Prognosis

Electrodiagnostic studies can predict which patients may have a progressive or deteriorating course. The likelihood of spontaneous recovery is greatest in those with the mildest electrophysiological abnormalities. In patients with persistent paraesthesias, abnormal two-point discrimination and any degree of muscle wasting, surgery will eventually be necessary. A history of elbow injury significantly worsens the outcome. The best surgical approach remains a matter of dispute and likely differs from patient to patient. A 27-year literature review was unable to formulate a uniform guideline for operative treatment.[7]

Radial Nerve Entrapment

Radial neuropathy most commonly presents with sudden painless wrist and finger drop. There may be associated paraesthesias or numbness over the dorsum of the hand. The clinical picture sets radial neuropathy apart from confounding conditions and generally helps in lesion localisation.

Radial neuropathy is most commonly due to compression at or around the spiral groove. Due to its more proximal innervation, the triceps muscle is spared. Elbow flexion may seem to be intact due to the biceps muscle compensating for the weakened brachioradialis muscle. More commonly, brachioradialis muscle palpation during elbow flexion reveals a flaccid tone. Motor deficit involves wrist and finger extensor muscles. Sensation is impaired over the dorsum of the hand, mainly in the region of the first and the second metacarpals. Radial

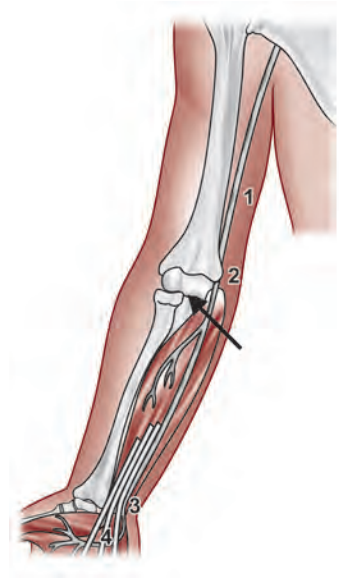

Fig. 3: Ulnar nerve entrapment at various regions of the upper limb: (1) Paralysie des amants; (2) Tardy ulnar nerve palsy; (3) Proximal portion of Guyon's canal; (4) Within palm (Bicyclist's paralysis); (5) Cubital tunnel syndrome (long arrow)

nerve injury proximal to the spiral groove is less common. In addition to spiral groove lesion manifestations, the triceps muscle is weak and the triceps deep tendon reflex is reduced or absent. When present, sensory loss may extend beyond the hand to the posterior forearm.

Lesions a few centimetres distal to the elbow result in posterior interosseous neuropathy. The acute to subacute progressive weakness involves one or more adjacent metacarpophalangeal joint extensors. Interphalangeal joint extension is innervated by the ulnar and median nerves and is, therefore, spared. Elbow pain occurs in 50% of these patients and usually clears in a few days. Tenderness can occur 5 centimetres distal to the elbow. Useful features are pain reproduction or exacerbation by pressure, resisted supination with 90-degree elbow flexion or middle finger extension, and relief by local anaesthetic injection. There is typically no sensory loss. The spared extensor carpi radialis brevis and longus muscles result in radial deviation on wrist extension.

Superficial radial neuropathy induces paraesthesias over the dorsum of the hand. At times, this may be painful. A handcuff or watchband may additionally compress the median and ulnar nerves. Superficial radial neuritis, or Wartenberg syndrome, is associated with pain at the radial styloid radiating to the hand and is exacerbated by ulnar deviation of the wrist. Tinel sign is usually positive over the junction of the middle-to-distal third of the radius.

Aetiology

Compression, trauma and entrapment are the main mechanisms of radial nerve injury. Tumour, systemic disease and birth trauma constitute less common causes.

Radial nerve compression is most frequently at or within close vicinity of the spiral groove.[55] The radial nerve, in "saturday night palsy", may be compressed during sedation, deep sleep, inebriation or by the head of a sleeping partner. Triceps muscle fibrosis induced by chronic analgesic intramuscular injection may cause severe progressive painless radial neuropathy. Radial nerve compression may occur more proximal due to inappropriate crutch pressure at the axilla, prolonged tourniquet application, frequent automated blood pressure cuff inflation or poor arm position during anaesthesia. Radial nerve compression at the axilla or arm may be associated with ulnar or median nerve dysfunction. Windmill pitchers may develop radial neuropathy at variable sites proximal to the spiral groove.[53] Due to its course around the spiral groove the radial nerve is injured in 15% of humeral fractures.[9]

The differential diagnosis of radial neuropathy includes C7 radiculopathy, posterior cord brachial plexopathy and extensor tendon rupture. Radial neuropathy can be confused with stroke due to apparent intrinsic hand muscle weakness. When the wrist and metacarpophalangeal joints are passively extended, patients with radial neuropathy can better activate median and ulnar-innervated lumbricals, thereby extending their interphalangeal joints. Similarly, wrist extension dramatically improves interosseus muscle strength. These manoeuvres eliminate most of the mechanical disadvantage in radial neuropathy. They do not, however, improve stroke-related hand weakness.

Radial neuropathy at the spiral groove is typically associated with motor conduction block. Additionally, 60–90% of cases display active denervation mostly due to secondary axonal loss. Distal muscle denervation may persist in 60% of cases for at least 2–4 years after full clinical recovery. In most instances, denervation involves the brachioradialis muscle as well as the extensor digitorum communis, extensor indicis proprius and the extensor carpi radialis.

Management

With few exceptions, conservative management with clinical and electrodiagnostic follow-up is the rule for radial neuropathies. Most patients with radial palsies induced by compression recover fully within 2–12 months. Faster and more complete recovery is anticipated with neuropraxia. All patients with radial neuropathy should wear a splint with passive dorsiflexion at the wrist and fingers. In the absence of clinical and electromyographic recovery of severe radial neuropathy, surgical exploration after 3–5 months is indicated, and intra-operative radial nerve conduction studies are helpful.

Indications for early exploration of post-traumatic radial neuropathy include complex humeral fractures or weakness developing after closed reduction of a simple fracture. Exploration of a simple humeral fracture may be delayed for 2 months to allow for spontaneous radial nerve recovery. Successful nerve graft induces return of function in 12–18 months. Delayed tendon transfers may restore wrist extension.

Conservative management of spontaneous superficial radial neuropathy includes prevention of external compression at the wrist, avoidance of repetitive wrist movements, nocturnal wrist splints and local anaesthetic or steroid injection. Otherwise, surgical decompression is effective as it is for traumatic radial nerve laceration.

Most patients with tennis elbow respond well to 6–12 months of conservative therapy including rest, activity modification, physical therapy, nonsteroid anti-inflammatory drugs and local steroid injection. Very few cases require decompression of the posterior interosseous nerve to reduce tension at the lateral epicondyle.

Sciatic Neuropathy

Sciatic neuropathy presents, usually acutely, with foot weakness, pain and sensory loss. Foot pain and dysaesthesia are common major symptoms in most patients. Not infrequently, signs of reflex sympathetic dystrophy (allodynia with skin, nail and bone dystrophic changes) become dominant and disabling. The foot weakness is commonly manifested as a foot-drop, which results in a

diagnostic challenge as sciatic neuropathy may imitate a peroneal neuropathy at the fibular head. In severe sciatic neuropathy, weakness of hamstrings (knee flexion) and gastrocnemius muscles (plantar flexion) is also present. The ankle jerk is usually depressed or absent. Sensory loss and dysaesthesia of the sole and dorsum of the foot and lateral leg are common.

Piriformis Syndrome

The sciatic nerve along with the inferior gluteal and pudendal nerves exits the pelvis through the lower part of the great sciatic foramen deep to the piriformis muscle. The piriformis is attached to the inner face of the bony pelvis and the greater trochanter. The nerve passes over the tendon of the obturator internus muscle and the gemelli. The development of the syndrome depends on muscular activity and hypertrophy. The symptoms are pain, paraesthesiae and motor weakness. Due to the involvement of the pudendal nerves the patient, along with sciatica, may have pain radiating to the groin.

Aetiology

Sciatic neuropathy is caused by external compression of the nerve, or by stretching around the hip during surgical procedures. Less common causes include injection injuries, vasculitis and gunshot or knife injuries.

The treatment of patients with sciatic neuropathy is mostly directed towards the management of pain with tricyclic antidepressants, anticonvulsants and topical analgesia. Initially, the foot-drop will require an ankle-foot orthosis. Leg elevation and stockings are useful when swelling is prominent. Surgical exploration and neurolysis or grafting is sometimes necessary in patients who do not show signs of re-innervation. In cases of sciatic nerve lesions due to a number of aetiologies, the presence of positive intra-operative nerve action potentials seems to indicate a better surgical prognosis. In those patients with nerve action potentials who underwent neurolysis, 87% of buttock-level injuries and 91% of thigh-level injuries attained at least Grade 3 functional outcomes post-operatively.[32]

Management

The treatment of the piriformis syndrome is controversial and often difficult. Conservative therapy includes stretching of the piriformis muscle by flexion, adduction and internal rotation of the symptomatic hip. Injection into the piriformis muscle with corticosteroids, preferably done under imaging guidance, may also result in relief of buttock pain. Botulinum toxin injection may reduce the pain in a significant number of patients.[20] Surgical exploration of the sciatic nerve in the region of the piriformis muscle is indicated only in cases resistant to conservative therapy. Abnormal bands or vessels constricting the sciatic nerve in the buttock should also be removed.[25] Section of the piriformis muscle is the most popular advocated procedure, but its value is uncertain. Sciatic nerve varices may respond to foam sclerotherapy, leading to complete obliteration of the offending vein.[46]

Peroneal Neuropathy

The most common causes of peroneal neuropathy include external compression, trauma, tumours or vasculitis.

Peroneal neuropathy usually presents with acute foot-drop. However, in some instances, the foot-drop develops subacutely over days or even weeks. Foot-drop may be complete, with failure to dorsiflex the ankle and toes, or partial. The foot may get trapped or may cause the patient to fall. Numbness while walking usually involves the dorsum of the foot and lower lateral leg; pain, however, is rare and, when present, is deep and ill-defined, usually located around the knee. On examination, the weakness is restricted to ankle eversion and ankle and toe dorsiflexion. Ankle inversion, toe flexion and plantar flexion are normal. An apparent weakness of ankle inversion is common with complete foot-drop, since inversion is best obtained with the foot slightly dorsiflexed. To avoid this misleading sign in a patient with foot-drop, the ankle should be dorsiflexed passively to 90 degree while testing ankle inversion. In a large study of common peroneal neuropathy,[2,29] 43% of cases were clinically misdiagnosed by physicians, including neurologists. Hypaesthesia to touch and pain is limited to the lower two thirds of the lateral side of the leg and dorsum of the foot. Tinel's sign may be elicited by percussion of the peroneal nerve around the fibular neck. Knee and ankle reflexes are normal. The hamstrings, glutei and quadriceps are normal. In selective deep peroneal neuropathies, which are much less frequent than common peroneal neuropathies, the sensory manifestations are lacking (except occasionally in the first web space), and ankle eversion is normal.

Table 2 shows the clinical differences between various causes of foot drop, which could be confused with peroneal neuropathy.

Diagnosis

Conduction block at the level of the neck of the fibula is a useful localising electrodiagnostic sign. Focal slowing is present in a minority of patients and is usually associated with conduction block. Conduction block can be found in 50–70% of patients with common peroneal nerve palsy related to postural positioning and weight loss.[3] Low amplitude or absent motor response (consistent with pure axonal loss) is observed in half of the patients, whereas pure conduction block and mixed lesions share the other half. At least three fourths of patients have a significant degree of axonal loss as revealed by a low distal compound muscle action potential. The MRI of the knee can be useful in the detection of tibiofibular joint cysts as a cause of suspected idiopathic peroneal nerve palsies.[6]

Table 2: Clinical differential diagnosis of common causes of foot drop

	Peroneal neuropathy at the fibular head	*L5 radiculopathy*	*Lumbar plexopathy (lumbosacral trunk)*	*Sciatic neuropathy (mainly peroneal)*
Common causes	Compression (weight loss, peri-operative), trauma	Disc herniation, spinal stenosis	Pelvic surgery, haematoma, prolonged labour	Hip surgery, injection injury, coma
Ankle inversion	Normal	Weak	Weak	Normal or mildly weak
Toe flexion	Normal	Weak	Weak	Normal or mildly weak
Plantar flexion	Normal	Normal	Normal	Normal or mildly weak
Ankle jerk	Normal	Normal (unless with S1)	Normal (unless with S1)	Normal or Depressed
Sensory loss distribution	Peroneal only	Poorly demarcated, predominantly big toe	Well demarcated to L5 dermatome	Peroneal and lateral cutaneous of calf
Pain	Rare, deep	Common, radicular	Common, can be radicular	Can be severe

Management

In managing acute compressive lesions, patients should be observed to allow for improvement by remyelination or reinnervation. Conduction block lesions (due to segmental demyelination) recover spontaneously in 2–3 months time, as long as further compression is prevented. Ankle bracing is important when the foot-drop is profound to prevent ankle contractures and sprains. Surgical intervention is appropriate in certain situations.[21]

- In cases of compound injuries when the nerve is lacerated and visibly discontinuous: This repair could be primary (at the time of suturing of laceration) or secondary (if local infection is feared). In cases with open wounds and when a nerve transection is suspected, surgery can be performed on an emergent basis and may be advisable in some cases, although factors favouring surgery have not been determined. Recovery in this group is uniformly poor.
- When clinical or electromyography (EMG) evidence for re-innervation has not been established in the tibialis anterior despite 4–6 months passing since the time of injury. Here, the nerve lesion is likely to be severe, at least of the third degree. In such cases, neuroma formation occurs in 66%, and surgery consists of neuroma resection and grafted nerve repair.
- In slowly progressive peroneal neuropathies, a nerve tumour, ganglion, cyst or, rarely, when true entrapment is suspected, the nerve is explored after appropriate electrodiagnostic localisation. Imaging studies, particularly MRI, are helpful in these situations.

One procedure for correction of such common peroneal nerve traumatic injuries is a 1-stage procedure of nerve repair and tibialis tendon transfer.[21] At 2-year follow-up, evidence of nerve regeneration is present in 90% of patients undergoing such a procedure.

Depending on the nature of the traumatic common peroneal nerve injury, different surgical procedures will be required. Neurolysis in patients with knee-level common peroneal nerve lesions with recordable intra-operative nerve action potentials led to 88% of the patients recovering useful function. In cases of nerve transection, end-to-end suture repair can lead to good recovery in 84% of patients by 24 months.[31] The length of graft required in traumatic lesions where graft repair is necessary impacts on outcome. When grafts less than 6 cm long are required, 75% achieve good peroneal function, whereas only 38% of patients requiring 6–12 cm grafts and 16% of patients requiring 13–24 cm grafts attained good peroneal function.[31]

Tibial Neuropathy

Tibial nerve injuries are best considered based on the anatomic site of the lesion. The divisions are arbitrary, but include the proximal tibial nerve, the distal tibial nerve or plantar nerves (including the individual plantar nerves at or distal to the tarsal tunnel), the interdigital nerves and the sural nerve.

Proximal Tibial Nerve

Due to its anatomic location, damage solely to this nerve is rare. It has been associated with Baker's cysts, trauma to either the knee or ankle, nerve sheath tumours, soleus muscle tendinous arch entrapment, and a host of rare and unusual causes including posterior tibial nerve impingement from a tibial spine fixation screw. More recently, tibial nerve injuries have been reported following subfascial endoscopic perforating vein surgery.

Due to the proximal nature of these lesions, patients present with weakness of foot plantar flexors and foot invertors, long toe flexors, and intrinsic foot muscles. Sensory loss usually involves the sole of the foot. It is important during the physical examination to palpate the popliteal fossa looking for evidence of a mass such as a Baker's cyst or neoplasm.

Distal Tibial and Plantar Nerves

The tibial nerve and its terminal branches, the medial and lateral plantar, and medial calcaneal can be compressed within the tarsal tunnel (the roof of which is formed by the flexor retinaculum) at the ankle. The most common pathology relates to external compression from shoes that are too tight or to plaster casts. Others include post-traumatic fibrosis, tendon sheath cysts, rheumatoid arthritis and hypothyroidism. The plantar nerves may be damaged within the tarsal tunnel or more distally, as they course through the arch and sole of the foot. The medial plantar nerve is injured more commonly than the lateral.

Clinical manifestations include foot and ankle pain along with paraesthesias on various areas on the sole of the foot depending on the particular terminal nerve involved. If there is sensory loss on the heel, usually the medial calcaneal sensory branch is involved, localising the lesion to within or proximal to the tarsal tunnel.

Digital Neuropathies (Morton Neuromas)

The inter digital nerves can become compressed between the adjacent metatarsal heads or stretched where they cross the deep metatarsal ligament. Although debated, the nerve in the third metatarsal interspace is most frequently involved. Joplin neuroma refers to a digital neuroma on the medial side of the great toe being compressed by ill fitting shoes or scarring after bunion surgery.[28]

Sural Neuropathy

The sural nerve can be injured by a Baker's cyst in the popliteal fossa or more distally by vein stripping or compression. The most common cause of an isolated sural neuropathy, currently, is nerve grafting or biopsy. After biopsy, the nerve may occasionally become hyperpathic, with unpleasant or painful paraesthesias experienced over the lateral side of the ankle and foot. The sural nerve can also be injured at the ankle by tendon sheaths and scar tissue. Sural nerve entrapment, localised to its course as it passes through the superficial sural aponeurosis, is described in athletes. Such entrapment results in chronic calf pain, exacerbated by physical exertion. Electrodiagnostic testing may be helpful in making the diagnosis. The results of surgical decompression are encouraging.[19]

Thoracic Outlet Syndrome

The term thoracic outlet syndrome (TOS) is a misnomer, as there are truly multiple forms of this syndrome, and the term thoracic outlet syndromes should always be used instead. Partially as a result of multiple syndromes being expressed as one, there has been great confusion and controversy about the thoracic outlet syndromes. Many physicians doubt the existence of thoracic outlet syndromes, while other physicians have a great deal of disagreement regarding the diagnosis and optimal treatment of the thoracic outlet syndromes. Problems with the diagnosis of TOS have led to great variance of incidences ranging 3–80 cases per 1,000 populations.

Clinical Manifestations

Before discussing the clinical manifestations, it is important to distinguish the different forms of TOS.

True neurologic or neurogenic TOS: This is the only type with a clear definition that most clinicians will agree with. The disorder itself is rare and is usually due to congenital anomalies, but presents in middle-aged women and almost always unilaterally. Symptoms include weakness and wasting of hand muscles, and numbness in the hand. Although pain can be a feature, it is often disproportionate to the development of sensory and even motor dysfunction within the hand. Here, the neurologic and electrophysiological abnormalities are more marked.

Non-neurogenic TOS: This is the common form of TOS, and also the most non-specific form. This is the highly controversial disorder, which frequently frustrates clinicians and leads to disputes in the literature. The most prominent symptom of this disorder is pain and neurologic/electrophysiological findings are limited.

Arterial TOS: Arterial TOS is rare and is also caused by a congenital anomaly. It affects both males and females, and is often found in young people. Symptoms may include hypersensitivity to cold in the hands and fingers, numbness or pain in the fingers, and finger ulcers (sores) or severe limb ischaemia (inadequate blood circulation) in unusual cases.

Venous TOS: This is also a rare disorder which affects both men and women. The exact cause of this type of TOS is unknown, but it has been reported as presenting suddenly following unusual, prolonged limb exertion.

Traumatic TOS: This syndrome may be due to either trauma, such as a motor vehicle accident, repetitive activities, or with hyperextension injury. The common presentation in this syndrome is pain and paraesthesias, and uncommonly, weakness.

Aetiology

There are three major causes of TOS: (1) anatomic; (2) trauma/repetitive activities and (3) neurovascular entrapment at the costoclavicular space.

1. *Anatomic:* Anatomical variants at the scalene triangle, often due to the anterior scalene muscle frontally, middle scalene muscle posteriorly, and the upper border of the first rib inferiorly, can account for at least some cases of neurologic TOS. Cervical ribs are an uncommon cause of neurologic TOS, but congenital fibromuscular bands may lead to as much as 80% of neurologic TOS.[23]

2. *Trauma or repetitive activities:* This is a more controversial cause of TOS and specifically of neurogenic TOS. Hyperextension injury during motor vehicle accidents, with subsequent fibrosis and scarring may lead to non-neurogenic forms of TOS. Musicians may be susceptible due to positioning of their shoulder in abduction or extension for long periods of time, although this is unlikely to lead to neurogenic TOS.
3. *Neurovascular entrapment:* Entrapment may occur in the costoclavicular space between the first rib and the head of the clavicle. This is a more frequent cause of non-neurogenic TOS.

True neurologic TOS usually presents with unilateral symptoms and signs, and often starts with pain. The typical patient has previously been described as a young, thin female with a long neck and drooping shoulders,[22,34] although the droopy shoulder syndrome may be mistaken for TOS. It is the lower two nerve roots of the brachial plexus, C8 and T1, which are most commonly (90%) involved, producing pain and paraesthesias in the ulnar nerve distribution. Often, pain may be the only feature for years, and the development of other symptoms occurs slowly. Pain is often described as dull and aching, and is felt over the lateral side of the neck, shoulder, axilla and parascapular region. Pain may be accompanied by paraesthesias, which are often intermittent and often can be nocturnal, leading to the patient waking up from sleep. Discomfort may be provoked with repetitive use of the arm, particularly with overhead activities. Both pain and paraesthesias over the arm are frequently localised over the medial forearm and the 4th and 5th digits. Sensory loss may occur over the same anatomical distribution, with a pattern clinically referable to the lower trunk of the brachial plexus. Weakness and muscle atrophy will tend to affect distal muscles of the arm, and classically affect the thenar muscles more than the hypothenar muscles.

Although much less common and even more disputed, the second most common anatomic pattern involves the upper nerve roots of the brachial plexus, C5, C6 and C7, with symptoms referred to the neck, ear, upper chest, upper back and outer arm in a radial nerve distribution. These patients present with pain and few neurologic or electrophysiological abnormalities.

A number of provocative tests have been described for TOS. The Adson, costoclavicular and hyperabduction manoeuvres are unreliable. Approximately 92% of asymptomatic patients have variation in the strength of the radial pulse during positional changes. Tinel's sign over the supraclavicular fossa has been described as a potential sign.

The elevated arm stress test (EAST) is possibly the most reliable screening test, although it is non-specific and evaluates all three types of TOS. This test can be performed by having the patient sit with the arms abducted at 90 degree from the thorax and elbows flexed at 90 degree. The patient then opens and closes the hands for 3 minutes. In patients with TOS, they cannot continue due to reproduction of symptoms.[22] In contrast, patients with carpal tunnel syndrome would be expected to have dysaesthesias in the fingers, but not shoulder or arm pain.

Differential Diagnosis

A number of diseases can mimic the presentation of TOS. In most clinical situations, TOS is a diagnosis of exclusion.

- Ulnar and median nerve entrapment
- Cervical disc herniation
- Cervical vertebral osteophyte formation
- Brachial plexitis
- Pancoast tumour
- Nerve sheath tumour
- Spinal cord tumour or other mass lesion
- Syringomyelia
- Multiple sclerosis
- Complex regional pain syndrome.

Diagnostic Workup

Nerve conduction studies and EMG can be helpful in the diagnostic evaluation of patients with suspected TOS.[34,56] In severe cases of true neurogenic TOS, nerve conduction studies may reveal the following characteristics:

- Decreased amplitude of ulnar sensory nerve action potentials
- Decreased amplitude of median compound motor action potentials
- Normal or slightly decreased ulnar compound motor action potentials
- Normal median nerve sensory nerve action potentials.

The EMG may reveal severe abnormalities in the intrinsic muscles of the hand in some cases. These electrodiagnostic findings are due to abnormalities within the lower trunk of the brachial plexus (C8-T1). All of the C8-T1 sensory fibres course within the ulnar nerve, accounting for the decreased ulnar SNAPs. The C8-T1 motor fibres are carried within both median and ulnar nerves, but the median motor fibres are preferentially injured due to their location within the lower trunk.

Imaging studies can be useful in the diagnosis of true neurogenic TOS. Cervical spine and chest X-rays can identify bony abnormalities, including cervical ribs or prominent, often "peaked" C7 transverse processes. Anomalous cervical ribs are found in approximately 10% of patients with TOS (compared to 0.5% in the normal population).The MRI and CT are most useful in the identification of conditions in the differential diagnosis of neurogenic TOS.

Management

For most patients with true neurogenic TOS, conservative treatment is reasonable to offer first. Conservative management includes the modification of behaviour

by avoiding provocative activities and arm positions. Improvement with purely conservative management of TOS ranges from 50 to 90%.[22,34,40,43,51]

Surgical intervention is usually indicated in the true neurogenic form of TOS, in which conservative management most often is unsuccessful. Surgical management for patients with the non-specific or non-neurogenic type of TOS is more controversial. The two most commonly used surgical approaches for the treatment of neurogenic TOS are the anterior supraclavicular and the transaxillary approach for resection of the first rib. The anterior supraclavicular approach is preferred by most neurosurgeons, as it provides for wide exposure of the supraclavicular plexus and middle two thirds of the first rib, where most of the congenital bands are located. The first rib can be resected using this approach. Relief can be expected in about 80% of cases.[43] The transaxillary approach with resection of the first rib is the technique preferred by most thoracic surgeons and many vascular surgeons.[47] The advantage of this approach is easy access for resection of the entire first rib without significant risk to neurovascular structures.

Since 2005, it has been seen that pectoralis minor syndrome (PMS) was associated with more than 75% of patients diagnosed with neurogenic TOS. Its recognition is important as many patients with suspected neurogenic TOS may be treated successfully with a simple, essentially risk-free pectoralis minor tenotomy. Should this fail, thoracic outlet decompression can always be performed at a later date.[49] The clinical picture is of pain or tenderness in the anterior chest wall and axilla together with physical findings of tenderness over the pectoralis minor tendon. Other symptoms include extremity pain, weakness and paraesthesia, similar to symptoms of neurogenic TOS. Recently, endoscopic transaxillary rib resection has been described for TOS.[12]

Meralgia Paraesthetica

This is a painful condition attributed to entrapment or injury to the lateral femoral cutaneous nerve at the site where the nerve leaves the pelvis. The patient with meralgia paraesthetica may complain of a dull ache, itching, numbness, tingling or burning sensation over the lateral and anterolateral thigh.[18,35,37,58] The pain associated with this condition may vary in intensity from mild to very severe and frequently occurs following activity with relief following rest. The lateral femoral cutaneous nerve originates from the posterior division of the L2 and L3 nerve levels and is a pure sensory nerve. Following emergence from the intervertebral foramina of L2 and L3, the nerve traverses the abdomen, first making an appearance at the lateral border of the psoas muscle, and then passing obliquely across the iliacus muscle towards the anterior superior iliac spine. The nerve then exits the pelvis just medial to the anterior superior iliac spine (ASIS) by traversing the fibres of the inguinal ligament. The nerve is surrounded by the tendinous fibres of the inguinal ligament at this point and makes a right-handed bend to change direction from a horizontal course in the pelvis to a more vertical course in the lateral and anterolateral thigh. Various hypotheses have been formulated for the cause of this condition based on the anatomical relationship between the lateral femoral cutaneous nerve and the structures associated with the inguinal region:

- The nerve may be angulated or compressed against a sharp edge of fascia as it pierces the iliac fascia prior to exiting the pelvis beneath the inguinal ligament.
- The nerve may be subjected to friction where it is wedged between the attachment of the inguinal ligament and the ASIS.
- The nerve may pass through the tendinous fibres of the inguinal ligament and be pinched at this site.

In diagnosing meralgia paraesthetica, care should be taken to rule out intraspinal, retroperitoneal, abdominal, or pelvic pathologies, diabetes mellitus, and L3 disc prolapse.[18,35] Clinically L3 disc prolapse may produce alteration of the patellar reflex. In contrast, the reflex will not be altered in meralgia paraesthetica.

Most cases of meralgia paraesthetica will respond to conservative care. Modalities that may prove helpful in the treatment of this condition may include ultrasound, electrical stimulation, or transverse friction techniques to break up possible adhesions affecting the lateral femoral cutaneous nerve at the inguinal region. Postural alterations and functional spinal problems should also be addressed in the management of this condition. Rarely, surgical release is required.

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Doyen of Indian Neurosurgery

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Preface

Since the publication of the second edition of this Textbook in 1996, phenomenal advances have been made towards improved understanding of the pathophysiology of various neurosurgical disorders, their diagnosis and therapy. Advances in molecular biology and genetics on one hand, the refinements of imaging technologies, introduction of image-guided techniques for neuronavigation, and refinements in endoscopic and minimally invasive procedures on the other hand have markedly reduced the morbidity and mortality of neurosurgery. Simultaneously, better availability of radiosurgery and safer endovascular approaches have led to the development of non-surgical therapy for a variety of lesions.

Recent years have witnessed a rapid increase in the number of well-equipped neurosurgical departments across the country providing both state-of-the-art services to the patients and training to specialists in the diverse subdisciplines of neurosurgery. It has been our endeavour to meet their needs for an updated account of the current knowledge of the subject.

The third edition of the textbook includes a comprehensive account of all the recent advances succinctly provided by a galaxy of outstanding contributors especially selected on the basis of their expertise and experience. Care has been taken to include relevant published literature both from India and abroad.

As in earlier editions, special attention has been given to tropical disorders not often adequately covered in publications of the West. This may be an additional attraction for neurosurgeons in other developing countries as also to those in the developed ones who often encounter such conditions in their practice.

The present editors deeply miss the invaluable, wise and experienced guidance of the Senior Editor Prof B Ramamurthi who was the moving spirit behind the earlier editions. The editors would like to thank all the contributors, their associates and the secretarial staff for their co-operation. The Jaypee Brothers Medical Publishers (P) Ltd, New Delhi, India deserve our special thanks for the excellent quality of the publication.

PN Tandon
Ravi Ramamurthi

Caraka Samhita

The early medical writer Caraka tells us that when setting out to learn about Indian medicine, we should have certain criteria in mind for choosing the texts we wish to study (Caraka. 3.8.3):

"A discerning person who wants to become a physician should start by selecting a text based on a consideration of his ability to cope with hard or easy tasks, the results he is after, the likely aftermath, the place and the time. After all, there are numerous physicians' manuals in circulation in the world, so he should apply himself only to a text which is extremely famous, which is used by scholars, which covers a lot of topics and is respected by qualified people. It has to be good for pupils of all three levels of ability, and it should not be flawed by repetitiousness. It should be derived from the tradition of the saints. The connection and the sequence of the text and commentary should be well organised. It should be solidly based, and have no corrupt or missing words. It should be full of significance, its ideas should follow in sequence and it should give importance to the exactness of what ideas really refer to. Its ideas should be coherent and its topics should not be haphazard. It should have both definitions and examples.

This type of text is like a flawless sun; it dispels darkness and throws light on everything."

The Roots of Ayurveda
Dominik Wujastyk

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Infections

AK Singh

60 Brain Abscess

Dharkar SR, Sardana VR, Purohit D

INTRODUCTION

Pyogenic brain abscesses are one of the common neurosurgical emergencies. Although the introduction of antibiotics may have reduced the incidence of brain abscess, it is still a condition which causes a formidable problem in this part of the world.[30] Over the past three decades due to improved diagnostic imaging, particularly with the advent of computed tomography (CT) scan and magnetic resonance imaging (MRI), improved neurosurgical techniques, improvement in neuroanaesthesia and critical care, a better understanding of the pathophysiology and management of intracranial hypertension and with the development of newer anti-microbials, the mortality rate due to brain abscess has reduced from 38% during the 1950s to 25% in the 1980s and 5–10% at present.[106] Despite this reduction in mortality, brain abscess remains a serious and potentially life threatening infection.

INCIDENCE

The incidence of brain abscess is comparatively higher in developing countries as compared to developed countries. In India it is approximately 8% of all intracranial space occupying lesions.[8,30] The annual incidence in the United States is 1 in 10,000 hospital admissions.[88] Brain abscesses are encountered about one sixth as frequently as bacterial meningitis and account for approximately 0.7% of all neurosurgical operations.[106] Several authors have reported a male preponderance (as high as 3:1).[72]

HISTORY

The first reference to brain abscess is attributed to Hippocrates, who in 460 BC, while reporting a febrile patient with purulent otorrhoea and delirium, postulated that intracranial infection was the primary focus and the ear involvement secondary with the ear canal draining the intracranial suppuration.[99] Although Morand (1768) described the disease along with a therapeutic proposal, including the first description of successful drainage of non-traumatic brain abscess,[37] Sir William Macewen was the first physician to diagnose, localise and suggest surgical treatment of brain abscess in a patient.[61] The therapy Macewen recommended for these lesions was drainage of the infective process and treatment of the underlying sinusitis.[62]

Macewen, the father of modern day abscess management, was the first to report 80% survival (8 out of 10 patients) following surgical drainage of temporal lobe abscesses,[62] which is still today a benchmark in the management of brain abscess and has been equalled only recently.[19] Dandy, in 1926, recommended aspiration as the primary surgical modality.[26] Vincent first advocated complete surgical extirpation of brain abscesses.[102]

AETIOPATHOGENESIS

Brain abscess develops either:

- In association with a contiguous suppurative focus
- After cranial trauma
- Haematogenous spread from a distant focus
- Cryptogenic origin
- Due to miscellaneous causes

In Association with Contiguous Suppurative Focus

Brain abscesses occurring due to local extension from contiguous infective foci, like traumatic, surgical, congenital, otic or paranasal infections, usually manifest adjacent to the predisposing focus. They occur as a result of either:

- Direct extension through associated osteitis or osteomyelitis
- Retrograde thrombophlebitic spread via diploic or emissary veins into the intracranial cavity
- Via local lymphatics

Bone infection of the walls of the paranasal sinuses or of the middle and inner ears is the usual precursor of brain abscess. The bone is infected through a necrotic area of mucosa, or by spread through lymphatics and veins penetrating the bone leading to osteomyelitis. In long standing cases caries of the bone leads to dehiscence, the common sites being the posterior wall of the frontal sinus, the tegmen tympani and the lateral part of the posterior surface of the petrous bone (Trautmann's triangle).[90] As compared to the Western countries, in India the commonest source of infection is middle ear suppuration, spread from paranasal sinuses being uncommon.[7,8]

The second line of defence is the dura mater which offers considerable protection against infection on account of its close and tough texture and its good blood

supply. The dura mater may completely resist infection so that an extradural abscess is formed. During the process granulation tissue covers the outer surface of the dura mater. Penetration of the dura mater probably takes place along the course of small vessels which traverse its thickness; they may thrombose and provide convenient pathways. In the majority of cases where a brain abscess is secondary to adjacent bone disease, the brain is adherent to the patch of inflamed dura mater. It is at this point that the abscess cavity usually is near the surface of the brain. This point of attachment is often described as the stalk of the abscess. Cases have been described in which the abscess has discharged its contents through the stalk, through a hole in the dura mater and in the bone, to the exterior.[90]

Otogenic Abscess

The commonest cause of brain abscess is spread of infection from the middle ear and mastoid, which in India accounts for 40–63.3%.[7,30] Typically brain abscesses related to otogenic infection are solitary and they most often develop in the inferior portion of the ipsilateral temporal lobe. In contrast to otogenic infections, mastoid infection typically leads to an abscess in the ipsilateral cerebellar hemisphere. Chronic otitis media and/or mastoiditis leads to intracranial extensions 4–8 times more frequently than does the acute disease. Cholesteatomas complicating chronic otitis or mastoiditis are additional risk factors, increasing the incidence of intracranial extension of infection from 23.2–74%.[65]

Paranasal Sinus Infection

Local spread from infection of the paranasal sinuses leading to abscess formation in the brain, accounts for approximately 15% patients.[12] However, because of earlier diagnosis and treatment of purulent sinusitis and development of more effective antibiotics, the incidence of paranasal sinusitis is decreasing. Most abscesses complicating infection in the frontal, ethmoid or maxillary sinuses occur in the frontal lobe. Intracranial abscess resulting from sphenoid sinusitis tends to occur in either the temporal lobe or the pituitary fossa.

Periodontal Infection

Brain abscess either by contiguous extension from dental infection or by haematogenous seeding occurs in 6–13% of patients.[65,91] They are more likely to occur after infection of the molar teeth, since the infection can spread between the muscles of mastication along the fascial planes to the skull. The site of the abscess is most commonly the frontal lobe, but temporal lobe abscess can also occur by direct extension. Unlike otogenic brain abscesses, odontogenic brain abscesses occur as sequelae of acute rather than chronic infection.[49]

Bacterial Meningitis

Rarely, brain abscesses can result as a complication of meningitis. They occur more frequently in neonates, particularly infants with gram negative meningitis. Cerebral abscesses have been associated with more than 70% of *Citrabacter diversus* meningitis in infants.[106]

Post-Traumatic

The incidence of brain abscess in penetrating and open head injuries is 3–17.2%.[30,76,80] These abscesses result from retained contaminated bone fragments, foreign bodies, hair, etc. However, some investigators have recently questioned the belief that retained bone fragments are the source of brain abscess formation.[16] High velocity bullet injuries or missile injuries devitalise brain tissue leaving fragments of metal or bones which may serve as foci for infection. In general, high velocity bullet fragments and even pellets do not present a significant risk for development of brain abscess because of heat sterilisation and, therefore, do not require removal.[89,106] Patients having skull base fractures with cerebrospinal fluid (CSF) fistula or bleeding through the ear and/or nose are always at risk of developing intracranial infection and rarely an abscess.[89] Post-traumatic abscesses may not develop immediately after the primary injury and in fact many years may elapse before such abscesses appear.[42,75]

Metastatic Abscess

Metastatic abscess results from haematogenous spread of micro-organisms from other parts of the body, frequently from chest infection like lung abscess, bronchiectasis, empyema and cystic fibrosis. Other remote foci of infection include wound and skin infections, osteomyelitis, pelvic infection, cholecystitis and other forms of intra-abdominal sepsis. About 5–18% of patients with cyanotic heart disease develop brain abscess. These patients are ten times more prone to develop brain abscess than patients with acynotic heart disease. Among cyanotic heart disease, Fallot's tetralogy is the most common cause for brain abscess.[98] Intracardiac right to left shunt allowing direct entry of blood containing bacteria to the cerebral circulation bypassing the pulmonary filter, hypoxaemia, metabolic acidosis, increased blood viscosity from compensatory polycythaemia resulting in low perfusion areas (microinfarcts) in the brain provide the perfect milieu where micro-organisms settle down and multiply to form an abscess.[9,40,78] Regardless of the source, haematogenous brain abscesses occur in the distribution of the middle cerebral artery, mostly in the parietal and frontal lobes with a predilection for the left side. Metastatic abscess formation usually begins at the corticomedullary junction (grey and white junction) where brain capillary flow is slowest.[89,106] They are more frequently multiple and are more likely to be multi-loculated. They tend to be less well encapsulated than those which occur by spread from a contiguous site.

Cryptogenic

In a number of cases in which no focus of primary infection can be found, they are embolic in nature and originate from minute lesions giving rise to bacteraemia.[5] Such bacteraemia may occur during surgical procedures on the tonsils[50] and teeth.[49]

Miscellaneous Causes of Brain Abscess

Brain abscesses may result as a complication of other non-neurosurgical procedures such as submucous dissection of the nasal septum,[45] cranial traction with Crutchfield skull tongs,[22,64] use of a halo orthosis[41,81] and secondary to bacteraemia following dilatation of oesophageal stricture and sclerosis of oesophageal varices.[3,24,33,87]

Post-Operative Abscess

Brain abscesses as a complication of intracranial procedures are rare as compared to local wound infection, cranial bone flap oestomyelitis, epidural abscess, subdural empyema or meningitis. Deep wound infections, cranial bone flap infections and the presence of CSF leak increase the risk of formation of brain abscess.

In about 10–20% patients of brain abscess no identifiable predisposing factor is found.[20,82,86]

MICROBIOLOGY OF BRAIN ABSCESS

The microbes responsible for the formation of an abscess depend on the pathogenic mechanism involved. In many instances more than a single bacterial species can be isolated from the brain abscess.

In non-traumatic brain abscess, streptococci including aerobic, anaerobic and microaerophilic streptococci are isolated in 60–70% of cases. These bacteria, particularly *Streptococcus milleri*, are part of the normal bacterial flora of the oral cavity, appendix and female genital tract. Bacteriosides and Enteric bacteria are recovered in 20–40% of cases and *Staphylococcus* in 10–15% of cases. *Staphylococcus* infection is usually caused by penetrating head trauma or bacteraemia secondary to endocarditis. *Clostridia* infections are most often post-traumatic. *Listeria monocytogenes*, a gram-positive bacillus with special tropism for the central nervous system (CNS), accounts for 10% of CNS infections. Brain abscess due to *Listeria* has a poor prognosis and is associated with a high mortality.[66] A high index of suspicion is needed to reach an early diagnosis and establish appropriate antibiotic treatment, which will improve the outcome.[84] *Klebsiella pneumoniae* is a very uncommon microbial agent to cause multiple brain abscesses in neonates that respond poorly to antimicrobial agents. *K. pneumoniae* brain abscess may occur in the absence of meningitis and even in the absence of any identifiable risk factors.[95]

PATHOGENESIS OF DEVELOPMENT OF BRAIN ABSCESS AND CAPSULE FORMATION

For adopting a rational approach to the management of brain abscess, it is valuable to have a better understanding of the pathogenesis and histopathology. The formation of brain abscess progresses through several well defined stages. Abscess development and maturation depends on a number of factors including local tissue oxygen tension, the underlying cause of infection, virulence of the offending organism, the type of organism (e.g. bacterial, fungal, etc.), and the host immune response. The development of brain abscess has been clearly delineated by Britt and Enzmann[15] in their classic experimental and clinical studies. Using a canine model of streptococcal abscess based on histopathological changes of development of brain abscess, Britt et al.[14] identified four stages in the encapsulation process namely:

- early cerebritis (1st to 3rd day)
- late cerebritis (4th to 9th day)
- early capsule formation (10th to 13th day)
- late capsule formation (day 14th and beyond).

The onset and duration of each of these stages is not absolute and may be altered by antibiotic therapy, administration of corticosteroids and alterations in the immune status of the host.

Early Cerebritis Stage (1st to 3rd Day)

It is characterised by the presence of a necrotic centre of purulent material accompanied by local inflammatory response surrounding the adventitia of blood vessels. This response is maximal on day 3 and results in marked oedema formation. The lesion is not demarcated from the surrounding brain at this stage. Histopathologically the early cerebritis stage is characterised by a core of purulent material surrounded by a zone of granulation tissue of variable thickness comprised of inflammatory cells, neovascularity and hyperplastic fibroblasts. Thrombosis of the local vasculature, perivascular cuffing and perilesional oedema is seen extending into the surrounding white matter.

Late Cerebritis Stage (4th to 9th Day)

The necrotic centre enlarges due to pus formation during the late cerebritis stage, which is surrounded by a zone of inflammatory cells and macrophages. Fibroblasts begin to lay down a reticular network, which is the precursor of the collagen capsule. Oedema is maximal during this stage and reactive astrocytes become evident.

Early Capsule Formation (10th to 13th Day)

The spread of infection and subsequent destruction of the parenchyma is limited by the important event of capsule formation which begins by the 10th day after the initial response to bacterial invasion. During this process, fibroblast activity infiltrates the brain surrounding

the zone of cerebritis, and collagen and reticulin fibres are deposited. The developing capsule is surrounded by an active zone of vascular hyperplasia and perivascular cuffing. Inflammatory cells may be observed infiltrating the adjacent leptomeninges if the abscess is near the brain surface. On the medial and ventricular side of the abscess capsule formation is slow and incomplete. This is believed to be related, at least in part, to the amount of cerebral blood flow and tissue oxygen tension adjacent to the developing capsule, which in turn may affect the ability of collagen to form triple helix strands. This probably explains the propensity for abscesses to rupture into the ventricular system rather than into the subarachnoid space and also may account for the predilection of daughter abscesses to form on the thinner side adjacent to the white matter.

Late Capsule Formation (14th Day and Beyond)

Late capsule formation is characterised by five distinct histologic zones:

1. Necrotic centre
2. Peripheral zone of inflammatory cells and fibroblasts
3. Dense collagen capsule
4. Layer of neovascularity just external to the capsule with residual cerebritis
5. Zone of oedema and reactive gliosis external to the capsule

This pattern has been confirmed by studies in other animal models as well as clinical observations[82,103] suggesting that it takes approximately 2 weeks from infiltration of the infective organism for a well formed abscess with encapsulation to develop in the majority of patients who have the capacity to mount a host response to the infection.[15,32,83,103]

Recent studies using an experimental mouse brain abscess model have found a complex role for Toll-like receptors (TLRs) in the pathogenesis of brain abscess. Toll-like receptor 2 (TLR2) has limited impact on the innate immune response during the acute stage of brain abscess formation induced by *S. aureus*, but influences adaptive immunity. In contrast, mice deficient in MyD88, a central adapter molecule for the majority of TLRs in addition to IL-1R and IL-18R, demonstrate severe defects in innate immunity coupled with exaggerated tissue destruction. Esen et al. feel that a better understanding of the roles for TLRs in both resident CNS glia as well as infiltrating immune cells will provide insights into how the immune response to bacterial infection can be altered to achieve effective pathogen destruction without causing excessive bystander damage of surrounding non-infected brain parenchyma.[34]

Syed et al. demonstrated that the pro-inflammatory cytokine tumour necrosis factor-alpha (TNF-alpha) enhances TLR2 expression in microglia, whereas interleukin-1beta has no significant effect on mice. The TLR2 expression was significantly attenuated in brain abscesses of TNF-alpha knockout mice. Their results indicate that in response to *S. aureus*, TNF-alpha acts in an autocrine/paracrine manner to enhance TLR2 expression in microglia and that this effect is mediated, in part, by activation of the nuclear factor-kappa β pathway.[96]

To delineate the importance of MyD88-dependent signals in brain abscesses, Kielian T et al. compared disease pathogenesis using MyD88 knockout (KO) and wild-type (WT) mice. Mortality rates were higher in MyD88 KO mice, which correlated with a significant reduction in the expression of several pro-inflammatory mediators, including but not limited to IL-1beta, TNF-alpha and MIP-2/CXCL2. These changes were associated with a significant reduction in neutrophil and macrophage recruitment into brain abscesses of MyD88 KO animals. Also, microglia, macrophages, and neutrophils isolated from the brain abscesses of MyD88 KO mice produced significantly less TNF-alpha, IL-6, MIP-1alpha/CCL3, and IFN-gamma-induced protein 10/CXCL10 as compared to cells from WT. They found the lack of MyD88-dependent signals had a dramatic effect on the extent of tissue injury, with significantly larger brain abscesses typified by exaggerated oedema and necrosis in MyD88 KO animals. They concluded that their findings indicate that MyD88 plays an essential role in establishing a protective CNS host response during the early stages of brain abscess development, whereas MyD88-independent pathway(s) are responsible for pathogen containment.[38,55]

Kielian et al. also addressed the importance of neutrophils in the early containment of *S. aureus* infection in the brain. Mice were transiently depleted of neutrophils before implantation of bacteria-laden beads. Neutrophil-depleted animals consistently demonstrated more severe brain abscesses and higher CNS bacterial burdens compared with control animals. *S. aureus* led to the induction of numerous chemokines in the brain, including macrophage-inflammatory protein (MIP)-1alpha/CCL3, MIP-1beta/CCL4, MIP-2/CXCL1, monocyte chemoattractant protein-1/CCL2 and TCA-3/CCL1, within 6 hours after bacterial exposure. Since neutrophils constitute the majority of the cellular infiltrate in early brain abscess development, their subsequent analysis focused on MIP-2 and KC/CXCL1, two neutrophil-attracting CXC chemokines. Both MIP-2 and KC protein levels were significantly elevated in the brain after *S. aureus* exposure. Neutrophil extravasation into the brain parenchyma was impaired in CXCR2 knockout mice and was associated with increased bacterial burdens. Their studies demonstrate the importance of the CXCR2 ligands MIP-2 and KC, and neutrophils in the acute host response to *S. aureus* in the brain.[53,54]

CLINICAL FEATURES

Brain abscess mostly occurs during the first two decades of life with a prediliction for males.[13,86] In infants they usually occur following septicaemia or meningitis and are mostly multiple (Fig. 1). The presenting features

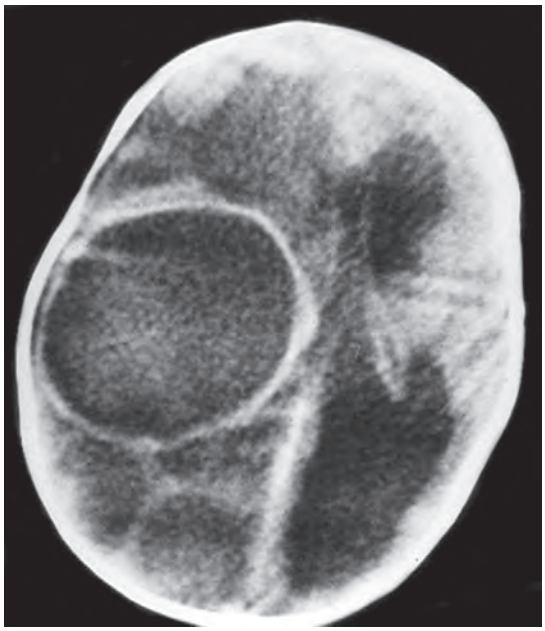


Fig. 1: Contrast computerised scan of an infant showing multiple abscesses

depend on the size, location, multiplicity of the lesion, the virulence of the organism, the host response, and the severity of cerebral oedema. The symptoms of brain abscess are indistinguishable from those of a tumour or a space occupying lesion. However, the symptoms of brain abscess are more rapidly progressive than those associated with a neoplasm[103] and are like rapidly expanding intracranial mass lesions. They include headache, seizures and focal neurological deficits.[84] The classical clinical triad of headache, fever and neurological deficit is seen in 50% of cases. Headache is usually constant, progressive and refractory to therapy, occurring in 70–97% of cases.[67,68,86,105] It is often generalised but may localise to the side of the abscess and increases in severity as the size of the abscess increases. Nausea and vomiting, which indicate raised intracranial pressure (ICP), occur in 25–50% of cases.[67,86]

Fever, which is usually low grade, is present in about 50% of cases.[67,86,105] However, in children fever occurs in 80% of cases.[85] Fever higher than 38.5°C indicates the presence of a systemic infection or concomitant meningitis.[21] Altered level of consciousness is present in approximately two-third of patients, ranging from mild confusion to coma.[63,67,86,105] Papilloedema develops in about 50% of cases, which is a relatively late event.[85]

Focal neurological deficits occur in more than 60% of cases.[63,67,86,105] The neurological deficit will depend upon the location of the abscess. An abscess in the posterior frontal and parietal lobe causes hemiparesis, whereas varying degrees of dysphasia and visual field defects are seen in a temporal lobe abscess. Cerebellar abscess manifests with ataxia and nystagmus. Pre-operatively, seizures occur in 30–50% of cases. Involvement of the III or VI cranial nerve may occur due to raised ICP.[63,67,86]

Infants usually present with progressively enlarging head, bulging fontanelle, separation of sutures, vomiting and seizures. Infants usually have irritability and poor feeding.

Adults with normal host response frequently show a rapid onset and progression of symptoms. In contrast, immunocompromised patients may have an insidious onset of symptoms, in which case high index of suspicion is necessary to make an early diagnosis.

LABORATORY INVESTIGATIONS

Routine laboratory studies are not very helpful in substantiating a diagnosis of brain abscess. The total leucocyte count is frequently normal and is only mildly elevated (less than 15,000 cells/cubic mm) in 60–70% of patients.[21,63,67] In cases of brain abscess with concomitant meningitis or acute systemic infection the WBC count may be elevated above 20,000 cells/cubic mm.[21] The erythrocyte sedimentation rate is elevated in about 90% of cases, but it is a non-specific indicator of inflammation.

Jamjoom[51] reported elevated serum C-reactive proteins (CRP) in 77% of patients with brain abscess. The CRP has been found to be a useful marker for differentiating brain abscess from other slowly progressive intracranial mass lesions. CRP levels return to normal after successful treatment and persistently elevated CRP indicates incomplete treatment.[51]

The blood cultures are usually negative. However, in patients with brain abscess associated with septic embolisation from an intravascular endothelial infection such as endocarditis or mycotic aneurysm it may grow organisms.

The CSF analysis is non-specific. There may be mild pleocytosis with WBC count lower than 100 cells/cubic mm unless there is co-existing meningitis.[67] The CSF protein contents are mildly elevated (usually < 100 mg/dl) and CSF glucose levels are generally normal except in patients with frank meningitis where CSF glucose is low. Cultures are usually sterile, particularly in patients who have been receiving antibiotics. Since the CSF findings are non-specific and lumbar puncture is potentially dangerous in the presence of an intracranial mass lesion and also easy accessibility to the CT scan, lumbar puncture should not be performed.

Molecular techniques can increase the number of identified microbial agents in cerebral abscesses. The ability of detecting bacterial pathogens directly from the clinical brain abscess specimens can be achieved by polymerase chain reaction (PCR) amplification and sequencing of bacterial 16S ribosomal deoxyribonucleic acid (rDNA). Bacterial 16S rDNA sequences provide reliable clues to the identification of unknown pathogens. The PCR analysis of 16S rDNA and sequencing may identify pathogens to the species level directly from brain abscesses. This approach is rapid and is useful, especially in the identification of slow-growing and fastidious organisms. Mycoplasma species, an emerging pathogen, is common and should be detected in these situations.[2,100]

RADIOLOGICAL INVESTIGATIONS

Advances in neuroimaging, most notably the routine use of CT scanning, have substantially improved the diagnosis and management of CNS infections in general and brain abscesses in particular. Diagnostic studies that have been used in the evaluation of patients with suspected brain abscess include plain radiography of the skull, pneumoencephalography, ventriculography, arteriography, radionuclide scan, CT scan and MRI.

X-Ray Skull

The skull radiographs are often normal in patients with brain abscess, but in some patients signs of raised ICP may be evident. In post-traumatic abscess, air inside the cranial cavity may be visualised. Evidence of paranasal sinusitis and mastoiditis can also be seen in the plain skiagrams of the skull.

Computed Tomography

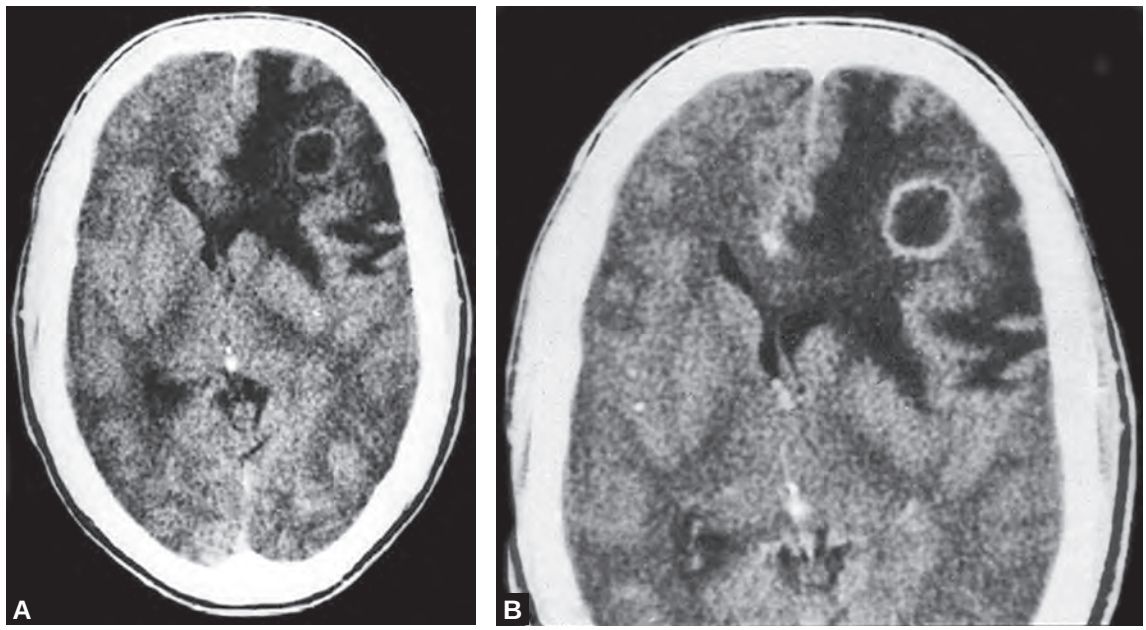
The CT scan has remarkably improved the ability to diagnose and localise pyogenic brain abcesses. Before the advent of CT scan, delay in diagnosis contributed significantly to the high morbidity and mortality. The CT scan has rendered diagnostic tests such as angiography, ventriculography, pneumoencephalography and radionuclide brain scanning virtually obsolete and of historical interest only. In addition to the diagnosis of the abscess *per se*, CT is excellent for detecting sinusitis, mastoiditis and soft tissue infections that may be predisposing factors for a brain abscess. Apart from early detection and accurate localisation, it provides valuable information regarding staging of an abscess, associated hydrocephalus, raised ICP, oedema, associated infection, pathology like subdural empyema, ventriculitis, meningitis, multiplicity of an abscess, loculations and to some extent the nature of the pus. This additional information has proved helpful in better planning and management of a brain abscess.[84,89,106] It is invaluable in assessment of adequacy of treatment and subsequent follow-up also.[89]

The classic appearance on a contrast enhanced CT scan is a lesion having a smooth, thin, regular wall with a decreased density both in the centre of the lesion (representing pyogenic material) and in the surrounding white matter (representing oedema). On non-contrast scan, the wall may be isodense or denser than the brain[84] (Figs 2A and B). Various authors have described CT scan findings as per staging of an abscess and demonstrated that the CT classification correlated well with the histopathologic stage confirmed on surgery or autopsy.[15,32]

Magnetic Resonance Imaging

The MRI is more sensitive than CT scan and is capable of detecting a brain abscess in the earliest stage of development.[1] Even the plain MRI is characteristic of brain abscess and is specific to make an accurate diagnosis. Additional advantages of MRI include better anatomic details, multiple imaging planes, lack of bony artifacts, especially in the posterior fossa and increased sensitivity for follow-up examination.[97]

Characteristic T1-weighted images show a peripheral zone of mild hypointensity relative to adjacent brain, representative of oedema formation, surrounding a central region of more marked signal hypointensity, indicative of the necrotic centre of the abscess. The capsule separates these two regions and appears as a discreet rim that is isointense to mildly hyperintense[46] (Fig. 3).



Figs 2A and B: (A) Non-contrast computerised scan showing isodence capsule wall of frontal abscess. (B) Contrast computerised scan of the same patient showing enhancing capsule wall

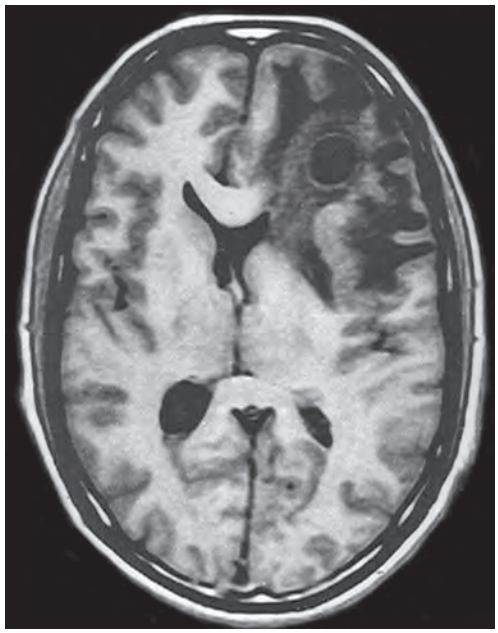


Fig. 3: T1-weighted magnetic resonance showing left frontal abscess

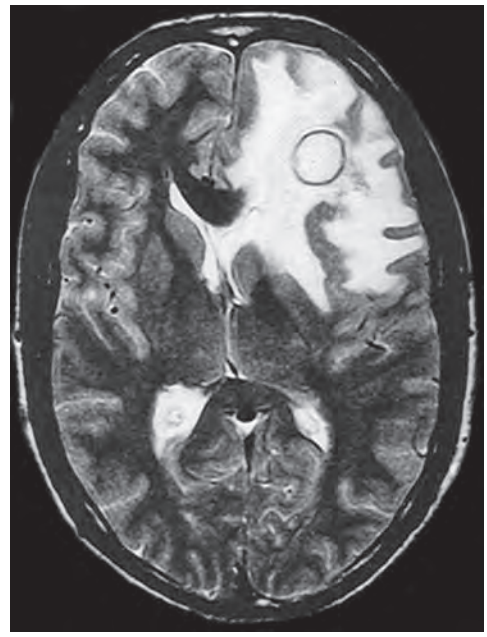


Fig. 4: T2-weighted magnetic resonance of the same patient showing hypointense rim at the margin of the abscess

On T2-weighted sequences the signal intensity of the zone of oedema increases markedly compared with the adjacent brain, while the central core is isointense to hyperintense compared with grey matter. The capsule now appears as a well defined hypointense rim at the margin of the abscess (Fig. 4).

Magnetic Resonance Spectroscopy

Magnetic resonance spectroscopy (MRS) has emerged as a powerful tool to non-invasively differentiate a brain abscess from a tumour.[79] The MRI when combined with *in vivo* MRS may help to better characterise cystic intracranial mass lesions.[77] There are lesion specific spectral patterns that may assist in tissue characterisation. Spectral pattern from MRS may permit differentiation of a brain abscess from necrotic or cystic tumours.[56] The presence of amino acids (AAs) on *in vivo*[1] H-MR spectroscopy is a sensitive marker of pyogenic abscess, but its absence does not rule out a pyogenic aetiology. The presence of acetate (Ac) with or without succinate (Suc) favours an anaerobic bacterial origin of the abscess, which may also be seen in some of the abscesses secondary to facultative anaerobes.[74] It might be possible also to differentiate tuberculous abscesses from pyogenic abscesses by using magnetisation transfer MRI and *in vivo* MRS, which could be of value in influencing the management of such cases.[44]

Diffusion Weighted Imaging

Ebisu et al.[31] described high signal intensity in the abscess fluid associated with low apparent diffusion coefficient. In contrast, necrotic or cystic tumours show low signal intensity in diffusion weighted imaging indicating a high apparent diffusion coefficient.

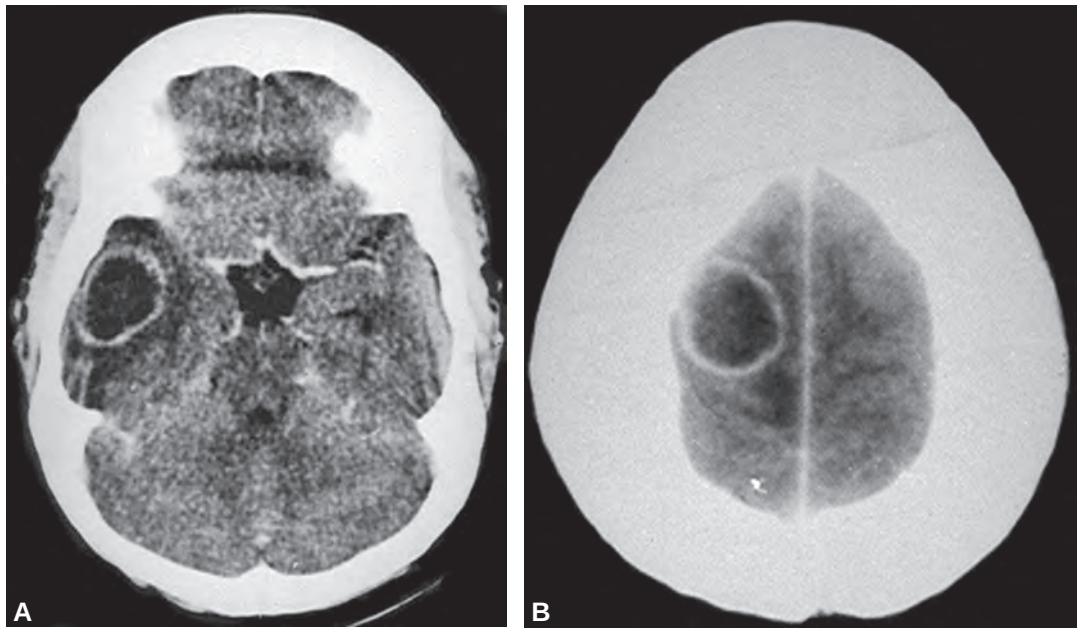
TREATMENT

The advent of CT scan and better understanding of pathogenesis have changed the management of brain abscess. Until the early 1970s surgery (aspiration, drainage, excision, etc.) was considered the method of choice for the management of brain abscess. The controversy over whether all brain abscesses require surgical treatment began in the early 1970s when Heineman and Braude[47] and subsequently other authors[6,10,23,83] published reports about non-surgical treatment of brain abscesses. Age, neurological status, location, number, size, loculations and stage of abscess formation influence the choice between conservative versus operative treatment. Each case must be individualised and treated on its own merit.[89]

Medical Treatment

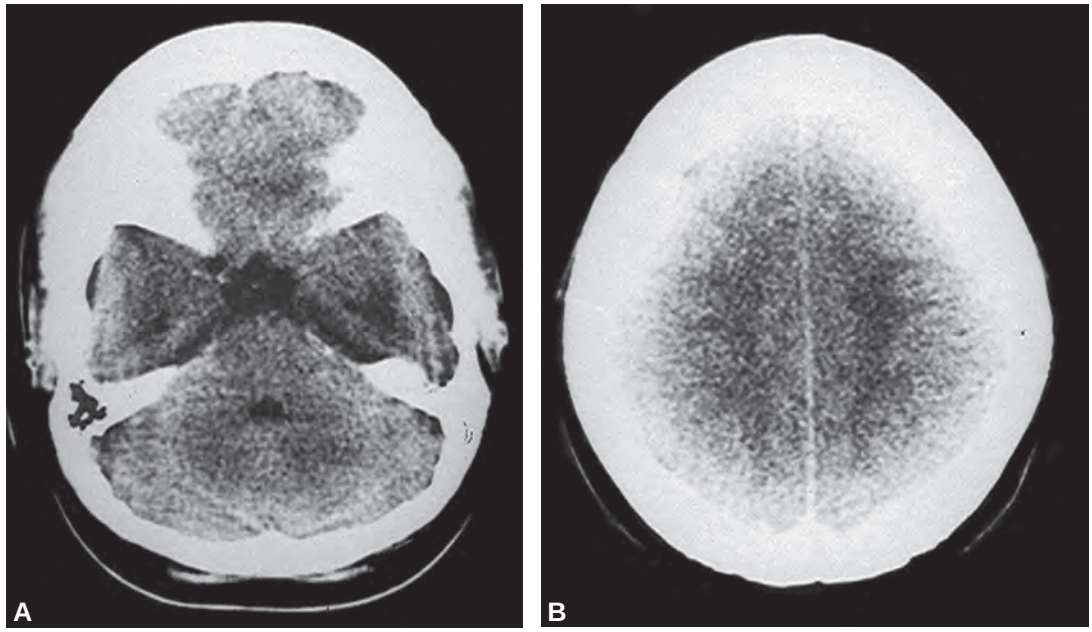
In selected patients, especially those in whom the abscess is still in the cerebritis stage and in those patients where the brain abscess is not associated with signs of raised ICP (clinically as well as on CT scan) and particularly those patients who have an abscess less than 3 cm in size, it can be managed conservatively with antibiotics alone[84] (Figs 5A and B, 6A and B). High-risk patients with bleeding diathesis caused by thrombocytopaenia (platelet count less than 30,000 cells/cubic mm) or coagulopathy where even minor surgery is contraindicated are best treated with medical treatment. Antibiotic therapy started early during the cerebritis stage or in small abscesses may result in complete cure.[89] However, serial CT scans are essential as an abscess may enlarge despite adequate antibiotics.[10,89]

Widespread use of antibiotics has reduced the mortality and morbidity associated with brain abscess. The



Figs 5A and B: Contrast computerised scan showing multiple abscesses in right temporal and frontal lobe

choice and efficacy of antibiotic depends on a number of factors including whether a particular antibiotic is bacteriocidal or bacteriostatic, type of microbials, concentration in CSF, whether it can cross the blood-brain barrier and blood CSF barrier, route and duration of therapy, the host response to infection, the concentration of the drug at the site of abscess and predisposing factors.[27,29,35,39,43,84,89] The concentration of antibiotic achieved in human brain abscess has been studied by Black et al.,[10] DeLouvois et al.[27] and Everett and Strausbaugh.[35] Antibiotics, like chloramphenicol, metronidazole, sulphonamides, isoniazid, rifampin and flucytosine, which penetrate well into normal brain and CSF, have potential utility for the treatment of brain abscesses.[84] When the permeability of the blood-brain barrier is altered by inflammatory conditions such as cerebritis and abscess, antibiotics that usually do not penetrate into CSF or brain tissue such as penicillin and cephalosporins, can penetrate well. Studies in experimental abscesses have demonstrated variable penetration of the aminoglycosides particularly gentamicin. Aminoglycosides are poor penetrators, especially into CSF and cannot be used intravenously to treat gram-negative meningitis. However, adequate correlation regarding chemical efficacy in the treatment of brain abscess and penetration capabilities of these antibiotics has not been done as in the case of meningitis.[84]



Figs 6A and B: Follow-up computerised scan of the same patient after 6 weeks of antibiotics, showing complete resolution of abscess

Evaluation of vancomycin in cases of Staphylococcal brain abscess has shown that the penetration of vancomycin is excellent; concentration of vancomycin in the abscess fluid was found to be 80% of the simultaneously obtained serum concentration.[60] In patients with meningitis the concentration of vancomycin in CSF is only 10–20% of the serum concentration. The correlation between penetration of an antibiotic into the infected area and the success of therapy has also not been well established.[84]

Pre-operative use of antibiotics would prevent the spread of infection during aspiration or surgical removal of the abscess. However, the possibility of obtaining false negative culture, particularly from a small lesion, is high with the pre-operative use of antibiotics.[84] Selection of antibiotics pre-operatively will be based on the aetiology of an abscess and organisms most frequently encountered. The best choice would be of those antibiotics which would cross the blood-CSF and blood-brain barrier. Later on, after obtaining the culture and sensitivity, proper antibiotics should be started. If no organism is identified, the antibiotic should be selected depending on the predisposing cause (primary source) and anatomic location of the abscess.[28,58] Earlier, penicillin and chloramphenicol were mainly used in treatment of brain abscess, particularly before cultures were obtained. They are now replaced with cefotaxime, vancomycin and metronidazole.[63]

Song et al. reported that in their series of 90 consecutive patients with brain abscess the rate of positive bacterial culture was only 12%. The outcome of superficial abscesses was better than those of abscesses in deep-seated locations ($p < 0.01$); multiple brain abscesses led to significantly poorer outcomes than unilocated abscesses ($p < 0.01$). There was no significant difference between the paediatric group and the adult group ($p > 0.05$). The differences in outcomes between intrathecal injection combined with systemic administration of antibiotics versus only venous administration could not be found ($p > 0.05$). They concluded that the effectiveness of tertiary-generation cephalosporin + vancomycin + metronidazole for bacterial brain abscess was 88%, and recommend combined antibiotics in cases with no positive cultures.[92]

The indications for non-surgical treatment are:
Patients who have a small abscess (less than 3 cm in diameter)

- Patients who have no signs of raised ICP
- Patient who is alert
- Clinically stable patient with no neurological signs
- Patient with multiple lesions
- Patients having high risk for surgery and anaesthesia

Patients in whom the diagnosis is firmly supported by identification of a predisposing factor, imaging studies, and patients in whom the organism has been identified presumably from culture elsewhere.[84,89]

Accurate assessment of therapeutic response can now be analysed with treatment-induced changes in diffusion tensor imaging indices [i.e. fractional anisotropy (FA) and mean diffusivity] in follow-up patients with brain abscess after treatment. The reduction in FA value reflects the down-regulation of the neuroinflammatory molecules in response to treatment of patients with brain abscesses.[71]

Surgical Treatment

Surgery is indicated to confirm the diagnosis, to obtain a sample for culture for identification of specific pathogens and sensitivity to particular antibiotics, and to remove as much purulent material as possible. Surgery should also be performed when there is clinical deterioration, significant mass effect, neurological deficit, multiple lesions in surgically accessible locations, doubtful diagnosis, presumably resistant organisms[89] and multiple loculations.

Many surgical procedures (including drainage, aspiration, excision) have been described for the treatment of a brain abscess,[19,84,89,93] but these days aspiration and surgical excision are the most commonly and widely used procedures. There is, however, some controversy whether aspiration or excision should be performed. In choosing between aspiration and excision various factors including surgical morbidity, success rate, and sequelae such as recurrence, seizure disorder, etc. should also be considered. Drainage is seldom used nowadays.[83]

Due to easy availability of CT scan for initial diagnosis and follow-up, these days aspiration of a brain abscess rather than primary excision has been widely used. Aspiration is a rapid and safe procedure, especially when the patient has markedly raised ICP and the abscess is located in an eloquent area. Aspiration is usually performed under local anaesthesia, except in children. It can be done with the use of stereotactic technique, real time ultrasound, particularly in infants with open fontanelle or under CT scan guidance. All these techniques provide precise localisation of an abscess. Stereotactic aspiration of an abscess is useful in a deep-seated abscess; abscess in the brainstem or thalamus, and even in a multi-loculated abscess. Callovini et al. treated three consecutive cases of thalamic abscess by stereotactic puncture as the first step, followed by histological analysis, external drainage and targeted intrathecal and systemic antibiotic therapy. They felt deep-seated abscesses behave differently as they are associated with an increased risk of intraventricular rupture and antibiotic resistance, which justifies a more aggressive and immediate surgical treatment.[18] CT or MR image-guided stereotactic aspiration via the suboccipital transcerebellar approach has been found an effective procedure for the treatment of brainstem abscesses. This procedure is less invasive than open surgery and can be performed even in patients in poor general condition.[11,70] Hellwig et al.[48] and Frisch and Manwaring[36] have reported encouraging results with endoscopic stereotactic aspiration of brain abscess. Kutlay et al. treated brain abscess patients with

stereotactic aspiration combined with antibiotics and hyperbaric oxygen (HBO) therapy. Their results indicate that the duration of antibiotic usage can be shortened with the use of HBO as an adjunctive treatment.[57]

Usually most abscesses respond to and reduce in size after repeated aspirations, particularly cerebellar abscesses, where burr hole aspiration is mostly sufficient.[17,69,105] If the abscess does not reduce in size and the quantity of pus does not subsequently decrease (even after 3–4 aspirations), excision of an abscess can be planned. The advantage of secondary excision over primary is that the surrounding oedema is significantly less after multiple aspirations. Post-traumatic abscesses containing bone fragment or foreign body, however, require primary excision. Proper and thorough wound toilet and removal of hair, foreign body, etc. are essential to prevent recurrence. Multi-loculated abscesses also mostly require secondary excision.

Su et al. reported an incidence of 20% of multiloculated abscesses in a series of 25 patients with pyogenic brain abscess. They conclude that excision seems to be the more appropriate surgical choice in multiloculated abscess, and prognosis can be as good as that for patients with uniloculated abscess. However, clinicians must carefully monitor these patients because the possibility of recurrence after surgery is significantly higher in patients with multiloculated abscess than in those with uniloculated abscess.[94]

Cerebellar and cerebellopontine angle abscesses, by virtue of their size and associated oedema, may obstruct the CSF pathways resulting in hydrocephalus, which may require immediate CSF diversion by adopting external ventricular drainage.[69]

Management of Multiple Abscesses

The detection rate of multiple abscesses has increased with the advent of CT scan and thus improved their management. They are mostly haematogenous and are often found in patients with cyanotic heart disease and in immunocompromised patients. Corticosteroids in particular are significant predisposing factors in patients with two or more brain abscesses.[25] They account for 5–50% of all brain abscess patients. Aspiration should be done in patients with large abscesses particularly those with neurological deficit and those which are accessible. Repeated aspirations reduce associated oedema and raised ICP. In patients who have one or more large abscesses and are not reducing on repeated aspiration, surgical excision may be considered. With regards to multiple brain abscesses due to *L. monocytogenes*, Cone et al. advocated therapy with high-dose ampicillin in combination with gentamicin as the drugs of choice, followed by trimethoprim/sulfamethoxazole and vancomycin. In general, antimicrobial therapy appears to be satisfactory treatment without surgical intervention.[25]

Role of Corticosteroids

The use of corticosteroids in the treatment of brain abscess is controversial. Corticosteroids significantly reduce cerebral oedema and mass effect that accompany brain abscess. Corticosteroids, however, inhibit the migration of leukocytes and diminish the effectiveness of the host response when used in the early cerebritis stage.[84,106] Administration of corticosteroids should, therefore, be avoided in the early stages of brain abscess development.

Whelan and Hilal[103] reported that administration of corticosteroids decreases enhancement of the abscess wall on CT scan and that withdrawal of corticosteroid occasionally results in increased enhancement despite clinical stability and eventual cure. Britt and Enzmann also observed decreased wall enhancement, but only in the cerebritis stage of abscess formation.[15,32] The majority of experimental evidence seems to indicate that steroids have more deleterious than beneficial effects.[106]

COMPLICATIONS

Epilepsy

Epilepsy is a common sequel of brain abscess occurring in 30–50% of patients.[4,20,52,67] The maximum frequency of seizures occurred during the 4th and 5th year after diagnosis.[106] Nielsen et al.[73] reported high incidence of seizures with frontal lobe abscesses. Patients treated with aspiration alone tend to have less seizures than patients in whom the abscess is excised.[20,59,67,86] Due to the high incidence of seizures, all patients with supratentorial brain abscess should be given prophylactic anticonvulsants for 1–2 years. The anticonvulsant should be tapered if the electroencephalography shows no epileptogenic activity. Patients having intractable seizures may sometime respond to temporal lobe resection or resection of the seizure focus.[106]

OUTCOME AND PROGNOSIS

With the introduction of CT, stereotactic techniques and broad-spectrum antibiotics, the outcome for brain abscess has dramatically improved, and depends on prompt awareness of the diagnosis and effective infection control. Tseng et al. found no association between outcome and other factors, including age, focal neurological deficits, seizures, laboratory findings, characteristics of the abscess, associated factors and treatment modalities.[101] The poor prognostic factors of brain abscess are poor glasgow coma scale, immunodeficiency and presence of underlying disease. Aggressive treatment with surgery, when indicated, and careful management of the aetiology might improve the outcome.[104] Once the abscess is cured, secondary operation is indicated to remove the primary cause, e.g. chronic mastoiditis, paranasal sinusitis, congenital heart disease, bronchiectasis, etc.

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61 Scalp and Skull Infections

Ravi Ramamurthi, Goutham Cugati

Scalp infections are encountered as a complication of scalp lacerations. They are also seen as a complication of various surgical procedures, like craniotomy, shunt surgery, from scalp electrodes used in deep brain stimulation and pin site infection for halo or skull pin traction.

SCALP LACERATIONS

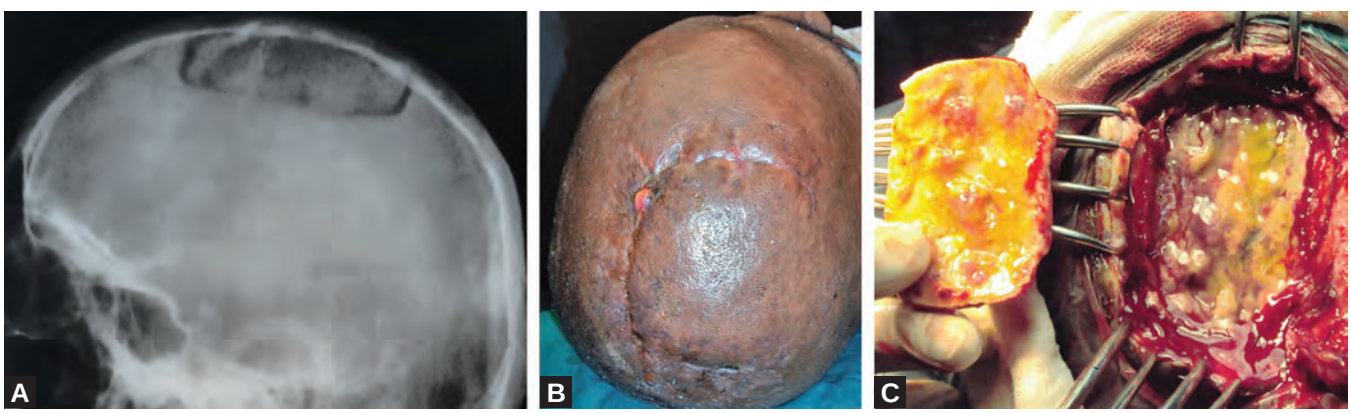
Most scalp lacerations heal without complications, but mismanagement of the same may end up in infections. Preventing scalp infections can be achieved by following the basic principles of wound management like reducing tissue contamination, meticulous wound toilet, debriding devitalised tissue, restoring perfusion in poorly perfused wounds and establishing a well-approximated skin closure without tension. Care has to be taken to remove any contaminants or foreign bodies within the wound. Continuous irrigation of the wound under moderate pressure reduces wound bacterial counts. Routine use of prophylactic antibiotics may be required if there is evidence of bacterial contamination or host risk factor. The patient's tetanus immunisation status should be evaluated, with the need for further immunisation determined as per US Centers for Disease Control and Prevention recommendations.

POST-OPERATIVE SCALP INFECTION

Accurate identification and evaluation of post-operative infection is very essential in neurosurgery as it can have devastating effects if left unattended. Narotam et al.[30] conducted a study of post-operative wound infections where the study group was divided into five categories as: (1) Dirty (brain abscess, ventriculitis, meningitis, etc.); (2) Contaminated (compound skull fractures, open lacerations, CSF fistulae, etc.); (3) Clean contaminated (entry into paranasal sinuses, transphenoid/transoral procedures, prolonged surgery, etc.); (4) Clean with foreign body (shunts, EVD, ICP monitors, DBS electrodes, etc.) and (5) Clean (ideal operating conditions). They have suggested that all abnormally appearing wounds be considered as wound infection as bacterial culture may not be positive in all the instances. With increasing degree of contamination, there was increasing rates of infection. The difference in rates of infection was very marked between the clean cases and the other four groups. The clean with foreign body and the clean contaminated groups had similar infection rates. Widespread use of permanent foreign materials has been an important predisposing factor.

CRANIOTOMY AND SCALP INFECTION

The incidence of scalp infection following a clean craniotomy varies from less than 1 to 5%[34] (Figs 1A to C and 2). Baumeister et al.[4] who conducted a meta-analysis found that 1–8% of craniotomy cases land up having post-operative infection necessitating removal of the bone flap and requiring secondary cranioplasty. The predisposing factors for post-craniotomy infection include:[16,19,30,34]



Figs 1A to C: Forty-year-old gentleman who underwent craniotomy for astrocytoma presented with post-craniotomy osteomyelitis. (A) Skull lateral X-ray showing lytic changes in the bone flap. (B) Clinical photograph showing discharging sinus along the operative scar. (C) Operative photograph showing infected bone with epidural collection of pus

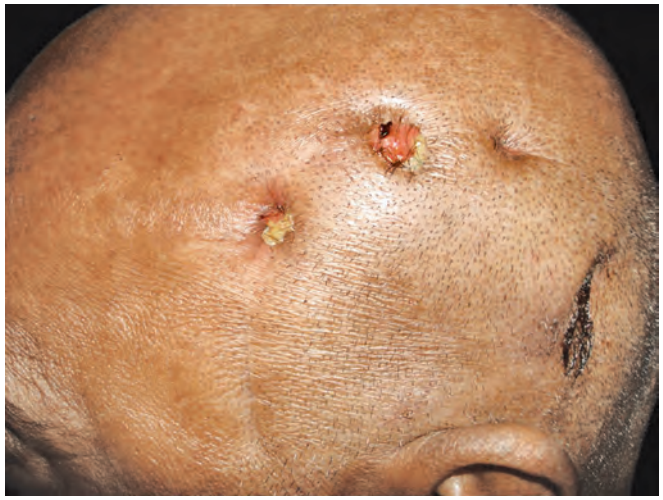


Fig. 2: Clinical photograph showing burr hole site scalp infection in a patient who has undergone craniotomy

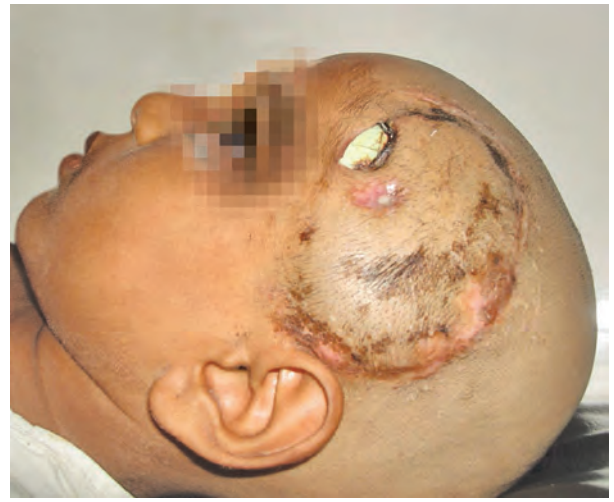


Fig. 3: Clinical photograph showing scalp infection and exposure of the acrylic in a patient who underwent cranioplasty

- Emergency level of surgery
- Long duration of surgery (>200 min)
- Duration of stay in ICU (>72 hrs)
- Penetration of paranasal sinuses
- CSF fistulae
- Multiple surgeries via same incisions
- Use of permanent implantable foreign materials (acrylic, metal wires, ventricular catheters, etc.) (Fig. 3)
- Tight haemostatic skin clips resulting in skin necrosis.

DEEP BRAIN STIMULATION AND SCALP INFECTION

Placement of the hardware in cases treated by deep brain stimulation has its potential complications of malfunction, lead migration, fracture, scalp erosion or infection. Spiotta et al.[44] have advocated two different approaches to address the problem of skin erosion or impending skin erosion in DBS patients. To tackle the above problem a temporo-parieto-occipital flap based on the superficial temporal artery with or without scalp expansion, and a scalp fasciocutaneous flap with or without cranioplasty can be used. Further refinement of the hardware is required to minimise hardware related complications.[44]

PIN SITE SCALP INFECTION

Various types of spinal immobilisation devices are in use for patients with spinal injury. Immobilisation using the Halo vest and Gardner Well's skull tongs requires placement of skull pins. In such patients pin site infection may be seen. In patients with Halo vest immobilisation, Van Middendorp et al.[46] have found pin site infection in 12% of 239 patients, and Botte et al.[8] and Garfin et al.[13] have found up to 22%. Pin site infection was mostly seen in those patients where the outer table was penetrated. *Staphylococcus aureus* has been the most common pathogen in these infections. Superficially infected pins can be managed with local pin care and oral antibiotics. Persistent or severe infections require pin replacement to a nearby site, parenteral antibiotic therapy, and incision and drainage as needed.[7]

OTHERS

Patients having presurgical scalp infections, like pediculosis capitis or scabies, are prone to peri-operative scalp infections. This problem is seen more in developing countries and in the paediatric age group. Early recognition of these conditions and prompt treatment is necessary.[41] If the neurosurgical procedure is not an emergency, as not the case always, then it is advisable to operate after complete treatment of local scalp infections.

Diagnosis

The infection may be superficial when the dermis and epidermis is involved or deep when the galea and the underlying bone are involved. *Staphylococcus aureus* is the predominant pathogen followed by hospital acquired pathogens like *Pseudomonas* and *Klebsiella*. Anaerobic pathogens and the gas forming *Clostridium* species infecting the scalp have also been reported.[47]

The patient may have evidence of local signs of infection like erythema, swelling, inflammation, tenderness and warmth. There may be a fluctuant collection or a discharging sinus with a serosanguinous or purulent discharge. The discharge needs to be sent for aerobic, anaerobic and fungal cultures. If tuberculosis is suspected, then tubercular culture also needs to be done.

Management

General risk factors for infection, like diabetes mellitus, obesity, malnutrition, chronic renal failure, advanced age and use of steroids, should be noted and appropriate measures taken to tackle them.

When the infection is superficial, oral antibiotics and anti-inflammatory agents are sufficient. If the infection is deep, it may require wound debridement along with administration of intravenous antibiotics depending

on the sensitivity of the organism. If the infection has spread to the bone, then, often it necessitates removal of the bone flap. A secondary cranioplasty will be required at a later date.[4] In cases of large scalp defects, there may be difficulty in scalp adaptation for cranioplastic surgery, especially in patients having scalp atrophy, poor nutritional condition and tense sutures. In such patients scalp expansion is effective. Instead of a hasty single sitting cranioplasty, two-stage cranioplasty can be done after tissue expansion with a scalp expander.[28]

There has been a controversy regarding shaving of the head for cranial surgery. Tokimura et al.[45] investigated 632 patients who underwent cranial surgery without head shaving and found no increased risk of wound infection. The low risk of infection was attributed to the use of the electrosurgical scalpel for skin and soft tissue dissection, which minimises bleeding and the probability of wound infection. Paolini et al.[33] who observed less than 1% of post-operative scalp infection have advocated shaving a small strip of hair along the planned wound. Closure of the wound was by intradermal sutures instead of traditional sutures or metal staples which requires removal in the post-operative period. Review of earlier studies and a search into the history of aseptic surgery shows that the practice of shaving the head does not have a scientific basis. There is no advantage in shaving patients in terms of reducing wound infection rates.[20] The use of depilatory agents has a lesser rate of infection than using razors.

General guidelines for prevention of surgical site infection were elucidated by Mangram in 1999.[25] Further information regarding the same may be obtained at www.cdc.gov/ncidod/dhqp/pdf/guidelines/SSI.pdf.

SKULL OSTEOMYELITIS

Although osteomyelitis can affect any bone in the body, involvement of the skull bones is a rare entity. One of the earliest reports of osteomyelitis of the skull was the one by Sir Percival Pott, where he described a subperiosteal abscess of the frontal bone occurring as a complication of trauma causing a puffy swelling in the forehead. Since then it derived its name, Pott's Puffy tumour.[35]

Pathogenesis

Haematogenous spread of infection to the skull is a rare entity. Skull osteomyelitis, in most of the instances, is a result of contiguous spread of infection. The probable sources of infection being:[9,21]

- Post-traumatic following compound fracture of the skull
- Post-craniotomy
- Sinusitis
- Intracranial infections
- Scalp infections
- Dental procedures
- Dermatological procedures
- Cryptic osteomyelitis

Osteomyelitis after craniotomy occurs in approximately 1.1–8.1% of cases and often necessitates bone flap removal[14] (Figs 1A to C). In a patient with spread from sinusitis, the frontal sinus is frequently seen as the offender. In patients with malignant otitis externa, especially in the paediatric population, spread of infection may result in osteomyelitis of the cranial base.[3] In a few instances the source of infection is not diagnosed as in cryptic osteomyelitis. Most of such cases have atypical/central type of skull base osteomyelitis. Such patients have been observed to have an immunocompromised state or other predisposing factors like diabetes.[10] In newborns, secondary to birth trauma, cephal haematoma, a subperiosteal collection of blood may be formed. Very rarely, due to bactraemia there may be colonisation of bacteria in the blood resulting in osteomyelitis.[27]

Pathogens

The common pathogens are microaerophilic streptococci, including *alpha-haemolytic Streptococcus, Staphylococcus, Peptostreptococcus*, bacteroides species and other anaerobes such as *Fusobacterium*. These organisms may be more common in this setting due to the relatively lower oxygen concentration in the frontal sinus, caused by compromised ostial patency.[37] Lee et al. have reported that *Pseudomonas* is the causative organism in 74% of 28 patients who were treated for skull base osteomyelitis.[22] In the report by Clark et al. who reported four cases of atypical skull base osteomyelitis, *Pseudomonas* species were isolated in three cases and a literature review by them showed *Pseudomonas* species in 8 out of 15 cases where a pathogen was isolated. Other organisms that have been reported include gram-positive organisms, *Aspergillus, Mycobacterium* and *Candida*.[40] In patients with immunocompromised state and prolonged steroid use organisms, like *Salmonella*,[5] *Cryptococcus* and *Treponema pallidum*, have been isolated.[2,17] There are a few reports of skull osteomyelitis from fungi like mucormycosis, madura mycosis and others.[38] A rare pathogen like *Propionibacterium acnes* has been isolated in a case of post-craniotomy osteomyelitis.[14]

Clinical Features

These patients present with generalised symptoms like fever, headache, vomiting, fatigue/malaise along with scalp tenderness and swelling. Pott's puffy tumour is the term given to a subperiosteal abscess of the frontal bone, usually presenting as a localised swelling of the soft tissues in the overlying region of the forehead, and is associated with localised osteomyelitis. It can be seen in the setting of frontal sinusitis or as a post-traumatic complication.[26,29] The incidence of this entity has come down in the antibiotic era. In some instances, there may be evidence of intracranial infection/abscess spreading to the calvarium and then extracranially to the soft tissues. It may mimic a calvarial bony tumour.[18,42]

Patients with skull base osteomyelitis can present with headache and a variety of cranial neuropathies, often a combination of VI and lower cranial nerve (CN) neuropathies. The source of infection in the form of ear infection needs to be looked for. In a typical case of skull base osteomyelitis the temporal bone is involved, whereas in atypical or central type of skull base osteomyelitis the sphenoid, occiput or the clivus can also be involved.[10]

Tubercular osteomyelitis rarely involves the upper extremities and non-weight-bearing bones. Skull involvement is exceptionally rare and is seen mainly in children. The lesions may be solitary or multiple involving both tables of the skull. They may form a scalp swelling with a sinus. Careful examination to look for other evidence of tuberculosis is required.[1]

If the treatment is inadequate (<4 weeks) or the patient is immunocompromised, then the patient may have recurrent infection. In chronic cases, the infection may persist for more than three decades.[31]

Investigation

Blood investigations often show an increase in the acute phase reactants like ESR, WBC count and CRP counts.[10] On plain radiographs, the skull lesions appear as lytic areas and these changes take several months to be seen. Initial CT scan may not show evidence of the disease, whereas in the later part of the disease evidence of lytic bony lesions is seen. Seabold et al. found no CT evidence of bone erosion in 13 out of 35 patients with biopsy-confirmed cranial osteomyelitis.[10,15,39] Once the treatment is completed, the changes on the CT take a long time to revert to normal. Hence, CT may not be a good choice to follow-up patients. On MRI the lesions appear hypointense in T1 and hyperintense in T2. In skull base osteomyelitis, it is very difficult to differentiate this condition as various conditions like skull base malignancies and other non-neoplastic conditions may mimic this entity. Various nuclear medicine imaging techniques, like gallium-67 scintigraphy, indium-111 white blood cell scans, technetium-99m methylene diphosphonate (MDP) bone scans and single-photon emission computed tomography (SPECT), have been used to investigate for postoperative osteomyelitis and also to follow-up patients on treatment.[23]

Lee et al.[22] classified the patients with skull base osteomyelitis using Technetium-99 SPECT into four grades:

1. Mild uptake
2. Focal mastoid/temporal bone uptake not reaching the midline
3. Petrous temporal bone uptake reaching the midline
4. Uptake crossing the midline, involving the contralateral temporal bone

Histopathological examination of the biopsy/debrided tissue is essential along with pyogenic, fungal and tubercular cultures as HPE may be non-diagnostic at times.[10]

Management

Surgical resection of the diseased bone with adequate clearance is required.[36] Post-operatively the patient has to be on long-term antibiotics for complete clearance of the infection. Pseudomonas being the commonest pathogen, antipseudomonal antibiotics have to be started empirically and once the sensitivity is available it may be changed, if necessary.[43] In various reports the duration of antibiotic treatment varied from 1 month to 6 months.[12] The Bone Infection Unit in Oxford, United Kingdom, recommends up to 6 weeks of intravenous treatment followed by 6–12 months of oral medication, guided by clinical response.[10] The patient needs to be started on ATT if the HPE is in favour of tuberculosis.[24]

In a few patients with troublesome chronic osteomyelitis, in spite of repeated debridement, the infection might persist. In such instances a combination of extensive surgical debridement and a free flap transfer is effective. A latissimus dorsi muscle flap with a split skin graft has been preferred by a few surgeons.[6] A multidisciplinary approach with an infection specialist and a plastic surgeon might be necessary for such cases.[10] In patients with malignant otitis externa, adjuvant hyperbaric oxygen improves the success of treatment by reversing tissue hypoxia, enhancing phagocytic killing of aerobic micro-organisms and stimulating neo-microangiogenesis.[11] Lee et al. have observed that long-term prognosis depends on the initial stage of presentation of skull base osteomyelitis as seen on SPECT.[22]

Complications of skull osteomyelitis include intracranial extension resulting in epidural, subdural or brain abscess, sinus thrombosis, cranial nerve palsies and death. Mortality from complications is 20–40%.[32] With accurate diagnosis and prompt treatment the complications can be avoided to get a better outcome.

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62 Subdural Empyema

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INTRODUCTION

The term subdural empyema (SDE) is used for suppuration in the pre-existing space between the dura and the arachnoid. The first patient with SDE reported to be operated upon was in 1869 by De la Peyronie, which was documented 10 years later.[32] Kubik and Adams[34] introduced the term "Subdural Empyema" which gained wide acceptance. Various other synonyms of this condition are pachymeningitis interna, purulent pachymeningitis, cortical abscess and subdural abscess.[32]

It has been described either intracranially or in the spinal canal, the latter localisation being quite rare. It is a rare, but serious illness with a declining mortality rate and rather frequent neurological sequelae. Morbidity and mortality in intracranial and spinal SDE directly relate to the delay in diagnosis and therapy.[17]

Although considered uncommon, subdural empyemas (SDEs) constitute 13% and 23% of all intracranial bacterial infections,[27,54] usually presenting with a fulminant clinical picture and rapidly progressive neurological deficit.

They occur more frequently in children than in adults. However, we have to consider subdural infection as one of the differential diagnoses in an elderly patient with subdural hygroma when a new abnormal density lesion develops in the subdural space.[66]

Intracranial SDEs, the majority of which are supratentorial in location, are common neurosurgical emergencies in developing countries, especially in the paediatric age group. They result in significant morbidity and mortality despite improvement in neuroimaging, surgical techniques and antibiotic therapy.[1,2]

Infratentorial SDE is a life-threatening rare complication of bacterial meningitis. Infratentorial SDEs constitute only a small portion of all cases with intracranial infectious diseases. Empyema should be considered in patients with suspected or proven bacterial meningitis and associated ear, nose or throat infection with neurological signs that suggest a posterior fossa lesion.[57]

The commonest source as reported in the Western literature is paranasal sinus infection[10,14] and otitis media, whereas trauma constitutes a major aetiological factor in the African continent.[39,50,62] Upper respiratory tract infection,[65] subdural effusion[64] and meningitis[52] can also be some important aetiological factors in the causation of SDE. Rare causes may include SDE secondary to the use of a halo fixator,[46] shunt surgery or after evacuation of subdural haematoma.[50]

The spread of infection into the subdural space can be due to direct extension through the bone and dura, which is the common route in patients with otitis media or mastoiditis. However, in SDEs secondary to sinusitis,[31] the mode of spread is usually by retrograde thrombosis of the dural and intracranial veins from septic thrombophletitis.[48] The location of a SDE varies according to the source of infection: frontal in case of sinusitis, occipital and temporal region in case of otitis media. Intracranial tubercular SDE in the paediatric age group is an extremely rare but curable entity.[2]

The pathological findings consist of an inflammatory process mostly in the subdural space, with a small group having associated meningitis. However, the secondary changes, e.g. venous thrombosis, cerebral oedema, haemorrhagic changes and superficial abscess formation are responsible for the overall clinical presentation and prognosis.[23,48]

The clinical presentation usually is dramatic. The majority of the patients have alteration of sensorium.[22,50] Features of raised intracranial pressure, headaches, nausea and vomiting are also quite common. Focal symptoms in the form of speech disturbances, hemiparesis and seizures may also be seen.[50] However, patients developing SDE after surgery, trauma or secondarily in a subdural haematoma may have an indolent course and are diagnosed only on suspicion. Infection in the wound might be the only clue.

Despite modern diagnostic and therapeutic modalities, delayed diagnosis of SDE is not uncommon and is associated with a significant mortality. The factors to be incriminated for rapid clinical deterioration in SDE are: (i) products of bacterial metabolism including toxins which may have a direct effect on neural and glial tissue[15] or (ii) venous obstruction and stasis leading to infarction secondary to cerebral venous thrombosis.[19,26,63] Diagnosis of SDE is based on a high index of clinical suspicion in the initial stages. The outcome is affected the most by the time interval between presentation of symptoms and operation.[55] If operated upon within 72 hours of onset of symptoms only 10% are disabled, but after 72 hours 70% are either disabled or dead.

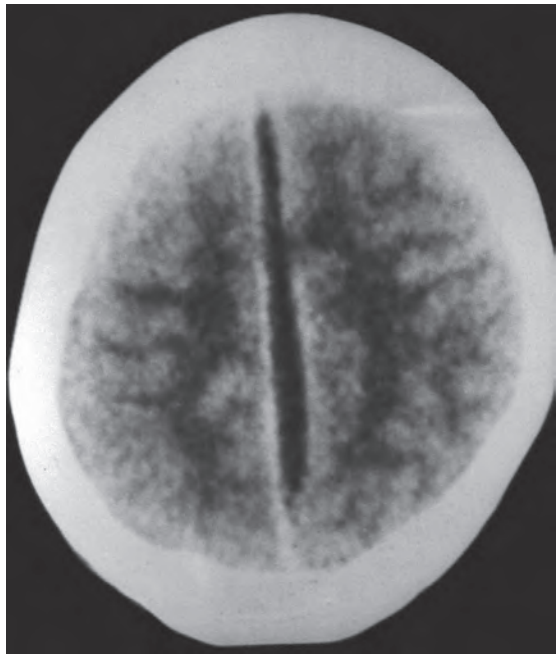

Fig. 1

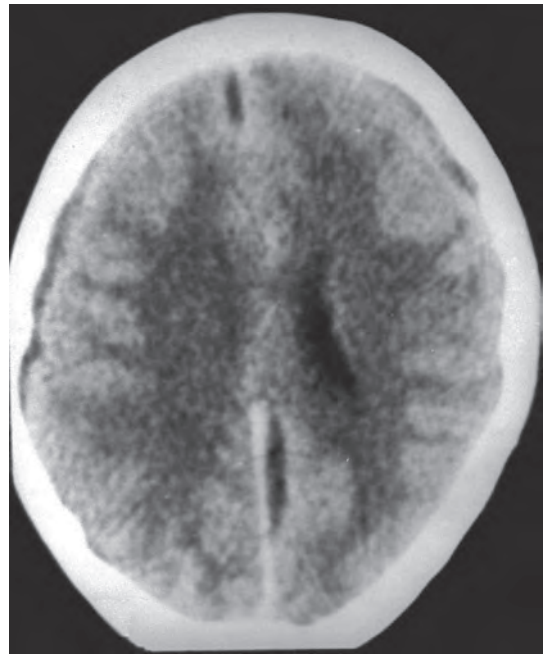

Fig. 2

Figs 1 and 2: CECT brain showing parafalcine subdural empyema

IMAGING

In the past, radioisotope scan had been a useful tool for diagnosis of SDE.[37,51] The CT scan[15,37,45] still remains the initial, common modality for diagnosis. Minimal midline shift and swelling of the ipsilateral hemisphere may be the only clue[20,53] as distinction of SDE from the surrounding brain is difficult in the acute phase prompting the need for serial CT scans with contrast enhancement[7,28,33,47,51] (Figs 1 and 2). Magnetic resonance imaging (MRI) has a major role in diagnosing and reducing mortality in subdural empyema as the actual empyema can be demonstrated in the acute phase using coronal and sagittal images, especially for collections near the base of skull, tentorium and over the convexity[12,61] (Fig. 3). However, in infants, the role of ultrasonography as a primary screening modality cannot be ignored.[13]

SDE have high signal intensity on diffusion weighted images (DWIs) and low signal intensity on ADC maps, with an ADC value lower than that of the normal cortical grey matter. Diffusion MRI can be valuable in distinguishing SDE from effusion and in the follow-up of subdural collections.[59] In earlier years angiography has been used for diagnosis.[30]

MICROBIOLOGY

The primary source of infection may have a relationship to the organism isolated from SDE. Aerobic, microaerophilic streptococci and anaerobic organisms are commonly isolated from empyemas secondary to paranasal sinusitis.[22,23] In post-traumatic or post-surgical cases *Staphylococcus aureus* is found. In children with SDE secondary to meningitis the organism commonly encountered is *Haemophilus influenzae* or *Streptococcus pneumoniae*. It is, however, not uncommon to isolate species of *Salmonella, Escherichia coli*[50] or other rare organisms.[16,24]

MANAGEMENT

SDE is a neurosurgical emergency which requires prompt intervention. Although no relationship exists between the mortality and the time taken to develop SDE,[42] a direct relationship exists between mortality and delay in referral[62] or a delay in treatment.[10,26,42] Seriously ill patients are claimed to have greater focal deficit.[42] The

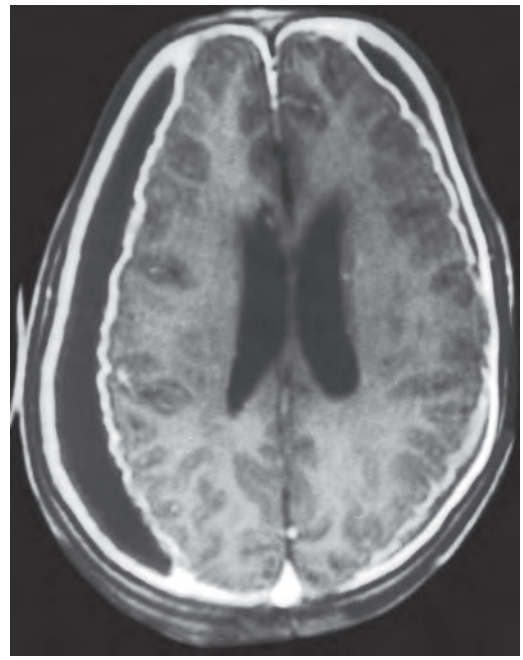

Fig. 3: Contrast enhanced MR (T1-weighted image) axial planar imaging showing convexity subdural empyema

extent of subdural pus accumulation has a statistically significant bearing on the chances of survival without severe disability, as extensive SDE involves the adjacent cortex, especially through widespread thrombophlebitis.

A wide range of options are available for the management of SDE. Surgery was the mainstay of treatment in the pre-antibiotic era. Subsequently surgery along with antibiotics helped to lower the mortality rates.[4,25,58] However, sporadic reports suggest that conservative management with antibiotic therapy for SDE has emerged as an accepted practice.[35,43,56]

Bradley and Shaw[10] considered early diagnosis followed by appropriate antibiotic therapy and early treatment of the primary source more important than rapid drainage of the empyema. Exploration of the paranasal sinuses and mastoids is suggested within 24 hours of the patient becoming stable.[9]

Proponents of surgical treatment of SDE claim an added advantage that it decreases the toxic and inflammatory influence on the brain and its blood supply which diminishes due to mass effect.[37] The advantage of surgery lies in achieving two main objectives, e.g. penetration of antibiotics into loculated areas of suppuration and identification of the offending organism.[6]

The type of surgical procedure is variable. Craniotomy or craniectomy is non-controversial for posterior fossa SDE. Percutaneous aspiration through an open fontanelle in infants or twist drill hole aspiration in children still remains a preferred method of treatment.[3,18,29,40,50]

SDE due to meningitis in infants is unique with respect to the pathophysiology, presentation and treatment. Early detection and removal of SDE lead to a favourable outcome.[36]

Bannister et al, in a review of 66 cases of SDE, reported gross difference in outcome based on burr holes or craniotomy.[4] There was a high mortality of 48% in burr holes in contrast to 8% in craniotomy. Burr holes are sometimes complicated by incomplete evacuation due to occlusion of a small dural opening by oedematous brain, and also in cases of multiloculated collections, parafalcine and posterior fossa empyemas.[4] Multiple burr holes are preferred in other series laying stress on treatment of the primary source,[10] early referral[5,62] and early diagnosis[44] in order to achieve better outcome. However, craniotomy has better outcome as it is possible to remove loculated pus and evacuate the SDE from the interhemispheric fissure.[15,58] A compromise between the two procedures can be brought about by preferring craniotomy for abscesses with thick pus and for abscesses in inaccessible areas like the interhemispheric fissure.[58] The role of a subdural drain is controversial.[8,21,41,49,50,59]

Early surgery can salvage most patients and obviate the need for permanent cerebrospinal fluid diversion procedures. Surgery (evacuation of empyema and mastoidectomy), antibiotics and management of hydrocephalus are the mainstays of treatment.[38]

Paediatric supratentorial SDEs, although rapidly fatal if not identified promptly, can be effectively managed with early surgical drainage; preferably craniotomy should be done.[2]

Statistically no significant relationship exists between different surgical procedures and the outcome in SDE.[42] For unconscious patients properly placed burr holes, located according to aetiology, clinical picture and CT scan, are the preferred procedure since, in the acute stage, the pus usually remains as an extended thin film. However, encapsulated pus in the chronic state with usually mild or no disturbance of consciousness needs a craniotomy.[50]

Mortality rates for SDEs range from 13 to 55%.[58] The level of consciousness has a significant bearing on the chances of survival and severe disability[42,60] reaching up to 80% in some series.[19] Fully alert or drowsy patients have a better prognosis than stuporous and comatose ones.[19,42]

The occurrence of seizures has no relationship with the outcome in SDE. Reports exist of 18% increase in incidence of seizures in frontal SDE in contrast to 100% in those located in the parietal region.[11] The duration of anticonvulsant therapy thus varies from a short period[15] to an indefinite period.[26]

Planning of treatment for an individual patient with SDE is based on several considerations.[50] Neurologically preserved patients without focal neurological deficit, and a localised area of pus on CT scan deserve a trial of conservative management. Patients with altered sensorium, deteriorating neurological status, focal deficit or failed conservative therapy demand surgical evacuation. A localised area of pus in the supratentorial compartment needs percutaneous needle aspiration and evacuation in infants or through burr holes in children and adults. Diffuse area of pus with midline shift, multiloculated or parafalcine SDE should be evacuated through craniotomies. All posterior fossa SDEs should have a craniotomy/craniectomy for evacuation. Follow-up CT scan is mandatory for all patients, whether treated conservatively or surgically. Once the patient improves, the relevant aetiological factor should be treated. Any residual pus with no improvement or deterioration in neurological status should be re-explored.

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63 Spinal Epidural and Intramedullary Abscess

Ashish Suri, Shashwat Mishra, Ajay Garg

SPINAL EPIDURAL ABSCESS

Spinal epidural abscess (SEA) is an uncommon pathology. In 1975, Baker et al.[3] had estimated their incidence at 0.2–1.2/10,000 hospital admissions. However, spinal epidural space infections are being noted more frequently in recent times as a result of increasing number of spinal surgeries, percutaneous spinal procedures, emergence of the human immunodeficiency virus epidemic and advances in spinal imaging modalities. Prior to the appearance of neurological deficits, the initial signs and symptoms of spinal epidural abscesses (SEAs) are non-specific and can erroneously be attributed to a plethora of commonly occurring spinal disorders. Due to their low incidence and confusing symptomatology, they continue to pose a diagnostic challenge. The SEAs, which escape recognition, can eventually result in permanent neurological deficits or even death due to systemic sepsis.

Relevant Anatomy and Pathophysiology

The spinal epidural space is a sleeve-like compartment between the dura and the periosteum and is filled with fat, epidural arteries and venous complexes. This compartment is developed well posterior and lateral to the thecal sac, but is only a potential space anteriorly where the dura and the periosteum are closely approximated. The posterior space is attenuated in the cervical region but enlarges in the midthoracic (T4-T8), lower lumbar and sacral (L3-S2) regions. When suppuration of the epidural space occurs, it spreads over several contiguous spinal segments[11,38,44] and is typically located in the posterior space. Epidural space collections anterior to the spinal cord generally result from infectious spondylitis or neoplastic affection of the vertebral bodies. Thus, in the Indian context, anteriorly located epidural abscesses are mostly noted in association with tubercular spondylitis. Tubercular epidural abscess occurring without an apparent spondylitis is rare. Tubercular epidural abscess in the absence of an osseous lesion have occasionally been described prior to the era of modern imaging. This was mostly due to the osseous lesion being missed on conventional X-rays. The SEAs most frequently occur in the thoracic and lumbosacral spine, which are also the most commonly accessed spinal segments in surgery and other procedures.[11–13]

The mechanism of spinal cord injury due to epidural abscesses remains unclear. The pathological mechanisms suggested include mechanical cord compression and septic thrombophlebitis with subsequent cord infarction. Although animal experiments[16] have suggested a primary role for mechanical compression in SEAs, some post-mortem studies[4] have also demonstrated infarction of the cord. Moreover, the appearance of cord damage due to either mechanism is indistinguishable on magnetic resonance imaging (MRI).

Epidemiology

The current annual incidence of SEAs stands at 2.5–3/10,000 hospital admissions.[39,44] All age groups are susceptible. However, SEAs are more frequently diagnosed in the 4th decade onwards. A male predominance has been noted in some studies.[11,35,38,39] The mortality rate for SEAs ranges from 6 to 32%.[17,25,39] Risk factors identified include predisposing medical conditions (diabetes mellitus, alcoholism and immunosuppression), spinal abnormalities, surgical intervention, spine trauma and presence of potential sources of infection (skin and soft-tissue infections, osteomyelitis, urinary sepsis, indwelling vascular access, intravenous drug use). *Staphylococcus aureus* is the commonest micro-organism isolated from these suppurations. Common microbial patterns seen in different clinical scenarios are listed in Table 1. Data from several series[12,25,39] suggest that in one half of cases, a contiguous spread of infection to the epidural space

Table 1: Risk factors and common micro-organisms causing spinal epidural abscesses

Risk factors	*Common micro-organisms*
Injected drug use	*Staphylococcus aureus, Pseudomonas aeruginosa*
Diabetes mellitus	Multiple
Recent invasive spinal procedures	*S. aureus, S. epidermidis*
Morbid obesity	Multiple
Skin infections or abscesses	*S. aureus, S. epidermidis*
Penetrating spinal trauma	*S. aureus, S. epidermidis*
Immunosuppression	Bacterial, mycobacterial, fungal
Transient bacteraemia	Multiple
Multiple medical illnesses	Multiple

occurs while haematogenous dissemination is responsible in a third. In the remaining cases, the source of infection remains unidentified.

Clinical Features

Fever, back pain and neurological deficits constitute the classical clinical triad of SEAs. However, this triad is recognisable only in a minority of patients.[10,14] Back pain is the most common and earliest symptom reported by patients. A staging system has been proposed describing the progression of symptoms in SEAs[21,33] (Table 2). The duration of these symptoms and the time of progression from one stage to another are highly variable between patients and may range from hours to months.[1]

It is apparent that clinical features of SEAs in the initial stages mimic common pathological spinal conditions. Radicular pain in the cervical and lumbar regions radiates to the extremities in classical patterns, but in the thoracic region, pain may vaguely extend to the chest or the abdomen, misguiding even the most discerning clinician.

The SEAs following invasive procedures (secondary SEAs) on the spine differ in clinical presentation from the spontaneously occurring SEAs (primary SEAs). The secondary SEAs occur in otherwise healthy individuals without significant comorbidities. Typically the patient presents with worsening pain at the surgical/puncture site along with tenderness and, occasionally, purulent discharge from the wound. The risk of developing SEAs following spinal epidural catheterisation has been variably estimated[5,7] to be around 1/1,350 procedures with the incidence of serious infections significantly increasing with prolonged placement of the catheter in the epidural space.

Patients developing spontaneous or primary SEAs following haematogenous dissemination of infection to the vertebral bodies or disc spaces develop discitis or osteomyelitis prior to the appearance of SEAs.

Isolated SEAs in tuberculous spondylitis are rare and the SEAs develop generally as a consequence of granulation tissue and purulent material spreading to the epidural space from spondylodiscitis of the vertebral segment(s). Due to the chronic inflammatory nature of the infection, the patients generally have back pain, systemic complaints (e.g. fever, anorexia, night sweats, weight loss, etc.) and neurological symptoms of prolonged duration. Spinal cord compression by epidural granulation tissue and caseous pus may be responsible for sudden neurological worsening in Pott's spine and may warrant urgent surgical decompression.

Table 2: Clinical staging of spinal epidural abscesses

Stages	*Clinical features*
I	Back pain
II	Radiating pain
III	Sensory deficits, motor deficits, and bladder and bowel dysfunction
IV	Paralysis

Diagnosis

Clinical findings, supporting laboratory data and suggestive imaging features are collated to establish the diagnosis of SEAs. However, it can be confirmed only by drainage of the abscess.

Laboratory Investigations

Routine laboratory studies reveal leukocytosis and elevated acute phase reactants (C-reactive protein), which are non-specific markers of any inflammatory process. Bacteraemia can be detected in up to 60% of cases,[10,11] especially where *S. aureus* is the likely causative organism. However, it is almost never seen in mycobacterial aetiology. Cerebrospinal fluid (CSF) examination typically reflects parameningeal inflammation with leukocytic pleocytosis and increased protein levels. The CSF cultures are usually negative and lumbar puncture carries a high risk of dissemination of the infective organism into the CSF. Moreover, the risk of neurological dissemination is compounded if the lumbar puncture is performed below the level of the spinal subarachnoid space block. Thus, a routine diagnostic lumbar puncture (except for myelography) should be avoided when a diagnosis of SEA is being suspected.

Imaging

Both contrast-enhanced MRI and computed tomography (CT)-myelography of the spine are highly sensitive (more than 90%) in diagnosing SEA.[22,38]

A plain radiograph or CT of the spine may reveal narrowing of the disc space and bone lysis to indicate the presence of discitis and osteomyelitis (which coexist with SEA in up to 80% of patients).[23] Similarly, radionuclide scanning (with technetium, gallium or indium) may show increased uptake, helping to identify the affected site. However, these imaging findings are neither sensitive nor specific for SEA.

The MRI is the imaging method of choice because it is non-invasive, multi-planar and without any radiation exposure. It delineates both the longitudinal and the paraspinal extension of the SEA and thereby helps in surgical planning. In addition, it may help to differentiate infection from cancer on the basis of the appearance and the signal intensity of the image.[32] The SEA is isointense to hypointense compared with the spinal cord on unenhanced T1-weighted images, and increased in intensity on proton-density and T2-weighted images[40] (Figs 1A and B). After contrast administration, SEA may show homogeneous enhancement, likely representing thickened, inflamed tissue with microabscesses or peripheral enhancement surrounding a central focus of low signal intensity representing a necrotic abscess, or a combination of both patterns.

Figs 1A and B: Spinal epidural abscess. (A) T2-weighted sagittal image showing posterior epidural abscess extending from D6-D11 spinal levels with spinal cord hyperintensity suggesting cord oedema. The core of the abscess is bright on T2-weighted image. (B) The rim enhances following gadolinium administration

Treatment

Prompt surgical drainage of SEA followed by appropriate systemic antibiotic therapy is almost always indicated to reduce the risk of sepsis and further neural injury.[31,37–39] In addition to blood cultures, other potential sources of infection are sampled prior to the initiation of systemic antibiotics.

Other treatment paradigms (applicable only in select cases with a small abscess and minimal symptoms) include systemic antibiotic therapy only and CT guided drainage of the abscess followed by antimicrobials.[40,42]

Pre-operative neurological status is an important predictor of outcome; hence early surgical intervention is appropriate. If profound neurological deficit persists for greater than 24–36 hours, recovery is unlikely following decompression. Depending upon the location of the abscess and surgical feasibility the epidural space is explored by laminectomy, hemilaminectomy or interlaminar fenestration. The purulent material and granulation tissue are then removed and samples collected for microbial culture.

Purely medical therapy may be considered in a few clinical scenarios. If the patient is a poor surgical risk, declines surgery or has complete paralysis of more than 3 days duration, antibiotic therapy is initiated following collection of samples for microbial culture and the patient is closely monitored for response. Very small abscesses without significant neurological symptoms may also be managed conservatively under close observation and frequent neurological assessment. Surgical drainage is indicated if the symptoms worsen or signs of sepsis appear during systemic antibiotic therapy. The abscess size can be monitored by Gd-MRI at a 2–4 week interval.[41]

While awaiting culture results, empirical antibiotic therapy must be directed against *S. aureus* (the most common pathogen), including coverage for methicillin resistant organisms and gram-negative bacilli, especially in scenarios where infection from gram-negative bacteraemia is likely, e.g. urinary tract infection.[13] However, it is important to remember that vancomycin is less active against methicillin sensitive staphylococci than β-lactams. Hence, documented methicillin-sensitive *S. aureus* is treated with nafcillin or cefazolin. The antibiotic regimen can be modified later on the basis of culture sensitivities.

The ideal duration of therapy is not well established and generally systemic antibiotics are recommended for a period of 6 weeks, as vertebral osteomyelitis frequently coexists with SEAs.

When SEA develops following spinal instrumentation or epidural electrode implantation, removal of the foreign material is necessarily required for elimination of infection. The role of steroids is controversial and may be used for temporary stabilisation while preparing for surgery.

For tubercular epidural abscesses, in neurologically intact patients, standard four-drug (HRZE) or five-drug (HRZES) antitubercular therapy is initiated. The patient is then monitored neurologically for therapeutic response. Although standard treatment guidelines for tubercular epidural abscesses are lacking, we generally intervene surgically when the patient deteriorates neurologically on antitubercular therapy. A costotransversectomy in the thoracic region and laminectomy in other spinal segments is the preferred approach for drainage of pus and removal of granulation tissue. At least 18 months of antitubercular therapy is recommended [1 month HRZES + 3 months of HRZE and 15 months of HRE (H = Isoniazid, R = Rifampicin, Z = Pyrazinamide, E = Ethambutol, S = Streptomycin)].

Outcome

The outcome for SEAs strongly correlates with the severity of neurological dysfunction before surgical decompression, making a case for early and aggressive surgical intervention.[3,12,28] If the duration of paresis is less than 24–36 hours, improvement is generally noted post-operatively. There is no conclusion that extent of elevation of erythrocyte sedimentation rate, C-reactive protein or MRI findings (canal compromise and number of vertebral segments involved) influence the ultimate outcome.

Uncontrolled sepsis, CNS spread of the infection or comorbid illnesses may ultimately result in mortality in up to 5% of patients. While the patient is recovering

neurological function, adequate measures should be taken to avoid the development of secondary complications such as decubitus ulcers, urinary tract infections, deep vein thrombosis and chest infection.

SPINAL INTRAMEDULLARY ABSCESSES

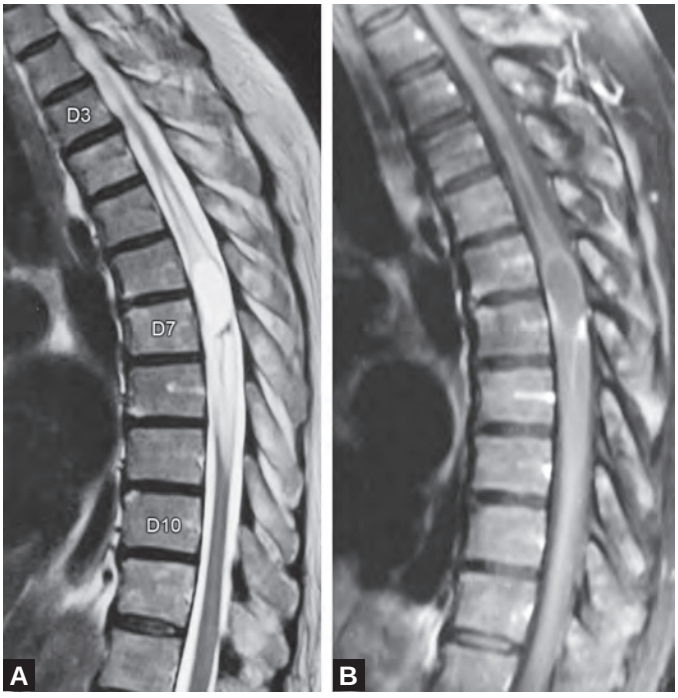
Intramedullary abscesses within the spinal cord are extremely rare, if one excludes cases where the infection spreads to the spinal cord from the contiguous vertebral body, disc space or a dermal sinus (Figs 2A and B). Only about 120 cases have been reported in the literature so far,[26] with the first case being described by Hart in 1830.[20]

The precise incidence of spinal intramedullary abscesses (SIAs) remains unclear. An autopsy series found only a single intramedullary abscess in 40,000 cases.[9]

Pathogenesis

Metastatic dissemination of infection from extraneous foci, contiguous spread from an infected dermoid, dermal sinuses, disc or vertebral bodies are commonly implicated in the causation of these abscesses.[6] Iatrogenic intramedullary abscesses, following surgical procedures on the spinal cord, may also occasionally be encountered. Compared with the pre-antibiotic era, haematogenous spread from septic foci has become infrequent in modern times.[6,30] Cryptogenic abscesses, with an unidentified primary source of infection now constitute the largest proportion.[2,6,26] In a review of 25 cases, the authors found the cervical and upper dorsal cord to be the commonest site of cryptogenic abscesses. Congenital midline neuroectodermal defects (spinal dysraphisms) were identifiable in 44% of the cases. The commonly noted stigmata of these dysraphic defects were pigmented naevi, sinus tract openings, blind dimple and inflamed skin nodule. Abscesses seen in this setting were common in the thoracolumbar region. Intramedullary abscesses are the common in the paediatric age group because of the frequent predisposing developmental spinal cord anomalies.[43]

Normally, the spinal cord substance is highly resistant to microbial colonisation. However, areas of subclinical spinal cord injury/ microinfarcts form a nidus for infection during transient bacteraemia. The stages of evolution of spinal intramedullary abscesses are similar to those seen in a pyogenic brain abscess. Areas of necrosis surrounded by purulent myelitis are seen in the initial stages. Later, a well-vascularised thick capsule surrounds the core of purulent material. Subsequent CSF dissemination and leptomeningeal spread of infection can complicate the clinical picture. Septic phlebitis with cord infarction may also contribute to cord damage.[6] Abscesses resulting from septic emboli have a predilection for the lower cervical and upper thoracic cord as these spinal segments have a relatively richer blood supply.



Figs 2A and B: Spinal intramedullary abscess. (A) T2-weighted sagittal image showing intramedullary abscess extending from D6, D7 spinal levels with spinal cord hyperintensity suggesting cord oedema. The core of the abscess is bright on T2-weighted image. (B) The rim enhances following gadolinium administration

Clinical Features

Pain, fever and rapidly progressive neurological deficits constitute the commonest symptomatology of SIAs.[6,26,30] Evidently, transverse myelitis and SEAs closely mimic the presentation of these abscesses and must be entertained in the differential diagnosis. Deterioration in sensorium and clinical features of sepsis are ominous and indicate leptomeningeal or systemic spread of infection. Fortunately, such complications are rare in the modern era with the availability of potent antimicrobials.

Staphylococcal species are the most common organisms isolated from these suppurations. The observed microbial pattern in relation to the proposed mechanism of infection is presented in Table 3.[6]

Management

Similar to pyogenic brain abscesses, generally a combination of medical and surgical therapy is considered appropriate for intramedullary abscesses. Surgical intervention is absolutely necessary in cases of abscesses associated with dermoids and epidermoids and dermal

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Gulati et al. described 11 cases of spinal suppuration-epidural, one case of subdural, and later, in 1983, VK Khosla and VK Kak reported 10 cases of spinal intramedullary abscess.[18,24]

Tandon and Pathak provided a detailed review on spinal tuberculosis including extradural, subdural and intramedullary lesions in Tropical Neurology.[45]

Table 3: Microbiology of intramedullary spinal abscesses

Mechanism of infection	*Microbiology*	*Antimicrobial therapy*
Contiguous spread from dermal sinus opening	*Staphylococcus epidermidis, S. aureus* and anaerobes	Vancomycin + cefotaxime + metronidazole
Following spinal surgery	*S. aureus, S. epidermidis,* Enterobacteriacea, Gram negative bacilli	Vancomycin + ceftazidime ± metronidazole
Haematogenous spread	Similar to primary source	Culture based
Cryptogenic	Listeria monocytogenes, Viridians streptococci, Hemophilus species, anaerobes	Ampicillin + cefotaxime + metronidazole

sinus tracts. However, medical management may suffice for small cryptogenic abscesses showing good neurological response to antibiotic therapy. A minimum of 4–6 weeks of parenteral antibiotic therapy is essential.

The standard surgical management entails laminectomy, midline myelotomy and drainage of the pus and excision of an underlying lesion if any.

Outcome

In the pre-antibiotic era, intramedullary abscess of the cord carried mortality as high as 90%.[2,6,43] The mortality rate has substantially declined to less than 10% with effective antimicrobial therapy in modern times. However, following successful treatment of intramedullary abscesses the prognosis for functional neurological recovery still remains grim.[2]

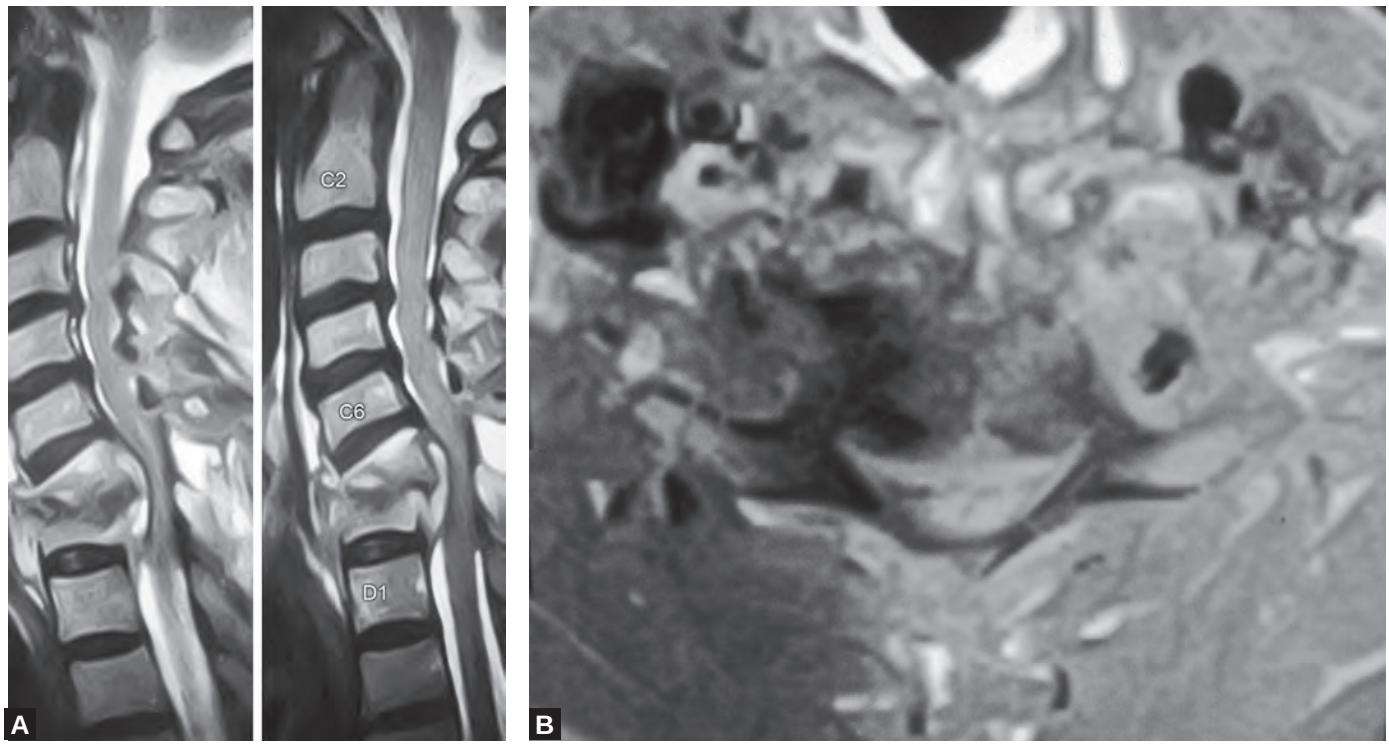
SPINAL INTRAMEDULLARY TUBERCULOMAS

Intramedullary tuberculomas in the spinal cord are extremely rare even in regions where tuberculosis is endemic. Nevertheless, it remains an important differential diagnosis of intramedullary lesions in the Indian population.

Intramedullary tuberculomas are encountered usually in the younger age groups and have been most frequently reported in the thoracic spinal cord.[29] However, they may affect almost all spinal segments.[15,34]

The patient may present with signs of subacute cord compression with classical signs of myelopathy. However, varied presentation, such as Brown-Sequard syndrome,[8] and acute urinary retention have also been reported.[15] The clinical presentation, however, is uncharacteristic and must be considered in context of the epidemiological setting and imaging features of the lesion.

The MRI appearance of intramedullary tuberculomas can vary according to the stage of evolution of the lesion. In the early stages, tuberculomas may be indistinguishable from myelitis with homogeneous enhancement of the cord (Figs 3A and B, Fig. 4). Eventually,



Figs 3A and B: Spinal tubercular spondylitis with epidural abscess. (A) T2-weighted sagittal image. (B) Axial image shows tubercular spondylitis C6, C7 spinal levels with anterior epidural abscess

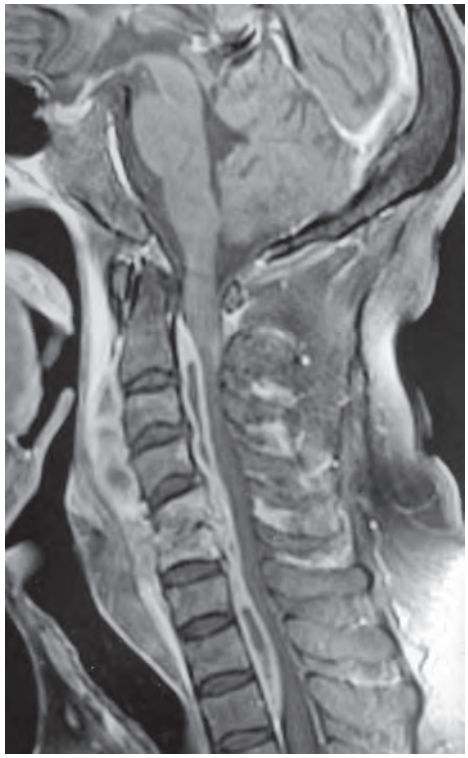


Fig. 4: Spinal tubercular spondylitis with epidural abscess. T1-weighted Gad DTPA enhanced sagittal image showing tubercular spondylitis of C5, C6 spinal levels with multiple cervical anterior epidural abscess

these lesions progress to the characteristic ring enhancing "target appearance" with a central hypointense core and hyperintense periphery on T2-weighted sequences along with evidence of expanded cord substance.[18,36]

The ideal treatment of intramedullary tuberculoma is controversial. Although, undoubtedly, tuberculomas exert mass effect upon the spinal cord, yet surgery on the cord is fraught with risk. A balanced approach is adopted, with the understanding that antitubercular therapy (12–18 months duration, standard four drug regimen) is the cornerstone of management (Figs 5A and B). In our experience, conservatively managed and surgically explored intramedullary tuberculomas showed comparable results.[34] Surgery is presently recommended for patients who worsen on antitubercular regimen with increasing mass effect or in patients with uncertain diagnosis.[27,29]

Improvement is generally seen with antitubercular therapy, unless the patient harbours a resistant form of the organism or the deficits are long-standing and established.

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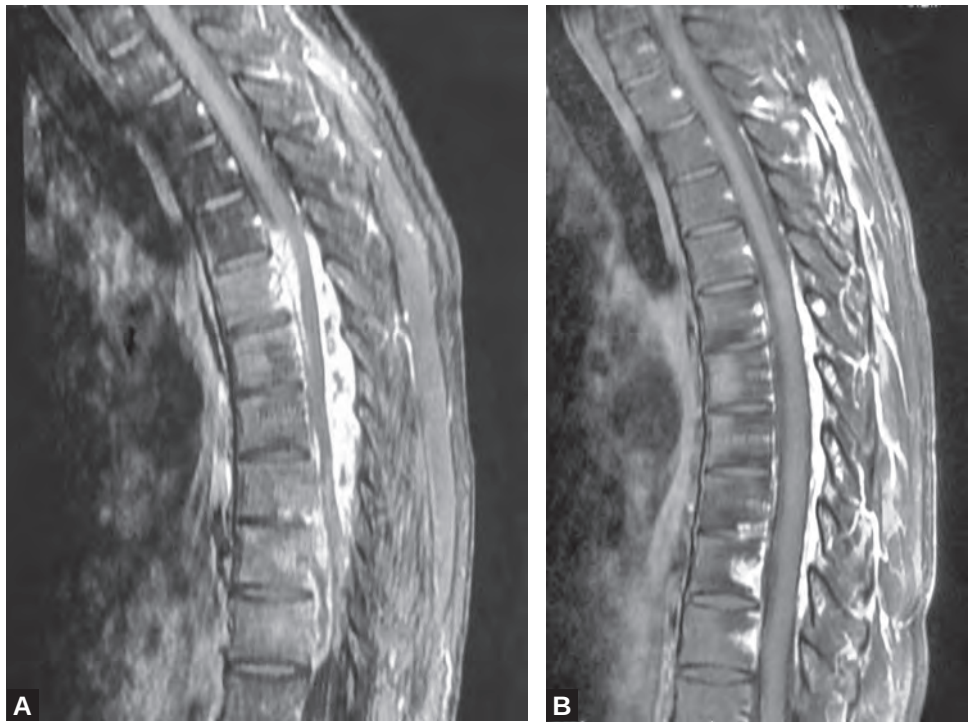

Figs 5A and B: Spinal tubercular spondylitis with epidural abscess—complete resolution with 18 months antitubercular therapy. T1-weighted Gad DTPA enhanced sagittal image (A) pre-treatment. (B) post-treatment

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64 Tuberculosis of the Central Nervous System

PN Tandon, Anil Pande

INTRODUCTION

Tuberculosis, a disease as old as recorded history, continues to exist in India and other developing countries and there is resurgence in the developed world consequent to the emergence of AIDS in epidemic proportions.[23,41,78,90,92,124,172,173,188] Worldwide, tuberculosis remains the leading cause of mortality from an infectious agent.[98] Approximately one-third of the world's population harbours *Mycobacterium tuberculosis* (*M. tuberculosis*). Individuals infected with *M. tuberculosis* have a 10% lifetime risk of developing the disease. Tuberculosis had affected 8.3 million patients worldwide in 2000.[165,166] The most dangerous form of the disease is neurotuberculosis. The manifestations of central nervous system (CNS) disease may involve the meninges and[1,9] parenchyma, or there may be focal involvement of the spinal cord and its adjacent osseous structures.[62,66] Cranial tuberculosis may be parenchymal (tuberculoma, abscess, encephalopathy), meningeal (meningitis, pachymeningitis)[56,122,135,137,202,204–206] or calvarial (osteomyelitis). Spinal tuberculosis can be vertebral[66] (caries or Pott's spine), meningeal (pachymeningitis, arachnoiditis) and parenchymal (spinal tuberculoma).[177] Craniovertebral junction tuberculosis has been reported on by Indians and others extensively.[60,91,99,134,178,184] Ramamurthi, in 2000, clarified that this entity should not be called a tuberculoma of the CV junction. Autopsy series of patients dying of tuberculosis identified CNS involvement in 19.3–42.2% of paediatric cases and in 2.9–5.9% of adult cases.[187] Children are commonly affected between 6 months and 4 years and adults between 20 years and 50 years. In addition to HIV-1 co-infection, other conditions associated with CNS tubercular involvement include recent measles infection and malnourishment in children; and alcoholism, malignancies, immunosuppressive medication and non-HIV immunosuppressive conditions in adults.

HISTORY

Hymns in the Rig Veda testify that the early Indo-Aryans (1500 BC) were familiar with this disease;[90] so were the Chinese, in the second or third millennia BC.[214] Egyptian mummies dating 3000 BC were found to have unequivocal evidence of skeletal tuberculosis.[32] The writings of Homer (900 BC), Hippocrates (400 BC) and Aristotle (350 BC) suggest the prevalence of this disease at that time.[127] Acid fast bacilli could be demonstrated in the spinal lesion of a Nazca culture child cadaver (approximately 700 AD) by Allison et al.[2] *M. tuberculous* DNA was identified in a pre-Columbian Peruvian mummy[170] and from a Bison fossil dating 17000 years ago.[164]

The infective nature of the disease was, however, not suspected till the early 18th century. Benjamin Marten, in 1722,[12] proposed that the cause of tuberculosis was "animaliculae or their seed, inimical to our "Nature" that can be transmitted by a "Breath" (a consumptive) emits from his lungs…. that may be caught by a sound person". Green, in 1835,[71] was the first to characterise tubercular meningitis and published the first description of the disease. The formal demonstration of its contagious nature was made in 1865 by Jean-Antoine Villemin.[212] It was only in 1882 that Robert Koch[97] isolated *M. tuberculosis* from crushed tubercles. It is interesting to note that, in the 18th century, CNS tuberculosis was primarily identified as "Dropsy in the Brain"[179] or "febris hydrocephalica".[113] The credit for recognising involvement of the meninges as the cause of hydrocephalus goes to Odier (1790),[130] even though the term meningitis was used for the first time by Herpin only in 1803.[79]

Charles Morehead (1847–48), working in Bombay, described the autopsy findings in a number of children with meningitis as undoubtedly tuberculous in nature. Ford[63] has been credited with the first description of a brain tuberculoma. Successful excision of such lesions was reported by Wernicke and Hahn,[217] Horsley[81] and MacEwen.[114] It is interesting to note that Blocq and Marinesco[21] described, in 1893, that a tuberculoma within the substantia nigra was responsible for Parkinson's syndrome. Spiller[185] observed, in 1905, two discreet tuberculomas in each anterior quadrant of the spinal cord in a patient with bilateral loss of pain and temperature sensations. This observation led him to advocate spinothalamic tractotomy for the relief of intractable pain. Scott and Graves[175] collected, in 1933, 815 cases of tuberculomas of the brain reported till then. Dott and Levin[58] reviewed the results of 91 patients operated upon by 17 British neurosurgeons. Most authoritative works in this field since 1950 have been by Indian neurosurgeons.[18,45,49,52,53,116,150,155,183,189,192]

PATHOGENESIS

The *M. tuberculosis* is member of the *M tuberculosis* complex that includes *M. africanum*, *M. bovis* and *M. microti*. The description that follows applies to CNS tuberculosis in general and not specifically to meningitis or tuberculoma. Though the TB bacillus was one of the earliest pathogenic organisms to be isolated, it is surprising that we still have a very inadequate knowledge about the pathogenesis of tuberculous infections. *M. tuberculosis* is an anaerobic, non-motile, non-spore forming bacillus that stains weakly gram-positive and the main cellular reservoir is tissue macrophages though the organism exists extracellularly. The bacteria resist decolourisation of carbol fuschin by acid alcohol in the Ziehl-Neelsen process due to the high lipid content of the cell wall. These mycobacteria are not fully understood with regard to their metabolism, host-pathogen interaction, mechanism of infection and damage and resistance by the host. It is still not clear how the pathogens get into the cells and then paralyse the protective machinery of the host cell leading to tolerance, and under appropriate circumstances to multiplication of the organisms. There are numerous macrophage receptors capable of binding *M. tuberculosis* that can participate in its internalisation including CD11b, CD14, the macrophage mannose receptor, scavenger receptor A and CD44.[107,112,115,211] Intracellular parasitism is accomplished by a variety of mechanisms that include altered trafficking of bacteria during endocytosis, interference with host Ca^{2+} signalling pathways and induction of maturational arrest of the phagosome. The mycobacteria then lie enclosed in the intracellular compartment that does not contain mature lysosomal enzymes.[24,139]

Recent molecular biological studies have revealed that *M. tuberculosis* contains diverse chemical substances, lipids, polysaccharides and tuberculoproteins which are responsible for the various immune phenomena, viz. resistance, sensitivity, virulence, granuloma formation and chronicity of infection. These immune responses are primarily cell mediated, involving a complex interplay of T and B lymphocytes and macrophages, and mediated by various lymphokines, and immunoglobulins. However, as of today, the nature of the antigen that stimulates the protective immune response, the type of cells involved in protection and the manner in which the macrophages kill the mycobacteria are not known. Although over a dozen somatic and secreted antigens have been cloned, the immunodominant antigen concerned with either virulence or protection has not been identified. In spite of phenomenal advances in molecular genetics, not a single gene involved in the pathogenesis of tuberculosis has been identified. Kinger and Tyagi[96] claimed to have identified and cloned genes differentially expressed in the virulent strain of *M. tuberculosis*. Many laboratories all over the world, including India, are currently engaged in this field. The entire sequence of the DNA that forms the genome of mycobacterium has been worked out.[64] Genomic libraries of several mycobacteria, including *M. tuberculosis*, have been constructed by several groups in India.

There is growing evidence to suggest that the host's genetic traits also play some role in determining susceptibility to infection. The classical study of Kallman and Reissner (1943) revealed that the risk of a contact consort developing tuberculosis is 7.1%. It was 11.9% in half-siblings, 25.5% in siblings and 87% in monozygotic twins. Increased phenotypic frequency of HLA-DR2 has been reported by Mehra[120] from Delhi and of HLA-A10, B-8 and DR2 by Pitchappan[140] from Madurai, India.

CENTRAL NERVOUS SYSTEM TUBERCULOSIS

Central nervous system tuberculosis is usually secondary to a haematogenous spread from a primary infection elsewhere in the body. Uncommonly, it could be the result of direct spread from a lesion in the neighbourhood, e.g. otitis media or spinal caries. There is enough clinical and experimental evidence to indicate that meningitis is the result of a discharge of tubercle bacilli into the CSF from a caseous focus ("Rich focus") in the brain or the meninges, and not a consequence of primary haematogenous spread.[194] In contrast, a parenchymatous tuberculoma is due to direct haematogenous spread to the brain. The inflammatory cells (lymphocytes, monocytes and plasma cells) accumulate in the subendothelial region of the vessel and with further cellular proliferation there is a displacement of the intact endothelium with or without tuberculoma formation, and this proceeds to complete involvement of the vessel with a contiguous inflammatory process. TNF-alpha is an important proinflammatory cytokine, once the bacteria enter the CSF. Infected monocytes and macrophages show increased expression of surface ICAM-1 and increased migratory activity across the endothelial and epithelial bilayers, activating intracellular signalling pathways and secretion of proinflammatory cytokines.[14,15,61,67,82,222] The precise reasons for a given patient developing either meningitis or a tuberculoma or both are not known. In an experimental study on rhesus monkeys, the nature of the lesion could be modified by manipulating the state of immunity or sensitivity of the animals.[80,193,197] This led to the conclusion that the nature of the lesion would depend upon the number of bacilli, their virulence and their site of deposition on the one hand and the state of immunity and allergy of the host on the other. It is important to realise that such a statement fails to provide a precise answer.

The majority of cases of CNS tuberculosis seen in India have been found to be due to the human type of tubercle bacillus (*M. tuberculosis* var. hominis). The bovine type of Tubercle bacillus, though a common cause of infection in Europe in the early years of this century,[22,72,86] is probably responsible for less than 5%. Isolated cases of meningitis have been attributed to avian[59,103] or atypical mycobacteria, both photochromogens and scotochromogens.[33,83,88,191,209] A scotochromogen was isolated from an

intracranial tuberculoma in one of our patients with disseminated tuberculosis. It is as yet difficult to say, if the coexistence of HIV infection or AIDS will alter the relative incidence of the various types of mycobacteria producing CNS tuberculosis.[31,36] The *Mycobacterium avium* complex was found in 50% of AIDS patients at necropsy. The presence of HIV-1 induced immunodeficiency is a powerful cofactor for the development of disseminated tuberculosis and, therefore, the proportion of extrapulmonary cases has increased. Berenguer et al. identified meningitis in 10% of HIV-1 co-infected patients when compared with 2% of non-HIV-1 co-infected individuals and 26% of HIV infected patients have meningeal involvement.[94,174] Patients with tuberculous meningitis can have associated tuberculomas or may develop them after successful initiation of antitubercular therapy.[6] Unal and Sultas[208] reported on 22 cases of intracranial tuberculomas; 8 of these were coexistent with tuberculous meningitis and 12 tuberculomas developed during therapy with ATT and steroids. They advise a careful follow-up of cases. Yaramis et al.[221] in their analysis of 214 cases of patients with tuberculous meningitis found tuberculoma in only 2%.

INTRACRANIAL TUBERCULOMAS

Incidence

There are distinct geographical differences in the incidence of intracranial tuberculomas, in different countries and even within a given country. In most developed countries, by the middle of the 20th century, there was a dramatic reduction in their incidence, though they had not been eradicated completely. Even before the AIDS epidemic broke out, there were several reports on tuberculomas from the UK,[3,118,138] the USA,[109,119,219] Spain and Canada, where most of the reported cases were among the immigrant population, the native Red Indians and the Eskimos.[4]

A higher incidence of tuberculomas among all intracranial space occupying lesions (ICSOLs) (above 10%) was reported from Bombay, while it was less than 5% in Delhi and Calcutta. No adequate explanation is available for such differences, especially when the overall incidence of tuberculosis or even tuberculous meningitis is not very different in these regions. It is interesting to note that in Nigeria[131] and Taiwan,[199] where tuberculosis is widely prevalent, the incidence of intracranial tuberculomas was around 1% only.

There has been a progressive decline in the incidence of intracranial tuberculomas.[147] Reports from Bombay indicated an incidence of 30.5% of all ICSOLs in 1963, 21.5% in 1968 and 12.3% in 1974.[54,105] Similarly, the reported incidence of 20% in 1960 from Madras came down to 14% in 1973.[153] These figures refer to the incidence of tuberculomas diagnosed in the pre-CT scan era. Since 1979, tuberculomas are being diagnosed much earlier and, in the majority of these, as there is no histopathological diagnosis it is difficult to assess the true incidence. The response to antituberculous therapy cannot always be taken as proof of pathology, as one encounters "disappearing lesions" in the CT which resemble a tuberculoma, but disappear in many instances without using antituberculous drugs.[48] With these limitations, one may state that the incidence of probable tuberculomas proved by CT has been on the increase.[152] Ramamurthi[149] encountered 381 cases of tuberculomas over a 28-year period between the years 1950–1978 (pre-CT era) and 246 cases over 12 years between 1979 and 1991 in the CT scan era. It should be emphasised, however, that the incidence of tuberculomas requiring surgical excision has gone down from 78.6% to 13.4%.

Pathology

Tuberculomas of the brain vary in size from less than a centimetre to 8–10 centimetres in diameter (Fig. 1). In its mature form it presents as a well-circumscribed, nodular, firm to hard, greyish-yellow relatively avascular mass. Some present on the surface of the brain, in which case they may get adherent to the dura. Rarely, it is known to cross the dural barrier and in an exceptional case has been seen to go through the overlying bone (Fig. 2). The lesion is surrounded by varying degrees of oedema and gliosis.[55] The so-called capsule of a tuberculoma is nothing more than compressed gliosed brain tissue. A true fibrocollagenous capsule does not exist, even though at surgery the lesion appears to shell out from the surrounding brain. The cut surface presents a creamish-white gritty caseating centre with crenated margins, surrounded by a firm to hard greyish rim of varying colour, composed of granulomatous tissue and compressed gliosed brain matter.

Microscopically, the lesion is a classical tuberculous granuloma,[46] with central coagulative necrosis surrounded by epithelioid cells, Langhans giant cells and

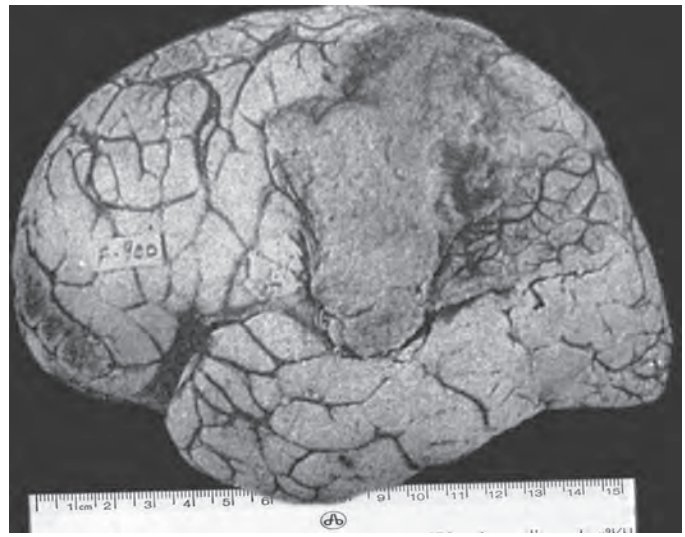


Fig. 1: Gross appearance of an unusually large tuberculoma presenting at the surface of the brain

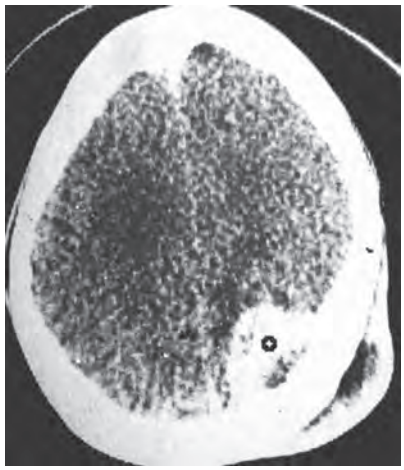


Fig. 2: CT scan showing a right occipital tuberculoma which involved the bone and presented as a subgaleal swelling

an admixture of lymphocytes and plasma cells (Fig. 3). There may be satellite granulomas at the periphery of the lesion and foci of perivascular infiltration may be seen further afield. A fibrocollagenous reaction is seen only where the lesion has reached the surface of the brain.

Careful examination of the central region of the mass may reveal acid fast bacilli in appropriately stained sections. As a rule, there is a paucity of organisms. Radhakrishnan et al.[144] have reported immunohistochemical demonstration of mycobacterial antigen within the cytoplasm of the giant cells and macrophages, while routine examination had failed to reveal any acid fast bacilli. In this connection, it is interesting to consider the possibility raised by Chandramukhi and Shankar,[34] that the evolution of a tuberculoma may not be dependent upon the presence of live tubercle bacilli. The tuberculoprotein or some of the antigenic components released by the destruction of the bacilli may, by complex immune reactions with a number of polyclonal and monoclonal antibodies, lead to the formation of the tuberculoma. They have demonstrated the variability of the immunoarchitecture of tuberculomas and find support for their hypothesis in the experimental work of Ridley.[161]

Besides the classical lesion described above, there are a variety of atypical manifestations of which practitioners in high endemic regions must be aware of.[213] Sinh et al.[183] described several of these atypical lesions.

Tuberculoma En Plaque

According to Pardee and Knox,[161] this type of tuberculoma was first demonstrated by French authors, notably Chantenesse[37] in 1884, under the term 'meningite en plaque tuberculeuse'. Ramamurthi and Varadarajan[150] reported that the angiographic appearance of such lesions may mimic a meningioma due to their increased vascularity. At surgery also, these are found to be adherent to the dura and may grossly resemble a meningioma en plaque. Welchman[216] described for the first time the CT appearance of this lesion.

Tuberculous Abscess

Tuberculous abscess of the brain has been known since the early days.[101,157,217] Dandy[44] referred, in 1932, to the existence of pus in some tuberculomas resembling a pyogenic abscess. It is important to differentiate a tuberculous abscess from a classical tuberculoma with central caseation, softening and liquefaction. A 'tubercular abscess' lacks granulomatous change, and histologically resembles a chronic pyogenic abscess, except that acid fast bacilli are seen in the pus.[141] A number of cases fulfilling these criteria have been described not only from India[35,57,123,151,171] but also from other countries[9,38,106,129,159,207,218] (Fig. 4). Tang et al.[198] reported, in 1991, a case of multiple tuberculous abscesses in the brain in a Chinese child who had tuberculous meningitis. We could produce a characteristic tubercular

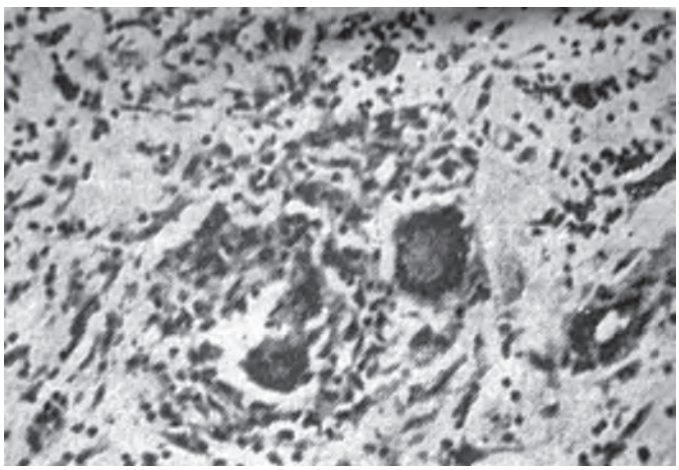


Fig. 3: Typical histological picture seen at the edge of a tuberculoma—giant cell and ill-defined epithelioid cells surrounded by lymphocytes

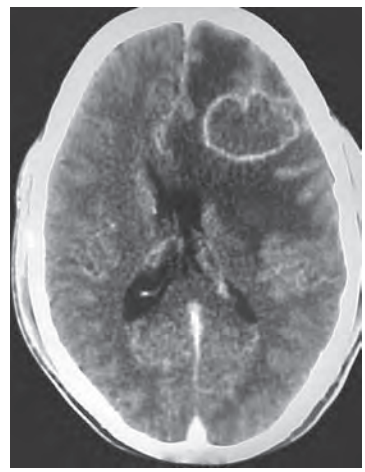


Fig. 4: CT scan of left frontal tubercular abscess—a unilocular hypodense lesion with a thin rim of enhancement

abscess in BCG vaccinated monkeys by injecting tubercle bacilli into the substance of the brain.[194] It is likely that abscess formation may be more frequent in AIDS patients than the classical tuberculoma due to immune suppression. Tuberculous meningitis and abscess, caused by *Mycobacterium avium* in a non-immunosuppressed woman, have been reported by Uldry et al.[207] Kumar et al.[104] reported on 6 cases and emphasised that a long clinical history and a thick walled abscess are indicative of a possible tubercular abscess and these can be aspirated, and rarely may require excision.

Cystic Tuberculoma

These tuberculomas are rare. The first case of cystic tuberculoma was reported by Dastur et al.,[51] in 1962, in a 4-year-old boy with hemiparesis. The cyst contained clear yellow fluid and the cyst wall had typical tuberculous pathology. There have been further reports of such cases from India.[127,158,168,183,186] Liberman et al.[110] reported a cystic tuberculoma containing green cloudy fluid in which acid fast bacilli were demonstrated. It has been suggested that these cases represent the various stages in the resolution of the necrotic core of some tuberculomas (Figs 5A and B). Sridhar et al.[186] have proposed a classification of cystic tuberculomas: Type I—intralesional cyst within tuberculoma; Type II—intralesional cyst at the periphery of the lesion; Type III—extralesional (the cyst is subdural in location) and Type IV—extralesional (the cyst lies between the lesion and the brain). The authors advocate that types I and II require radical excision whereas types III and IV require excision of the solid part alone.

Multiple Grape-like Tuberculomas

Another rare presentation is in the form of a grape-like cluster of multiple immature tuberculomas.[192] These may resemble a cluster of cysticercus cysts. It has been postulated that some of the large mature tuberculomas develop as a result of coalescence and caseation of such multiple lesions (Fig. 6).

Microtuberculomas

With the advent of the CT scan, a large number of cases who presented with a solitary small disc or ring, 5–7 mm in diameter, surrounded by perifocal oedema were reported from all over India. In some cases such small lesions could be multiple or be associated with a large tuberculoma elsewhere in the brain (Fig. 7). It is now, obvious that this CT morphology could be due to a variety of conditions, cysticercosis, "microabscess", non-specific encephalitis, etc., but at least some of these have proven to be tubercular on biopsy.[20] Such a lesion may represent the initial stages of evolution of a tuberculoma. These have been observed at autopsy in cases of tubercular meningitis.[47,142,195]

Calcified Tuberculoma

Calcification is uncommon in a tuberculoma and is reported in 2–6% of cases.[5,8,150] However, occasionally, a tuberculoma may present as a fully calcified mass. It is important to realise that such a lesion is not inactive or healed. A very high incidence (60%) of calcification has been reported in Eskimos and Canadian-Indians.[4]

Tuberculous Encephalopathy with an "Inconsequential" Tuberculoma

Dastur and Udani,[49,50] have drawn attention to the occurrence of diffuse brain damage in children with tuberculosis with a minimal or no inflammatory lesion, meningitis or significant granuloma. The condition is characterised by obvious oedema with varying degrees

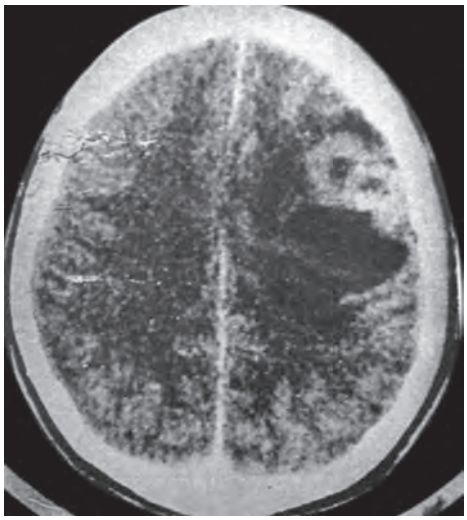


Fig. 5A: Contrast CT scan showing a parietal tuberculoma with a posterior cystic component

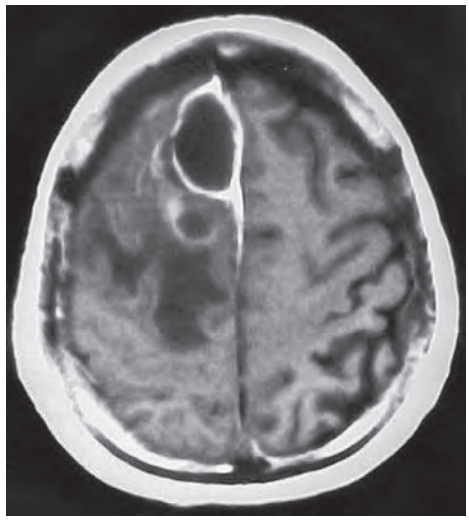


Fig. 5B: MRI axial view showing right parafalcine cystic tuberculoma

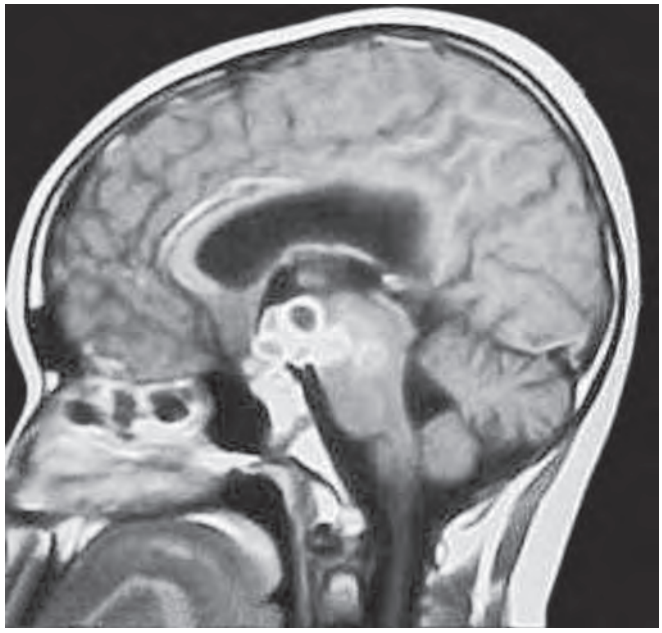


Fig. 6: CT scan of tuberculoma brain—grape-like cluster

of perivascular myelin loss and, in some, even haemorrhagic leucoencephalopathy. They have designated it as 'tuberculous encephalopathy' and attributed it to an allergic reaction to proteins liberated from lysed tubercle bacilli. We had demonstrated a somewhat similar pathology in hypersensitised monkeys challenged with a small number of tubercle bacilli.[194] Wisniewski and Bloom[220] produced evidence in favour of a hypersensitivity mechanism for this type of pathology. Crowle et al.[43] have further elaborated on the chain of complex cellular and molecular events constituting the mechanisms in human tuberculosis.

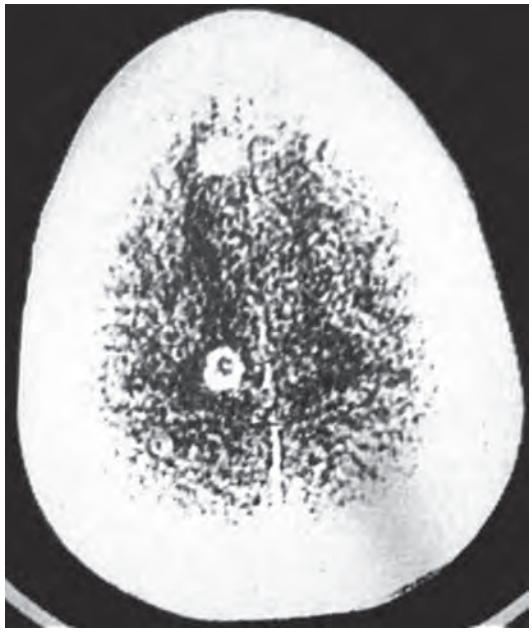


Fig. 7: Contrast CT showing microtuberculomas in the left frontal and parietal regions

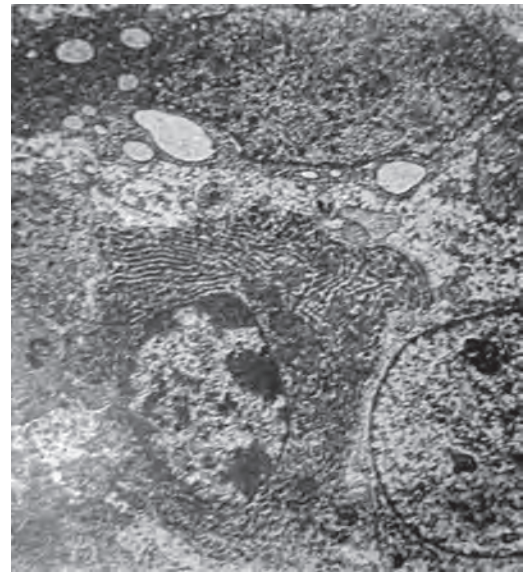


Fig. 8: Electron micrograph of the periphery of a brain tuberculoma—at the top a macrophage is seen with a large nucleus and vacuolated cytoplasm, in the lower half, a plasma cell is seen with the characteristic rough endoplasmic reticulum and peripheral heterochromatin in the nucleus. A part of another large cell with a very pale nucleolated nucleus possibly an epithelioid cell, is seen in the lower right corner

Microscopy

Dastur and his colleagues, in a series of publications, have provided details of electron microscope (EM) studies of brain tuberculomas (Figs 8 and 9). In addition to describing the fine structure of these lesions, including evolution of the epithelioid cells, they elaborated the ultrastructural basis of vasculopathy in and

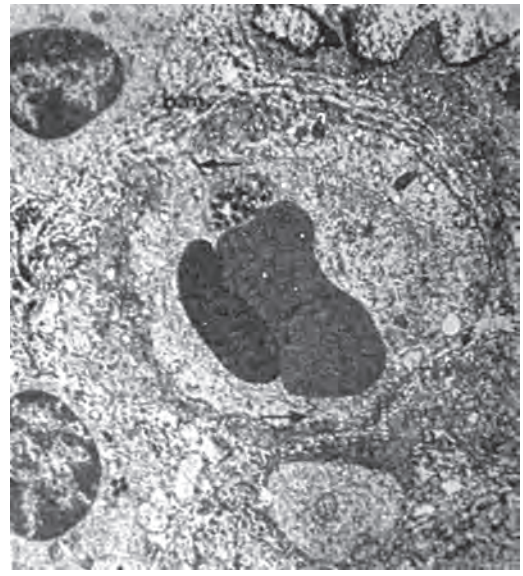


Fig. 9: Electron micrograph of a tuberculoma brain—showing an entire blood vessel, possibly a venule, with two intact endothelial cells and normal tight junction (arrow). Two RBCs and a platelet are seen in the lumen. Note the two lymphocytes on the left and the two epithelioid cells on the right infiltrating the vessel wall

around a tuberculoma. EM examination of the reactive border zone revealed the varied pleomorphic cellular, vascular and necrotic reactions characteristic of these lesions. It was demonstrated that a variety of cells surrounding the central necrotic area participate in phagocytosis. All these cells were large mononuclear cells, the commonest being the epithelioid cell. They demonstrated the evolution of the epithelioid cell from a mononuclear cell and also showed that overt macrophages full of secondary lysosomes and phagosomes contained ingested osmophilic debris. A feature of these cells was their proclivity to fuse with their fellows, forming characteristic Langhans giant cells which also retain the capacity for phagocytosis. These varied responses probably resulted from a delayed type of hypersensitivity to a very small quantity of antigenic tuberculoprotein in the absence of demonstrable tubercle bacilli, which were hard to discover in these lesions. Dastur and Dave[45] had also studied the ultrastructural morphology of blood vessels in tuberculomas. They observed marked proliferation of the basement membrane into concentric layers in the vessels in the reactive border zone. They postulated that the proteinaceous material in the basement membrane may act as an antigen and be responsible for the vasculitis and brain damage associated with tuberculomas.

Clinical Features

The symptoms and signs of an intracranial tuberculoma resemble those of other intracranial tumours. There is no clinical feature which could unequivocally provide the diagnosis. There are, however, certain findings which collectively may suggest a possible diagnosis.

Age and Sex

There is no age immune to CNS tuberculosis, but 60–70% of patients with tuberculomas are below the age of 20 years. The youngest child seen by us was 9 months old and the oldest patient was 69 years old. Ramamurthi[154] reported that 111 out of 280 tuberculomas (40%) were in children. Dastur[53] found 50% to be below the age of 10; 59% below the age of 15 and 83% below the age of 25 years. A higher incidence has been reported in females, but in the author's experience this does not appear to be significant.

Sites

Tuberculomas may occur at any site within the brain; the cerebrum and cerebellum, owing to their bulk, are the most common sites (Figs 10 and 11). The cerebellum was found to be a more frequent location in children and the cerebral hemispheres in adults. This observation no longer appears to be true with much earlier diagnosis being made now with CT scans. The surgical verification of the lesion is also much less frequent, as few cases require surgical excision as compared to four decades earlier.

Tuberculomas have been documented in the intrasellar region, brainstem, thalamus, basal ganglia, mesencephalon, cerebellopontine angle, optic chiasma, the pineal region, in the ventricles and the aqueduct[13,19,20,27,52,53,68,70,85,116,133,182,216] (Figs 12A and B, 13). CT and magnetic resonance (MR) scans reveal a much higher incidence of multiple lesions than was suspected earlier,[17,18] about 15–20% of patients having multiple lesions. Tuberculomas in different stages of evolution and varying in size often coexist. Intracranial extraparenchymal tuberculomas have been reported in the pituitary

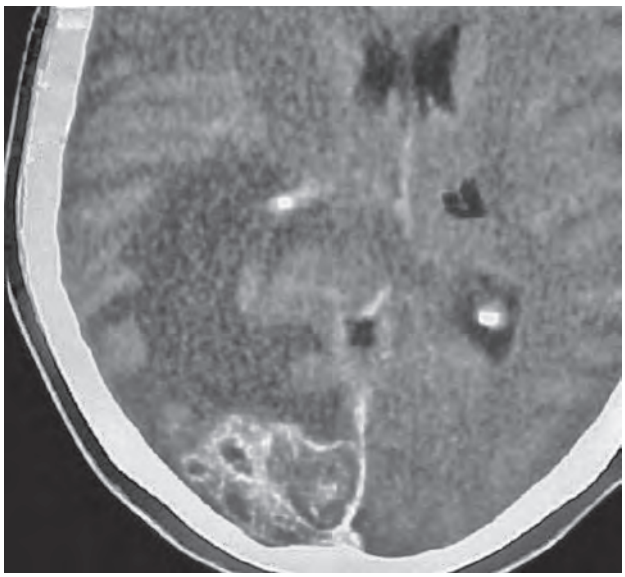


Fig. 10: Contrast CT scan of the brain showing enhancing tuberculoma in the right occipital lobe which is surfacing and minimal shift of the posterior falx to the left due to mass effect

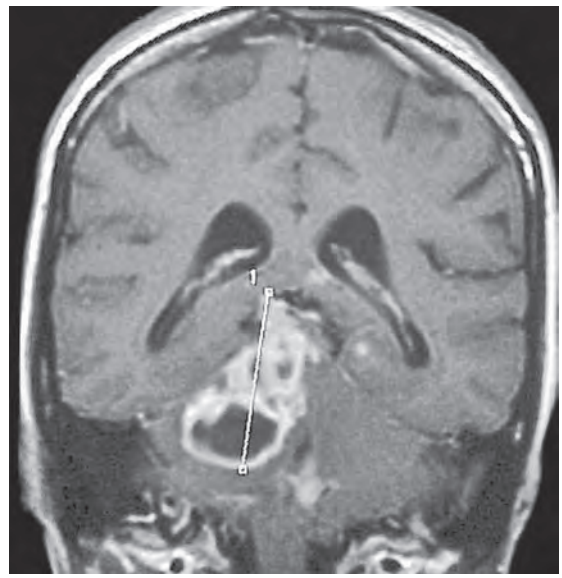
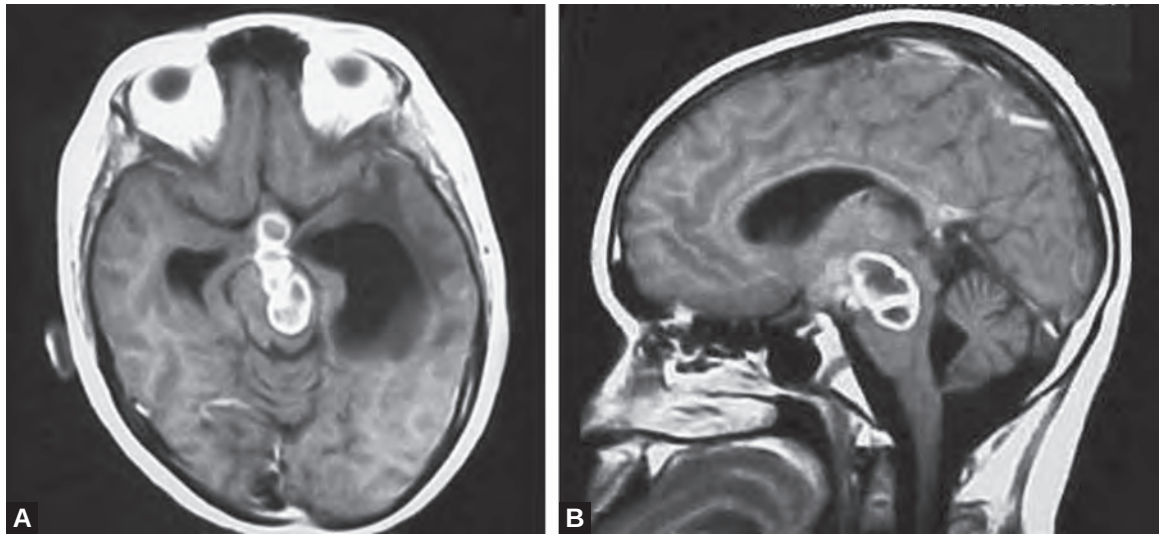


Fig. 11: Contrast MRI of the brain showing infratentorial tuberculoma



Figs 12A and B: MRI of the brain axial and coronal views showing brainstem tuberculoma

fossa,[28,39,40,100,102,160,181] in the superior orbital fissure and involving the lesser wing of the sphenoid.[21,189]

Symptoms and Signs

Tuberculomas generally, present as slow-growing intracranial space occupying lesions. The constitutional symptoms and signs of an inflammatory lesion are uncommon. Unlike patients with tuberculous meningitis, those with a tuberculoma often look physically well-preserved.[148] A history of fever is recorded in no more than 10–20%. A history of exposure to a person with open pulmonary tuberculosis, especially a close relative, should arouse the suspicion of tuberculous aetiology in a patient suspected to harbour a brain tumour. Concomitant evidence of healed or active tuberculosis acquires great significance. Mayers et al.[119] reported the coexistence of an active extracranial tubercular lesion in 50% of patients and an abnormal chest X-ray in 30%. Mathai[117] identified positive chest X-rays in 51% of 200 cases of intracranial tuberculomas. It is important to remember that in a community in which tuberculosis is as prevalent as in India, patients with neoplastic lesions may have extracranial tubercular lesions as was observed by Mathai[117] in 12.5% of cases. The association of a clinically manifest tuberculoma with tubercular meningitis is uncommon. This was reported in only 3 out of 200 cases by Mathai.[117] However, a much higher incidence of coexistence of the two has been reported in patients investigated by CT or coming to autopsy.[47] A tuberculoma may, uncommonly, appear for the first time after the initiation of antitubercular therapy for tuberculous meningitis or a coexisting tuberculoma may enlarge following treatment.[25,33,77,108,126,195,200]

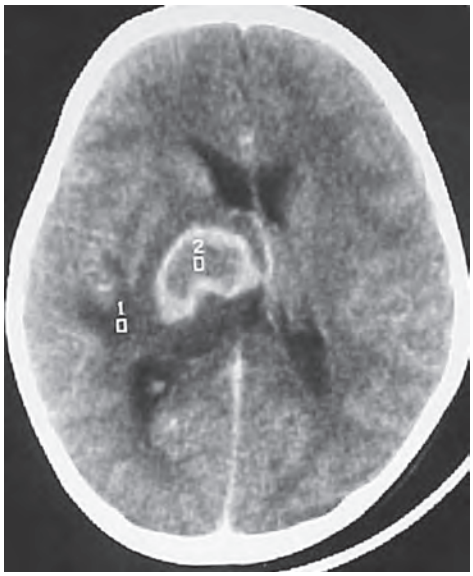


Fig. 13: Contrast enhancing CT scan showing a thalamic tuberculoma

Focal seizures are frequently the first symptom. Symptoms and signs of raised intracranial pressure are seen in large tuberculomas. Focal neurological deficit, appropriate to the site of the lesion, is observed in approximately 50%. A higher incidence of false localising signs and focal seizures in patients with cerebellar tuberculomas was reported by Dastur and Desai.[52] These were most likely due to multiple lesions, not detected by the investigations available then, viz. ventriculography or angiography. An interesting comparison of the clinical features of 107 cases each of brain tuberculomas and gliomas has been provided by these authors.

Investigations

None of the currently available diagnostic procedures, either singly or in combination, are able to provide an unequivocal diagnosis of an intracranial tuberculoma. Efforts are underway to develop specific and sensitive immunodiagnostic tests, but so far these fall short of the desired accuracy.

The erythrocyte sedimentation rate is often raised, though it may be normal. The Mantoux test is generally positive, though Arseni[5] found it positive in 25%

only. A negative Mantoux test does not rule out tuberculoma, nor does a positive test establish the diagnosis. A plain X-ray of the chest is mandatory as an active tubercular lesion significantly increases the possibility of an intracranial mass being a tuberculoma. PCR is a useful diagnostic aid.[132] Plain X-rays of the skull may show signs of raised intracranial pressure and, uncommonly, calcification.

Computerised Tomography

The computerised tomography (CT) morphology of intracranial tuberculomas has been well-documented in a series of publications since 1976.[111] Welchman[216] has provided a comprehensive account and concludes that the CT appearance of tuberculomata in the majority of cases is sufficiently characteristic to permit a positive or high probability diagnosis.

The CT morphology depends on the stage of evolution and the maturity of the lesion. The important CT characteristics[16,18] are summarised below (Fig. 14):

- In a non-contrast enhanced scan tuberculomas are generally, isodense with the surrounding brain. However, hypodense or slightly hyperdense lesions are well-documented.
- These enhance markedly on administration of contrast.
- Perifocal oedema, usually quite out of proportion to the size of the lesion, is common.
- The lesions manifest in one of the following three forms:
  1. Small discs and rings measuring less than a centimetre. They are sharply outlined and homogeneously enhancing, surrounded by perifocal low attenuation representing oedema (Fig. 15).
  2. A large ring, usually 1–2 cm in diameter, with a uniformly enhancing periphery and central lucency, though not as marked as in a pyogenic abscess (Fig. 1). In a few cases, there may be a central dense nidus producing the so-called "target sign" of Welchman.[216]
  3. Large nodular masses with an irregular outline.
- Multiple lesions representing one or more of the above varieties, occurring in the same patient, are seen in 15–20%.

It must be realised that in spite of the accumulated experience over the years, CT does not provide an unequivocal diagnosis of brain tuberculoma. CT findings considered with the clinical features can, however, provide enough justification for instituting medical therapy.

Magnetic Resonance Imaging

Intracranial tuberculomas usually show complete hypointensity, isointensity or central hyperintensity with a hypointense rim on T1-weighted images and isointensity and/or hypointensity on T2-weighted images.[74–76,215] However, some tuberculomas have been found to be hyperintense on T1 and hypointense on T2 images. Gadolinium MR may show thin rim enhancement in a tuberculoma.[169] Gupta et al.[75] correlated the MR images with histopathology. They concluded that the intensity of a tuberculoma on T1-weighted images depends on the number of macrophages, the degree of fibrosis, gliosis and lipid contents. Lipids are the major contributor to the low-signal intensity on T1 images. Solid caseation appeared hypointense and liquid appeared hyperintense on T1-weighted images. The characteristic hypointensity of intraparenchymal tuberculomas is not found in most other space occupying lesions. It is obvious that the MR image morphology may show

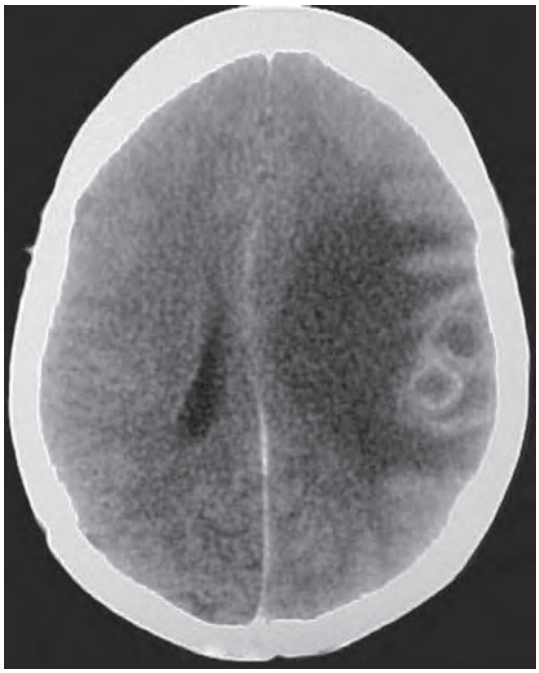


Fig. 14: CT scan showing right parietal tuberculoma with surrounding oedema and mass effect

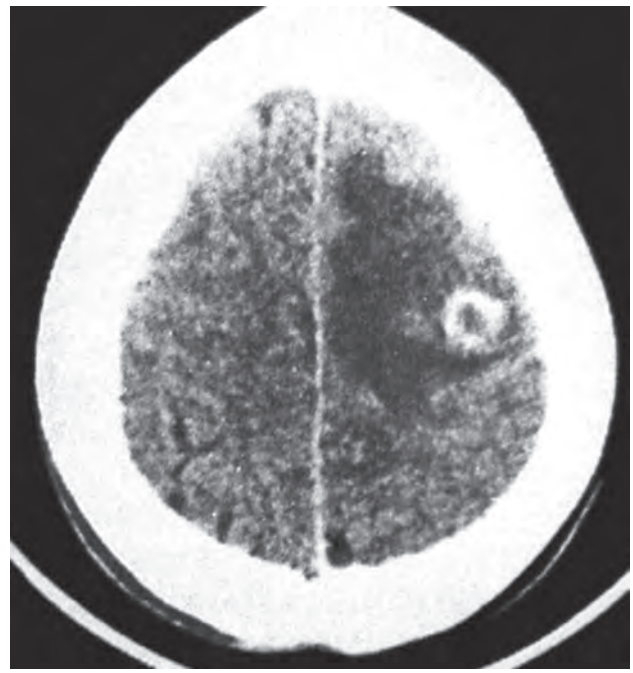
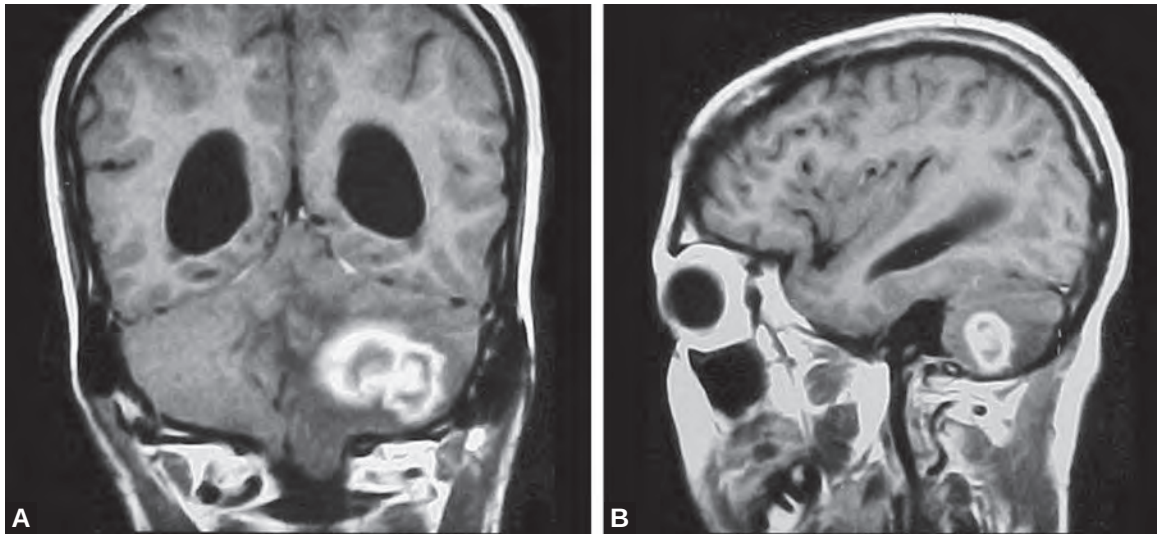


Fig. 15: CT scan showing a small ring lesion in the right parietal region



Figs 16A and B: MRI—coronal and sagittal views of gadolinium enhancing tuberculoma in the left cerebellar hemisphere

variations from lesion to lesion and within the same lesion depending upon the stage of evolution and its histopathological characteristics (Figs 16 to 19).

Magnetic Resonance Spectroscopy

In vivo, proton MR spectroscopy[11,88-90,155] of the hypointense lesions shows a characteristic lipid peak on stimulated echo acquisition mode (STEAM) and point resolved spectroscopy sequence (PRESS).

Stereotactic Biopsy

When the diagnosis of a lesion, suspected to be a tuberculoma, is in doubt, one may start a trial of antituberculous treatment or do a stereotactic biopsy. Stereotactic biopsy gives a definite diagnosis to enable the treatment to be based on firm grounds.[26] Vedantham et al.[210] have advocated CT guided stereotaxy to avoid empirical treatment of small brain masses.

Treatment

Till 1970s, emboldened by the availability of antitubercular chemotherapy, neurosurgeons advocated excision of tuberculomas as the treatment of choice.[73,192] This attitude was dictated by the uncertainty of preoperative diagnosis, inability to follow-up reliably the effect of medical treatment and the earlier experience of post-operative meningitis following partial excision. No doubt there were several reports of cures following chemotherapy alone,[4,149,150,163] but in most of these cases there was no objective verification of the diagnosis.

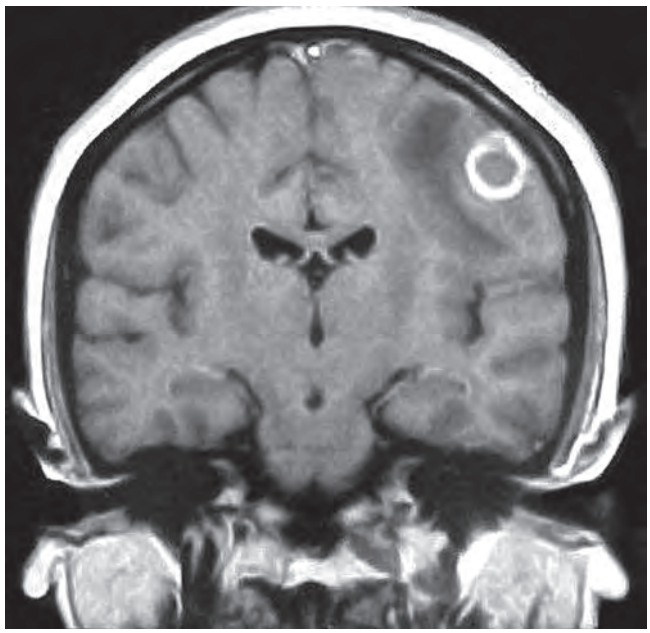


Fig. 17: MRI coronal view showing left parietal solitary ring enhancing tuberculoma with surrounding oedema

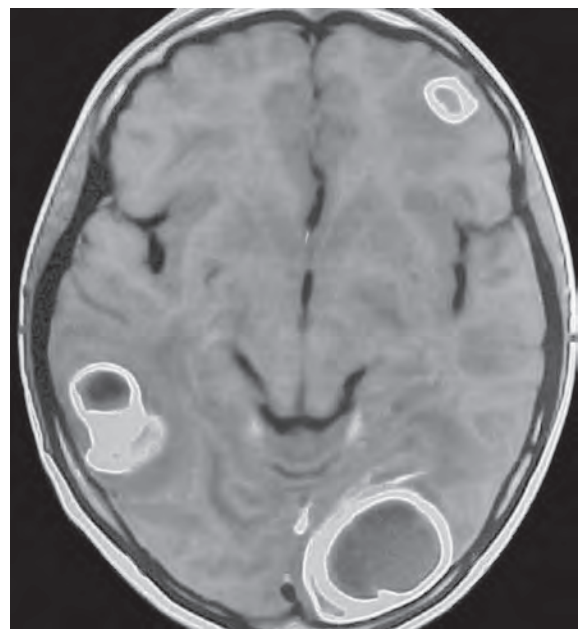


Fig. 18: Post-contrast MRI of the brain showing multiple ring enhancing lesions of various sizes in both hemispheres

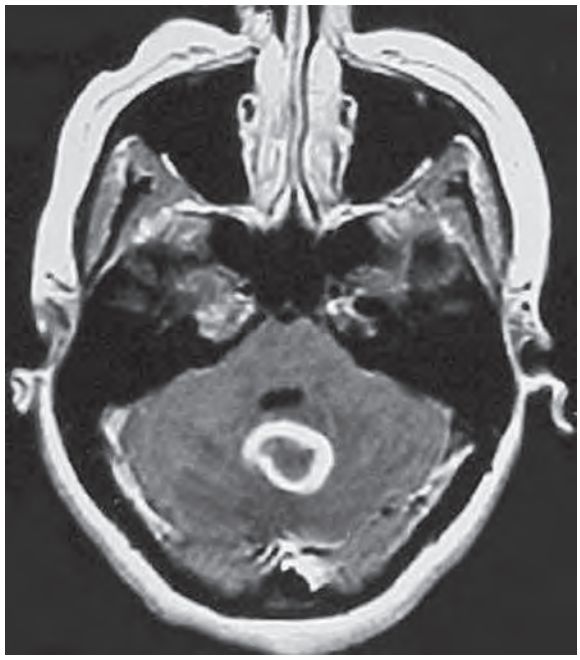


Fig. 19: T1-weighted axial MRI scan of a patient with vermian tuberculoma

With the availability of CT, the diagnosis has become more reliable and the effect of treatment can be evaluated non-invasively.[7,18] This has radically changed the indications for surgery.[190,196] It is now generally, agreed that surgery is indicated: (a) if vision or life is threatened due to a severe increase in intracranial pressure and (b) when the diagnosis is in doubt. In all patients with a reasonable suspicion of a tuberculoma, with no imminent threat to vision or life, a course of multi-drug antitubercular chemotherapy is initiated. Steroids may be added in case CT or MR response to treatment is closely monitored. As a rule, clinical improvement is obvious within 2–3 weeks and significant reduction in the size of the lesion can be documented by CT or MR within 4–6 weeks. Complete resolution of the lesion depends on its size, and is seen as early as 10–12 weeks for small lesions and even large lesions may resolve completely in 6–8 months time.[18-20,108,138,190] Medical treatment may not resolve all tuberculomas. The lesion may develop central liquefaction,[133] may remain unchanged[20] or even paradoxically increase in size.[10,126,146] The reason for the lack of response and the paradoxical response is not clear. There is enough evidence to suggest that this is not only due to drug resistance of the bacilli but also due to factors as yet unknown. A number of these cases ultimately respond to continued therapy and carefully worked out combinations of antitubercular drugs including, if necessary, streptomycin injections. Rajkumar et al.[146] found that the atypical response was seen from 3 weeks to a year of therapy and well-formed lesions more than 3 cm have a greater risk of paradoxical increase.

There are two controversial questions in respect of medical therapy: (1) The ideal combination of drugs and (2) The duration of the treatment. There have been some prospective trials conducted by the Tuberculosis Research Centre of India and Indian Council of Medical Research (ICMR) at Chennai, India. Among the antitubercular drugs, rifampicin, isoniazid, pyrazinamide and streptomycin are bactericidal, and the former three penetrate the blood-brain barrier both in the presence and in the absence of inflammation.[128] Hence, ideally, these constitute the important first line of drugs. After the initial treatment with three drugs, any two of these three or only INH and ethambutol are used for another 12–15 months. Para-aminosalicylic acid (PAS) and streptomycin are seldom used now, though they were in use for many years. Recently, streptomycin had to be reintroduced in some patients in whom there was no adequate response to a three drug regimen. The ICMR research study group[145] recommended a reduction in the duration of therapy to ensure adequate compliance, which reduces the chance of recurrence and to overcome drug resistance induced by irregular therapy. An intermittent regimen gave equally good results with less toxicity. The group concluded that short course chemotherapy gives good results in tuberculosis of the spine and in brain tuberculomas.

In spite of these recommendations, we are reluctant to reduce the treatment to less than 18 months, except in cases of a solitary microlesion described earlier. Pandya and his colleagues[69,133] do not favour short-term chemotherapy for CNS tuberculosis. Poonnoose et al.[40] reported that 75% of patients with biopsied and partly resected tuberculomas exhibited residual lesions even after 18 months of treatment and caution that the duration of ATT should be based on radiological response and some may require prolonged periods of ATT.

It is important to realise that most antitubercular drugs have side/toxic effects. These should be assiduously looked for and patients should be warned to report immediately, if any untoward reactions are observed. Liver toxicity is a real problem with the use of rifampicin. It may be better to evaluate liver function periodically by appropriate tests. There is a risk of optic neuritis when ethambutol is used. It is desirable to use pyridoxine (10 mg) as prophylaxis against peripheral neuritis encountered with the use of isoniazid and ethambutol. The ototoxic complications of streptomycin are well known.

The causes of non-response to antitubercular therapy were identified as inappropriate drug therapy (needing the addition of another drug), bacterial resistance and the lesion not being a tuberculoma. In cases not responding even after a change in therapy and the addition of steroids, the possibility of a glioma is high and stereotactic biopsy or surgical excision is indicated.[167]

Multi-Drug Resistant Tuberculosis

Multi-drug resistant tuberculosis is becoming a common problem and results from inappropriate dosage, use of a single drug or inadequate duration of therapy. The resistance is influenced by bacterial genome changes.[30,136] The coexistence of HIV/AIDS infection increases the chances of developing multi-drug resistance.

Role of BCG

The protective nature of BCG vaccination is well-proven.[121,125,162] Farinha et al,[62] in an analysis of patients with CNS tuberculosis over 20 years, found that no patient who had received BCG vaccination died or had severe neurological sequelae.

Surgical Treatment

The indications for surgery have already been described above. It is desirable to initiate chemotherapy, preferably a few days prior to surgery, if the patient is not already on it. Administration of pre-operative corticosteroids is also desirable. The guiding principles for surgery are:[155]

- Total excision of easily accessible lesions in non-eloquent areas of the brain must be done. No attempt should be made to excise large tuberculomas en-masse. Piecemeal removal or initial debulking does not increase the risk of meningitis if the patient is covered with antitubercular drugs.
- Subtotal or partial excision of lesions situated in or near eloquent areas.
- No attempt should be made to excise aggressively tuberculomas attached to vital structures like the brainstem or the major dural venous sinuses.
- Simple evacuation of the central liquefied caseous material from a tuberculoma or pus from a tubercular abscess may be adequate for treatment of deeply situated lesions, i.e. those in the thalamus, basal ganglia and brainstem.[156] This may preferably be carried out stereotactically.[19]
- Small, circumscribed lesions, the so-called microtuberculomas could be excised stereotactically, if the diagnosis is in doubt.
- Residual lesions, or in cases of multiple tuberculomas, the lesions that have not been excised, respond to chemotherapy.
- A ventriculoperitoneal shunt may be required for patients with gross hydrocephalus.
- The CUSA (ultrasonic aspirator) can be very useful in debulking a large tuberculoma. Chiasmal decompression may be required for a suprasellar tuberculoma developing during treatment for tuberculous meningitis.[29,42,43,65,84,95,118,176,201]
- Endoscopy[87,180] has a role in management of associated hydrocephalus and can be used to do ETV, fenester the septum, break loculations and reduce the need for multiple shunts.

In short, even when surgery is indicated, it is better to be conservative rather than risk an undesirable neurological deficit. With the use of modern techniques, the mortality and morbidity of surgery are negligible.

Reviewing an experience of 40 years, Ramamurthi,[149] in 1993, pointed out the changes that have taken place in the presentation and management of tuberculomas in the CT era. Of the 380 patients with tuberculomas seen between 1950 and 1978 (the pre-CT era), 303 (78.6%) required surgical treatment. Between 1979 and 1999 (the CT era), of the 246 patients seen only 13.4% required surgery. During the CT era smaller lesions are diagnosed early, long before the ICP rises. On a presumptive diagnosis from the CT, antituberculous treatment was started and the majority of cases responded to therapy, as proved by serial CT studies. It is obvious, of course, that in all these patients the pathology has not been proven by histology. Some of them could have been what have been termed 'disappearing lesions' whose aetiology is not clear and may be multi-fold. Puri and Gupta, in 1994,[143] evaluated with MR these focal CT lesions in 67 patients and identified four distinct groups: 38 (56%) were diagnosed as tuberculomas; 12 (17.9%) as cysticercosis; 1 as abscess and the rest (23.8%) were classified as non-specific. The non-specific lesions were hyperintense on T2-weighted and hypointense or isointense on T1-weighted and resolved completely in 5 months without any antitubercular therapy.

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65 Tuberculous Meningitis

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INCIDENCE

In spite of the intensive public health measures adopted by governments and various agencies, tuberculosis continues to be a major problem, and tuberculous meningitis (TBM) a major cause of neurological morbidity and mortality all over India and the developing countries. The incidence of TBM, in patients with tuberculosis, has been reported to vary from 7% to 12%. TBM is a disease of childhood, with the maximum incidence around 3 years. It is uncommon before 6 months of age and rare before the age of 3 months. The incidence in adults is increasing and adults account for 50% of patients. There is a resurgence of TBM in the developed countries due to the prevailing AIDS epidemic. Since 1995, an increase of 15% in the incidence has been reported.[1,23,39,139,150,152,153,164] The BCG vaccine was introduced in 1921 and the protective efficacy of this vaccine against miliary tuberculosis and tubercular meningitis is proven. The children who have been vaccinated with BCG have a better outcome than those who have not been protected.[5,6,17,74,81,112]

AETIOPATHOGENESIS

Much of the characteristic pathology of TBM is recreated with the subarachnoid injection of tubercular protein alone. The spectrum of CNS tuberculosis is varied,[149] and both the host and bacterial genotype influence the development of disseminated disease.[22] A cascade of proinflammatory cytokines (e.g. tumour necrosis factor, TNF alpha, interferon, Gamma-cytokines) influence the cell mediated response.[97] TBM is correctly characterised as a meningo-vasculo-encephalitis as the meninges, parenchyma and vasculature are all involved. There is a thick subarachnoid tubercular exudate caused by basal arachnoiditis. The small and medium sized arteries that traverse the exudates develop an inflammatory tuberculous arteritis and the adventia and intima develop typical tubercular granulomatous lesions.[162] The intima may be damaged by fibrinoid hyaline degeneration and this leads to vascular occlusion by a reactive subendothelial cellular proliferation.

EARLY DIAGNOSIS

The protean manifestations of this disease may mimic almost any neurological disorder affecting the central nervous system.[130,144,147,154,156] Constant awareness of the disease and clinical suspicion are prerequisites for diagnosis. Usually the clinical features include fever, meningismus, nausea and vomiting, and neurological deficits including cranial nerve involvement, motor paresis and a bulging fontanelle in infants. Only less than 20% of patients with TBM present with fever, hence, the absence of fever does not exclude the possibility of TBM. In 1994, the Ahuja criteria[1,4] were proposed to aid in the diagnosis of TB meningitis.

Modified criteria of Ahuja[126] are useful to diagnose the disease and include the following:

A. *Clinical*—Fever with or without change in the temperature over a period of 2 weeks with or without any cause (mandatory), loss of appetite, irritability, headache, vomiting, meningeal signs, convulsions and focal neurological deficits; known contact with sputum positive adult tuberculosis (optional).
B. *Cerebrospinal Fluid (CSF)*—Pleocytosis with more than 20 cells/mm^3, lymphocytes more than 60%, protein more than 100 mg% and sugar less than 60% of corresponding blood sugar.
C. *Radiological*—Computerised tomography (CT) studies of brain showing two or more of the following:
    1. Exudates in the basal cisterns or in the Sylvian fissures
    2. Hydrocephalus
    3. Infarcts
    4. Gyral enhancement
D. *Extraneural tuberculosis*—Active tuberculosis of lungs, gastrointestinal tract, lymph nodes, skeletal system as evidenced by appropriate radiological or microbiological evidence or by the presence of caseation necrosis on histological examination.

Diagnosis of TB meningitis is classified into four groups based on the above clinical and laboratory criteria.

1. Definitive TBM:
    a. Clinical criteria
    b. Bacterial isolation from CSF or diagnosis at autopsy
2. Highly probable TBM:
    a. Clinical criteria
    b. All three of B, C and D
3. Probable TBM:
    a. Clinical criteria

b. Any two of B, C or D
4. Possible TBM:
   a. Clinical criteria
   b. Any one of B, C or D

These criteria have been modified by adding Mantoux reaction and contact history. The modified Ahuja's criterion has a sensitivity of 83% and a specificity of 63%.[126] If diagnosed and treated early, the disease is curable with minimal or no residual neurological disability.

LABORATORY INVESTIGATIONS

CSF examination at the least suspicion is essential.[86,90] Apart from changes in cells and proteins, enzyme-linked immunosorbent assay (ELISA) tests are most useful.[68,72] The polymerase chain reaction (PCR) is useful in the rapid diagnosis of tubercular meningitis and has a sensitivity varying from 31% to 60%.[8,100,101,103,109,128] Microscopic observation drug susceptibility (MODS) assay format detects the presence of 65 kD hsp antigen which is specific to *M. tuberculosis* and is a reliable diagnostic marker of TBM.[7,80,91] of IgG reactivity to lipoarabinomannon (LAM) in the CSF is very useful in the early diagnosis of TB meningitis and is superior to PPD in the diagnosis of TBM. The novel wide range qualitative nested real time PCR assay for mycobacterium tuberculosis DNA is used to rapidly diagnose TBM and is a useful and advanced assay technique for assessing the clinical treatment course of TBM.[140,142] Culture of the bacteria takes 2–6 weeks. Centrifugation and filtration methods are used to increase the yield of positive cultures.[125] The isolation rates for the BACTEC 12B medium and LJ medium were 93% and 39%, respectively.[58,159] Notwithstanding the recent advances, a totally reliable diagnostic test is still not available.

LATE DIAGNOSIS AND COMPLICATIONS

If diagnosed late, the course of the disease is prolonged with numerous complications like hydrocephalus, arachnoiditis, infarcts and tuberculoma. In addition, many chronic and localised forms of the disease appear with atypical manifestations, posing diagnostic and therapeutic problems and often require surgical help. A thorough knowledge of these problems is essential for neurosurgeons practising in the developing countries in the East and the West.

The most common complication of tubercular meningitis where surgery is helpful is post-meningitic hydrocephalus resulting from a blockage of the CSF pathways as a result of inflammation, the incidence of which may range from 38% to 80%. Tubercular meningitis may also present with raised intracranial pressure (ICP), mimicking a brain tumour, cerebral abscess or tuberculoma.[85] A progressive hemiparesis due to vascular involvement in tubercular meningitis may resemble an intracranial space occupying lesion. Occasionally, a tuberculoma may follow or be associated with tubercular meningitis.[137,138] Basal arachnoiditis due to tuberculosis may be localised and cause neurological deficits or hydrocephalus. Compression of the optic chiasma may result in impairment of vision.[34] Spinal arachnoiditis, often associated with meningitis, may result in spinal cord compression.[37] The different aspects of the disease and its presentation are described here as many of these conditions may simulate other surgical problems and may require surgical relief.

Acute Stage of the Disease

Raised Intracranial Pressure Pathogenesis

TBM may present primarily with the problem of raised ICP.[93] Most of the cases of TBM are associated with raised ICP, which is caused by brain oedema, increased proteins in the CSF, poor absorption of CSF and obstruction to CSF flow. In the early stages, there is a mild increase in ICP due to the general inflammatory processes. Later, cerebral oedema with associated tuberculous encephalopathy occurs, possibly on the basis of an allergic reaction. The large arteries at the base of the brain get occluded or compressed with resulting ischaemic oedema and infarction in the affected territory. In some, softening of the brain may occur without major arterial involvement.[30,155] Increased proteins in the CSF retard CSF absorption and lead to raised ICP. Radioisotope studies have shown no significant obstruction to the flow of CSF from the ventricular system to the subarachnoid space in the acute stage.[141] However, in later stages the obstruction to CSF flow may be at a variety of sites—aqueduct, fourth ventricle, tentorial opening or the arachnoidal villi. It may even be at more than one of these sites.[145]

Diagnosis and Treatment

A patient with TBM and associated acute intracranial hypertension may present with an alarming picture of impaired level of consciousness and decerebrate spasms. These patients are usually young and the signs of meningitis minimal. The correct diagnosis can be arrived at only by an examination of the lumbar CSF. Hence, it is wiser for neurosurgeons in countries where TB meningitis is widely prevalent to bear in mind such an uncommon clinical presentation and in suspected cases to resort to a careful LP for the purposes of examination, preferably after CT studies. The risk of lumbar puncture in the presence of raised ICP is minimised by anti-oedema measures like IV mannitol which helps to reduce cerebral oedema. CT studies may show acute oedema with compressed narrow ventricles or hydrocephalus with a dilated ventricular system. The addition of acetazolamide and furosemide, to antituberculosis chemotherapy, is effective in controlling ICP.[123] If acute hydrocephalus still develops, repeated ventricular tapping or external ventricular drainage with a closed system is essential to reduce ICP.[14] This may directly be done through suitably placed burr holes or after inserting an Ommaya reservoir.

Subacute and Chronic Stage of the Disease

Tuberculous Endarteritis

Vascular involvement in TB meningitis is usually a tuberculous endarteritis affecting the smaller blood vessels and resulting in multiple focal neurological signs, due to localised areas of infarction. In late cases, these areas get calcified and are visible in the plain X-rays as irregular small areas of dense calcification. Such calcification is more common than the one seen infrequently in tuberculomas. The resultant clinical picture will vary with the areas involved, e.g. hypopituitarism or hypothalamic obesity in association with basal calcification.

Involvement of Large Arteries

The large arteries may be displaced, kinked or obstructed by the tuberculous exudates at the base of the brain. The siphon of the internal carotid artery, its bifurcation and the proximal segments of the middle cerebral artery are most commonly involved. Occasionally, the anterior cerebral artery may also be narrowed or occluded. The affected artery shows changes of periarteritis and a massive subintimal fibrosis, narrowing or occluding the lumen. These changes have been demonstrated by arteriography[50,51,87,117,162] and in autopsy studies by Dastur et al.[29,31,32] Of the 33 cases of TBM studied by Wadia and Singhal[161] with carotid arteriography, narrowing of the siphon of the internal carotid artery and the proximal segments of the anterior and middle cerebral arteries was seen in 17 cases. Narrowing of the arteries was seen most frequently in those with a neurological deficit and thus suggested infarction as the probable cause of hemiplegia. Cerebral infarction occurs in 14–38% of children with TBM and the most common vessels involved are the medial striate and thalamostriate arteries.

Tuberculomas and Tuberculous Abscess

These may infrequently follow TBM. More often, these occur in patients without any history of previous TBM.[110,157] They can also appear during or after completion of antitubercular therapy.[36,69,113] They manifest as a space occupying lesion, requiring appropriate investigations and treatment. CT or MR helps to localise the lesion, which may be excised with complete relief (see the chapter on Tuberculosis of the Central Nervous System). Kumar et al.[76,77] reported on six cases of tubercular abscess. These are characterised by an encapsulated collection of pus containing viable tubercular bacilli and 50% of the cases developed TB abscess while on ATT for TB meningitis. Only multilocular abscesses or those with thick capsules required excision, the rest were managed with aspiration and ATT. Poonoose and Rajshekhar[107] found that 46% of patients being treated for tuberculomas had residual lesions on imaging 2 years after treatment. Muthukumar et al. described concurrent syringomyelia and intradural extramedullary tuberculoma as a late complication of TBM.[57,94,105,135] Extended treatment may be required in such cases.

Basal Meningitis

Plaque simulating a neoplasm: as the disease becomes more chronic, the meningeal exudates become firm, organised and adherent to the base of the brain. In some areas the exudates becomes plaque-like, a few millimetres thick, almost like a granuloma, whilst the rest of the exudates clear up.[35] At times, when the process has become more chronic and localised, woody hard fibrosis of the leptomeninges may produce a bizarre clinical picture without clinical evidence of meningitis.[54] Such cases may simulate posterior fossa tumours, foramen magnum lesions or intracranial abscesses.[35] MR is helpful in differentiating these conditions. In these cases, the disease, though localised, is still in an active form.[141] The patient may present with headache, vomiting and drowsiness, and mild pyrexia is present. The clinical picture often simulates a posterior fossa neoplasm if a definite history of TBM is not available. The CT shows a dilatation of the ventricular system with no enlargement of the subarachnoid space. The fourth ventricle may be displaced and distorted. At surgery, a thick carpet of granulation tissue is seen obliterating the cisterna magna and the exit foramina of the fourth ventricle. It is better to avoid posterior fossa exploration in such cases. A ventriculoperitoneal shunt is more effective.

Hydrocephalus

More often, the exudates get organised and there is a fibrous obliteration of the subarachnoid space. The disease dies down, but hydrocephalus develops and leads to progressive mental deterioration and impairment of the level of consciousness. The hydrocephalus may be communicating or non-communicating.[16] Lampreche et al.[79] found non-communicating hydrocephalus in 58.5% and communicating in 41.5% of shunted cases.

The raised ICP in subacute and chronic TBM is essentially due to the hydrocephalus produced by the obstruction of the CSF pathways.[95] Blockage of the arachnoid villi contributes to the production of hydrocephalus.[119,120] A common site of obstruction is in the basal cisterns like the cisterna pontis, interpeduncularis and ambiens. In the majority of cases, the hydrocephalus is of the communicating variety as confirmed by isotope cisternography. At times, the exudates block the foramen of Munro or the foramina of Luschka and Magendie preventing the exit of CSF from the fourth ventricle. Blockage of the aqueduct of Sylvius may be caused by the exudates or by ependymitis with local oedema, or an associated small intrinsic tuberculoma.[111] Usually, a combination of these factors is responsible for the hydrocephalus, and this was demonstrated by RIHSA studies of CSF circulation by the author in 1975.[146] The block at the level of the foramen of Monro may lead to the necessity of two shunts or an endoscopic fenestration of the septum.

Clinical Picture

This depends upon the stage of the disease when hydrocephalus sets in. In the acute stage, when the symptoms

and signs of meningitis dominate, the development of hydrocephalus is heralded by increasing ICP, while the systemic and meningitic signs appear to be responding to treatment. Infants develop a bulging fontanelle, enlarging size of the head and increasing drowsiness. Upadhyaya et al.,[158] in a series of 70 cases of TBM and hydrocephalus in children five months to 11 years of age, found fever, altered sensorium, vomiting and convulsions as the common symptoms. Disturbed state of consciousness, decerebrate rigidity, meningeal signs and focal neurological deficits may be observed. These signs may develop any time during the course of the illness, even after a few months of an apparent arrest of the disease. In some cases, the initial acute illness may be mild or be modified by inadequate therapy, the patient thus presenting for the first time with evidence of raised ICP.

On the other hand, hydrocephalus may manifest months after the treatment for meningitis has been completed. At this stage, there are no clinical features of meningitis or systemic toxaemia. The patient presents with symptoms and signs of raised ICP, only the history indicating the aetiology.

Amongst adults, one occasionally sees a patient presenting with raised ICP, with or without any neurological deficit, and with no clinical evidence of meningitic or infective pathology. Investigations reveal a communicating hydrocephalus. CSF examination or a contrast enhanced CT may reveal the inflammatory nature of the lesion. The possibility of tuberculosis being the cause of the condition is often presumptive.

Investigations

In the acute stage, CSF examination reveals evidence of meningitis, predominantly lymphocytic pleocytosis, raised proteins and diminished sugar. In the chronic stage, the CSF may be normal or may show mild pleocytosis and increase in proteins. Coexistent syndrome of inappropriate secretion of antidiuretic hormone (SIADH) and cerebral salt wasting syndrome should be diagnosed and treated. Polyurea, hyponatraemia, volume depletion and increased sodium excretion are pointers.[25,118]

Computerised tomography: It establishes the diagnosis of hydrocephalus and may suggest a possible tuberculous aetiology.[10,13,16,19,62,98,99,115,121,137,158] Ozates et al. reported that abnormal CT scans were seen in 98% of patients and hydrocephalus was seen in 84%.[99] Basal exudates can be detected and their severity ascertained. Such exudates, characteristic of TBM, are not diagnostic and can be seen in other bacterial, fungal[24] and carcinomatous meningitides.[98]

The most specific feature of TBM is hyperdensity in the basal cistern area prior to IV contrast medium administration, and the most sensitive feature is basal enhancement (Fig. 1).

The severity of hydrocephalus can be quantified in the CT by planimetric measurement of the surface area of the brain and the ventricle.[158] The degree and significance of hydrocephalus is calculated by the Ventricular Size Index, which is a ratio of the bifrontal diameter over the frontal horn diameter. A VSI range of 30–38% signifies mild hydrocephalus, 39–45% moderate hydrocephalus and severe hydrocephalus is indicated by VSI of 46% and above. Periventricular lucency indicates transependymal CSF flow and is caused by elevated ICP or spread of the inflammatory process. CT also reveals the presence or absence of infarcts and tuberculomas which have a direct relevance to therapy and prognosis. Abnormal CT scan findings may persist even after 6 months and despite good clinical improvement.

SPECT reveals more frequent abnormalities compared with EEG and CT scan.[63] Cortical hypoperfusion with or without basal ganglia hypoperfusion is associated with

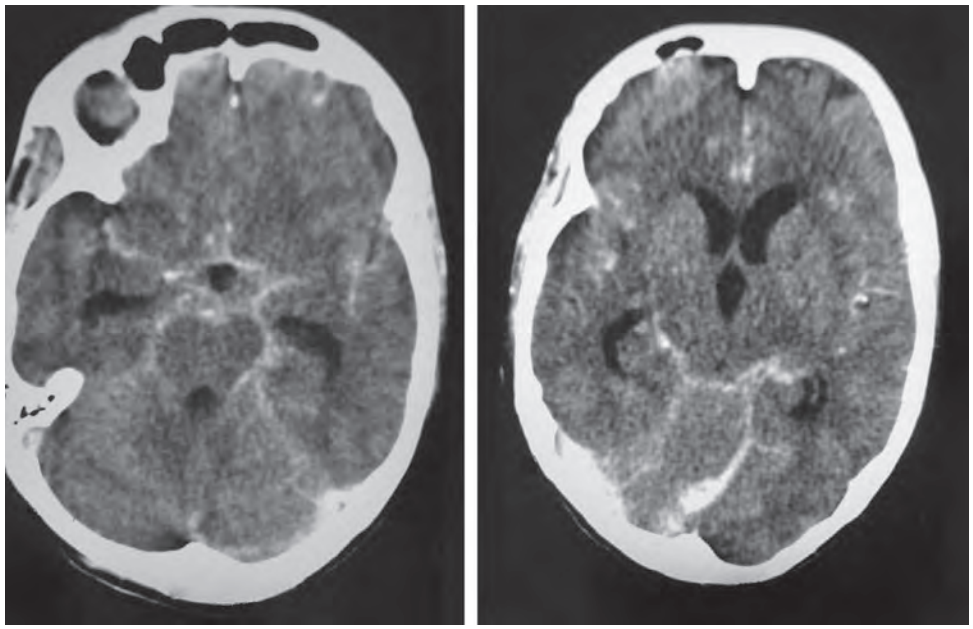

Fig. 1: CT scan of the brain showing post-contrast enhancement of the basal exudates

frontal rhythmic intermittent delta activity (FRIDA) and diffuse slowing on EEG.[62,88] BAER and VEP may have a role in evaluating these patients and show characteristic changes.[9]

Magnetic resonance imaging: Reactive diffuse meningeal enhancement occurs in the early period of tubercular meningitis on contrast medium enhanced T1 weighted MR; this later becomes limited to the basal regions.[100] The most specific feature of TBM is hyperdensity in the basal cisterns prior to administration of contrast medium. Magnetisation transfer MRI[65] is an important modality to detect infectious meningitis of different aetiology and the visibility of the meninges on precontrast T1 weighted MTMRI images is highly suggestive of TBM.

Treatment

Sir Hugh Cairns[21] was a pioneer in suggesting a CSF diverting procedure for post-meningitic hydrocephalus in tuberculosis in 1951. Since then the scope of surgical management has increased due to availability of shunt systems and the endoscope.[3,11,46,114,131,133,148] In those subacute and chronic cases of TBM, which have developed hydrocephalus, a ventriculoperitoneal shunt is indicated.[69] Mild hydrocephalus (VSI 30–35%) is treated with acetazolamide (20 mg/kg/day in three divided doses). It is important to remember that mild to moderate hydrocephalus, in the acute stage of the disease, is reversible following medical treatment of the meningitis and resolution of the basal exudates.[42,121,145] On the other hand, it is imprudent to delay the shunt in the face of impaired sensorium, increasing ICP or progressive neurological deficits.[15,134] In a series reported by Karande et al.,[67] hydrocephalus was seen in 84% of patients and 56% required shunt surgery.[27] It is not necessary to wait for the CSF to become free of evidence of active disease before shunt insertion. In patients with CSF protein higher than 1 gram/litre, an external ventricular drain is inserted initially which is converted into a VP shunt when the protein level becomes near normal.

A large volume of evidence has accumulated to show that dissemination of the disease is rare if the shunt is inserted under adequate cover of chemotherapy, even whilst the disease is active. There are, however, reports of the occurrence of military tuberculosis after a ventriculoatrial shunt and of tuberculous peritonitis after a lumboperitoneal shunt.[50]

After the insertion of the shunt, most of the patients show gradual recovery, even though the CSF may continue to show some abnormality. The level of consciousness improves and the neurological deficit regresses.[158] Long-term follow-up studies by Bhargava et al.,[16] showed that shunt surgery was followed by significant reduction in the size of the ventricles, but only rarely did the ventricles return to normal or near normal size. There was a close relationship between the cerebral mantle thickness and later intellectual attainments. Series dealing with post-tubercular hydrocephalus treated by shunt placement indicate that early shunt placement in cases of mild to moderate hydrocephalus leads to a better outcome. In HIV positive patients with TBM hydrocephalus a poor prognosis is common.[66,95]

Endoscopic surgery: Confirming that the hydrocephalus is non-communicating is very important in the management of hydrocephalus secondary to TB meningitis. Jha et al.[60] elaborated that endoscopic third ventriculostomy[61] can fail in the presence of advanced clinical grade, extra-CNS tuberculosis, dense prepontine cisternal adhesions and unidentifiable third ventricular floor anatomy. An associated tuberculoma in the brain can be associated with a successful outcome of the ETV.[59,60] The endoscope can also be used to fenestre loculations and the septum, thereby reducing the number of shunts.[41,165]

Corticosteroids: The use of steroids under ATT cover is advocated and improves outcome. Girgis et al.,[44] from Cairo, found that the addition of dexamethasone to antituberculous chemotherapy significantly reduced mortality and morbidity in patients with TBM, and this has been well validated.[2,108]

The use of steroids decreases cerebral oedema, and the production of cytokines and other chemicals in the immunopathogenesis of TBM.[151] Corticosteroids are given during the first month of treatment with IV dexamethasone (0.6–1.2 mg/kg/day in three divided doses) for 1 week followed by oral prednisolone (2 mg/kg/day in three divided doses). Corticosteroids affect outcome by reducing hydrocephalus and preventing infarction.[151]

Antituberculous drugs: Streptomycin was introduced in 1946[136] and since then a number of first-line and second-line antitubercular drugs have been introduced. The first-line drugs used are isoniazid, rifampicin and pyrizinamide, all of which are bactericidal. Ethambutol, a bacteriostatic drug or streptomycin in children too young to be monitored for visual acuity, are included in the initial treatment regimen if there is a possibility of drug resistance.[113] *Rifampicin* is given orally (10 mg/kg). It is contraindicated in jaundice and pregnancy and has adverse effects of liver toxicity, GI symptoms and rarely shock and respiratory collapse. *Isoniazid* is given orally or by the intramuscular route (3–10 mg/kg). It is contraindicated in drug induced liver disease and has adverse effects like peripheral neuropathy, psychosis, optic neuritis and, occasionally, lupus syndrome. *Pyrazinamide* is given orally (20–30 mg/kg) and is contraindicated in liver damage and can cause hepatitis. *Ethambutol* is given orally (15 mg/kg) and is contraindicated in optic neuritis and can cause optic neuritis, colour blindness and peripheral neuritis. *Streptomycin* is given as intramuscular injections (1 gm/day) (20–25 mg/kg). It is contraindicated in pregnancy and old age and can cause ototoxicity and renal damage.

The duration of ATT (short term/long term) is controversial and many neurosurgeons prefer to give 18 months of antituberculous drugs. However, Rajeshwari et al.[110] found satisfactory outcome after 9 months of ATT in 108 patients of tuberculomas. Goel et al.[45] reviewed 35

cases of TBM and found that short-term treatment was associated with recrudescence of TBM and a higher incidence of infarcts and neurologic sequelae. The problem of multidrug resistance[20,38,70] is very real and is seen in 2.4% of isolates.[96,104]

Anticonvulsants: Anticonvulsants are necessary because of the high incidence of seizures in patients with TBM. Patwari et al.[106] proposed a protocol that includes the consideration of clinical, EEG and radiological findings. Patients with focal or generalised seizures or tonic spasms that occur more than once, or associated with abnormal scans or EEG findings are started on anticonvulsants.

Results

The improvement depends upon the pre-operative condition of the patient.[82,83] Patients with prolonged pre-operative coma and semicoma show only marginal improvement. However, if a shunt is inserted when the level of consciousness is good, the results are gratifying. Most of these patients become alert, the hemiplegia improves and they may regain normal speech. Even in advanced disease the vision may return. Several series of patients treated with shunt surgery reported from India[26,89,102,158] and elsewhere[19,92] have established the safety and utility of shunt operations. Palur et al.,[102] from Vellore, India, reviewed 114 patients who underwent shunt surgery for hydrocephalus due to TBM. The patients were graded according to their sensorium. Palur grade I (headache, vomiting, fever and neck stiffness with normal sensorium and no neurologic deficit), Palur grade II (normal sensorium with neurologic deficit), Palur grade III (altered sensorium but easily arousable with or without dense neurological deficit) and Palur grade IV (deeply comatose, decerebrate or decorticate posturing). The best results were seen in grades I and II. They advocate early shunt surgery in these grades. For the others, external ventricular drainage is placed and if this results in improvement of the neurological status within 48 hours, shunt surgery was done. Bhargava et al.[15] emphasised the prognostic value of the amount and density of the exudates as seen in a contrast enhanced scan. The presence of thick exudates was associated with poor prognosis for survival and residual brain damage. The usual complications of shunt surgery like shunt obstruction, displacement, etc. may occur and need to be dealt with appropriately.

The pathology, in patients who show neurological recovery, is more likely to be vascular ischaemia rather than infarction. The blood flow is reduced as the dilated ventricles cause a narrowing of the arteries by elongation and stretching. A satisfactory restoration of blood flow, consequent on relief of hydrocephalus, results in neurological improvement.

Prior to the introduction of shunt surgery, direct intervention to relieve the obstruction locally has been performed on many occasions. These procedures are risky and are better avoided.

SEQUELAE OF THE DISEASE

Long-term sequelae[64] are seen in 78.5% of patients with 55% having cognitive impairment, 40% having motor deficit, 37% optic atrophy and 23% having cranial nerve involvement. These sequelae were common in patients who presented with deficits and altered sensorium. These patients need follow-up and there is the possibility of late development of tuberculomas after completing the ATT course successfully. Schoeman,[124] in analysing 76 cases of TB meningitis treated with modern antitubercular drugs and aggressive ICP management, found only 20% of children were functioning at normal level with 80% having cognitive impairment.

Optochiasmal Arachnoiditis

Defective vision following TBM is not an uncommon disability. The optic nerves may primarily be affected in an ischaemic process leading to primary optic atrophy. Loss of vision may also be due to compression of the visual pathways by basal meningitis. Fibrosis occurring near the optic chiasm may cause irregular field defects or blindness due to optochiasmal arachnoiditis. Choroidal tubercles, commonly described in textbooks, are rarely seen.[20] Blindness may also result from prolonged increase of ICP. When a child is brought with a complaint of blindness following TBM, plain X-rays of the skull are valuable in indicating raised ICP. In case the plain X-rays are normal and the visual defect is irregular, CT or MR has to be done to visualise the chiasmatic cisterns. In selected cases surgery around the chiasm may lead to improvement in vision.

Malnourishment

Malnourishment is common in patients with TBM, especially children, with nearly a third being malnourished. Shunt infection and dysfunction is related to the patient's nutritional status. Early pre-operative nutritional status screening and its optimisation may decrease the morbidity and mortality of shunt surgery for hydrocephalus. Jain et al.[47] studied 124 patients with hydrocephalus and in 66 patients the aetiology was TBM. They found that post-operative complications were significantly higher in undernourished patients and serum albumin was the most significant predictor of post-operative mortality.

Endocrine Signs

Involvement of the pituitary and hypothalamus, due to ischaemia, may lead to obesity, diabetes insipidus or hypogonadism.[78] Such a picture, when associated with field defects and primary optic atrophy, may simulate a neoplasm in the chiasmal region. SIADH is often observed in children with TB meningitis. Electrolyte disturbance in the form of hyponatraemia is very common and is seen in 42–85% of patients. Incidence of SIADH in 89% of patients was reported in one series.

Tuberculous Spinal Arachnoiditis

Incidence

Tuberculous spinal arachnoiditis is generally a complication of meningitis. It has been reported in 10–30% of cases, either during the course of treatment of TBM[71] or several months or even years after the arrest of the disease.[56,116,143,160] Isotope cisternography in patients undergoing treatment for TBM revealed a much higher incidence of spinal involvement than clinically suspected.[145,146]

Primary spinal TBM, though described in the early years of this century,[53,55] failed to be recognised as a clinicopathological entity till recently. A paper by Harbitz, in 1922,[53] which provided a detailed pathological account of this condition has generally been overlooked. Isolated cases were reported under a variety of titles. Singh et al.[132] and Bawa and Wahi[12] described such cases under the title of spinal TBM. In a series of publications, Wadia and Dastur[12,164] have elaborated the clinical, radiological and pathological features of this condition. This condition is certainly more common than would appear from the number of publications on the subject.

In some cases, the disease may start primarily as spinal meningitis. This is due to rupture into the subarachnoid space of a tuberculous focus (tuberculoma) on the surface of the cord, as described by Harbitz.[53] In some cases, the spinal lesion may spread to involve the cranial cavity resulting in a full fledged picture of TBM. Wadia and Dastur[163] observed that the secondary cranial lesion was more proliferative, while the spinal lesion was more organised and tenacious. Lumbar spinal arachnoiditis may occur in TBM, secondary to an irritation caused by repeated administration of intrathecal streptomycin,[33] a procedure seldom practised nowadays. Described as early as 1871 by Michaud, quoted by Garceau and Brady,[43] transdural spread of infection to the spinal meninges in cases of caries spine, though uncommon, has been well documented.

Pathology

Tuberculous spinal arachnoiditis usually occurs concomitantly with TBM. The spread of infection from the cranial cavity to the spinal canal is responsible for those cases associated with a known case of TBM. In these cases, besides the cranial basal exudates, there is often a thick exudate in the spinal theca. At times the cranial basal exudates may be slight, whereas the spinal involvement may be quite marked. The maximum involvement is in the dorsal or dorsolumbar region. The leptomeninges are infiltrated with fibrinopurulent exudates in varying stages of organisation depending upon the stage and duration of the illness. The longitudinal extent of the lesion is variable, involving only a few segments or extending throughout the spinal canal. It surrounds the spinal cord, varies in its thickness and is generally more marked on the posterior surface. Macroscopic nodular tubercles may be seen on the surface pointing to the diagnosis. The dura is adherent to the exudates overlying the spinal cord. In chronic cases, the fibrocollagenous tissue may acquire a woody hardness. The cut surface of the cord is atrophic and soft due to oedema. There may be one or more tuberculomas in the substance of the cord.

Microscopically, the characteristic tubercular lesions, fibrinous exudates, caseation necrosis, granulomas[18] with epithelioid cells, Langhans giant cells, lymphocytes and plasma cells are obvious. Interestingly, besides the arteritis, a common feature of tuberculous infection, phlebitis was found to be more pronounced both by Hughes[55] and Dastur and Lalitha.[28]

With the passage of time, the exudates get organised and tuberculous granulation tissue is found to envelop the cord. Occasionally, fibrosis sets in and thick fibrous tissue may either constrict the spinal cord or the spinal nerve roots or both, producing a myeloradiculopathy.[160]

Clinical Features

The possibility of the coexistence of spinal arachnoiditis with TBM is considered when such a patient develops root pains, weakness of the lower limbs and sphincter disturbances. This is confirmed by lumbar puncture, which reveals evidence of a partial or complete block with increase in the protein content of the CSF with a variable lymphocytic cellular response. The glucose tends to be low. RIHSA cisternography, studied by Tandon et al.,[145] showed early evidence of spinal arachnoiditis even before the clinical manifestations appeared.

When spinal arachnoiditis is not associated with the cranial manifestions, it presents essentially as spinal cord compression. In the acute stage, there may be systemic manifestations like malaise and pyrexia. Both in the subacute and chronic stages of the disease, root pains, progressive paraparesis or quadriparesis with sphincter involvement are the presenting features. As the lesion is usually diffuse, one often finds a mixture of a level of sensory loss and extensor plantar responses that suggest a high dorsal lesion, and absent reflexes in the lower limbs. Lumbar puncture reveals a partial or complete block with the CSF showing increased proteins and a mild cellular lymphocytic response.

Lumbar myelogram may show an incomplete block, with the contrast flowing very slowly in small fragmented globules or a complete block with an irregular margin. The block is likely to be at a level lower than the expected clinical level. Cisternal myelogram shows the upper level of the block which often confirms a very extensive lesion. Rarely, one may see in the myelogram a curvilinear outline suggestive of a cyst. Intramedullary cavitation or cysts may also be seen.[40,134] Water soluble contrast myelography, CT myelography or MR helps to reveal the level and the extent of the arachnoiditis or cysts.

Magnetic Resonance Findings

TB leptomeningitis is characterised by loculation of the CSF, subarachnoid nodular lesions, nerve root thickening

and clumping seen in the lumbar region, or complete obliteration of the subarachnoid space. Gadolinium MR may show linear enhancement of the surface of the spinal cord and nerve roots or plaque-like enhancement of the dura-arachnoid complex. Intramedullary lesions, like tuberculomas, cord oedema and cavitations, are well seen.[52,75,84,94,122,129] Increase in CSF intensity on T1 weighted images leads to loss of cord CSF interface or a shaggy outline. Sharma et al.[127] advocated contrast enhanced MRI as the first line of investigation for evaluation of suspected tuberculous arachnoiditis. As there is usually a long segment involvement, extended FOV image should be acquired for the whole spine in all patients.[49,73]

Treatment

Having established a diagnosis of spinal arachnoiditis, the treatment is essentially medical. Antituberculous drugs, with a full course of steroids, may be of help in a fair number of patients. Intrathecal administration of hydrocortisone 25 mg or methyl prednisolone twice a week may help in the further resolution of the exudates. Gourie Devi[48] has found intrathecal administration of hyaluronidase useful in the treatment of TB spinal arachnoiditis. Recurrence is not uncommon and similar medication may have to be repeated. The prognosis in such cases is not encouraging.

Surgery may be offered only if the diagnosis is in doubt, if the lesion is fairly localised and not diffuse or if the imaging is suggestive of a cyst at the expected clinical level.

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66 Tuberculosis of the Spine

Sridhar K

HISTORY

The classical paper by Percival Pott entitled, "Remarks on that kind of Palsy of the lower limbs which is frequently found to accompany a curvature of the spine, and is supposed to be caused by it, together with the Method of Cure", has led to paraplegia of tuberculous origin being named Pott's paraplegia.

INCIDENCE

The world has nearly 30 million people suffering from tuberculosis.[170] Of all the patients with tuberculosis, nearly 1–3% has involvement of the skeletal system. Vertebral tuberculosis is the commonest form of skeletal tuberculosis, most series reporting an incidence of up to 50% of osteoarticular tuberculosis.[43,49,67,104,120,126,132,171] Tuli[170] from Banaras reported that out of a total of 1,074 cases of osteoarticular tuberculosis, 440 cases affected the spine.

Spinal tuberculosis can occur at any age and affects both sexes equally. When tuberculous disease was ubiquitous in all countries of the world, spinal tuberculosis was found to be most common in the first three decades of life.[148,165,170] In recent decades, with the near abolition of tuberculosis in the developed countries and preventive measures undertaken in the poorer countries, there seems to be a shift in the incidence to older age groups.[103,164] The pattern of the disease in the developed countries appears different from that in the developing countries.[29,44,70,71,95] In the developed countries and urban populations, tuberculosis of the spine affects more commonly the elderly, while in the developing countries it is still a disease of the young adult. The disease was uncommon in the advanced countries of the world.[27,95] However, the frequent and easy communication facilities and exchange of population and the emergence of HIV infection and intravenous drug abuse[40,85,102] are leading to an increasing incidence.[62,76,77]

PATHOLOGY AND PATHOGENESIS

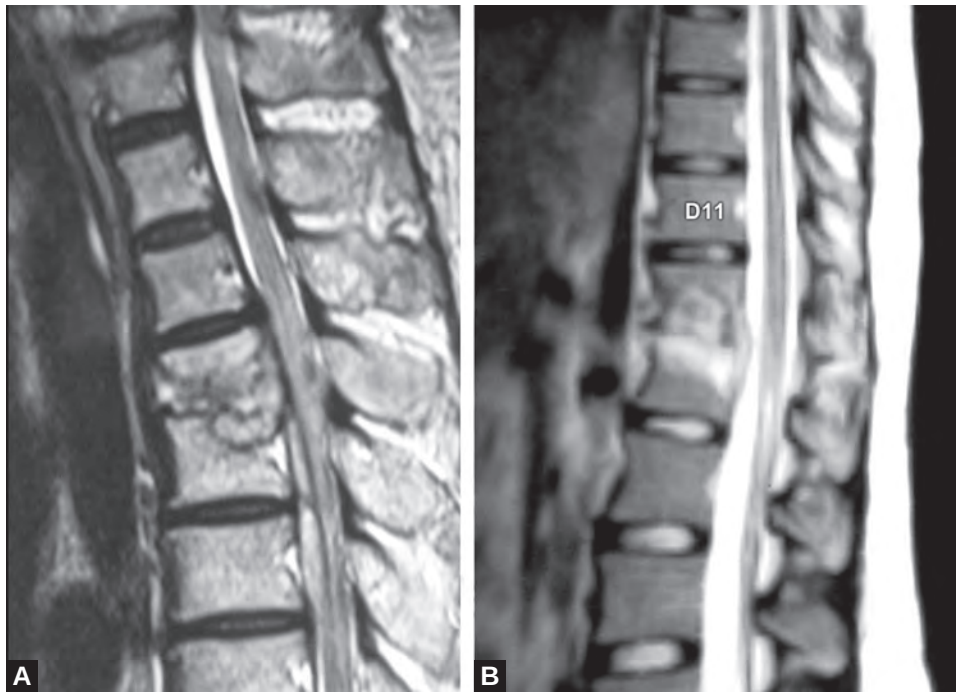
Tuberculosis is the prototype of a granulomatous disease in man. The tubercle comprises of an organised microscopic aggregation of plump rounded histiocytes (macrophages) that vaguely resemble epithelial cells and are therefore called epithelioid cells. At the margin of a cluster of epithelioid cells there may be some Langhan's multinucleate giant cells, formed by the fusion or internal nuclear divisions of macrophages. Around this is a collar of plump fibroblasts interspersed with mature macrophages and lymphocytes. The tubercles thus formed grow by expansion and coalescence. The characteristic caseation occurs in the central region of the epithelioid cells. The caseous material may soften and liquefy. Marked exudative reaction is a common feature of spinal tuberculosis. The incidence of exudative response is much higher amongst patients from developing countries.[75] A "cold abscess" is composed of serum, leucocytes, caseous material, bone debris and bacilli. It can penetrate the ligaments and migrate along fascial planes, often presenting far from the site of infection.[165, 170]

Route of Infection

The spinal disease is always secondary to a primary lesion, usually from a visceral focus, and occurs due to haematogenous spread.[95,165,170] Involvement of different parts of the spine and the presence of associated visceral lesions imply a bacillaemia causing the spread of infection from the primary focus. Infection may reach the spine due to a bacillaemia or through the Batson's plexus of veins. The primary focus may be active or quiescent and may be in the lungs, mediastinal lymph nodes, kidneys or other viscera. Simultaneous involvement of the paradiscal part of two contiguous vertebrae suggests spread of infection via the common blood supply to the region (Figs 1A and B). On an average, an involvement of 3.4 vertebrae was reported in two series[57,103] and 3.8 in another.[120] Kaila et al.[79] found the incidence of non-contiguous multilevel involvement to be as high as 71.4% when screened with whole spine magnetic resonance imaging (MRI).

Types of Lesions

Classically, four types of involvement of the spinal column have been described in spinal tuberculosis: (i) a paradiscal lesion which arises from arterial spread of the infection (Figs 1A and B); (ii) the central type of vertebral body involvement of one or more distant or adjacent vertebrae (this is often associated with tuberculous meningitis as the spread of the infection is via the Batson's plexus of veins); (iii) the anterior type with



Figs 1A and B: Paradiscal location of caries spine as seen on sagittal MRI T2-weighted images. (A) C7-T1 caries. (B) D12-L1 caries

cortical bone destruction (Fig. 2) and (iv) appendiceal type (Fig. 3).[37,165,170]

The paradiscal lesion (Figs 1A and B) begins in the vertebral metaphysis, erodes the cartilage plate and destroys the disc. The cartilaginous end plate acts as a barrier, but once invaded, destruction of the disc progresses rapidly due to its relative avascularity,[147] and the infection goes on to involve the adjacent vertebrae. The early resorption of the disc leads to narrowing of the disc space, although with progressive involvement of the body and accumulation of debris, the space may sometimes be widened.[95]

In the central type of lesion the infection begins in the midsection of the body instead of the metaphysis. It extends centrifugally to involve the whole body. Following the infection, marked hyperaemia and osteoporosis occur. The body, which is thus softened, easily yields under gravity and muscle action, leading to compression, collapse and bony deformation.[95,170]

Anterior lesions lead to cortical bone destruction beneath the anterior longitudinal ligament. Spread of the infection in the subperiosteal and subligamentous planes, allows extension of the infection to adjacent bodies without involvement of the intervening disc space.[95] Stripping of the periosteum results in loss of the periosteal blood supply to the body. This, along with thromboembolic phenomena, periarteritis and endarteritis can lead to ischaemic reactions of the bone contributing to the vertebral collapse[32,46,164,165,170] (Figs 2 and 4A and B).

In the appendiceal type the pedicle, the lamina, the articular process or the spinous process is affected primarily (Fig. 3).

Infection and infarction lead to the formation of bone and cartilage sequestrae. The granulomatous debris and infective material may be compressed between normal bony and ligamentous structures, and get pushed along tissue planes, resulting in lateral extension, retropulsion into the spinal canal or propulsion anteriorly.

Tuberculous spondylitis commonly occurs in the thoracic spine followed by the lumbar and cervical spines (Fig. 5)[14,63,95,96,164] Tuli[170] found a higher incidence in the cervical spine and thought it to be due to a larger number of paediatric patients in his series.

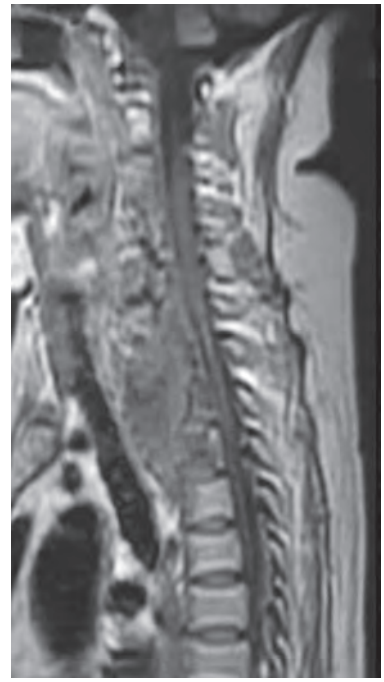


Fig. 2: Sagittal MRI T1-weighted image showing tubercular involvement of vertebral bodies from C5 to T3

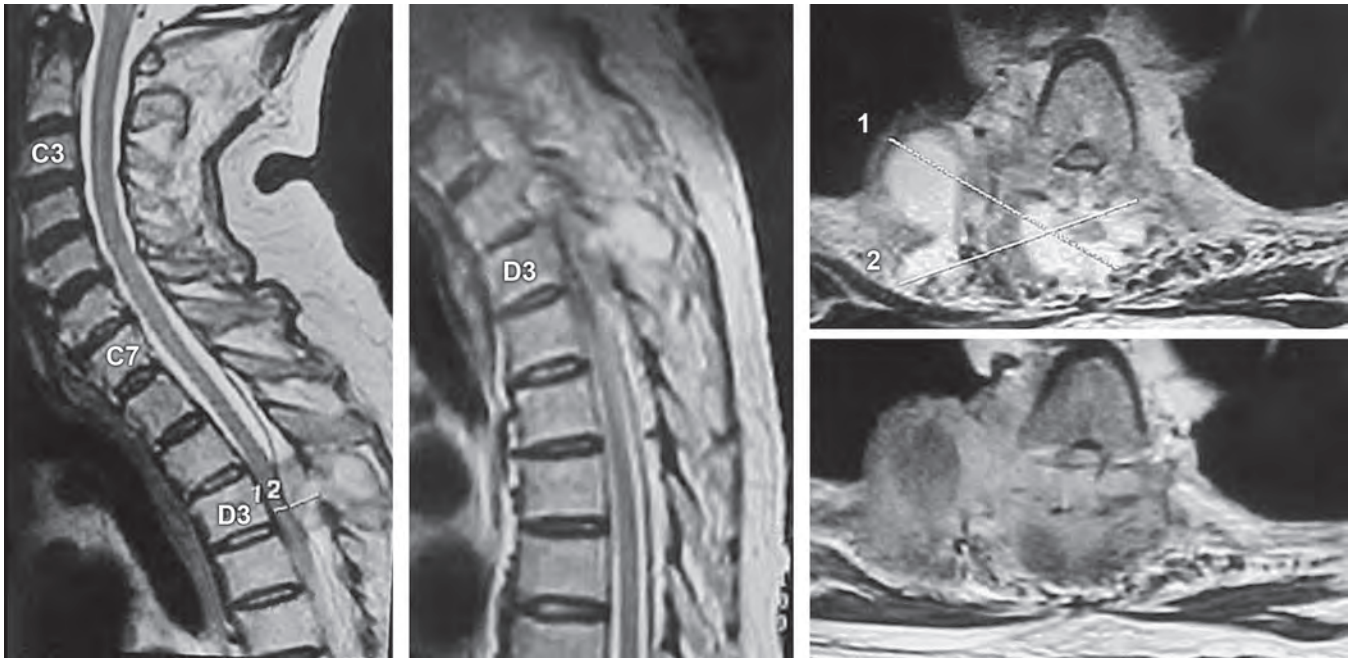
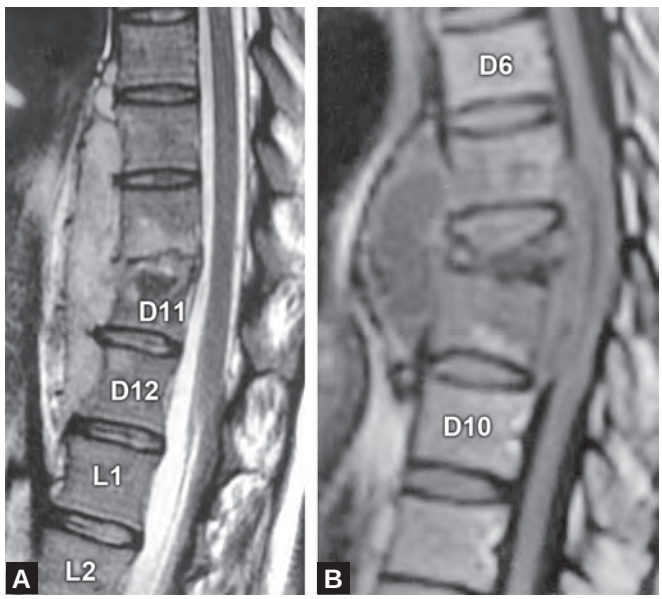


Fig. 3: Sagittal MRI scan showing apendicular dorsal caries at D3 with dorsal epidural collection causing cord compression. Axial MRI T1-weighted and T2-weighted images showing the extent of involvement of the posterior elements

Neurological Involvement

Neurological involvement is the most serious of the complications of spinal tuberculosis. The overall incidence of neurological complications varies between 10% and 40%.[24,70,75,120,126] Janssens and de Haller[71] reported neurological involvement in 46% of their cases, while Friedman[44] reported 8 patients (12%) with paralysis in a series of 64 adults. Reporting on a prospective series of 45 cases of the lower cervical spine, Prabhakar et al. found cord compression in 37.8% of patients.[134] The risk of paraplegia is highest in lesions of the cervico-dorsal region,[164,165] although Tuli[170] reported a higher incidence amongst those with mid thoracic lesions. Out of 200 patients with neural involvement, Tuli found the lesion to be in the mid-dorsal region in 139.[170] Involvement of the cauda equina in the lumbar and lumbosacral regions is seen less frequently.

The spinal cord may be involved during any phase of the disease, in the active phase within the first 2 years or in later years after the disease has become quiescent.[24,150,162] The severity of the neurological deficit can be graded depending on the degree of motor involvement.[47,90]



Figs 4A and B: Sagittal MRI of two different patients showing prevertebral collection in dorsal caries

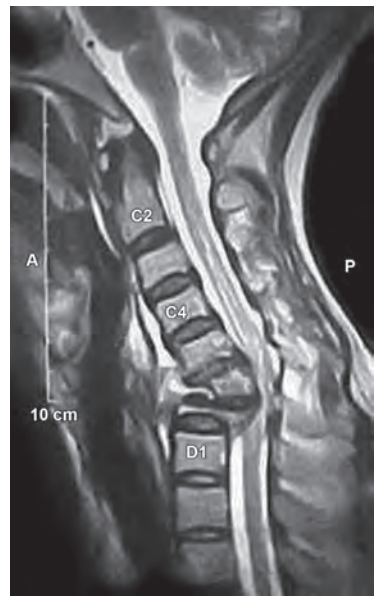


Fig. 5: MRI cervical spine sagittal view in a patient with tubercular involvement of C6,7 showing gross dislocation and severe cord compression

The cause of paraplegia in most cases is compression of the spinal cord[106,120,145,150,165,170] due to one of the following mechanisms:[58]
(1) In active disease: (a) abscess (fluid or caseous); (b) granulation tissue; (c) sequestrated bone and disc; (d) pathological subluxation or dislocation of vertebrae.
(2) In healed disease: (a) transverse ridge or bone anterior to the spinal cord; (b) stretching or attrition of the cord due to spinal deformity; (c) fibrosis of the dura.
In a given case more than one factor may contribute to the pathogenesis.

Other causes are infective thrombosis of the cord, and the spinal tumour syndrome. Non-compressive pathologies may rarely lead to neurological deficits. There is no proof that the paraplegia can be caused by toxic or vascular reactions in the cord secondary to the presence of active tuberculosis in close relationship to the dura,[164,165] as was proposed by Butler.[24]

Pathology

The extradural mass, caused by an abscess, sequestrae or granulation tissue, fills the epidural space and spreads around the dural sac, thus compressing the spinal cord. It may get adherent to the dura, which becomes thickened by the formation of new fibrous tissue on its outer surface. The granulation tissue causes loss of function by not only direct compression of the cord, but also by impeding venous drainage, thus causing cord oedema. As a rule the dura constitutes a very good barrier against the spread of infection. Rarely, the barrier is broken and the infection spreads intradurally to result in focal or diffuse meningitis, arachnoiditis or a granuloma.[58,143]

The usual pathological lesion in the cord, in the early stages, is a vacuolar type of myelin degeneration seen in the lateral or anterolateral columns.[44,169] This is more diffuse than seen in ischaemic lesions and may be secondary to venous obstruction. Wallerian degeneration above or below the lesion is uncommon in spite of considerable myelin damage at that level. Autopsy findings in chronic cases show vacuolisation and myelin degeneration.[44]

Acute severe lesions of the cord may be produced where there is rapid collapse of a vertebral body with the cord stretched over a relatively intact intervertebral disc or when sequestrae are pushed backwards into the spinal canal by a sudden angulation (Fig. 6).[150] Infarction of the spinal cord may occur due to endarteritis, periarteritis or thrombosis of the arterial supply of the cord.[95,164,170] An important radicular supply to the cord may be compromised occasionally at the intervertebral foramen before it enters the dura.[164,165,169] Angulation of the spine on healing may lead to the formation of a bony ridge or spur called 'an internal gibbus' on the anterior wall of the spinal canal, resulting in a slow and progressive paraparesis.[165,170]

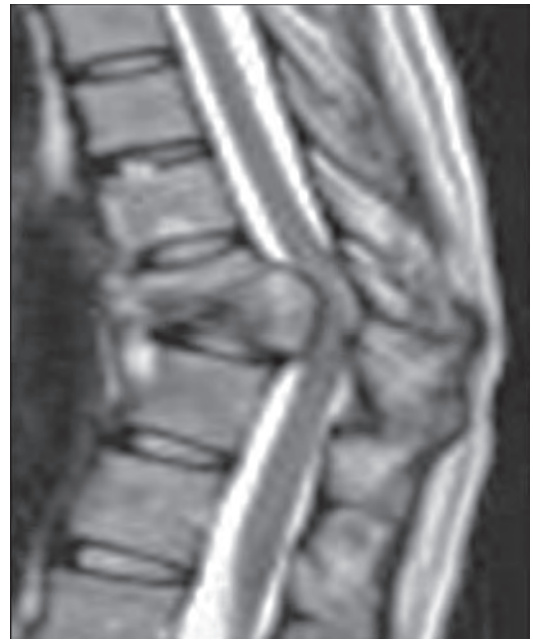


Fig. 6: Sagittal MRI T2-weighted image showing collapse of the body with retropulsion causing cord compression

CLINICAL PRESENTATION

The clinical picture has three components: (1) the systemic illness; (2) the osseous lesion and (3) neurological complications.

As with tuberculosis elsewhere in the body, there may be malaise, pyrexia, loss of appetite and weight, and night sweats. Fever was seen in 32% of patients reported by Alothman et al. from Saudi Arabia.[5] Back pain is a predominant clinical feature.[70] The spine is stiff and painful on movement, with spasm of the paravertebral muscles. The associated localised muscle spasm is so characteristic, that an experienced physician usually suspects the disease immediately. Progressive backache is so often seen, that many authors are of the opinion that tuberculosis must be considered in its differential diagnosis when the patient belongs to an endemic region.[29] A soft tissue swelling or mass is often obvious and in late cases a draining sinus may be seen. Tuli[170] reported a 20% incidence of palpable cold abscesses, while Janssens and de Haller[71] had an incidence of 57%. Angulation of the spine in the form of a kyphosis or gibbus was seen in 95% of the cases seen by Tuli.[170] This he felt was due to the poor socio-economic condition of the patients and their ignorance of the disease process, resulting in late presentation to the hospital. Weakness of the legs (69%), gibbus (46%), pain (21%) and a palpable mass (10%) were the most common clinical features seen in 694 cases reported by Turgut.[175] Heroin addicts have been noted to have a distinct presentation with an acute toxic febrile illness associated with pain, weight loss, anaemia and neurological deficit.[4,42,62] Rare forms of presentation include abdominal symptoms, occasionally leading to unwarranted surgery before the correct diagnosis is made.[64]

Jain and Sinha, on evaluating the ASIA scoring system and Tuli's classification for assessment of the neurological status of patients with tuberculosis of the spine, found both systems wanting. In their study they found the Tuli system insensitive to early detection of improvement or deterioration, while the ASIA system failed to score all types of neurological involvement. They have suggested a new staging system for Pott's spine.[66]

Associated Lesions

The incidence of associated visceral lesions (of the lung, kidney or lymph nodes) varies between 40% and 50% in different series.[44,132] Bahemuka and Murungi[10] found tuberculosis outside the nervous system in 33% of cases and Chan et al.[29] found pulmonary tuberculosis in 25% of their cases. Simultaneous involvement of other bones and joints has been reported to be between 12% and 15% in patients with caries spine.[44,170]

Neurological Deficit

The degree and extent of the neurological deficit depends on the site of the disease, the direction of spread and the pathological changes produced.[165] While usually the onset of symptoms is slow and progressive, in a small percentage of cases the paraplegia may be of sudden onset and nearly complete from the beginning. Tandon and Pathak[164] have divided the clinical picture of Pott's disease into four groups: (1) Paraplegia arising in a known case of spinal tuberculosis; (2) Paraplegia as the presenting symptom of spinal tuberculosis; (3) Spinal tumour syndrome and (4) Paraplegia due to tuberculosis of the posterior neural arch.

Lesions of the posterior neural arch, including the lamina and pedicle, while reported to be rare by orthopaedic surgeons[147] are more frequently seen in neurosurgical practice.[7,53,114,121,141,164,165] This is probably due to the higher incidence of neurological morbidity in these cases[7,114,164,165] and to the increasing use of the CT scan and the magnetic resonance (MR).[61] Kumar[89] studied 27 cases of tuberculous involvement of the posterior elements of the spine and proposed a four-point classification based on the site of the lesion, the stage of the lesion, the presence of associated lesions and of neurological deficits. Baibus and Garbuz have, after studying 2,500 patients with tuberculosis of the spine, also classified the neurological condition into five grades.[134]

IMAGING

Plain X-rays

The paradiscal lesion is the commonest lesion seen. Narrowing of the disc space is the earliest radiological finding on plain X-rays, and when associated with a loss of definition of the paradiscal margins of the vertebra, the diagnosis of tuberculosis is obvious. Lytic areas in the metaphyseal regions of the body may not be seen early, as foci less than 1.5 cm in diameter are not demonstrable on a conventional radiograph.[147] At least 30–40% of calcium should be lost before a radiolucent area is visible on a plain X-ray.[170] Sclerosis may be seen in up to 50% of patients at presentation.[23]

The central type of disease arises from the centre of the vertebral body, which loses the normal bony trabeculae and may show as areas of destruction. Occasionally, and especially in children, the body may be ballooned out as a result of the accumulation of inflammatory debris which expands the weakened cortical bone.[59] Towards the later stages, the diseased vertebral body may show a "concertina" collapse[170] and may resemble a collapse due to secondary deposits.

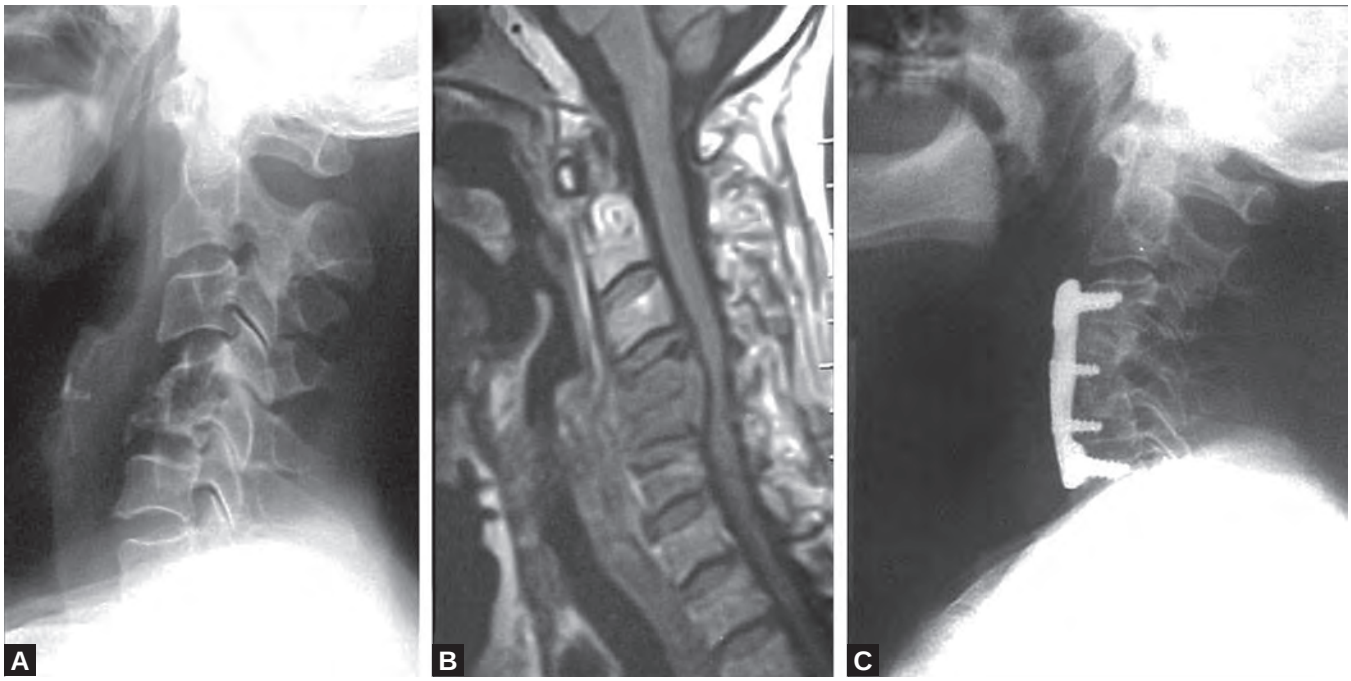
In the anterior type of lesion, the infection begins beneath the anterior longitudinal ligament. This results in erosion of the peripheral parts of the vertebral body (in front and on the sides), which is seen well in the lateral or oblique views as shallow excavations. Destruction of the anterior surface of the vertebral body due to a tense paravertebral abscess may simulate scalloping due to an aneurysm of the abdominal aorta.[149] The tendency for erosion is greater when the aorta is in close proximity to the paravertebral abscess as the transmitted pulsations compound the pressure caused by the abscess. Stripping off of the periosteum deprives the bone of its blood supply, making the bone more liable to the destructive and scalloping effects of the lesion (Figs 7A to C).

Lesions of the pedicle, transverse process and the spinous process appear as erosion of the region involved and may be missed in the plain X-rays unless specifically looked for.

Wedge collapse of adjacent vertebrae with paradiscal bone destruction causes forward angulation of the spine and when this involves a large number of adjacent vertebrae a severe kyphotic deformity results. Rarely, a lateral curvature and deviation may be seen and is caused by the greater destruction of a vertebral body on one side.[60] The final effect is due to a combination of lateral deviation and lateral rotation.[52] Tuli[170] is of the opinion that lateral shift occurs where there is involvement of the posterior spinal articulations along with the usual paradiscal lesions.

A paravertebral shadow is seen on the plain X-rays due to the presence either of an abscess or extension of tuberculous granulation tissue. An abscess produces typical radiological findings depending on its size and location: an abscess in the cervical region causes a widening of the space between the pharynx and the vertebral body and upper thoracic abscess causes a squaring of the superior mediastinal shadow when small, or a V-shaped shadow when large, shifting the apices of the lungs laterally and downwards; abscesses below D4 take up a typical fusiform shape; and those below the diaphragm produce a widening of the psoas shadow.

CT scan is useful in assessing the destructive lesions in the vertebral column. It is considered by most authors to be the investigation of choice for spinal tuberculosis.[9,25,99,129,145,155,157,176] Based on a study of 30 patients



Figs 7A to C: (A) Pre-operative X-ray of the cervical spine showing destruction of C4 and C5 vertebrae. (B) Pre-operative MRI of the cervical spine showing destruction of C4 and C5 vertebrae with epidural soft tissue compression. (C) Post-operative X-ray of the cervical spine showing anterior cervical plating from C3 to C6

with clinical suspicion or diagnosis of spinal tuberculosis, Jain et al. classified the findings on CT scan into fragmentary, osteolytic, subperiosteal, and localised and sclerotic types.[69] The fragmentary type was most common followed by the osteolytic variety. Vertebral body destruction, intraspinal extension, paravertebral soft tissue masses, extension of involvement into the neural arches and calcification can be seen on plain scans.[129] With contrast, rim enhancement may be seen around a multiloculated fluid collection. Coppola et al.[33] found destructive osseous changes associated with adjacent soft tissue masses showing a characteristic rim enhancement. In all their cases CT demonstrated more extensive involvement than could be seen on plain radiographs (Fig. 8). CT helps to diagnose spinal tuberculosis in the initial stages.[25] Inaccessible fixed areas of the spine, difficult to see in conventional radiographs, are seen with ease on axial CT sections.

Calcification, representing retained bone fragments, seen with paraspinal collections and in regions of bone destruction, is said to be pathognomic of tuberculous infection. It represents the lack of the necessary proteolytic enzymes in *Mycobacterium tuberculosis* that are necessary to lyse the bone.[69,76]

Magnetic Resonance Imaging

The advantages of MR include high resolution, direct multiplanar imaging, detection of marrow infiltration

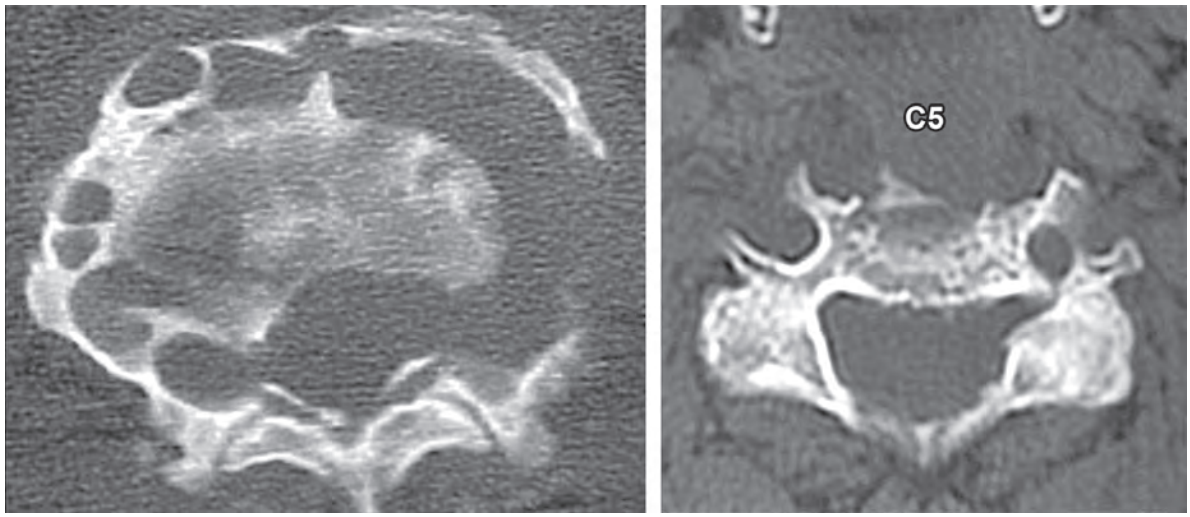


Fig. 8: CT axial views of a patient with cervical caries showing significant bony destruction

and the early detection of intradural infection.[18,89,176] The technique used should be modified, depending on the site and extent of the infection, using spin echo and T1-weighted imaging for localisation. Extradural extension of the disease is better visualised with either a T2-weighted image or a short T1 inversion recovery technique (STIR).[21,113,152,153,159,160,168] The latter technique has a higher sensitivity, but is less specific than the T2-weighted images.[13,39] Both are useful in showing vertebral and intradural disease, but epidural spread may not be detected early, as the abnormal signal obtained may be isointense with CSF,[152] Sagittal T1-weighted images using contrast are necessary to detect early epidural spread of the infection.[133,153] The involvement of the paraspinal soft tissues is best seen in coronal sections.[6,34,153,154]

MR is also helpful in revealing associated lesions like intraosseous abscesses, paraspinal cold abscess, vertebral body and disc collapse, spinal deformity, skip lesions, epidural and intraspinal extension, involvement and compression of the cord or nerve roots and appendicular lesions (Figs 9 to 11).

T1-weighted images may show a decreased signal from the affected vertebral marrow, reduced disc height, involvement of the paraspinal tissues and extradural extension. The T2-weighted images show an indiscriminately increased signal from the marrow, discs and soft tissues. The use of gadolinium enhanced imaging is advantageous. Post et al.[133] have shown that contrast MR imaging provides: (a) excellent anatomical delineation of all epidural abscesses, differentiating them from the compressed thecal sac when this was not possible by plain MR; (b) localisation of those portions of paraspinal masses most likely to yield a positive percutaneous biopsy; (c) identification of foci of active infection from those which had responded adequately to therapy and (d) unequivocal detection of early vertebral and disc space infection. Contrast MRI is useful, especially in the diagnosis of abscesses: rim enhancement being characteristic of tuberculosis.

Response to therapy may be seen as an increase in the signal intensity on T1-weighted images from the affected vertebra. This has been found to correlate well with clinical signs and symptoms. However, radiologically evidenced progression of bone destruction may be seen up to 14 months after the initiation of anti-tubercular therapy. This should not be taken as an indication of treatment failure.[23] Jayasundar et al. have reported excellent specificity in diagnosis with Proton MR spectroscopy.[72] Distinguishing spinal tuberculosis from other spinal diseases, especially pyogenic and fungal spondylitis and also metastatic disease of the spine is important. Features that are indicative of a tuberculous infection are: (1) calcification within a paravertebral abscess, (2) presence of a large paravertebral abscess, (3) involvement of more than two vertebral levels, (4) involvement of the posterior elements, (5) multicentric disease, (Figs 12A to E) (6) subligamentous spread and (7) heterogeneous MR signal.[76] MRI can distinguish tuberculous from pyogenic infection in most instances.[30,54] Shankar et al. have reported that CT perfusion could also help in differentiating spinal inflammatory from neoplastic lesions.[151]

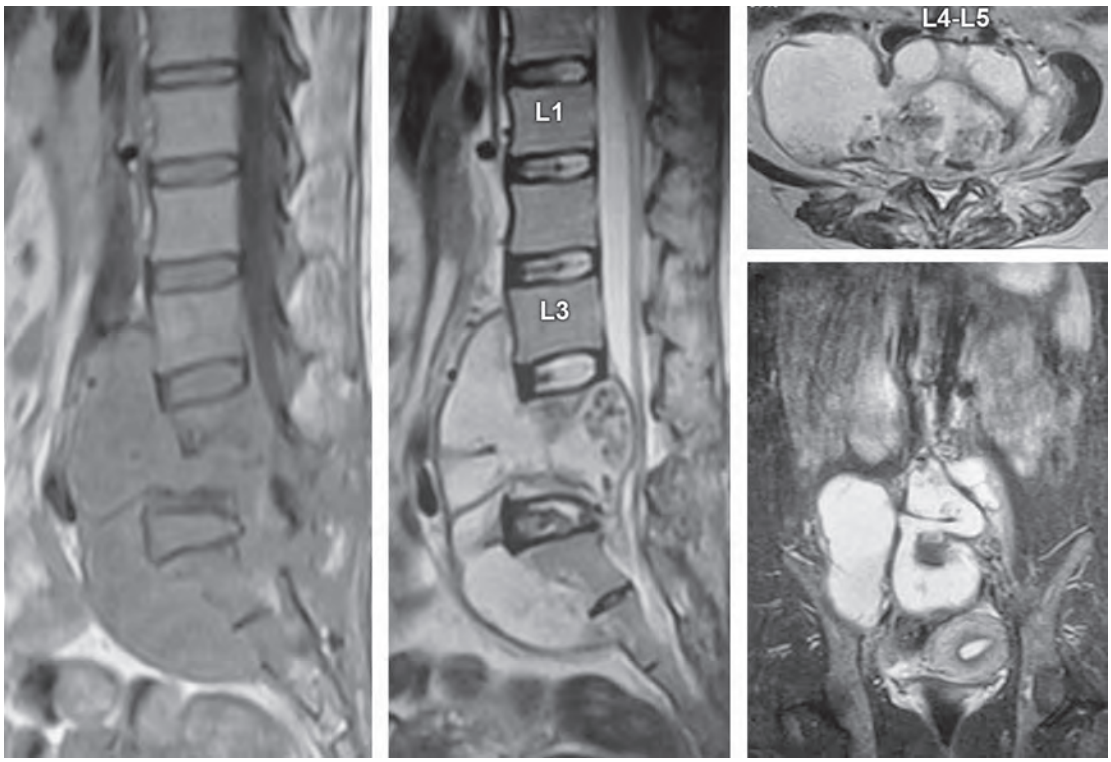


Fig. 9A: MRI of a patient with lumbosacral caries showing significant pre- and paravertebral cold abscess along with compression of the thecal sac and the exiting nerve roots

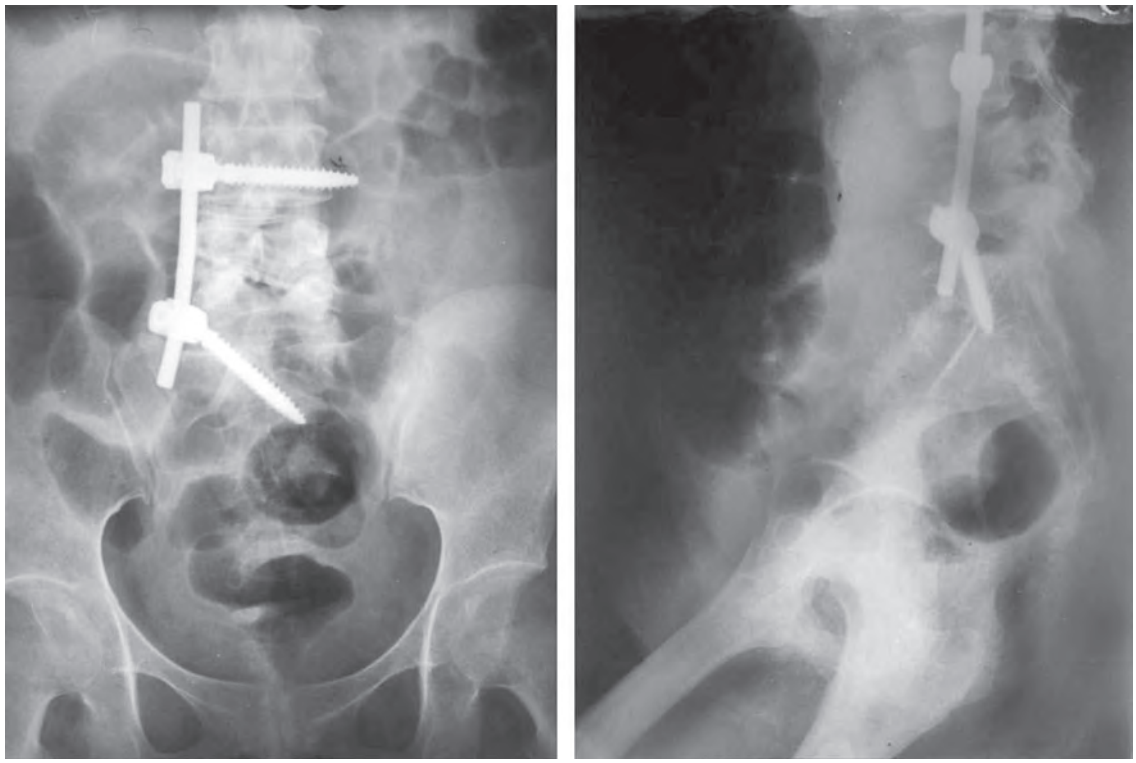


Fig. 9B: Post-operative X-rays showing spinal fixation

Radioisotope Bone Scans

While bone scans are useful in delineating osteomyelitis, in spinal caries, Technetium scans may be negative in one-third of cases and gallium scans negative in two-thirds.[97,135] Their diagnostic value is limited and of historic interest only.

TREATMENT

Evolution of Treatment

In ancient India, the Atharvans (1800–1000 BC) used to treat cases of skeletal tuberculosis with sunshine and "Sipudru", a herbal preparation.[38] Hippocrates and

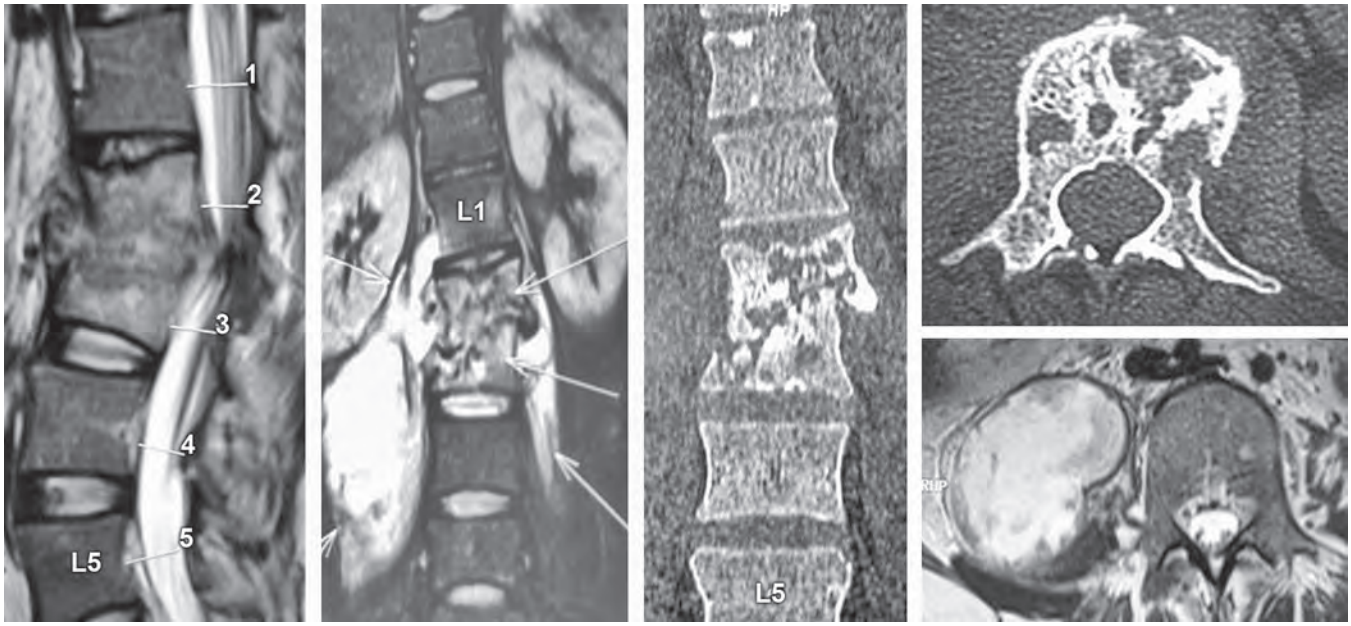


Fig. 10A: Imaging of a patient with L2,3 caries showing large paraspinal and psoas abscess with bony destruction causing dislocation

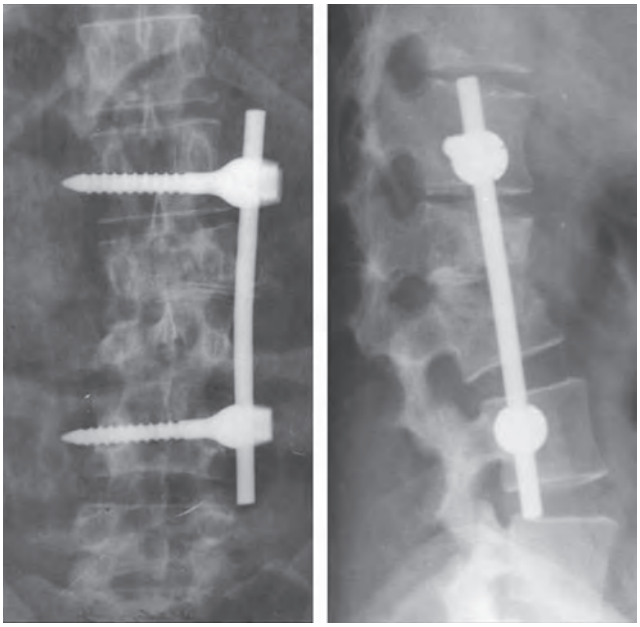


Fig. 10B: Post-operative X-rays showing spinal fixation done by the retroperitoneal approach

Galen tried to correct the kyphotic deformity due to spinal caries by manual pressure, traction and mechanical appliances, but with little success.[170] The orthodox conservative treatment in modern times was entirely constitutional and included recumbency and immobilisation by body casts, plaster beds and braces, but the results were often unsatisfactory[35,91] and the healing took many months or even years. This led surgeons to attempt direct surgical procedures. Unfortunately, these had disastrous results so that Calot in 1930[26] remarked, "the surgeon who, so far as tuberculosis is concerned, swears to remove the evil from the very root, will find only one result awaiting him—the death of his patient". The surgical procedures performed in the pre-antibiotic era included the created abscess (Pott 1779), laminectomy (Chipault 1896), laminotomy (Fraser), costotransversectomy (Menard 1894), posterior mediastinotomy (Obalinski), lateral rachiotomy (Capener 1933) and anterolateral decompression (Ito 1934, Dott and Alexander 1947). Tuli has provided an excellent historical review of spinal tuberculosis.[48,92,174]

Posterior Fusion

Albee, in 1911[3,4] and Hibbs in 1912,[55,56] introduced posterior spinal fusion. This provided internal stability to the diseased spine, and helped to avoid recurrence of the disease and the development of paraplegia. It also shortened the period of immobilisation. Bekalim[17] reviewed the results of posterior spinal fusion before the use of anti-tubercular therapy and found that 40–80% of patients were "healthy and fit for work", 60% were "improved" and 14–19% "not healed". However, kyphosis could develop in spite of the posterior fusion and there was also an appreciable incidence of pseudoarthrosis following the procedure. Long-term follow-up showed that paraplegia could still occur in some patients, in spite of a posterior spinal fusion. Hallock and Jones[53] found that 23 out of 192 operated cases developed paraplegia subsequently. It became apparent that the surgery did nothing for the diseased bone where the organisms may remain quiescent until reactivated.

Antibiotic Therapy

The introduction of anti-tubercular drug therapy dramatically improved the results of non-operative therapy and of posterior spinal fusion.[17,45,158] The most spectacular effect of the drugs was the disappearance of sinuses, ulcers and abscesses and the elimination of post-operative dissemination of the infection.

Such a dramatic improvement in the prognosis encouraged surgeons to adopt total excision of the lesion along with anti-tuberculous chemotherapy. This was the standard treatment between 1950 and 1960.[57,58,108,170]

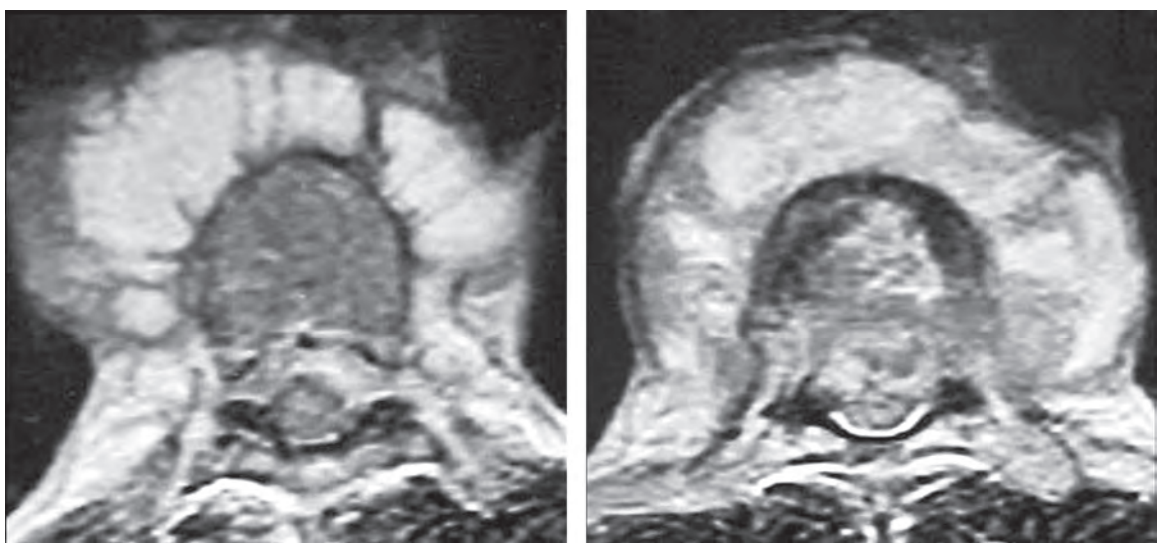
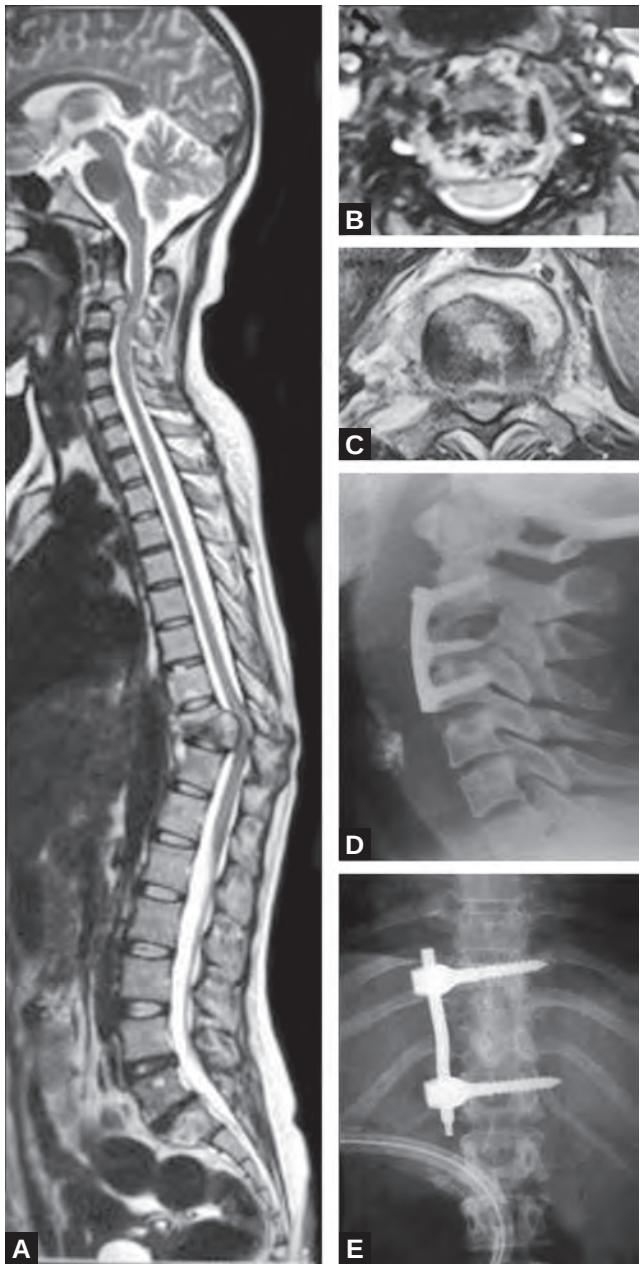


Fig. 11: Axial MRI showing a paraspinal collection in a patient with caries spine



Figs 12A to E: MRI of the entire spine showing evidence of concurrent cervical and dorsal caries. (A) Sagittal MRI of the entire spine. (B) MRI axial of the cervical spine. (C) MRI axial of dorsal spine. (D) Post-operative X-ray lateral view of cervical spine. (E) Post-operative X-ray AP view of dorsal spine

Conservative Therapy

Conservative therapy had many advocates and has successfully been used in many countries. Friedman[44] treated 64 patients with Pott's disease by the administration of anti-tubercular drugs, bed rest and braces and 50 patients had good results. Laminectomy had to be done in eight patients who developed paresis.

Bed Rest or Ambulation

Should a patient with tuberculous disease of the spine be immobilised in bed with a plaster cast, or can he be ambulant? Controlled studies[84,107] by the Medical Research Council, UK, compared the results of ambulatory outpatient treatment with bed rest inpatient therapy. At 18 months the response rate was 66% for the inpatients and 58% for the outpatients; while at 36 months the rates were 84% and 88%, respectively. The mean total vertebral loss and angulation of the spine were a little more in the ambulatory group. Neurological outcome was the same in both groups. Later studies by the MRC[110] showed that ambulant chemotherapy achieves good results when treating children with tuberculosis of the thoracic and lumbar spines.

Our policy is to advise our patients on chemotherapy to have bed rest without immobilisation for 4–6 weeks till the pain and spasm disappear and the general health improves. They are then allowed to get up, but wear braces which can be discarded after a period of 6–8 weeks. The chemotherapy is continued for 18 months (Figs 13A to D). The family members and contacts are checked for the presence of tuberculous infection at the beginning of the treatment.

Excisional Therapy and Grafting

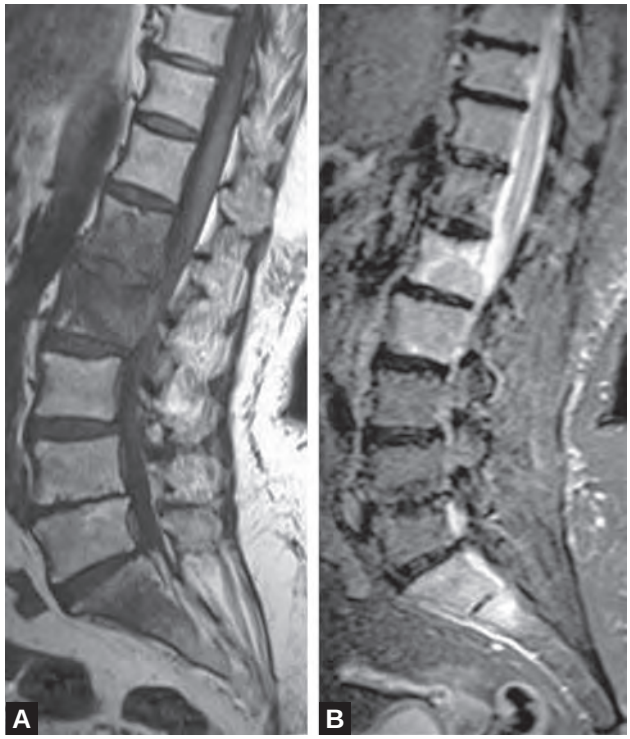
Excisional therapy has given good results and is widely followed. Where there is extensive destruction and sequestra, evacuation of tuberculous pus and debris and removal of sequestra of disc and bone result in the opening up of new vascular channels in the ischaemic areas with reduction of general toxaemia and reduction in total healing time.

Paus[132] treated 37 cases with anti-tubercular drugs and ambulation, and achieved complete working capacity in 35. Of the 86 cases treated by him with direct surgery and anti-tubercular drugs, 94% achieved complete working capacity, while 11% required reoperation for either relapse or failure. A similar experience was reported by Somerville and Wilkinson[161] who treated 130 patients by direct operation and achieved sound healing in 92% with a relapse or recurrence rate of 12.5%. However, they achieved similar results in 105 patients treated non-surgically with only anti-tubercular therapy.

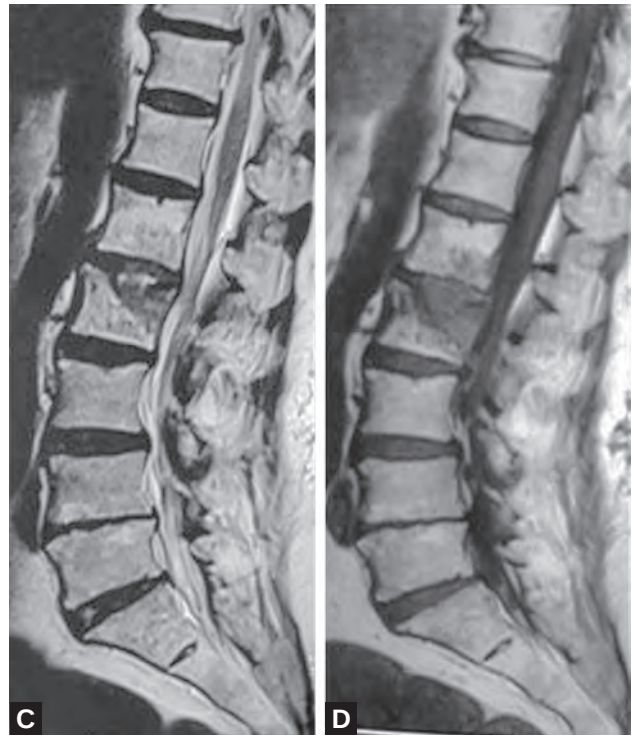
Tuli[170] is of the opinion that cases without extensive destruction and sequestration would heal without surgical intervention. Indications for surgery proposed by him include, progressive bone destruction, increase in the size of the abscess, failure to respond to conservative therapy, uncertainty in diagnosis, recrudescence of local disease and development of neural complications or pain in the spine due to mechanical instability.

Bone Grafting

After excisional surgery, should bone grafting be done? Neville and Davis[123] reported 92% bone fusion in those patients who were treated with surgical fusion and 50% bone fusion in patients who had only drainage of the abscess. Hodgson et al. in 1960[58] reported on a series of 412 patients treated by radical removal of the diseased area and anterior spinal arthrodesis. The mortality was



Figs 13A and B: MRI of the lumbosacral region showing tubercular involvement of L1, L2, S1 and S2



Figs 13C and D: MRI of the lumbosacral region showing resolution of the tubercular lesions after 6 months of anti-tubercular therapy

2.9% and no patient developed paraplegia after operation. They advise surgery for all patients with early tuberculosis of the spine and believe that it should supplant conservative treatment in most instances.[57-59,177] Chu[31] reported satisfactory healing in 71 of 74 consecutive patients treated by the method of Hodgson.

The Medical Research Council Working Party on Tuberculosis of the Spine[109] studied 119 patients with tuberculosis of the thoracic and lumbar regions who underwent excisional surgery with or without bone grafting. Bony fusion occurred earlier and in a higher proportion of patients in the group with bone graft, but at 5 and 10 years there was little difference between the two. At 10 years, there was a small reduction in the angle of kyphosis in the bone grafted group and a small increase in the angle in the no grafted series. These changes had occurred early and had persisted subsequently.

Instrumentation

Instrumentation helps to produce rigid fixation of the involved segments of the spine to allow uninterrupted healing, as movement in and around the spinal cord is still possible after anterior strut grafting. The instrumentation procedures also prevent any increase in spinal deformity that may occur in the course of healing. Bailey et al.[11] supplemented their surgery with posterior arthrodesis, whenever the graft spanned more than two disc space levels. Kemp et al.[81] used posterior fusion if the infection involved more than two vertebral bodies, so that immediate stability was achieved.

The problem associated with instrumentation in the presence of infection is the possibility of persistence of a focus of infection.[50,51] Biomaterial-centred infections are related to the preferential adhesive bacterial colonisation on inert surfaces.[105,124,125] Mycobacteria produce less biofilm than other bacteria. Oga et al.[125] Louw[100] and others[10,68,129,144] using instrumentation have followed up their cases and have not encountered problems related to the persistence of infection or reactivation.[74]

The type of instrumentation used is of individual choice and is also dependent on the age of the patient. The fixation devices and techniques are variable. It is essential that all internal implants are MR compatible, to permit future MR examinations of the patient.

Factors Influencing Results

The decision on the type of surgical therapy depends on many factors which include the general health of the patient, the presence of concomitant infection elsewhere, the facilities available for surgery and the avoidance of secondary infection. Prolonged disease, undernutrition and the presence of disease elsewhere influence the overall results and additional measures may have to be adopted. Rajasekaran and Soundarapandian[137] reviewed 81 patients, eight years or more after treatment with debridement and anterior arthrodesis. Arrest of kyphosis with good improvement was seen in 48 patients (59%) who had minimal destruction of the vertebral body, limited excision of bone, short graft, marked intraoperative correction of deformity and involvement of the lower lumbar segments. The unfavourable factors

were extensive vertebral destruction necessitating a graft spanning more than two disc spaces, the involvement of thoracic vertebra or a marked pre-operative kyphotic deformity. As the graft was found to be stable only in 41% of their cases, they concluded that it was unwise to rely solely on the graft to prevent vertebral collapse, especially in patients whose grafts spanned more than two disc spaces. They suggested additional measures like extended period of non-weight bearing, posterior arthrodesis after 6–12 weeks and the prolonged use of a brace until complete consolidation was achieved.

Surgery for Paraplegia

Surgery to decompress the spinal cord is indicated in patients: (i) who fail to respond to conservative treatment; (ii) develop paraplegia while on appropriate chemotherapy; (iii) patients in an advanced stage of disease when delay in decompression is risky; (iv) patients with posterior neural arch disease; (v) those with "spinal tumour syndrome" and (vi) if the diagnosis is in doubt.[108,164,165] Relief of pressure on the spinal cord by the most appropriate technique is the aim of treatment when paraparesis starts to appear. Bed rest and anti-tubercular therapy alone have been found sufficient in mild paraparesis. However, if there is no obvious improvement within two or three weeks, surgical decompression becomes necessary. Simple drainage of the cold abscess would be sufficient in those cases where the tension inside the abscess is the cause of cord compression. In cases where the cord is compressed due to debris, sequestra or granulation tissue, a direct approach becomes necessary. Laminectomy is an unsatisfactory procedure except in a few cases when the compressing element is posterior, as in tuberculous disease of the neural arch, or in spinal tumour syndrome. In most cases, a lateral or an anterior approach to the diseased area, with radical removal of the compressing material is indicated. This opportunity may also be utilised to fuse the spine anteriorly, in those cases where the patient can stand the prolonged surgery. Many reports indicate the usefulness of this approach to surgical therapy.[1,2,36,61,82,95,107]

The route of approach has to be tailored to the level of the lesion, the amount of compression and the general health of the patient. Korkusuz et al. in 1989,[86] reporting on 108 patients, described an extrapleural, extraperitoneal approach for those patients with lower thoracic and upper lumbar spinal involvement. The approach was recommended, especially for those patients with compromised pulmonary reserve.

Delaying surgical decompression for too long in the presence of paraplegia may lead to problems, like extradural fibrosis, which may be difficult to eradicate.

Conservative Approach Justified

Many authors, like Pattison,[131] argue that the case for urgent early surgical intervention in the treatment of Pott's paraplegia may have been overstated. He reviewed a series of 89 consecutive cases of Pott's disease, out of which 85 were treated conservatively. Around 83% of these returned to normal life and full activity. Of 41 patients, who deteriorated neurologically in the first 3 months, 37 recovered completely. Moon et al.[115] treated 75 cases of spinal tuberculosis conservatively, with a favourable outcome in 95% of cases. They recommend that the conservative regime be used confidently, especially in less privileged countries where adequate facilities for hospital treatment may not be available.

RECENT TRENDS IN THE MANAGEMENT OF SPINAL TUBERCULOSIS

The aims of treatment are to confirm diagnosis, achieve bacteriological cure, prevent and/or treat deformity and neural compression. With technological advancements in the field of spinal imaging, early diagnosis of spinal tuberculosis is possible. With better chemotherapeutic drugs available that reach pus, granulation, caseous material and bone, non-operative management has become more effective, especially in cases diagnosed early.[67,78,87,116,173] The fourteenth report of the MRC working party on tuberculosis of the spine has clearly shown that the 5-year report of the 6 and 9 months courses of isoniazid plus rifampicin was excellent and similar to that of the 18 months course of ethambutol plus PAS. They, however, found the 9 months ethambutol plus PAS regime inferior to the others.[119]

Radical resection has been defined as excision of the disease focus to uncover the dura mater as completely as possible until healthy bleeding bone is reached.[65] Debridement, on the other hand, has been defined as removal of pus, granulation tissue, caseous tissue and loose sequestrated bone from lesions and also part of the viable bone needed to decompress the spinal cord leaving a relatively stable spine.[67] It is now recommended that radical excision is not necessary for infective spinal lesions, like tuberculosis, where effective anti-tubercular chemotherapy is available. The indications for surgery are well defined as is the extent of surgical decompression.[22,117,122,130,146] In cases of tuberculous infection of the lumbosacral region, Rajasekharan et al. feel that surgery is indicated in the group who are younger than 10 years old, as they have a tendency to a greater kyphosis.[138]

When one considers spinal instability related to tuberculosis it is essential to remember that the pathophysiology is different compared to trauma. Pathological fractures, involvement of the anterior and posterior spinal elements, translation or dislocation of the destroyed vertebrae, and long segment disease with kyphosis should all be considered as signs of instability. Mehta and Bhojraj proposed a classification system using MRI, dividing patients into four groups based on the treatment received. In their opinion the appropriate surgery for each case could be planned based on MRI findings.[111] Lesions affecting the vertebral body should be decompressed anteriorly. Performing a posterior decompression

like a laminectomy is not recommended as it removes the healthy segment of the spinal column and renders the spine unstable.

In the cervical spine the anterior approach is presently established as the approach of choice. In the case of thoracic tuberculosis, a transthoracic transpleural approach gives an excellent exposure of the diseased segments. However, in the presence of compromised pulmonary function, systemic morbidity factors and extensive disease, the risk of surgery increases and one may opt for an extrapleural anterolateral exposure. Jain et al. reported that the extrapleural anterolateral approach provides the surgeon the exposure to perform anterior decompression as well as a posterior instrumentation at the same sitting with decreased morbidity.[68] The lumbar and lumbosacral spine may be approached retroperitonially.

Video-assisted thoracoscopic surgery (VATS) has been used by a few surgeons for short segment disease where there is no lung disease and especially for biopsy or for decompression of a cold abscess.[73,101] The surgeon should be prepared to convert to an open thoracotomy at all times.

Jain and Dhammi found, in their review of PubMed in 2006, 1,097 patients underwent anterior or posterior instrumentation for tuberculous spondylitis.[12,67] Of the cases reviewed, the kyphosis correction on instrumentation was 30–35 degrees pre-operatively to 15–18 degrees post-operatively. On follow-up, the loss of kyphosis correction was a mean of two degrees for those who underwent posterior instrumentation and 2.3 degrees for those patients who underwent anterior instrumentation. While the majority of authors prefer to stabilise the diseased segments using internal fixation, Moorthy et al.[118] found good clinical and radiological outcome in patients with subaxial cervical spine tuberculosis who were not instrumented. Klockner and Valencia, in a retrospective study, concluded that in single level disease with no major substance loss, anterior debridement and grafting alone was adequate. They recommend the use of instrumentation in the presence of multi-level disease and extensive kyphotic deformity.[83] Rajasekaran is of the opinion that there is an average increase of 15 degrees deformity in all patients who are treated conservatively and 3–5% of patients finally have a deformity that is greater that 60 degrees. Surgery, therefore, must be done early and stabilisation by instrumentation gives a good result.[139] Various types of implants have become available to the surgeon to internally stabilise the spine. Despite the availability of systems that are biomechanically better, Jain and Dhammi argue that in some cases, especially in long segment disease, fixators like the Hartshill rectangle are still a reasonable option as they take purchase against the posterior healthy segment of the vertebra and a single healthy vertebra on either side of the diseased segment could give adequate stabilisation.[67] Many authors presently prefer anterior instrumentation done at the same sitting as the debridement.[19,112] Ramani et al. reporting on a mean 36 months follow-up of 61 patients with subaxial cervical spine tuberculosis found that anterior reconstruction of the column using titanium plates and locking screws provides segmental stability and is a useful adjunct in preventing a kyphotic deformity[142] Benli et al. comparing anterior instrumentation systems, did not find any significant difference between rod-screw and plate instrumentation systems even at 5 years follow-up.[20] However, there are some who still prefer posterior instrumentation following an anterior decompression.[68,93,163,166]

Late Onset Paraplegia

Years after the primary disease of the spine, paraplegia may develop due to recrudescence of active disease at the original site or as a result of chronic compression and ischaemia of the cord due to pronounced kyphosis. Anterior decompression is helpful for these patients.

Hsu et at.[61] treated twenty-two patients with late onset paraplegia by anterior decompression and fusion, and reviewed them seven years later. Twelve patients had active disease at the internal kyphus and, in two, a soft healing bony ridge was the cause of cord dysfunction. In the eight patients with healed disease, hard bony ridges compressed the cord. The response to anterior decompression was faster, better and safer in patients with active disease. Nine patients recovered completely and three significantly. In patients with healed disease, anterior decompression was technically more difficult and the recovery less satisfactory and with significant complications. Rajeswari et al. reported on five patients who developed paraplegia even after successful treatment of the initial disease. MRI was useful in diagnosing the exact cause of the late paraplegia, and surgery could be offered in selective cases.[140]

Correction of Kyphosis

In many cases, proper posturing and wearing of braces when indicated, help to correct a tendency for kyphosis. In patients with kyphosis, correction can be attempted successfully during excisional surgery and bone grafting. Occasionally, special measures may be required.

Louw[100] reported 19 patients with thoracic or thoracolumbar spinal tuberculosis treated by anterior debridement, decompression and vascularised rib grafting. This was followed either during the same procedure or 14 days later by multi-level posterior osteotomies, instrumentation and fusion. The average pre-operative kyphotic angle of 56 degrees was reduced to 27 degrees post-operatively and 30 degrees at follow-up. Around 95% of the patients had normal neurological function at 14 months and the rest could walk with crutches.

Rajasekaran and Shanmugasundaram[136] studied 90 cases with spinal caries and compared the angles of the gibbus deformity. They were able to predict the

final angle of the gibbus with 90% accuracy in patients who were not treated surgically. The ability to predict the final angle of the gibbus allows the surgeon to select the patients who will require radical resection and bone grafting to prevent a severe kyphosis. Other authors[170] have found that multiple vertebral involvement, active growth and thoracic lesions were responsible for excessive increase in kyphosis. Correction of kyphosis is presently done at the time of debridement surgery with elegant instrumentation systems that are available.

Indications of Surgical Therapy

The experience of many surgeons in the treatment of Pott's paraplegia suggests the following useful criteria for deciding on surgical therapy:[170,178]

- Neurological signs not improving or worsening within 4 weeks of adequate conservative and drug therapy
- Development of neurological signs with progression while on adequate therapy
- Recurrence of neurological signs after improvement
- Rapid onset paraplegia
- Paraplegia with flexor or painful spasms
- Posterior spinal disease with spinal tumour syndrome
- Prevertebral cervical abscess with difficulty in deglutition
- When the diagnosis is in doubt
- Late onset paraplegia
- Correction of kyphosis.

CRANIOVERTEBRAL TUBERCULOSIS

Tuberculous disease involving the structures at the craniovertebral junction requires special mention, due to the difficulties in early diagnosis and the possibility of serious complications. Craniovertebral tuberculosis is rare, forming less than 1% of spinal tuberculosis;[172] however, it seems to be more frequent in the developing countries as is spinal tuberculosis itself. Teaching hospitals in India may see two or three cases every year.[80,128]

Amongst Karapurkar's[80] 31 cases, 13 were between 20 and 30 years of age, seven between 10 years and 20 years and five below 10 years. There was a female preponderance of nearly 2:1.

Karapurkar[80] described five types of clinical presentations:

1. The commonest was that of progressive pain in the neck, restriction of movement and torticollis. The pain radiates to the occipital region. Neurological deficit is usually progressive, but may be stuttering or sudden. Some patients in this group had no neurological deficit.
2. Low grade fever, progressive neck pain and stiffness without any neurological deficit.
3. Fever, neck pain, difficulty in swallowing and an oropharyngeal bulge.
4. Neck pain and stiffness associated with dysphagia and involvement of the lower cranial nerves.
5. Fever, neck pain and progressive quadriparesis starting in one leg, successively followed by the other and then the upper limbs.

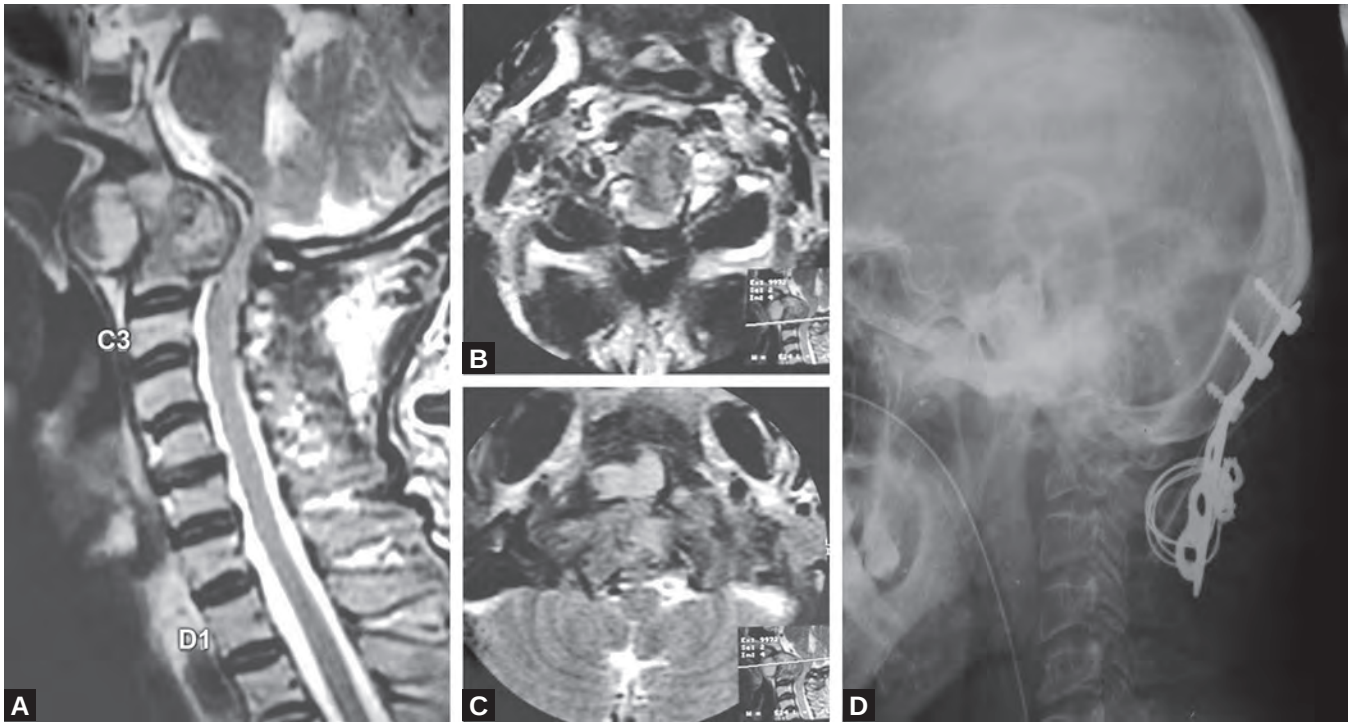
Tuberculosis of the craniovertebral junction may cause atlantoaxial dislocation, upward translocation of the dens, cervicomedullary compression by tubercular abscess or direct invasion by tuberculous disease.[41] According to Pandya[128] this is the cause of the neurological problem and not hyperaemic decalcification and loosening of the ligaments, as suggested by several authors earlier.

Plain skiagram of the CV junction may sometimes fail to reveal the diagnosis. Special oblique views and tomograms are helpful. Osteolytic erosions, subluxation of the atlantoaxial articulations and increase in the retropharyngeal space are to be looked for. CT scan and MR findings are conclusive[88] (Figs 14A to D).

Treatment

John Hilton first described a case of tuberculous atlantoaxial dislocation and stressed the importance of rest.[98,127,128] Both conservative and surgical therapy has been advocated.[94] Skull traction is indicated when there is subluxation.[27] If adhesions have formed, reduction may be achievable only after excision of the diseased tissue.

Traction and anti-tubercular drugs are the principal modes of therapy[170] and stability may be achieved within 3–6 months. The neck may be immobilised by a halo vest or a four post-cervical collar and the patient is allowed normal activities. Chadha et al. are of the opinion that CV junction tuberculosis can be management adequately using conservative methods regardless of the extent of bony erosion.[28] Surgical decompression is indicated in patients who do not stabilise spontaneously or if there are progressive neurological signs. All diseased bone, synovium and granulomatous tissue are removed; and after reducing any subluxation by traction, anterior fusion is performed using homologous iliac or rib grafts inserted into troughs across the lateral facet joints. Following such a transoral decompression, halo traction is used till radiological union (8–17 weeks) becomes apparent, or else a posterior fusion and internal stabilisation may be done as second stage surgery.[41] Sinha et al. have reported their results with a transcervical retropharyngeal approach for their cases, all of whom underwent a posterior fixation also.[156] Teegala et al. have suggested a scoring system and management algorithm, where the patients are divided into one of three grades.[167] Behari et al. have divided their patients into four clinical grades and based management options on the clinicoradiological presentation.[16] Anti-tubercular therapy was continued for 18 months in all patients. While a conservative neck immobilisation was adopted in patients with milder degrees of deficits (Grades I and II), those with severe deficits and



Figs 14A to D: (A to C) Sagittal and axial MRI showing tubercular involvement of the craniovertebral junction with significant pressure over the cervicomedullary junction. (D) Post-operative X-ray after anterior decompression followed by foramen magnum decompression and occipitocervical fixation

significant cervicomedullary compression underwent anterior decompression and posterior fusion. Direct posterior fusion was performed on patients with a reducible dislocation. Arunkumar and Rajshekhar are of the opinion that patients with CV junction tuberculosis are ideally managed with an anterior decompression followed by occipitocervical fusion as this provides immediate neurological improvement, stability and allows early mobilisation.[8]

Bapat et al. have compared traditional occipitocervical fusion techniques with transarticular screw fixation in tuberculous atlantoaxial instability.[15] They have reported early brace free mobilisation, 100% fusion and a patient satisfaction rate of 90.90% in the transarticular group compared to 83.16% fusion and patient satisfaction of 62.5% in the occipitocervical fusion group.

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67 Surgery for Leprosy

Sridhar K

INTRODUCTION

Leprosy, in spite of being a bacterial disease, remains to be eradicated completely from the world. "If leprosy is a disease of the skin alone, it can be easily eliminated, but it is also and mainly involves the nerves and this makes the disease more formidable"—Bourrel. Even after the disease process has been controlled or eliminated, the residual sensory and motor deficits produce a crippling deformity. This creates the need for corrective surgery, to restore the patient to his occupation and to society. Surgery for leprosy involves improvement of function and appearance, the former being more important. The deformities and disabilities, which require surgical correction, are due either to the direct involvement of the tissues by the disease process or due to anaesthesia produced by the nerve involvement. The paralysis produced by the nerve involvement can be corrected, but the pathology produced as a result of anaesthesia can only be prevented by due care of the hands, feet and eyes. With the correction of motor paralysis, the patient starts using the hands and feet more and more, increasing the risk of trophic ulceration in such patients.

HISTORICAL REVIEW

One of the earliest recorded descriptions of leprosy is found in the works of Susrutha, who wrote his treatise on surgery "Susrutha Samhitha" in the 6th century BC. He describes many types of "Kushta" and distinguishes leprosy from vitiligo and other conditions. Mention about anaesthesia, paraesthesia and loss of sweating are found in his description, so also the facial disfigurement. The earliest skeletal remains, which showed signs of leprosy, were found in El Bigha in Upper Egypt, which dates back to the 6th century AD. Some references to this disease are found in the Bible.

Surgical procedures for leprosy developed only during the 20th century. As early as 1953, Gudagnini[15] suggested nerve decompression to prevent deformities. Surgical decompression was weighed against medical treatment alone and was debated for long in the past. But the works of Gudagnini, Carayan and Hunt,[4] Vaidhyanathan,[32] Pandya[26] and Palande[24] clearly emphasise the benefits of early decompression of the nerves. Tendon (FDS) transfer for paralysed hands was pioneered by Stiles (1922) and popularised later by Bunnell[3] during the Second World War. Later Brand,[2] Fowler,[11] Zancolli,[34] Srinivasan[30,31] and Palande[25] described various procedures for claw hand correction and opponens palsy.

EPIDEMIOLOGY

During the period between the mid-sixties and the mid-eighties, the global prevalence of leprosy was estimated to be around 10–12 million. After the successful implementation of multidrug therapy (MDT),[21] the incidence came down remarkably and, as per 1991 WHO data quoted by Noorden,[20] the prevalence was estimated to be around 5.5 million in the world, and India contributes nearly 3 million of these. The incidence of deformity, including in those patients already cured of the disease, was estimated to be around 2–3 million. In our series at the V.H.S. Sakthinagar, the incidence of deformities is 11.7%.

As per the WHO weekly epidemiological record[33] dated 14th July 2000, the global prevalence has come down to 2.2 per 10,000 and among the 11 endemic countries in the world, the prevalence is 4.1 per 10,000. India has a prevalence rate of 5.0 per 10,000. In stark contrast to 1991 situation, during January, 2000 only 495,073 registered cases were there in India.

PATHOLOGY OF NERVE INVOLVEMENT

Common Sites

Starting with the classical studies by Khanolkar,[18] a number of Indian pathologists have contributed a great deal towards understanding the pathogenesis and pathology of neural lesions in leprosy. Dastur from Mumbai has made major contributions in this field.[6–9] A detailed review of the subject has been provided by Antia.[1]

The nerve gets involved either during the normal course of the disease or during a reactive phase. The nerves which are usually involved are the ulnar, the median and the radial nerves in that order in the upper limb, and the common peroneal and the posterior tibial nerves in the lower limbs. The facial and the trigeminal nerves are the only cranial nerves commonly involved. The superficial radial, the superficial peroneal, the greater auricular and the sural nerves which are purely sensory, when involved, show thickening which may help in establishing the diagnosis. These are of little surgical importance except for taking a nerve biopsy.

The reason why some nerves are involved at specific sites is not clear. Some common anatomical features have been noted in these nerves at these specific sites:

- The affected nerves lie at a comparatively superficial plane where the temperature is low.
- The site of involvement is near a joint where there is constant motion.
- The involvement is near an area of constriction like an osseofibrous tunnel, intermuscular septum or retinaculum.
- The nerves lie over bony prominences.

The ulnar nerve is the commonest nerve to get involved; the common site of involvement being proximal to its passage under the osseofibrous tunnel behind the epicondyle. Rarely, it is involved near the wrist proximal to its passage through Guyan's canal.

The median nerve, which in its proximal part lies deep behind the muscle bellies, becomes superficial near the wrist and it is here, before its passage through the flexor retinaculum, that it is involved. Commonly, the proximal thickening is noticed where it is crossed by the flexor digitorum superficialis to the fingers. Hence, median nerve palsy is commonly at a lower level; the long flexors of the fingers and thumb escape and only the intrinsic muscles of the hand are paralysed. The common peroneal nerve, like the ulnar nerve, is involved as it curves round the neck of the fibula and produces a foot drop. The posterior tibial, like the median nerve, gets involved before it enters the flexor retinaculum near the ankle.

Branches of the VII cranial nerve, mainly the ones supplying the orbicularis oculi and frontalis, are involved as they cross the zygomatic arch and are near the temporomandibular joint.

Entry of Bacilli into the Nerve and Establishment of Neuritis

Various theories have been postulated regarding the mode of entry of the bacilli into the nerves:

- Phagocytosis by Schwann cells in the outer layers of the dermis and once engulfed the bacilli travel by contiguity from Schwann cell to Schwann cell or within the axons. There are many objections to this theory.
- Penetration of the perineurium. The perineurium is a formidable barrier in leprosy and this explanation is also not satisfactory.
- The most plausible hypothesis is that the bacilli enter via the endoneurial blood vessels.[10,17,27] Bacteraemia is a normal finding in patients with untreated lepromatous leprosy.

Once the bacilli enter the nerves, they multiply and produce an inflammatory response and the antigens, which leak out, produce an immunological response. Both the inflammatory and the immunological responses promote nerve damage. Depending on the immune response of the body, the pathology of destruction varies from the tuberculoid to the lepromatous spectrum. In the tuberculoid variety, the host resistance is high and the immunological reaction is primarily responsible for the destruction. At the opposite end of the spectrum is lepromatous leprosy, where the host resistance is very poor and bacilli enter and multiply unchecked. However, the multiplication is a slow process. Borderline leprosy produces a mixed picture.

Nerve Damage in Reactions

Type I Reaction (Reversal or Upgrading Reaction)

This occurs most commonly in the borderline type of leprosy and tends to develop in the early months of treatment. It may also occur in untreated cases. The existing lesions flare up with erythema and oedema due to an increase in the immune response. In borderline leprosy, there are surviving Schwann cells enclosed in rigid inflammatory tubes. During the reaction, the pressure within the tubes increases rapidly causing demyelination. The damage is sometimes very rapid without even pain or tenderness. Hence, decompression becomes urgent to preserve function.

Type II Reaction (Erythema Nodosum Leprosum)

Erythema nodosum leprosum (ENL) is an immune-mediated complication of leprosy presenting with inflammatory skin nodules and involvement of multiple organ systems including the peripheral nervous system, often running a protracted course. Immune complex production and deposition as well as complement activation have long been regarded as the principal aetiology of ENL.[16]

Here, crops of new lesions appear and the nerve damage is a slow process with the formation of antigen-antibody immune complexes. These are usually found in patients with lepromatous leprosy who are under treatment for months or years. Nerve decompression is not urgent as the disease process is slow and conservative treatment can be tried for an adequate period. The vasa nervorum may get involved in both the reactive phases and in the natural process of the disease and contribute to the nerve damage. This may not be relieved by simple decompression, as there is no pressure build-up inside the nerve.

Nerve Abscess

These are focal areas of necrosis involving one or more fascicles. Early in the disease, the fascicles change from a greyish to a yellow colour and undergo liquefaction. Initially, the epineurium thickens around the area of inflammation and as the pressure builds up, the epineurium may give way and the contents track outside the nerve, forming a paraneural abscess which may reach the skin. Surprisingly, a fair amount of nerve function may remain even in cases with large abscesses and hence, careful evacuation of the abscess is to be done without interfering with the surviving fascicles to prevent further damage.

CLINICAL FEATURES OF NEURITIS

Local pain in the area of involvement of the nerve, sometimes, excruciating and not relieved by analgesics is a common symptom. Absence of pain does not rule out

neuritis; sometimes neuritis may progress rapidly, without any appreciable discomfort. Pain, numbness or tingling in the distribution of the affected nerve is noticed by many patients.

Thickening of the nerves, generally at specific sites (described above) is common. Thickening of the ulnar, lateral popliteal, greater auricular, radial cutaneous and median nerves can be easily made out. This feature is an important sign in suspecting the diagnosis. Occasionally, when only one nerve is thickened, diagnosis may be difficult and a biopsy may be needed. Pain and restriction of movement may be present on stretching the nerves by moving the adjoining joint.

Sensory loss along the distribution of the nerve is an important clinical feature. The loss is usually patchy. The common areas of sensory loss are: (a) the pulp and proximal phalanx of the little finger and the hypothenar area (the ulnar nerve); (b) the pulp and proximal phalanx of the index finger and the tip of the thumb (the median nerve); (c) a small area around the anatomical snuff box (the superficial radial nerve) and (d) the lateral border and the sole of the feet (the posterior tibial nerve). Glove and stocking anaesthesia may be present in advanced cases, but careful examination will reveal some islands of intact sensation.

Motor weakness occurs in the concerned muscles, with evidence of wasting. For rapid assessment, the abductor digiti minimi and the first dorsal interosseous function will give an idea of ulnar nerve involvement. The function of the abductor pollicis brevis will demonstrate the involvement of the median nerve. Opposition of the thumb to a straight little finger will show the integrity of the median and the ulnar together. Making the patient cross the index over the middle finger, keeping it straight, will test the integrity of the intrinsic muscles. It is impossible to do this in the presence of an ulnar palsy. With this background assessment, a diagnosis of nerve involvement can be made. Nerve conduction studies may support the diagnosis.

DIFFERENTIAL DIAGNOSIS

The diseases most commonly confused with leprosy include:

I. Those associated with spinal cord diseases like syringomyelia, amyotrophic lateral sclerosis and motor neuron disease.
II. Those associated with peripheral nerve lesions:
    1. Damage by pressure such as spinal root compression, carpal tunnel syndrome and Bell's palsy.
    2. Polyneuritis:
        i. Hereditary—Hypertrophic interstitial neuropathy, peroneal muscular atrophy.
        ii. Metabolic—Diabetes, poryphyria, amyloidosis.
        iii. Deficiency—Vitamin B_1 and B_{12}, especially associated with malnutrition and alcoholism.
        iv. Toxic—Lead, mercury and alcoholism
        v. Malignant—Carcinoma of bronchus.
III. Those associated with muscle disease—myopathies.
IV. Those associated with trophic changes—diabetes, tabes dorsalis.

The salient features of nerve involvement in leprosy can be summarised as: localised irregular nerve enlargement in an endemic area is almost always due to leprosy. Muscle weakness is always of the lower motor neuron type and never involves the girdle or trunk muscles. Sensory loss is patchy and mixed. Position sense is always preserved. The central nervous system (CNS) is never damaged and the reflexes are normal.[28]

TREATMENT

Medical

In the past, medical treatment for the control of leprosy was mainly with monodrug therapy using Dapsone. Now, with the advent of MDT, the control of the disease is much better. As per the National Leprosy Eradication Programme Operational Guideline 1988[20] depending on the severity of illness, the patients are divided into two categories, viz. "paucibacillary" in less severe cases and "multibacillary" in more severe cases.

For the paucibacillary disease, a 6 month regimen with Dapsone 100 mg daily and Rifampicin 600 mg once a month is given as a supervised dose. For the multibacillary cases, the treatment is for 2 years. Dapsone 100 mg and Clofazamine 50 mg are given daily. Rifampicin 600 mg and Clofazamine 300 mg are given once a month under supervision. The patients are followed up regularly to watch for progress, sensory and motor involvement and reactions.

Treatment of Acute Neuritis

Prednisolone given in high doses is useful as an anti-inflammatory drug and as an immunosuppressant. The initial dose of 50–60 mg/day is gradually stepped up under supervision. Before and during the course of treatment, sensory and voluntary muscle testing is to be done to keep track of any deterioration in nerve function, especially muscle weakness. Other anti-inflammatory drugs are also administered along with steroids. Thalidomide and Cyclosporine A have also been used. During this period, anti-leprosy treatment should be continued. The muscles affected must be rested and splintage of the affected part with the muscles in the resting position is necessary.

Surgical Decompression

If there is progressive nerve involvement under medical treatment, decompression is necessary. In type I reaction, the progress may be rapid and if no response is detected in 8–10 days, it is better to decompress. Earlier the decompression is done, before permanent nerve damage sets in, the better are the results. Vaidhyanathan[32] clearly demonstrated the benefits of early decompression. In the ENL type of reaction, a conservative line of management may be followed.

Indications for Decompression

If any of the following occur in spite of full medical treatment, decompression is indicated:

- Progressive nerve deficit.
- Sudden increase in nerve deficit indicating an active increase in the internal nerve pressure.
- Increase in the intensity of pain and tenderness in the nerve.
- Positive stretch sign.
- For the ulnar nerve, a positive compression sign and pain elicited by flexion and ulnar deviation of the wrist with the fingers closed.
- Pain as the ulnar nerve slides forward on flexion of the elbow.

Ulnar Nerve Procedure

The skin incision is started about 7 cm above the medial epicondyle, carrying it anteriorly around the epicondyle down into the forearm for about 5 cm below the epicondyle and exposing the common flexor origin. The deep fascia is incised, the medial intermuscular septum is divided and the osseofibrous tunnel behind the epicondyle deroofed by cutting the olecranon ligament. The nerve is released in the forearm between the heads of the flexor carpi ulnaris by cutting the fibrous origin. The release of these constricting areas relieves the external compression. Medial epicondylectomy is done to prevent repeated trauma to the nerve during movement. To relieve the internal compression, median epineurotomy is done by incising the thickened epineurium along the whole length of the affected segment. This is the minimum which must be done, but most authors feel that at least the superficial hemi-circumference of the nerve should be freed from the epineurium by cutting away the thickened portion, leaving the vascular supply from the bed undisturbed. Only if multiple abscesses are seen, are these deroofed carefully.

Anterior transposition of the ulnar nerve is generally not recommended, as freeing an inflamed nerve totally from the bed over a long segment would compromise the vascularity.

Carayan, in 1957[4] and 1962,[5] proposed fascicular endoneurolysis. This type of fascicular dissection must be done only under magnification, taking care to preserve the anastomosis between the various fascicular bundles inside the nerve and is possible only by specially trained surgeons.

Median Nerve

The carpal tunnel is deroofed to relieve the external compression.

Radial Nerve

The nerve is rarely compressed by the fibrous arch from which the lateral head of the triceps originates and where the nerve is in the radial groove. The fibrous band is cut to relieve it.

Common Peroneal Nerve

The fibrous origin of the peroneus longus compresses the nerve and it is to be cut where the nerve winds around the neck of the fibula. The results of conservative management are quite encouraging in involvement of the common peroneal nerve and hence, decompression is rarely indicated.

Posterior Tibial Nerve

Decompression of this nerve has been extensively studied by Palande et al.[23] The incision is made behind the medial malleolus for 6 cm above and 6 cm below, extending it up to the lower border of the calcaneum. The flexor retinaculum is incised and the neurovascular bundle is released by incising the thickened sheath. The inferior calcaneal bands are cut and the nerve is released up to its division into plantar branches. Palande claims excellent results both in terms of sensory recovery and healing of plantar ulcers.

PARALYTIC DEFORMITIES

Hand

To understand the mechanism of the deformities and the restoration of function, one must know some basic concepts about the function of the hand. The prehensile functions of the hand are: (i) grasp; (ii) pinch; and (iii) hook. Srinivasan,[31] during the early seventies, has added one more function which he calls as "the syringing function" like pushing the piston of a syringe, holding it between two fingers. Among these if grasp and pinch can be restored useful function of the hand results.

In an ulnar claw hand, as the intrinsic muscles are paralysed, the metacarpophalangeal (MP) joints are kept hyperextended and the arch gets reversed with the convexity on the palmar side. The interphalangeal (IP) joints are kept flexed due to the paralysis of the interossei. The hand is unable to initiate even the first phase of grasp, which requires the diametrically opposite position. The aim is to restore MP joint flexion and IP joint extension to enable grasping.

In median nerve palsy, the abductor pollicis brevis and the opponens pollicis are paralysed and the patient is not in a position to rotate the thumb medially. Usually, as the ulnar nerve is also weak and the intrinsics paralysed, the index finger does not move as required, and the thumb cannot press against the index, and pinch is not possible. The primary aim in restoring pinch is to provide abduction and rotation of the thumb, so that it can oppose the other fingers.

I. The procedures adopted to restore function in the hand are:
   a. Dynamic tendon transfer
   b. Static procedures
II. The procedures to correct secondary deformities include release of skin contracture, capsulotomy and arthrodesis.

DYNAMIC TENDON TRANSFER

Eighty per cent of the patients with deformities in leprosy require minor surgery and the rest require major surgery. Tendon transfer is the only option available in cases of deformities like Simian hand, ulnar claw hand, wrist drop and failure of the metacarpals.[29]

General Principles

- In any paralysed part, when a tendon transfer is done, the available muscle power is redistributed and hence, one cannot expect full return of power and function, but improvement can be effected.
- Tendon transfers are possible only when the joints concerned are supple and mobile. Therefore, any skin or capsular contractures, when present, are to be attended to before the tendon transfer is performed.
- It is preferable to transfer a synergistic muscle, as re-education is easy, e.g. wrist extensor for metacarpophalangeal flexion, wrist flexor for extension.
- The tendon is to be routed as directly as possible to the new location of insertion.
- The power of the muscle transferred must be at least Gr. IV, so that at least Gr. III power may be obtained if the transfer is to be meaningful.
- The functional loss of the transferred tendon should be acceptable.

Claw Hand

The most common paralytic deformity in leprosy is the claw hand.[19] Applying the above principles, appropriate tendon transfers help to improve claw hand. After correcting the extension of the MP joint, the IP joints are extended by the long extensors. The pinch function of the thumb is restored by using the flexor digitorium sublimis going to the ring finger. Techniques have been perfected by surgeons experienced in the field of leprosy rehabilitation.

Foot Drop

When there is lack of improvement after conservative treatment or when the patient comes with an established foot drop, the options are to give the patient a foot drop splint or offer a dynamic transfer. Dynamic transfer gives the patient a permanent solution. The most common method which is used is the tibialis posterior transfer, as suggested by Ober.[22]

Facial Palsy

Commonly, the zygomatic branch of the facial nerve is involved in leprosy and leads to lagophthalmos. Early correction of this deformity is necessary to prevent exposure keratitis. When the cornea is also involved due to direct involvement by the bacillus or due to trigeminal nerve involvement, corneal sensation is also lost. Therefore, it is imperative to correct the disability to prevent blindness.

Initially, the eye is protected with oily drops applied frequently to prevent drying of the cornea. Patients can be administered steroids to see if the palsy improves with conservative treatment. The facial nerve recovers faster, if it responds to conservative treatment. A maximum period of 3 months of this treatment can be tried and that too if the patient is co-operative enough to apply the eye drops properly. Surgery is indicated if medical treatment fails to provide relief within three months.

Tarsorrhaphy

This is a passive procedure, wherein the palpebral fissure is narrowed and the cornea remains covered during sleep. Normally, a lateral tarsorrhaphy is done to avoid injury to the canaliculi which are situated medially, but Fritschi[12] prefers medial tarsorrhaphy and claims excellent results. The superficial nature of the dissection, according to him, prevents any damage to the canalicular system. Whatever be the site, it is preferrable to do a Z-plasty and interchange the triangular flaps of the upper and lower eyelid so as to narrow the palpebral fissure.

Kuhnt-Szymanowsky Procedure

When the lower eyelid is flabby and severe ectropion is present, tarsorrhaphy alone is not enough. In this procedure, an incision is made just outside the ciliary margin in the lower eyelid and the incision is extended on to the cheek laterally. The whole of the eyelid skin is pulled outward, the excess skin removed and sutured. This corrects the ectoprion and supports the eyelid against the globe.

Dynamic Transfer

Temporalis transfer is the commonest dynamic procedure used for lagophthalmos. The patient is able to close the eyelid consciously by biting his teeth and the tone of the temporalis keeps the palpebral fissure narrowed, even when it is relaxed. The patients can be trained easily and a near normal appearance can be achieved by meticulously adjusting the tension.

MISCELLANEOUS SURGICAL CONDITIONS

Contractures

Skin and capsular contractures are noticed in the hands and feet of patients with long standing disease. Most of these contractures respond to serial splinting with POP. When there is no improvement, surgical release is done either by a Z-plasty, excision of scar and skin grafting, or local flap over cover. Capsular contracture needs capsulotomy and mobilisation. Especially in the hand, all contractures are to be attended to before any tendon transfer is contemplated. If the finger joints cannot be released, then it is better to arthrodese them in a functional position.

Trophic Foot Ulcer

Dressing of the wound and rest in a light POP cast will help to heal plantar ulcers. If osteomyelitis is demonstrated, scraping or sequestrectomy is necessary. Palande claims good results with posterior tibial nerve decompression along with conservative management. Once the ulcer

heals, proper foot wear made of microcellular material is to be used with relief on pressure points.

Facial Deformities

A mini facelift will help remove the thick coarse wrinkles in the face, especially in the nasolabial region, and make the facial appearance more acceptable. Loss of eyebrows, which is another prominent feature, can be reconstructed with a free graft from the scalp. A hypertrophic and lax ear lobule can be reduced to normal size. The depressed nose is a result of mucosal involvement and subsequent contracture. The dorsum collapses and the nose appears as if it has been tucked in. Gillies[13,14] described the procedure of release of the scar through the sulcus of the mouth and pulling the nose outward. The raw area created in the inner aspect of the nose is covered by an inlay skin graft. Later a bone graft can be applied to the dorsum as a second stage procedure.

Gynaecomastia

Gynaecomastia is commonly noticed in lepromatous leprosy. Reduction of the breast through a periareolar incision is the procedure of choice.

With modern surgical techniques, many of the disabling and disfiguring deformities caused by leprosy can be corrected, resulting in both physical and emotional improvement of the patient.

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68 Cysticercosis

BS Sharma, Sarat Chandra P

INTRODUCTION

Cysticercosis is a zoonotic parasitic disease caused by infection with the larval stage of the pork tapeworm *Taenia solium (T. solium)*.[27,41,47] In humans, the parasite commonly infests the central nervous system (CNS), where it produces a pleomorphic clinical disorder called neurocysticercosis (NCC).[11] Cysticercosis is currently considered the most common parasitic disease of the CNS, affecting thousands of individuals living in developing countries and in industrialised nations with a high index of immigration of people from endemic areas.[24,110]

This disease represents a major health problem in many of the developing countries. Endemic subcontinents include Central and South America, Eastern Europe and Asia. Conservative figures mention 50,000 deaths every year due to NCC, and no less than 20 million people infested by cysticerci.[18,49] The disease is widely prevalent in countries like Mexico.[77] General autopsy incidence has been reported up to 3.5–4%.

According to the International League Against Epilepsy, cysticercosis is probably the single most common cause of acquired epilepsy in the developing world, where prevalence rates of active epilepsy are twice those of developed countries.[18,49] These numbers indicate only the tip of the iceberg, as the actual prevalence of human cysticercosis is not known.

LIFE CYCLE AND PATHOGENESIS

Life Cycle

T. solium has a complex two-host life cycle. Humans are the only definitive hosts and harbour the adult tapeworm, whereas both humans and pigs may act as intermediate hosts (Fig. 1).

The Adult Worm

The adult *T. solium* is a hermaphrodite and inhabits the small intestine of man, where it attaches to the bowel wall by its suckers and hooks. It has a head (scolex) outfitted with four suckers and a double crown of hooks, a narrow neck and a large body (strobila) that measures 2–4 metres and is composed of several hundreds of units (proglottides).

Disposition of Gravids

Gravid proglottides are frequently detached from the distal end of the worm and are excreted in the faeces. Each proglottid contains as many as 50,000–60,000 fertile eggs, which can remain viable for a long time in water, soil and vegetation. In places with deficient disposal of human faeces, pigs may ingest stools contaminated with *T. solium* eggs.

The Larval Stage (Intermediate Host-Pig)

Once ingested by the pig, the invasive oncospheres (embryos) in the eggs are liberated by the action of gastric acid and intestinal fluids and actively cross the bowel wall, enter the bloodstream, and are carried to the muscles and other tissues where they develop into larval vesicles or cysticerci.[42]

Ingestion of Larvae by Humans

When humans ingest undercooked pork meat infected with cysticerci, the larva evaginates in the small intestine, its scolex attaches to the intestinal mucosae and it begins forming proglottides.

Humans are Accidental Intermediate Host

Humans act as intermediate hosts for *T. solium* by accidental ingestion of *T. solium* eggs, leading to development of cysticercosis.[40]

The mechanism by which eggs cross the bowel wall and lodge in human tissues is the same as that described in pigs.

Pathogenesis

The main sources from which humans acquire cysticercosis are ingestion of food contaminated with *T. solium* eggs and fecal-oral contamination in tapeworm carriers.[44] In addition, poor hygienic practises in food handling by *T. solium* carriers represent a threat to their communities. Improperly cooked vegetables or improperly washed salads represent an important source of contamination.

The cysticerci are fluid-filled vesicles consisting of two main parts: (1) the vesicular wall and (2) the scolex (Fig. 2). The vesicular wall is a membranous structure composed of three layers: (1) an outer or cuticular layer;

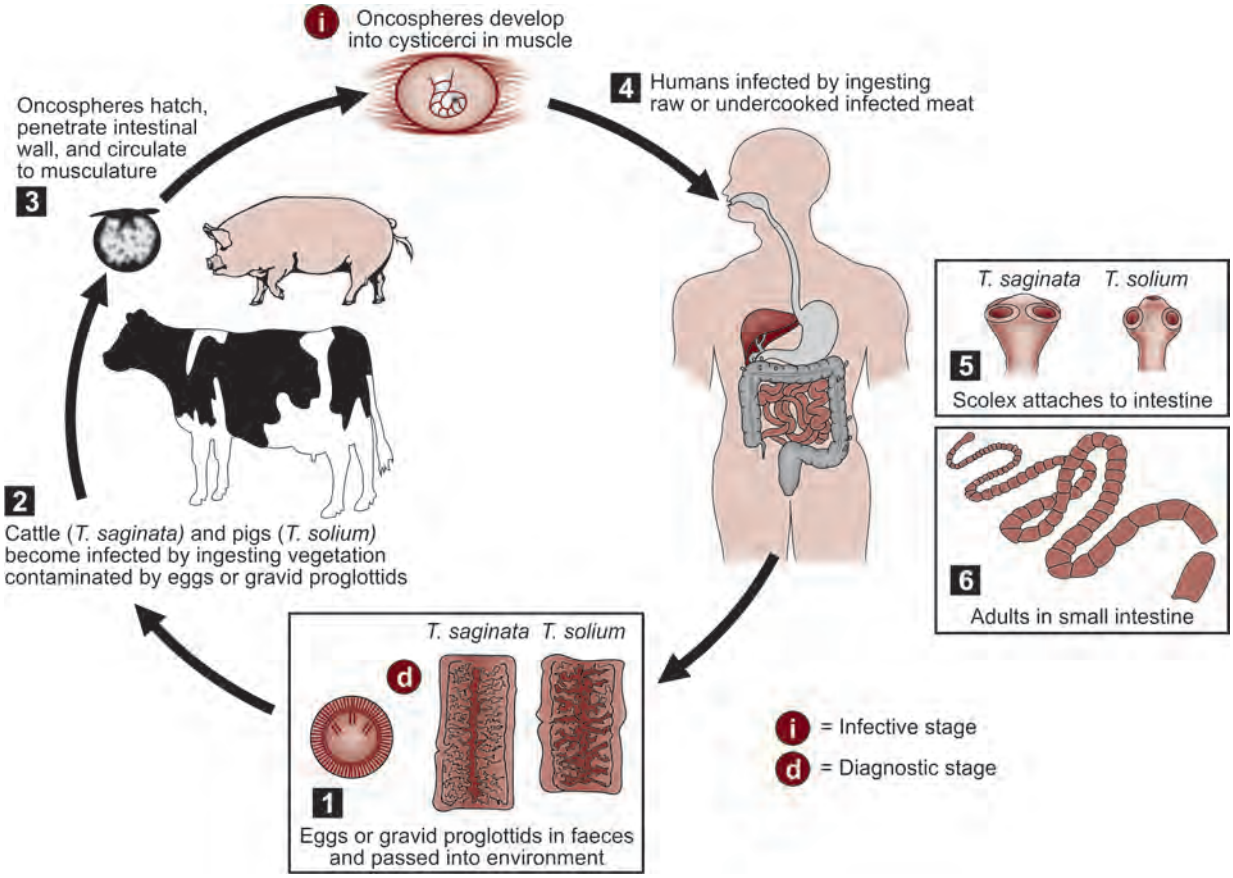


Fig. 1: Life cycle of *T. solium* (pig tapeworm) and *T. saginata* (cattle tapeworm). Note: Humans normally behave as definitive hosts by lodging the adult worms. However, either by regurgitation of eggs, igestion of food contaminated with cysticercal eggs or by orofecal contamination, they become accidental intermediate hosts and develop cysticercosis

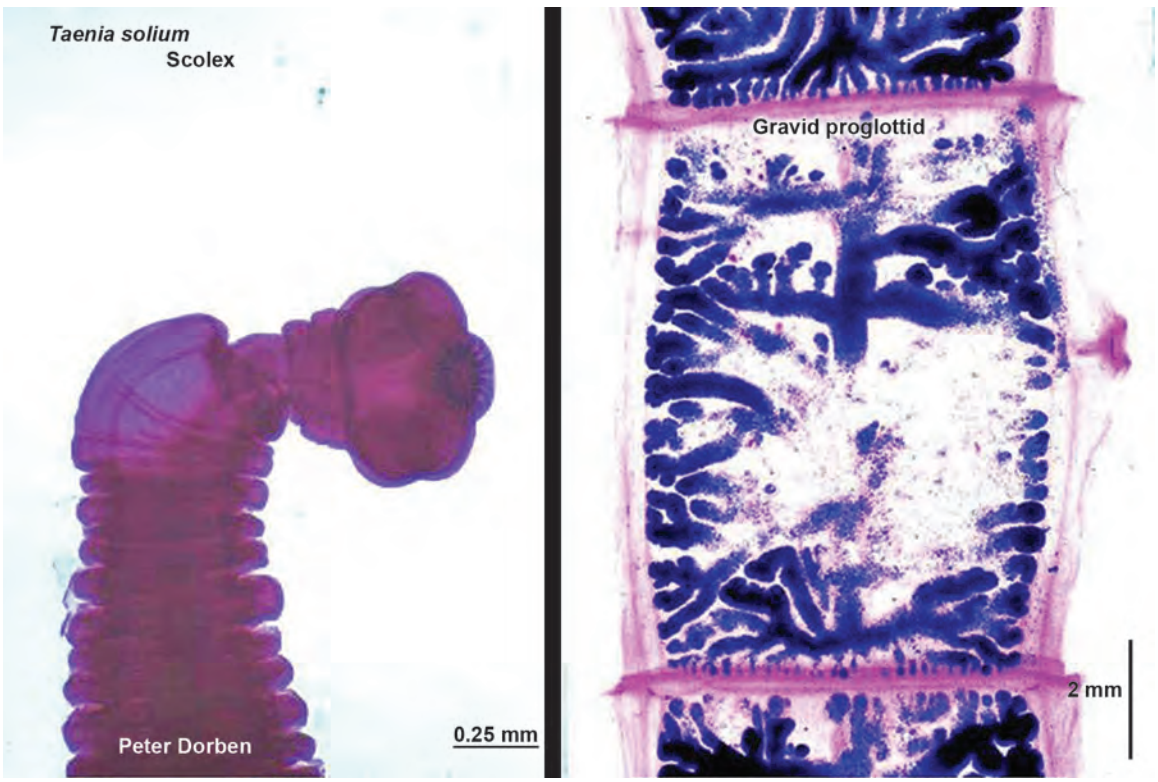


Fig. 2: Microscopic section of the scolex of *T. solium* and gravid proglottides

(2) a middle or cellular layer with pseudoepithelial structure and (3) an inner or reticular layer.[37] The invaginated scolex has a head or rostellum armed with suckers and hooks and a rudimentary body or strobila that includes the spiral canal.

Cysticerci in the brain parenchyma are usually small and tend to lodge in the cerebral cortex or the basal ganglia. These cysts rarely measure more than 10 mm because the pressure of the brain parenchyma usually does not allow further growth of the cyst, but giant cysticerci have been described.[103] The most common location of *subarachnoid cysticerci* are the Sylvian fissure and the basal cisterns.

Ventricular cysticerci may be small or large are usually single, and may or may not have a visible scolex. They may be attached to the choroid plexus or may be freely floating in the ventricular cavities. The most common location of these cysts is the fourth ventricle, although they may also be found in the third and lateral ventricles. Intraventricular cysts tend to acquire large size (Wani et al. 1981) (Fig. 3).

Spinal cysticerci may be intramedullary or located in the subarachnoid space, and their morphology is similar to those cysts located in the brain.[37]

Cysticerci located in the basal CSF cisterns may undergo a disproportionate growth of their membrane, with extension processes attached to each other, which tend to gather in clusters resembling a bunch of grapes (*racemose cysticercosis*)[7] In these cases, the scolex is frequently absent and cannot be identified even after microscopic examination. It is believed that their scolex regresses as the result of a hydropic degenerative process[78] resulting from the availability of space or the continuous entrance of CSF into the vesicles. It is a common practise to refer to cysts that have a scolex as *Cysticercus cellulosae*, and those without a scolex as *Cysticercus racemosus*; however, such terminology may create confusion because they are both forms of the same parasite—*T. solium*—and commonly coexist in the same patient.

Stages of Involution of Cysticerci

After entering the CNS, cysticerci are in a vesicular stage in which the parasites are viable and elicit little inflammatory changes in the surrounding tissues. Cysticerci may remain for a long time in this stage because the host develops a state of immune tolerance to the parasites, caused by active immune evasion mechanisms of the cysticerci. After a variable and undetermined time (estimated to be several years on the basis of the classic epidemiological studies in English soldiers returning from India),[33] cysticerci enter, as the result of immunologic attack from the host, a process of degeneration that ends with the death of the parasite. This continuation of involution has been classified by Escobar into four stages which these cysticerci pass through in this degenerative process, namely: *viable; colloidal; granular nodular* and *nodular calcified cyst*.[37] Each stage of development is characterised by specific changes in the parasite and in the surrounding brain parenchyma as well as with a distinctive appearance on radiological studies (Bhargava 1983).

Pathologic Changes in the Central Nervous System

NCC may lead to multiple of pathologic lesions in the CNS. Apart from the diversity in number, location, size and shape of parasites, the inflammatory reaction around cysticerci usually induces various changes in the brain parenchyma, meninges, cerebral ventricles and spinal cord.

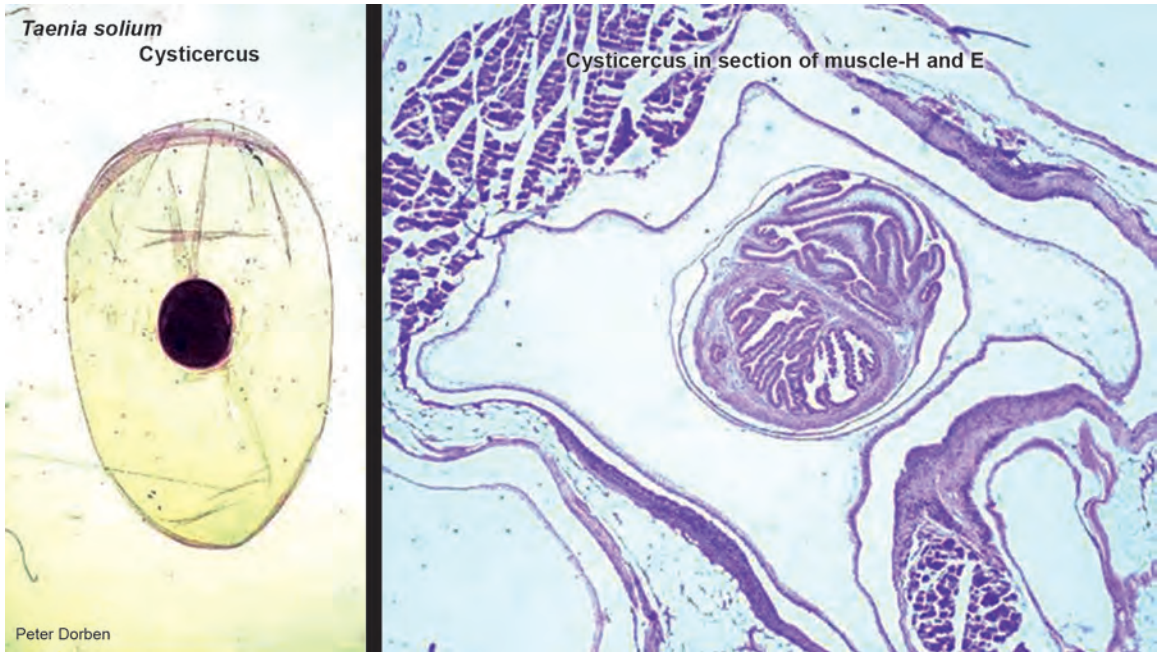


Fig. 3: Section of muscle showing the parasite impregnated within it

Parenchymatous

The inflammatory reaction surrounding parenchymal brain cysticerci is mainly composed of lymphocytes, plasma cells and eosinophils, and is usually associated with some degree of oedema and reactive gliosis, and varies according to the stage of development of the cysticerci.

Massive cerebral infections may cause an encephalitic picture (*cysticercotic encephalitis*) because of overwhelming inflammation around many parasitic cysts, a syndrome that occurs more frequently at younger ages and in women.[85] In contrast, some patients may tolerate hundreds of intraparenchymal cysticerci with only minimal symptoms.[45] In the latter presentation, infestation with the adult tapeworm is frequently found. In some of these cases, intraparenchymal or subarachnoid cysticerci may occasionally grow to exaggerated dimensions, with diameters that may reach 10 cm or more ("giant" cysticercosis).[103] In such cases, symptoms result from the mass effect exerted by the parasite.

Single small enhancing lesion (SSEL) is the commonest form of NCC in India.[94] It commonly presents with simple partial, partial complex, simple partial with secondary generalisation or generalised seizures. Tuberculous granuloma, microabscess, focal meningoencephalitis, postictal enhancement, neoplasm and vascular lesion should be considered in the differential diagnosis.[81–83] Chandy et al.[15] showed that 12 out of 15 patients with SSELs proved to be cysticercosis.

Meningeal

Meningeal cysticerci elicit an intense inflammatory reaction in the subarachnoid space, with formation of a dense exudate composed of collagen fibres, lymphocytes, multinucleated giant cells, eosinophils and hyalinised parasitic membranes. This causes abnormal thickening of the leptomeninges at the base of the skull, from the optochiasmatic region (*optochiasmatic arachnoditis*) to the foramen magnum. The optic chiasm and cranial nerves arising from the ventral aspect of the brainstem are usually entrapped in this dense exudate, leading to visual field defects and other cranial nerve dysfunction. Luschka's and Magendie's foramina may be occluded by the thickened leptomeninges, with the subsequent development of hydrocephalus. Blood vessels, mainly those arising from the circle of Willis, may also be affected by this inflammatory reaction. The walls of small penetrating arteries are invaded by inflammatory cells, leading to a proliferative endarteritis with occlusion of the lumen (*cysticercal vasculitis*). In addition, large vessels may be occluded by atheroma-like deposits resulting from disruption of the endothelium; this vascular involvement may result in the development of a *cerebral infarct*.[10] For some unexplained reasons, this type of pathology is very common in patients from Latin America and Mexico, as well as is also seen very infrequently in India.

Table 1: Causes of hydrocephalus

1.	Direct obstruction by intraventricular cysts
2.	Cysticercal meningitis
3.	Ependymitis (obstructive by granular proliferations and communicative by reducing absorption)

Intraventricular and Subarachnoid

This form of NCC is seen in 15–54% of cases (Table 1).[3,64] The oncosphere reaches the ventricular cavity by way of the choroid plexus. It migrates through the ventricular system, occluding vital communication corridors causing acute episodes of ventriculomegaly with sudden death or mass effect with focal compression. Thirty-eight per cent of patients are present with rapid clinical deterioration. Larval death initiates ependymitis and occlusion of ventricular outlets producing hydrocephalus.[3,63,100] This form has a rapidly progressive clinical course demanding prompt action. It tends to occur in isolation in the majority of cases; however, parenchymatous disease may be associated in 24%.[112] The fourth ventricle is the commonest site (53%) followed by third ventricle (27%), lateral ventricle (11%) and the aqueduct (9%). Isolated cystic lesions within the lateral ventricle are mobile (migratory) and transventricular migration is usually towards the fourth ventricle due to the effects of gravitational forces favouring migration of the cyst from superior cavities to inferior ones (Wani et al. 1982). This results in entrapment of cyst in the fourth ventricle due to the small size of foraminae of Luschka and Magendie. Ventricular entrapment may occur secondary to ependymitis causing a double compartment syndrome.[3]

Spinal

This form occurs in 1.6–13% of cases with NCC. The clinical features depend upon site of lodgement of parasite. Two forms of spinal NCC are recognised.

Leptomeningeal (Extramedullary) form: It is 6–8 times more common than the intramedullary form. This occurs by downward migration of larva from the cerebral to the spinal subarachnoid space.

Intramedullary form: This form is uncommon. It occurs through haematogenous spread. The parasite commonly lodges in the thoracic spinal cord according to the percentage distribution of blood flow to the spinal cord.[20,92]

EPIDEMIOLOGY

NCC is the most common parasitic disease of the CNS and a rather frequent neurological disorder in many countries of Latin America, Africa and Asia. In addition, massive immigration of people from endemic to non-endemic areas has caused a recent increase in the number of cases of NCC in some developed nations where this condition was considered eradicated.[91,110] According to the World Health Organisation (WHO), more than 2 million people harbour the adult tapeworm and many more are infected with cysticerci.

T. solium carriers are infective sources of cysticercosis, endangering everyone coming into contact with them. Indeed, epidemiological studies suggest that almost every newly diagnosed patient with cysticercosis has been infected by someone harbouring *T. solium* in the patient's close environment. In endemic areas, NCC accounts for 10–12% of all hospital admissions to neurology departments. In addition, this disease is a major cause of epilepsy in developing countries, where the prevalence of active epilepsy is almost twice at Western countries (Ahuja and Mohanta 1982). NCC is an important public health problem: it affects people of productive ages and causes an estimated 50,000 deaths every year, and many times that number of patients is left with irreversible brain damage.[105]

Neurocysticercosis in Developing Countries

With the possible exception of Chile, Argentina and Uruguay, all Latin American countries are endemic for cysticercosis. Studies from Mexico, Peru and Ecuador documented that up to half of patients with adult-onset seizures had evidence of NCC by neuroimaging studies and that NCC is a leading cause of hospital admissions and neurosurgical procedures.[26,45] Among these, Mexico and Peru are the countries where the disease has been more extensively studied. Necropsy studies from general hospitals have shown that the prevalence of NCC in Mexico ranges from 2.5 to 3.6%.[26] Major studies have documented a high prevalence of infection throughout Latin America, especially in Brazil,[4] Colombia[74] and Ecuador,[24] where NCC is also a leading cause of seizure disorders. The endemia of cysticercosis in Latin America is related to the poor socioeconomic conditions of the inhabitants and the lack of public awareness about the nature of this disease, its form of transmission and the harm that it produces in human beings.

The endemia of cysticercosis in Asia and Africa is mainly related to the religious practises of their inhabitants. As the Quran prohibits the consumption of pork, taeniasis and cysticercosis are almost unknown conditions in Muslim regions of Asian countries. On the other hand, NCC is endemic in areas where pork is massively consumed under poor hygienic conditions, such as in most sub-Saharan African countries,[36] in India[109] and in several other countries of Southeast Asia. Whereas in some of these countries NCC is a common disease, its prevalence is still underestimated due to the lack of diagnostic facilities in rural areas where the cases reported actually represent the "tip of the iceberg".

This disease was uncommon in developed nations till recently. However, cases of NCC are now being reported more commonly with influx of emigrant population.[56,64,72]

Cysticercosis in India

The disease is widely prevalent in India, but the exact incidence is not known as no major epidemiological study has been carried out. The first reported case is attributed to Krishnaswami in 1912.

Solitary cysticercus granuloma[62,107] accounts for 60% of NCC cases reported from India,[79] and have also been described in other regions of the world where this disease is endemic.[31,71] A relationship between NCC and Japanese encephalitis has been suspected, the former predisposing to the latter (Liu et al. 1957). An autopsy study reported from Bangalore found 33% cases of Japanese encephalitis having coexistent cerebral cysticerci (Shankar et al. 1983).

CLINICAL MANIFESTATIONS

Clinical manifestations of NCC are varied and nonspecific, and recognition of a typical syndrome is not possible.[24,26,27,72] This pleomorphism is related to individual differences in the number, size and topography of lesions and in the severity of the host's immune response to the parasites (Shankar et al. 1994). Epilepsy is the most common form of presentation of NCC and usually represents the primary or sole manifestation of the disease. Seizures occur in 50–80% of patients with parenchymal brain cysts or calcification, but are less common in other forms of the disease.[26,27,45,47] In endemic regions, the presence of recent-onset seizures in otherwise healthy middle-aged individuals is highly suggestive of NCC.[4,24,47]

Most of these patients have normal neurological examinations. In general examination, it is important to look for any subcutaneous, submucosal, subconjuctival or intramuscular swellings (Fig. 3). The routine practise of neuroimaging and serological studies in every patient with adult-onset epilepsy is mandatory to confirm or exclude the diagnosis of NCC.

A variety of focal neurological signs have been described in patients with NCC, particularly in those with strategically located parenchymal brain cysts and in those with large subarachnoid cysts[28] (Ahuja et al. 1978). Pyramidal tract signs, sensory deficits, cerebellar ataxia, signs of brainstem dysfunction and involuntary movements are among the most common focal signs observed in patients with NCC. These manifestations usually follow a subacute or chronic course, making the differential diagnosis with neoplasms or other infections of the CNS difficult on clinical basis alone. Focal signs may also occur abruptly in patients who develop a cerebral infarct as a complication of subarachnoid NCC.[10] Such infarcts are usually small and induce lacunar syndromes (ataxic hemiparesis or pure motor hemiparesis), although large infarcts associated with severe neurological deficits have also been reported in this setting.[29]

A number of patients with NCC present with increased intracranial pressure that may be associated with seizures, focal neurological signs or dementia. Hydrocephalus, related to cysticercotic arachnoiditis, granular ependymitis or ventricular cysts, is the most common cause of this syndrome.[39] In these cases, intracranial hypertension has a subacute onset and a slowly progressive course that may be punctuated by episodes of sudden loss of consciousness related to movements of the head (Bruns' syndrome) when

the cause of hydrocephalus is a fourth ventricle cyst.[89] Increased intracranial pressure also occurs in patients with giant cysts and in patients with cysticercotic encephalitis. The latter is a particularly severe form of NCC that occurs as the result of a massive cysticercus infection of the brain parenchyma inducing an intense immune response from the host resulting in severe brain oedema and raised intracranial pressure. This condition is more frequent among children and young women and is characterised by a clinical picture of subacute encephalitis associated with clouding of consciousness, seizures, diminution of visual acuity, headache, vomiting and papilloedema.[85]

Clinical manifestations of spinal NCC are also nonspecific, and the differential diagnosis with other diseases of the spinal cord is not possible on clinical grounds alone. Arachnoiditis is characterised by root pain and weakness of subacute onset, and cysts in the cord parenchyma usually present with motor and sensory deficits that vary according to the level of the lesion.[9] The various clinical manifestations of NCC are depicted in Table 1.

RADIOLOGICAL INVESTIGATIONS

Plain X-rays of muscles and skull may show cigar-shaped calcification. In the CT scan, single or multiple, variable sized, low density rounded cystic lesions with a small hyperdense eccentric mural nodule (spot) representing the scolex giving a "starry night" effect in the parenchyma, are suggestive of NCC. Ring enhancement occurs either due to inflammatory reaction or granuloma formation. Perilesional oedema is seen around dying cysts. The ventricles look small and throttled. The encephalitic variety shows extensive oedema (Bhargava 1983). Degenerated cysts are seen as single or multiple pin head size calcified dots without preferential localisation. Additional extracranial cysts in the temporalis or nuchal muscles with a honeycomb appearance may be seen.[108]

Plain and intravenous contrast CT may not delineate an intraventricular cyst. It demonstrates hydrocephalus and a round enlargement of the fourth ventricle. Ventricular or periventicular enhancement suggests ependymitis. In cases of hydrocephalus, contrast CT ventriculography is required for localisation of CSF obstruction and to confirm the actual presence of the parasite. This may be performed by intrathecal injection of contrast. A regular rounded filling defect similar to an inverted cup suggests the presence of a cyst. CT scan performed in different positions may define its mobility in addition,[89] whereas a cul-de-sac suggests inflammatory obstruction. A cyst within the third ventricle may mimic a colloid cyst.[21,70]

MR imaging is quite specific (Fig. 4). The number, clumps, multiplicity and additional cysts in other locations are well delineated by this non-invasive diagnostic tool. It differentiates the various stages of evolution, i.e. live, dying and calcified cyst.[58] These are described here in detail. Fluid in live cysts parallels CSF in its intensity. The scolex appears as a mural nodule of high-signal intensity on T1 and low-signal intensity on T2 weighted images like a hole with a dot or pea-in-a-pod. There is no perilesional oedema at this stage.[102] In a degenerated cyst, the fluid becomes turbid (colloid vesicular stage) appearing as high-signal intensity in the T1 image. In the granulonodular stage on gadolinium injection, ring enhancement (isointense on T1 and hypointense on T2 image) occurs and there is a variable degree of perilesional oedema. However, calcified cysts are better delineated by CT scan. The racemose type cysts are seen as large lobulated cysts without a scolex, whereas the cellulose type contains a scolex inside a vesicle. An intraventricular cyst is well delineated with a small metacystode inside the cysts.[50] Abnormal enhancement after gadolinium suggests ependymitis and ventricular entrapment.[76] MRI is useful on follow-up to see the disappearance or reduction in the number and size of cysts in patients on treatment.

The degeneration occurs via a sequence of events, which may be differentiated with MR imaging studies:[73]

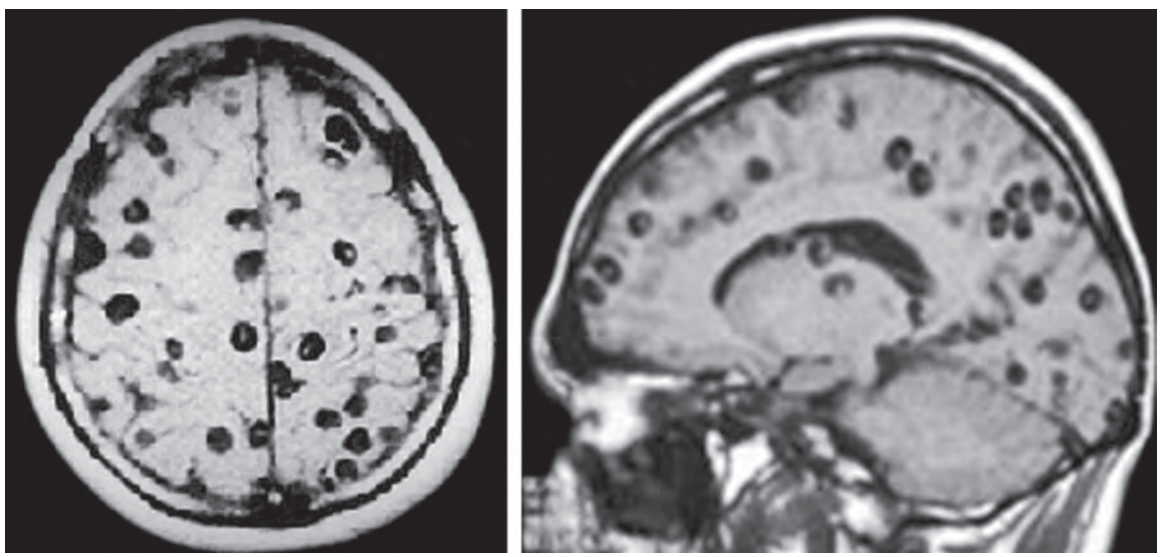


Fig. 4: MR imaging, axial and sagittal sections, T1 sequence showing severe infectation by the parasite

1. *Vesicular stage (active, live or developing cyst form)*: This presents as a fine, brittle, translucent membrane of uniform thickness with a small denser area corresponding to the scolex and containing colourless transparent fluid similar to CSF intensity on MRI. The scolex appears as a mural nodule of high-signal intensity on T1 and low-signal intensity on T2 sequences like a hole or pea-in-a-pod. There is no perilesional oedema. This type of cysticercosis cellulosae is common in the brain parenchyma. Cysticerci developing in the ventricle and subarachnoid spaces reach a larger size without a scolex, with a membrane of irregular thickness and usually clustered in multiple vesicles like raceme called cysticercus racemosus.
2. *Colloid stage (degenerating cyst)*: The membrane becomes thick and opaque and clear fluid is replaced by whitish gel appearing as high-signal intensity on T1 weighted images.
3. *Granular stage*: The gel undergoes calcium deposition. Ring enhancement occurs after gadolinium injection and there is variable degree of perilesional oedema.
4. *Calcified stage*: This appears as hypo-intensities on both T1 and T2 sequences.

DIAGNOSIS

Diagnosis of NCC is made when there is history of exposure in an endemic area, positive stool examination, peripheral blood or CSF eosinophilia, CSF lymphocytosis, positive immunological tests in blood and CSF, viz. Complement fixation test (CFT), Enzyme-linked immunosorbent assay (ELISA) and Enzyme linked immunoelectrotransfer blot assay (EITB).[18,42,45]

NCC is a common disease, but its diagnosis remains problematic. The most common clinical manifestations—seizures, headache and focal deficits—may be caused by a variety of neurological conditions. Neuroimaging studies are usually abnormal but, in most cases, not pathognomonic. Serological tests have been developed to support the diagnosis. However, older tests had low specificity and current assays have decreased sensitivity in patients with single lesions.[80,86] In 1996, Del Brutto, Rajshekhar and a panel of experts from various centres proposed certain diagnostic criteria for cysticercosis, based on the objective evaluation of clinical, radiologic, immunologic and epidemiologic data.[52] Whereas these criteria have proven useful in the diagnosis of this parasitic disease, concern has been raised about the specificity of some of them.[13,52,90] In 2001, a more simplified and comprehensive criteria[25] was proposed as the earlier one was more for patients (apart from nervous system cysticercosis) with exclusively muscular or cutaneous cysticercosis. These criteria are clinically more relevant as cysticercosis outside the nervous system rarely produces manifestations and is usually not relevant clinically. These criteria are shown in Table 2.

Table 2: Revised diagnostic criteria for neurocysticercosis

Categories of Criteria	Criteria
Absolute	1. Histological demonstration of the parasite from biopsy of a brain or spinal cord lesion
	2. Cystic lesions showing the scolex on CT or MRI
	3. Direct visualisation of subretinal parasites by funduscopic examination
Major	1. Lesions highly suggestive of neurocysticercosis on neuroimaging studies*
	2. Positive serum EITB† for the detection of anticysticercal antibodies
	3. Resolution of intracranial cystic lesions after therapy with albendazole or praziquantel
	4. Spontaneous resolution of small single enhancing lesions‡
Minor	1. Lesions compatible with neurocysticercosis on neuroimaging studies§
	2. Clinical manifestations suggestive of neurocysticercosis‖
	3. Positive CSF ELISA for detection of anticysticercal antibodies or cysticercal antigens
	4. Cysticercosis outside the CNS ¶
Epidemiologic	1. Evidence of a household contact with *T. solium* infection
	2. Individuals coming from or living in an area where cysticercosis is endemic
	3. History of frequent travel to disease-endemic areas

ELISA = Enzyme-linked immunosorbent assay

*CT or MRI showing cystic lesions without scolex, enhancing lesions or typical parenchymal brain calcifications.
†Enzyme-linked immunoelectrotransfer blot assay using purified extracts of *T. solium* antigens, as developed by the Centres for Disease Control and Prevention (Atlanta, GA).
‡Solitary ring-enhancing lesions measuring less than 20 mm in diameter in patients presenting with seizures, a normal neurological examination, and no evidence of an active systemic disease.
§CT or MRI showing hydrocephalus or abnormal enhancement of the leptomeninges, and myelograms showing multiple filling defects in the column of contrast medium.
‖Seizures, focal neurologic signs, intracranial hypertension and dementia.
¶Histologically confirmed subcutaneous or muscular cysticercosis, plain X-ray films showing "cigar-shaped" soft-tissue calcifications, or direct visualisation of cysticerci in the anterior chamber of the eye

As in the original publication,[25] the revised criteria include four categories—absolute, major, minor and epidemiologic—so are classified on the basis of their individual diagnostic strength (Table 2). *Absolute criteria* allow unequivocal diagnosis of NCC, *major criteria*

Table 3: Degrees of certainty for the diagnosis of neurocysticercosis

Diagnostic Certainty	Criteria
Definitive	1. Presence of one absolute criterion
	2. Presence of two major plus one minor and one epidemiologic criterion
Probable	1. Presence of one major plus two minor criteria
	2. Presence of one major plus one minor and one epidemiologic criterion
	3. Presence of three minor plus one epidemiologic criterion

The presence of two different lesions highly suggestive of neurocysticercosis on neuroimaging studies should be considered as two major diagnostic criteria. However, positive results in two separate types of antibody detection tests should be interpreted only on the basis of the test falling in the highest category of diagnostic criteria

Adapted from reference [57]

strongly suggest the diagnosis but cannot be used alone to confirm the disease, *minor criteria* are frequent but non-specific manifestations of the disease and *epidemiologic criteria* refer to circumstantial evidence that favour the diagnosis of cysticercosis.

The revised criteria are simpler, containing only definitive and probable diagnosis as the diagnostic guidelines (Table 3).[25] A brief description of each criterion is provided here.

Absolute Criteria

Histological Demonstration of the Parasite from Biopsy of a Brain or Spinal Cord Lesion

Visualisation of the scolex with its suckers and hooks, or the presence of parasitic membranes in the histologic sections confirms the diagnosis.[75] However, biopsy of calcified cysticerci only may not confirm the diagnosis, as the characteristic scolex or the membranes are not seen in this.

Cystic Lesions Showing the Scolex on CT or MRI

A large number of imaging findings have been described for NCC (Fig. 4). From these, only the presence of cystic lesions along with a scolex should be considered pathognomonic.[35] The scolex is visualised as a bright nodule within the cyst. This produces the so-called *"hole-with-dot"* imaging that is seen in some vesicular cysts located in the brain parenchyma, the subarachnoid space or the ventricular system.[60] This finding is more clearly seen on MR images.

Direct Visualisation of Subretinal Parasites by Funduscopic Examination

Because the retina is considered part of the CNS, patients with subretinal cysticerci may be considered to have NCC. This, however, does not apply to patients with cysticerci in the anterior chamber of the eye. Subretinal cysts are usually located over the macula and have a yellowish colour with a central dark spot corresponding to the scolex. Subretinal cysticerci may rupture the retinal layers and enter the vitreous. In such a situation *in vivo* evagination and invagination movements of the parasite may be observed and is considered confirmative of CNS cysticercosis.[65]

Major Criteria

Lesions Highly Suggestive of NSS on Neuroimaging Studies

Among a myriad of imaging features, only a few have been described to be highly suggestive. These include: cystic lesions without a scolex, single or multiple ring or nodular enhancing lesions and parenchymal round calcifications. Such CT and MRI findings may also be observed in other diseases of the CNS and must be interpreted with caution to avoid over diagnosis of NCC, particularly in HIV-infected patients or in those with evidence of a systemic disease.[25,74] A common neuroimaging finding in NCC is the presence of intracranial lesions in different evolutive stages, i.e. calcifications and cystic or ring-enhancing lesions.[27]

Positive Serum Enzyme-Linked Immunoelectrotransfer Blot Assay (EITB) for the Detection of Antibodies to T. Solium Glycoprotein Antigens

Although many serologic assays for human cysticercosis have been reported, most of them are limited in value due to poor sensitivity and specificity. Only tests based on detection of antibodies specific for *T. solium* antigens are reliable for clinical diagnosis and epidemiological studies. To date, these are limited to those based on the use of purified glycoprotein antigens derived from *T. solium* cysticerci. The current assay of choice is EITB using partially purified antigenic extracts.[104] This assay has been documented to have a specificity approaching 100% and a sensitivity of 94–98% for patients with two or more cystic or enhancing lesions. A major weakness of this test is frequent false negative results in patients with single intracranial cysticerci, in which fewer than 50% test positive. The detection of antibodies to antigens of 26 kDa and 8 kDa by immunoblot using a crude antigenic preparation of *T. solium* cysticerci has been shown to approach 100% specificity.[55] This assay has been less extensively assessed than that using purified *T. solium* glycoproteins described previously, but has the potential advantage of the antigen preparation being simpler. The results need to be interpreted with more care, however, due to the presence of a number of non-specific interactions with antigens with molecular weights close to those of the specific antigens. This assay is less sensitive than the glycoprotein based antigen EITB.[87]

Spontaneously Resolving Small Single Enhancing Lesions

Single enhancing lesions may occur in several infectious and neoplastic diseases of the CNS. However, Rajshekhar and Chandy[78] demonstrated that when those lesions fulfil a rigid set of clinical and radiological criteria, the diagnosis of NCC can be established with a sensitivity of 99.5% and a specificity of 98.9%. Solitary cysticercus granulomas measure less than 20 mm in diameter may be associated with oedema not severe enough to displace the midline, and occur in patients with seizures, a normal neurological examination and no evidence of an active systemic disease. When those lesions resolve spontaneously, either disappearing or transforming into a calcified nodule, the diagnosis of NCC is almost certain. Solitary cysticercus granuloma accounts for 60% of NCC cases reported from India[79] and have also been described in other regions of the world where this disease is endemic.[31,71] Care should be taken not to interpret resolution of an intracranial lesion with the use of steroids as definitively indicative of NCC, because other diseases that may present with similar neuroimaging findings are known to respond to steroid therapy.

Resolution of Intracranial Cystic Lesions after Therapy with Albendazole or Praziquantel

Several studies have shown that cysticidal drugs hasten the destruction of cysticerci[8,46,95] and the disappearance of intracranial cystic lesions or their transformation into calcified nodules after therapy with either albendazole or praziquantel should be considered as a strong factor favouring the diagnosis of NCC.

Minor Criteria

Lesions Compatible with NCC on Neuroimaging Studies

Some imaging features are not strong enough to be included in the major criteria.[74] They have thus been classified under minor criteria. These include CT or MRI showing hydrocephalus or abnormal enhancement of the leptomeninges and myelograms showing multiple filling defects in the column of contrast medium. So are multiple filling defects seen on myelogram suggesting presence of spinal subarachnoid cysts.

Clinical Manifestations Suggestive of Neurocysticercosis

Large series have shown that seizures, focal neurological deficits, increased intracranial pressure and intellectual deterioration are the most common clinical manifestations of NCC.[27,47,72,109] These features have thus been included under minor criteria. More than 70% of symptomatic patients develop seizures, which in many of these cases are the primary or sole manifestation of the disease.[4,24,26,45,74] Several studies have shown that NCC is the single most common cause of adult-onset epilepsy in developing countries, and the presence of recent onset seizures in an otherwise healthy middle-aged individual coming from an endemic area is highly suggestive of NCC.[4,24,74] Other clinical manifestations of the disease include focal neurological deficits, signs and symptoms of increased intracranial pressure and intellectual deterioration.[93]

Positive CSF Enzyme-Linked Immunosorbent Assay (ELISA) for Detection of Anticysticercal Antibodies or Cysticercal Antigens

The detection of anticysticercal antibodies by serum ELISA has been used for the diagnosis of cysticercosis in endemic regions.[16,88] However, recent studies have demonstrated a large number of false-positive and false-negative results.[84] In contrast, the detection of anticysticercal antibodies by ELISA using CSF was 87% sensitive and 95% specific, and remains a useful tool for the diagnosis of NCC in areas with limited access to the EITB assay.[75] However, this test may falsely be negative in patients with parenchymal brain cysticercosis or in those with inactive disease, and it may falsely be positive in other helminthic infections.[88] However, the specificity of this assay has not been adequately assessed on samples of patients with other diseases. Pending further experience with the use of this test, it should only be considered as a minor diagnostic criterion. Several other serodiagnostic tests have been proposed for immunodiagnosis of cysticercosis. These assays are not sufficiently well standardised at this time for inclusion as diagnostic criteria (Fig. 5).

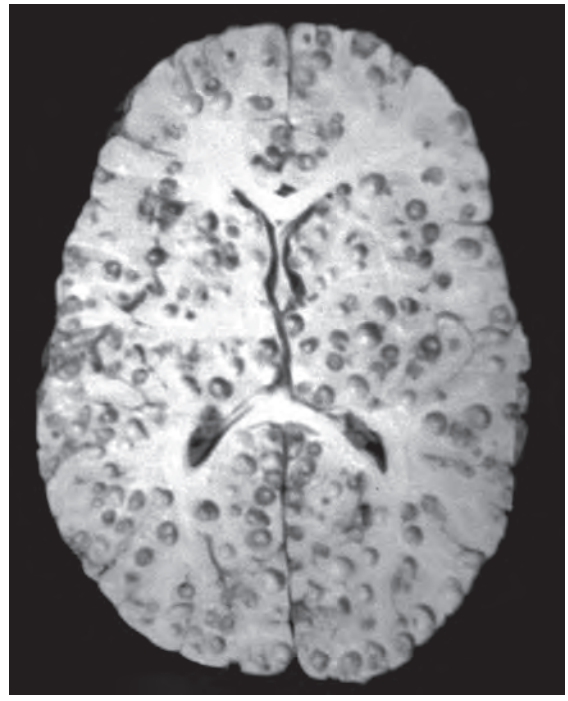


Fig. 5: Cut section of a brain showing heavily impregnated cysticercal cysts

Cysticercosis Outside the Central Nervous System

From the pioneering studies of McArthur[68] and Dixon and Lipscomb,[33] it was considered that the presence of soft-tissue calcifications or palpable subcutaneous cysticerci in a patient with seizures strongly suggests the diagnosis of NCC. This may be true, but in endemic regions a patient may have systemic cysticercosis and neurological manifestations due to an unrelated cause. Therefore, a probable or even a definitive diagnosis of cysticercosis outside the CNS only provides circumstantial evidence favouring the diagnosis of NCC. Definitive diagnosis of extraneural cysticercosis requires one of the following: (1) histological demonstration of the parasite from biopsy of a subcutaneous nodule; (2) plain X-ray films showing multiple "cigar-shaped" calcifications in thigh and calf muscles; (3) direct visualisation of a cysticercus in the anterior chamber of the eye or (4) positive EITB test. Since the latter is already considered a major criterion for the diagnosis of NCC, only the three previously enumerated findings should be included in this category of minor diagnostic criteria for NCC.

Epidemiologic Criteria

Epidemiologic data, including the place of birth, residence and travel history, provide important information when evaluating patients with suspected NCC. Cysticercosis is endemic in Latin America, sub-Saharan Africa and in some regions of Asia, including the Indian subcontinent, China, Korea and Indonesia. The disease is rare in most European countries, in North America, in Oceania and in some muslim countries of Asia and Africa.[2] However, in these areas, it may occur in the immigrant population. Clinicians must be aware that NCC is an infection acquired from a human tapeworm carrier and the disease is sometimes diagnosed in persons born in non-endemic countries who have never travelled to endemic regions.[14,91] In such cases, it is of value to search for a close contact—usually a household contact—with a tapeworm infection. This finding will support the diagnosis of NCC in a patient with suggestive clinical, radiological and immunological criteria and, by treating the tapeworm carrier, will permit the elimination of the source of contagion. A definitive diagnosis of *T. solium* infection can only be established when the scolex or a gravid proglottid is available for microscopic examination.[42] A probable diagnosis can be suspected in those with history of having passed proglottids in faeces as well as in those with positive stool examinations for *Taenia* eggs or with a positive coproantigen test.[1] These latter criteria should only be considered as probable indicators of *T. solium* infection because they may represent an infection with *Taenia saginata*. It may be pointed out that positive stool examination was an exception than a rule in proven cases of NCC.

TREATMENT

The mainstay of NCC is medical management. However, some cases do require some form of surgical intervention either to treat the pathology itself (e.g. cyst excision) or to treat the consequences of the pathology (e.g. hydrocephalus). NCC has been classified depending upon the location of cysts,[96] clinical presentation,[106] prognosis[38] and viability of cysts.[26]

Treatment of NCC principally consists of control of seizures, oedema and intracranial pressure followed by definitive treatment. This can be accomplished with both medical and surgical modalities, which are complementary to each other.

Medical Treatment

A brief review of medical treatment will be provided before dealing with the surgical aspects. Cysticidal drugs, namely albendazole and praziquantel, have been shown to be effective in all forms of NCC.[2,8,32,46,95]

Albendazole in a dose of 15 mg/kg/day for 8 days is reported to be more effective than praziquantel in a dose of 50–100 mg/kg/day for 15 days. The duration of treatment ranges 8–21 days and 1–30 days for albendazole and praziquantel, respectively. Recently, ultrashort single day therapy with praziquantel 75 mg/kg/day divided in three 25 mg/kg/doses each, given at 2 hourly intervals (7–9–11 AM) has been introduced.[8,46,95] Four hours later (3 PM), 10 mg dexamethasone intramuscular or 80 mg oral prednisolone is given followed by the same doses of steroids for the next three mornings. As the half life of praziquantel is 2–3 hours, a four-hour interval between praziquantel and anti-inflammatory treatment is without pharmacological conflicts. Steroids prevent secondary inflammatory reactions triggered by acute destruction of the parasite. Long-term steroid therapy depends on parasitic load and inflammation.[19] Wadia et al.[108,109] have cautioned against the use of cysticides in the disseminated variety. Such patients should be monitored in an intensive care unit and steroids and mannitol must be used to decrease the oedema along with cysticidal treatment.

Cysticides induce destruction of 96% of the parasites located in the brain parenchyma including giant or large clumps of cysts. In the intraventricular form, 80% of cysts completely disappear and another 10% decrease in size.[2,8,46,95] Prompt elimination of the cyst prevents chronic inflammation and granuloma formation (focus of epilepsy) around the cyst in the parenchymatous form and ependymitis and ventricular entrapment in the intraventricular form.[8]

If cystic lesions remain unchanged on repeat MRI, 1–2 months after praziquantel therapy, an additional course of praziquantel is given. However, in partial response to a cysticidal drug, administration of the other cysticide (albendazole 15 mg/kg/day in two divided doses for 8 days) is better than repetition of the same drug.[95,99]

Currently, albendazole 15 mg/kg/day for 2 weeks is the treatment of choice in patients with uncomplicated fourth ventricle NCC without hydrocephalus. Repeat albendazole therapy or an additional course of praziquantel 100 mg/kg/day for 2 weeks may be required in non-responders.[34,56] In patients with hydrocephalus, a ventriculoperitoneal shunt should be inserted and steroids in the form of dexamethasone 10 mg intramuscular or prednisolone 80 mg orally should be started prior to cysticidal treatment to reduce the risk of shunt block. Menezes et al. (1996)[70] reported that cysticidal treatment in the intraventricular form may be disastrous due to development of ventriculitis and recurrent obstruction of ventricular drainage system.

Corral et al. (1996)[20] successfully treated intramedullary spinal cysticercosis with cysticidal therapy. In the meningeal form, cysticidal treatment may only give marginal benefit and the prognosis is poor because of hydrocephalus, meningeal fibrosis and multiple brain infarcts secondary to vasculitis. In these patients, administration of 50 mg prednisolone three times a week is useful in preventing or diminishing chronic inflammation.[60,99]

Symptomatic Medical Therapy

Since most patients with NCC have seizures, antiepileptic drugs are frequently used. In patients with calcifications, the administration of standard doses of a single, first-line antiepileptic drug, e.g. phenytoin or carbamazepine, usually results in adequate control of seizures. Whether the control of seizures (always with antiepileptic drugs) in patients with viable parenchymal brain cysts is aided by antiparasitic therapy is still to be conclusively demonstrated. Prospective evidence is inconclusive,[12,69] whereas retrospective studies demonstrated a strong association between seizure control and the use of praziquantel or albendazole: seizures were adequately controlled in 83% of patients who received antiparasitic therapy but in only 27% of those who did not. The optimal length of antiepileptic drug therapy in patients with NCC has not been determined. Successful antiepileptic withdrawal is difficult to achieve. One prospective study showed that up to 50% of albendazole-treated patients had relapses after withdrawal of antiepileptic drugs, after 2 years free of seizures.[30] Prognostic factors associated with seizure recurrence included the development of parenchymal brain calcifications as the result of albendazole therapy and the presence of recurrent seizures and multiple brain cysts before the institution of antiparasitic therapy. In a large prospective study of patients with focal epilepsy due to antiepileptic drug alone was found to be adequate therapy. Additional of cysticial drug provided no statistically significant advantage.

Corticosteroids are also frequently used in patients with NCC. They are usually administered at the time of antiparasitic therapy to decrease neurological symptoms resulting from the death of the parasite. Also, steroids represent the primary form of therapy for cysticercotic encephalitis, where up to 32 mg/day of dexamethasone may be needed to reduce the brain oedema accompanying this condition.[27,85] Corticosteroids may be used alone or in association with mannitol at a dosage of 2 gm/kg/day. High doses of intravenous dexamethasone are also of value in the acute treatment of patients with cysticercotic angiitis to avoid the risk of recurrent cerebral infarcts[29] followed by chronic oral therapy with dexamethasone (10 mg/day) or prednisolone (50 mg/day) to ameliorate the inflammatory reaction in the subarachnoid space that initially caused the angiitis. The same protocol of chronic corticosteroid therapy may be followed in patients with diffuse cysticercotic arachnoiditis causing hydrocephalus and progressive entrapment of cranial nerves at the base of the brain. In both conditions, corticosteroids should be administered until the inflammatory reaction in the subarachnoid space subsides; serial cytochemical analysis of CSF determines the optimal time for corticosteroid withdrawal. Absolute indications for corticosteroid administration during antiparasitic drug therapy include the management of patients with giant subarachnoid cysticerci, ventricular cysts, spinal cysts and multiple parenchymal brain cysts. In most of these cases, corticosteroids must be administered before, during and even some days after the course of antiparasitic drugs to avoid the risk of cerebral infarcts, acute hydrocephalus, spinal cord swelling and massive brain oedema.

Surgery

In general, surgery is required when:

- The diagnosis is uncertain.
- Cysts exhibit tumour-like effect (oedema and/or mass effect) which are refractory to medical treatment.
- Hydrocephalus.
- Intraventricular cysticerosis is diagnosed.
- Presence of acute or sub-acute rise of ICP.

For parenchymatous type of cysticercosis, the following surgical approaches are recommended.[3,17,99,112]

Stereotactic excisional biopsy/open craniotomy and cyst removal is recommended in cases of a single giant cortical cyst or large clumps exhibiting tumour like behaviour, if the lesion is in a surgically accessible area, is producing progressive deficits or not responding to cysticidal therapy. This approach may also be used when diagnosis is uncertain, e.g. SSEL with atypical features, and worsening or not responding to cysticides or in cases of multiple lesions.

Supratentorial decompressive craniectomy/craniotomy/ lobectomy is undertaken when the pseudotumour type of oedema is refractory to medical treatment, particularly in the disseminated variety of the disease frequently seen in India.

For Intraventricular and subarachnoid forms of NCC, the surgical procedure usually used which includes a shunting procedure for managing hydrocephalus, cyst removal or excision through a posterior fossa craniotomy

for fourth ventricle/subarachnoid cysts and supratentorial open or stereotactic craniotomy for subarachnoid third or lateral ventricle cysts.

Endoscopic Excision

More recently, endoscopic excision has been advocated both for supratentorial and infratentorial intraventricular cysts. Endoscopic third ventricular cyst removal may be carried out very effectively using a rigid rod lens endoscope through a frontal burr hole. The foramen of Monro may be identified on entering the lateral ventricle by noting the presence of the choroid plexus and the thalamostriate vein. It is not uncommon in long standing hydrocephalus to find multiple perforations within the septum; hence it is important to identify the correct portal of entry into the third ventricle. It is usually not possible to remove the cyst *in toto*, and the cyst usually gets ruptured during removal. Some authors have hence advocated intraventricular injection of steroids to prevent an anaphylactic reaction.[5,22] In a recent review, Bergsneider et al.[6] have reported a series of 10 cases of intraventricular cysticercosis cysts presenting with hydrocephalus. Combined endoscopic removal of the cysts with a third ventriculostomy and/or a septal pellucidotomy gave excellent results. They have advocated endoscopic removal of cysts as the primary therapy of intraventricular cysticercosis and were able to avoid shunts. Endoscopic removal of fourth ventricular cysts has also been described.[6] This may be achieved by using a paramedian suboccipital burr hole as a portal of entry. In a small ventricle, a pre-operative ultrasound or image guided neuronavigation may be used to reach the fourth ventricle. Overall, endoscopic removal of cysts is a minimally invasive procedure, reduces blood loss and operative time and provides excellent visualisation of the anatomy.

Spinal Neurocysticercosis

For spinal cysticercosis, excision needs to be undertaken.[9] Intramedullary and clumped leptomeningeal cysts producing symptoms by mass effect and not responding to cysticidal drugs may be removed via laminectomy or laminoplasty. When diagnosis is in doubt, surgery also helps in obtaining a histopathological diagnosis.[20,92]

Surgery has been considered to be therapeutic procedure of choice for intraventricular cysticercosis (Figs 6A and B),[2,5,6,22,66] but successful treatment with cysticidal drugs in this location has raised some controversy. Proano et al.[76] now consider cysticidal drugs as the treatment of choice for uncomplicated intraventricular NCC without hydrocephalus. Surgical removal of the cyst prevents acute complications, like sudden death, and chronic complications like ventriculitis and ventricular entrapment.[2,22]

Excision of simple cysts in the absence of radiographic or surgical evidence of arachnoiditis or ependymitis may be performed with stereotactic localisation, craniotomy and microsurgical techniques. Madrazo et al.[67] proposed the pipette suction technique for atraumatic extraction of intraventricular NCC. Here they have devised a special long pipette, which may be attached to the cyst, and it may be removed without rupturing the cyst. Madrazo et al.[67] considered cyst rupture a dangerous event, whereas other do not share this view.[5,6,22,66] However, in all cases of intra-operative rupture large doses of glucocorticoids and vigorous intraventricular lavage with Ringer's lactate solution (at body temperature) is advocated. While selecting the surgical approach for intraventricular NCC, the surgeon should consider:[2,5,22]

- Presence of associated ependymitis with its implications in accomplishing complete excision of cyst and the need for a shunt.
- Presence of ventricular entrapment (double compartment syndrome).
- Potential of cyst migration with posture and frank transition from one ventricular cavity to the other.
- Potential for increase in size of the cyst with local mass effect.
- Potential for rapid clinical deterioration and/or sudden death.
- Potential for presence of additional cysts at other sites.
- Feasibility of stereotactic/endoscopic excision/aspiration in lateral and third ventricular cysts.
- Selection and institution of surgical approaches that establish alternative routes of CSF flow, e.g. fenestration of the septum pellucidum. Following surgical excision or shunt, cysticidal therapy may be given to take care of cysts present at other locations or for treating small intraventricular NCC not seen during surgery.

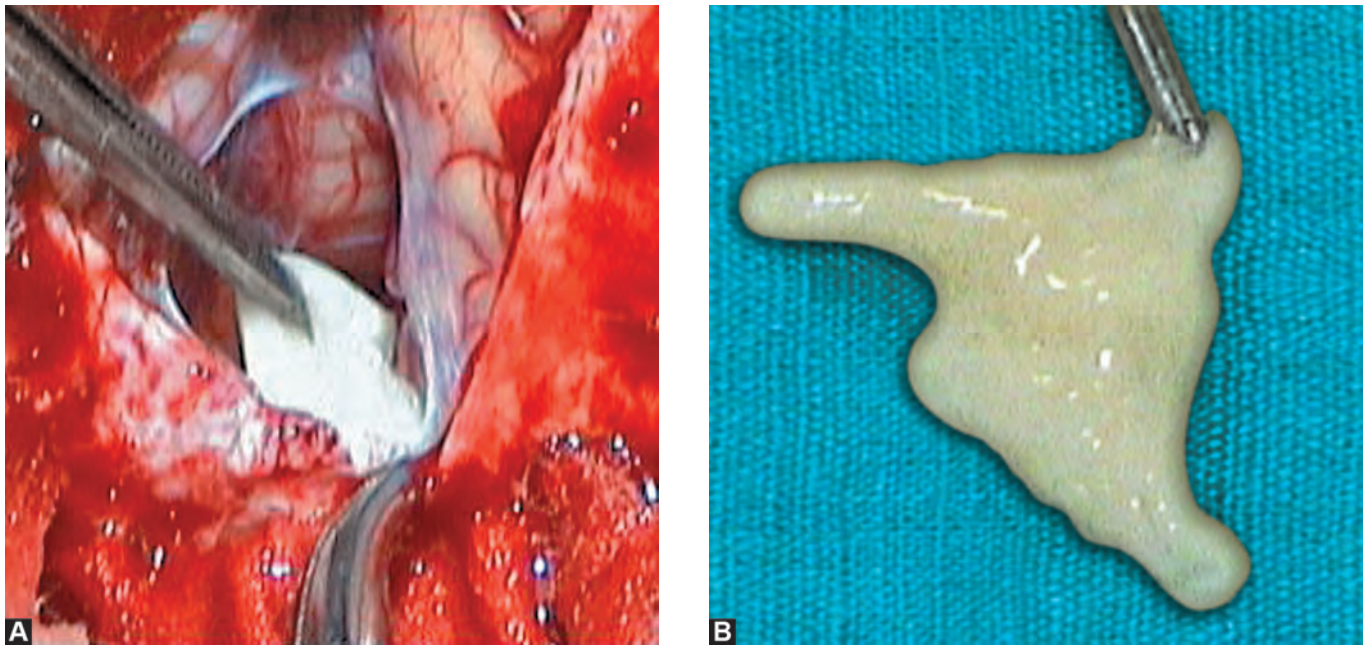
Shunt

Insertion of the ventriculoperitoneal shunt is indicated in the presence of hydrocephalus.[97] Shunt is associated with high percentage of complications like blockage and infection. Shunt obstruction rate is 50% within the first 4 months.[61,101] Intermittent long-term prednisolone therapy after V.P. Shunt reduces shunt malfunction and may improve the functional status of the patient.[102] Prednisolone is started within the first post-operative week in doses of 50 mg three times a week.

Sotelo et al.[94,98] introduced a new shunt system devoid of a valve mechanism with drainage capacity limited to physiological parameters of CSF production to avoid over-drainage and occlusion. This shunt system has shown to have 96% functional results.

PREVENTION AND CONTROL

Transmission of *T. solium* has largely been eliminated in developed countries by improving public sanitation and meat inspection. Due to economic reasons, this approach has consistently been failed in areas where pigs are raised by peasant farmers.[23,54]



Figs 6A and B: Intra-operative photographs showing removal of a fourth ventricular cysticercal cyst

The cycle of *T. solium* may be interrupted by intervening at the human level (tapeworm carriers—the only infective source for human and porcine cysticercosis) and at the pig level (infected pork—reservoir for human taeniasis). Tapeworm carriers play a key role in transmission of infection. Because they rarely have significant symptoms and are usually missed by routine stool examination, detection is often problematic. Stool examination to detect parasite antigen is more sensitive,[27] but is not widely available. A recently described serologic test for tapeworm carriers will enhance the detection of carriers.[111] Human infection with adult tapeworms is prevented by freezing or adequate cooking of measly pork.

Another important source of human cysticercosis is through fecal-oral contamination, and hygienic measures, such as adequate hand washing, proper education, periodical deworming, that reduce the risk are highly recommended.[52] Transmission through consumption of uncooked vegetables and fruits (e.g. use of improperly washed salads) is yet another source of contamination. Hence, eating salads or raw fruits from street side vendors should be avoided.

The introduction of oxfendazole as effective and cheap single-dose therapy for porcine cysticercosis permitted the design and execution of combined pig-human chemotherapy interventions.[51–53]

Apart from the control measure to be tested, monitoring the effect of an intervention requires the use of simple epidemiological indicators. Human seroprevalence is useful, but cannot be used easily to demonstrate changes in infection patterns, because antibodies to cysticercosis persist in man for years, even after successful treatment. Studies in Peru[43] have shown that infection in pigs, monitored by serology, is a useful indicator of both the prevalence of cysticercosis infection in a community and the changes in infection intensity over time.[111] Similarly, the rate of infection that occurs in uninfected (sentinel) pigs over time can be used to estimate the intensity of *T. solium* infection in the community.[51] In most cases, the prevalence of porcine infection correlates well with the prevalence of human cysticercosis. These indicators of porcine infection can be used to evaluate the effect of control programmes in communities, because they are measures of the intensity of *T. solium* egg environmental contamination of the community. In most rural communities, pigs are kept for less than 1 year, so that a new cohort is available yearly. The use of the pig as an indicator permits the results of control programmes to be easily and cheaply evaluated.

Other than improvement of sanitary conditions and changes in porcine-rearing practises, development of an effective vaccine against porcine cysticercosis may prove the best potential tool for eradication of the disease. A recombinant vaccine has been developed for *Taenia ovis* that can provide nearly complete protection.[59,61] This vaccine is currently commercially available in several countries. A *T. solium* homologue of a *T. ovis* vaccine antigen has been cloned.[48] Development of such a vaccine is hampered at the present time by the lack of a simple, reproducible model of animal infection in which vaccine candidates may be tested.

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69 Hydatid Disease

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Hydatid disease is caused by the parasite tapeworm (Taenia) *Echinococcus* (Platyhelminth). *Echinococcus* has been recognised since the times of Hippocrates (410–379 BC) and Galen (131–210 AD) who described hydatid cysts of the liver.[23] In the 17th century (1626–1694). Redi and Hartmannus Tyssen[54] established that hydatid disease was caused by an animal. Guesnard reported the first case of cerebral hydatid cyst, while vertebral hydatidosis was first described by Chaussier in 1807.[15] In 1808, Rudolph coined the term *Echinococcus* to describe the vesicular worms.

PARASITOLOGY

There are two main varieties of *Echinococcus*: (i) *Echinococcus granulosus*, causing the classical hydatid disease, prevalent in various parts of the world and (ii) *Echinococcus multilocularis*, uncommon and reported only from some parts of Europe.

Echinococcus granulosus produces hydatid cysts in man and in other animals and is endemic in sheep rearing areas. Its larval form is called the hydatid cyst. The definitive hosts of the are the various carnivores, the important one being the dog. The mature tapeworms live in the small intestines of the dog. The intermediate host includes all mammals, especially sheep. Man gets infected occasionally by accidental contamination of the hand with the faeces of infected dogs or by ingestion of food infected with the ova. There are variations in the host-parasite relationship between different animal species. In parts of North America, wild animals are involved. In Great Britain, horses have been found harbouring hydatid cysts. In the Madurai district of Tamil Nadu, 20% of the slaughtered cattle were found to have hydatid cysts.[40] Human beings are infested by eating contaminated food, or from the fingers as a result of fondling dogs whose skin may be contaminated by the ova of the worm. The dog, in its turn, is infected by eating the offal of infested sheep. In man, the eggs, after reaching the stomach, lose their enveloping layer, thereby releasing the hexacanth embryos. The hexacanth embryo passes through the wall of the gut into the portal system and then to the liver, where a hydatid cyst may develop. The embryo can successfully pass through the capillary filters of the liver and lungs and get entry into the systemic circulation and thus reach the central nervous system,[30] the cranium and the vertebrae. The liver is affected in about 65% of cases, the lungs in about 15–20% and the brain in about 2–5%.

EPIDEMIOLOGY

Echinococcosis is widely distributed in the whole world, being most common in sheep and cattle rearing countries such as Uruguay, Argentina, Australia,[63] New Zealand and South Africa. The disease is also relatively common in Europe and Central Asia. In India, the disease has been reported from different parts of the country, but is more common in the Kurnool district of Andhra Pradesh, in Punjab and in the Madurai district of Tamil Nadu.[52]

CEREBRAL ECHINOCOCCOSIS

Incidence

Hydatid cysts constitute only a small percentage of space occupying lesions of the brain. There were only two cases of hydatid cysts, among the 2,000 cases in Cushing's classic series.[19] In New Zealand, 1% of all intracranial space occupying lesions[14] are hydatid cysts. At the Institute de Neurologia of Montevideo hydatid cysts constituted 3.64% of intracranial space occupying lesions in adults and 24.3% in children[22] during a period of 13 years from 1958 to 1971.[7] Ramamurthi et al.,[50] in Madras, found an incidence of 0.2%. A similar incidence was found by Raja Reddy et al.[49] in Hyderabad, Dharker et al.[21] in Gwalior and Sardana et al.[60] in Jaipur.

Pathology

The hydatid cyst is unilocular, slow growing and may attain a large size in the liver, lungs and spleen. The cysts are somewhat smaller in the brain, although a cyst measuring up to 12.5 cm in diameter has been reported.[21] The cyst wall is made up of three layers: (1) the outer layer is thin; (2) the intermediate layer is made up of laminated chitinous material and (3) the inner one is the germinal layer. To the inner layer are attached brood capsules, containing scolices, which are the heads of the embryonic worm. The fluid in the cyst is watery and colourless, but, occasionally, may be whitish or yellow. It contains scolices, brood capsules (referred to as hydatid sand) and, occasionally, daughter cysts. The cyst

is well delineated from the surrounding brain. Cerebral cysts are nearly always single, large and confined to the white matter. Multiple hydatid cysts represent a secondary form of the disease, resulting from either rupture of a cyst in the left side of the heart,[5,10] or traumatic, spontaneous or surgical rupture of the primary cerebral hydatid cyst.[7,20,23,25,27,75] Secondary cysts lack a brood capsule and are infertile.[45,61] For unknown reasons, the hydatid cyst has a predilection for the white matter.[17]

Cerebral hydatid cysts are more common in children and young adults. They are mostly supratentorial and tend to occur in the distribution of the middle cerebral artery.[35,69] Infratentorial involvement is unusual.[2,8,48] Rarely, hydatid cysts are found in the supratentorial as well as the infratentorial compartments.[37,60] Hydatid cysts have been reported at unusual sites, e.g. cavernous sinus.[54,55] Multiple primary hydatid cysts in the brain are rare.[10,43] A subdural hydatid cyst can grow to a large size and resemble intracerebral cysts. As the hydatid cyst grows in size, it compresses and distorts the surrounding brain tissue and displaces blood vessels. There is no neural tissue reaction, unless the cyst is disturbed. Daughter cysts are more frequent in the brain than elsewhere.[6] A rare instance of infection in a hydatid cyst has been reported.[24] The cyst may cause raised ICP by its size and/or interference with cerebrospinal fluid (CSF) pathways. The cyst, as it grows, may produce asymmetry of the cranium, and localised thinning, erosion and bulging of the calvarium overlying the cyst. The cyst does not infiltrate the bone. The average growth of a hydatid cyst has been estimated at about 1.5 cm/year[62,70] to 10 cm/year.[45]

Clinical Features

Cerebral hydatid cysts are most commonly seen in children and in young adults.[61] While in adults, focal neurological signs predominate children primarily present with features of raised intracranial pressure.[35] Cracked-pot resonance (McEwen's sign) is common in children. Macrocrania or swelling of the head over the area of the hydatid cyst is seen quite commonly.[12,21,26,38,42] Papilloedema occurs not infrequently and may progress to secondary atrophy.[2,12,21,26,38,44,53,73] The cyst is located most commonly in the posterior part of the cerebral hemisphere and hemianopia is an important sign. Contralateral hemiparesis may be present. Mental changes are more frequent in adults and seizures more frequent in children. Minimal contralateral cerebellar signs may be present and may lead to faulty localisation.

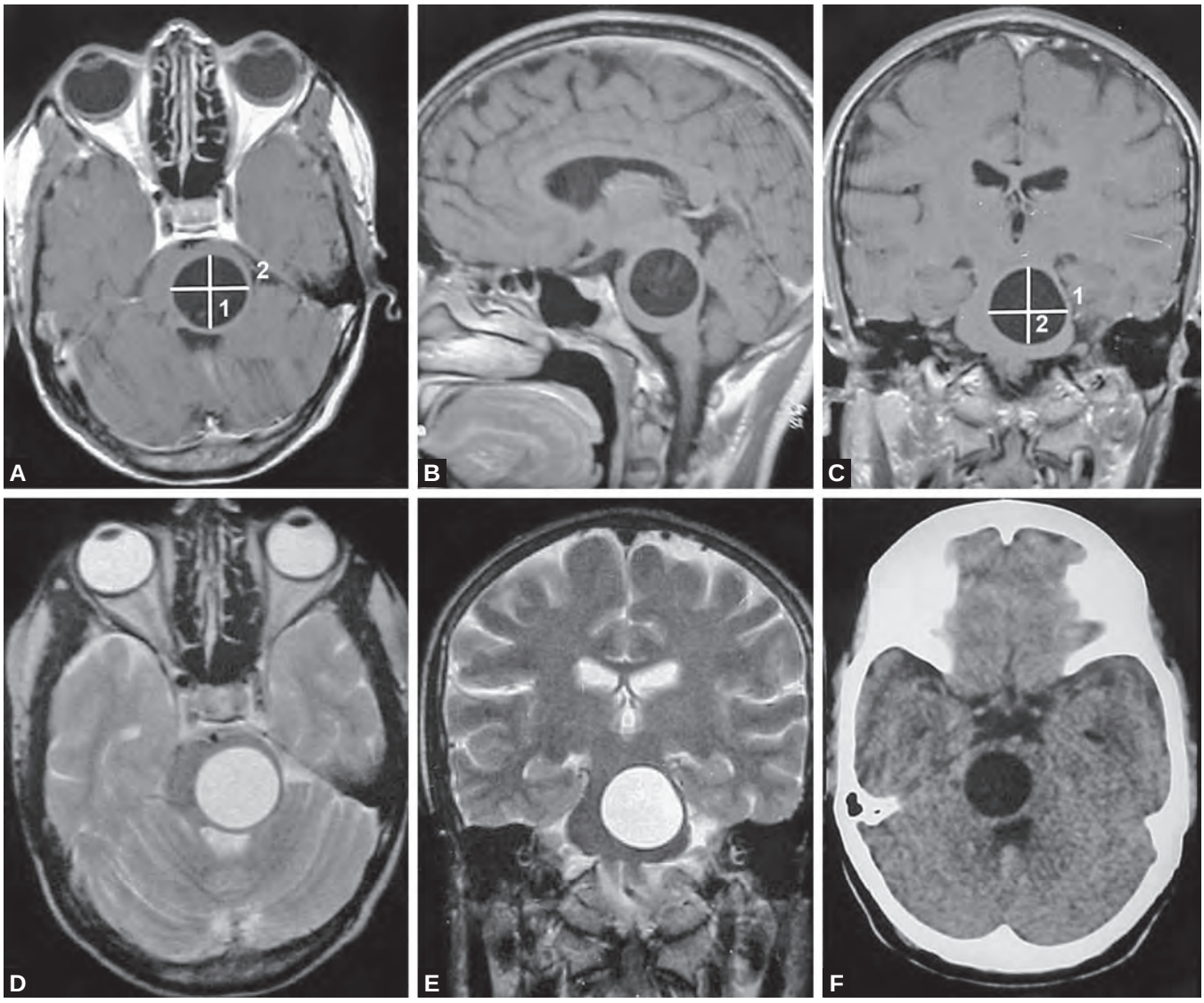
Arana-Iniguez[6] has described what is known in Uruguay as the tetrad of Schroeder: (a) a patient who is a country dweller; (b) in good general condition; (c) with the picture of raised intracranial pressure and (d) without marked focal findings. This tetrad was seen in 86% of his cases. This is, however, not specific for hydatidosis.

Diagnosis

A raised eosinophil count in the blood, a positive Casoni's intradermal skin test and Weinberg's complement fixation test may be of help in diagnosis. Arana-Iniguez[6] has proposed that when there is suspicion of hydatid disease, indirect haemagglutination, immunoelectrophoresis and indirect immunofluorescence should be carried out. As a screening test, radial double diffusion and latex agglutination tests should be performed. Positive results may then be confirmed by immunoelectrophoresis and indirect immunofluorescence and negative ones by electrophoresis and electrosineresis.

Radiological examination of the skull may show evidence of raised intracranial pressure. The skull vault overlying the cyst may show localised thinning, erosion and bulging. Angiograms show marked displacement of the vessels which curve around the periphery of a circular avascular area. There are no abnormal vessels. Rarely a blush may be noted if the surrounding tissue is inflamed but this carries less significance than in tumours.

The CT scan reveals an intraparenchymal hypodense lesion with a clearly defined margin (Fig. 1F). The cyst fluid has the same density as that of the CSF, but hydatid sand, if present, may increase the attenuation values. Rarely, the margin may show enhancement.[3] This occurs when the cyst is infected.[11,36] Peripheral enhancement has also been reported in an extradural cyst.[37,60] There is usually significant ventricular shift and hydrocephalus may be pronounced.[2] Perilesional oedema and mural nodules are significantly absent, thus differentiating the lesion from a brain abscess and other cystic tumours except in a rare case.[9] Calcification may be seen rarely.[2,57] On the MR, the unilocular cysts are large and spherical with thin walls which partially reach the brain surface. The contents of the cyst are generally indistinguishable from the CSF.[16,72] In MRI scan, these lesions have high signal intensity on T2-weighted images and low signal intensity on T1-weighted images, and are slightly hyperintense with respect to CSF on balanced images[33,47,51,76] (Figs 1A to E). After contrast administration, the walls of these lesions may or may not enhance mildly. A secondary process involving the cyst, such as calcification, infection, rupture of entodermic membrane or perifocal oedema, may also be identified. MR imaging is believed to be more sensitive and reliable than computed tomography (CT)[1,74] in depicting the pericyst layer, which appears as a halo, or in showing perilesional oedema. In formulating a differential diagnosis, the most difficult lesions to distinguish from hydatid cyst are arachnoid cyst and epidermoid tumuor. Epidermoids usually have a slightly hyperintense signal intensity on proton density weighted MR images and they usually engulf nerves and vessels, whereas arachnoid and hydatid cysts displace adjacent structures. Racemose cysticercosis in the subarachnoid space should also be considered in the differential diagnosis.



Figs 1A to F: (A to E) Pre-operative MRI of the brain showing distinct rounded lesion in the brainstem which is hypo-intense on T1-weighted images and hyperintense on T2-weighted images. (F) Pre-operative CT scan of the brain study showing hypodense lesion in the brainstem with well-defined margins

CSF examination does not contribute to the diagnosis.[69] The presence of a proved hydatid cyst elsewhere in the body would suggest a similar aetiology for a suspected intracranial lesion.[33,47,51,76]

Treatment

Treatment of a hydatid cyst is surgical. The aim of surgery must be total removal of the cyst without rupturing it so as to prevent contamination of the operative field with living scolices (Fig. 2). To achieve this, the surgeon must be familiar with the external surface of a hydatid cyst, in case one is unexpectedly encountered. The technique which has been found most useful is that described by San Julian and Arana-Iniquez.[4,58,59] They recommend that the craniotomy should be large and that the cyst wall be exposed by a series of radiating cortical incisions, termed Dowling's episiotomies. It is advisable to cover the surrounding exposed brain with lintines soaked in normal saline to prevent contamination of the surrounding brain by accidental rupture of the cyst. The head is then lowered so that the cyst is dependent, facilitating its expulsion which is helped by gently irrigating the cleavage plane between the cyst and the brain with saline. This simple technique is possible, because of the absence of adhesions between the cyst wall and its bed. A thin cyst wall, periventricular location and micro-adhesions to the surrounding brain tissue were the main surgical problems resulting in rupture in about 12% of cases resulting in distal deposit of secondary cysts elsewhere on follow-up.[31] If accidental rupture of the cyst occurs, irrigation with hypertonic saline (3%) is recommended in the hope of destroying the scolices in the operative field through osmotic desiccation. If the cyst is completely removed without spilling its contents, complete cure can be expected.

Intracystic injection of 10% formalin, 0.5% silver nitrate, hydrogen peroxide or 1.0% acqueous iodine hypertonic saline has been used to destroy residual larvae.[2,12,32,42,62] It is, however, not advisable to do this in cerebral lesions.

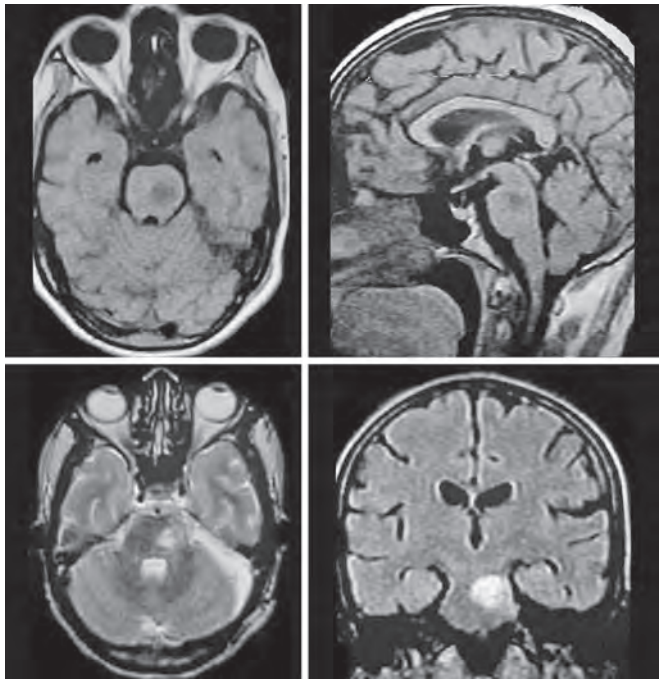


Fig. 2: Post-operative MRI of the brain showing total excision of the brainstem hydatid cyst

Saline injection into the opposite lateral ventricle has also been performed to facilitate the removal of cysts without spillage.[41] Aspiration or opening of the cyst should be avoided, unless removal cannot otherwise be accomplished.[61] In deep-seated cysts located in eloquent and vital areas such as the brainstem, management by internal decompression by aspiration followed by extirpation of the cyst wall, protecting the surrounding cisterns and CSF spaces may be done without anaphylaxis or dissemination.[72] After primary infestation, the host develops an immunologic response that is protective against re-infection but not effective against the lodged parasite. The absence of anaphylaxis has been explained by evasion of the host immune attack against the parasite by the suppression of T-lymphocyte function and inhibition of macrophage-lymphocyte interaction. Rapid decompression caused by evacuation of a large cyst may result in disturbances in autoregulatory mechanisms, which need to be watched for in the postoperative period. Occasionally, when there is previous spillage or added infection, the cyst becomes adherent to the surrounding brain and removal without rupture becomes difficult.[56]

Praziquantel does not pass through the hydatid cyst wall,[46] but high levels are seen in the CSF. As it has a powerful lethal action on free scolices,[28,67,71] it may be used in the event of spillage of the cyst fluid. Although protoscolicidal agents do not penetrate large hydatid cysts in sufficient quantity,[18] highly soluble albendazole can be used over a prolonged period for the treatment of small multiple cysts in inaccessible sites.[28,29,39,40,68] A combination of praziquantel and albendazole is more effective than either drug used alone.[67]

HYDATID DISEASE OF THE CRANIUM

Hydatid disease of the cranium is exceptionally rare.[58] Among all the cases of hydatid disease, less than 2% occur in the bones. Of these almost 50% affect the vertebrae and only 2–3% occur in the skull, the rest being located in the long bones of the body. Arana-Iniguez[7] came across only 11 cases of hydatid disease of the skull, accounting for 6.5% of his cases of echinococcosis affecting the nervous system.

Hydatid disease of the cranium is a primary disease. It initially invades the diploe and, as it grows, it widens the diploic space. Subsequently, it extends in both directions. As it erodes through the inner table, it extends freely in the extradural space causing compression of the brain. Multiple vesicles are formed both in the bone and in the extradural space reaching a considerable size. The dura is rarely invaded. It is extremely rare to have simultaneous cerebral and cranial vault extradural involvement in a single patient.[60] When the outer table of the skull is pierced, large subgaleal collections occur which may form fistulae after bursting through the scalp.[58]

Clinical Features

When the disease invades the outer table of the skull, a small firm lump is usually felt beneath the scalp. Further extension of this could lead to a soft swelling of the scalp which may ultimately result in fistulae formation. With erosion of the inner table and formation of a large extradural mass, signs of raised intracranial pressure appear. Basal lesions produce cranial nerve palsies.

Diagnosis

Plain X-rays of the skull demonstrate destruction of the skull, and CT defines the extent of the disease. Ring-like calcifications in the lesion[32] and extensive calcification in the cyst have also been reported.[13,64] Eosinophilic granuloma, cystic fibrous dysplasia and calvarial epidermoid tumour/ cyst, in particular, must be considered in the differential diagnosis of intraosseous hydatid cyst.[65] Computerised tomography scanning demonstrates a sharply marginated lytic skull defect more frequently involving the outer table than the inner table. Serological tests mentioned previously have great utility in the diagnosis of cranial hydatidosis.

Treatment

Treatment of cranial hydatidosis consists of complete excision of the affected bone. Total resection of the cyst via a craniectomy without rupture is the recommended management. Extradural hydatid cysts of intraosseous origin, however, may be difficult to excise completely because of their adherence to the dura, and osseous trabeculae. This, of course, is not possible when the disease affects the base of the skull. Patients with intraosseous hydatid cysts should be treated with albendazole for at least 3 months and monitored for up to 12

months before they are considered cured.[34,66] Steroids are helpful in relieving cranial nerve palsies, if any. The efficacy of biological treatment by means of inoculation with hydatid antigens remains a matter of dispute.

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70 Other Parasitic Infestations of the Brain

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COENEUROSIS CEREBRALIS

Coeneurosis, a rare infection in man, is caused by *Coeneurosis cerebralis*, the larva of the dog tapeworm Multiceps multiceps (Taenia multiceps). The life cycle is similar to that of *Echinococcus granulosus*. Systemic infection, though reported from many countries,[1,2,3] is the most common in tropical Africa.[6] *Cerebral coeneurosis*, however, has been reported only from temperate climates.[9] Infection in humans is via the faeco-oral route. The ingested ova hatch in the intestine. After migration through the intestinal walls, the larvae settle in the viscera where they metamorphose into the cystic form or coeneurosis.[5] The cyst in the brain is usually single and unilocular, with sizes of up to 5 cm having been described.[7] Occasionally, multiple cysts may be present, forming grape-like collections resembling the racemose variety of cysticercosis.[8,9] These are found in the ventricles, usually the fourth, or in the subarachnoid cisterns. Though Kuper et al.[6] thought that the coeneurosis cysts develop only in the CSF pathways they have also been described in the cerebral hemispheres[1,7] and in the spinal cord.[10] The arachnoid around the cyst is thickened. Unlike in hydatid cysts, the wall of the coeneurosis is thin, opaque and milky white.[9] It is not surrounded by a fibrous capsule nor does it show a laminar structure. Multiple scolices project into the cavity of the cyst. Occasionally, however, the cyst may be sterile. The surrounding brain may show astrocytic proliferation and changes of chronic inflammation. Meningeal adhesions and vessel thrombosis have also been reported.[4] Diagnosis is usually retrospective. Treatment is surgical excision of the cyst.

SCHISTOSOMIASIS (BILHARZIASIS)

This is an ancient disease, the parasite having been found in the bodies of the Pharaohs in the Nile valley. Infestation by Schistosoma annually affects approximately 200 million people worldwide.[3]

PARASITOLOGY

The parasite belongs to the group of trematodes or flukes and three varieties have been recognised: *S. japonicum, S. haematobium* and *S. mansoni. S. japonicum* is found in China, Japan, Philippines and Burma,[8] *S. haematobium* in Africa and *S. mansoni* in Africa, West Indies, South America and the Middle East. A few cases of *S. haematobium* have been reported from Maharashtra, India.[8]

Man is the definitive host, while the intermediate host is a freshwater snail. Infection occurs in human beings as a result of bathing or wading in infected water. The adult worms live in the veins and travel to different parts of the body via the nervous plexuses. The eggs and the adult worm may travel through the veins to the brain or the spinal cord. The lungs are the common site of infestation. The most important schistosomal disorders are the vesical or urinary form caused by *S. haematobium* and the intestinal form caused by *S. mansoni*. Involvement of the central nervous system (CNS) in Schistosomiasis is uncommon.

Route of Involvement

S. haematobium prefers to settle in the pelvic venous plexus, especially the vesical, while *S. mansoni* and *S. japonicum* prefer to settle in the haemorrhoidal-portal vein tributaries. The most common route of infection of the CNS is through the venous communications described by Batson. The adult worm lies in the pelvic venous plexus and the ova are carried via the anastomoses between the pelvic veins and the vertebral venous plexus. This explains the more common involvement of the conus medullaris. Adult worms themselves may, occasionally, enter the spinal canal presumably via this route.[32] Another possibility is that a gravid schistosome may find its way into the cerebral venous system (occasionally, it may enter the spinal venous plexus and the spinal canal).[4] A third possibility is that the ova are discharged into the pulmonary blood stream, from which they are disseminated as arterial emboli.[13] The eggs may also embolise to the brain via pulmonary arteriovenous shunts or portal-pulmonary arteriovenous shunts. This physiological situation is more likely to occur in advanced hepatosplenic and cardiopulmonary schistosomiasis and may explain the high incidence of asymptomatic CNS involvement in these patients.[28,29,36] Pre-existing trauma with some disruption of tissue may enable the ova to get a hold once they gain access to the nervous system.[23] Such a history of injury has been recorded by several authors.[4,19,23]

S. japonicum has been noted to infest the brain, but almost never the spinal cord,[20] while *S. mansoni* and *S. haematobium* clinically involve the spinal cord more frequently than the brain.[36] *S. mekongi* and *S. intercalatum* have never been reported to cause ectopic CNS lesions.[13]

The reason for the differential involvement of the CNS by different species is not entirely clear, but it is likely that the physical characteristics of the egg influence venous access to the CNS. The ova of *S. japonicum* are much smaller than those of the other species and are generally produced in much greater numbers daily. This may account for their relatively frequent deposition in the brain. Conceivably, the large size and protruding spines of *S. mansoni* and *S. haematobium* eggs result in a tendency to lodge in the lower vertebral plexus and spinal cord.[13]

Since, the parasite inhabits the portocaval venous system, cerebral schistosomiasis and myelopathy are forms of ectopic schistosomiasis.[12] Depending on the parasite species and localisation of the eggs within the CNS, a variety of neurological syndromes may occur. Infestation of the brain may result in acute encephalopathy, seizure disorders, mass lesions and paresis.[6,19,25]

CEREBRAL SCHISTOSOMIASIS

Though clinically apparent involvement of the CNS in schistosomiasis is rare, cerebral involvement is almost always due to *S. japonicum*.[31,39] Clinically silent ova deposition in the brain occurs frequently in severe hepatosplenic schistosomiasis.[24] Shimitzu (1935) reported the first case of surgically verified cerebral *S. japonium* granuloma.

Schistosoma Japonicum

The ova of *S. japonicum* have a strong tendency to localise in the brain, especially in the cerebral cortex, basal ganglia and internal capsule.[19] The main neurological manifestations include: (i) diffuse meningitis and/or encephalitis; (ii) varying degrees of motor deficit from cortical, subcortical or capsular lesions and (iii) syndromes simulating brain tumours.[19]

On CT scanning, a variety of abnormalities may be seen including focal contrast-enhancing mass lesions and parenchymal lucencies with or without oedema.[40] Multiple focal lesions may also be seen. Magnetic resonance imaging (MRI) demonstrates one or more areas of hypointense and hyperintense signals with contrast enhancement.[21,39] These findings are, however, non-specific as are the other laboratory findings of eosinophilia and CSF pleocytosis.[19]

Histopathologically, the affected areas show inflammatory changes around the ova, with oedema, parenchymal necrosis, cellular infiltration with giant cells and granuloma formation and occasionally, vasculitis.[19] Often, a fibrocaseous mass is formed which closely resembles a tuberculoma.

Schistosoma Mansoni and Schistosoma Haematoma

Though ova are commonly detected in the brain tissue of chronic fatal *S. mansoni* and *S. haematobium* infections, these are usually clinically silent.[27] In post-mortem studies, ova of *S. mansoni* have been found mainly in the cerebral and cerebellar cortex and the leptomeninges.[27] Histopathological changes vary from no inflammation to massive granulomatous reactions. Focal arteritis and vascular lesions have also been noted.[27,29] Levy et al.[24] have reported encephalitis in a series of eight patients. Large tumoural masses[1,15] and cerebral and subarachnoid haemorrhage[30,35] have also been reported.

In most cases, the diagnosis is presumptive and is based on an epidemiological history, ova in the stool, systemic signs of hepatosplenic infestation, neurological signs and radiological findings. In endemic regions, where other parasitic infestations are prevalent and the differential diagnosis includes non-parasitic granulomas, a tissue diagnosis may be necessary. CT or MR guided stereotactic biopsy of the lesion or CT guided stereotactic craniotomy and excision of the lesion may be helpful in such cases. These are invasive procedures and require excellent support from pathology and microbiology services.[13]

Treatment

Antischistosomal drugs, corticosteroids and surgery are the modalities of therapy available for treating NS.[39] Praziquantel is the drug of choice for *S. japonicum* infestation. A single dose is capable of complete clinical cure and resolution of mass lesions and oedema on CT.[39,41] The post-treatment inflammatory exacerbation of lesions is not seen in schistosomiasis, unlike in cysticercosis.[13] Ferrari et al. treated schistosomal myeloradiculopathy (SMR) with PZQ (60 mg/kg/day for three days) given in two daily doses at a 4 hour interval and prednisone (1.5–2.0 mg/kg/day) administered in three daily doses or methylprednisolone 500 mg every 12 hour for 5 days followed by prednisone as described above. This high dose of prednisone is maintained for about 3–4 weeks, followed by progressive reduction over several weeks.[33,38] The duration of therapy has not been defined, though prolonged courses have been recommended.[13,33,34] The immediate prognosis is good but some patients have residual neurological deficits. Epilepsy is a common problem and status epilepticus is the most common cause of death.

SPINAL SCHISTOSOMIASIS

The spinal cord may be involved in schistosomiasis.[18] SMR is less frequent than the cerebral disease.[39] This may be in the form of granulomatous masses involving the conus medullaris or cauda equina, acute or subacute transverse myelitis,[5,9,17,35] radiculitis from granulomatous root involvement[5,14] or rarely an anterior spinal artery

occlusion syndrome.[37] Spinal cord disease is almost always caused by either *S. mansoni* or *S. haematobium*.[39]

Granulomatous intrathecal lesions involving the lower spinal cord, conus medullaris and cauda equina are the most commonly reported lesions.[13,14,35] The lesion appears as a yellowish, amorphous or rubbery granuloma with a tendency to extend along the nerve roots of the cauda equina.[14]

Patients with schistosomal myelopathy are predominantly male with a mean age at presentation of 28 years for *S. mansoni* and 19 years for *S. haematobium*.[34] An acute or subacute onset, with a flaccid are flexic paraplegia including sphincter dysfunction, is the typical mode of presentation. Progression of symptoms could mimic Guillain-Barré syndrome.[26] The systemic features of acute schistosomiasis often precede or accompany the onset of spinal symptoms.[13] The disease more frequently starts with lumbar pain and/or pain in the lower limbs, usually of a radicular nature, which is followed, often within hours to a few days, by muscular weakness and sensory impairment in the lower limbs, almost always associated with autonomic dysfunction, particularly bladder dysfunction.[39]

The presentation of schistosomal transverse myelitis is similar to that of granulomatous myelopathy. The pathogenesis is not clear. It may be an allergic or hypersensitive reaction or may be related to a critical disturbance in blood supply. Like in granulomatous myelopathy, this form of spinal schistosomiasis also primarily involves the lower spinal cord and conus.

In an endemic region, diagnosis of spinal schistosomiasis can be made by the characteristic radiological findings. Routine laboratory investigations provide supportive evidence of hepatosplenic or genito-urinary infestation.[13] The classical myelographic appearance is a partial or complete block extending at least the length of a vertebral body, usually at T12-L1 level, with trifid edges and signs of an intramedullary lesion.[11] On CT with intrathecal contrast, the lower cord or conus may be expanded in an irregular fashion, with irregular beading and matting along the nerve roots of the cauda equina.[17,20] In schistosomal transverse myelitis, CT myelography may be normal or equivocal with later studies showing atrophy of the cord.[9,17] MR imaging will show moderate expansion of the distal spinal cord in all cases. The abnormality is isointense to the cord in T1 and patchily hyperintense in T2-weighted spin-echo images. Three forms of contrast enhancement occur: (1) intramedullary nodular; (2) peripheral and (3) linear radicular.[21,34,36,38]

Treatment

Praziquantel and oxamniquine are used against *S. mansoni* and praziquantel and metrifonate against *S. haematobium*. The drugs not only kill the parasite but also reduce the immunological reactions.[10,35] Ischaemic changes within the spinal cord may occasionally be reversed.[7] The role of corticosteroids is controversial with reports of both benefit and the lack of it.[5,16,17,23,35] With appropriate drug therapy, Scrimgeour and Gajdusek[35] reported a reduction in the mortality rate from 72% to 11.5% from 1965. Recovery is achieved in 54% of cases in 1 week to 4 months' time. It is essential that treatment be instituted early so that there is a greater probability of recovery.[40]

The role of surgery is limited. Laminectomy is an important adjunct, especially for patients who develop acute paraplegia with spinal block or whose condition deteriorates while on medical therapy. In diffuse granulomatosis, a small but adequately selected biopsy should be taken and the dura left open.[13] The surgeon must ensure that further damage does not occur to the already compromised cord.[2,22,35]

PARAGONIMIASIS

Paragonimiasis or "lung fluke infestation" is caused by tissue invasion by the adult trematode of the genus paragonimus. Human infestation is most commonly by *P. westermani*, though other species, e.g. *P. mexicanus*, *P. africanus* and *P. kellicotti*, also cause human disease.[6] Humans acquire paragonimiasis by ingesting immature forms of the parasite (metacercariae) in raw or undercooked food containing freshwater crabs or crayfish. There is no direct human transmission. The ingested metacercariae of paragonimus undergo ex-cystation in the duodenum, penetrate the intestinal wall and enter the peritoneal cavity. Most worms penetrate the diaphragm and enter the pleural space. They ultimately invade the lung parenchyma and encapsulate near the bronchioles. After a 6–8 week maturation period, the adult worm releases eggs which pass into the bronchial tree. The eggs are passed out of the body in the sputum or if swallowed, in the faeces. The eggs hatch into miracida in freshwater and infest snails, the intermediate hosts. Cercariae which are released in turn into the water encyst themselves in the muscles of crayfish and freshwater crabs.

Human paragonimiasis is endemic in East Asia (e.g. Korea, Japan, China, Taiwan, Philippines, Thailand), West Africa (e.g. Gambia, Nigeria, Congo valley) and in Central and South America (e.g. Mexico, Peru, Columbia, Costa Rica).[6] In India, it has been reported in the Eastern parts, viz. Assam and Bengal.

Chronic pulmonary disease is the most common result of paragonimus infestation and clinically presents as rusty sputum, haemoptysis and pleuritic chest pain. CNS involvement in paragonimiasis ranges from 0.8% to 26.6%,[1,11,14] forming the most common focus of extrapulmonary infestation.[2,4,18]

The pathophysiology of cerebral paragonimiasis is uncertain. The worms are thought to migrate from the lungs through the perivascular soft tissue in the jugular foramen to the CNS.[2,8] Brain infestation has also been shown to occur as emboli.[8,9] The temporal and occipital lobes are the most frequent sites though, occasionally, lesions have been found in the parietal lobe.[6]

Patients with cerebral paragonimiasis are usually young[2,8,10] and have symptoms for years before diagnosis.[1] Pulmonary symptoms occur before or simultaneously with cerebral symptoms. The clinical picture of CNS paragonimiasis is variable with considerable overlap of the different clinical syndromes: Meningitis, arachnoiditis (cranial or spinal), mass lesions, visual disturbances and seizure disorder.[5,6] Meningitis, seizures, visual disturbances and motor deficits are the most common presentations.[6,12] A deteriorating mental status with personality changes, disorientation and depressed levels of consciousness may also be seen.

Oh[13] has divided the varied presentations into: (i) a meningitic form; (ii) a subacute encephalitic form; (iii) a mass lesion; (iv) dementia; (v) epilepsy and (vi) a presentation with hemiplegia.

Spinal lesions are mostly lower thoracic and lumbar in location and include extradural granulomas and cysts, which may extend over several vertebral segments.

In the acute phase of infestation meningoencephalitis occurs. Granulomas and cysts result from chronic infection. Histologically, the lesions are seen as having a central necrotic zone surrounded by a layer of collagen. The eggs of the parasite are found in the necrotic tissue close to the collagen and are surrounded by foreign body giant cells. Mature worms are rarely seen in the brain.[16]

Diagnosis

Laboratory studies show peripheral eosinophilia in 20–50% of patients[6] and anaemia and leucocytosis in 10–30% of patients.[10] Supportive evidence of infestation can be got by the demonstration of ova in the sputum, faeces, pleural or peritoneal fluid or from lung biopsy. Serological studies, while sensitive, are not specific for CNS disease, and also cannot distinguish between active disease and prior infection.

Electroencephalography is abnormal in almost all cases of CNS paragonimiasis, with findings of focal epileptogenic activity and focal slowing.[2,6] Chest radiographs are abnormal in 70–100% of cases. Plain X-rays of the skull show calcification in 40–70%.[2,4,11] Higashi et al.[2] have described the calcification as "aggregated oval or round cystic calcifications with an increased peripheral density". Multiple cystic calcifications which look like "soap bubbles" are highly suggestive of paragonimiasis.[10]

In acute or subacute cases, CT scan shows multiloculated crowded abscess like cysts in the temporoparietal or temporo-occipital regions and with surrounding oedema with ring enhancement on contrast.[7,17] In chronic cases, soap bubble calcification with cerebral atrophy and hydrocephalus may be seen.

In pulmonary paragonimiasis, the same lesions resembling clusters of grapes can be seen on chest radiographs. The ring enhancing cerebral lesions are 1–3 cm in diameter and round or oval. The walls of enhancing masses are smooth and 1–4 mm thick. If no normal brain tissue is interspersed among the conglomerate granulomas, the lesion may be mistaken for a single lobulated neoplasm with multi-focal necrotic centres. The presence of conglomerated, multiple ring-enhancing lesions (grape-cluster appearance) with surrounding oedema was the most characteristic finding at the early stage of cerebral paragonimiasis. Non-specific CT or MR features include non-enhancing oedema-like lesions, parenchymal haemorrhage including haemorrhagic infarction, and irregularly enhancing solid lesions.[3,15]

On histopathology, arachnoiditis, granulomas and encapsulated abscesses may be seen.[2,4] In the granuloma, a central area of caseous necrosis is seen, as also the parasite ova and giant cells. Calcification may be seen in chronic lesions.

The treatment of CNS paragonimiasis is primarily medical.[6] Praziquantel is the drug of choice and there is significant response. Bithionol, though effective against pulmonary disease, is not effective in cerebral disease. Corticosteroids may be needed if there is worsening of symptoms due to increased local inflammation. Surgery may be required to control secondary complications, e.g. hydrocephalus or when the disease and symptoms are progressive while on medical therapy.

STRONGYLOIDIASIS

In humans, the intestinal nematode strongyloides stercoralis produces a broad spectrum of clinical illness. The manifestations of the infestation in an individual are dependent on the balance between the host and the parasite.[3]

Infection by *S. stercoralis* occurs by the penetration of the skin by the filariform larvae of the nematode. The larvae then enter the lung through the pulmonary circulation, from where they enter the alimentary canal. Larval development occurs in the duodenum and small intestine. An individual harbouring, the worms may be asymptomatic. Autoinfection and hyperinfection may lead to a state of disseminated strongyloidiasis, in which penetration of all major organs occurs. During this dissemination the major neurologic sequelae of the infestation occur.

There is a worldwide distribution of strongyloides stercoralis. Measurable rates of infection have been reported from Central and South America, Africa, Europe, Southeast Asia, the Caribbean and the South Pacific.[4,7]

Clinically, patients present most commonly with gastrointestinal symptoms (including the "swollen belly syndrome" of Papua New Guinea), cutaneous manifestations (larva currens), chronic urticaria and respiratory symptoms. Human immunodeficiency states pre-dispose towards the development of disseminated strongyloidiasis, especially where the disease is endemic. The nature of the immune defect also appears important. Corticosteroids, especially, have been found to stimulate

egg production and larval development, while depressing the host's cell-mediated immunity at the same time.[8]

The parasite, in the rhabditiform larval stage, gains access to the CNS and the systemic circulation. The neurological symptoms and signs described include headache, changes in mental status, meningismus, focal seizures, motor or sensory deficits and loss of consciousness.[1,11,19] For some unknown reason, bacterial meningitis, due to enteric pathogens, is commonly associated with CNS strongyloidiasis.[2,3] A variety of pathologies have been seen, including: Parenchymal abscesses, intravascular parasites causing parenchymal infarction, intraparenchymal and leptomeningeal larvae without tissue response, and intraparenchymal larvae in granulomata.[11,14,15,20] Degenerating larvae are usually surrounded by a modest inflammatory response, while actively migrating larvae do not excite any host response.[3] It is thought that patients with defects in cellular immunity are most at risk, although the contributions of humoral immunity and eosinophilic response are not yet understood. Hyperinfection with strongyloides stercoralis was thought to be rare in acquired immunodeficiency syndrome (AIDS), despite endemicity in areas where infection with human immunodeficiency virus is highly prevalent.[17] Further surveillance is needed in geographically susceptible populations.

Diagnosis

A definitive diagnosis of strongyloidiasis requires the identification of the larval forms in body fluids or tissue specimens. Isolation of the larvae from CSF is not common and may require repeated sampling and centrifugation to increase the yield.[3] Serological assay to detect the IgG antibody to strongyloides stercoralis antigen has a sensitivity of 85–95%. However, cross reactivity with other parasitic infestations does occur.[6,13] Eosinophilia which is found in chronic infestation may be absent in hyperinfection or disseminated disease.

Treatment

The drug of choice is thiabendazole[10] which is given orally in two 25 mg/kg doses daily for 2 days. A success rate of about 80% is reported, though up to 23% of cases have side effects referable to the CNS. In hyperinfection, the drug is given for 5–7 days. Invermectin (50–400 mg/kg) has also been found to be effective.[12] Steroids must not be given and, if already started, must be withdrawn. Periodic examination of the stool specimen should be carried out in immunosuppressed individuals for surveillance and appropriate therapy instituted with thiabendazole, albendazole or ivermectin to prevent hyperinfection and its complications.[1,5,9,16,18]

Morality with disseminated strongyloidiasis approaches 60%, even with appropriate therapy. Recurrence of symptoms may occur even years after treatment and repeated courses of therapy may have to be given.[3]

TRICHINOSIS

Trichinella spiralis is endemic in all areas of the world except Australia and some islands of the Pacific Ocean. The parasite is a gut and tissue dwelling nematode. While the clinical manifestations of *T. spiralis* infections are varied, most infestations are asymptomatic.[8] Only 5–10% of infected persons may have significant morbidity or may die due to involvement of the cardiopulmonary or CNS.[6] Involvement of the CNS occurs in 10–20% of patients and is usually associated with heavy Trichinella infection. The mortality rates may be as high as 50%.[12]

Human infestation is due to ingestion of meat containing the larvae. The ingested larvae transform into the infective larvae in the stomach. They then pass into the small intestine where they moult four times and are transformed into sexually mature adult worms which attach to the duodenal and jejunal mucosa. New born larvae, released by the female worm, penetrate the gut mucosa and migrate into the draining lymphatics and vessels. Systemic dissemination occurs mainly into tissues with a high blood flow. The larvae encyst in their new surroundings and may remain viable for several years even if they calcify. Kratz, in 1866, recognised neurological involvement due to Trichinella, while Frothingham, in 1906, related to the presence of the parasite in the brain to focal neurological signs.[8]

Systemic manifestations of the infestation coincide with the life cycle of the parasite. Patients suffer diarrhoea and abdominal cramps within 1–2 weeks of infestation. On systemic dissemination, fever and intense myalgias occur, especially in the extraocular muscles and the masseter. Periorbital oedema, conjunctivitis, headache and subconjunctival and subungual petechiae may also occur.[1]

Neurological complications occur in 10–24% of cases.[3,6] Patients most commonly present with symptoms and signs of meningoencephalitis (96%), focal paresis (73%) and delirium (71%).[8] Later signs include persistent drowsiness, disorientation and emotional lability. Cerebral invasion occurs during the 2nd week, the larval migratory stage, producing varying degrees of encephalitis manifested by emotional instability, psychotic behaviour, delirium, insomnia, inattentiveness, disorientation, lethargy, headache or memory loss. They are frequently mild and evanescent, but can be severe and prolonged in certain cases. During the 3rd week (the encystment stage) localised or focal nervous system involvement may occur. When focal involvement occurs, it is often superimposed on previous meningeal or encephalitic symptoms and is rarely the sole manifestation.[3,10,12]

Focal deficits occur with encystment of the larvae.[5] These include sphincter dysfunctions, cranial nerve palsies, seizures, vertigo, anisocoria, decreased auditory acuity and ataxia.[4] When hypotonia is present, it is most likely due to primary muscle involvement.[9] Peripheral nerves may also be involved. Occlusion of cerebral

venous sinuses causing extensive venous infarction and intracerebral haemorrhage may also occur.[12]

The manifestations of CNS and peripheral nerve trichinosis are due to granulomatous inflammatory reactions which surround the larvae or parasite antigens. Pathological findings in CNS trichinosis include infiltration of the pia-arachnoid by lymphocytes, macrophages, fibroblasts and gitter cells. Perivascular inflammatory changes with occasional granuloma formation may be found around the Virchow-Robin spaces.[9] Glial cell nodules and occasional periventricular haemorrhages may also be seen.[8] A diffuse eosinophilic meningoencephalitis is rare.

Treatment

A definitive diagnosis of *T. spiralis* infestation can be made by identification of the larvae in muscle, usually by biopsy of the gastrocnemius or other large muscles in which there is pain. Laboratory tests, such as eosinophil count, though sensitive are not specific for trichinosis. A modest elevation of muscle enzymes, e.g. creatine kinase and lactate dehydrogenase, occurs in about 50% of subjects. CSF studies are neither sensitive nor specific, as in up to 75% of cases the CSF may be normal.[2,4] While serodiagnostic test by ELISA has a high degree of sensitivity, its specificity is only about 60% due to its cross reactivity with other nematodes.[8]

The role of imaging in trichinosis is not yet established. CT scan of the brain may appear normal despite neurological signs of trichinosis.[4,11] In other cases, the CT may show multiple nodular or ring-like lesions, with contrast enhancement or ring calcification.[7] MR imaging in trichinosis has still to be defined though there are stray case reports.[4]

There are no antihelminthics with documented efficacy against CNS trichinosis.[9] Thiabendazole or mebendazole may be used but their usefulness is doubtful. Corticosteroids may be used as an adjunct.

The overall prognosis in cases of CNS trichinosis is related to the severity and intensity of the initial infection, the host defence mechanisms, the structural damage which has occurred and the effectiveness of the antihelmenthic and anti-inflammatory therapy.[8]

CEREBRAL SPARGANOSIS MANSONI

Sparganum mansoni is the larva of *Spirometra mansoni*. The incidence of this infestation is especially high in Japan, though cases have also been reported from Korea, China and South East Asia.[2,5,11]

Human infection may be via: (a) drinking water containing Cylops, the first intermediate host; (b) eating raw freshwater fish, frogs or snakes, the second intermediate hosts or (c) by the application of infected tissue (frog poultice) to a raw wound. Human infection is most often by the larva.[11] Soft tissues, such as the subcutaneous tissue of the abdominal wall, are the most common sites of parasitism. Brain involvement is rare.[4,6] Yamashita et al.[11] found only 19 cases of cerebral sparganosis in their review of the literature.

Cerebral sparganosis presents with focal signs and convulsions.[3,8,11] The offending lesion is a granuloma in the cortical or subcortical tissues of the brain. However, the worms may move causing a shift of focal signs and symptoms. On the CT scan, an extensive hypodense area with nodular enhancement different from that seen in paragonimiasis or cysticercosis is seen. The hypodensity is thought to be due to the movement of the worm and the protease enzyme released by it. The presence of white matter hypo-attenuation with dilatation of the adjacent ventricle, irregular or nodular enhancing lesions, small punctuate calcification and a change in the location of the enhancing nodule on the follow-up CTs are characteristic. Occasionally, subcortical haemorrhages are also noticed. Brain MRI demonstrated multiple cystic areas of hyperintensity on T1-weighted images with rim enhancement and areas of hyperintensity on T2-weighted images. Moon et al.[7] reported that areas of hyperintensity on T1-weighted images and areas of hypointensity areas on T2-weighted images were detected only in MRI. They believed that these changes in signal intensity represented petechial haemorrhage and may be due to capillary or venous injury by the migrating worm,[2,10] but cyst formation is uncommon.[1] ELISA is the only specific investigation available preoperatively.[11] It is quite difficult to differentiate sparganosis from cerebral tumours on CT and laboratory data pre-operatively. The diagnosis is usually confirmed by post-operative histological examination.[11]

As there is no effective chemotherapy, surgical excision of the granuloma is the only treatment.[10] Larvae being the most common infective agent recurrence is uncommon once the granuloma is removed. Prevention is important and care should be taken in respect to the food eaten, especially for those visiting endemic regions.

VISCERAL AND OCULAR LARVA MIGRANS

Visceral and ocular larva migrans (VLM and OLM) are zoonoses, which occur when humans become an accidental host for the larval stage of a parasitic helminth. Beaver coined the term "visceral larva migrans" to differentiate it from creeping eruption or cutaneous larva migrans.[1,2,3] Classic causes of VLM and OLM are: Toxocara sp. and *Baylisascaris procyonis*. The other agents implicated include nematodes, like Gnathostoma sp., Angiostrongylus cantonensis, and cestodes like Spirometra sp. (which cause sparganosis) and Taenia multiceps (which cause coeneurosis). Visceral larva migrans due to *T. canis* has a worldwide distribution, including Canada, England, France, Germany, New Zealand, Australia, Africa, Turkey, Malaysia and India.

Toxocara canis has three, possibly four, types of life cycle. First is the classical pathway, embryonated ova in soil being ingested by the dog (the natural host) with larvae migrating from the intestine through the liver and

lungs to return to the intestine to become adult forms capable of perpetuating the life cycle. A second type of life cycle is characterised by migration of larvae from the lungs to somatic tissues of the female, there to remain dormant until pregnancy when they become active and migrate across the placenta to infect the foetus *in utero*. For this reason, the majority of newly born puppies may be infected and may eliminate advanced stages of larvae in the faeces. A third type of life cycle occurs when these larvae are ingested by the dog or possibly by humans. When swallowed they become adult forms and produce fertile eggs within the gastrointestinal tract so that the liver-lung migratory pathway is not essential for larval maturation. A fourth kind of life cycle may not be important for transmission of parasites from or to man, but may have relevance concerning the clinical expression of human toxocariasis. This life cycle involves the phenomenon of paratenesis, a term introduced by Beaver[2] to define situations in which there is "passage of infective-stage larvae without essential development through a series of transport (paratenic) hosts to the final host with the transport hosts serving at the same time to maintain the infective-stage larvae from one season of transmission to the next." Two features of this phenomenon are noteworthy. The tissue distribution of the larvae is unique for each type of transport host, involving primarily the liver in some, the skeletal muscles in others and the CNS in many. A second feature is the extraordinary capacity of the larvae to maintain viability for long periods. In the monkey, experimentally infected with canis, larvae may remain alive and infective for at least 10 years. Thus, the parasite is capable of passing through several intermediate hosts, for example, rodents and other small mammals, before coming in contact with and infecting its natural host, the dog. Although man has been referred to as an aberrant or unnatural host for canis, it is possible that man is an intermediate host and that visceral larva migrans is a clinical expression of paratenesis. A consideration of the different types of life cycle indicates several ways in which man may become an intermediate host for the parasite. The most common route of infection is ingestion of soil containing larvae or embryonated ova. Another and less frequent way of becoming infected includes close contact with nursing bitches or puppies and in particular hand-to-mouth spread of larvae or eggs in the environs. Since third-stage larvae may be present in this type of setting, it is possible, although extremely unlikely, that infection with adult canis may be acquired.[6]

Zoonotic ascarid larval infection is frequently asymptomatic. The classical picture of VLM can be found in a child one to five years of age, presenting with fever, hepatomegaly and pulmonary infiltrates. The blood picture shows leucocytosis with eosinophilia and hypergammaglobulinaemia.[1] Neurologic manifestations include neuropsychiatric disorders, seizures, encephalopathy, meningoencephalitis and transverse myelitis.

OLM due to *T. canis* presents as unilateral visual loss and strabismus. Four clinical syndromes are described: (1) a peripheral granuloma involving the retina; (2) a raised lesion at the posterior pole; (3) diffuse endophthalmitis and (4) papillitis. These may result in heteropsia or macular detachment.

The diagnosis is by a combination of clinical signs and laboratory testing. The latter includes serodiagnosis and extraction of the larvae from biopsy tissues.

As most of the manifestations of LM are due to host response to dead and dying larvae, the administration of antihelminthics can potentially exacerbate the disease. Diethylcarbamazine or thiabendazole may be given in combination with corticosteroids and antihistaminics.[4,5]

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71 Spinal Hydatidosis

Harjinder S Bhatoe

Echinococcosis or hydatid disease is the larval stage of infection caused by cestodes of the genus *Echinococcus*, whose life cycle involves two mammalian hosts. The definitive hosts are carnivores, in whom the adult worm is present in the intestines. Classic cystic echinococcosis is caused by the larva of *Echinococcus granulosus (E. granulosus)*, a species adapted to dogs and a wide variety of domestic and sylvatic animal intermediate hosts (e.g. sheep, buffalo, etc.). The large size, often attained, is responsible for neurological pathogenicity and morbidity.

LIFE CYCLE AND SPINAL IMPLANTATION

After ingestion of protoscolices originating from fertile hydatid cysts, sexual maturity of the adult tapeworm is reached within 4–7 weeks. The fully mature adult *E. granulosus* is a small tapeworm approximately 3–7 mm in length. It firmly attaches to the mucosal wall of the small intestine of the canine host. Development from ovum to oncosphere takes place *in utero* in the adult worm. The oncosphere measures about 0.018 mm and is bilaterally symmetrical, possessing three pairs of hooks, muscle fibres and glands that aid in penetration and locomotion in the intermediate host. The oncosphere and its surrounding membrane are called the cestode eggs. These eggs are shed with faeces into the external environment, and remain viable on the furry coat of the canine. These eggs reach the alimentary canal of the intermediate hosts by ingestion (close contact with dogs, contamination of water, foodstuffs, salads, etc.). Their own lytic secretions facilitate the oncospheres to hatch, and their passage through the gut mucosa. Entry into the circulatory system occurs:

- Through the portal system, when the preferred site of implantation is the liver
- Lymphatics

Once the oncosphere passes through the liver, it enters into the pulmonary circulation where it can evolve into a pulmonary hydatid. Passage into the systemic circulation can lead to any of the organs becoming the site for implantation. Spinal implantation can occur via the systemic circulation, or through the valveless epidural venous plexus that communicates with the pelvic and retroperitoneal venous channels; the circulation in the epidural venous plexus is transiently reversed during straining and Valsalva manoeuvre. Once the oncosphere reaches its preferred site, cystic development begins by degeneration of the oncospheral stage and emergence of the vesicular metacestode stage. The cyst expansively grows by concentric enlargement. In general, hydatid cysts increase in diameter by 1–5 cm each year. Under natural conditions, transmission and perpetuation of echinococcosis is the result of predator-prey relationship between the hosts, and man is an accidental host where the parasite reaches a dead end. However, transmission in synanthropic cycles is considerably modified by human behavioural factors.

INCIDENCE

The human form of echinococcosis is more common in warmer climates, especially in rural and farming communities where sheep rearing is an important occupation. While skeletal hydatid constitutes 2.8–3% of human echinococcosis, spinal involvement occurs in one third to half of these cases.[2,24] Spinal hydatid was first described by Churrier in 1807, which was reported in 1819,[41] and is considerably rare when compared to cranial hydatid. There have been case reports from India,[4,6,7,13,38,39,44,47] and Iyer et al.[22] reported the largest Indian series of five cases collected over a period of 12 years. Worldwide, the largest series of 24 cases has been reported by Sami et al.[42]

PATHOGENESIS AND PATHOLOGY

Spinal hydatid is always primary, i.e. due to the implantation and development of the larva in the affected organ.[1] The primary lesion in the bone is characterised by multiple infestations through the arterial circulation or via the epidural venous plexus through portovertebral channels whenever the flow in the latter is transiently reversed (as during straining or Valsalva manoeuvre). The embryos lodge preferentially in the vascularised region of the centre of the vertebral body. Growth occurs within the intratrabecular space, destroying the bone-like tumour and eliciting no inflammatory response. The organism spreads beneath the periosteum and ligaments.[2] Formation of vesicles replaces the medullary tissue and bony architecture is destroyed by pressure, with widening of bony canals resulting in formation of rounded areas of rarefaction; eventually, the pedicles, adjacent ribs and laminae are eroded. The unyielding

nature of the osseous compartment restricts cyst expansion resulting in fragmentation and conglomeration of daughter cysts.[18] Perforation of the cortex and periosteum results in extraosseous extension, which may be extraspinal, paraspinal or intraspinal. Spinal cord compression occurs once, when the bony centre has been perforated. Spinal cord compression may also result from transforaminal extension of the cyst into the spinal canal,[6] and there may be a dumb-bell extension of the cyst into the spinal canal.[21,37] Adjacent vertebrae may be involved by extension beneath, the anterior longitudinal ligament, and rarely across the intervertebral disc. The intervertebral disc is relatively resistant to invasion;[33] discal involvement has been reported in a 76-year-old male who was earlier operated upon for extraspinal hydatid cyst.[26] Discal involvement probably occurred due to direct implantation or via vascular dissemination. Extraspinal extension leads to encystment of the lesion by a common adventitial membrane.

The fully developed metacestode (hydatid) of *E. granulosus* is typically fluid-filled and unilocular, but multiple communicating chambers also occur. Structurally, the cyst consists of an inner germinative layer of cells supported externally by a characteristic acidophil staining, acellular, membrane of variable thickness. Cytoplasmic extensions of the germinative layer unite to form a syncitium, which is differentiated into numerous microtriches. The microtriches project peripherally into the laminar layer towards the host tissues surrounding the cyst. Surrounding the parasitic cyst is a host-produced granulomatous adventitial reaction of extremely variable intensity. Small secondary cysts, called brood capsules, bud internally from the germinative layers and by polyembryony. They then produce multiple protoscolices. A protoscolex is a scolex with the rostellum and suckers deeply withdrawn into the post-sucker region. In humans, the slowly growing hydatid cysts may attain a volume of many litres and contain thousands of protoscolices.

Primary infection with *Echinococcus* larva elicits an early immune response in the intermediate host as evidenced by specific antibody and cellular responses.[43] The immune response is biphasic: an early response that is directed against the recently hatched preimplantation stage of the larva, and the second against the established metacestode at the site of formation of hydatid cyst. Immune mechanisms in the first phase are more effective in destroying the larva than those against the established metacestode.[43] In *E. granulosus* cysts, the protective mechanism is probably related to sequestration of the parasite by the laminated and germinative membranes and host capsule, which greatly limit the exchange of high molecular weight substances between the host and the parasite.

CLINICAL FEATURES

Spinal hydatidosis is a slow growing lesion usually seen in the third or fourth decades of life. Clinical presentation is determined by the vertebral level of involvement and the degree of spinal cord compression. An expanding cyst in the vertebral body gives rise only to persistent backache, which worsens with passage of time. A diffuse paraspinal swelling may be visible externally, while craniovertebral junction involvement may present with a visible mass in the oropharynx and nasopharynx.[8] There are no specific features diagnostic of the lesion and the diagnosis may be suspected in patents living in endemic areas, or in those people who have stayed in endemic areas. Spinal hydatidosis has been reported in a married couple.[31] Almost all reported cases have myelopathy as their presenting feature. The onset is insidious in the form of easy fatigability, stiffness of the limbs with difficulty in brisk walking or doing fine skilful motor work with the hands. However, if the cyst is intramedullary or intradural extramedullary, myelopathy sets in early and is more severe as compared with predominantly vertebral involvement. A pathological fracture of the vertebra or vascular involvement may cause acute paraplegia. The continued slow growth of viable cysts precludes regression or spontaneous cure.[25] Spinal echinococcosis has been classified into five clinical subgroups:[9]

a. Primary intramedullary hydatid cyst: Rarest form of spinal involvement, myelopathic features are early and progressive.[35]
b. Intradural extramedullary hydatid cyst.[10,24,39]
c. Intraspinal extradural hydatid cyst.[45,48]
d. Hydatid disease of the vertebra: This is the commonest form of spinal involvement seen clinically, where a growing cyst encroaches upon the spinal canal. Thoracic and lumbar spinal involvement occurs in about 75% of all cases with vertebral echinococcosis.[18] Multiple vertebral involvements are rare[27] as it is the involvement of the cervical spine and the sacrum.[29,36] Association of vertebral with costal involvement is considered as a diagnostic of vertebral echinococcosis.[19]
e. Paravertebral hydatid disease: The spinal canal may be invaded secondarily by cysts located in the mediastinal, retroperitoneal and paraspinal regions.[16,20,40]

IMAGING

Plain Radiographs

Plain radiographs may reveal an osteolytic lesion of the vertebral body (with destruction of the areolar pattern of the bone). There may be erosion of transverse processes, adjacent ribs and pedicles. Preservation of discs is a common finding. The enlargement of the cyst results in punched out radiolucent areas initially without sclerosis. Sclerosis around the radiolucent area may be seen later in the course of the disease. Vertebral collapse due to a pathological fracture along with a paravertebral soft tissue shadow may be seen in advanced stages of the disease. A paravertebral mass is often seen, which may be fusiform in appearance. Many of these patients have already had treatment with antituberculous therapy for variable periods.[7] Chest radiograph may show an associated pulmonary hydatid.

Magnetic Resonance Imaging

Since the first description of magnetic resonance imaging (MRI) appearances of vertebral hydatid by Mikhael et al.,[32] MRI is now the imaging modality of choice for diagnostic evaluation of spinal echinococcosis. MRI provides accurate details of the intradural and extradural compartments together with multiplanar imaging, so that the exact relationship of the cyst with the surrounding structures is known and the surgical approach can be planned. Typically, the cyst appears as a multiloculated hypointense mass on T1-weighted images, which is brightly hyperintense on T2-weighted imaging (Fig. 1). Marani et al.[30] and Tekkok and Benli,[45] while reporting MR imaging findings in patients with spinal echinococcosis, found signal intensity alterations on T2-weighted images. The intensity differences may reflect the viability of the cyst. Whereas a viable cyst appears hypointense on T1-weighted images with isointense or mildly hyperintense cyst wall, it is the T2-weighted sequence that indicates whether the cyst is viable.[23] A decrease in hyperintensity and an increase in hypointensity from a collapsed cyst indicate a non-viable cyst.[23,45] Proton density weighted images are also useful in determining cyst viability[45] and gadolinium enhancement correlates well with various stages of cyst degeneration.[11]

Computed Tomography

With increasing utilisation of MRI in the evaluation of myelopathy, the role of CT has become more specific. Detection of calcification in the cyst wall, delineation of bony erosion and size of intraosseous cysts and assessment of adjacent bony architecture prior to instrumentation are the principal uses of CT.

SEROLOGICAL DIAGNOSIS

While imaging is the mainstay of pre-operative diagnosis in spinal hydatid disease, serologic tests may be useful in confirming presumptive imaging diagnosis. The limitations of serodiagnosis must be kept in mind to interpret the findings correctly. False positive reactions with tests using whole hydatid cyst fluid antigens occur frequently in the presence of helminthiasis, malignancies and chronic immune disorders. Regardless of localisation, antibody detection tests are least sensitive in patients with intact hyaline membranes, although cysts in the bone stimulate the formation of antibody regularly in contrast to those cysts that occur in the liver, lung, etc.[43] Rupture of the cyst is followed by an abrupt rise in antibody titre. Enzyme linked immunoabsorbent assay (ELISA) and indirect haemagglutination or indirect immunofluorescence tests are highly sensitive procedures for screening of serum for diagnosis of hydatid infestation.[14] Confirmation can be obtained with an immunoblot assay for specific antigen-antibody bands or gel diffusion for echinococcosis arc[5] protein. However, serological tests may falsely be positive in 5–25%. The patients with neurocysticercosis, a condition that shares the endemicity and imaging appearances with echinococcosis.[49] Eosinophilia is present in less than 25% of infected persons.

In seronegative cases, a presumptive diagnosis may be confirmed by demonstrating protoscolices or hydatid membranes in the liquid obtained by percutaneous aspiration of the cyst contents. Ziehl Neelsen stain is particularly useful for easy identification of the elusive hooklets.[3] Closed aspiration under ultrasound or CT guidance combined with medical treatment appears to be safe and is now a standard practice.

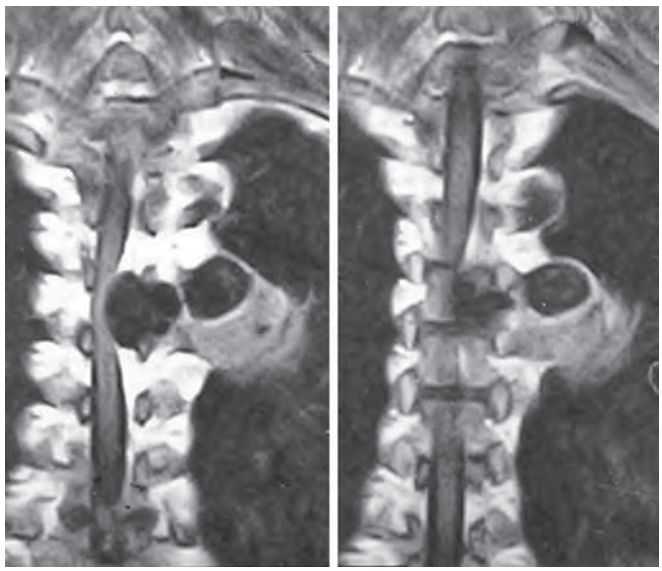

Fig. 1: MRI showing multiloculated hydatid cyst with dorsal cord compression

SURGICAL MANAGEMENT

Surgery is the mainstay in the definitive management of spinal echinococcosis, especially in the presence of compressive myelopathy. The aim of surgery is to preserve and improve neurological function and provision of spinal stability with eradication of the parasite. The exact location of the cyst determines the surgical approach to the lesion. Posterior exposure may be made by laminectomy, especially in the presence of an intradural cyst.[1] Extensive involvement of vertebral bodies requires an anterolateral transthoracic approach. Vertebral body resection and stabilisation by instrumentation and fusion can be carried out.[18,46] A combination of anterior and posterior approaches may be required. Spinal fixation can be done as a first step, before excision of the cyst.[8] A reasonable suspicion of hydatid cyst can be made from pre-operative imaging studies, and appropriate precautions should be taken to prevent spillage of cyst contents. Scolicidal-soaked gauze should be packed around the cyst wall. Hypertonic saline and formalin are best avoided in the vicinity of neural tissue; instead of aqueous iodine in glycol (Betadine®) is used. A layer of isotonic saline-soaked gauze is first placed over the neural tissues, and scolicidal-soaked gauze is then placed over the saline-soaked gauze to avoid direct contact of neural tissue with scolicidal solution.

Inspite of attempts at extensive exposure for radical excision, the cyst may be removed incompletely.[15] Spillage from a viable cyst should promptly be recognised and antianaphylactic measures instituted. All patients, irrespective of the extent of resection of the cyst, must receive albendazole or mebendazole in the post-operative period.

MEDICAL MANAGEMENT

Medical management of hydatid disease has evolved over the past several decades, and drug treatment can now be recommended for many patients. While one-third patients can be cured of their disease, nearly 30–50% have favourable response in the form of regression of cyst size. Small isolated cysts respond better than the large multiloculated ones and those with thick calcified walls. Both albendazole 10–15 mg/kg/day and mebendazole 40–50 mg/kg/day have been effective. Drug treatment may have to be administered continuously or punctuated by treatment-free intervals for a period of three to six months. These drugs can also be administered pre-operatively to inactivate the scolices, altering the integrity of the membrane and thus safe surgical manipulation of the cyst(s); clinical evidence of this approach however is lacking.[43] There have been reports of reduction in cyst size with medical treatment after incomplete cyst excision.[5,17] These drugs are teratogenic and are contraindicated during pregnancy. All patients must undergo MRI after 12 months of treatment: static size, reduction in the cyst size or disappearance of the cyst indicates effective therapy.[12]

PERCUTANEOUS ASPIRATION, INJECTION, REASPIRATION (PAIR)

According to the WHO advisory group, PAIR is indicated in inoperable cases and those who refuse surgery.[50] The procedure involves percutanous puncture using sonographic guidance, aspiration of substantial amounts of liquid contents and injection of scolicidal agent (e.g. 95% ethanol and 0.5% cetrimide) for at least 15 minutes, followed by reaspiration.[28] Concurrent treatment with albendazole/mebendazole improves the efficacy and safeguards against spillage and secondary implantation.

PREVENTION OF ECHINOCOCCOSIS

Echinococcosis is a major health care problem in endemic regions like Turkey and Australia, and Kashmir in India. In the Madurai district of Tamil Nadu, 20% of the slaughtered cattle were found to have hydatid cyst.[34] CNS involvement can cause major morbidity and mortality, especially in cases of rupture of these cysts. Prevention of human echinococcosis involves the dual approach of regular deworming of dogs and ensuring meat hygiene. Infected animal carcasses have to be destroyed, so that these are not consumed by dogs. All these measures involve a concerted effort on the part of medical and veterinary personnel, and public health authorities.

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72 Fungal Infections

Anil Pande

GENERAL CONSIDERATIONS

Fungi are everywhere and an estimated 70,000–150,000 different species exist around us.[25,75,101] Only a small fraction of these cause human fungal infections. These are members of the phylum thallophyta, but lack chlorophyll. They do not have the usual plant structure, lacking stem, leaves and roots. They may be unicellular or multicellular. Many are dimorphic, that is, they can take two different types of form; a unicellular (yeast form) and a multicellular (mycelial form). The mycelial forms can be septate or non-septate, that is branched or unbranched. They may be capsulated or non-capsulated. The fungal cell wall is of great complexity and this polysaccharide capsule is of great use in characterising these lesions, and in protecting them and the fungal cell wall components. Ergosterol, chitin and beta 1,3 and 1,6 glucans are the targets of antifungal agents excepting flucytosine, which acts due to its antimetabolite effect. The human immune system, normal colonising bacteria and fungus and low pathogenicity are all responsible for the rare occurrence of these infections. Whenever the immune system wavers in its effectiveness in extremes of age, disease and debilitation or, whenever immunosuppression occurs due to AIDS, diabetes, drugs or blood dyscrasias, the fungi find a foothold.

Fungi are thus basically simple plants, lacking chlorophyll; they are parasites or saprophytes thriving on other living or dead organisms. Fungal infections of the central nervous system (CNS) have been recognised since the end of the 19th century. Paltauf, in 1885, reported a case of cerebral mucormycosis.[110] Von Hanseman in 1905 reported from Germany, a yeast isolated from the cerebrospinal fluid (CSF). Since then, numerous reports of cryptococcal and other fungal CNS infections have appeared.[44,51,58,59,158,160,161] In India, after the publication of a case of intramedullary cryptococcal granuloma by Ramamurthi et al.[120] in 1954, and blastomycosis of the spinal cord in 1956, many cases of fungal infections of the brain and spinal cord have been reported.[4,9,18,28,35,38,88,97,118,123,132] Recently, they are being encountered more frequently as opportunistic infections in patients whose host defence mechanisms have been compromised due to disease or due to techniques of immune suppression and immune modulation used for managing malignant and autoimmune diseases[146] and for organ transplantation.[155]

The factors that have contributed to the increasing incidence of fungal infections are:

- Prolonged use of broad-spectrum antibiotics and the use of antimetabolites and steroids.
- Social evils such as drug addiction and substance abuse.[3,87]
- Diseases like diabetes mellitus, renal failure, malnutrition, AIDS and systemic lupus erythematosus.[79,147]
- Increase in international travel with the risk of environmental exposure.[146]
- Longer survival of patients with lymphoproliferative malignancies.[28]
- Larger ageing population.
- Near drowning episodes.

CNS mycoses can also affect healthy individuals without any of the predisposing factors mentioned above.[19,93,96,119,140] Asha et al.[7] from India reported that 17 out of 25 of their patients with fungal infections of the CNS were not immunologically compromised. This is also a common observation in other centres in India.[31] In contrast to the Western literature, poor nutritional status, antibiotics, steroids and parasitic infestations have been cited as causes of reduced host defences and increase of CNS fungal infections in India. Also a hot dry climate with high aspergillus spore content is cited as a cause of increased cases reported from India.

Mycotic infections enter the differential diagnosis of many neurological conditions, even in an apparently fit individual. They produce a wide range of pathology depending on the host response to the fungus: Inflammatory reactions, chronic round cell inflammation, chronic suppuration, granulomatous inflammation, calcification, infarction, hypersensitivity and/or antibody production.[8,111]

CLASSIFICATION

Fungi are classified as follows:

Pseudo Mycetes

Blastomycetes, Candida, Coccidiodes, Cryptococcus, Histoplasma, Paracoccidiodes and Sporotrichum.

Septate Mycetes

Aspergillus, Cephalosporum, Cladosporum, Diplo-rhinotrichum, Hormonodendrum, Paecilomyces, Penicillum.

Non-Septate Mycetes

Absidia, Basidobolus, Cunninghamella, Mortierella, Mucor, Rhizopus.

Fungi Like Bacteria[109]

PATHOGENESIS

The pathogenicity of fungi is attributed to their neurotropism, and to the altered defence mechanisms in the host.[28] Fungi causing systemic and CNS infections possess thermotolerance and resist phagocytosis by capsule formation, intramacrophage germination and toxin production. Fungi can grow either as yeast or moulds at different times of their life cycle. This is known as dimorphism. The morphology and size of the fungus determine the pathology of these lesions. Small yeast forms (Blastomycosis, Coccidiodes, Cryptococcus and Candida) reach the small arterioles and capillaries and produce meningitis and subpial ischaemic lesions. Intermediate size pseudohyphae (Candida) obstruct small blood vessels leading to necrosis and abscess formation. The larger hyphal forms (Aspergillus, Zygomyces, Cladosporium) block larger vessels and give rise to large infarcts. Disorders of phagocytic function predispose patients to develop CNS aspergillosis, mucormycosis and candidiasis.[141] Impairment of cell-mediated immunity predisposes to CNS Cryptococcal, Histoplasma, Coccidioidal and Blastomycotic infections. Impairment of granulocyte function predisposes to Candida, Aspergillus and Zygomycetes.[41]

Recently, in some fungi, cytoplasmic hormone receptors have been demonstrated, which interact with human corticosteroid and sex hormones. The receptors have been reported in *Candida albicans, Coccidioides immitis* and *Paracoccidioides brasiliensis*.[86,116] This discovery has aided our understanding of the growth and virulence of pathogenic fungi.

Basically, fungi affecting the CNS can be divided into two groups:

1. Pathogenic or Endemic fungi: They affect healthy hosts. These are endemic in various parts of the world.
2. Opportunistic fungi: These fungi usually cause infections in immunologically compromised hosts and in the presence of predisposing factors (diabetes, malignancies, renal failure, AIDS, etc.).

Many other miscellaneous fungi, like Penicillum, Curvularia, Alterneria, Cephalosporium, Paecilomyces, Fusarium, Pseudoallescheria, Rhizopus arrhizus, Rhodotorula, Trichosporon and Ustilogo, can cause CNS mycosis on rare occasions.[49]

Pathogenic Fungi

The site of primary infection is usually in the lung and rarely in the skin. In addition, primary lesions may occur in the mucosa of the mouth and pharynx as in paracoccidioidomycosis and in the gastrointestinal tract as in histoplasmosis[131] The organisms spread to the CNS by the bloodstream from the primary site. Rarely, meningitis may ensue due to direct spread from osteomyelitis of the skull or vertebra, e.g. *Coccidioides immitis*. Direct spread can also occur from the paranasal sinuses and middle ear.

Opportunistic Fungi

The primary site of entry in aspergillosis and cryptococcosis is the lung, with subsequent bloodstream spread to involve the CNS.[129] Some fungi (Aspergillus, Zygomyces) spread directly from the nose and paranasal air sinuses and less often from the ears. Occasionally, the brain is directly infected after a head injury or craniotomy.[129] In candidiasis, the normal commensal multiplies and enters the blood at any site where there is a defect in normal surface defence mechanisms.

Meningitis

The prototype fungus that primarily causes meningitis is *Coccidioides immitis*. Involvement of the leptomeninges is typically widespread, the basal meninges being maximally involved.[73] The basic pathologic lesion of coccidioidomycosis is a combination of suppurative and granulomatous inflammation. In the infected tissue, the endospores are surrounded by polymorphs[27] and in granulomas the spherules are surrounded by mononuclear cells and giant cells. The chronic inflammatory response results in thickening of the meninges, hydrocephalus, arteritis, cranial nerve palsy and infarctions. Other fungi (Blastomyces, Paracoccidioides and Histoplasma) may also cause meningitis. As in tuberculosis, there may be spinal meningitis in blastomycosis where there is an extradural infection of the vertebrae and intervertebral discs.

Meningoencephalitis

Fungi, like *Cryptococcus neoformans* and the Candida species, are prone to cause meningoencephalitis. In cryptococcosis, cystic clusters of fungi are spread throughout the brain with little or no surrounding inflammatory response and predominantly involving the basal ganglia and the cortical grey matter.[27] Large focal collections of fungi with inflammatory cells (cryptococcomas) may be observed in rare cases. The cystic lesion contains a gelatinous polysaccharide material. This polysaccharide antigen is detectable in spinal fluid and serum, and forms the basis of a commercially available latex agglutination test, which is 90% sensitive and highly specific for diagnosis of cryptococcosis.

Brain Abscesses/Infarction/Haemorrhages

Aspergillus, Zygomycetes, Blastomyces, Paracoccidioides and Candidiasis cause these lesions, as also Nocardia,[68], Actinomyces,[113] and Coccidioidomycoses.[94] Some dermatiaceous fungi produce brain abscess, especially in

the frontal lobes, even in the absence of a disseminated lesion, e.g. *Cladosporium trichoides* and Phialophore.[45]

Disseminated candidiasis mainly produces microabscesses, though macroabscesses, glial nodule formation, granulomas and fungal balls may also be found. Rarely, Candida may directly invade blood vessels causing haemorrhage, necrosis and infarction. Vasculitis is characteristic of invasive aspergillosis and mucormycosis. Direct spread occurs from the paranasal sinus to the brain with subsequent vasculitis, especially in diabetic patients.

CLINICAL FEATURES

There are no pathognomonic signs or symptoms of fungal infection of the CNS. However, a constellation of specifically affected organs and some characteristic pathological features help the physician towards a presumptive diagnosis. In non-endemic areas, a history of travel to a region of the world where the organisms grow, may point towards the correct diagnosis. A history of near drowning episode is inquired into. Occasionally, there may be no neurological symptoms or signs.

The clinical features may be divided into the following groups:[100]

Meningeal Syndromes

The common symptoms are headache, nausea, vomiting, neck stiffness and fever. In 40% of the cases of cryptococcosis, visual impairment, diplopia and papilloedema occur.[160] Cranial nerve palsies may also be seen. Alteration of the mental status may be caused by encephalitis or hydrocephalus. Seizures may occur. Focal signs due to arteritis, granuloma or abscess may be present. In patients with AIDS, cryptococcal infection may cause retrobulbar neuritis,[53,83] choreoretinitis,[142,144] internuclear ophthalmoplegia[151] and reverse ocular dipping.[125] The clinical picture of meningitis varies in the immunocompromised and non-compromised hosts with a paucity of symptoms and signs in the former.

Space Occupying Lesions

Granulomas, abscesses or hydrocephalus cause symptoms and signs relating to the affected area. There may be features of increased intracranial pressure.[42,142] Aspergillosis typically presents in this way. An intraventricular fungal mass has been reported.[78] In blastomycosis, the patient has progressive paraplegia with sensory manifestations and sphincter disturbances. Blastomycosis may also involve the vertebrae and the intervertebral discs producing a gibbus simulating caries spine.[4] Extradural or intradural cryptococcal granulomas have been reported in the spinal cord, producing features of compressive myelopathy.[10,12,120]

Rhinocerebral Syndrome

This syndrome presents with orbital pain preceded by a watery nasal discharge, which becomes bloody and purulent. There is facial oedema with proptosis and visual loss. Involvement of the carotid artery produces hemiparesis. Subsequently, the trigeminal nerve and the adjacent brain may be involved.[112,145] This is classically found in zygomycosis, where blackish necrotic areas called eschars are seen on the hard palate or the nasal turbinates. Rhinocerebral mycosis has a high morbidity and mortality, despite institution of aggressive management.[69,148] Allergic fungal sinusitis can lead to formation of a "fungocoele", which expands with time causing bony destruction and intraorbital and intracranial extension, but characteristically is non-invasive and can be removed bluntly leaving the mucosa intact. Transsphenoidal, trans-ethmosphenoidal, endoscopic transnasal and, rarely, transbasal bifrontal approaches may be utilised. Prolonged antifungal treatment is not required, but steroids help.[85]

Stroke Syndromes

Aspergillosis or zygomycosis may produce sudden onset of a focal deficit due to invasion of blood vessels. Rarely, subarachnoid haemorrhage may occur due to rupture of a mycotic aneurysm.[60,64,117,157] Unlike bacterial mycotic aneurysms, fungal mycotic aneurysms occur in the larger arteries.[60] Candida infection may result in an embolic stroke.[62]

Skull Base Syndromes

Orbital apex syndrome, cavernous sinus syndrome, proptosis with or without ocular palsy, polyneuritis cranialis and orbitocranial syndrome may occur.

Spinal Syndromes

Myelopathy and radiculopathy due to involvement of the vertebral column, and extradural, intradural and intramedullary lesions may be seen.

DIAGNOSIS

Suspicion of CNS mycosis is the most important initial step in the diagnosis. Laboratory tests should be directed to discover evidence of immunological compromise and of fungal infection elsewhere in the host.[17,33]

Evidence of Fungal Infection in the Central Nervous System

Cerebrospinal Fluid Examination

i. *CSF protein* is elevated and glucose diminished. In aspergillosis with deep-seated granulomas, the CSF is normal. If a high protein level is found (1.0 gm/dl or more), subarachnoid block should be considered.[146] High levels of proteins, often greater than 1.0 gm/dl are not uncommon in cases of cryptococcal meningitis even in the absence of a spinal block.
ii. *Cell count*: A mononuclear pleocytosis is seen ranging between 20 cells/cubic mm and 500 cells/cubic mm,[115]

but, occasionally, in candidiasis and zygomycosis, there may be a polymorphonuclear increase.

iii. *Cytological examination* of the CSF may occasionally reveal the fungus. For cryptococcal meningitis, India ink preparation is a simple and effective test. It is positive in approximately 50% of all cases and the sensitivity increases to 80% in patients with AIDS.[146]

iv. *Positive cultures* confirm the diagnosis of fungal meningitis, but may be difficult to obtain or may take a long time. Cryptococcal meningitis shows a positive culture in 75% of patients and Coccidioidomycosis meningitis in 30–50% of patients. Blastomycosis and histoplasmosis rarely yield positive cultures. It may be necessary to centrifuge and culture the sediment. Candida yields positive culture within a few days and Cryptococci within 7–10 days, while Histoplasma and Coccidioides require longer incubation periods of up to 6 weeks.

v. *Immunological tests*: In cryptococcal meningitis, the latex agglutination test for capsular polysaccharides in CSF is positive in 90%. False positivity may occur in 20%. In CNS coccidioidomycosis, complement-fixing antibody is found in 95% of patients in the range of 1:2–1:25. CSF antibody to Histoplasma has been found by both complement fixation and radioimmunoassay. False positivity occurs in 50%. In sporothrix meningitis, CSF antibody in a titre of 1:8 or more is detected by the latex agglutination or ELISA test.[128,137]

Imaging Techniques

CT or MR scan may reveal features of meningitis, granulomas, hydrocephalus, infarction or spinal cord compression. In rhino-orbital syndromes, CT or MR is especially helpful. CT scan usually underestimates the degree of involvement by the organism, and shows paranasal sinusitis, small areas of bony destruction, and absence of separation of periosteum from the medial orbital wall. The granulomas appear as irregular hypodense lesions with irregular and minimal contrast enhancement and disproportionate perilesional oedema. For example, in cryptococcal meningitis the scan may be normal in up to 40%.[47,67] The MRI is very useful to visualise ocular muscle or nerve involvement and will show involvement of the paranasal sinuses or mastoid involvement. Granulomas have a low T2 intensity compared with surrounding hyperintense cerebral oedema. MR can be used to follow treatment response in fungal meningitis.[163] This characteristic low intensity in T2 is due to high levels of iron, magnesium and manganese in the fungus. Diffusion weighted imaging is useful in detecting early lesions and in differentiating these from progressive multifocal leukoencephalopathy and neoplasm. MR spectroscopy in aspergilloma is non-specific with high choline, low creatinine and lactate with no N-acetyl aspartate.[71] Cryptococcus pseudocysts which are formed due to the dilatation of the Virchow Robin spaces with mucoid gelatinous material produced by the capsule of the organism are seen in clusters in the basal ganglia and thalamus and are pathognomic of cryptococcal infection. Deep cerebral infarcts are seen as areas of hyperintensity on T2W1 images. Ring enhancing T2 heterointense lesions with irregular walls and non-enhancing intracavitary projections having a low ADC are indicative of a fungal abscess. Spinal involvement shows disc involvement or sparing, heterogeneous marrow signal alteration and extensive extraosseous involvement and variable bony deformity and destruction. Rarely, CNS fungal infection can present with subarachnoid haemorrhage due to rupture of a mycotic aneurysm or thrombosis of large vessels[53,62] and these require conventional angiography as CT angiography may miss small aneurysms.

The authors have proposed a classification of Rhinocerebral fungal infections depending on the extent of the lesion (Figs 1 to 5)[138] (*Reproduced with permission from Neurology India*).

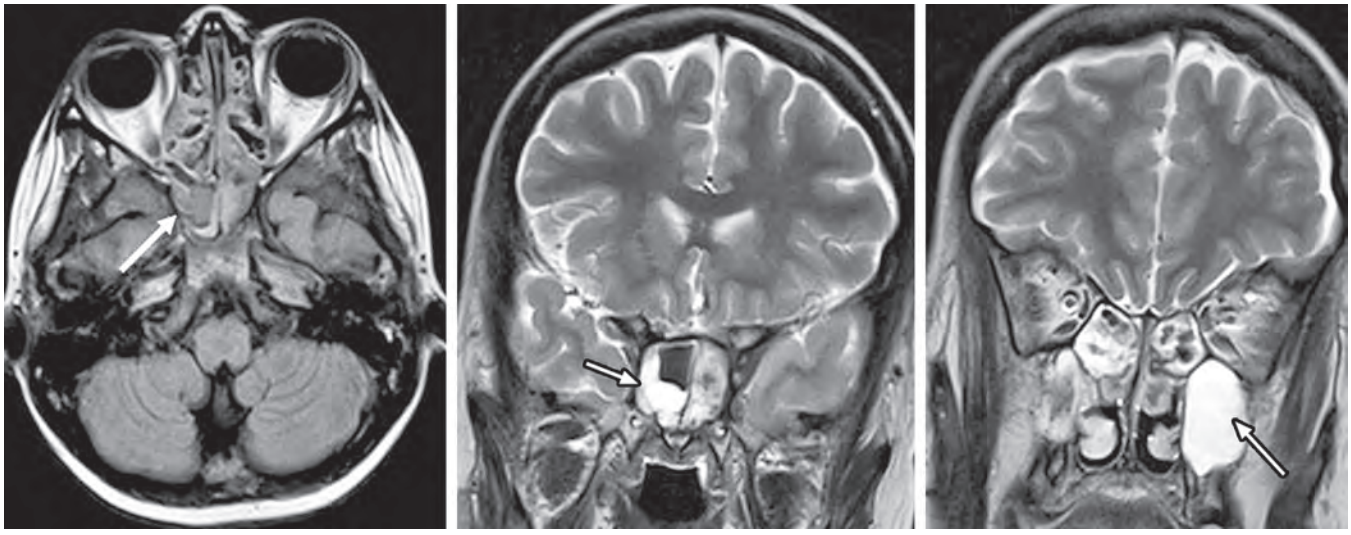

Fig. 1: MRI of the brain showing evidence of fungal infection in the ethmoidal and maxillary sinuses (arrows). Infection is limited to the sinuses and not involving the dura or extending intracranially (Stage I)

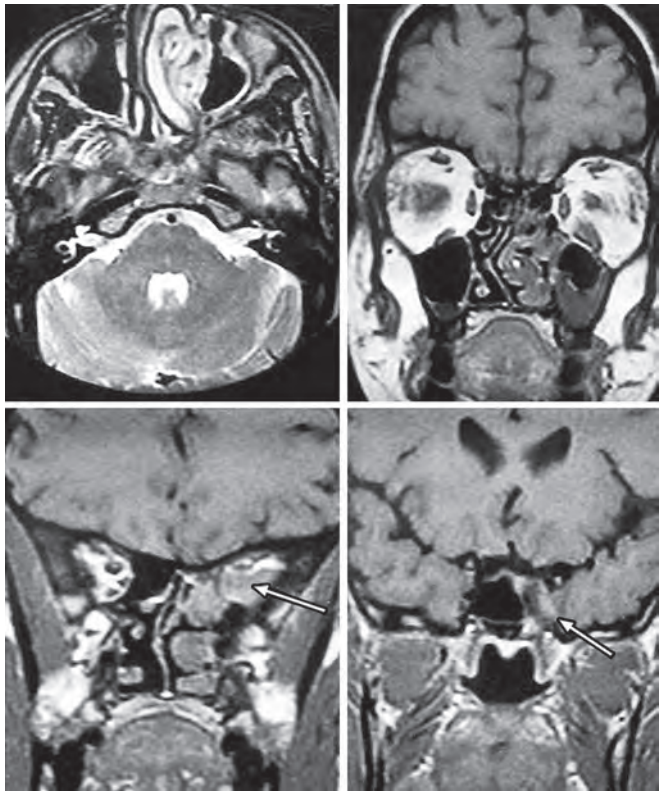

Fig. 2: MRI of the brain showing pansinusitis with erosion of the bone and without dural breach or parenchymal spread (Stage II)

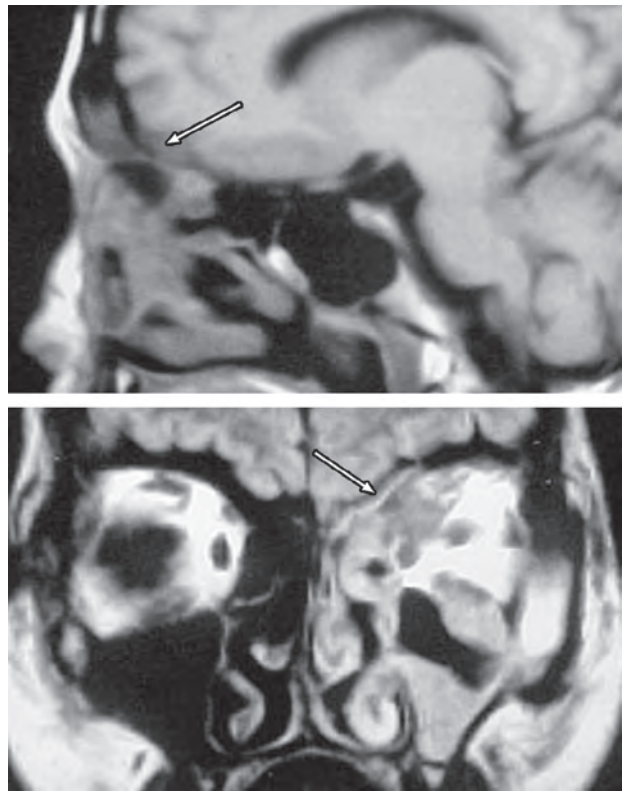

Fig. 3: MRI of the brain showing evidence of infection in the ethmoidal sinuses with skull base erosion and spread to the dura seen as dural thickening (arrow) (Stage IIIA)

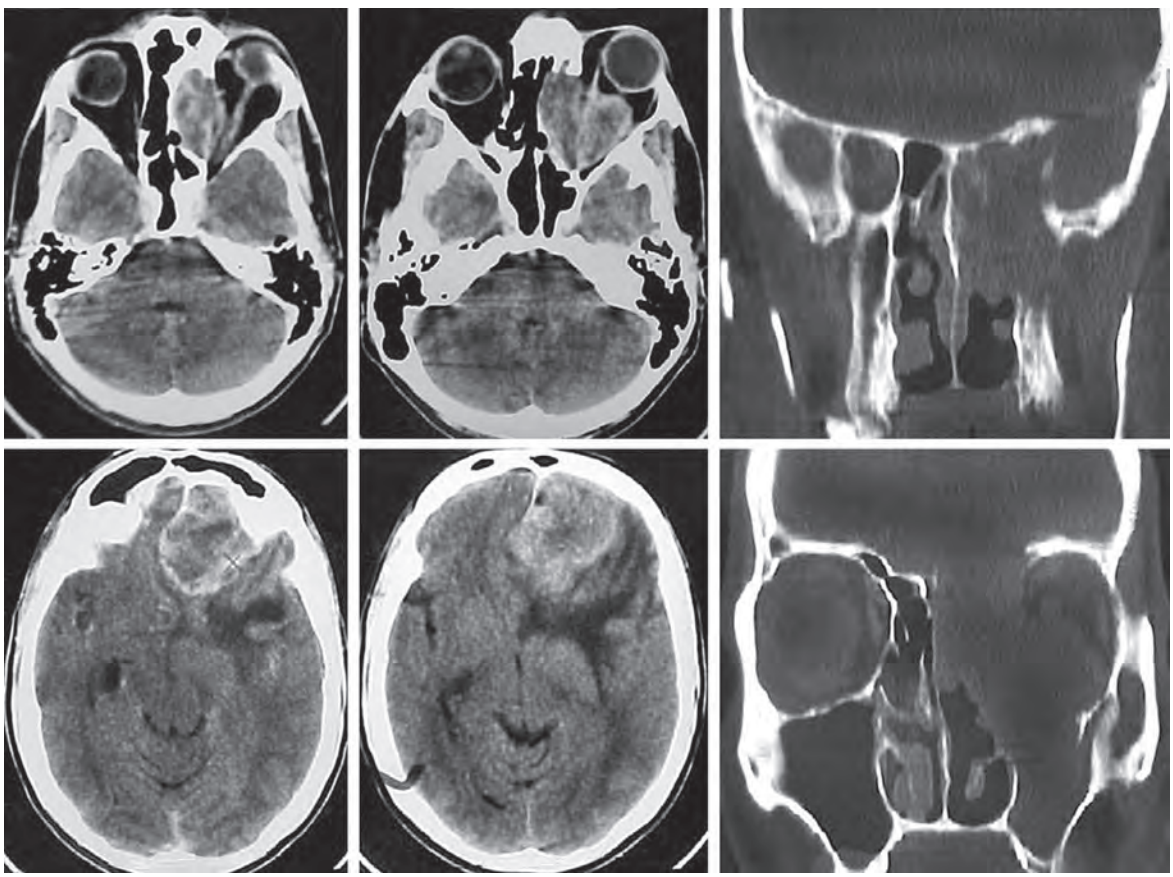

Fig. 4: CT of the brain showing infection in the maxillary and ethmoidal sinuses with extension into the orbit. There is evidence of erosion of the skull base and spread to brain parenchyma with perilesional oedema (Stage IIIB)

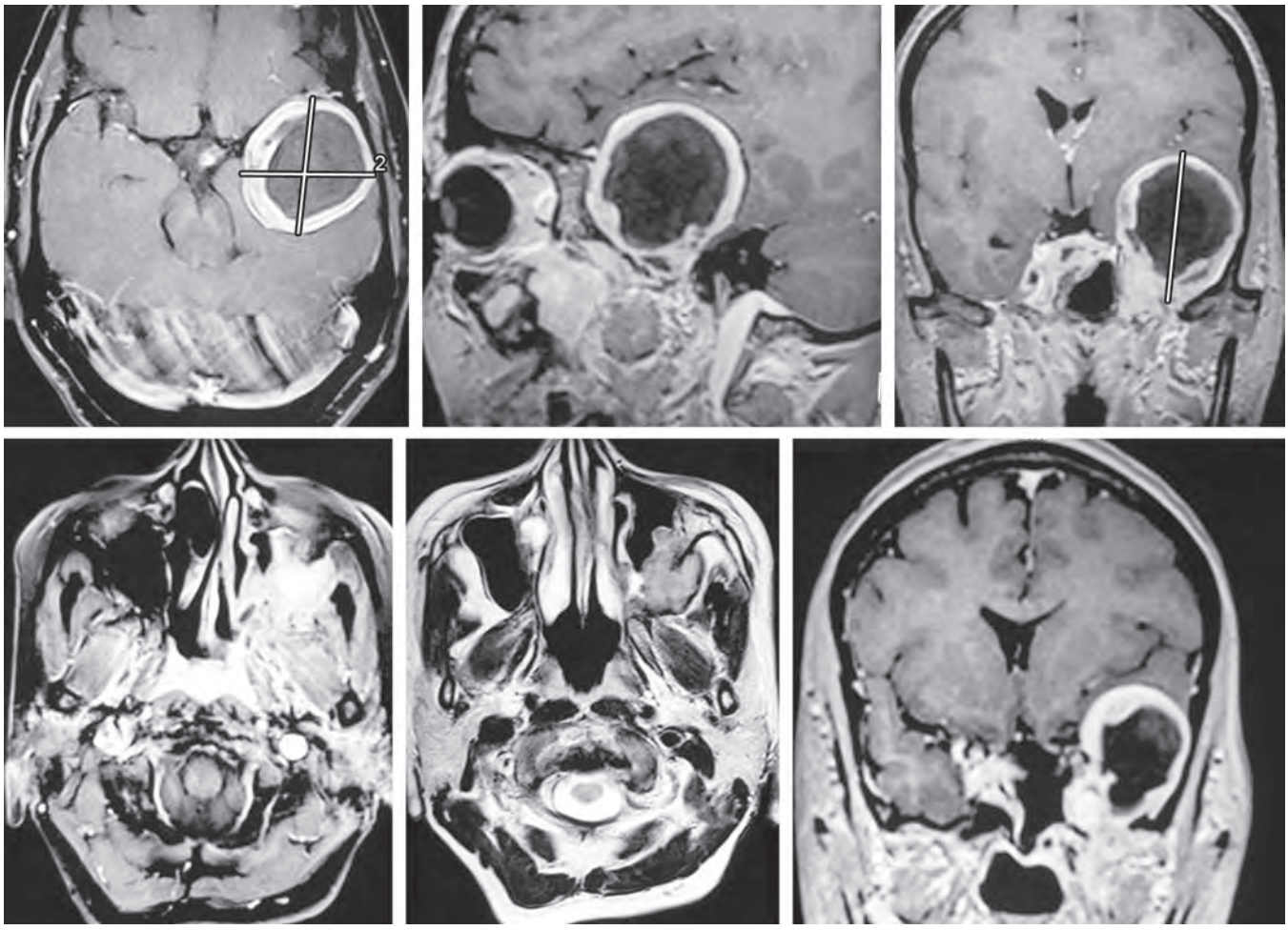

Fig. 5A: MRI scan of the brain. Well circumscribed extra-axial lesion measuring 4.3 x 4.5 cm in the temporal base with erosion of the skull base and involvement of the dura. There is evidence of the disease in the maxillary sinus (Stage IIIA)

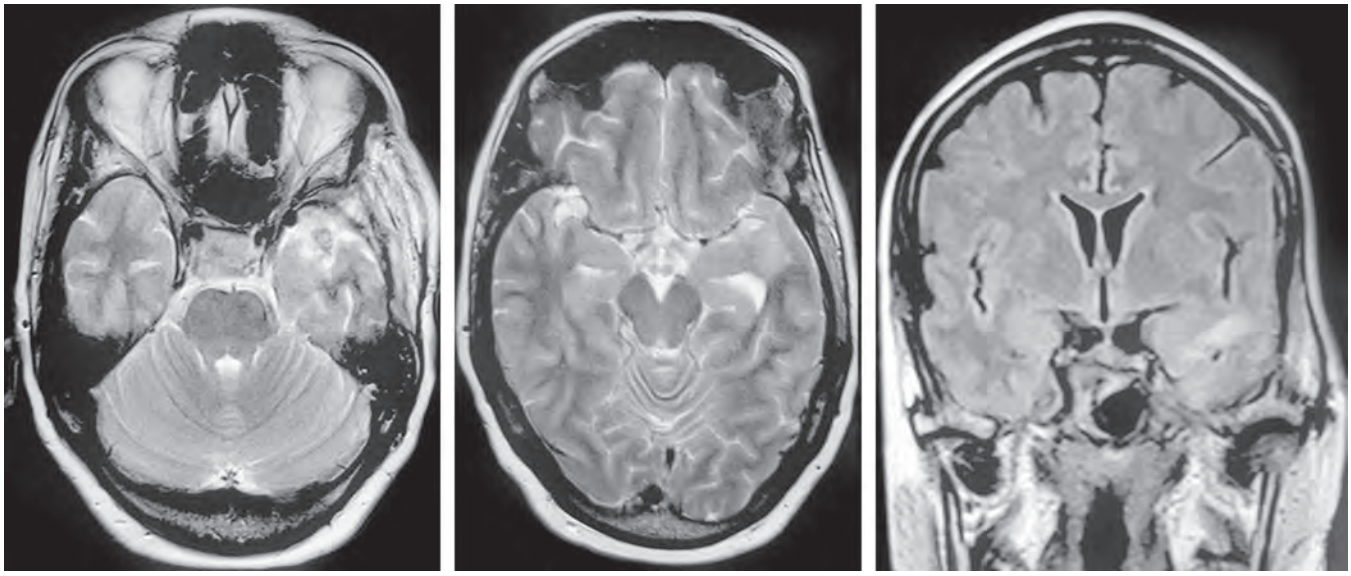

Fig. 5B: Post-operative contrast MRI of the brain showing total excision of the intracranial lesion

Stage I: Purely rhino-sino-orbital.
Stage II: Involvement of the bone without dural breach in addition to sinus involvement.
Stage IIIA: Spread of infection from the sinus to the skull base, involvement of the bone and breach of the dura.

Stage IIIB: Infection involving the brain parenchyma.

Stage IV: Fulminant meningoencephalitis and large infarcts.

Biopsy

When a diagnosis cannot be made otherwise, biopsy of the lesion may become necessary. In every case where a granulomatous lesion is encountered, investigations for fungi should be done in addition to histopathology and culture sent for pyogenic organisms. The specimen should be sent in normal saline and stained with Periodic Acid Schiff stain or Grocott's methanoamine silver stain, especially for aspergillosis and zygomycoses. In the case of Cladosporium and other dermatiaceous fungi, hematoxylin and eosin stain is adequate.

Evidence of Fungal Infections Elsewhere in the Host

Searching for the source of infection elsewhere in the body is essential, e.g. lung, skin, bone and sinuses using X-rays and serological tests; and identification of the organisms by smear, culture, histopathology from pus, sputum, blood and skin. Skin tests for Coccidioides, Histoplasma or Blastomyces may indicate exposure to the particular fungus.

Evidence of Immunological Compromise

Complete blood count and blood chemistry are carried out to identify predisposing conditions, such as leukaemia, lymphoma, diabetes mellitus, renal failure and AIDS.

TREATMENT

Non-Specific Measures

a. Control of predisposing factors which are mentioned earlier.
b. Treatment of intracranial hypertension, e.g. mannitol and furosemide.

Specific Measures

Antifungals can be classified as:

Polyenes: Amphotericin, Nystatin

Azoles: Miconazole, Ketoconazole, osaconazole, Ravucon-azole, Voriconazole, Eberconazole, Itraconazole.

Antimetabolic: Flucytosine

Antiprotozoal: Atovaquone

Echinocandins: Caspofungin, Misafungin, Aniducafungin

The antifungal agents commonly used are amphotericin B, flucytosine and azole derivatives.[124] The duration of the treatment is from 4 to 6 weeks. Immunocompromised patients take longer to experience remission. The treatment should continue till active systemic or CNS infection has disappeared. Long-term maintenance therapy is considered in immunocompromised patients.

Other drugs under trial: Amphotericin B encased in liposomes reduces toxicity to the host, allowing administration of higher doses of the drug. Voriconazole is considered the gold standard of systemic antifungal treatment and is superior to conventional amphotericin and has improved survival rates in patients with cerebral aspergillosis.

Capsofungin and Posaconazole are other agents, and combination therapy is preferable. Amphotericin B deoxycholate given as a continuous infusion, with appropriate saline loading through a dedicated line is a safe and affordable treatment option with similar toxicity profiles compared to expensive lipid based formulations.[124] Rifampicin given with amphotericin B potentiates the activity of the polyene against multiple yeasts, including Candida, Histoplasma and Cryptococcus.[92] Immune based therapies for fungal infections are at an exploratory level and merit further evaluation in clinical trials.[114]

Surgical Management

Surgery may entail stereotactic biopsy and, if possible, aspiration of an abscess. Stereotactic craniotomy can be useful to place an appropriate flap and localise the lesion.[18,61,119,143]

Besides diagnostic biopsy, surgery may be needed for CNS mycoses.[57] Brain abscesses, especially Blastomyces and Histoplasma abscesses, can surgically be removed and treated with amphotericin. Large cryptococcomas (greater than 3 cm) in accessible locations should also be considered for surgery.[50,120,166]

Drainage of the paranasal sinuses with excision of the granuloma is indicated in the rhinocerebral syndrome. Focal infection with Cladosporium requires surgical removal of the lesion.[70] Hydrocephalus may require shunt surgery. Insertion of the Ommaya type reservoir helps in prolonged intraventricular or cisternal chemotherapy. Spinal compression requires surgery to remove granulomas or abscesses.

PROGNOSIS

In most fungal infections, the prognosis depends on the duration of the disease before the diagnosis and on whether any underlying disease can be controlled. Specific prognosis factors have been identified in cryptococcal, candidal and coccidioidal meningitis.

Poor Prognostic Factors

1. Cryptococcal meningitis:[39]
   i. Initial positive India ink test.
   ii. High CSF opening pressure.
   iii. Low lumbar CSF leucocytes (less than 20/cu mm)
   iv. Cryptococci isolated from extraneural tissue.
   v. Absent anticryptococcal antibody.
   vi. Initial CSF or serum cryptococcal antigen titre greater than 1:32.
   vii. Corticosteroid therapy for lymphoreticular malignancy.

2. Candidal meningitis:[14]
   i. An interval from the onset to diagnosis of more than 2 weeks.
   ii. CSF glucose level below 35 mg/dl.
   iii. Development of intracranial hypertension or focal neurological deficit.
3. Coccidioidal meningitis:[20]
   i. Presence of hydrocephalus.
   ii. Presence of an underlying disease.
   iii. Non-Caucasian races.

Without treatment, fungal meningitis is a fatal disease. In CNS coccidioidomycosis, virtually all the patients die within 2 years. By administering amphotericin B directly into the CNS the mortality has decreased to less than 50%.[146]

CRYPTOCOCCOSIS

Cryptococcus neoformans has a worldwide distribution and is associated with soil enriched by pigeon droppings. It is also known as Torula histolytica. The disease may be seen in patients with disorders of the reticuloendothelial system[32,105,144,161] and also in previously normal individuals.[43,56,126,154,159] The route of infection is through the respiratory system, which may result in a subclinical infection or a cavitating lesion in the lung.[48,159] It is disseminated via the bloodstream and, when it reaches the CNS, commonly causes meningitis.[32,82,122] Verse, in l9l4, first reported cryptococcal meningitis.[122] The first case published from India was by Krainer et al. in 1946.[76] Since then there have been more case reports.[9,13,74,118,120] Cryptococcosis appears to be the commonest type of mycosis in AIDS. Involvement of the CNS is in the form of basal meningitis,[130] meningoencephalitis and mass lesions such as granulomas or cysts.

Cerebral Cryptococcosis

Pathology

Meningitis is localised mainly to the cerebral and cerebellar hemispheres, and the meningeal exudate is made up of a minimal inflammatory response.[133] The leptomeninges become thickened and the infection spreads along the distended Virchow-Robin spaces. The formation of perivascular granulomas, similar to tubercles, has been noted.[105,133] Changes in the brain are seen near the surface, but may extend deeper. Recent foci distort rather than destroy the brain tissue and produce gelatinous pseudocysts. There is only a minimal inflammatory reaction and this is usually delayed.[152] When present, it consists of lymphocytes, plasma cells, eosinophils and multinucleate giant cells. The nuclei of the giant cells are more centrally located than in the Langhans' cell and may contain cryptococci.[133]

There is a change in infection trend due to the marked improvement of the quality of life produced by the highly active antiretroviral therapy.[130]

Cryptococcal mass lesions may be seen in the subependymal regions of the thalamus and basal ganglia.[1] Multiple lesions may be found in up to 35% of cases.[11] Patients are mostly male and in the fifth decade.[1,11] Both cystic and granulomatous lesions have been identified.[48,89] The cerebral hemispheres are involved in 56%, the cerebellum in 10% and the spinal cord in 17%. Multiple organ involvement may be seen in up to 25% of cases.[65] The granulomas are greyish pink in colour and appear grossly encapsulated.[65] Some may be attached to the overlying dura. These are firm to hard in consistency. Histologically, the lesion presents the picture of a histiocytic granuloma. Depending on the tissue reaction, the lesion may appear gelatinous or granulomatous. Caseation is not seen. Staining techniques used for fungi, like PAS or mucicarmine, reveal the fungus, which appears as small yeast-like bodies approximately the size of an erythrocyte. These may be single or grouped in a jelly-like mass.

Spinal Cryptococcosis

Involvement of the spinal cord by Cryptococcus is quite rare. In 1951, Carton and Mount[24] reported one case of a cryptococcal granulomatous mass involving the spinal cord. In their review of the literature, they found ten cases with spinal cord involvement. In the same year, Ley et al.[82] described the successful removal of a cervical cord cryptococcal granulomatous mass, with good recovery of the patient. In 1954, Ramamurthi and Anguli[120] from India reported an intramedullary cryptococcal granuloma of the spinal cord which was removed surgically.

Pathology

Involvement of the spinal cord by Cryptococcus is usually in the form of compression by a granulomatous mass. This may be an infiltrating extradural mass,[84,123] an intradural extramedullary granuloma[24,82] or an intramedullary granuloma.[120] The lesion presents the picture of a histiocytic granuloma.[122] Caseation is not seen. Davidson, in 1968,[32] described spinal arachnoiditis due to Cryptococcus, a complication of cryptococcal infection of the CNS not described before.

Diagnosis

The diagnosis of cryptococcal involvement of the spinal cord should be considered in any patient with a subacute or chronic presentation, especially when superimposed on a previously existing debilitating disease. The chest X-ray may show the pulmonary pathology. CT and MRI show meningitis, granulomatous lesions and hydrocephalus. The CSF may be used for culture and serodiagnosis. While encapsulated budding cells may be seen in up to 90% of cases, their absence does not rule out the diagnosis.[32,161] The latex agglutination test for detection and titration of the polysaccharide capsular antigen is of diagnostic and prognostic value.[63,161]

Treatment

Treatment of cryptococcal infection is by a combination of amphotericin B and 5-fluorocytosine (Flucytosine), which provides the best opportunity for a cure.[15,154] Patients treated with amphotericin alone have a higher mortality and the organism becomes resistant to flucytosine when used alone.[161] Miconazole has been used intravenously and intrathecally, but its place in treatment regimes is less certain than the older drugs.[150] Garlic tablets were used as supplementary therapy by Tjia et al.[154] and the mortality was low. While cryptococcal meningitis is generally fatal if untreated,[161] there are reports of good recovery without drugs after removal of a granulomatous mass.[120] Elevated CSF pressure occurs in 75% of patients and is treated by repeated lumbar punctures, and lumbar drain or shunts are resorted to when these measures fail resulting in frank hydrocephalus.

ASPERGILLOSIS

Aspergillus species are among the commonest saprophytes and are found abundantly in the soil and decaying vegetation. *Aspergillus fumigatus* is the most common cause of granulomatous infection in man and in a recent series it was identified in 63% of cases. In the majority of cases infection occurs through haematogenous spread from a pulmonary or gastrointestinal focus.[23,36,102,103,165] Infection may be associated with an immunocompromised state[23,79] and may also occur during intravenous drug abuse,[72] open heart surgery,[34] trauma, etc. Infection may also start in the paranasal sinuses and mastoids and spread to the surrounding tissues[96,97,131] and the basal dura.[98] Cerebellar aspergilloma has been reported.[46] Generalised aspergillosis spreads to the nervous system in about 18–50% of cases,[23] both by direct and by haematogenous spread.[26,36] Rarely, it may be a post-surgical infection.[40] Aspergilloma refers to a large granuloma which sometimes is literally a ball of fungal elements.

The organism shows a high affinity for blood vessels. The vessel walls are invaded, resulting in secondary thrombosis and haemorrhage. Involvement of small vessels may lead to multiple small haemorrhagic infarcts.[104,161] Larger vessels, like the carotid artery or the basilar artery, may also be involved. Subarachnoid haemorrhage may occur from the rupture of mycotic aneurysms.

Abscesses may form and may be single or multiple. They are seen as pale areas with petechiae or as necrotic and haemorrhagic areas with a central cavitation. The most striking histological picture here is the vascular invasion and thrombosis. The degree of inflammation varies according to the stage of the infection and the individual patient. Granulomatous masses occur, either in association with a chronic infection or as a solitary mass. Microscopically, these are made up of aggregates of lymphocytes, plasma cells and epithelioid cells in necrotic tissue, with varying amounts of collagen. Langhans' type of giant cell may occasionally be seen.[31]

Clinically meningeal irritation is not a common feature, unlike in Cryptococcus infection. Focal deficits in the presence of immunocompromise should arouse the suspicion of infection.

Spinal aspergillosis is uncommon.[23] The infection may present with bone involvement, occasionally simulating spinal tuberculosis,[91] as an epidural abscess,[22,29] or there may be direct involvement of the spinal cord.[139] It may also present as infection of the disc space in patients who have undergone previous laminectomy,[90] or as part of the picture of systemic dissemination of the infection.[161]

Diagnosis of aspergillus is made following biopsy and culture of the fungus.[95] Patients with invasive aspergillosis may produce specific antibodies which may be detectable by ELISA, double diffusion or counter immunoelectrophoresis. As the aspergillus is not a member of the normal microflora, the detection of antibodies becomes significant.

As antifungal drugs are not very effective against aspergillus, excision of the mass lesions is the treatment of choice.[6,24,134,161] Operative decompression may be required for patients with granulomatous masses causing cord compression. Complete excision may not be possible and may cause cord damage. Amphotericin B in combination with 5-fluorocytosine are the drugs of choice. Recently, good results have also been achieved with imidazole derivatives, e.g. ketoconazole and miconazole. Itraconazole in high dose (16 mg/kg/day) is given. The prognosis of established CNS disease is poor. Voriconazole alone, or in combination, is currently the drug of choice.[136]

NORTH AMERICAN BLASTOMYCOSIS

Blastomycosis is a fungal infection caused by *Blastomyces dermatitidis*. It is a soil saprophyte and is endemic in the Mississippi and Ohio River valleys and the south-eastern parts of the United States of America, though occasional cases are being reported from Canada, Mexico, India, Africa and Latin America.[14,21,37,53,73,81] The infection is acquired by inhalation of air-borne spores and the formation of a primary pulmonary focus. The infection most commonly affects middle-aged healthy males who have a history of high alcohol consumption.[23] Involvement of the CNS follows haematogenous spread either directly or to adjacent bony structures with associated abscess formation.[121,149,161] CNS involvement by abscess, granuloma and meningitis has been reported.[49,161] The incidence of bone involvement in cases of systemic blastomycosis is about 30%.[127] The bones involved are, in the order of frequency, the vertebrae, ribs, tibia, skull and the tarsal and carpal bones.[30,52,162] Meningitis may be diffuse or localised to the base of the brain close to an abscess. It may occasionally be the result of spread from an extradural lesion. A thick fibrinopurulent exudate may cause obstructive hydrocephalus, the clinical course of which may be subacute or chronic.[55,133] Abscesses, if long standing, are enclosed in a thick capsule infiltrated

by plasma cells. The centre of the abscess contains caseous necrotic material with neutrophils and lymphocytes and is surrounded by epithelioid and Langhans' like giant cells.

Spinal blastomycosis commonly infects the thoracic and lumbar vertebrae, often leading to kyphosis.[23,77,161] Clinically and radiologically the disease may simulate tuberculosis.[23,37,161] Radiological findings include osteolytic lesions with minimal surrounding reactive bone changes and narrowing of the disc spaces with an adjacent paraspinal abscess. Vertebral collapse occurs late and there is a segment-to-segment spread.[52] Granulomatous lesions occurring in and around the spinal cord are difficult to differentiate from other causes of cord compression, except when presenting as a complication in pre-existing meningitis.[16]

The diagnosis is established by biopsy, fungal stains and appropriate cultures. There are no reliable serological tests for blastomycosis.[16,23,161] Treatment is by surgical removal of the lesion wherever possible and a full course of amphotericin B, which may cure the disease.[37,76,153,161]

NOCARDIOSIS

Nocard, in 1888, first described a granulomatous disease in cattle caused by a slow growing soil saprophyte. Nocardiosis is caused by organisms belonging to a group of actinomycetes. They are neither true bacteria nor fungi. *Nocardia asteroides* is common in the soil and in decaying vegetation, and is the only one of its group able to infect the CNS.[23] Though it may infect previously fit individuals, nocardiosis has a propensity for causing disease in debilitated, immunosuppressed individuals or those receiving immunosuppressive agents.[49] It has also been associated with AIDS.[23,161] Primary infection is pulmonary or cutaneous,[1,3] with the CNS involved in up to 44% of patients.[23,122]

In the brain, Nocardia produces abscesses, granulomas and meningitis. Abscesses may be single or multiple and are generally secondary to haematogenous spread. Microscopically, the abscesses have a fibrous wall infiltrated by neutrophils. Small abscesses occasionally coalesce to produce a large lesion.[133] Granulomatous lesions are rare. Microscopically, there are no giant cells. Meningitis occurs usually due to an underlying brain abscess. Clinically, systemic illness is apparent and the clinical signs are dependent on the location of the abscess or granuloma. Rarely cranial osteomyelitis and a cranial epidural abscess may occur.[161]

Treatment is with sulphonamides in combination with trimethoprim (4–8 g/day in divided doses for 6–12 months); erythromycin, amikacin, clindamycin and minocycline are also used. While occasionally good results have been achieved with medical therapy alone, drainage of the abscesses or surgical excision may be required for diagnosis and to relieve intracranial pressure.

Spinal involvement is rare and is usually a vertebral osteomyelitis, the organisms reaching the bone by haematogenous dissemination, or by contiguous spread between the retropleural veins and the Batson's plexus.[23]

Most patients present with signs of cord compression, often masquerading as a neoplasm or other granulomatous diseases, with which it often coexists.[164] Rarely, it may present as an extradural granuloma producing cord compression.[106] Spinal nocardiosis must be treated like any other spinal infection, and material must be obtained for histopathology and culture. Surgery is indicated in the presence of neurological deficits, when a decision must be made about decompressing the cord. Many drugs, e.g. sulphonamides, aminoglycosides, trimethoprim, rifamycin and ampicillin have anti-nocardial activity and have been used with good results.

COCCIDIOIDOMYCOSIS

Coccidioides immitis is a soil saprophyte in certain arid regions of the United States of America, Mexico and Central America. Infection results from inhalation of the spores, resulting in a primary pulmonary infection. The disease primarily affects previously healthy individuals.[20] Most infections are subclinical and, in endemic areas, a majority acquire immunity as the result of an asymptomatic primary pulmonary infection. Dissemination occurs in less than 0.5% of patients and about half of these patients run the risk of CNS involvement.

The organism elicits a granulomatous reaction in the CNS. The basal meninges may be studded with small granulomata containing plasma cells, lymphocytes, epithelioid cells and giant cells. Blood vessels may be involved. Occasionally, large intraparenchymal lesions may be formed either as granulomas or abscesses. Cranial osteomyelitis may also occur.

The clinical picture is mostly one of chronic meningitis similar to that of tuberculous meningitis. Hydrocephalus may supervene. Occasionally, patients may present with signs of a large space occupying lesion in the brain.

Vertebral infection may occur in the course of disseminated infection with coccidioidomycosis.[161] While the thoracic and lumbar spines are commonly involved,[23] occasionally the cervical spine may also be infected.[66] Clinically, the lesions present either acutely with pain and tenderness around the involved vertebra or chronically with sinus formation and paraspinal abscesses. Neurological involvement occurs with bone collapse or compression by epidural abscesses. Radiologically there may be involvement of the body, laminae, transverse processes or contiguous ribs, the intervertebral disc space being relatively spared. Sclerosis occurs as a late response to destructive lesions. Vertebra plana has also been reported.

Diagnosis is by a general examination to look for subcutaneous nodules, erythema nodosum or erythema multiforme. CSF, though being abnormal, is not specific for diagnosis. Serum and CSF antibodies are reliable indicators

of disease activity.[20,161] CT scan may show intense basal enhancement or granulomatous lesions. MRI shows evidence of meningitis, granulomas and hydrocephalus.

Large intracranial lesions require surgical excision. Decompression and stabilisation procedures may be necessary in spinal infection when there is a neurological deficit. Amphotericin B and ketoconazole are recommended drugs for the disease. Amphotericin B lipid complex has been found effective[5] as also itraconazole.[156] Prognosis in disseminated disease is not good. Coccidioidomycosis may be fatal, even without systemic dissemination, due to meningeal involvement.

CANDIDIASIS

Candida albicans is a true yeast and a normal constituent of the human flora. It is the single most common cause of human fungal infection: 27 out of the 57 cases of fungal infections of the CNS studied post-mortem by Carey[23] were due to candidiasis. Most of the Candida infections are due to infection from the oropharynx, skin, intestine and vagina of healthy individuals. In most clinical cases, infection is opportunistic and is found in association with surgical or other trauma, immunosuppression, prolonged antibiotic usage, drug abuse or AIDS. Infection in a previously healthy individual is also known. CNS infection is by haematogenous spread, though occasionally direct spread does occur through the oral cavity, orbit or middle ear following surgery or trauma. CNS involvement occurs in 50% of patients with systemic candidiasis and up to 80% of patients with Candida endocarditis.[59] CNS candidiasis may present as meningitis, a granuloma or as an abscess.[14] In the early stages, the lesions resemble haemorrhagic infarcts. These later develop into abscesses and granulomas without a central focus of necrosis.

Seventy per cent of patients with *Candida meningitis* have an extracranial focus of infection. Chronic meningitis with basal exudates may cause multiple lower cranial nerve palsies and/or hydrocephalus.

Candida granulomas are multiple and are most commonly located at the junction of the grey and white matter.[56] Mycotic aneurysms and abscesses are the other presentations of cerebral candidiasis. Occasionally, a patient with candidial endocarditis may present with a stroke due to embolic phenomena.

Candidiasis of the CNS cannot be identified by skin tests. Meningitis can be diagnosed by lumbar puncture and analysis of the CSF.[135] When mass lesions are suspected, CT or MR scan is the investigation of choice. CT scans in an immunocompromised patient may show areas of low density without enhancement. A high index of suspicion is necessary to diagnose Candida on culture as most often the growths are dismissed as contaminants.

Treatment is by removal of the source of infection at the earliest with control or stabilisation of the underlying debilitating disease. Untreated meningitis has a morbidity of 80%, while cure rates in patients with meningitis are about 90%.[14,59] Candida abscesses have a poor prognosis, death being usually due to multi-system failure. Definitive treatment of active infection is with amphotericin B alone (0.6–1.0 mg/kg daily in four divided doses) or in combination with 5-fluorocytosine (100–150 mg/kg daily in four divided doses). Mass lesions require surgical excision for diagnosis and as definitive treatment. Itraconazole, ketoconazole and nystatin may be used as prophylaxis in susceptible patients.

MUCORMYCOSIS

The clinical spectrum of mucormycosis is produced by several genera of fungi including Rhizopus, Rhizomucor and Absidia. Almost invariably, infection with this group of fungi is associated with some other significant disease like diabetes or with drug addiction.[54] The majority of patients have poorly controlled diabetes mellitus, the predisposing factor in such cases being the acidosis rather than the hyperglycaemia.[31] Renal transplant patients, patients with sepsis or severe dehydration and patients with haematological malignancies are affected.

The organisms spread by direct extension along nerves, blood vessels and cartilage. Entry into the CNS is from adjacent structures such as the paranasal sinuses or the orbit. The rhinocerebral form is the commonest type of penetration and is seen in 80–90% of cases.[1] Brain abscess may develop secondary to the pulmonary focus and is seen in immunocompromised patients. Like aspergillus, these organisms show a strong tendency to involve blood vessels. Mucormycosis should always be thought of while examining inflammatory or necrotic tissue from the orbit or nasal region. Microscopically, polymorphs are seen, clustered mainly around blood vessels. Non-septate hyphae with right angle branching are seen in large numbers around and within the walls of the blood vessels of the brain and meninges. A granuloma with giant cells is seen only rarely.[31]

The classical clinical picture of the rhinocerebral form is a poorly controlled diabetic patient with facial or periorbital pain and nasal discharge. Epistaxis may occur. Examination of the nose may reveal gangrenous changes in the turbinates. Black necrotic lesions may be seen on the hard palate. These are not pathognomonic for mucormycosis, as they may also be seen in Pseudomonas and Aspergillus infections.[56] External ophthalmoplegia and proptosis are common findings, and there may be loss of vision may secondary to central retinal artery occlusion. This finding is important, as vision is usually not lost early in bacterial cavernous sinus thrombosis. Eighty per cent of the patients have meningeal involvement by the time clinical signs become apparent. The fungus advances along the base of the brain and may cause facial nerve palsy. Carotid artery involvement may cause cerebral infarction and focal deficit, which is seen in one-third of the patients. Upwards extension of the infection through the orbital roof may result in a frontal lobe abscess.

A high index of suspicion is needed to diagnose mucormycosis, as isolation rates are very low.[11] Diagnosis is however on histology, as reliable serological tests have not been developed.

Mortality is high in this condition even with early institution of medical therapy with amphotericin B (0.6–1.25 mg/kg daily) as penetration of the drug into infected tissue is likely to be poor because of vascular occlusions and gangrene. With aggressive management, the mortality has been brought down to 15% in some series. The value of hyperbaric oxygen is unproven. Despite advances in surgery and antifungal medication, a mortality of 50–63% has been reported in large series.

PSEUDOALLESCHERIA BOYDII

The fungus *Pseudoallescheria boydii* and its asexual (synanmorphic) form the Scedosporium apiospermum is the causative factor of the Madura foot, a chronic suppurative infection common in the southern parts of India.[107] It is found in the soil, polluted water, sewage and manure. In 1964, a case of brain abscess was described and it is being diagnosed with greater frequency, especially in people who survive near drowning.[2,80,108] Direct entry from trauma, haematogenous spread from the lungs, and from IV cannulas and from infected sinuses and lumbar puncture can affect the CNS. Young adult males are the usual victims. After near drowning, signs and symptoms develop after 15–30 days, and can cause a spectrum of lesions: abscess, ventriculitis and ependymitis. The fungus is resistant to amphotericin and is sensitive to miconazole. It is treated with combination of antifungal drugs (terbinafine, caspofungin and voriconazole).[99]

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73 Viral Infections

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Viral infections of the central nervous system (CNS) are of interest to neurosurgeons, as they may have to treat the acute phase of some infections, help in establishing diagnosis by brain biopsy, or deal with the sequelae of viral infections like persistent pain or intractable epilepsy. The possibility of virus aetiology of CNS tumours is also an area of interest.

Recently, interest in viral infections has been renewed due to many factors: the emergence of HIV/AIDS; the increasing use of immunosuppression; the possibility of an increase in viral diseases due to the prevention of bacterial infections; rapid growth of the basic knowledge of virus biology and of CNS structure and function; improved diagnostic techniques enabling better study of viral infections of the CNS and the development of effective antiviral agents.[41,43]

Viruses are minute particles (virions) measuring 20–300 nm in diameter. They consist of only one type of nucleic acid either DNA or RNA, which is surrounded by a protein unit called capsomere, enveloped in a lipid membrane. Viruses may destroy a cell completely, live in it for many years to get reactivated, stimulate the cell to unrestricted growth or disrupt cell function without causing death of the cell.

The CNS seems especially susceptible to viral infections, due to its lack of capacity for regeneration and its complicated metabolic pattern. The presence of a blood-brain barrier, and a limited immune response, also contribute to this susceptibility. *Neurotrophism* refers to the affinity of a virus for a particular neural cell, and *Neurovirulence* is the ability of the virus to produce neurological disease.

Viruses enter the body through the skin, the gastrointestinal tract or the respiratory system. The spread of viruses in the body occurs through the bloodstream as in enteroviruses and measles and mumps viruses, or through the nerves as in polio, herpes and rabies. Neural spread is via axoplasmic transport through axons to the sensory ganglia. Viral spread along neurons may also occur via the perineural lymphatics or the Schwann cells surrounding the axons. It is the presence of specific viral receptors on the neural cells that makes the specific neurons susceptible. The other factors that determine susceptibility are the state of differentiation and mitotic activity of the neural cells, the density of the neural and supporting cells and the various CNS immune responses to viral infections.[43]

Immune responses induced in the body to viral infections may be humoral and directed against the virus particles, or cell mediated directed against the infected cell during which virus specific cytotoxic lymphocytes are generated. A variety of cytokines and lymphokines, such as interferons that limit viral replication, are also produced. Depressed cell mediated immunity leads to the development of viral diseases like subacute sclerosing panencephalitis (SSPE) due to measles virus, progressive multifocal leucoencephalopathy (PML) due to JC virus and encephalitis due to the herpes simplex virus (HSV) and the varicella zoster virus (VZV).[5,64,73] Depressed cell immunity may also lead to persistent polio or echovirus infections of the CNS.

Viral encephalitis may be produced by both conventional viruses and unconventional viruses.[5] The characteristics of conventional viruses have been described. The unconventional viruses, also called slow viruses or prions, contain protease resistant proteins, but neither DNA nor RNA.

Our understanding of viral diseases has been advanced considerably by recently developed technologies like improved methods of serological diagnosis, molecular diagnostic methods and neuroimaging techniques like MR and SPECT. Polymerase chain reaction (PCR) is considered the first line investigation for viral meningitis and encephalitis as a patient with a positive PCR result is 88 times as likely to have a definite diagnosis of viral infection of the CNS as a patient with a negative result.[40] Nucleic acid amplification methods have improved the detection of common (HSV, Enterovirus and VZV) and uncommon viral pathogens. The advantages are that the results of these tests are available more quickly and are more sensitive than viral cultures. Other viral causes of meningoencephalitis, such as arboviruses (including West Nile), can be identified by detection of IgM and IgG antibodies in CSF.[58,86]

HERPES SIMPLEX ENCEPHALITIS

Herpes simplex encephalitis (HSE) virus is the most common cause of viral encephalitis.[92] These viruses are of two types (HSV-1 and HSV-2) which, although morphologically identical, are composed of two antigenetically different viral agents.[60,65] Type I spreads through the oral route and Type II through genital contamination. HSE occurs in about one person per million per year[85] and

may occur at all ages and in both sexes. HSV-1 induces apoptosis (programmed cell death, or "cellular suicide") in neuronal cells, and it causes virtually all cases of HSE in immunocompetent older children and adults.[2,17] It can also cause sporadic necrotising encephalitis in adults.[74] The definition of intractable cases of HSE was developed as follows:[39]

- Cases of HSE that develop to an apallic state and lead to fatality
- Prolonged cases that require more than 6 months' hospitalisation
- Recurrent cases.

Maximum involvement is seen in the temporal and inferior frontal lobes. Oedema and haemorrhages are the prominent features. Lymphocytic infiltration, perivascular cuffing, necrosis and intranuclear inclusion bodies are also seen. The progression of symptoms simulates a tumour and uncal herniation can occur.

Following oral sores (cold sores), the patient develops headache, fever, disturbed consciousness with personality changes and seizures. Seizures may be the presenting feature in 50% of patients with HSE due to involvement of the highly epileptogenic frontotemporal cortex. The occurrence of seizures denotes a poor prognosis.[62] These viruses are also associated with Alzheimer's disease by interacting with the components and receptors of lipoproteins.[19,59]

CSF shows lymphocytosis and the EEG is pathognomonic with periodic high voltage discharges confined to the temporal region.[70] The diagnostic gold standard is the detection of HSV DNA in the cerebrospinal fluid by PCR. The HSV PCR has been noted to have a high sensitivity, around 96–98%. In cases with negative results but high clinical suspicion, the test should be repeated after 3–7 days, as the detection of virus may be difficult in the first few days of illness.[86] HSV-1 DNA may be recovered from the trigeminal ganglion in as many as 50% of ganglia sampled at autopsy.[69] Computed tomography (CT) and MRI show oedema and haemorrhages in the frontotemporal regions.

Brain biopsy from the temporal region with isolation of the virus was for many years a diagnostic measure. With immunofluorescence and electron microscopy, the diagnosis from the biopsy material can be confirmed within a few hours in the majority of cases.[76]

Adenine arabinoside (ara-A) was used as the specific treatment for a long time. Presently acyclovir is the drug of choice. Acyclovir is administered in a dose of 30 mg/kg body weight divided into three daily doses mixed with 100 ml of IV fluids and given over a 1 hour period.[12] The prompt response to early administration of acyclovir in suspected cases is diagnostic and has mostly eliminated the need for brain biopsy. Newer medication, like valacyclovir which provides a high bioavailability of acyclovir 3-fold to 5-fold higher than that obtained with oral acyclovir, is also in use.[80] When symptoms of raised intracranial pressure are present, hyperventilation and diuretics are indicated. If medical measures fail, temporal lobectomy should be done to relieve raised ICP.

Neonatal HSE is caused by HSV II. The infection is acquired by the infant during delivery. The mortality is high. When the mother has genital herpes, it is recommended that caesarean section is performed before the rupture of the membranes to prevent the child from acquiring the infection.

HERPES ZOSTER (VARICELLA ZOSTER)

Varicella (chickenpox) virus may cause meningoencephalitis, transverse myelitis, Guillain-Barré syndrome (GBS), Reye's syndrome or acute cerebellar ataxia. Recovery from meningoencephalitis and ataxia without residual defect is common.[68] Reye's syndrome and GBS may occur in association with other viral infections also. This virus can also cause vasculopathies which can lead to ischaemic infarction of the brain and spinal cord, as well as aneurysm formation, subarachnoid and cerebral haemorrhage, carotid dissection and, rarely, peripheral arterial disease.[32]

Herpes zoster is a late manifestation of varicella infection, and is often a reactivation of latent viral infection of the posterior root ganglion. Other areas where this virus can become latent are the nerve cell bodies, and also in the non-neuronal satellite cells of the cranial nerves or autonomic ganglia.[42] It is more common in the elderly and may affect the trigeminal, the geniculate or the dorsal root ganglion. Motor complications, like facial palsy or localised wasting of muscles, may occur in about 5% of cases. Facial nerve involvement in cephalic herpes zoster occurs in about 12% of patients, causing the Ramsay Hunt syndrome.[1] HSV can cause herpes zoster associated cerebral angiitis.[33] These can be seen as ovoid, round lesions at the grey-white matter junction on imaging.[86] Acyclovir is effective in treating herpes zoster and is helpful in reducing pain. This is given in a dosage of 10 mg/kg every 8 hours for 10–14 days.[23,86] Post-herpetic neuralgia may be a distressing phenomenon requiring treatment. Newer drugs, like valacyclovir and famciclovir, are considered to have similar or even superior efficacy and good safety and tolerability.[87]

RAMSAY HUNT SYNDROME

Also known as herpes zoster oticus, geniculate neuralgia or herpes zoster auricularis, it involves the facial and auditory nerves which accounts for 12% of all cases of facial nerve palsy.[63] It is the second most common cause of atraumatic peripheral facial nerve paralysis.[57] Vesicular eruptions may manifest on the pinna, tragus, in the auditory canal and on the tympanic membrane, as well as anywhere in the facial nerve distribution (Figs 1 to 3). The presenting complaints are hearing impairment, nystagmus, vertigo, facial nerve palsy (mimicking Bell's palsy) and loss of taste sensation in the anterior two-thirds of the tongue. The site of the lesion causing vestibular symptoms in RHS could be in the labyrinth, and/or in the superior and inferior vestibular nerve.[66]

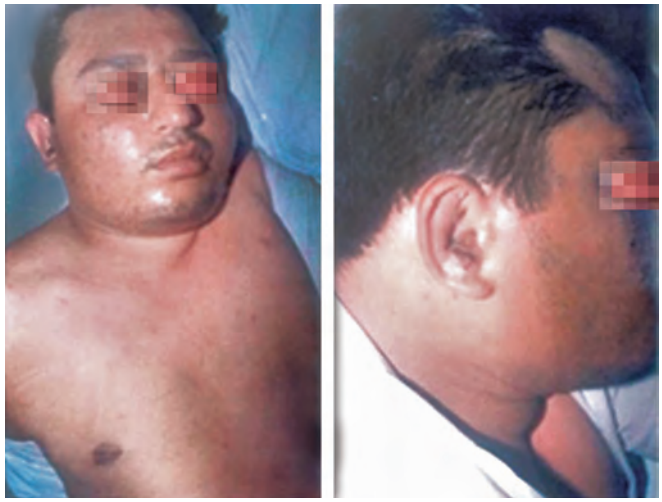

Fig. 1: Clinical photograph of patient showing vesicular rash on right ear pinna, facial nerve palsy and varicelliform rash on the face and trunk [Source: Meher R, Varshney S, Gupta P, et al. Herpes Zoster Oticus with Ménière's syndrome complex. The Internet Journal of Otorhinolaryngology. 2006;(4):2]

Compared with Bell's palsy, patients with zoster oticus often have more severe paralysis at onset and are less likely to recover completely.[57] Petrositis with multiple cranial nerve palsies is also seen in RHS.[25] At times there can be isolated CN VIII paresis without involvement of the facial nerve.[52] Magliulo et al. have described post-operative reactivation of RHS in a patient operated upon for acoustic neuroma.[54] Bilateral Ramsay Hunt syndrome has also been reported in diabetic patients and these patients should be treated with appropriate metabolic control, NSAIDs and intravenous acyclovir, which should be started at the earliest.[83]

Varicella zoster virus DNA level in saliva helps in understanding the kinetics of the viral reactivation in the facial nerve, as well as in the oropharyngeal epithelium, in patients with Ramsay Hunt syndrome.[29] This virus can be diagnosed using real time PCR in cerebral spinal fluid analysis.[30]

Brainstem auditory evoked response shows a significant increase in latencies of waves II and V and interpeak latencies of I-III, I-V suggesting cochlear or retrocochlear involvement or involvement at more than one site along the auditory pathway in Ramsay Hunt syndrome. Pure cochlear hearing loss is not common.[93]

MRI study of the brain shows enhancement of the facial nerves, along with the extent of intratemporal lesions of the facial nerve, especially in the labyrinthine segment[44] (Figs 4 and 5). 3D-FLAIR could be a useful diagnostic tool in the early stages of Ramsay Hunt syndrome which shows high signals in the cochlear and vestibular apparatus which is due to high protein content which is not detected by T1-weighted and T2-weighted MRI.[81]

Acyclovir and steroid therapy is an advisable treatment modality to improve the recovery rate of facial nerve function in Ramsay Hunt syndrome.[45]

REYE'S SYNDROME

This is of neurosurgical interest due to the cerebral oedema and high intracranial pressure seen in the condition. The syndrome was described in 1963. The administration of aspirin during a viral illness in children has been identified as a probable cause of this syndrome.[35] Some children who are recovering from viral infections may become ill with headache, vomiting, confusion and restlessness due to acute cerebral oedema and hepatic failure due to fatty infiltration of the liver. Serum ammonia levels are elevated and sugar levels are low.[35] Urgent treatment with hyperventilation, diuretics like mannitol or furosemide, and control of hypoglycaemia is indicted. The mortality rate is high.

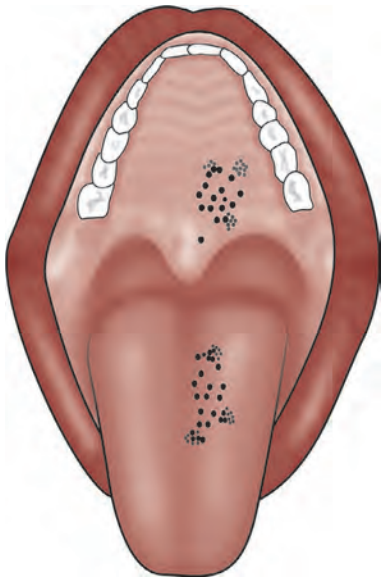

Fig. 2: Schematic representation showing vesicles on the tongue

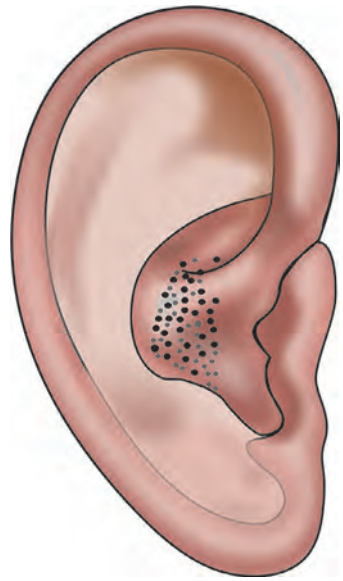

Fig. 3: Schematic representation showing vesicles in the ear

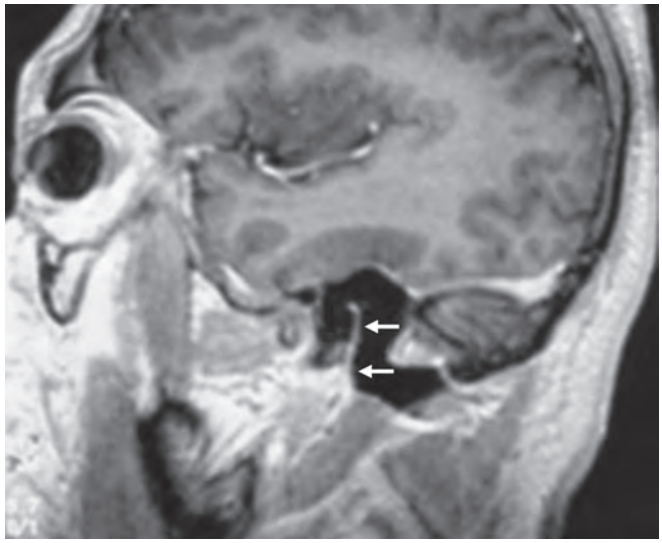

Fig. 4: Parasagittal contrast enhanced MRI images demonstrating enhancement of mastoid segment of facial nerve (arrows) [Source: Meher R, Varshney S, Gupta P, et al. Herpes Zoster Oticus with Ménière's syndrome complex. The Internet Journal of Otorhinolaryngology. 2006;(4):2]

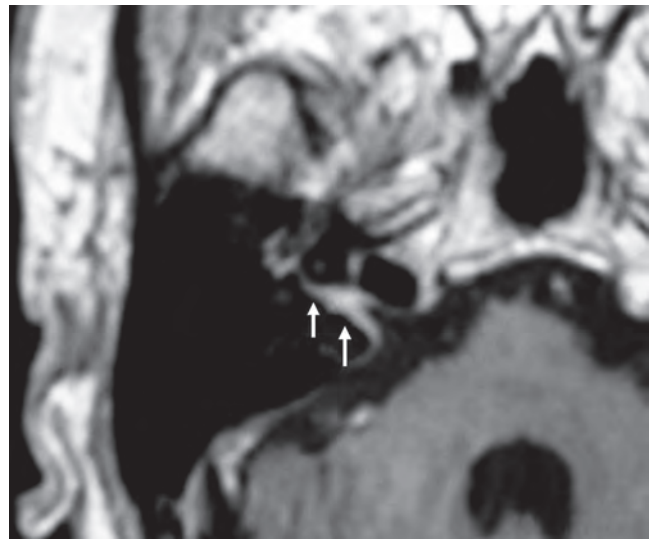

Fig. 5: Contrast enhanced axial MRI images demonstrating enhancement of right VII and VIII nerve in canalicular course [Source: Meher R, Varshney S, Gupta P, et al. Herpes Zoster Oticus with Ménière's syndrome complex. The Internet Journal of Otorhinolaryngology. 2006;(4):2]

CREUTZFELDT-JAKOB DISEASE

Creutzfeldt-Jakob disease (CJD) is caused by slow viruses or prions that cause Kuru. The neurosurgical interest is brain biopsy to establish the diagnosis. Extreme care is needed during such a procedure to prevent transmission of the disease to other patients and to the surgeons. The other human disease caused by slow viruses is Gerstmann-Straussler syndrome. CJD presents as a subacute dementia, evolving over weeks to several months and is accompanied by pyramidal, extrapyramidal and cerebellar signs. The iatrogenic route is the only route of transmission (contaminated surgical instruments such as EEG electrodes, organ transplants such as cornea transplants and growth hormone prepared from human pituitaries). Mad cow disease caused by consumption of infected beef is a variant of CJD which acquired epidemic proportion in the UK.

POLYOMA VIRUS

These viruses cause progressive multifocal leucoencephalopathy (PML). Although rare, it causes a fatal brain disease. They are also associated with novel neurological disorders such as granule cell neuronopathy and virus encephalopathy, and also cause meningitis. Other diseases caused by these viruses are the immune reconstitution inflammatory syndrome (IRIS).[84]

RABIES VIRUS

This belongs to the Lyassavirus group of the Rhabdoviridae. It contains a single stranded RNA with a helical symmetry. Six to seven nanometres spike projections are present on the envelope and on electron microscopy it has a characteristic bullet-shaped appearance; the virion measures 130–240 x 80 nm. The commonest mode of transmission in man is by the bite of a rabid animal or the contamination of scratch wounds by virus infected saliva. Other modes of transmission are mucous membranes of the mouth, conjunctiva, anus and genitalia, aerosol transmission and infected corneas.

Following inoculation, the virus replicates in the striated or connective tissue at the site of inoculation and enters the peripheral nerves through the neuromuscular junction spreading to the CNS in the endoneurium of the Schwann cells. Finally, there is widespread CNS involvement with the neurons infected with the virus showing structural abnormalities.

Within 2–3 weeks of the rabid dog bite the patient suffers with flu-like symptoms. Soon after, the symptoms expand to slight or partial paralysis, cerebral dysfunction, anxiety, insomnia, confusion, agitation, abnormal behaviour, paranoia, terror and hallucinations, progressing to delirium.[13] These symptoms progress to hydrophobia, brain damage and finally death.

The method for diagnosing rabies is by performing PCR or viral culture on brain samples taken after death. The diagnosis can also reliably be made from skin samples taken before death.[14] Inclusion bodies called Negri bodies are 100% diagnostic for rabies infection, but are found in only about 80% of cases in the saliva and CSF.[20]

One dose of *human rabies immunoglobulin* (HRIG) and four doses of rabies vaccine over a 14-day period should be administered following a bite by a suspected rabid animal. As much as possible of this dose should be infiltrated around the bites, with the remainder being given by deep intramuscular injection at a site distant from the vaccination site.[71]

ENTEROVIRUS CENTRAL NERVOUS SYSTEM INFECTIONS

Approximately 26% of adult aseptic meningitis cases for which an aetiological agent is identified are caused by enteroviruses.[49] These cause hand, foot and mouth disease in association with brainstem encephalitis.[96]

PCR of CSF has proven to be a sensitive test with great cost-saving capabilities, as the patients with positive PCR tests tend to have shorter hospital stays, fewer tests performed and receive IV antibiotics for less time.[4] MR imaging shows hyperintensities in T2-weighted images in the brainstem and spinal cord. The major CNS lesions are in the medulla oblongata, pons, midbrain and the dentate nuclei of the cerebellum. Other lesions are seen in the spinal cord, thalamus and putamen.[77] Pleconaril is an effective drug along with adjuvant corticosteroids.

H1N1 VIRUS

A new pandemic arose in the United States in April, 2009 which was swine-origin influenza A (H1N1) virus. The H1N1 virus usually causes febrile respiratory symptoms including fever, cough, sore throat, etc.[16] These symptoms are usually self-limiting, but they can cause neurological symptoms like seizures and altered sensorium with abnormal electroencephalograms.

The findings on MRI in brainstem encephalitis include pontine enlargement and increased signal lesions in the pons. MRI is superior to CT for detecting brainstem encephalitis.[15,28] Oseltamivir and rimantadine are useful in therapy.[8]

EPSTEIN-BARR VIRUS

Epstein-Barr virus (EBV) causes aseptic meningitis, encephalo-myelo-neuritis and neuritis. The EBV neuropathies present with ophthalmoplegia, lumbosacral plexopathy, and sensory or autonomic neuropathy. The association of the virus with neurological disease was suggested by a positive serum heterophile antibody titer, and later by the presence of EBV DNA, antibody or both in CSF.[3] CSF from patients with EBV infection of the nervous system contains mainly EBV-specific CD8+ T cells, a few CD4+ T cells and no CD19+ B cells.[51]

EBV infects B and T lymphocytes of more than 90% of the general population before adulthood. Primary infection results in transient viraemia, followed by a rapid immune response. EBV replicates in the oropharynx and is transmitted through oral secretions. It is estimated that neurological complications occur in 1–5% of individuals with infectious mononucleosis. Virtually all CNS lymphomas in AIDS patients contain EBV DNA.[53] These also cause infectious mononucleosis, nasopharyngeal carcinoma, Burkitt's lymphoma, Hodgkin's disease and lymphoproliferative disease in immunocompromised individuals.[11]

CYTOMEGALOVIRUS

Cytomegalovirus (CMV) produces neurological disease predominantly in infants with congenital infection. Neurological complications include microcephaly, seizures, hypotonia, acute brachial plexopathy and spasticity. In immunocompetent adults, the most common neurological complication of CMV infection is Guillain-Barré syndrome.[21] CMV polyradiculopathy in patients with AIDS begins insidiously as a cauda equina syndrome with paraesthesias and distal weakness (usually asymmetric), incontinence, and sacral-distribution sensory loss.[24] CSF might show neutrophilic or mononuclear pleocytosis, or an elevated protein and depressed glucose content. Imaging studies (MRI) show enhancement in the ventricular ependymal and focal disease has been attributed to CMV vasculitis or demyelination. Characteristic owl-eyed cytomegalic inclusions and CMV-specific antigens have been found in brain tissue and blood vessels of AIDS patients with subacute encephalopathy.

An international panel that developed guidelines for treatment of CMV diseases in adults with AIDS receiving highly active antiretroviral therapy recommended treatment with intravenous ganciclovir, intravenous foscarnet, or a combination of the two drugs.[91]

HUMAN HERPES VIRUS 6

Human herpes virus 6 (HHV-6) causes Roseola. This virus causes neurological complications primarily after bone marrow or stem cell transplantation,[95] presenting as limbic encephalitis.[89]

Diagnosis is confirmed by detection of HHV-6 DNA in the CSF. RT-PCR (98%) is more specific than PCR (84%) in diagnosing active infections. As HHV-6 becomes latent in cells of the monocyte-macrophage lineage,[46] the detection of HHV-6 DNA and antigen in brain tissue is likely to reflect HHV-6 reactivation from latency in blood mononuclear cells trafficking through the brain in patients with inflammatory CNS disease. CD46 is a HHV-6 receptor that is expressed mostly in macrophages and cells lining blood vessels, and less often in cells of neuronal origin. HHV-6 expresses proinflammatory cytokines that are cytotoxic to oligodendrocytes and induce caspase-independent apoptosis.[46] HHV-6 has also been shown to inhibit G1–S-phase transition in glial precursor cells, which are important in remyelination.[18] Treatment includes ganciclovir, foscarnet or both. Real-time fluorescent probe CSF PCR has been used to follow the effects of antiviral therapy on HHV-6 DNA levels in the CSF.[94]

JAPANESE ENCEPHALITIS

This is caused by Flavi virus. It is the most common vaccine-preventable cause of encephalitis in Asia.[26,36] Among the affected individuals 20–30% of patients die, and 30–50% of survivors have neurological or psychiatric sequelae.[38,67]

After an incubation period of 5–15 days, symptoms develop. These include fever, headache and other non-specific symptoms. The classical description of JE includes a Parkinsonian syndrome with mask-like facies, tremor, cog wheel rigidity and choreoathetoid movements.[61,79] Seizures are common, especially among children.[47,48,61,72,75,78] Status epilepticus, brain hypoxia, increased intracranial pressure, brainstem herniation and aspiration pneumonia are the most common complications associated with poor outcome and death.[37,47,78,79]

Microglial activation following JEV infection has been found to influence the outcome of viral pathogenesis. Activated microglia secrete cytokines, such as interleukin-1 (IL-1) and tumour necrosis factor alpha (TNF-α), which can cause toxic effects in the brain. Other soluble factors, such as neurotoxins, excitatory neurotransmitters, prostaglandin, reactive oxygen and nitrogen species, are secreted by activated microglia. In JE, the tight regulation of microglial activation appears to be disturbed, resulting in an autotoxic loop of microglial activation that possibly leads to bystander neuronal damage.[31]

MRI of the brain is better than CT for detecting JEV associated abnormalities such as changes in the thalamus, basal ganglia, midbrain, pons and medulla.[61,90] Thalamic lesions are the most commonly described abnormality; although these can be highly specific for JE in the appropriate clinical context, they are not a very sensitive marker of JE.[22]

JEV infections are confirmed most frequently by detection of virus-specific antibody in CSF or serum. Acute-phase specimens should be tested for JEV-specific immunoglobulin M (IgM) antibodies using a capture enzyme-linked immunosorbent assay (MAC ELISA).[6,7,10,55,56,88] More recent studies have shown the utility of nucleic acid amplification tests (NAAT) for diagnosing JE in some patients with encephalitis or aseptic meningitis, but this method still lacks the sensitivity needed for routine diagnosis.[50,82] JEV-specific IgM antibodies can be measured in the CSF of most patients by 4 days after onset of symptoms and in serum by 7 days after onset.[7,10]

No specific antiviral agent or other medication to mitigate the effects of JEV infection is available.[34] An inactivated mouse brain-derived JE vaccine (JE-MB) has been available since 1992 for use in travellers aged greater than or equal to 1 year. Three doses are administered subcutaneously on days 0, 7 and 30 through the subcutaneous route.[9] In March 2009, the Food and Drug Administration (FDA) approved a new inactivated Vero cell culture-derived JE vaccine (JE-VC) for use in persons aged greater than or equal to 17 years.[27] This is given in two doses of 0.5 ml each by the intramuscular route administered 28 days apart.

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74 AIDS and the Neurosurgeon

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HISTORICAL PERSPECTIVE

It was in the early 1980s that a number of gay men in New York and California suddenly began to develop rare cancers and opportunistic infections. The cause for it soon became obvious that they were suffering from a common syndrome which was later named as the acquired immunodeficiency syndrome (AIDS). In 1981,[4] the discovery of human immunodeficiency virus I (HIV I) was made by Barre'-Sinoussi, Montagnier and colleagues.[2] Subsequently, a second virus has been isolated from Western Africa and has been named HIV II.

THE VIRUS

HIV is a type of RNA virus, known as lentivirus[2] which is sub-grouped under the Retroviruses, and attacks the immune system. Lentivirus means 'slow virus' because it takes long to produce symptoms in a patient. HIV virion is icosahedral in shape. The envelope contains two major proteins (gp 120 and gp 41) which form external spikes and it has nine genes. Three genes (gag, pol and env) are needed to make the structural proteins for the new virus particles. HIV is a zoonotic infection, similar viruses have been found in a number of different animals, including sheep, horses and cattle. It is now generally accepted that the lentiviruses are descendants of Simian immunodeficiency virus, which affects Monkeys.[1,5,14]

HIV virus has been found in the body fluids like semen, cervical secretions, plasma, CSF, tears, saliva, urine and breast milk. The concentration of virus in these fluids varies considerably and the most infectious are semen, cervical secretions and blood. The most common modes of transmission are by intimate sexual contact, (anal, vaginal or oral),[32] transfusion of infected blood products, use of contaminated needles, and from mother to child *in utero* or at birth.

Receptive anal intercourse has a strong association with HIV because only thin rectal mucosa separates the semen from the susceptible cells and trauma may be associated with it, leading to direct inoculation into the blood. Occupational risk of acquiring HIV in health and related field workers is around 0.3% with a needle prick, which was contaminated with blood from a HIV positive person.

PATHOGENESIS

Once the virus has gained entry into the body of the host, it attaches to a special glycoprotein called CD4 present on the helper/inducer T cells. This allows the viral envelope to fuse with the cell membrane, and contents of the HIV particle enter the cell. Inside the cell the viral enzyme, reverse transcriptase, converts viral RNA into DNA, which attaches to the human DNA by the HIV enzyme integrase. This provirus may lie dormant for a long time but, on activation of the cell, the HIV gene is converted into messenger RNA using the human enzymes and it is transported outside the nucleus, where it is used as a blueprint for producing new HIV enzymes and proteins. These together form new viral particles which are released from the cells and infect new cells, starting the cycle again. CD4 helper T cells are important for a strong immunological response against foreign antigens. They secrete interleukin 2, interferon, and B cell growth and differentiating factors. They also help in activating CD8 T cells, B cells and macrophages. The defects in immunity are not only explained by the quantitative abnormalities of the lymphocytes, but also by the qualitative defects of the CD4 responsiveness caused by HIV. The defect in the B cells leads to generalised hypergammaglobulinaemia and can depress B cell responsiveness to new antigens. Therefore, the immunodeficiency of HIV is mixed where both humoral and cellular immunity are affected.

The virus directly causes a variety of neurologic effects, mostly due to release of cytokines and other neurotoxins by the infected macrophages and microglia. HIV mediated effects on neurons and oligodendrocytes are felt to involve indirect pathways where viral proteins, like gp120 and Tat, trigger the release of neurotoxins from the macrophages and also from the astrocytes. Impairment of excitatory neurotransmitters and calcium flux are also implicated for neurological deterioration.

CLINICAL FEATURES[7,19,25,35,37,44]

The complications of HIV related infections and neoplasms affect virtually every organ system. This varied clinical spectrum of illness ranges from an acute seroconversion illness to a chronic asymptomatic carrier to full blown AIDS. The acute HIV syndrome is seen in 50–70% of individuals infected with HIV, approximately

3–6 weeks after the primary infection. The typical symptoms are fever, pharyngitis, lymphadenopathy, headache, retro-orbital pain, arthralgias, myalgias, lethargy, malaise, anorexia and nausea. Neurological features may include meningitis, encephalitis, peripheral neuropathy,[34] myelopathy, dermatological rash and mucocutaneous ulceration. These symptoms occur with an initial burst of plasma viraemia. Symptoms can persist for one to several weeks and gradually subside, with development of the immune response. In most patients, the primary infection with or without this syndrome is followed by a period of prolonged latency. The median time for untreated patients is around 10 years, from the initial infection to the development of clinical disease. HIV disease with active replication continues during this latent asymptomatic period and this progression directly correlates with the HIV RNA levels. The hallmark of progressive disease is declining number of CD4 lymphocytes and a low CD4/CD8 ratio. Patients with positive HIV serology and who have ever had a CD4 lymphocyte count below 200 cells/mcL or a CD4 lymphocyte percentage below 14% are considered to have AIDS, because the resulting state of immunodeficiency with such low levels of CD4+ T cells count is severe enough to predispose the individual to opportunistic infections and neoplasms and hence for clinically apparent disease.

When symptoms of HIV occur they are remarkably non-specific and may be seen with other diseases as well. Physical examination may entirely be normal and abnormal findings range from completely non-specific findings of generalised lymphadenopathy to highly specific findings of hairy leukoplakia of the tongue, Kaposi's sarcoma and cutaneous bacillary angiomatosis. Systemic complaints include fever, weight loss and night sweats. Weight loss involves disproportionate loss of the muscle mass and is attributed to multiple factors like anorexia, nausea, vomiting, malabsorption, recurrent diarrhoea and increased metabolism due to fever.

Pulmonary diseases, like *Pneumocystis pneumoniae*, are one of the most common opportunistic infections associated with AIDS; other infections include bacterial, mycobacterial and viral pneumonias. Apical infiltrates and disseminated disease associated with mycobacteria are more common in AIDS patients when compared with immunocompetent persons. The 'anergy' skin tests like Mantoux are not accurate in classifying these patients. Multidrug resistant tuberculosis in this subset of the population is increasing. Other lung diseases associated with HIV are Kaposi's sarcoma, non-Hodgkin's lymphoma and interstitial pneumonitis.

Gastrointestinal manifestations include oral candidiasis or hairy leukoplakia which is caused by Epstein Barr virus, angular cheilitis, recurrent aphthous ulcers, candidial oesophagitis, hepatic disease due to infections (mycobacteria, CMV, hepatitis B/C) and neoplasms like lymphomas, acalculous cholecystitis, enterocolitis and malabsorption syndrome.

Endocrine dysfunctions are hypogonadism in men and thyroid function abnormalities.

Skin manifestations include viral infections (herpes simplex, herpes zoster, molluscum contagiosum from poxvirus), bacterial infections (Staphylococcal boils, furuncles, impetigo; bacillary angiomatosis due to *Bartonella hensalae* and *Bartonella quintana*) seborrhoeic dermatitis, xerosis, psoriasis and skin malignancies.

HIV related malignancies include Kaposi's sarcoma, Non-Hodgkin's lymphoma, primary CNS lymphoma (PCNSL) and invasive cervical carcinoma.

NEUROLOGICAL MANIFESTATIONS OF ACQUIRED IMMUNODEFICIENCY SYNDROME

With the ever increasing number of cases of AIDS in the developing countries the problem of HIV infected patients seeking neurosurgical consultations is increasing. It is believed that 40–60% of all patients with acquired immunodeficiency syndrome will develop neurological symptoms with one-third of these presenting initially with their neurological complaint.[26,30,31,36,39,42,43] Only 5% of patients dying of AIDS have a normal brain on autopsy. The CNS complications of AIDS as shown by the study of Levy et al.[30] and Shankar et al.[39] are summarised in Table 1.

It can be seen from Table 1 that, in the Indian setting, the incidence of cryptococcal and (especially) tubercular infections is much higher as compared to the Western literature. Likewise the incidence of PCNSLs has also been quoted to be much less.

PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA

Primary CNS lymphoma is a primary intracranial tumour occurring commonly in patients who are immune suppressed and typically in AIDS. However, its incidence has been quoted to be very low.[39,45] More than 90% are associated with Epstein Barr virus infection[13] and 20% of all cases of lymphomas in AIDS are due to PCNSL; these are seen to occur in 10% cases of AIDS.[27] Mean CD4+ count at the time of diagnosis is around 50/μL; thus due to severe immune suppression the prognosis is poor. In the immune competent population PCNSL occurs in the later age group, i.e. 50–60 years, median age being 54 years[33,36] (in immune compromised patients median age at diagnosis is 34 years). There is an increasing trend in incidence of PCNSL in the immune competent population.

Most PCNSLs are diffuse large B cell Non-Hodgkin lymphomas and they occur more commonly in the frontal lobes, deep nuclei and periventricular region in the supratentorial compartment, while in the infratentorial compartment the commonest location is the cere bellum.[21,33,38,41] They present with seizures, headache, cranial nerve deficits, altered sensorium and features of mass effect, associated with systemic features of fever, night sweats or weight loss.[21]

Table 1: CNS complications of AIDS (320 patients)[30] (clinical: 588; autopsy: 134)[39,45]

Complication	*Levy et al. (%); clinical*	*Chandra PS et al. (%); clinical*	*Shankar et al. (%); autopsy*	*Wadia et al. (%); clinical*
Viral syndrome				
Sub-acute encephalitis	17			
Atypical aseptic meningitis	6.5			
Herpes-simplex encephalitis	2.8			
Progressive multifocal leukoencephalopathy	1.9			
Viral myelitis	0.93			
Varicella zoster encephalitis	0.31			
Non-viral infections				
Toxoplasma gondii	> 32	12	20	
Cryptococcus neoformans	13	25	30	67
Candida albicans	1.9			
Coccidioidomycosis	0.31			
Treponema pallidum	0.62			
Atypical mycobacteria	1.9			
Mycobacterium tuberculosis	0.31	30	20	19
Aspergillus fumigatus	0.31			
Bacteria (*E. coli*)	0.31			
Neoplasms				
Primary CNS lymphoma	4.7	uncommon	uncommon	uncommon
Systemic lymphoma with CNS involvement	3.8			
Kaposi's sarcoma	0.93			
CVA				
Infarct	1.6			
Intracerebral haemorrhage	1.2			
Miscellaneous/Unknown	7.8			

Imaging (MRI) shows multiple ring enhancing lesions (one to three), usually in the deep white matter (Figs 1A to H). They usually present with multiple ring enhancing lesions with mild mass effect and oedema on CT. On MRI, unlike non-AIDS cases where homogeneous enhancement of contrast is seen, these patients have target lesions on T2-weighted images (hypointense centre with surrounding hyperintensity). Higher incidence of multicentric lesions is seen in AIDS patients compared to non-AIDS cases of PCNSL.

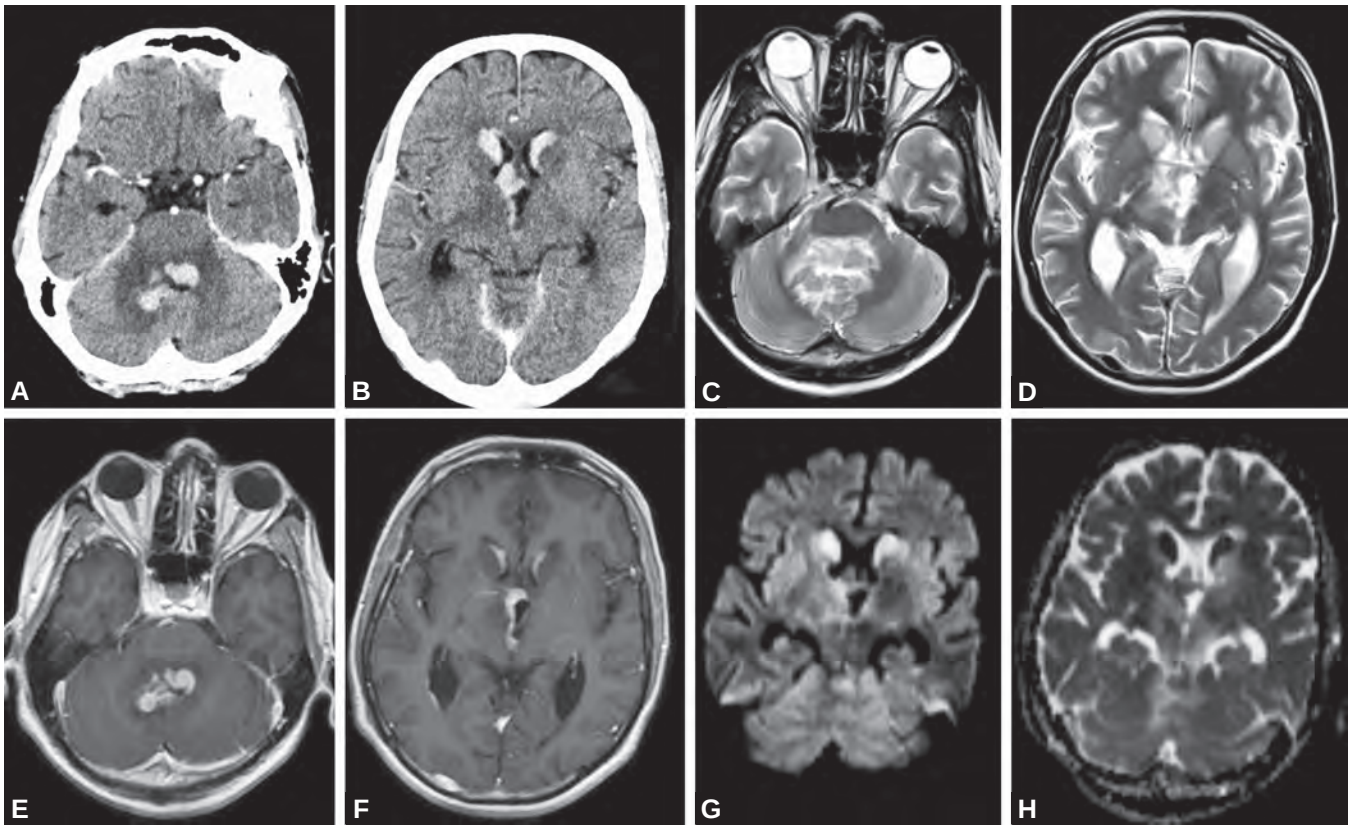
Differentiation with toxoplasmosis may be difficult needing confirmatory brain biopsy in solitary lesions or when trial toxoplasmosis therapy has failed. Surgical decompression does not alter the prognosis and the role of surgery is usually limited to biopsy, for which stereotactic techniques are commonly used as the lesions are often deep seated.

The treatment of choice, once the diagnosis is confirmed by biopsy, is whole brain radiation therapy, a total of 40–50 Gy given in 1.8–3 Gy daily fractions along with corticosteroids. This produces partial response in more than 90% of the patients. Median survival for patients with AIDS is less in comparison to the immune competent patients where it is 10–18 months. Survival advantage is seen with the addition of intraventricular methotrexate and IV folinic acid (leucovorin),[9] but in patients older than 60 years radiation is not recommended in conjunction with methotrexate due to increased risk of leukoencephalopathy and dementia. In patients with AIDS the highly active anti-retroviral therapy which affects the CD4+ count is also important for the final prognosis. In AIDS, the median survival is 3–5 months only.[9,10]

PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

It is usually a fatal viral disease caused by a polyomavirus called "JC virus". The antibodies for JCV are present in 60–80% of adults, but usually remain latent[11] and cause PML specifically in patients who are immunocompromised, e.g. AIDS, allograft recipients,[11] patients receiving chemotherapy, drugs (like natalizumab and infliximab[29]), chronic steroid therapy and autoimmune disorders (like SLE). It is believed that PML occurs more commonly in HIV infection in comparison to any other immune suppressive condition because HIV infection of the brain makes JCV more active in the brain.[11] There has been an extremely low incidence of PML in India, and this may be due to some factors such as viral strain differences as well as HIV and JC virus interactions.[40]

PML is characterised by progressive damage or inflammation of the white matter of the brain at multiple locations. Focal myelin loss occurs with sparing of the axon cylinders, causing impairment in transmission of the nerve impulses. These are surrounded by the enlarged astrocytes and abnormal oligodendroglia with eosinophilic inclusion bodies. Symptoms include



Figs 1A to H: Primary CNS lymphoma. (A and B) Contrast enhanced CT scan images show (A) Periventricular homogeneously enhancing lesions in the dorsal pons. (B) Around the third ventricle and frontal horns of lateral ventricles. (C and D) The lesions are isointense on T2-weighted images with surrounding oedema. (E and F) On post-gadolinium T1-weighted images, homogeneous enhancement is seen within the lesions and around the right occipital horn. On diffusion-weighted images, the lesions are (G) Bright on diffusion trace image. (H) Dark on ADC maps suggesting restricted diffusion

cognitive impairment, blindness, cranial nerve or motor weakness, sensory deficit and ultimately coma. PML is like other demyelinating diseases but, since oligodendrocytes, which are myelin producing cells are destroyed, it progresses more rapidly and leads to death within a few months. The median survival with PML in patients with AIDS is 6 months, but longer survival is also seen. Confirmatory diagnosis of PML is made by testing for JC virus in CSF or in brain biopsy.

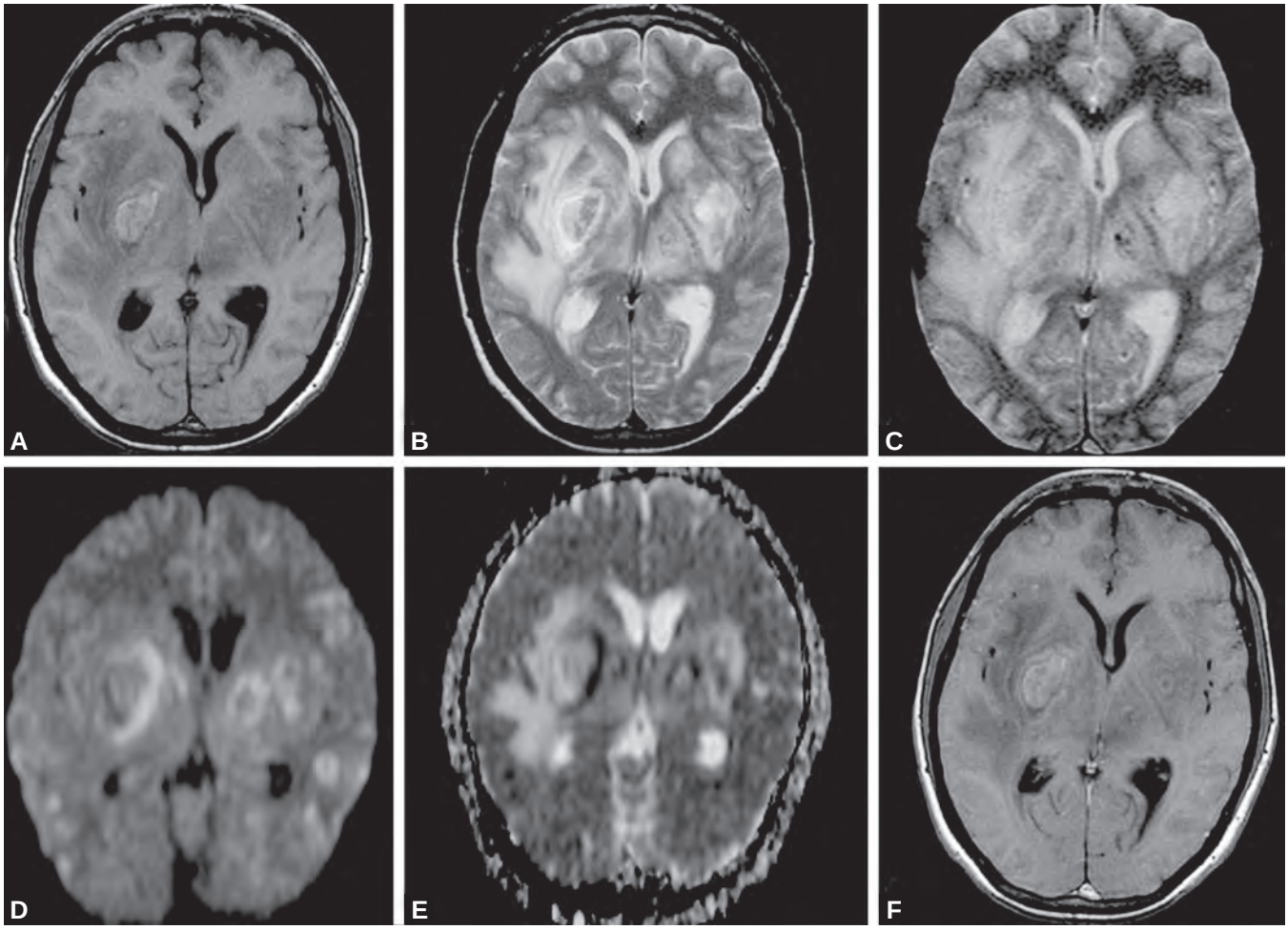
CT scan shows areas of diffuse low density and MRI shows high intensity areas on T2-weighted images. The virus attacks the oligodendrocytes and hence there is progressive involvement of the white matter. Contrast enhancement is absent because there is absence of inflammatory response. Extensive white matter high signal on T2 weighted/FLAIR (fluid attenuated inversion recovery) is therefore the hallmark of this disease with sparing of the cortical grey matter.[11]

No enhancement on contrast, no mass effect, no oedema and more ill defined borders help in distinguishing it from toxoplasmosis. The lesion may be solitary in 36% of CT and 13% of MRI scans.

No treatment is effective, although some promise has been shown with the use of antiretroviral therapy initially, as the immunity improves.[12] However, patients on highly active antiretroviral therapy (HAART) can develop a rare fatal complication of immune reconstitution syndrome which increases the damage caused by the infection.

TOXOPLASMOSIS

It is the most common cause of a space occupying lesion of the CNS in patients with HIV.[39,45] Patients present with headache, focal neurological deficits, seizures and cognitive deficits. Imaging studies show typical peripheral contrast enhancing lesions which have a predilection for the basal ganglia (Figs 2A to F). The major differential diagnosis may be lymphoma and distinction between the two may be impossible in some cases. Features that favour toxoplasmosis are basal ganglia involvement, variable contrast enhancement, ring enhancement and micro haemorrhages. AIDS related lymphoma, in contrast to classical lymphoma, can also be cortical and tends to involve the grey and white matter, is associated with leptomeningeal thickening and is occasionally subependymal or wholly intraventricular. For a single lesion on MRI, an empiric trial of toxoplasmosis therapy may be instituted and MRI is repeated after 2 weeks. If the lesion has not decreased in size, then biopsy of the lesion is indicated to confirm the diagnosis. Toxoplasmal infection can also cause meningoencephalitis and encephalopathy.[39] This usually occurs when CD4 titres fall below 200/mcL.



Figs 2A to F: Cerebral toxoplasmosis. (A) Axial T1-weighted image and (B) Axial T2-weighted image showing multiple ring lesions in bilateral basal gaglion and subcortical white matter. The core of the lesions is (C) Hyperintense on T1-weighted image and (D) Hypointense on T2-gradient image suggesting bleed within the lesions. On diffusion-weighted images, the lesions have (D) Incomplete peripheral hyperintense rim on DWI and dark rim on ADC maps suggesting peripheral diffuse restriction. (E and F) On gadolinium administration, faint enhancement is seen within the lesions, especially subcortical lesions. (*Courtesy*: Dr Ajay Garg, Assistant Professor, Dept of Neuroradiology, AIIMS)

MENINGITIS

Cryptococcal Meningitis

This has been reported to be the commonest opportunistic infection in India[39,45] ranging 25–67%. Diagnosis in patients with AIDS, presenting with features of fever, headache and meningismus is based on positive latex agglutination test (CRAG positive = 70%) or positive spinal fluid examination for *Cryptococcus*. Classical meningial signs may or may not be present. Meningismus is present in less than 20%. Treatment with Amphotericin B and flucytosine for 6–8 weeks is moderately effective in eradicating the infection.

Carcinomatous Meningitis

This can occur in patients with lymphoma, presenting with features of multiple cranial nerve involvement and meningeal signs. CSF may not show any abnormality, but biopsy is diagnostic. Radiotherapy to the skull base and intrathecal methotrexate are the available treatment options, but the prognosis remains poor.

Aseptic Meningitis

It can occur in 1–2% cases of recently infected individuals.[12] A more indolent aseptic meningitis is seen in around 60% cases of HIV carriers.[23] CSF examination is suggestive of meningitis, but serological and culture tests are negative. HIV has been isolated from the CSF, and is believed to be the pathogenic organism.[22]

TUBERCULAR INFECTION

It is one of the most common infections associated in HIV-AIDS in India has been dealt in the chapter on Tuberculosis of the Central Nervous System.

AIDS ENCEPHALOPATHY AND AIDS DEMENTIA COMPLEX

HIV encephalopathy is a part of acute HIV syndrome. HIV associated progressive encephalopathy is a syndrome complex seen in children while, in adults, the AIDS dementia complex (ADC) is also known as HIV

associated dementia complex. These are characterised by cognitive, motor and behavioural features. It is associated with advanced age and lower CD4+ counts. With the use of HAART, a less severe dysfunction, minor cognitive disorder (MCMD) has become commoner than ADC. Clinical features include impaired mentation, decreased work productivity, inattentiveness, memory loss, decreased libido, apathy, depression, sleep disturbances, psychosis and, rarely, seizures. Motor abnormalities include weakness and imbalance of gait. At a later stage global dementia with memory loss and impaired speech may develop leading to a persistent vegetative state. In children regression of milestones is the prominent feature with inability to acquire new skills.[18] The neuropsychological examination corroborates the above findings. Frontal release signs, tremors, hyper-reflexia, increased tone and impaired co-ordination may be seen later.

CSF studies show elevated protein (60%) and immunoglobulin IgG (80%). The CSF is usually acellular but mononuclear infiltrates may be seen in 25%. Presence of oligoclonal bands, HIV antibodies and testing of HIV in CSF using PCR (best) may also yield positive results. Neuroimaging studies may reveal diffuse cortical atrophy with periventricular hyperintense signals in T2-weighted images in MRI. EEG shows generalised slowing in the later stages. Biopsy is not indicated but, if done for another reason, may show cortical and subcortical neuronal loss and infiltrates of microglia, lymphocytes and multinucleated giant cells. Microgliosis is often perivascular and vacuolation may also be seen. HAART is the treatment of choice[3,18] and drugs with good CSF penetration (lamivudine, stavudine, zidovudine, indinavir, nevirapine) should be used. The role of NMDA antagonists, acetylcholine esterase inhibitors, antioxidants and chemokine receptor antagonists is being studied. Tricyclic antidepressants or neuroleptics should be used for the depressed and agitated patients, respectively. The mean time from first symptom to death is 5.6 months. Poorer prognosis is associated with lower CD4 counts, higher HIV RNA levels, anaemia, low body mass index, higher constitutional symptoms and lower educational levels.

HIV MYELOPATHY

Myelopathy is a late presentation of HIV disease and most patients will have concomitant HIV encephalopathy.[17] Vacuolation of the white matter of the cord is seen. The syndrome is similar to Vitamin B_{12} deficiency and, therefore, a nutritional cofactor is believed to be involved. The diagnosis is of exclusion and patients presenting with spastic paraparesis with paraesthesias leading to incontinence should be evaluated by lumbar puncture to also rule out CMV polyradiculopathy. Lymphomatous deposits in the epidural space can cause cord compression in HIV and hence an MRI or CT scan to exclude the above should be done. Transverse myelitis due to herpes zoster or CMV can occur.

PERIPHERAL NERVOUS SYSTEM

HIV may cause inflammatory polyneuropathies, sensory neuropathies and mononeuropathies. Around 30% of patients with AIDS may develop peripheral neuropathy.[30] Presenting features are tingling, numbness and pain in the lower limbs. Symptoms are out of proportion to objective findings on examination. This is believed to be due to the direct effect of HIV on the nerves and is improved with zidovudine. However, drugs like stavudine and didanosine, can also cause peripheral neuropathy. Patients on these drugs, presenting with neuropathy, should be switched to other regimes. Evaluation to rule out other causes, like alcoholism, thyroid disease, vitamin B_{12} deficiency and syphilis, should be done. Gabapentin has been seen to provide symptomatic relief and response to amitryptyline is uncommon. A Guillain-Barré syndrome like demyelinating neuropathy is seen in HIV infected patients and it usually occurs before frank immunodeficiency develops. Improvement with plasmapheresis supports the immune mediated causation.

CEREBROVASCULAR DISEASE

Cerebrovascular complications occur in up to 7% of these patients[30] and autopsy has revealed lesions in one-third of patients. Infarction may be secondary to nonbacterial thrombotic endocardial embolus and cerebral lymphomas can cause intracerebral bleed. Hypercoagulable states in HIV are documented and even thrombocytopaenia due to HIV and CMV is seen leading to ICH.

OTHER UNCOMMON NEUROLOGICAL PRESENTATIONS

1 *Myopathy*: Zidovudine can also cause myopathy. If creatinine kinase levels are greater than 1000 units/L then the dose of zidovudine should either be decreased or stopped.
2 *Retinitis*: CMV retinitis is the most common cause of visual diminution in patients with AIDS and, therefore, visual complaints in HIV patients must be evaluated urgently. Other rare retinal infections can be by herpes virus and *Toxoplasma*.

DIAGNOSIS OF HIV

The tests for HIV include antibody and antigen assays. HIV antibody testing conventionally is done by ELISA, which is a good screening test (sensitivity >99.9%), showing 50% positivity by 22 days and 95% by 6 weeks. To avoid false positive results in repeated tests, confirmation must be done by Western Blot which, when combined with ELISA, yields specificity of greater than 99.99%. Indeterminate results may be seen in HIV II infection, autoimmune diseases, pregnancy and early HIV infection. HIV rapid antibody test produces results in 10–20 minutes and is utilised as a screening procedure and the results need to be confirmed with the standard tests as described above. Complete blood count in HIV cases

may show anaemia, neutropaenia and thrombocytopaenia. Absolute CD4 lymphocyte count (< 200 cell/mcL) is the most widely used predictor for disease progression. The percentage of CD4 lymphocytes may be more accurate (<14%). HIV viral load tests can measure the actively replicating viruses and they are better for diagnosis in acute HIV infection before seroconversion.

MANAGEMENT OF INTRACRANIAL LESIONS

HIV cases are on the rise and due to frequent involvement of the nervous system neurosurgical consultations are being frequently sought for brain biopsy, as the diagnostic dilemma often persists despite rapid progress in the diagnostic and neuroimaging techniques. PML is usually identifiable on neuroimaging, but it might be impossible at times to differentiate toxoplasmosis from lymphoma and, therefore, it is imperative to obtain baseline toxoplasmosis titres of all AIDS patients. The toxoplasmal titres are positive in the general population in 80–90% of cases by adulthood due to the ubiquitous nature of this organism. The chances of toxoplasmosis are higher with serum antibodies greater than 1:16 (usually > 1:256). Thus, patients in whom titres change over a period of time and neuroimaging shows presence of multiple ring enhancing lesions, particularly in the basal ganglia region, they have higher chances of having toxoplasmosis. The treatment of choice for toxoplasmosis is Pyrimethamine 200 mg loading dose, followed by 75–100 mg/d with sulphadiazine 75 mg/kg per orally loading dose then 25 mg/kg every 6 hours. Folic acid tablets (10 mg) should be given along with each dose of pyrimethamine. In cases of sulpha drug allergy, sulphadiazine may be replaced with clindamycin; other alternative treatment options for complete intolerance are spiramycin and atovaquone. When empirically started, check MRI should be done in 2–3 weeks, because both clinical and radiological response is evident by then.[6] In case of good response the dosage can be decreased to 50% of the above doses in 6–12 weeks time, but they are continued throughout the remainder of life. However, in case of no response with the toxoplasmal therapy, biopsy should be done.

PCNSL is suspected in single ring enhancing lesions with neurological deterioration in AIDS. A lumbar puncture should be done in such cases if imaging is not suggestive of mass effect. Around 10 ml of CSF is needed for cytology and is positive for PCNSL in 10–25% of the patients. CSF analysis for PCR amplification of JC virus and Epstein Barr virus can also be done. Biopsy may be needed to confirm the diagnosis prior to starting radiotherapy. Some recommend early biopsy to prevent inadvertent delay in trial of antibiotic therapy, while other centres have even recommended empiric radiation therapy for highly suspicious cases of lymphoma.

BIOPSY IN AIDS

Biopsy is recommended in the following settings in AIDS cases:

- Lesions are atypical for toxoplasmosis
- Negative toxoplasmosis titres in the presence of intracranial space occupying lesion(s)
- Patients who fail to respond to empirical treatment for toxoplasmosis
- Presence of extraneural neoplasm or infectious disease process involving the CNS.

As most of these lesions are usually deep and the risk of open biopsy in AIDS is higher, stereotactic biopsy must be preferred in appropriate cases. The success rate in reported series is as high as 96% with low morbidity and mortality.[28]

Biopsy should be taken from the centre of the lesion which is most accessible and located in the least eloquent area of the brain. All biopsy specimens should be subjected to histopathological examination and microscopic examination for TB and fungus. Immunoperoxidase staining is done for *Toxoplasma* and cultures done for TB, fungi and bacteria.

RISKS IN HEALTH PROFESSIONALS

Professionals working in surgical wards are especially exposed to higher risk of infections.[16,24] This is especially true for hepatotrophic and HIV viruses. Around 2.5% of HIV infections ascertained in 35 million health care professionals worldwide is the consequence of percutaneous injuries with sharp objects.[46] It is seen that damage to the surgeon's skin occurs in 1 per 10–50 surgical procedures depending on the surgical subspecialty. Studies also show that the percentage of patients infected with hepatotrophic viruses and HIV among those admitted to the surgical wards is often greater than that observed in the general population or among blood donors and, therefore, the risk of infection in health care workers from such subset of patients is higher.

There is increasing concern among the operating room staff from the increasing risk of transmission of HIV due to needle stick injuries. The risk of HIV infection from a HIV positive patient after a needle stick injury is around 0.3%. There has also been public debate about the risk of patients who undergo surgeries acquiring these viruses from infected surgeons.

The Centre for Disease Control has recommended universal precautions for the protection of health workers from blood or body fluids that may contain HIV or hepatotrophic viruses. These precautions are based on the fact that a large number of patients with these diseases are frequently asymptomatic carriers who are not easily diagnosed and, therefore, it is imperative to consider body fluids and blood of these patients as infected and to take adequate precautions. Universal precautions should apply to blood, semen, vaginal secretions, CSF, synovial fluid, pleural fluid, peritoneal fluid, pericardial fluid and amniotic fluid. These do not apply to urine, sweat, faeces, vomitus, nasal secretions, sputum and saliva unless containing blood. The most effective way of protection is by consistent use of protective gloves, impervious gowns, face mask and goggles.

The precautions recommended for staff during surgery are:

- Have vaccination against hepatitis B
- Cover all cuts and abrasions with waterproof dressings
- Do not pass sharp instruments hand to hand
- Do not use hand needles
- Do not guide needles with fingers
- Do not re-sheath needles
- Dispose of all sharp instruments safely into approved containers
- Put disposables and waste into yellow clinical waste bags for incineration.

ADDITIONAL PRECAUTIONS WHEN CARING FOR KNOWN HIV POSITIVE AND HIGH-RISK PATIENTS

- Consider non-operative management
- Remove unnecessary equipment from theatre
- Observe highest level of theatre discipline
- Have only experienced surgeons and health care workers in the operation theatre
- Use double glove, high efficiency masks, eye protection, boots, impervious gowns, closed wound drainage
- Use disposable anaesthetic circuitry or appropriate method of decontamination
- Disinfect theatre floor with hypochlorite.

TRANSMISSION FROM HEALTH WORKERS TO PATIENTS

It is extremely difficult to quantify the risk of transmission from health care workers to patients, but it must be very low because large volumes of blood from the health care workers would need to enter the patient's bloodstream. The risk is probably much lower than the risk of transmission from patient to health care worker. There is a single report that a Florida dentist with AIDS transmitted HIV to five patients. The mechanism of this transmission is still speculative as the dentist died before his techniques could be verified. By August 1992, there was no report of transmission of HIV from an infected surgeon or other member of the operating theatre staff to a patient. Estimates of the risk of such transfer range from 1:48,000 to 1:10,00,000.[8,20]

PRECAUTIONS FOR INFECTED HEALTH WORKERS

The General Medical Council recommends that all staff who think that they have been at risk of infection should be confidentially tested and that where HIV or hepatitis B virus infection is detected special counselling and expert advice should be sought.[15] If the health care worker is E-antigen or HIV positive, he or she should stop performing invasive procedures.

INVASIVE PROCEDURES TO BE AVOIDED BY E-ANTIGEN OR HIV POSITIVE HEALTH WORKERS

- Surgical entry into tissues, cavities or organs
- Repair of major traumatic injuries
- Cardiac catheterisation and angiography
- Vaginal or Caesarean deliveries or other obstetric procedures during which bleeding may occur
- Manipulation, cutting or removal of any oral or perioral tissue, including tooth structures, during which bleeding may occur.

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SECTION

8

Vascular Disorders

SN Mathuriya

75 Subarachnoid Haemorrhage

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INTRODUCTION

Subarachnoid haemorrhage (SAH) is a neurological emergency characterised by haemorrhage into the subarachnoid space, which is normally filled with cerebrospinal fluid. It is one of the most important causes of acute severe headache and needs to be always considered in its differential diagnosis. In population-based studies, SAH has been estimated to occur at an annual incidence rate of 10.0–10.9 cases per 100,000.[58] Although population-based studies indicate that the condition is not very common in the general population, it is of great importance to diagnose the condition at the earliest because of the associated high morbidity and mortality. Hence, awareness, early diagnosis and management play a paramount role in achieving the goal of reduced morbidity and mortality.

EPIDEMIOLOGY

Few data bases exist regarding the exact incidence of SAH, with variations in data-based on the diagnostic modality used. The incidence of SAH varies between geographical areas. There is also racial, sex and age-related variations. The overall incidence of SAH is approximately 9–10.5/100,000 population/year.[10,49] Finland and Japan have the highest incidence of SAH in the world, with rates between 15.1 and 29.8 per 100,000 population per year,[10,20,37,68] whereas the rates have been documented to be as low as 2.2 per 100,000 population/year in Dijon, France,[22] and about 2 per 100,000 population/year in China.[37] The incidence of SAH in India has not been evaluated by population-based studies in detail, although it had been reported to be lower around 3–4 per 100,000 from hospital-based data.[5]

The incidence is reported to be 1.24–1.6 times more in women compared to men.[10,49] Differences in incidence have also been noted between ethnic groups living in the same geographical areas and exposed to similar risk factors. SAH is reported to be higher in Hispanics and Blacks compared to Whites.[44]

The incidence of SAH has been found to be relatively constant over time. The incidence increases with age.[88] Below 50 years of age, the incidence among men and women are similar, while beyond 50 years, the incidence is higher among women.[10] Autopsy data indicates a high incidence of unruptured aneurysms in the general population. The incidence varies depending on the size of aneurysms taken into consideration. Housepian et al. had reported that 5% of the population harboured aneurysms based on autopsy studies,[33] while prevalence of incidental intracranial aneurysms was found to be 1% in studies of unselected angiograms.[4] Although the prevalence of aneurysms in autopsy studies is high, the incidence of SAH is around 9–10.5/100,000 population/year.[10,49] This indicates that only a small per cent of aneurysms rupture during life. According to the multicentric study conducted under the aegis of ICMR (1970–75) among 404 consecutive autopsies at New Delhi and Chandigarh, there were five aneurysms and one AVM discovered.

AETIOLOGY

The most common cause of SAH is trauma. However, among SAH due to non-traumatic causes, 85% are due to ruptured cerebral aneurysms. In a small proportion of cases, connective tissue disorders have been implicated as the cause of SAH. These include Ehlers-Danlos syndrome, pseudoxanthoma elasticum, polycystic kidney disease and neurofibromatosis type I.[18,69] The other causes of SAH include AVM, dural sinus thrombosis, intracranial arterial dissection, mycotic aneurysms, bleeding diathesis and drug-induced SAH.[18] In about 20% of the cases, no cause can be ascertained. In peri mesencephalic SAH aneurysms are the cause in less than 10% of the cases. It is postulated to be of venous origin and considered to be a benign form of SAH.[18] The various causes of SAH have been discussed in Table 1.

Table 1: Causes of subarachnoid haemorrhage

• Trauma
Vascular
• Ruptured intracranial aneurysms
• Arteriovenous malformations
• Tumours with haemorrhage
• Pituitary apoplexy
Vasculopathy
• Collagen vascular disease
• Amyloid angiopathy
• Arterial dissection
Haematological
• Anticoagulant therapy
• Leukaemia
• Hepatic or renal disease-induced coagulopathy
Drugs:
• Cocaine, amphetamine, ephedrine

CLINICAL FEATURES

Headache is a very common ailment in the general population. A high index of suspicion and careful understanding of presentations of SAH is needed for early and accurate diagnosis. In the general population, migraine is 1,000 times more common than SAH.[78] A careful focussed history and examination helps in identifying patients with SAH.

The most common and classical presentation of SAH is the sudden onset of severe headache, often described as "the worst headache of one's life". The headache is acute, peaks rapidly, wakes the patient if asleep and persists for days in spite of treatment. It is often holocranial, may sometimes be localised to one side or to the occipital region. The sensorium is often altered in patients with SAH due to sudden raise in intracranial pressure. Transient loss of consciousness can occur in 33% of patients and around 20% may be comatose at presentation. Seizures occur in about 20% of patients with SAH.[78] Seizures often occur with MCA aneurysms, Pcom aneurysms, intracerebral haematoma and hypertension. Sometimes neck pain may predominate over cranial symptoms.

Among the patients who present with acute onset severe headache and are neurologically normal, around 12% have SAH.[45,50,56] Nearly 50% of SAH present only with mild symptoms. The following points in history should carefully be evaluated to identify these patients:

- Onset of headache: abrupt onset/during exertion
- Severity
- Quality: distinct/unique
- Associated symptoms: nausea, vomiting, seizure, diplopia
- Alternate causes for headache
- Enquire about: alcohol consumption, smoking, hypertension, cocaine use
- Family history or past history of SAH

Many patients with SAH give history of mild headache with nausea or vomiting suggesting a minor bleed prior to the ictus. This is referred to as "warning leak or sentinel haemorrhage". Sentinel haemorrhage is reported to occur in 40–50% of patients with SAH and is usually noted within 2–8 weeks prior to SAH.[46,57] Verweij et al., in their study, reported that only 50% of patients with warning headache consulted physicians.[92] CT scan of the brain is usually not very reliable in diagnosing or ruling out sentinel haemorrhage.

The patient's level of sensorium, presence of focal motor deficits and cranial nerve palsies, if any, should be recorded on examination. Meningismus or nuchal rigidity is noted in 50% of patients due to meningeal irritation following SAH. It can manifest within 6–24 hours after SAH. The patient also needs to be evaluated for systemic effects of SAH in detail before surgical management. Examination of the fundus may reveal papilloedema, subhyaloid, retinal or preretinal haemorrhage in 20–40% of patients.[59] Ocular haemorrhage in SAH can be subhyaloid, intraretinal or vitreous. Subhyaloid haemorrhage results in bright red blood near the optic disc obscuring the underlying retinal blood vessels.

Certain clinical features in a patient with SAH can suggest the specific location of the aneurysm. Visual symptoms can occur due to aneurysms in the region of the Acom, ophthalmic and superior hypophyseal segments of the internal carotid artery, giant aneurysms of Pcom and anterior choroidal artery. Aneurysms of the posterior communicating artery cause third nerve palsy with pupillary involvement.

Multiple cranial nerve palsies can occur in a cavernous carotid aneurysm. They can present with acute retro-orbital pain, decrease in visual acuity, proptosis and paresis of cranial nerves III, IV and VI. A ruptured cavernous carotid aneurysm does not result in SAH but causes carotid cavernous fistula. An intradural extension of the aneurysm can result in SAH. Hypothalamic dysfunction and diabetes insipidus are more common in patients with anterior communicating artery aneurysms. Basilar bifurcation aneurysms can present with third nerve palsy, chiasmal compression or Weber's syndrome. Intraventricular haemorrhage and hydrocephalus can occur.

Grading of Clinical Status

The clinical condition of the patients with SAH needs to be evaluated and documented in a uniform manner to record periodic changes in the condition, for comparing the data and outcome across the studies and for prognostication based on the clinical condition of the patient. Various clinical grading methods have been proposed for evaluating patients with SAH. Hunt and Hess classification[34] (Table 2) and World Federation of Neurosurgical Societies (WFNS) grading[14] (Table 3) are the most commonly used systems for evaluation.

When there is any associated serious systemic disease, like diabetes mellitus, hypertension, severe arteriosclerosis, chronic pulmonary disease or severe vasospasm seen on angiography, the patient is placed in the next less favourable Hunt and Hess grade (Table 2).

Table 2: Hunt and Hess classification of SAH

Grade	*Clinical features*
0	Unruptured
1	Asymptomatic or mild headache, slight nuchal rigidity
2	Moderate-to-severe headache, nuchal rigidity, no neurological deficit other than cranial nerve palsy
3	Mild focal deficit, lethargy, confusion
4	Stupor, hemiparesis
5	Coma, extensor rigidity

Table 3: World Federation of Neurosurgical Societies grading scale for SAH

Grade	*GCS*	*Focal deficit*
1	15	Nil
2	13–14	Nil
3	13–14	Present
4	7–12	Absent or present
5	3–6	Absent or present

MISDIAGNOSIS OF SUBARACHNOID HAEMORRHAGE

In spite of advances in diagnostic modalities and their better availability, missed diagnosis of SAH is very common. It occurs in 12–51% of patients with SAH on their first consultation with a physician.[15,42,55,60,89] In 75% of cases, the misdiagnosis occurred in the emergency department or the physician's office. The true estimate of the frequency and impact of missed diagnosis cannot be ascertained from hospital records as 12–50% of SAH patients who have rebleeding may die without being hospitalised.[7,70] The missed diagnosis is often attributed to: (1) lack of awareness; (2) failure to do relevant investigations and (3) failure to interpret the investigation results. The most common error was failure to perform CT leading to misdiagnosis in 73%, while misinterpretation of CT or LP results caused misdiagnosis in 16% of cases.[42] The common clinical misdiagnoses made were migraine/tension headache, viral infection, hypertension/encephalopathy, sinusitis, meningitis, etc. Patients with good clinical grade (Hunt and Hess I and II) and small volume bleed had higher chances of missed diagnosis. The significance of the missed diagnosis cannot be overemphasised since rebleed rates are 48% in those misdiagnosed, which reduce to 2% in those correctly diagnosed.[55] Nearly 20% of the patients with good initial clinical grade were misdiagnosed, and these patients had a four-fold increase in the likelihood of death at 12 months and worse functional recovery and quality of life among those who survive.[42]

INVESTIGATIONS

The threshold for investigating a patient with sudden onset of severe headache for the first time in life should be very low. CT scan of the brain is the investigation of first choice, because it has high sensitivity to detect acute haemorrhage, is non-invasive, easily available, relatively low cost and can suggest the possible location of an aneurysm. Other modalities to detect SAH include lumbar CSF analysis and MRI of the brain.

Computed Tomography Brain

CT brain is the most commonly performed investigation in SAH. Subarachnoid blood appears in plain CT scan as a hyperdensity in the subarachnoid space. The hyperdensity of the blood is related to the concentration of globin in the haemoglobin molecule. The identification of subarachnoid blood in CT scan depends on the amount of bleed, density of blood and the time interval between the ictus and imaging. Blood with low haematocrit values does not appear hyperdense in CT scan.[73] If a CT scan is performed within 24 hours after ictus, subarachnoid bleed will be evident in 95–98% of patients who have blood demonstrated on lumbar puncture.[39,86] As time elapses, haemolysis and dispersion of blood in the CSF occurs, reducing the sensitivity of CT in detecting SAH. Only 58% of SAH can be detected by 5 days and at 1 week,[34] only 50% of patients have a positive CT scan.[87] A thin layer of SAH adjacent to a bony structure can be missed in CT and thin slices may need to be performed for its detection.[48] Structures that can mimic SAH include calcification of the basal arteries, falx, partial volume artifacts and streak artifacts. They can be recognised by their focal nature and can be differentiated from SAH. MR imaging, especially the FLAIR sequences may be a better imaging modality to detect subacute SAH.

The amount of bleed has been graded by Fischer et al. and this can predict the outcome of patients with SAH[19] (Table 4). The amount of subarachnoid blood directly correlates with the risk of vasospasm. Patients with Fischer's grade 3 SAH have the highest risk of developing vasospasm.

The location of an aneurysm causing SAH can be predicted in the majority of cases based on the cisterns involved. Intracerebral haematoma in the temporal lobe can occur following rupture of MCA or Pcom aneurysm. Acom aneurysm bleed can cause gyrus rectus bleed. An ICA bifurcation aneurysm can result in intracerebral haemorrhage extending into the putamen and thalamus, although slightly anterior and inferior to the usual location of hypertensive intracerebral haemorrhage. Subdural haematoma can occur due to bleed from MCA or Pcom aneurysm.

Lumbar Puncture

Lumbar puncture is the gold standard against which other investigations have been compared for their sensitivity in diagnosing SAH. Since the sensitivity of CT brain for detecting SAH is very high and it being non-invasive, it is considered the investigation of first choice. SAH may not be detected in CT if the amount of bleed is very little or a longer time has elapsed between the ictus and the time of investigation.[30] A lumbar puncture is

Table 4: Fischer's grading of subarachnoid haemorrhage

Grade 1	No detectable blood on CT scan
Grade 2	Diffuse thin SAH Vertical layers < 1 mm thickness
Grade 3	Localised clot and/or thick SAH vertical layer > 1 mm thickness
Grade 4	Intraventricular or intracerebral clot with diffuse or no subarachnoid haemorrhage

performed when the clinical presentation of the patient is highly suggestive of SAH and the CT scan is negative.

In around 3% of patients with sudden headache, CT scan performed within 12 hours will be normal. A lumbar puncture is usually positive in these patients if it is done after 6 hours, preferably 12 hours after SAH which allows for the formation of metabolites of haemoglobin.[86] Bloody CSF that remains uniformly blood stained when collected in four tubes is highly characteristic of SAH. The collected CSF is centrifuged and analysed. If the lumbar puncture is performed a few days after the ictus, then the supernatant fluid will reveal xanthochromia and crenated RBCs will be detected in the sediment. Xanthochromia is the most characteristic feature of SAH and occurs due to lysis of RBCs in the CSF, which imparts the yellow colour. It appears as early as about 3 hours after the ictus and persists for about 3 weeks. The sensitivity was 100% at 2 weeks and 70% at 3 weeks.[91] Xanthochromia may sometimes not be visible and spectrophotometric analysis needs to be performed for detection.[83] A traumatic lumbar puncture can mimic subarachnoid haemorrhage (SAH). It can be differentiated from spontaneous SAH by the fact that the blood in the CSF clears in serial collecting tubes.

Angiography

Four-vessel catheter angiography is the gold standard investigation for detection of aneurysms, despite the recent surge of alternate techniques, like CT and MR angiography, which are non-invasive. Angiography is mandatory in all patients with a CT diagnosis of SAH and in patients with acute onset third cranial nerve palsy with pupillary involvement. It establishes the cause of SAH in 85% of patients. The risks of angiography needs to be considered while subjecting the patient for the procedure, which include contrast reactions, nephrotoxicity, puncture site haematoma, transient neurological deficits (1%) and permanent complications (0.1–0.5%). The overall complication rate is around 7%, with the majority of them being puncture site haematomas.[27,94]

In 15–20% of patients with SAH, angiogram may be negative and this can be due to interpretive errors, cerebral vasospasm, spontaneous thrombosed aneurysms, vascular lesions of the spine or spinal neoplasms.[39,80,84] These patients require a repeat angiogram after 2–6 weeks. Angiogram is often negative in perimesencephalic SAH, where blood is located in the interpeduncular and perimesencephalic cisterns. This cannot be differentiated from a basilar artery aneurysmal bleed; however, a repeat angiogram is unnecessary in this pattern of SAH if an initial good quality angiogram does not demonstrate any aneurysm.[71] This condition is associated with good outcome and rebleed is unusual.[83] Conditions, like pregnancy-induced hypertension, sympathomimetic drug abuse, bleeding dyscrasias, antiplatelet agents and anticoagulants, can result in SAH and when detected, they have to be corrected.

Computed Tomography Angiography and Magnetic Resonance Angiography

CT angiography and MR angiography have been performed for detection of aneurysms as an alternative to catheter angiography. The main advantage of these procedures is the non-invasiveness. CT angiography can be performed rapidly even in patients not medically fit to undergo angiography, and as an emergent procedure in patients with acute deterioration. It can also be used as a screening tool in the patient group with high risk for aneurysms like those with collagen vascular disease and polycystic kidney disease. The main disadvantages of the procedure include contrast-related reactions and nephrotoxicity. The presence of intracerebral haematoma, calcification or aneurysmal clips can affect the interpretation of the images. Small posterior communicating segment aneurysms may be missed by CT angiography.[93]

Catheter angiography is considered the gold standard, while all other procedures are compared against it for assessing their sensitivity and specificity. The sensitivity of CT angiography varies between 77% and 100%, while the specificity ranges from 79 to 100% as reported in literature.[31,40,41,93,97] This depends on the size and location of the aneurysm, and the experience of the interpreter. For aneurysms of size 5 mm or more, the sensitivity of the procedure is better (95–100%), while it significantly decreases (64–83%) when the size of the aneurysm is less than 5 mm.[93]

MR angiography has a sensitivity of 85–100% for aneurysms larger than 5 mm size, while the sensitivity falls to 56% for aneurysms smaller than 5 mm. The specificity of MRA for aneurysms ranges from 92–100%.[2,23,32,35] The disadvantages of MRA include longer procedure time, difficulty to perform in emergent settings and in critically ill patients. MRA can be performed in pregnant patients, and as compared to CT angiography, can avoid the risk related to iodinated contrast and radiation.

MANAGEMENT OF SUBARACHNOID HAEMORRHAGE

Despite early diagnosis and management, the 30-day mortality of aneurysmal SAH approaches 50%. Most deaths occur in the first week after the ictus. Around 10% die before reaching the hospital and 25% die within 24 hours.[3,7,70] The natural history of SAH is grim even among good grade patients. The 3-month mortality rate among patients who reach major medical centres is approximately 25%.[16] The leading causes of death include large intraparenchymal haematoma, acute hydrocephalus, raised intracranial pressure, myocardial ischaemia, cardiac arrhythmias, pulmonary oedema, respiratory failure, rebleed and ischaemia secondary to vasospasm.[74] The level of consciousness at the time of admission is the most predictive clinical factor of SAH. The 6-month mortality rate among comatose patients was 71%, whereas only 11% of initially alert patients die during the same period.[1]

SAH results in a wide gamut of changes in the patient, affecting multiple systems in varied ways. The goals of medical management include:

- General care, stabilisation of acutely ill patients
- Obliteration of the ruptured aneurysm at the earliest
- Prevention of complications and sequelae of SAH

Acute Management

Patients with SAH need to be managed in medical centres with adequate expertise to treat this disease. Acute life-threatening complications need to be anticipated and treated. These patients have to be managed in an ICU by trained nurses.[54]

Most of these patients experience photophobia due to SAH and hence bright lighting is avoided in the room. A water mattress or pneumatic mattress can be used to prevent deep venous thrombosis. Analgesics are administered to alleviate headache. Patients may be agitated due to brain injury, hydrocephalus, raised intracranial pressure or a full urinary bladder, which need to be taken care of. Sedatives are administered to reduce agitation. Straining at stools should be avoided and hence a good laxative is prescribed.

Intravascular volume depletion is common following SAH.[6,43,75] Disturbances of water and electrolytes occur in about one-third of patients with SAH. They occur more commonly in critically ill patients.[96] Hyponatraemia and volume depletion correlate with poor prognosis.[95] In the past, hyponatraemia in patients with SAH was attributed to SIADH and treated accordingly. It is now recognised that the more common cause for hypovolaemia is cerebral salt wasting (CSW).[95,96] The mechanism of water and sodium depletion in CSW has been correlated with disturbances in levels of atrial natriuretic peptide and C-type natriuretic peptide, as well as direct neural effects on renal function.[26] The clue to diagnosis is excretion of larger amounts of sodium and chloride in urine. There is volume contraction, unlike SIADH where there is fluid retention or euvolaemia. A proper diagnosis of CSW or SIADH should be made as management is very crucial and can be harmful if the condition is not diagnosed and treated properly. Assessment of volume status by careful recording of input and output, Na^+ and Cl^- balance, daily body weight recording, or laboratory tests such as elevated haematocrit or BUN: creatine ratio help in planning therapy.[26] Hypovolaemia predisposes to high incidence of cerebral vasospasm. Hence, patients with SAH should be hydrated well to maintain a central venous pressure of about 12–14 mmHg. Crystalloids are infused at the rate of 125 ml/hour to maintain the central venous pressure.

Arterial hypertension is common in SAH resulting from elevation of catecholamines and rennin production by hypothalamic disturbances.[9,39,81] The other reasons for hypertension include raised intracranial pressure, agitation, seizure, pain or vomiting. Hypertension after SAH has been found to correlate with increased risk of vasospasm and mortality, and recurrent bleed.[81] Rapid and steep reduction in blood pressure might be dangerous, resulting in drop in cerebral perfusion in patients with vasospasm and raised intracranial pressure, leading to neurological complications. The level of hypertension that mandates treatment is not known. Moderate hypertension in a patient with mean blood pressure less than 120 mmHg may be reactive and need not be corrected.[81,90] The initial approach should be to control pain and agitation which can reduce blood pressure. A mean pressure greater than 120 mmHg should be treated with the goal of cautious reduction. Randomised trials have not been performed evaluating the benefit-risk relationship of antihypertensive therapy in the hyperacute phase of SAH prior to surgical or endovascular therapy.

Anti-oedema therapy with 20% mannitol is instituted in the presence of diffuse cerebral oedema following SAH. The treatment with mannitol should be monitored closely to prevent electrolyte imbalance, especially sodium imbalance. An external ventricular drainage may be required in the presence of acute symptomatic hydrocephalus, although there is a risk of rebleed following sudden decompression of the ventricles.

The cornerstone in medical management of SAH includes triple H therapy (hypertension, hypervolaemia and haemodilution) and calcium antagonists. Triple H therapy has been shown to be effective in prevention and treatment of cerebral vasospasm. Nimodipine, a cerebroselective calcium channel blocker, has been found to reduce the risk of poor outcome and secondary ischaemia after aneurysmal SAH. Considering the potential benefits and modest risks of this treatment, oral nimodipine is currently indicated in patients with aneurysmal SAH. Intravenous administration of calcium antagonists is not recommended for routine practise on the basis of the present evidence.[12]

The reported incidence of seizure in patients with SAH is 25%, most of which occur within the first 24 hours.[62,79] Routine practise presently is to prescribe prophylactic anticonvulsants to patients with SAH. Platelet aggregation has also been considered to play a causative role in secondary brain ischaemia following SAH. Hence, some authors have attempted to add antiplatelet therapy in patients with SAH. A Cochrane review of all randomised controlled trials of antiplatelet therapy revealed a trend towards better outcome in patients treated with antiplatelet agents, possibly due to a reduction in secondary ischaemia, although the results were not statistically significant, but antiplatelet agents could also increase the risk of haemorrhagic complications. On the basis of the current evidence, treatment with antiplatelet agents in order to prevent secondary ischaemia or poor outcome cannot be recommended.[13]

Raised intracranial pressure following SAH presents with depression in sensorium, and can occur due to various causes like intracerebral haematoma, intraventricular haematoma, hydrocephalus, cerebral oedema and mass effect secondary to cerebral ischaemia. General

treatment strategies for managing raised ICP include head end elevation, fluid balance, anti-oedema measures, correction of hyponatraemia, prevention of hypoventilation and hypercarbia, treatment of fever and agitation. Specific measures include evacuation of intracerebral haematoma, external ventricular drainage for intraventricular haematoma or hydrocepahlus.

Hydrocephalus is a common acute complication of SAH, reported to occur in 25% of cases in the acute phase.[72] It can occur due to intraventricular haematoma, subarachnoid blood blocking the subarachnoid spaces and/or arachnoid villi. Prolonged presence of extensive subarachnoid clot is associated with hydrocephalus. Hydrocephalus following SAH can be classified according to its time of appearance as: (1) acute: < 12 hrs; (2) subacute: a few days after ictus and (3) delayed: weeks to years after SAH. Acute hydrocephalus is an important cause of raised intracranial pressure and coma. Subacute hydrocephalus is a cause of gradual decline in sensorium 7–10 days following SAH. Delayed hydrocephalus often manifests as subacute dementia. Approximately 16–34% of patients have CT evidence of acute hydrocephalus. Most patients have decreased level of consciousness; some may be asymptomatic. Acute hydrocephalus predisposes to increased morbidity and mortality, and is correlated with subsequent development of vasospasm and ischaemic complications. Management is guided by the clinical situation. The patient can be just observed and medically managed, monitored with serial CT scans and treated with serial lumbar punctures, if required. Although acute hydrocephalus may resolve spontaneously, some patients require temporary CSF diversion procedures.[24,28]

SAH disrupts brain integrity and function and results in multi-system involvement including cardiovascular, respiratory, metabolic, haematological and immunological dysfunction. A patient with SAH needs to be closely monitored for these events and promptly treated to improve the outcome of disease management.

The various changes that can occur following SAH include:[77]

- *Cardiovascular*: Arterial hypertension, intravascular volume depletion, congestive heart failure and decreased cardiac output and left ventricular dysfunction. ECG reveals ST depression, T wave inversion and QT prolongation, and arrhythmias. Creatine kinase-MB and troponin I levels are raised in serum.
- *Respiratory*: Cardiogenic pulmonary oedema, acute lung injury, acute respiratory distress syndrome (ARDS), neurogenic pulmonary oedema (NPE), pneumonia and pulmonary embolism.
- *Metabolic*: Hyponatraemia due to SIADH or cerebral salt wasting, hypernatraemia and stress hyperglycaemia.

Cardiac arrhythmias can be detected in almost all patients during the first few hours of SAH.[11,53,61] In 20%, arrhythmias can be severe and life-threatening. Changes resembling those seen in acute myocardial ischaemia can be seen in 25–80% of patients. It is assumed that release of catecholamines by the posterior hypothalamus is responsible for the development of cardiovascular complications of SAH. Presumably, marked elevation of norepinephrine leads to hypokalaemia, systemic hypertensive effects, left ventricular strain and coronary artery spasm.[21,67,98] Neurogenic pulmonary oedema is rare and occurs in critically ill patients. This complication is frequently attributed to greater sympathetic activity resulting from acute cardiac changes.[47]

Prevention of Rebleed

Prevention of rebleed is the cornerstone of management of SAH. Torner and colleagues found that the period of greatest risk for rebleeding is the first 24 hours after the ictus, which peaked at approximately 4% during this time.[82] In a Swedish series, 9.6% of all patients admitted within 24 hours of SAH had very early rebleed; most of them died.[29] The cumulative rate of rebleed during the first 2 weeks after SAH is approximately 15–20%.[82] Recurrent haemorrhage is a feared complication of SAH, because it is one of the leading causes of death and morbidity.[29,65] Broderick reported rebleed as the cause in 50% of deaths occurring within 2 days following SAH.[7] The mortality rates in patients who have a rebleed are approximately twice as much as in those who have a single bleed. Even in centres performing early surgery, rebleeding remains a major cause of poor outcome.[64] Early treatment to obliterate the ruptured aneurysm either by surgical clipping or endovascular coiling is most important, which will be discussed in the following chapters.

PATIENT OUTCOME FOLLOWING SUBARACHNOID HAEMORRHAGE

SAH results in significant morbidity in spite of optimal treatment. Large studies have reported a 30-day mortality of around 40% following SAH.[17,37,51] A population-based analysis from the United States had documented an overall mortality rate of 2.77 per 100,000 person years following SAH, in the last two decades.[38] Among all those patients who suffer from SAH, roughly one-third of them die acutely, one-third survive with significant residual cognitive and motor deficits restricting functional independence, while only one-third of patients recover well from SAH to get back to normal daily activities.[51,52,58] The cognitive dysfunction following SAH is significant, resulting in deficits in verbal and non-verbal memory, psychomotor speed, executive function, visuospatial function and pattern recognition. It can also result in emotional lability.[25,51,76] Due to these widespread cognitive and motor deficits, only about 50% of the survivors of SAH were able to return to the same level of work prior to the bleed.[8,36] This disease commonly affects people at younger and productive age, resulting in considerable loss of manpower and additional burden to the family and society. An unfavourable outcome was found

to be associated with increasing age, worsening neurological grade, ruptured posterior circulation aneurysm, larger aneurysm size, more SAH on CT scan, presence of intracerebral haematoma and co-morbid factors like hypertension, diabetes mellitus, myocardial infarction, etc. The variables during hospital stay, which influence outcome, include fever, symptomatic vasospasm and cerebral infarction. Among all these, the most important factors which influence outcome are cerebral infarction, WFNS grade, age, occurrence of fever and symptomatic vasospasm.[66]

PERIMESENCEPHALIC SUBARACHNOID HAEMORRHAGE

Perimesencephalic haemorrhage is defined as blood confined to the cisterns around the midbrain, usually in the interpeduncular and prepontine cisterns, sometimes in the quadrigeminal cisterns. Around 2.5–5% of these patients have aneurysms of the basilar or vertebral artery.[83,85] Thus, perimesencephalic SAH needs to be investigated with DSA or high quality CT angiography. Headache in these patients develops gradually in comparison to aneurysmal SAH. Patients are usually conscious, occasionally confused. Rebleeding is very rare, almost unknown in perimesencephalic SAH. The cause is not known with certainty. An arterial cause is ruled out by a normal angiogram. It is assumed to be due to rupture of veins; the basis being that, in these patients, the perimesencephalic veins drain directly to the dural sinuses instead of the vein of Galen. A repeat angiogram is unnecessary in this pattern of SAH if an initial good quality angiogram does not demonstrate any aneurysm.[71] This condition is associated with good outcome, and rebleed is unusual.[83]

CONCLUSION

SAH is one of the most devastating neurosurgical emergencies. A low threshold for investigating a patient with sudden severe headache is mandatory to detect the disease. CT scan is the best imaging modality for detecting SAH. Obliteration of an aneurysm at the earliest by either microsurgery or endovascular techniques is the standard of care at present. SAH has far reaching systemic implications which need to be understood and managed to obtain optimal outcome following the disease. Further research is necessary in this field to manage the modifiable factors, like vasospasm, rebleed and systemic sequelae, which form the major cause for the morbidity secondary to SAH.

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76 General Principles of Management of Intracranial Aneurysms

Mathuriya SN

INTRODUCTION

Intracranial aneurysms (IAs) affect 5–10% of the general population[77] and represent a major public health problem. It is estimated that 2.3% of the population have undetected aneurysms,[54] a fraction of which will rupture and lead to devastating consequences. In the absence of trauma, intracranial aneurysm (IA) is the leading cause of subarachnoid haemorrhage (SAH) and accounts for approximately 85% of the cases.[61]

The incidence of aneurysmal SAH in most of the Western countries is approximately 9/100,000 population, but in Finland it is approximately 20/100,000.[133] In the United States, the incidence of SAH is 6–9/100,000; about 28,000 ruptures occur per year.[90] This number may be even higher in other countries, such as Finland, where the incidence has been reported to be much higher. This is likely due to higher rates of rupture of existing aneurysms, rather than a greater number of aneurysms *per se*.[107,113] Progress in understanding the pathogenesis of IA has been hampered by its multifactorial nature. SAH due to rupture of an IA is a serious neurosurgical emergency with a poor prognosis. Approximately 12% of patients die before reaching medical attention[77] and 40% of patients die in the hospital.[45,56,84,115] Only 25% of those who live past the 1st month recover completely, leaving the majority of survivors requiring long-term care[32,41]

Aneurysmal SAH accounts for 3–11% of all strokes, 5% of stroke deaths, and more than one-quarter of potential life years lost through stroke as this is common in comparatively young individuals and, hence, a productive age group.[32] Although the latter half of the 20th century has seen great advances in the diagnosis, treatment and prevention of complications of SAH; the overall outcome has shown only modest improvement.[90] Due to the devastating sequelae of aneurysmal SAH, surgical or endovascular intervention before rupture is considered to be of paramount importance. Guidelines have been established to assist in the decision making between treatment and careful monitoring, with the goal of prophylactically treating those aneurysms that are likely to rupture. Attempts to identify risk factors and the pathophysiology leading to aneurysm formation and rupture have had limited success, although there has been noteworthy progress of late, particularly in the study of aneurysm genetics.[90]

One large multi-centre trial suggested that IAs larger than 10 mm had a risk of rupture of 1% per year, with smaller aneurysms having a much lower risk. However, this initial data conflicted with clinical experience in which a significant number of patients present with SAH owing to aneurysms smaller than 10 mm in size. Furthermore, the data contradicted a previously published series in which aneurysms smaller than 10 mm were at greater risk of rupture.[57,58] Other than aneurysm size, the conditions that lead to aneurysm formation and rupture have not been fully delineated. Contributing to the disease are a number of well established risk factors such as sex, hypertension, smoking, alcohol, low body mass index and drug use.[45,55] These risk factors, however, fall short of a complete explanation. Recent studies suggest that, in addition to these, genetic factors also contribute to the pathogenesis of IA. Given the large number of familial cases and increased incidence with other genetic diseases such as adult polycystic kidney disease (ADPKD),[90] a genetic contribution to aneurysm formation and rupture has long been speculated. Studies have reported that the incidence of familial aneurysms is 10%.[106] The degree to which each risk factor contributes to an individual's aneurysm is likely to be patient-specific. It is considered that both genetic and environmental factors may work independently and/or synergistically to form IA.

GENETICS

Recent advances in genetic disorders and vascular abnormalities have revealed several alterations in genes and gene products involved in the remodelling of the extracellular matrix (ECM). The dynamic nature of the ECM has been theorised to go awry, leading to diminished support of the vasculature, ultimately resulting in an aneurysm. Supporting this notion, the content and structure of collagen and elastin (ELN), the predominant elements in the wall of the aneurysm, are significantly altered. The ECM-related proteins discussed below have been identified in genetic disorders and could be related to IA formation.[90]

These are ELN, elastase 2 (ELA), alpha-1-antitrypsin (AAT), collagen III (COL3A1), endothelial nitric oxidase synthetase, polycystin (PKD1) and fibrillin (FBNI).[21] Neder et al.[131] have identified the 1p35–36 locus in a large family with IAs. Genome-wide sibling pair and kindred

studies have also incriminated 2p13, 7q22.1, 11q25, 14q22 and 19q13.3 as harbouring susceptibility genes. Notable heritable connective tissue disorders which have been associated with IAs include polycystic kidney disease, Ehlers-Danlos syndrome type IV, Marfan's syndrome, neurofibromatosis type I, pseudoxanthoma elasticum (PXE) and AAT deficiency.

Several loci have been identified for the ADPKD gene on chromosome 16 (PKD1) as well as on gene 4 (PKD2). Mutations in gene encoding proα_1 (III) chain of COL3A1 on chromosome 2 are the cause of Ehlers-Danlos syndrome IV.[84] Several vascular disorders have been associated with AAT deficiency, viz. arterial aneurysms, spontaneous arterial dissections and arterial fibromuscular dysplasias. Patients with AAT deficiency are at increased risk of developing IAs as antitrypsin deficiency may cause breakdown of subcutaneous septa resulting in cutis laxa.[115] Antitrypsin gene is located on chromosome 14. It is a highly polymorphic gene which has 75 variants. The locus has been designated as "Pi" for protease inhibitor.[15]

Marfan's syndrome occurs due to mutations in gene encoding fibrillin-1 (FBN-1). FBN-1 is a glycoprotein that is one of the major components of microfibrillin, which in turn is an important constituent of the ECM. FBN-1 plays an important role in maintaining the structural integrity of connective tissue. Neurofibromatosis-1 is caused by mutation in gene (NF-1) encoding neurofibrin, a protein with a centrally located domain homologous to guanosine triphosphatase-activating protein. It is postulated that neurofibromin may have a regulatory role in the development of various connective tissues including vascular connective tissue.

Several cases associated with PXE have been reported. Pathogenesis of PXE appears to involve abnormal elastic fibres. Both autosomal recessive and dominant varieties have been mapped to chromosome 16p13.1.[124]

CLINICAL FEATURES OF RUPTURED ANEURYSMS

The hallmark of SAH is sudden, usually severe headache in about 80% of cases and 45% complain of brief loss of consciousness. About 35% have nuchal rigidity. Aneurysmal rupture can lead to sudden death in about 12–15% of cases. A variety of other symptoms may develop before aneurysm rupture. They depend on the site and size of the aneurysm and include hemiparesis, dysphasia, extraocular muscle impairment, visual loss, visual field defect, localised headache and seizures and, sometimes giant thrombosed aneurysms may present as a mass lesions.[140] Prior to frank bleed, many patients experience warning symptoms, the so-called "sentinel symptoms". These are reported to occur in as high as 60–70%. These consist of headache, retrobulbar pain and nuchal pain.

Ruptured aneurysms at specific sites may produce distinct clinical features. Anterior cerebral artery (ACA) aneurysm rupture may produce brief weakness of the lower extremities bilaterally. Middle cerebral artery (MCA) aneurysms may produce hemiparesis, paraesthesias, hemianopsia and dysphasia. Seizures occur more commonly with anterior circulation aneurysms and more so with MCA aneurysms. Third nerve palsy or unilateral retro-orbital pain suggests an aneurysm arising at the internal carotid artery-posterior communicating artery junction. Third nerve involvement can also occur with aneurysms originating in the superior cerebellar artery (SCA). Carotico-ophthalmic aneurysms and superior hypophyseal aneurysms may produce unilateral visual loss or even bilateral field defects. Focal neurological deficits after SAH may be due to mass effect from giant partially thrombosed aneurysms, vasospasm, seizures or haematomas in an intracerebral or subdural location. In about 25% of patients with SAH there may be vitreous haemorrhage.[112,140]

Editors' comment: Multi-centric study "Epidemiological Study on Subarachnoid Haemorrhage in India" (1972–75) published by the Indians Council of Medical Research, 1984, and a paper by Sambasivan et al. (Neurology India 1984;32:17) provide valuable information on the subject.

CLINICAL PRESENTATION OF UNRUPTURED ANEURYSMS

Unruptured aneurysms may be discovered incidentally or present with neurological symptoms. Raps et al.[105] investigated the presenting symptoms in 111 patients with unruptured aneurysms. They found that, although 51% of these aneurysms were asymptomatic, 17% presented with acute symptomatology, and 32% presented with chronic symptomatology. Acute neurological symptoms included ischaemia (37%), headache (37%), seizures (18%), and cranial neuropathies (12%). Chronic neurological symptoms included headache (51%), visual deficits (29%), weakness (11%) and facial pain (9%). As expected, larger aneurysms tended to present with neurological symptoms because the average aneurysm sizes for these three groups were 1.1 cm, 2.1 cm and 2.2 cm in maximum diameter respectively. In addition, symptomatic aneurysms tended to be located along the proximal internal carotid artery (ICA) with diameters never smaller than 3 mm.

DIAGNOSIS

The diagnosis of SAH due to rupture of IA is made on the basis of clinical suspicion corroborated with non-contrast computed tomography (CT) scan findings, which shows the amount and location of the bleed and, thus, may point towards the vessel from where the bleed has occurred. At times, when the history is suggestive of SAH, but CT is inconclusive, a lumbar puncture may be required. But the main stay of the diagnosis is CT angiography (CTA) which is undertaken after plain CT points to a vessel from which the bleeding has occurred.

Plain CT brain can mostly accurately predict the nature and location of the underlying vascular lesion. Clotted blood is characteristically seen as a high attenuation lesion in the subarachnoid cisterns. The length of time for which the high attenuation persists depends upon the amount of blood in the subarachnoid space, with 90% positivity during the first 5–7 days, 88% positivity within 5 days and 57% positivity up to 6–14 days after the bleed. The location of SAH may give information about the probable aneurysm site, such as anterior interhemispheric fissure (IHF), suggests bleed from the anterior communicating artery (A.Com); distal IHF suggests rupture of a distal ACA aneurysm; unilateral Sylvian fissure suggests rupture of an MCA aneurysm; blood in the suprasellar cisterns is indicative of an ICA aneurysm; interpeduncular cistern bleed points to basilar top aneurysm (basilar top An); prepontine + cerebellopontine angle cisterns suggests a basilar trunk and vertebrobasilar aneurysm and isolated intra IV ventricular bleed is suggestive of distal posterior inferior cerebellar artery (PICA) aneurysm. Frontal intracerebral haemorrhage (ICH) is seen in A_1, A.Com, internal carotid bifurcation and M1 aneurysms. Temporal ICH is seen in MCA aneurysms. Basilar top and postero superiorly directed A.Com aneurysm may produce pure intraventricular haemorrhage (IVH) only.[119]

Computed Tomography Angiography

Spiral and multi-slice CT is used for three-dimensional (3D) pictures to investigate the cause of SAH. The examination includes the area between the first vertebral body and the vertex in order to visualise the intracranial arteries, after intravenous injection of 100 ml contrast medium using a pressure injector. Image reconstruction is done using section thickness of 0.75 mm, overlapping steps of 0.5 mm, and 12 cm field of vision (FOV). Changes in attenuation values are measured with a region of interest placed within the internal carotid arteries and the spiral scan is automatically started as soon as a threshold of 80 Hounsfield units (HU) is reached. Good quality CTA not only depends on the acquisition parameters, but also on post-processing, which should be performed on a fast workstation, capable of real-time 3D volume rendering. There are several methods to analyse the CTA volume.[128] First of all it is mandatory to explore source images in order to identify the aneurysm; partial thrombosis or calcification should be recognised on source images before 3D processing. Multi-planar reformation is the method of choice at the beginning of the evaluation to confirm the aneurysm and to create coronal, axial, sagittal, or oblique sections, followed by maximum intensity projection (MIP) which, however, has a limited utility in CTA due to the higher attenuation of the skull compared with intracranial arteries. With MIP, small aneurysms can be missed, as they are masked by the signal of their parent vessels averaged into the same two-dimensional (2D) plane. Shaded surface display (SSD) and volume rendering technique (VRT) are less straightforward than MIP and require the user to define thresholds for the selection of voxels on the basis of their HU. The VRT uses all voxels within a volume, avoiding the loss of information typical of MIP and SSD techniques. The "ideal" threshold to depict intracranial arteries has to be found interactively and depends on several parameters, including the injection rate of the contrast medium and cardiac output. Once the aneurysm is identified, the volume-rendered 3D images are used for depiction of the position and spatial orientation of the aneurysm neck and sac, characterisation of arterial branching patterns at the neck and depiction of the relationship of the aneurysm to local and regional bone anatomy. An accurate anatomical evaluation is useful for assessment of the suitability of an endovascular approach for aneurysm treatment. The average sensitivity of CTA for the detection of IAs is about 90%. However, for aneurysms less than or equal to 3 mm diameter sensitivity is reduced to 61%, whereas the detection rate increases to 96% for aneurysms with a larger size.[138] More recent studies found overall detection rates of up to 97%,[138] and in some centres CTA has almost completely replaced intra-arterial digital subtraction angiography (IADSA) in patients with SAH[28] (except when dynamic flow study is mandatory). Villablanca et al.[135] reported a CTA sensitivity of 98–100% compared with 95% with IADSA, suggesting a central role for CTA in the evaluation of all patients with symptomatic and potentially asymptomatic IAs.

Four-Dimensional Computed Tomography Angiography

Four-dimensional computed tomography angiography (4D CTA) entails multi-slice CTA with a retrospective electrocardiographic-gated (ECG-gated) reconstruction algorithm by use of technology that was developed initially to examine coronary arteries. It is a novel technology that includes time dimension, which is repeated within the cardiac cycle. This is an important difference between 4D CTA and conventional cerebral angiography. The purpose of 4D CTA is to clarify the value of aneurysm wall pulsations and actual haemodynamic behaviour on the diagnosis and treatment of patients with aneurysm.[49]

Technique

In 4D CTA, angiographic images of the region around the circle of Willis are acquired by using multi-section helical CT systems in ECG-gated mode with a tube current of 260 mA and a tube voltage of 135 kV. The helical pitch/tube rotation speed is usually 0.7–1.2/0.4 seconds per rotation with the 4-row system, and 2.0–2.4/0.4 or 0.5 seconds per rotation with the 8-row system and 2.0–4.0/0.4–0.6 seconds per rotation with the 16-row system may also be used. Images are reconstructed by using the ECG-gated reconstruction method (with the R-R interval divided into 20 phases at 5% intervals). A total of

100 ml of non-ionic contrast medium (iopamidol) with an iodine concentration of 370 mg/ml is injected intravenously at a rate of 3 ml/sec by using an automatic injector. Scanning is started after a delay time of 20–23 seconds following the start of injection or by using the bolus-tracking function of the CT scanner.

Electrocardiographic-gated reconstruction: In the cardiac cycle, systole corresponds to the period from 0 to 50% of the R-R interval, with maximum contraction occurring at approximately 25%. The pulse wave generated during systole propagates towards the periphery at a speed of 4–6 m/s in the aorta and 8–12 m/s in the muscular arteries.[37] Pulsation of IAs can be observed during the period from 45 to 55% propagation of the pulse wave into IAs. About 84% of aneurysms rupture at the dome, 14% in the wall and 2% at the neck.[49] In particular, the presence of a bleb is important as an indication of the rupture site. In 4D CTA studies, the pulsation can be observed only in a bleb on the aneurysm which subsequently can be confirmed at the time of clipping.[37]

Magnetic Resonance Angiography

Although magnetic resonance angiography (MRA) has given very good results in detecting aneurysms in acute SAH,[137] it is often impractical in severely affected patients, due to long examination time, low spatial resolution compared to digital subtraction angiography (DSA), high cost, sensitivity to motion artifacts and difficulty in demonstrating vessels with low flow. These limitations make intracranial MRA a preferred screening modality only for specific groups at higher risk of harbouring an aneurysm than the general population, e.g. diseases of connective tissue such as Ehlers-Danlos type IV, ADPKD, fibro-muscular dysplasia, neurofibromatosis type 1 and AAT deficiency. The MRA is also recommended in families with greater than or equal to 2 first-degree relatives with SAH.[124] Unlike CTA and IADSA, MRA has the advantage of high sensitivity to the flow phenomena and, therefore, cerebral vessels can be displayed without contrast medium administration. Three basic MRA techniques are currently utilised:

1. Time-of-flight (TOF)
2. Phase-contrast (PC)
3. Gadolinium enhanced MRA.

All these techniques are based on 2D or 3D acquisition of flow-sensitive images of intracranial vessels with background suppression and production of angiographic projections for visualisation of the intracranial vasculature. The 3D (volume) acquisitions are preferred for the intracranial arteries, as lower gradient amplifier demands allow reduced echo time as well as higher signal-to-noise ratio, which may be used to achieve greater spatial resolution. For screening examinations 3D TOF MRA has almost replaced PC MRA, which is characterised by longer duration and lower spatial resolution due to a larger imaging matrix. Currently, a standard 3D TOF MRA investigation of the cerebral vessels is performed with multiple overlapping volumes (three to five) from the foramen magnum to the pericallosal artery, fat saturation, magnetisation transfer and high resolution matrix (256 × 512) to increase vessel-to-background contrast, rectangular FOV and 8–10 minutes acquisition time. Selective spatial saturation is often used in arterial TOF studies where a saturating pulse applied distal to the imaging volume is used to suppress venous blood. Spatial resolution is critical for depicting smaller aneurysms and also to minimise the effects of turbulent flow in large aneurysms. Compared with CTA, MRA has the disadvantage of a limited coverage of the intracranial vasculature. The average sensitivity and specificity of MRA for the detection of IAs is, respectively, 87% and 95%. However, sensitivity for aneurysms with a size of 3 mm or below drops to 38%, whereas the sensitivity for aneurysms with a larger diameter is 94%.[138] Aneurysms with a small sac or neck diameter, or which stem laterally to the feeding vessel will tend to receive little flowing blood, and thus are less conspicuous on 3D TOF magnetic resonance (MR) angiograms. Within a large aneurysm, recirculation can lead to saturation of the blood signal and compromise the angiographic contrast between the lumen of the aneurysm and the surrounding static tissue. More recently, gadolinium-enhanced MRA has been done for the evaluation of larger aneurysms with turbulent flow, usually underestimated in size by the traditional technique.[86] Although particularly useful for MR examinations with both a large coverage volume and high spatial resolution, until now contrast enhanced MRA has not reached widespread use, due to the lack of contrast of proximal arteries against enhanced venous structures near the cavernous segment of the ICA.

Intra-Arterial Digital Subtraction Angiography

Angiography is still required for pre-operative planning. The IADSA is the accepted diagnostic procedure of choice for the assessment of IAs and for the pre-operative treatment planning of patients and after a negative CTA or MRA examination in a patient with SAH.

A four-vessel IADSA is still the most sensitive tool to detect an IA and is the gold standard. This is ideally performed with selective injection of the ICAs and vertebral arteries within 24 hours of the bleeding. The IADSA usually succeeds the CT/CTA examination, which often indicates the appropriate vessels where the aneurysm takes origin from. When multiple aneurysms are discovered, in general, the larger and more irregular aneurysm seen on arteriograms is likely to have bled. A nipple irregularity is as highly significant as a focal mass effect or vasospasm.[92] The DSA should include sufficient views, including lateral, anteroposterior or angled anteroposterior, oblique and basal, and an unsubtracted film also is necessary. Adequate demonstration of neck size is important for planning aneurysm clipping, as well as in predicting the success of treatment with the Guglielmi detachable coils, because total occlusion is more likely in aneurysms whose neck is 4 mm or less.[23]

The primary advantage of IADSA over other imaging modalities is the high resolution. The selective

intra-arterial injection of iodinated contrast medium ensures optimal enhancement of the intracranial arteries with superior resolution compared with that of CTA or MRA. Very small diameter vessels and perforators can be imaged only on IADSA. This information is mandatory at certain locations. However, in some cases, IADSA may lead to ambiguity due to its inability to project the aneurysm sufficiently, leading to a less than optimal definition, therefore impairing the choice of the optimal treatment method.

3D rotational angiography reveals aneurysms not seen on conventional DSA and allows a clearer depiction of anatomic details which are important for therapeutic planning.[40] It serves as a useful adjunct to IADSA, providing precise measurements necessary for endovascular coiling.[31,131]

Figures 1–27 show various investigations related to the diagnosis of intracranial aneurysms.

LOCATION OF INTRACRANIAL ANEURYSMS

Aneurysms commonly arise at the bifurcations of major arteries and from branching sites. Most saccular aneurysms arise in the circle of Willis or the MCA bifurcation. Approximately 86.5% of all IAs arise in the anterior (carotid) circulation and about 10% of IAs arise in the vertebrobasilar circulation. About 3.5% of IAs occur at miscellaneous locations like the SCA and the anterior

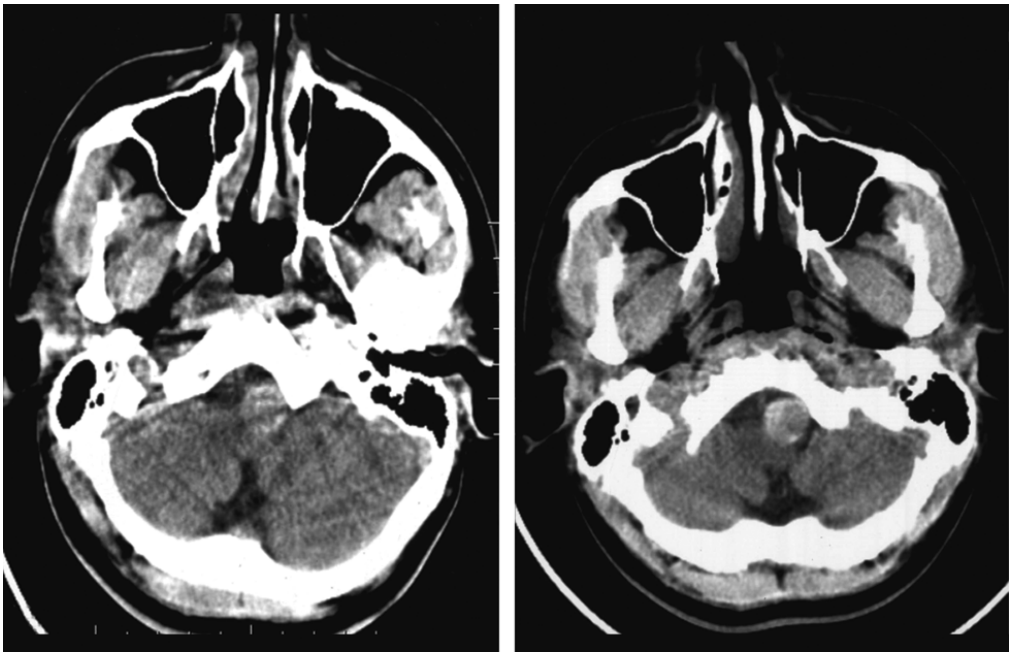

Fig. 1: Computed tomography—perimedullary bleed left (posterior inferior cerebellar artery aneurysm)

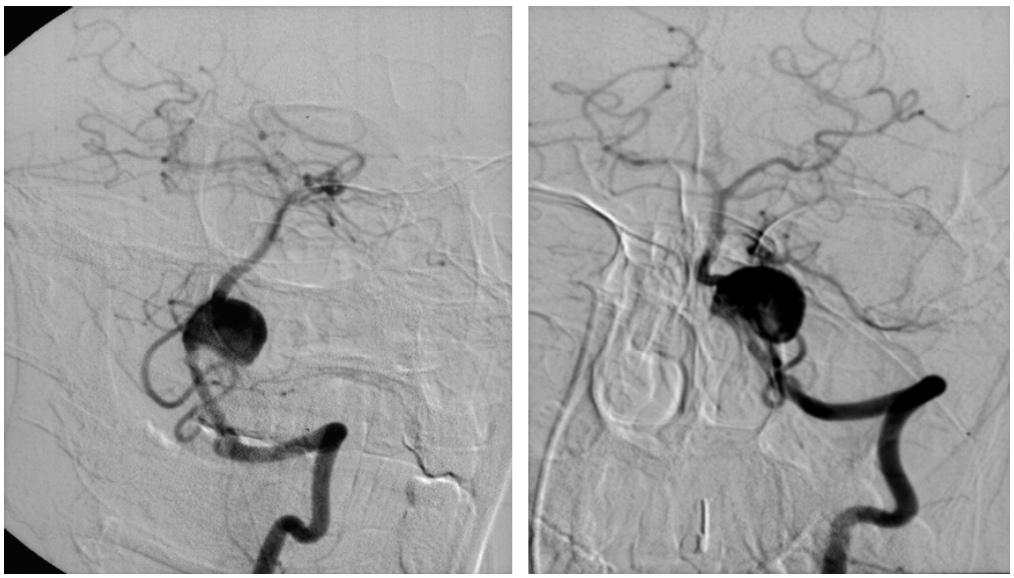

Fig. 2: Digital subtraction angiography—large posterior inferior cerebellar artery aneurysm (left)

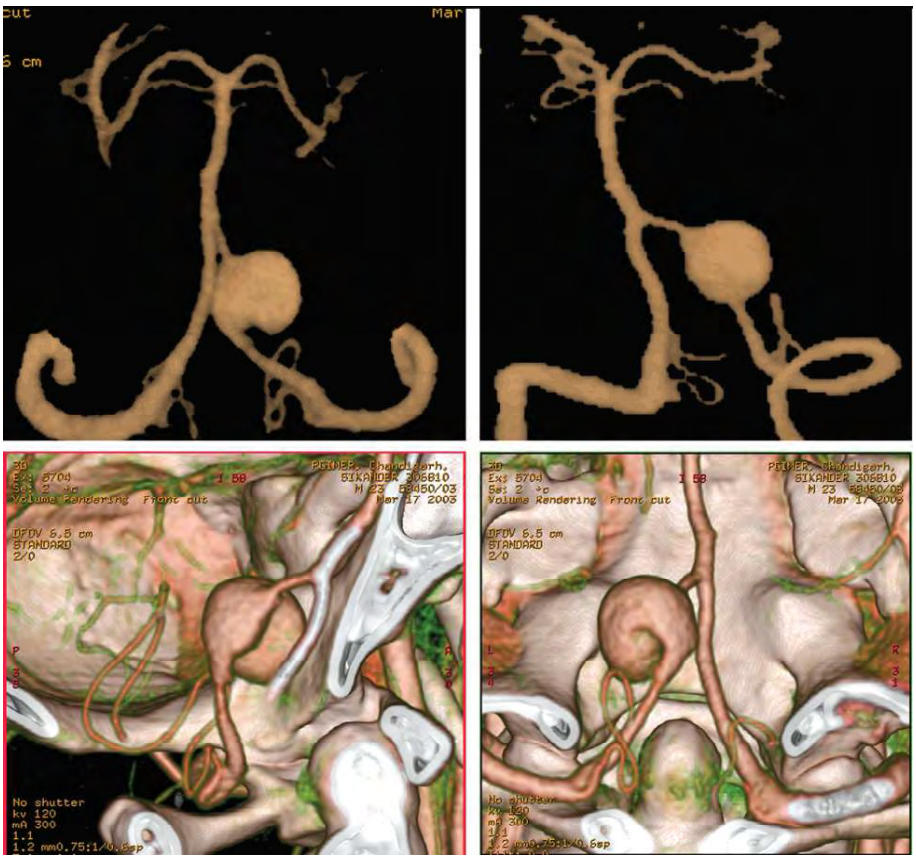

Fig. 3: Computed tomography angiography—large posterior inferior cerebellar artery aneurysm (left)

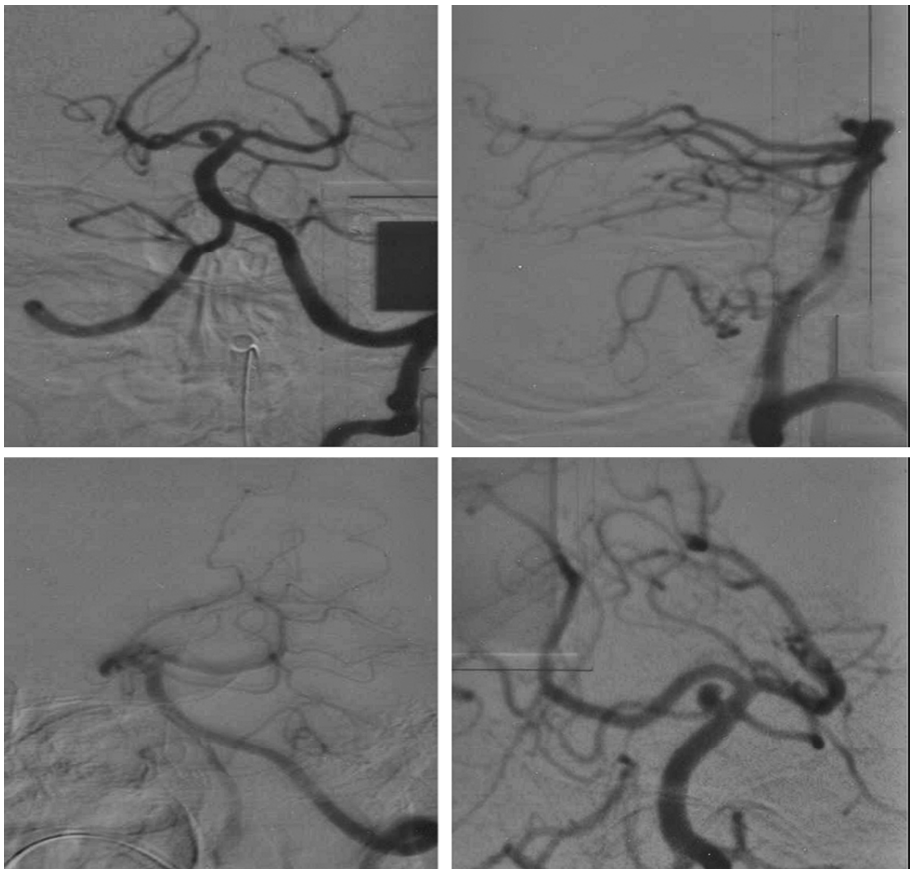

Fig. 4: Digital subtraction angiography—right superior cerebellar artery aneurysm

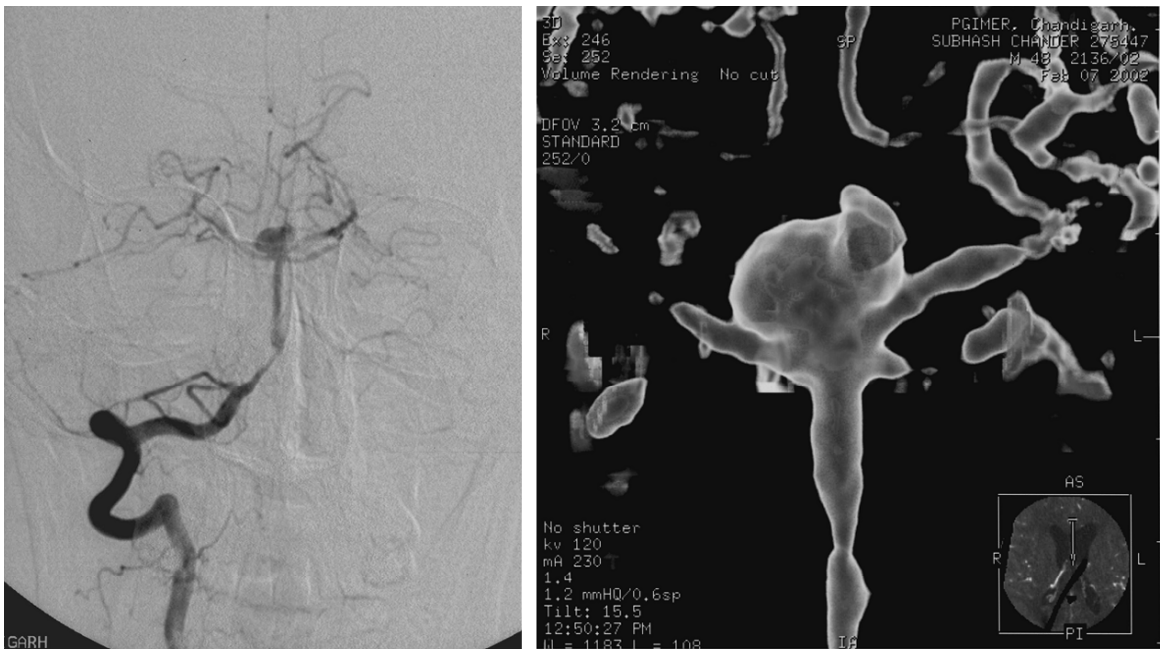

Fig. 5: Digital subtraction angiography and computed tomography angiography—basilar top aneurysm with ruptured nubbin

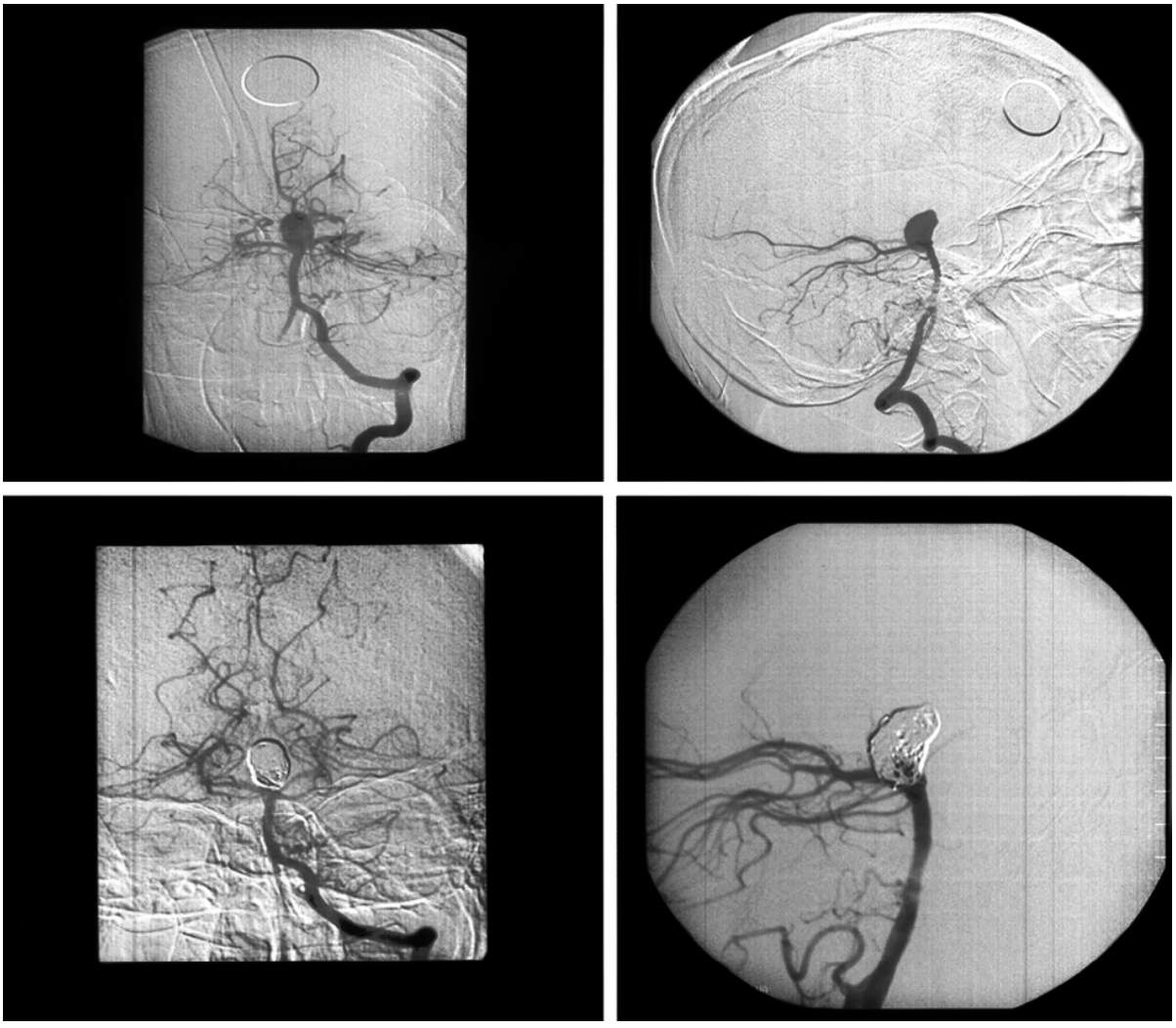

Fig. 6: Digital subtraction angiography—basilar top aneurysm coiled

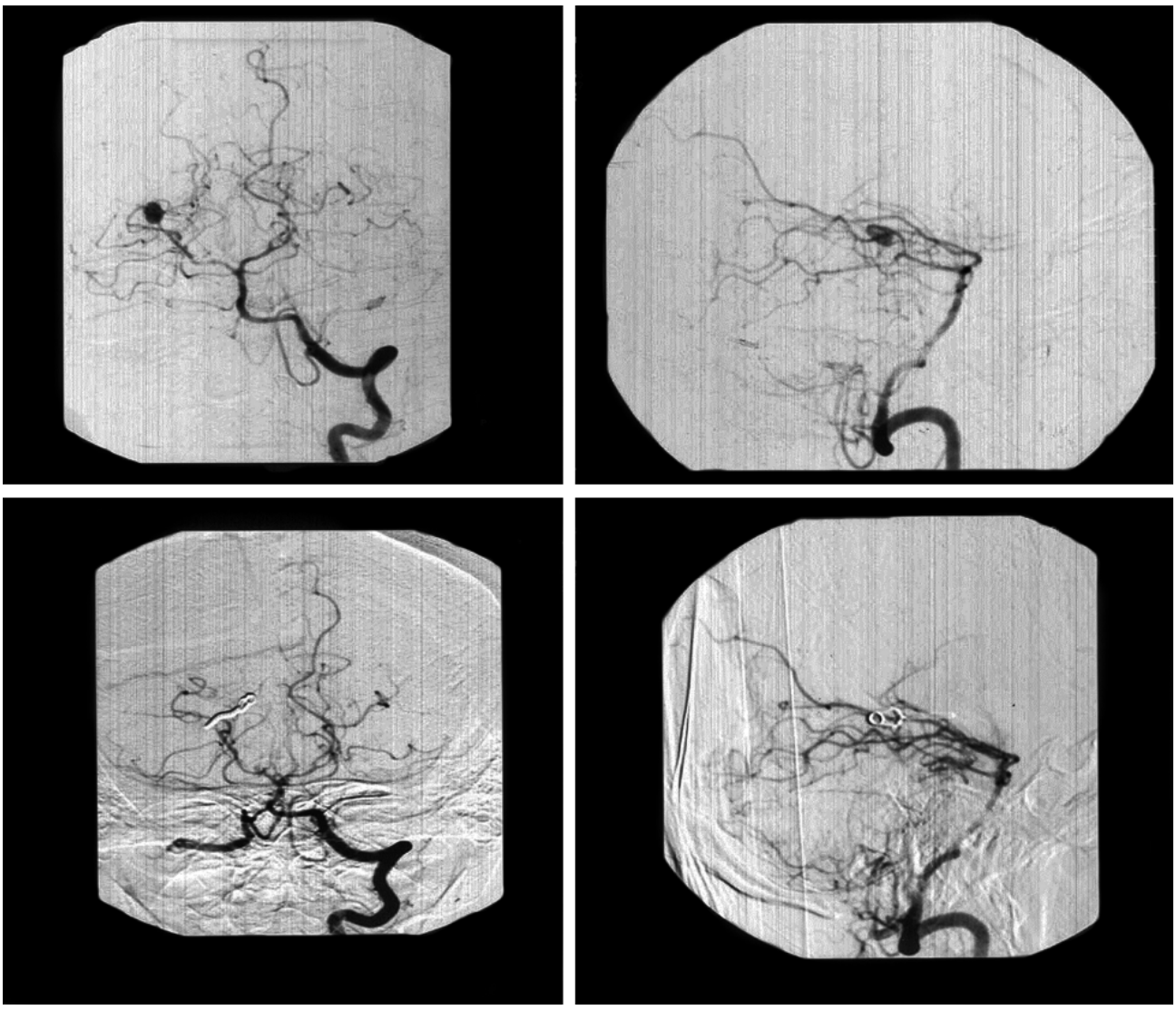

Fig. 7: Digital subtraction angiography—P3 aneurysm clipped

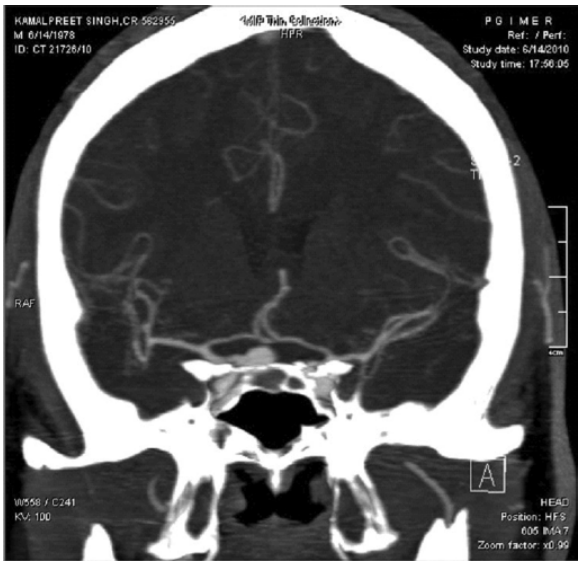

Fig. 8: Computed tomography angiography—right superior hypophyseal artery aneurysm

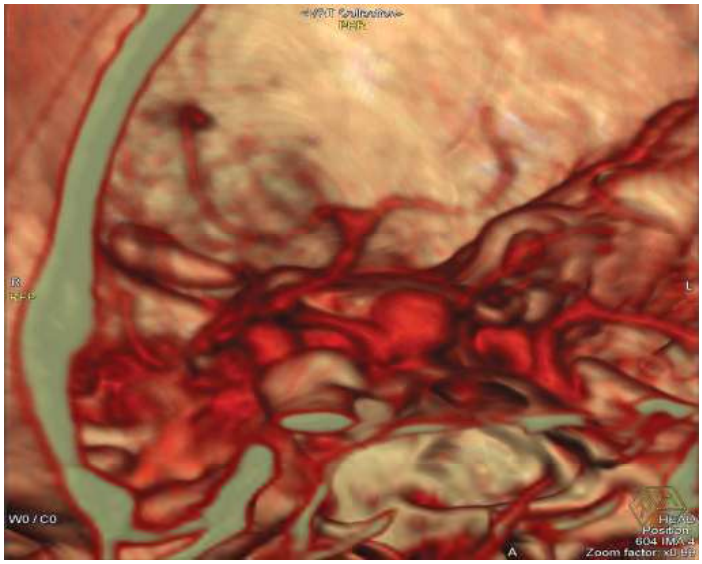

Fig. 9: Computed tomography angiography—showing right superior hypophyseal artery aneurysm

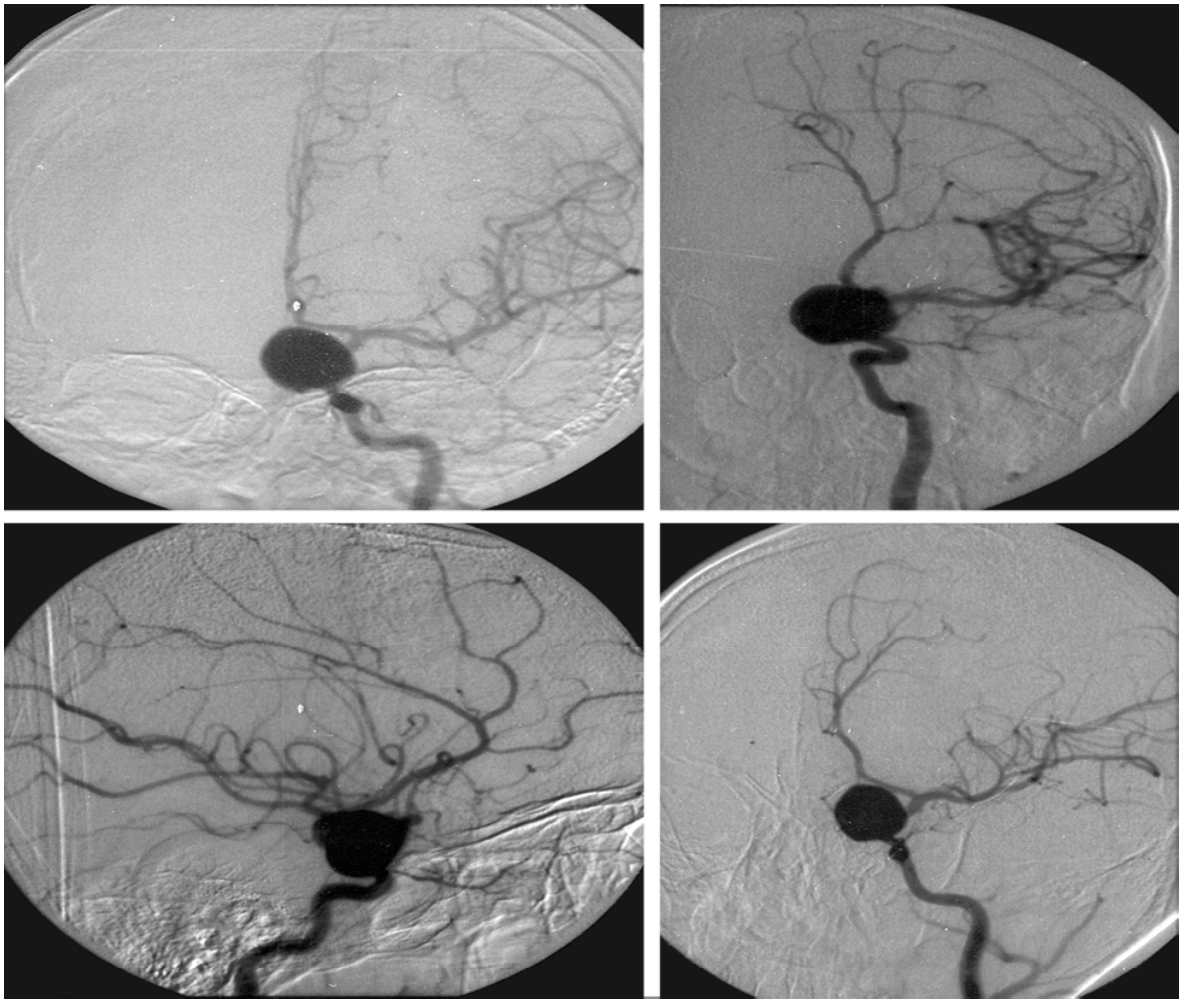

Fig. 10: Digital subtraction angiography—giant left carotico-ophthalmic artery aneurysm

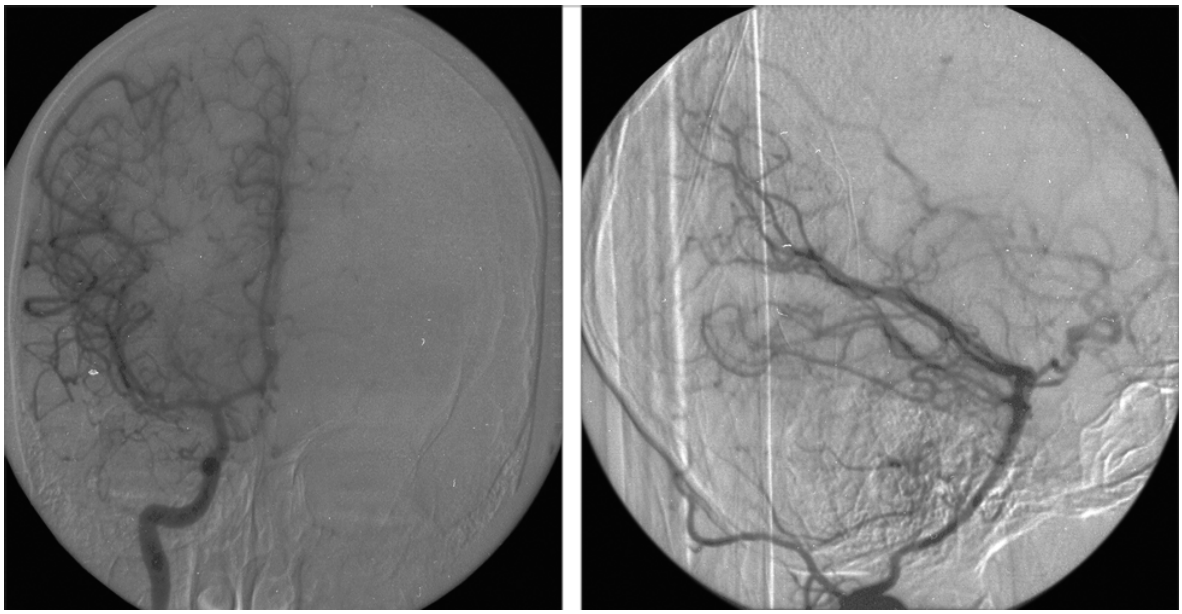

Fig. 11: Digital subtraction angiography—no cross-circulation from right to left, good cross-circulation from vertebral to carotid in a patient with a large left sided carotico-ophthalmic artery aneurysm

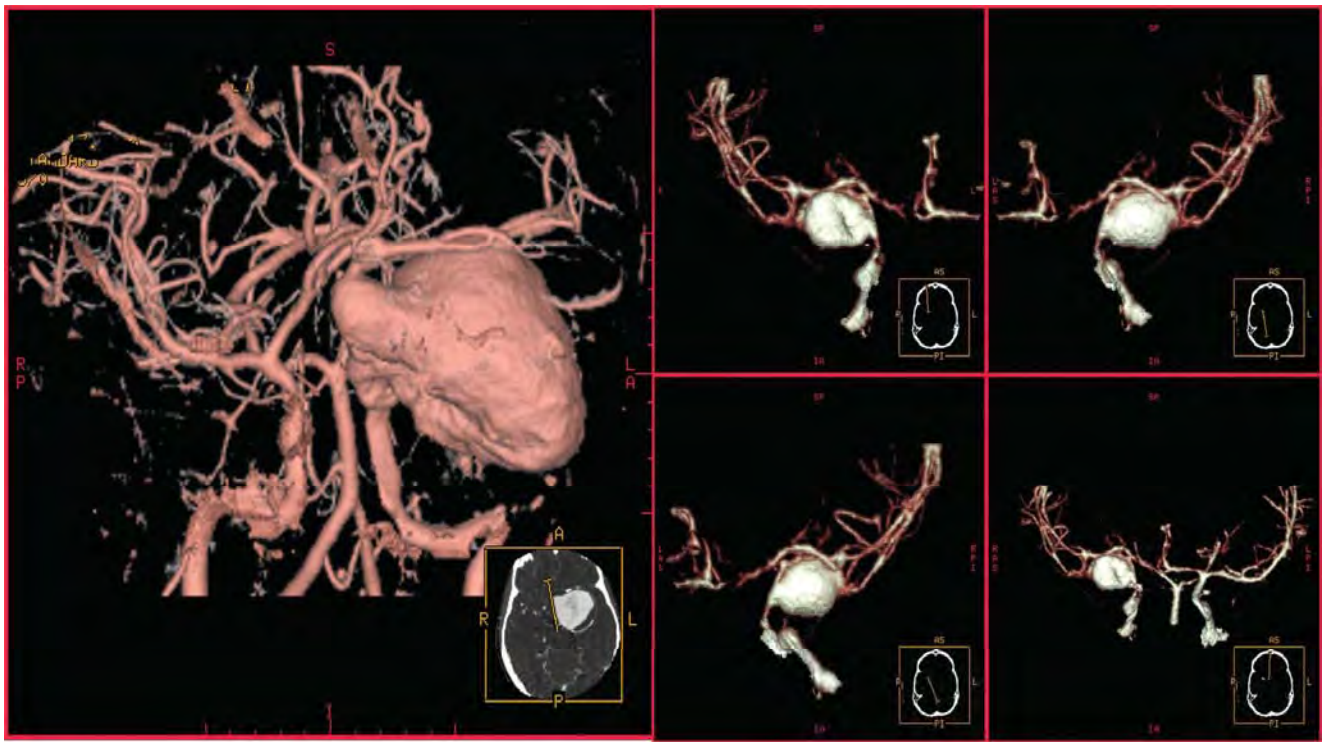

Fig. 12: Computed tomography angiography—giant paraclinoid aneurysm left

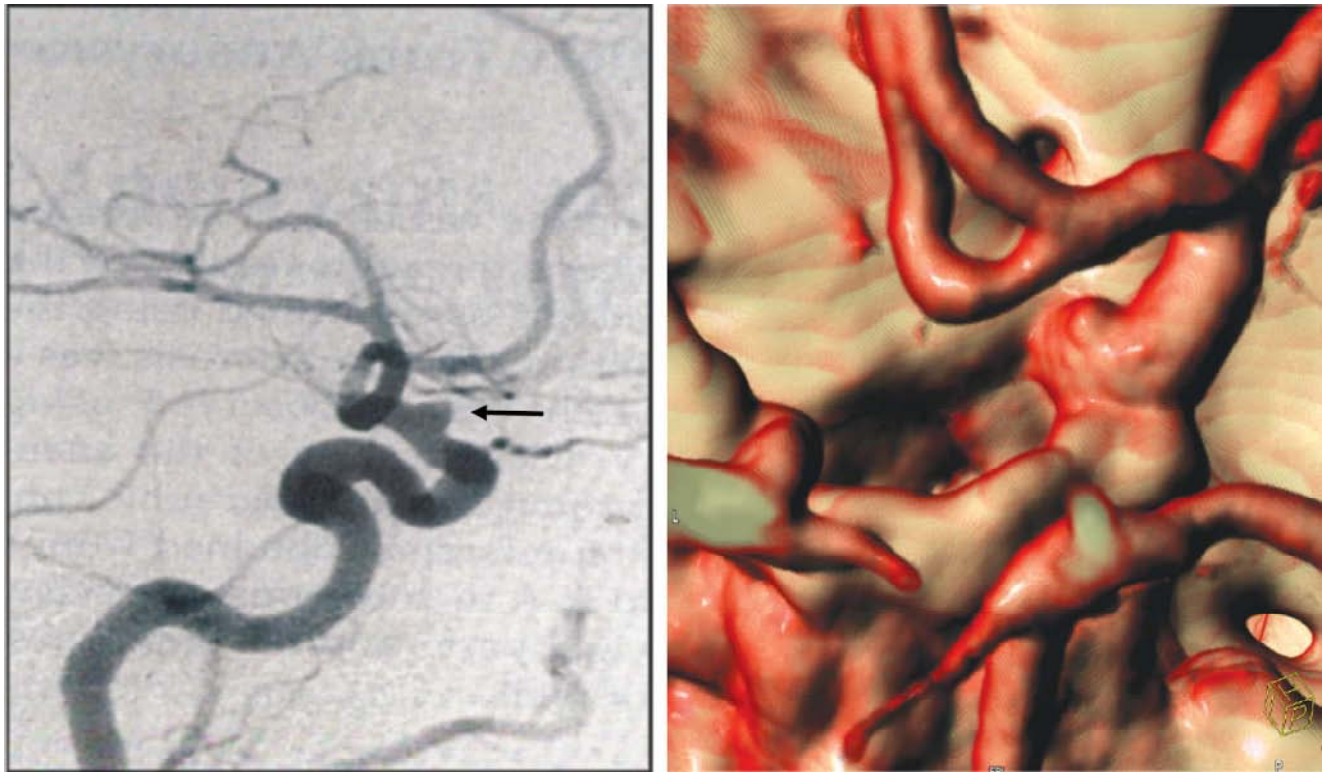

Fig. 13: Digital subtraction angiography + computed tomography angiography—dorsal internal carotid artery blister aneurysm

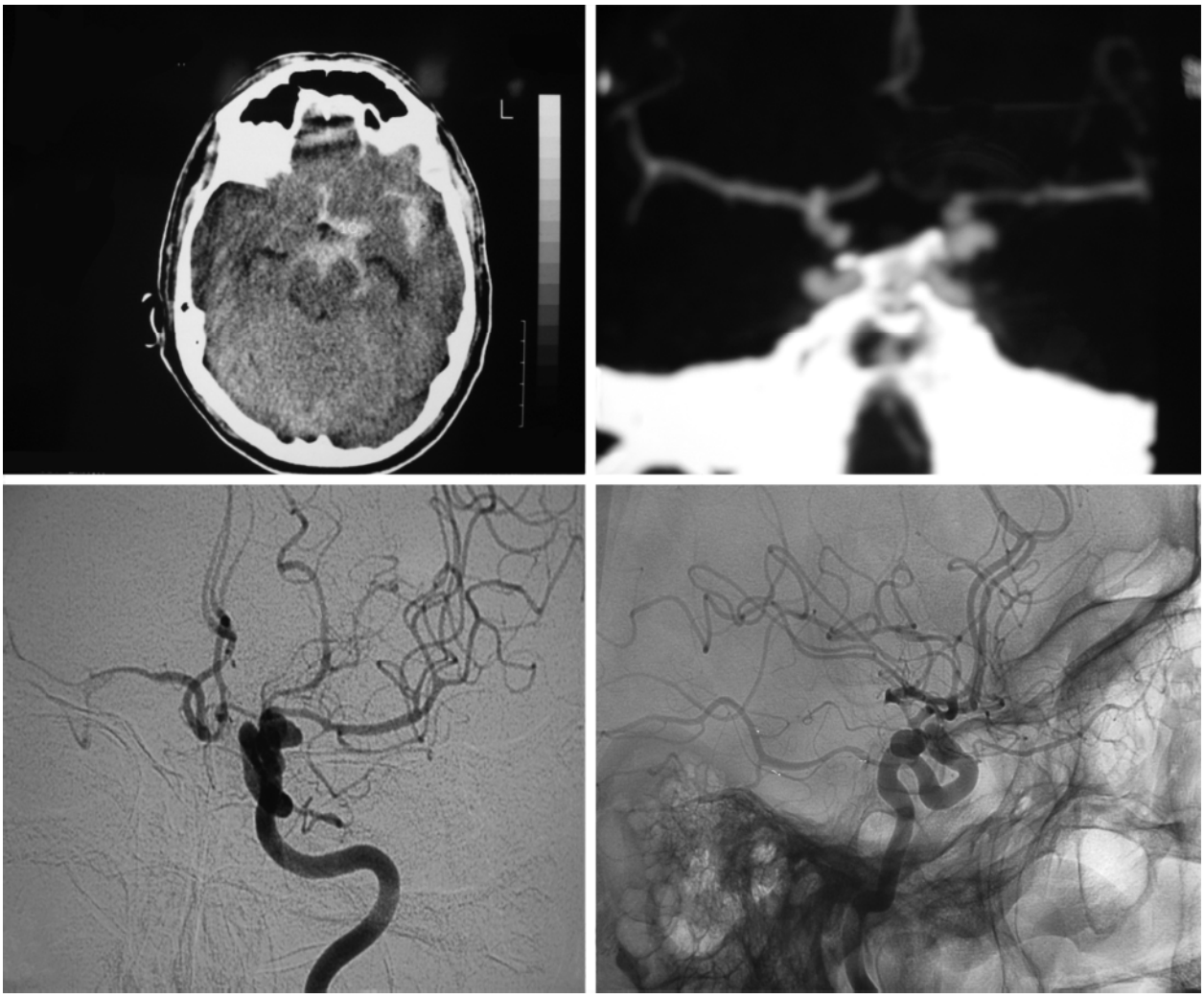

Fig. 14: Computed tomography angiography and digital subtraction angiography—Sylvian peri-mesencephalic bleed due to ventrolateral internal carotid artery aneurysm left

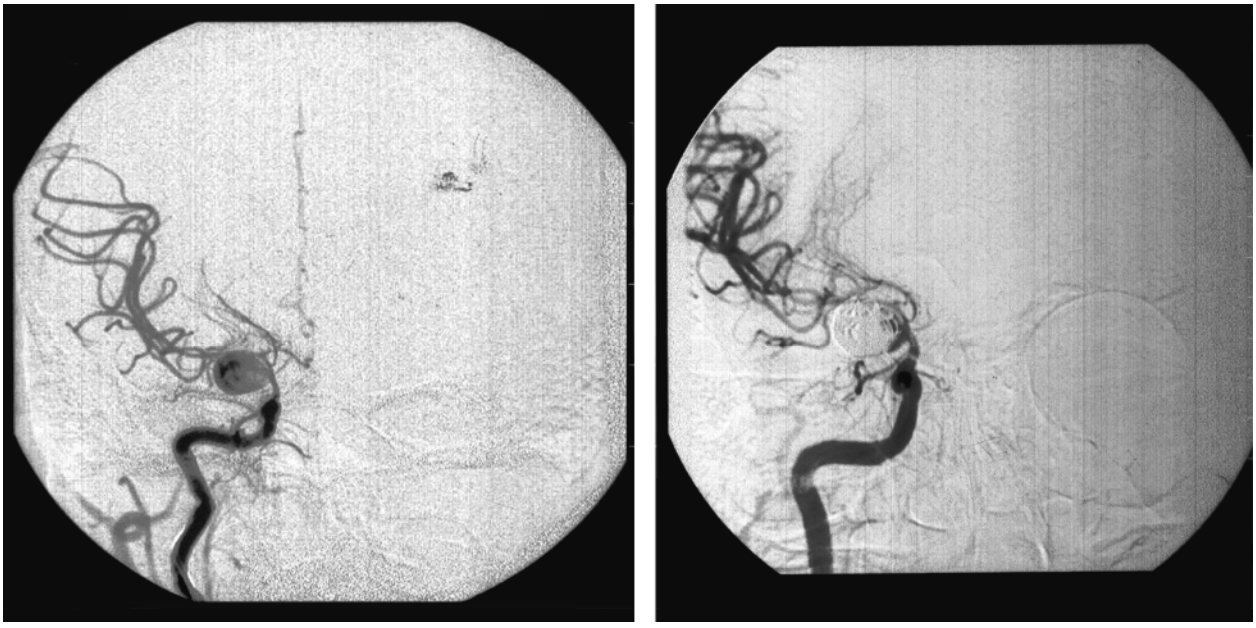

Fig. 15: Digital subtraction angiography—large right posterior communicating artery aneurysm coiled

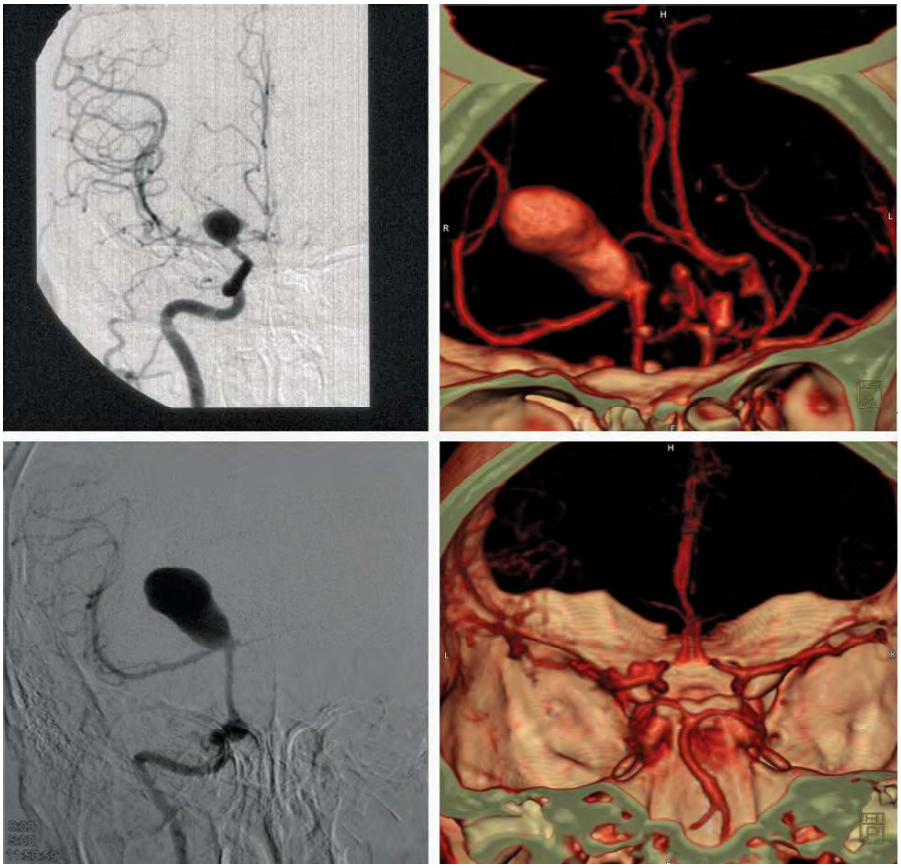

Fig. 16: Digital subtraction angiography and computed tomography angiography—giant internal carotid artery bifurcation aneurysm

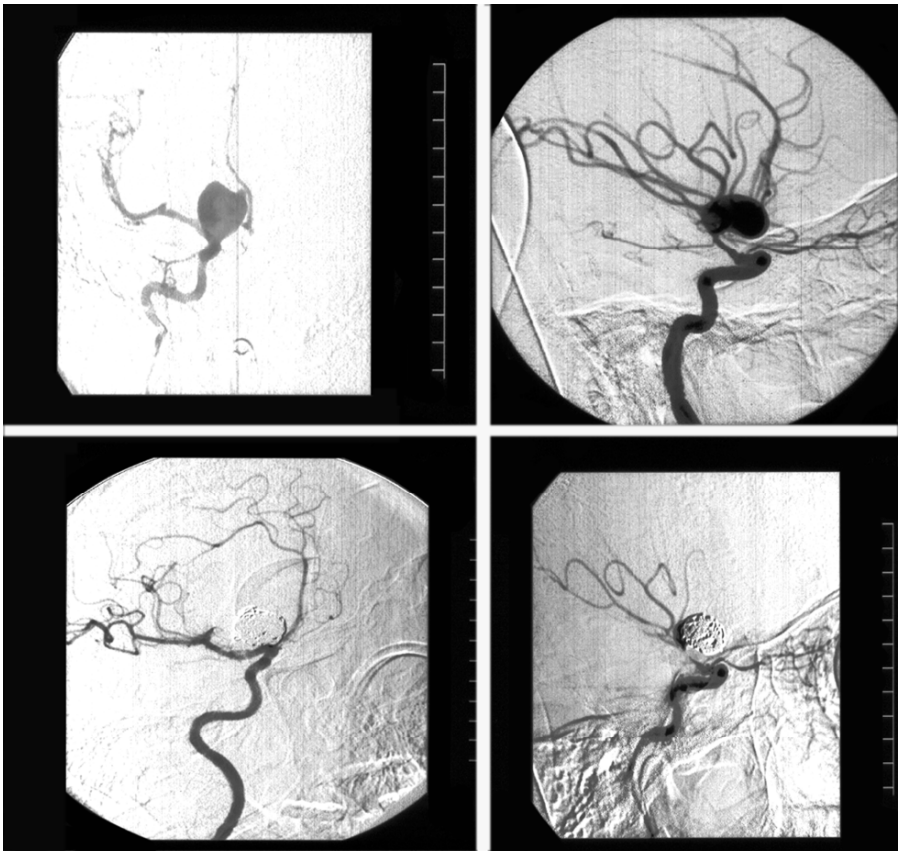

Fig. 17: Digital subtraction angiography—large internal carotid artery bifurcation aneurysm coiled

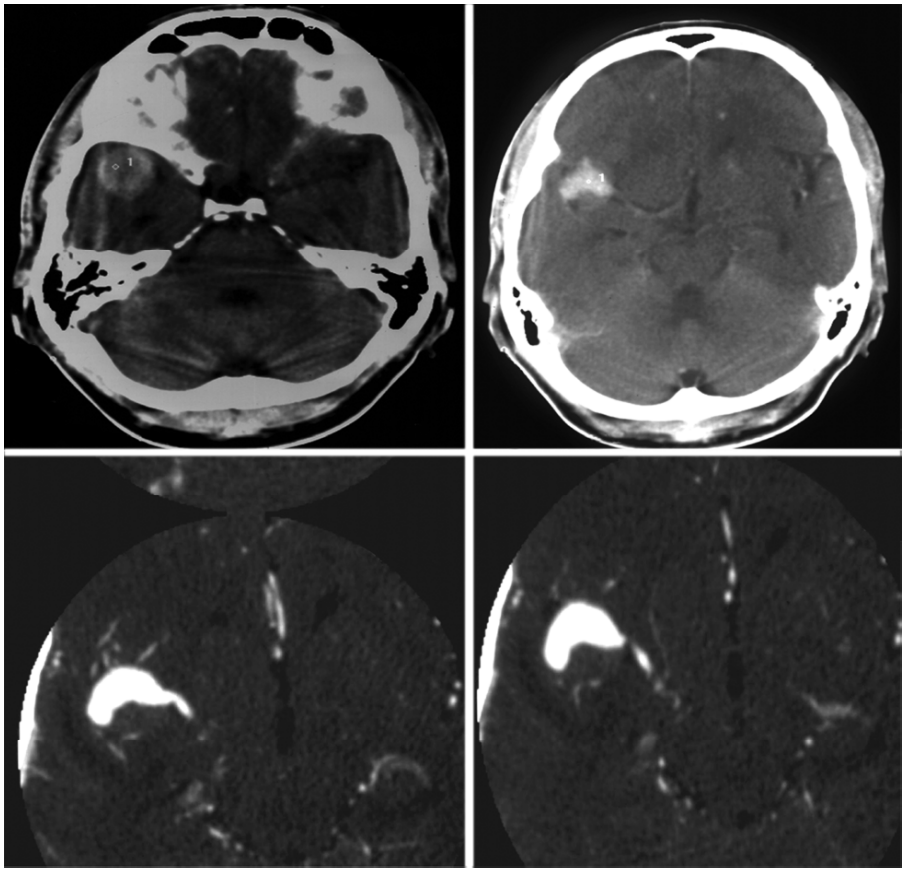

Fig. 18: Computed tomography and computed tomography angiography—right Sylvian bleed due to right fusiform middle cerebral artery aneurysm

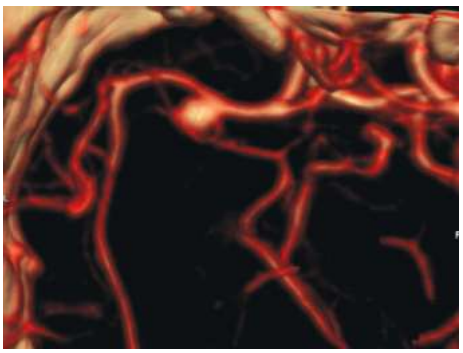

Fig. 19: Computed tomography angiography—right M1 aneurysm

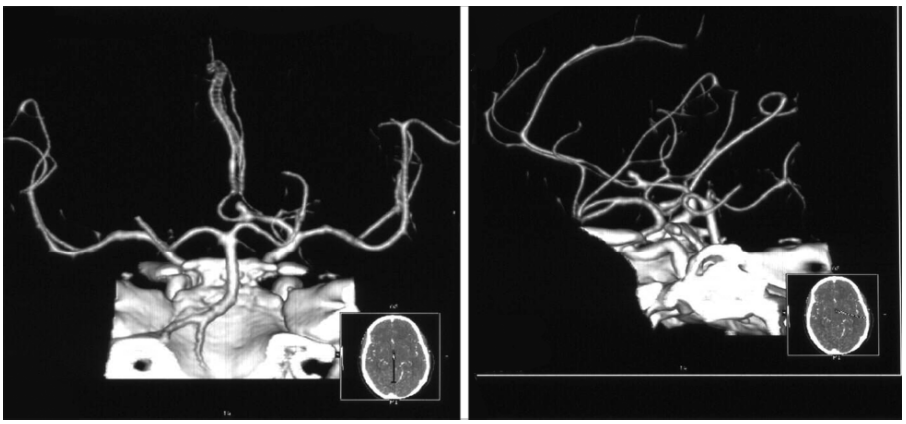

Fig. 20: Computed tomography angiography—anterior communicating artery aneurysm

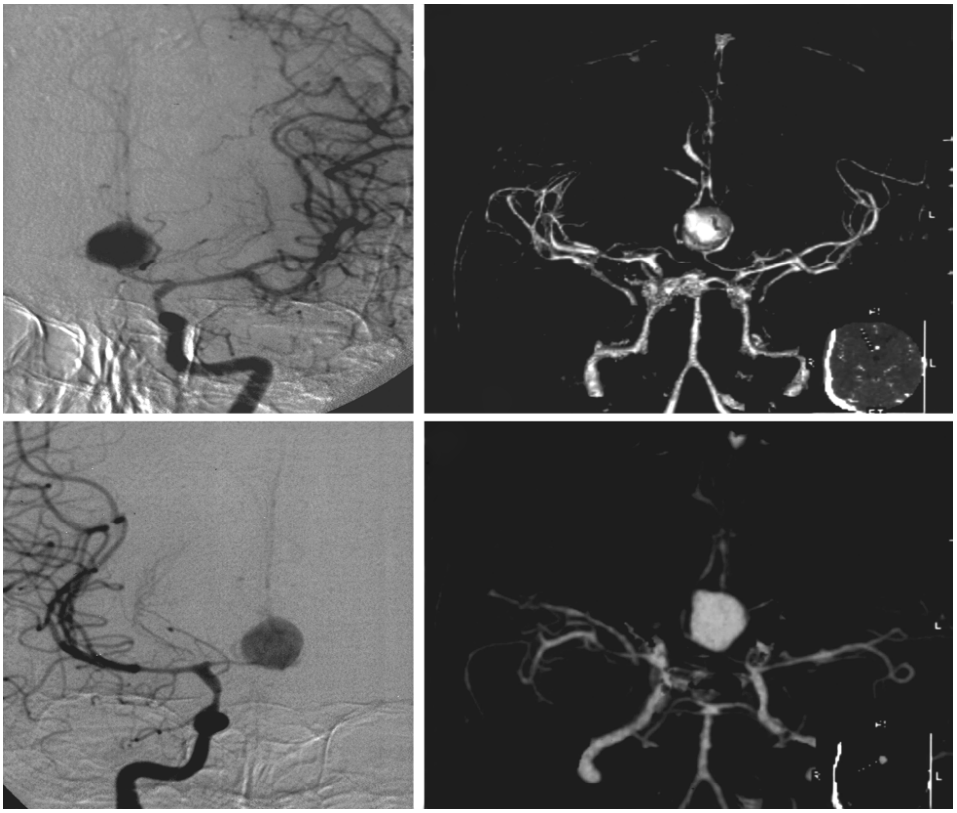

Fig. 21: Digital subtraction angiography and computed tomography angiography—large anterior communicating artery aneurysm filling from both sides

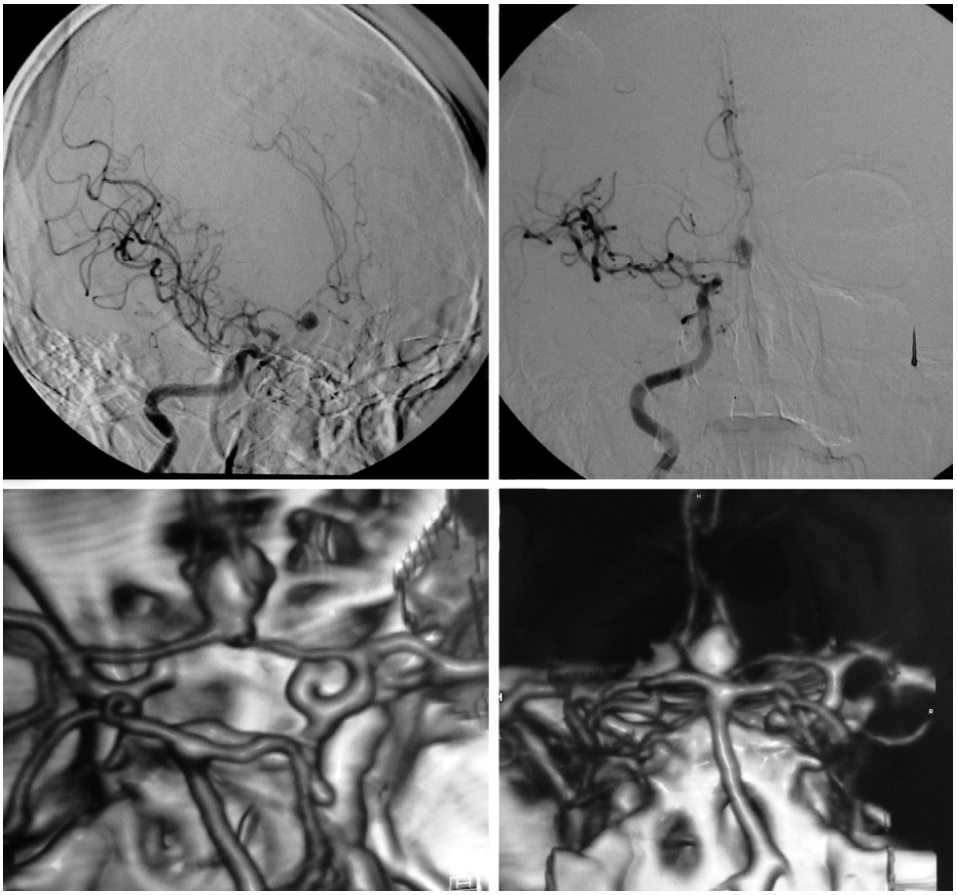

Fig. 22: Digital subtraction angiography and computed tomography angiography—anterior communicating artery aneurysm

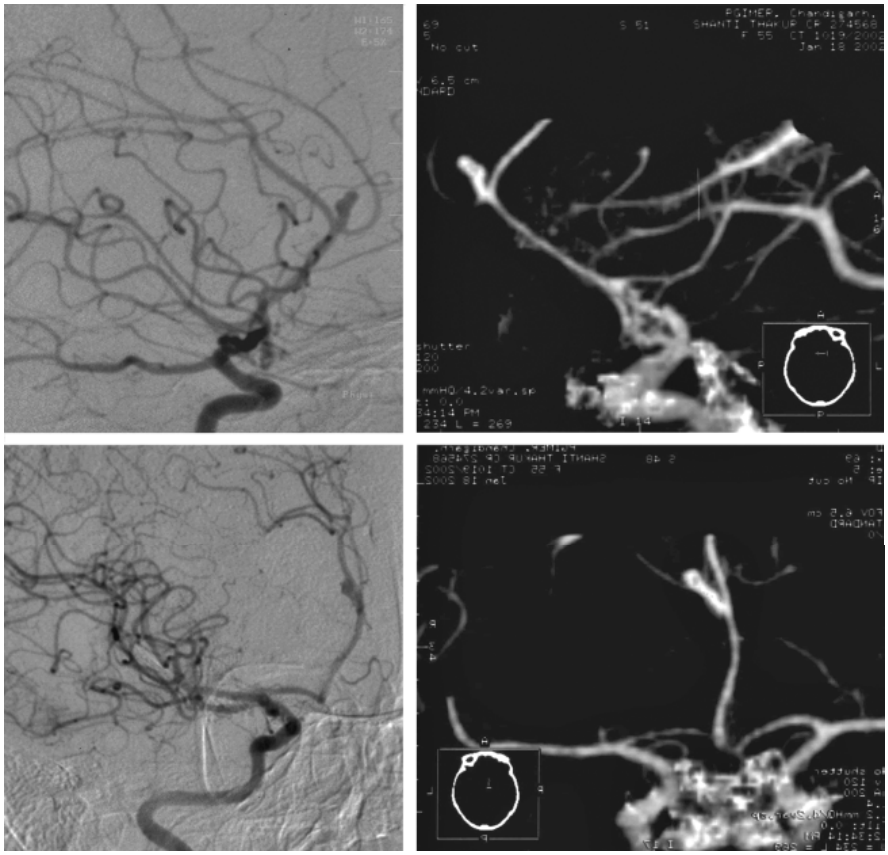

Fig. 23: Digital subtraction angiography and computed tomography angiography—distal anterior cerebral artery aneurysm

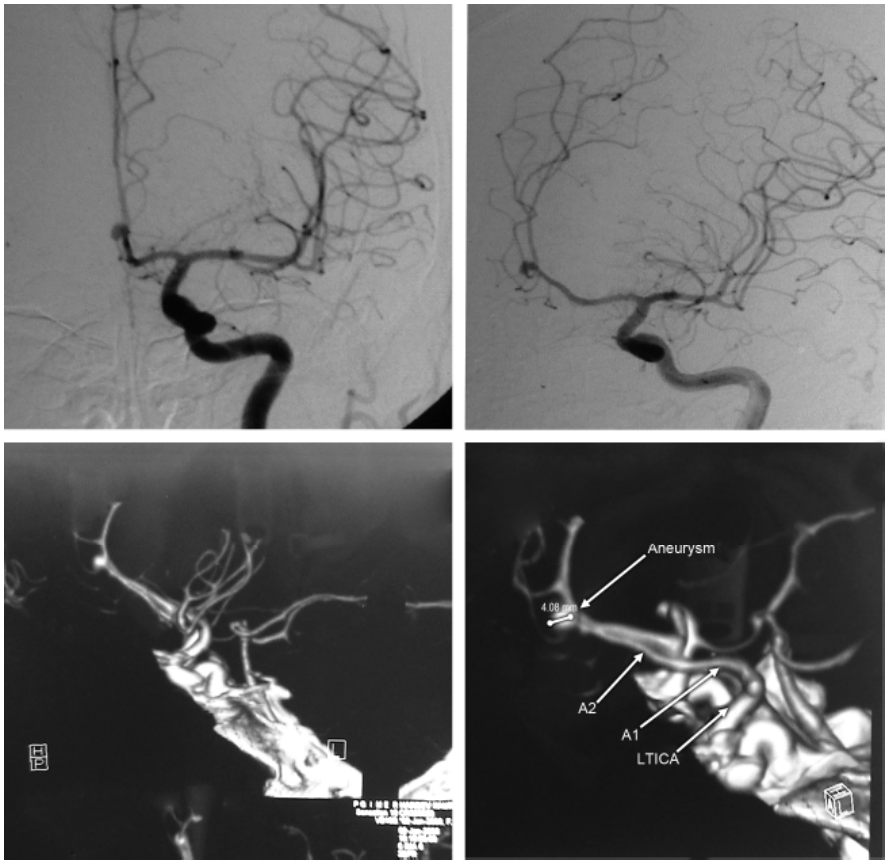

Fig. 24: Digital subtraction angiography and computed tomography angiography—distal anterior cerebral artery aneurysm

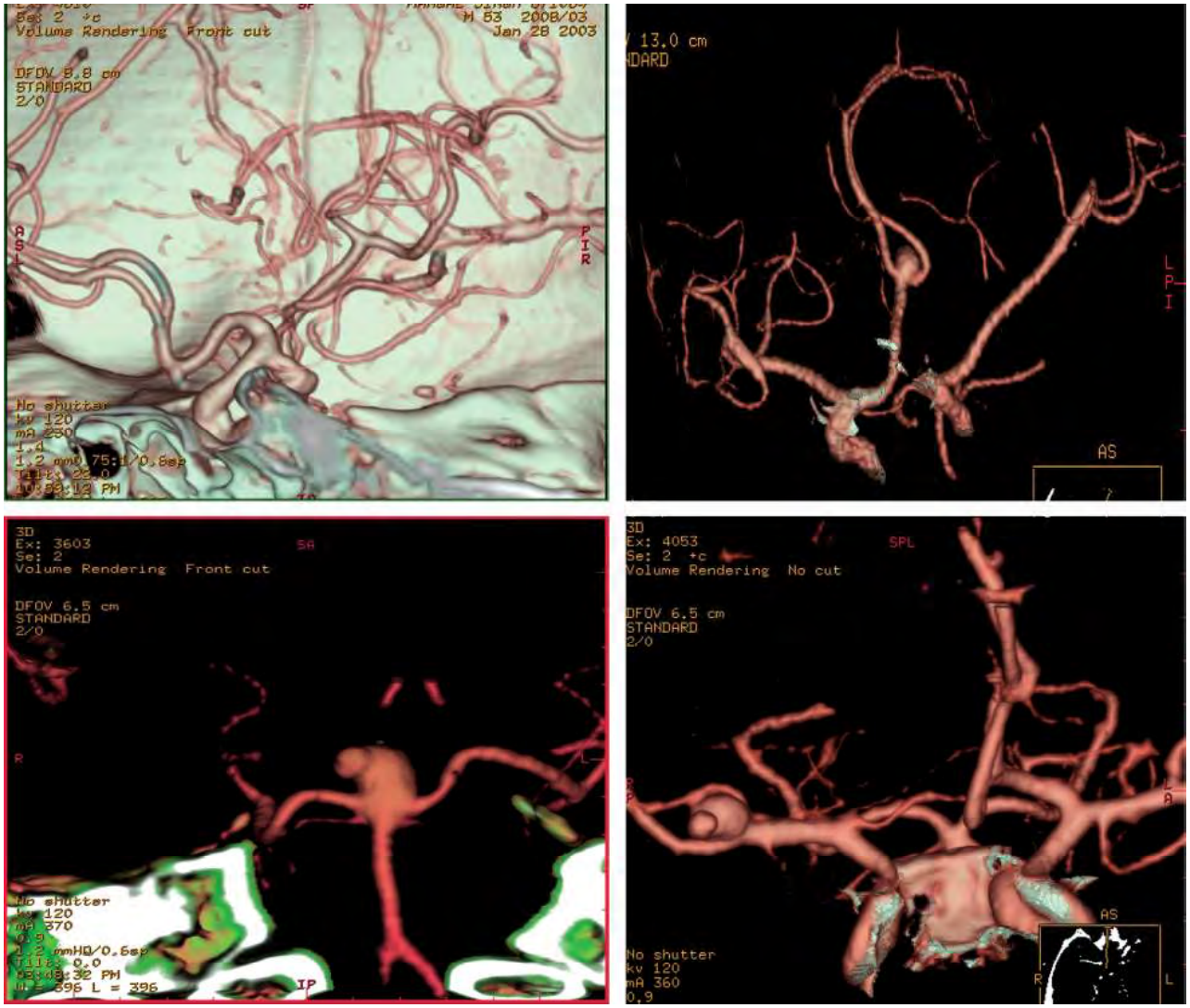

Fig. 25: Computed tomography angiography—multiple aneurysms

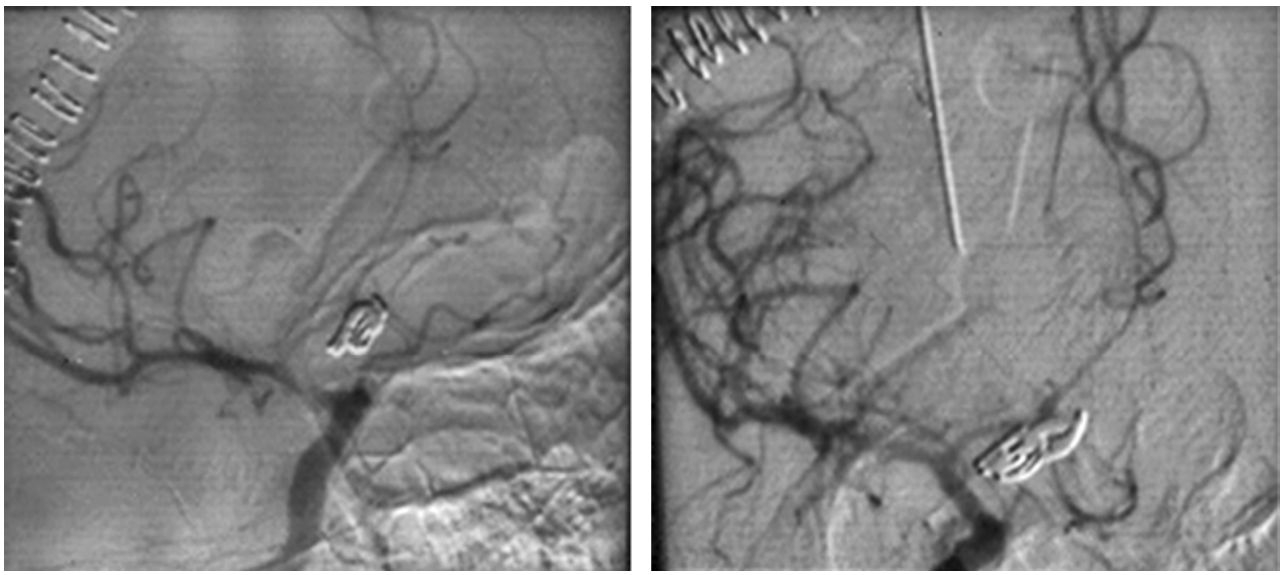

Fig. 26: Digital subtraction angiography—vasospasm relieved after intraventricular sodium nitroprusside instillation

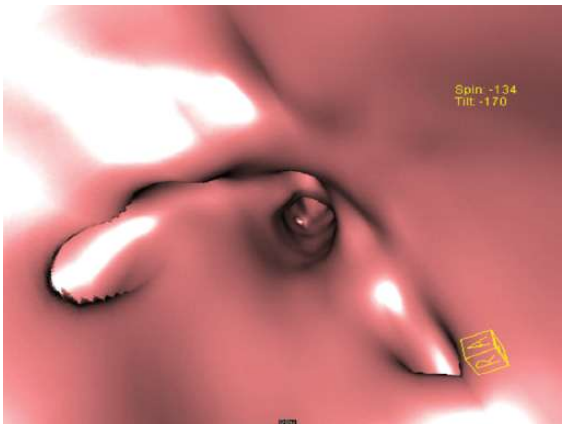

Fig. 27: Computed tomography angiography—angioscopic view showing openings of M1, two M2 division and aneurysm neck

inferior cerebellar artery. Common locations include the A.Com (30%), the junction of the ICA and the posterior communicating artery (P.Com) (25%) and the MCA bifurcation (20%). The ICA bifurcation (7.5%) and the pericallosal/callosomarginal artery junction account for the remainder (4%). Around 7% arise from the basilar artery bifurcation, and the remaining 3% arise at the origin of the PICA where it comes off the vertebral artery. Saccular aneurysms are uncommon in locations other than the sites mentioned above. Aneurysms that develop at distal sites in the intracranial circulation are often caused by trauma or infection. Non-traumatic distal aneurysms, particularly along the ACA, have a high frequency of multiplicity and spontaneous haemorrhage. The authors' operative experience shows the distribution as under:

Location 1992–2009			
A. com	*1114*	*43.0%*	
MCA	*590*	*22.8%*	
P. com	261	10.0	
ICB	**158**	**06.1%**	
DACA 141	05.4%		
DICA 11	00.4%		
ICA	**73**	**02.9%**	
M1	39	01.5%	ICA Aneurysms 22.2%
Distal MCA	24	01.0%	
COPH	**65**	**02.5%**	
A1A2	32	01.2%	
ACA	8	00.3%	
PICA	26	01.0%	
Basilar tip	12	00.5%	
PCA	6	00.2%	
BAS SCA	7	00.3%	
ANT. CHOR	**17**	**00.7%**	
CAV	5	00.2%	
		2588	

AGE AND SEX DISTRIBUTION

Aneurysmal SAH commonly occurs in the age group of 40–60 years with a peak incidence in the fifties. This is two decades older when compared to SAH due to arteriovenous malformations and one decade younger when compared with hypertensive intracerebral haematoma. It thus, occurs in the population at their most productive age.

The following bar diagram (Fig. 28) shows the incidence of aneurysmal SAH in different age groups (NB: In neonates only 19 cases have been reported so far).

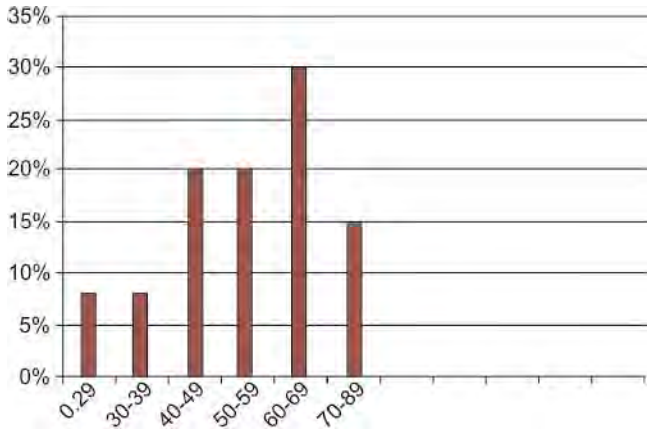

Fig. 28: Incidence of aneurysmal SAH in different age groups

The majority of epidemiological surveys have reported a higher incidence of SAH in women than men.[10-12,48,52,62,98,103,130,131] This observation, however, is not universal. Two large population-based registries found a higher frequency in men[46,113] and a third found no gender related differences at all.[29] Although the source of this variability is not completely understood, differences in age distribution may provide a partial explanation because the relationship between gender and incidence is age dependent.[63,113] Aneurysmal SAH is more common in males than females in childhood and adolescence.[10,24,99] This, however, reverses and, by the sixth decade of life, more women have aneurysmal SAH than men. The reason for gender-related differences is unclear. Longstreth and his colleagues[79] have proposed that hormonal factors may play a role in the pathogenesis of aneurysmal rupture. Gender does not predict the severity of presentation, outcome or survival from SAH.[48,63] Although mortality rates in women are higher than in men,[48,53,130] no significant differences in case fatality rates have been reported.[35,98] This suggests that women are more likely to die from SAH only because they are more likely to experience SAH.

MANAGEMENT OF ANEURYSMS

Patients with ruptured IAs should be treated as soon as possible after the haemorrhage to prevent re-bleeding and to provide adequate medical treatment of vasospasm.

Until recently, the standard method of treatment for IAs has been surgical clipping, however, during the last decade the introduction of Guglielmi detachable coils has completely revolutionised the management of patients with IAs.[31] The endovascular treatment of cerebral aneurysms consists of filling the aneurysm sac with soft platinum coils through a microcatheter which is usually placed at the neck of the aneurysm. The choice of treatment depends upon the anatomical characteristics of the aneurysm, mainly the size, location, neck width and the clinical condition of the patient. The dome:neck ratio should also be measured, since it significantly affects the ability to completely coil the aneurysm.[28] Patients with poor Hunt and Hess grades, namely 4 and 5, are generally poor neurosurgical candidates and can benefit from endovascular treatment. Patients with a basilar top aneurysm are good candidates for endovascular coiling, as surgery is limited by the small working space at a depth and the presence of perforating arteries to the brainstem. MCA aneurysms are less suitable for coiling, as the secondary branches are close to the neck and the neck is usually wide. Although the results of endovascular treatment of small aneurysms (< 10 mm) and aneurysms with small necks are promising, the rate of success is less in aneurysms with larger diameters and wider necks.[135,137] One of the major disadvantages of coiling is the chance of partial re-canalisation of the aneurysm even in the first few months after a successful procedure due to coil compaction. Different options for aneurysm treatment have been recently proposed, among which combined treatment of large-neck aneurysms with intracranial dedicated stents and coils, balloon-assisted coiling (the so-called remodelling technique) and bioactive coils which promote complete neck endothelisation.[86]

The therapeutic management of SAH has considerably changed since the publication of the International Subarachnoid Aneurysm Trial study, the only randomised trial which compared endovascular coiling with surgical clipping in ruptured aneurysms.[92] The study shows that endovascular intervention with detachable platinum coils in patients with ruptured IAs can improve the chances of independent survival compared with neurosurgical clipping of the neck of the aneurysm. The results indicate that embolisation with coils is a reasonably safe procedure with a low complication rate, not only in patients with a ruptured aneurysm, but also in patients with an unruptured aneurysm and in patients with a basilar bifurcation aneurysm. Introduction of flow diverters is a useful addition to existing endovascular therapy. Although the natural history of ruptured aneurysm has been well defined, there is still controversy regarding the natural history of unruptured aneurysms, particularly those aneurysms which are less than 10 mm in size.[23]

ANEURYSMS IN NEONATES AND CHILDREN

Aneurysms are uncommon in children as compared to adults. IAs account for 5–6.8% of cases.[72] The reported incidence is higher in females as compared to males,[59] but Lasjaunias reports that the incidence is higher in males up to 2 years of age and, thereafter, the incidence is higher in females. Posterior circulation aneurysms are more common in children than adults, i.e. 39% in children versus 5% in adults.[72]

Intracranial Aneurysms in Neonates

IAs are extremely rare in neonates and only 19 cases have been reported in the literature. The clinical presentation of SAH in this age group is often non-specific. The mean age at diagnosis is 13 days. There is a slight female predominance (M/F = 7/10), as in adults. This contrasts with the male predominance shown in paediatric aneurysms.[59,78,87] Clinical presentation is extremely variable.[59] Common clinical manifestations are irritability (44%), seizures (44%), alteration of consciousness (31%), bulging fontanelle (31%), vomiting and failure to thrive (25%), and opisthotonus (25%), all of which can be linked to SAH.[125] Other manifestations are apnoea, cyanosis (36%) and fever (13%). No patient presented with focal neurological deficit due to mass effect.

Diagnosis

To confirm a suspected neonatal aneurysm, transfontanelle cranial ultrasonography should be undertaken first and if it fails to show the aneurysm, then an MRA should be performed and, finally, a CTA if the MRA is not sufficient. Conventional cerebral angiography remains a gold standard technique, but bears significant risks in the neonate.[126]

About 56% of neonates had MCA aneurysms and 28% had posterior circulation aneurysms which is in keeping with the general paediatric incidence.[72,122,125] Aneurysms of the PICA are extremely rare in this age group.[18] Over three quarters of neonatal cases involve large (> 10 mm) or giant lesions (> 25 mm), which is also similar to the paediatric population.[24,64,125] Posterior circulation aneurysms and large or giant aneurysms are more frequent in neonates and children than in adults. There was one mycotic and two traumatic aneurysms and the remaining were congenital.

Treatment

Most neonatal aneurysms have been treated conservatively (58%), whilst 37% were managed surgically. Surgery is usually better tolerated in young children than in adults.[42] Indication for surgery depends on the type of aneurysm. For example, dissecting aneurysms with extensive vessel wall damage and no evidence of mural haematoma have a strong tendency to re-bleed and, therefore, need aggressive management.

In contrast, dissecting aneurysms with mural haematomas frequently thrombose spontaneously and can be managed conservatively.[72] Although endovascular interventions are routinely used in the treatment of vein of Galen malformations, often wrongly called aneurysm of the vein of Galen, their application in the treatment of IAs in the very young has been reported in only a few cases,[64,102] with only one case[122] in the neonatal period.

Complications

In children, the overall tolerance to SAH seems better than in adults.[72,74] This is probably due to less sensitivity to post-haemorrhagic spasm, which is a major cause of morbidity and mortality in adults.[27] Vasospasm associated with haemorrhage is usually well tolerated in the paediatric age group with a relatively low incidence of ischaemic deficits,[24,72,125,126] and there also seems to be less incidence of delayed vasospasm.[18] Ferrante[24] et al. even claim that vasospasm is not found to be a significant contributing factor in morbidity or mortality. According to Patel and Richardson,[102] the absence of cerebral infarcts on necropsy studies (even in patients with angiographic evidence of vasospasm) combined with the absence of cerebral atherosclerosis might explain the low incidence of mortality and morbidity of ruptured IAs in the first two decades of life, in contrast to adults in whom up to 60% have infarcts.

Outcome

General outcome in the paediatric aneurysm population is better than in adults. In neonatal aneurysms, favourable outcome was seen in 59% of cases, but mortality was as high as 41%. Considering the progress in diagnosis and surgical treatment made in the 1980s, if we take into account only the cases described after 1980, the mortality rate drops down to 25%. Mortality in the first 48 hours after first bleed is reported to be 11% in early childhood and 14–34% in adults.[78]

The prognosis is poor for ruptured aneurysms in neonates if they are left untreated.[18] Of the 11 aneurysms conservatively treated, seven (64%) died. In the group of aneurysms treated by surgery or embolisation, only one died (14%) despite surgery, but it is important to note that he was initially treated conservatively until he re-bleed a month later.

The prognosis also depends on the aneurysm location. Neonatal MCA aneurysms carry a better prognosis than posterior circulation ones. This has been attributed to the tendency for intracerebral haematomas to be at peripheral sites (due to peripheral location of aneurysm), the rarity of vasospasm and the good functional compensation of the young brain. Tekkok and Ventureyra[126] suggest that the plasticity of the infant brain allows the possibility of recovery even in a seriously sick child, provided aggressive and appropriate treatment is considered early. Early diagnosis and treatment increase rates of favourable outcome,[59,81,122] but long-term prognosis is unknown.[125]

Intracranial Aneurysms in Children

The commonest site in paediatric patients is the ICA bifurcation followed by the MCA bifurcation and the vertebrobasilar system.[72,76] Large and giant aneurysms are commoner in children as compared to adults. The reported incidence is 20–45%. The incidence of multiple aneurysms is less in children as compared to adults.[18,27,38,59,64,72,74,76,78,81,87,102,122,125,126]

The aetiology and pathogenesis of paediatric aneurysms are not clear. While Allison et al.[4] regard it as a congenital disease, Agid et al.[2] do not consider it to be truly of congenital nature. Sekhar and Heros,[116] and Stehbens[123] suggest that it is due to an interplay between the structural changes in the vessel wall and stress. Lasjaunias et al.[72] suggest that aneurysms in children are a result of expression of various vessel dysfunctions which result in transient or permanent failure to repair a partial insult. In addition to congenital conditions (Marfan's syndrome, Ehler-Danlos syndrome, polycystic kidney disease, PXE, sickle-cell anaemia, tuberous sclerosis), infection (bacterial endocarditis) and trauma (closed and penetrating head injury, irradiation) also contribute to the aetiology of aneurysms in paediatric patients.

The presenting features of IAs in the paediatric population are different from those in adults. The incidence of SAH in previous reports has varied from 35 to 100%.[44,104,110] Sharma et al.[120] reported that the incidence of SAH was 82% in their case series, and the majority (86%) of those who presented with SAH had good Hunt and Hess grades. Liang et al.[76] report that the most common presentation was acute severe headache caused by SAH. The incidence of SAH was 46%, which was lower than that reported by others. Besides SAH, the presentation in this group included focal neurological symptoms from mass effect such as proptosis, diplopia, hemiparesis, chronic or intermittent headache, dizziness and so on. The incidence of mass effect was remarkably higher (54%) than in other reports. There can be seizures in about 18% cases.[120]

Treatment

Just as for aneurysms in adults, the treatment for paediatric IAs has undergone significant evolution in recent years. At present, multi-modal treatment strategies are widely used as a standard approach and have, therefore, resulted in significant improvement in patient outcomes.[2,120] The choice of treatment method for a given aneurysm is made by a multi-disciplinary team of neurosurgeons and interventional neuroradiologists. Surgical clipping or endovascular treatment can be decided according to site and size of the aneurysm. Children withstand surgery better than adults due to greater brain functional capacity and better vascular status.[72] The endovascular approach is preferred whenever possible technically, and is less dependent on the patient's

clinical situation because the majority of aneurysms in the paediatric population are either large or giant and/or in the posterior circulation.[76]

ANEURYSMS IN THE EIGHTH AND NINTH DECADE

Elderly patients with aneurysmal SAH account for up to 40% of all patients treated conservatively and surgically.[66] The percentage of elderly patients undergoing surgical treatment varied from 7 to 30% of all aneurysmal SAH patients.[47,70,97]

Advanced age is one of the recognised risk factors for poor outcome in aneurysmal SAH patients.[61,70,97] In the international co-operative study of the timing of aneurysm surgery, Kassell et al.[61] in 1990, clearly demonstrated the linear correlation between age and outcome. Conversely, some studies have shown that increasing patient age was not a risk factor associated with unfavourable outcome in the elderly.[22,34,47]

Horiuchi et al.[43] have shown that the important predictors of outcome of patients in the eighth decade of life were age, clinical pre-operative grade and pre-operative CT findings. By contrast, in the ninth decade, clinical pre-operative grade and pre-operative CT findings, but not age, were significant factors in the prognosis. These results indicate that there are some differences in clinical characteristics between these two decades of life. Favourable outcomes of surgically treated elderly patients have varied from 39.6 to 60%.[34,43,47,141] There is controversy whether poor grade patients be treated conservatively or surgically, but recent studies show that even poor pre-operative grade patients made a good recovery indicating that results of conservative management can be catastrophic. The site and size of aneurysms do not have much bearing on the outcome in the elderly.[141] Other important factors in addition to clinical grade are associated co-morbidities, Fisher grade, associated ICH/IVH, pupillary status and the intracranial pressure.

FUSIFORM ANEURYSM

Fusiform aneurysm (FA) is defined as a circumferential arterial dilatation resulting from pathological involvement of the entire artery.[5,13,25,95,117] All aneurysms exhibit a spindle shape when viewed externally.[16] Conceptually there is still confusion as to the aetiological, clinical and radiological features of FAs. Many investigators have applied the term "atherosclerotic" as the cause of FAs.[19,20,25,88,91] In fact, advanced atherosclerotic arteries have a slightly fusiform appearance. However, the classic dissecting aneurysm also has a fusiform appearance.[88] Several authors have recently reported the presence of FAs caused by dissection.[5,6,13,14,16,25,36,39,42,65,69,82,88,89,91,93,117] Therefore, all cases of FAs based on external view without consideration of aetiology were included in this study except well known typical cases of dissecting aneurysm of the vertebral artery.

The age and sex distribution of patients with FAs differ from those with saccular aneurysms. The mean age of patients is 45.1 years and the male:female ratio is 1.4:1. This contrasts with that of patients with saccular aneurysms.[5,13,16,19,20,25,42,75,88,93,95,96,108,117,136,142]

The clinical features of FAs are categorised morphologically. They can progress from a small focal dilatation or vessel narrowing to a relatively thick-walled, tortuous dilatation and elongation of the artery. FAs can be incidental or asymptomatic, discovered during work up for unrelated symptoms. They can present as a non-specific headache without haemorrhage or other neurological signs or symptoms, as ischaemia, transient ischaemic attack or complete stroke, as mass effect with or without seizure, or as haemorrhage, subarachnoid or intraparenchymal. Patients with small, large and giant aneurysms with focal dilatations of their lumen had SAH rates of 80%, 62% and 23%, respectively, whereas ischaemic symptoms, such as transient ischaemic attack or complete stroke, were the presenting feature in 31%. Haemorrhage is the most common presentation in patients with small lesions with focal dilatation, whereas ischaemic symptoms are the most common presentation of patients with stenosis or occluded vessels.[88] FA of the vertebral artery can present with hemifacial spasm due to mass effect.[114]

About 75% of FAs are seen in the anterior circulation and the rest in the posterior circulation. Dissection has been proposed as the main underlying cause of FAs and most commonly involves the posterior circulation, especially vertebral and basilar arteries.[6,14,16,19,20,25,36,51,65,69,75,80,82,89,91,93,109,113,136] Dissecting aneurysms can originate in any region of the anterior circulation, such as the ICA,[51,96,108,114,136,142] MCA,[6,26,31,50,59,68,79,80,100,118,134,137] the ACA[6,36,65,69,73,89,94,136] and rarely in the anterior choroidal artery.[82] The MCA is the most common site for spontaneous FAs (75%), followed by ICA and ACA.[16] Of the MCA, FAs 69% originate proximal to the MCA genu (M1 segment), 21% at the insular (M2) segment and 10% at distal (M3 or M4) branches.[16] Various aetiological factors for FAs have been proposed, including atherosclerosis, vessel dissection and association with other diseases such as Von Recklinghausen's disease, fibromuscular dysplasia, systemic lupus erythematosus and various collagen-associated vascular diseases.[13,16,100,117] Park et al.[101] found vessel dissection to be the leading cause, followed by atherosclerosis and collagen disease, or unknown factors.

Pathogenesis

The initial event in the formation of atherosclerotic FAs is thought to be lipid deposition in and beneath the intima. This disrupts the internal elastic membrane and infiltrates the muscular wall.[136] Intramural haemorrhage and rupture of the atheroma leads to transmural extension of the thrombus and thickens the intima to create the fusiform shape of the aneurysm.[88,136] Rupture of the vasa vasorum by shear forces or by stress on the luminal

wall then causes intimal tear and fracture of the internal elastic membrane. This permits bleeding into the arterial wall to form a haematoma.[16,51] If the dissection occurs between the internal elastic lamina and the media, the vessel lumen becomes narrow or occluded with an intramural haematoma and the patients present with ischaemic symptoms.[6,16,42,51,88,136] If dissection occurs between the media and adventitia, the aneurysm can rupture and the patient will present with SAH or ICH.[6,16,51,136] An intramural thrombus that ruptures into the lumen will cause distal embolisation and further expansion of the intramural clot will lead to vessel occlusion.[113] After the vessel is occluded by intramural clot, it can re-canalise and enlarge the dissection both laterally and longitudinally. A serpentine channel forms as the disease extends longitudinally, combined with varying degrees of intraluminal thrombosis.

Treatment of Fusiform Aneurysms

It depends on the presence and type of symptoms, the lesion size and location, and the risk of any accompanying intervention. Day et al.[16] have suggested guidelines for the treatment of patients with dissecting aneurysms of the MCA. They recommend that most small and some large focal dilatations, especially those that are asymptomatic, should be treated conservatively unless serial neuroimaging assessment indicates significant enlargement over time. However, the appearance of symptoms requires aggressive intervention. Lanzino et al.[69] and Nikawa et al.[93] also recommend conservative treatment in patients with dissecting aneurysms without neurological deterioration or re-current SAH due to of the possibility of spontaneous evolution of a dissecting aneurysm. In general, the authors agree with the recommendation of conservative treatment for non-symptomatic dissecting aneurysms. However, we recommend clipping using encircling clips for focally dilated dissecting aneurysms if they are found during surgery for another symptomatic aneurysm, and aggressive surgical treatment for FAs which are not caused by dissection, due to the possibility that they will progress. Day et al.[31] and several other authors[6,20,69,109,136] recommend that patients with stenotic or occlusive lesions presenting with acute ischaemic symptoms should be treated conservatively. Kurino et al,[82] learning a lesson from their patient with a dissecting aneurysm in the MCA who presented with ischaemic symptoms and who had a poor outcome after conservative treatment, recommend surgical revascularisation distal to the compromised artery. The authors agree with the policy of conservative treatment for patients with stenotic or occlusive lesions and acute ischaemic symptoms. Park et al.[101] from their experience of a case with a fusiform dilatation dissecting aneurysm in the PICA with cerebellar ischaemic symptoms, which bled later after conservative treatment and was subsequently treated successfully with endovascular methods, recommend consideration of aggressive treatment with endovascular or surgical methods for focal dilating FAs. Direct "aneurysm only" clip application was associated with a high rate of re-growth of the lesion or re-bleeding caused by preserving flow in the normal half of the affected vessel, despite excellent intra-operative aneurysm obliteration.[16,93] Therefore, many authors recommend proximal occlusion or trapping with or without resection combined with end-to-end anastomosis or external carotid-internal carotid (EC-IC) bypass,[6,13,16,25,36,39,42,69,108,117,136] but there is no consensus on this issue. Many authors recommend occlusion of the aneurysm and parent vessel by endovascular methods.[14,75,78,114]

MANAGEMENT OF RUPTURED ANEURYSMS

There is no controversy that ruptured aneurysms need to be tackled either surgically or by endovascular treatment or by combined treatment, but the important consideration is the status of the patient at the time of presentation. Patients who are in good Hunt and Hess grade/World Federation of Neurosurgeons Scale are treated at the earliest while poor grade patients are initially managed conservatively and once they improve then they are taken up for definitive treatment. Once detected or suspected to harbour an aneurysmal bleed the patient is put on bed rest, analgesics are administered and the patient is adequately hydrated. Routine haematological investigations including coagulation profile and biochemical investigations are done to evaluate the patient for CTA and surgery. A CTA is asked for to see the location of the ruptured aneurysm, its relationship with the parent and other vessels, and configuration. In the majority of cases it suffices, but in some cases an IADSA needs to be done in addition. Transcranial Doppler (TCD) sonography is performed to evaluate the flow velocities in the intracranial vessels, which not only serves as a baseline value, but also gives an idea about vasospasm. Medical treatment other than that mentioned above is required in cases in a poor grade where surgical treatment is held in abeyance for some reason.

Surgical Principles

Positioning and Craniotomy

Almost all anterior circulation aneurysms, the majority of basilar top and P1-P2 junction aneurysms can be operated upon by the standard pterional craniotomy. At times some modification to it may be necessary as is required in distal MCA and A2 segment aneurysms. A fronto-orbito-zygomatico temporal craniotomy may be required for some basilar top aneurysms.

For a standard pterional craniotomy the patient is positioned supine and an arterial line is introduced for invasive monitoring of blood pressure. The head is fixed with a three or four pin fixator and is rotated 15–20 degree to the opposite side. The neck is extended and head elevated by 30 degree. A generous scalp flap is raised and a frontal burr hole is made anterior to the coronal suture 3 cm away from the midline and this can be used for external ventricular drainage during surgery.

After raising the bone flap the lateral part of the sphenoid ridge is drilled.

Further Steps

- Good extradural haemostasis should be obtained. The dura is opened at the base and the Sylvian fissure is split. The optic nerve and the ICA are identified and CSF is let out from the optic, carotid and interpeduncular cisterns. If the brain does not relax, the frontal horn may be cannulated and CSF let out. Brain retraction should be as minimal as possible and the face of the spatula should be parallel to the brain surface.
- Arachnoid dissection is the next important step. The arachnoid should be dissected extensively mainly using sharp instruments.
- The intracranial arteries, as far as is possible, should be dissected on their ventral surface as there are hardly any perforators originating from this surface of the vessel. Adequate vascular control is imperative. It helps when the aneurysm ruptures intraoperatively. Proximal and distal control should be achieved after exposing the parent artery and space is made so that a temporary clip can be applied in case of need. The distal artery must be exposed to expose the anatomy of these segments. Sometimes, the distal portion of the parent vessel opposite the side on which the aneurysm arises should be exposed before the neck of the aneurysm is dissected.
  The neck of the aneurysm is dissected before the fundus and all the perforating branches should be separated from the aneurysm neck and the neck should be dissected all around before the clip is passed around the neck of the aneurysm. Blind application of one or both blades of the clip should be avoided and the perforators should be safeguarded. In most cases both the blades of the clip can be visualised by extending the dissection to expose the neck and fundus. After the aneurysm is clipped, the area should be inspected to make sure that the clip is not kinking or obstructing a major vessel or compromising the wall of the main vessel and that the clip has not included any perforators. At no time the entry of the clip in the space created should be forced. In case there is an arterial bleed at the time of clip application, the clip is applied. If the bleeding stops subsequent to clip application a more thorough dissection should be done to see if there is non-inclusion of any vessel in the clip, compromise of the main vessel lumen or incomplete clipping of the neck. In case the bleeding increases or continues after clip application, the clip is removed and a temporary clip is usually applied. If bleeding settles on clip removal adequate dissection is performed beyond the small rupture point. In case prolonged temporary clipping is required it should be intermittent. About 5 minutes of clipping with around 10 minutes of reperfusion in between. It is better if temporary clipping is done under neuroprotection measures.
- If the facility exists then indocyanine green angiography should be used to visualise the adequacy of aneurysm clipping and any vessel compromise by the clip. If available, the surgeon must use intraoperative Doppler sonography to measure the flow velocities in the proximal and distal arteries after clipping of the aneurysm.

Figures 29–32 show operative photographs related to the management of intracranial aneurysms.

MANAGEMENT OF COMPLEX ANEURYSMS

General principles remain the same as that for any other aneurysm. The details are discussed in the specific Chapters.

TRAUMATIC INTRACRANIAL ANEURYSMS

Smith was the first to report about a post-traumatic middle meningeal artery aneurysm after autopsy in 1829,[121] but it was not till 1934 that a traumatic intracranial aneurysm (TICA) was demonstrated angiographically.[129] About 500 cases of TICA have been reported so far. The incidence of TICA is about 1% in adults, but in children TICA contributes to about 30% cases of all IAs.[134] The reason why the incidence is high in children could be due to lower incidence of saccular aneurysms in children.[127] TICAs are commonly seen in young adults in their twenties. This group is more vulnerable to risk of blunt and penetrating trauma. There is

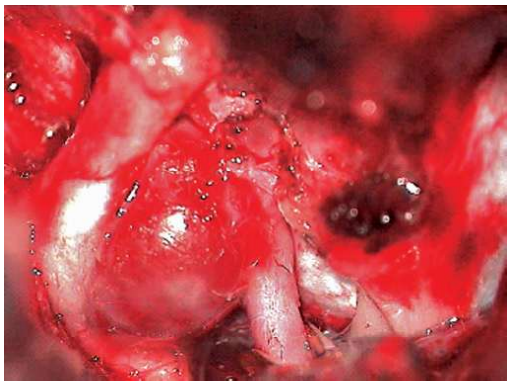

Fig. 29: Operative photograph—giant carotico-ophthalmic artery aneurysm

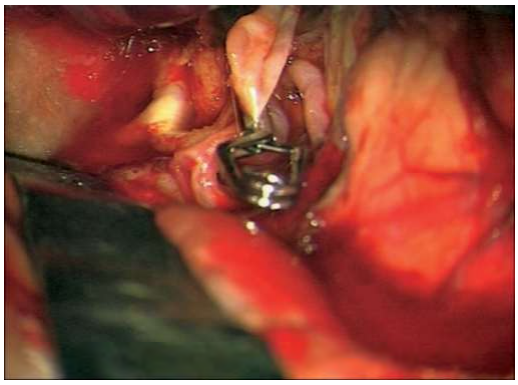

Fig. 30: Operative photograph of clipped large anterior communicating artery aneurysm

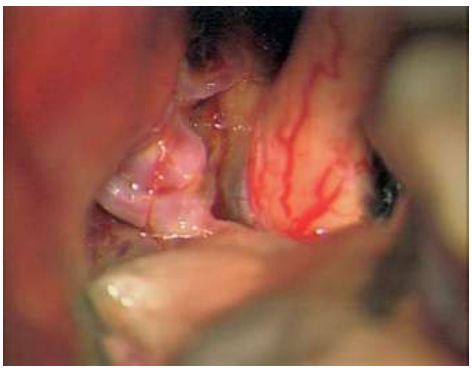

Fig. 31: Operative photograph—anterior communicating artery aneurysm

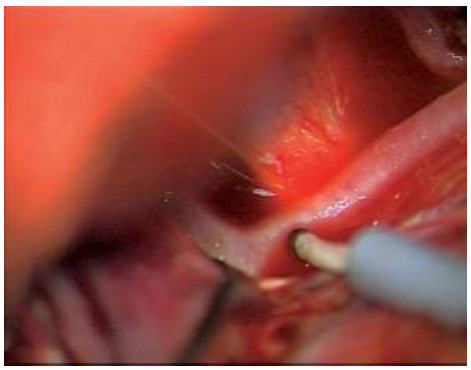

Fig. 32: Operative photograph—microvascular Doppler insonating anterior cerebral artery

a male predominance. The male:female ratio is reported as 12:1[87] and 50:1.[33] In children TICA can occur with less severe trauma and shaken-baby syndrome can lead to TICA.[67] The relative incidence of TICA varies according to aetiology; blunt trauma in 60–70%, penetrating injuries in 16–26% and iatrogenic in about 10%.[7,17,134]

TICAs can be classified in numerous ways either on the basis of aetiology into blunt trauma or penetrating injuries, or iatrogenic injuries.[30] Penetrating injuries are further subclassified into secondary to missile injuries or secondary to stab injuries. Alternatively they can be classified on the basis of anatomy into extracerebral (middle meningeal artery) or intracerebral groups. The latter is again subdivided into two groups as proximal to the circle of Willis which includes ICA supraclinoid and infraclinoid segments and vertebrobasilar artery and distal to the circle of Willis which includes subcortical and cortical branches.

Pathogenesis

The mechanism of TICA formation is different for different aetiologies. While a shearing injury of the vessel or entrapment of a cortical branch within a widened linear skull fracture or tearing process which occurs while a freely mobile vessel is rubbed against a fairly hard edge explains TICA formation in blunt trauma; a low speed bullet injuring the vessel wall explains a TICA following a missile injury. Pathologically TICAs can be classified into three groups:

1. True aneurysms (resulting from partial laceration of the vessel wall, i.e. injury to the intima or adventitia or both)
2. Pseudo or false aneurysms
3. Mixed aneurysms.

In a pseudo-aneurysm there is complete disruption of the arterial wall and subsequent haematoma formation which undergoes fibrous reorganisation enclosing the lumen and forms the wall of the aneurysm. A mixed aneurysm occurs when a true aneurysm ruptures forming a false aneurysm attached to it. TICAs are usually seen on the secondary branches, while saccular aneurysms occur on the large blood vessels at the base of the brain or major branches. TICAs are located along the course of the artery often near the sharp edges, while saccular aneurysms are at the bifurcation of major vessels.[30]

Clinical Presentation

A patient with TICA gives a history of trauma which could be blunt or penetrating. Blunt trauma is usually a major trauma in adults and minor trauma in children. The patient may present either awake or may have any degree of altered sensorium. A person who is awake usually complains of headache. Cranial CT shows haemorrhage which could be either intraparenchymal, intraventricular, subarchnoid or subdural. Initial management focuses on diagnosis and management of the presenting head injury. Delayed depressed levels of consciousness, seizures and new neurologic deficits point towards TICA.[71] Alternatively, a supraclinoid TICA may present with headache, memory changes and visual loss. An infraclinoid TICA can present with diabetes insipidus or compressive cranial nerve palsies caused by an enlarging aneurysm.[83,85] An intracavernous TICA can rupture into the cavernous sinus leading to caroticocavernous fistula formation. A triad of unilateral blindness, cranial base fractures and recurrent epistaxis should lead to suspicion of an ICA injury originating at the base of the brain. Aneurysms of the distal branches like the pericallosal produce deficits that correspond to their location. In about 10–20% of the cases the aneurysm may be asymptomatic. In infants a growing aneurysm can lead to a growing skull fracture.

Editorial comment: In a very large series of growing skull fracture the editor (PN Tandon) did not find a single case of this aetiology.

TICAs can be diagnosed by delayed CTA or MRA. Although TICAs can occur within a few hours after injury, most develop over days and may be missed by angiography. Angiographic features suggestive of TICA include delayed filling and/or excessive delay in emptying of the sac, lack of relationship with arterial branching, irregular appearance and absence of a neck.[1]

A small number of TICAs can thrombose spontaneously with time,[26] but TICAs typically enlarge and rupture and, therefore, it is recommended that once diagnosed, a TICA should be excluded from the circulation regardless of size and location, either surgically or by endovascular means.[30] A large proportion of TICAs, particularly those located close to skull base, result from rupture of an entire arterial wall.[9] The location at the skull base and rupture of the entire vessel wall during surgery are two great problems. In such situations, ICA trapping with or without EC-IC bypass is a better option[17] or endovascular aneurysm obliteration is another option.

Endovascular procedures have their own associated morbidity. A high neck:fundus ratio may make an endovascular procedure difficult. Placement of a balloon or coil directly into a pseudo aneurysm may lead to massive haemorrhage. In such situations endovascular trapping or occlusion of the parent artery with detachable balloon or endovascular stent placement appears to be a safe procedure.[132]

POST-OPERATIVE MANAGEMENT OF INTRACRANIAL ANEURYSMS

In the post-operative period, vasospasm and development of hydrocephalus are the main causes of neurological worsening in addition to other causes such as electrolyte imbalance.

Post-operatively patients are assessed neurologically, and with TCD and CT scan. Patients at risk of developing vasospasm are monitored closely in the intensive care unit. All patients are given nimodipine, starting within 4 days of SAH and continued for 21 days regardless of admission grade. There is controversy regarding this and many surgeons do not give nimodipine. The usual dose for an adult is 60 mg 4th hourly.[3,8] Neurological status is watched carefully and TCD studies are done to detect vasospasm early. Rising values of TCD velocities guides the timing of more aggressive therapy.

The mainstay of medical treatment is triple H therapy where volume expansion is achieved with packed blood cells, and colloids or hypertonic saline solution.[118] As per the literature and the author's experience starch solutions should be avoided due to risk of coagulopathy. A central venous line is inserted for aggressive invasive monitoring. A central venous pressure of greater than 8 mmHg or pulmonary wedge pressure greater than 14 mmHg is usually enough to dilute the haematocrit to less than 35%. An adequate level of haemoglobin should also be maintained. This volume expansion maintains the blood pressure at the desired level. In case the situation demands it, the systolic blood pressure can be raised to 180–200 mmHg with the help of vasopressors.[60] The mean should be 30 mmHg higher than the baseline mean.

Endovascular therapies for vasospasm are used when either aggressive medical therapy fails or when the TCD velocities rise, or when there are several risk factors for vasospasm. Transluminal balloon angioplasty is used to mechanically dilate the segment of the large arteries such as ICA, MCA and ACA A1 segment. The effect of angioplasty lasts for 7 days which corresponds to the duration of vasospasm.[111,139] Smaller vessels, such as the A2 segment, are not amenable to angioplasty and are instead treated with intra-arterial papaverine or verapamil.[111]

Hydrocephalus is a common complication with SAH due to A.Com aneurysms, especially when there is a significant intraventricular bleed. More than half of the patients may require either external ventricular drainage or a permanent ventriculoperitoneal shunt.[116] Fenestration of the lamina terminalis at the time of surgery appears to reduce the need for ventriculoperitoneal shunting.

Patients with A.Com aneurysms are susceptible to electrolyte abnormalities of which hyponatraemia is frequently seen (incidence 18%) lasting 1–5 days after surgery.[68] This is treated with normal saline infusion, supplemental salt intake and if need be with hypertonic saline infusion.[111]

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77 Vasospasm and Its Management

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INTRODUCTION

The term "vasospasm" is used to denote an abnormal, inappropriate or unnatural constriction of the vascular lumen. Cerebral vasospasm results in a decrease in cerebral blood flow, disturbance in autoregulation and delayed cerebral ischaemia (DCI). Despite the fact that cerebral vasospasm has been the subject of the most intensive laboratory and clinical investigations, its cause still remains uncertain and the management is difficult. This angiographic narrowing is seen in cerebral[43,50,52] and spinal vessels.[107] It generally involves medium and large sized cerebral arteries and usually occurs between the 4th day and 14th day after subarachnoid haemorrhage (SAH). It is maximal during day 6–8th and spontaneously resolves by the 12–14th day and rarely may be sustained over 2 weeks.[244,262,283] Aneurysmal SAH has an incidence of 6–16 per 100,000. Early reports[216] of vasospasm as being less common in India were due to the condition being unrecognised and under-reported. Around 30–70% of aneurysmal SAH patients will develop cerebral angiographic vasospasm with delayed neurological defects manifesting in 30–50% of patients. Vasospasm causes death and disability in 12–17% of SAH patients and is the most important factor in the eventual outcome.[35,45,132,133,305] Vasospasm can also occur following traumatic brain injury[30,158,181,203] with or without SAH. It has been seen following cranial surgery,[111,154] lumbar puncture, brain tumour bleed,[67] hypothalamic injury and following cranial infections.[149] Thacker et al.[267] cited vasospasm and an autonomic storm due to the venom as a plausible explanation of the symptom complex of multiple cerebral infarcts and bilateral optic neuropathy with limb ischaemia, following scorpion bite. In women with eclampsia transcranial Doppler (TCD) regularly picks up vasospasm in all the great cerebral arteries.[27] Arterial narrowing has been seen in migraine and in non-infectious vasculitis. Vasospasm accounts for 3–7% of all strokes and carries a mortality rate as high as 40% and is more serious than re-bleeding as a cause of death and disability due to cerebral ischaemia and infarction.[64,116] Delayed cerebral vasospasm has traditionally been recognised as the most treatable cause of morbidity and mortality from SAH. The physiological and cellular events of acute brain injury, which occur during the first 24–72 hours following aneurysm rupture are also contributing factors along with delayed cerebral vasospasm to the final patient outcome.[25,26]

BRIEF HISTORICAL OVERVIEW OF VASOSPASM

Endo et al.[55] highlighted the landmarks in the study of vasospasm and this knowledge is important to understand the complexity of the problem of vasospasm and may suggest further direction of research. Roy and Sherrington,[225] in 1890, suggested that the intrinsic control of cerebral circulation depends upon the local metabolic and functional need. Richardson and Hyland,[55,250] in 1941, were advocates of the hypothesis that strokes could be due to aneurysmal vessel thrombosis. In 1951, Ecker and Riemenschneider[52] published a classic paper which began the modern era of vasospasm management and they presented six cases of vasospasm, all in patients after SAH. Vasospasm was seen to be greatest near the site of the ruptured aneurysm. They also noted that vasospasm was a self-limited process, because it was not seen in angiograms performed 26 days after SAH. They stated that "It is probable that arterial spasm plays an important role following spontaneous rupture of saccular aneurysms of or near the circle of Willis." They confirmed angiographically the spasm of cerebral arteries and its relationship to cerebral aneurysms. Vasospasm was defined as a change in calibre of arterial vessels based on two consecutive cerebral angiograms performed under identical conditions at different time intervals.[52] Denny-Brown,[43] in 1951, reported cases where neurological deterioration occurred due to hypotension and narrowing of major blood vessels. Although Denny-Brown did not directly correlate deterioration with vasospasm, he linked these changes with neurological signs in patients with strokes.[151] This significant observation was not noticed but, over time, it became evident that vasospasm was an important cause of death and disability in patients with SAH. Logue[55,250] implicated vasospasm and re-bleeding as causes of neurological deterioration in patients with aneurysmal SAH and Bebin[55,250] implicated the role of vasospasm in the mortality and morbidity in patients with aneurysmal bleed.[174,176] In 1956, the first observation of vasospasm during surgery for intracranial aneurysms was published by Logue et al.[55,250] Penfield et al.[197,250] in 1958 published an article on "manipulation hemiplegia" and attributed

vasospasm to be the cause of this untoward complication of epilepsy surgery. Pool et al. in 1958[55] demonstrated that vasospasm could be induced by surgical manipulation and counteracted by local application of papaverine. Lindsay Symon and his coworkers[250,259-261] did a lot of work on elucidating disordered cerebrovascular pathology in aneurysmal SAH and autoregulation dysfunction leading to development of focal ischaemia. Symon also demonstrated that angiographic vasospasm may be asymptomatic. Stornelli and French[55,250] reported on their experience in treating 28 patients after SAH from a ruptured aneurysm. The appearance of vasospasm on angiographic studies was more common in patients who died after surgery than in those who recovered post-operatively. These authors concluded that intracranial vasospasm was a key factor in the determination of outcome after aneurysmal SAH. In 1964, Glen Kindt and Sayeed Farhat, two residents of Edgar Kahn, began the use of hypertensive agents to reverse hemiparesis due to vasospasm. Farhat and Schneider further studied this phenomenon in clinical cases and Kindt along with McGillcuddy Keller, Pritz and Gianotta studied the addition of hypervolaemia to hypertension to treat vasospasm. In 1965, Allcock and Drake[3] presented a series of patients with SAH in whom post-operative angiograms were obtained. Vasospasm was seen in 51% of patients who underwent surgery within 3 days of haemorrhage, in 61% who received surgical treatment 6–10 days after SAH, and in 9% of patients who underwent surgery 10 days post-SAH. The interval between SAH and angiography was 3.7 days in patients with and 6.9 days in those without vasospasm. Weir[282] made measurements at 8 predetermined positions on 627 sets of angiograms from 293 patients with aneurysms. A ratio between the sum of the vessel diameters in the subarachnoid space to the sum in the base of skull and neck was calculated and plotted against time. They reported that vasospasm has its onset in man about day 3 after SAH, is maximal at days 6–8 and is gone by day 12. There was a tendency for patients in poor clinical grades to have more vasospasm. The patients with most vasospasm had a significantly higher mortality than those with the least. The idea, that vasospasm was associated with high morbidity and mortality rates, lead to the norm for delayed surgery for ruptured aneurysms. Kennedy[250] postulated that blood if removed from the subarachnoid space by irrigation, could decrease the risk of vasospasm. In 1979, Allen et al.[4] showed that acute and chronic vasospasm in dogs could be reversed by the calcium antagonist nifedipine. Based on this observation, a human trial of another calcium antagonist, nimodipine, was initiated.[119] Allen et al.[4] found that a neurological deficit due to vasospasm occurred in 8 of 60 patients receiving placebo compared with 1 of 56 receiving nimodipine. Saito et al.[226] on the significance of vasospasm in the treatment of ruptured aneurysm and the time period of vasospasm found that there were no deaths among 20 patients operated upon within the first 3 days after SAH. Post-operative vasospasm was always mild in these cases, when it occurred, probably because blood clot or blood-stained cerebrospinal fluid (CSF) was removed by operative procedures. Sundt et al.[254] advocated a delay of surgery till meningismus is gone. In 1976, Suzuki et al.[255] analysed more than 1,000 aneurysm cases and found excellent outcomes when surgery was performed during the first few days after SAH. They hypothesised that early surgery decreased the likelihood of vasospasm by removing blood products surrounding cerebral arteries. Evidence confirming the timing of vasospasm was provided by Weir and his colleagues,[283,284] Peerless,[193-196] Wilkins,[289-292] Fox,[68,69] Gianotta,[72] Batger,[15] Macdonald,[152,153] Kassell[112-117] among others have been important contributors to the study of the phenomenon of vasospasm and its management.

INCIDENCE

The incidence of vasospasm following aneurysmal SAH varies from 20% to 40% in different large series.[66,171,185,195,196,223,226,237,289] Komotar et al.[132,133] estimated an incidence of 6–16 per 100,000 populations for aneurysmal SAH and this was the aetiology in 5–15% of stroke patients with a high overall mortality ranging from 30% to 70%. There are reports that patients with vasospasm have a significantly higher mortality and morbidity,[3,226] while others[171,238,242,243,289] could not find any consistent effect on mortality and morbidity. Ramamurthi[216] in 1969, reported a low incidence of intracranial aneurysms in India and south-east Asia, but had cautioned that the reason could be due to a poor pickup rate. Aneurysmal SAH affects 10 per 100,000 populations in the Western world.[271] The incidence of SAH and vasospasm in India is comparable to the rest of the world and has to be estimated. Sengupta[238] observed that a congenital anomaly of the Circle of Willis adversely affects the surgical results in patients with vasospasm. The incidence and time course of symptomatic vasospasm parallels that of arterial vasospasm.[260] However, although 40–70% of patients have evidence of arterial narrowing confirmed by angiography (Angiographic vasospasm) or Doppler ultrasound, only 20–30% develop the clinical syndrome (Symptomatic or clinical vasospasm).

CHRONOLOGY

Angiographic spasm is usually seen on doing cerebral angiography 7 days after the SAH (it may be seen as early as 3 days after the haemorrhage), but is not seen angiographically before the 3rd day. If seen earlier after SAH it is due to an earlier episode of bleed. The vasospasm is maximal during 7–8 days (4–14 range) following bleed and usually subsides in 2 or 3 weeks. Brawley et al.[19] demonstrated a biphasic response of cerebral vasospasm in experimental SAH. The acute phase starts within minutes and lasts up to 1 hour. The chronic phase begins 4–24 hours after the bleed. Three phases in the evolution of chronic vasospasm

were proposed by Kapp et al.:[109] (1) an initial muscular contraction; (2) secondary injury to the arterial wall due to injury to the internal elastic lamina and (3) the further cascade of repair. Suzuki[256] recognised that early spasm is induced by mechanical stimulation and serotonin, and the second phase by release of oxyhaemoglobin from haemolysis of the clot. Endo et al.[55] and Suzuki[256] found that the severity of vasospasm depended on the reactivity of the vessel and prolongation of vasospasm was dependent on the quantity of vasospasmogenic substances. Oxyhaemoglobin is maximally released on the 7th day and then it gets converted to methaemoglobin which disintegrates into haeme and globulin which get absorbed by the 15th day. Thus, the onset of vasospasm and its resolution correspond to the time taken for the lysis of erythrocytes and the final clearance of the breakdown products from the subarachnoid CSF spaces. Sano and Saito[228] in their survey of 443 cases of intracranial aneurysms identified 68 cases with pre-operative vasospasm. There was no case in which vasospasm was identified during the first 4 days after SAH, while 66% of the cases exhibited vasospasm between the 6th and 9th days after SAH. Eight cases died from vasospasm before surgery and 8 cases had renewed bleeding mainly when vasospasm began to subside. The duration of vasospasm was on an average 14 days, ranging from 8 days to 24 days.

Immediate or Acute Vasospasm

Immediate vasoconstriction after SAH has been observed in a number of experimental studies.[288] The role of this sudden spasm may be protective. Westermair et al.[286] showed that acute vasoconstriction occurs even in SAH of a minor extent and may contribute significantly to a perfusion deficit in the acute stage after SAH. The oscillating pattern of regional cerebral blood flow (rCBF) in the period of early recovery after SAH resembles the pattern of synchronised vasomotion.

Early Spasm

It is the spasm seen after 25–30 minutes after SAH.[179] Early vasospasm, which is defined as arterial narrowing seen on diagnostic angiography within the first 48 hours of aneurysmal rupture, is a rarely reported and poorly defined phenomenon in patients with SAH. This early spasm, seen in animal experiments, is not often seen perhaps because imaging is rarely done immediately after the rupture of the aneurysm. Factors contributing to early spasm have been elaborated by Nagai et al.[179]

Late Vasospasm

This is the spasm which appears on day 3–14 and occasionally lasts for 2–3 weeks. Rarely vasospasm may be seen after 2 weeks of SAH.

RISK FACTORS FOR DEVELOPING VASOSPASM

Several factors including a large volume of blood on CT, an initial loss of consciousness, poor grade of SAH (poor neurological condition), pre-existing hypertension, basilar artery aneurysms, an anatomically incomplete circle of Willis and smoking, and other correlates, like age less than 50 years, hyperglycaemia, the duration of unconsciousness after SAH, the plasma level of brain natriuretic peptide (BNP), have been suggested as predictors for the development of cerebral vasospasm after SAH.[29,48,59,112,142] Hop et al.[88] found that the duration of unconsciousness after SAH is a strong predictor for the occurrence of DCI. Gonzalez et al.[76] proposed the vasospasm probability index, a combination of TCD velocities, cerebral blood flow and clinical risk factors to predict cerebral vasospasm after aneurysmal SAH. Badjatia et al.[14] studied the relationship between blood glucose levels (mg/dL) and occurrence of symptomatic vasospasm and clinical outcomes after aneurysmal SAH and they concluded that mean inpatient blood glucose value was associated with the development of symptomatic vasospasm and thus is a target for therapy to prevent vasospasm and improve clinical outcomes.

Chandy et al.[28] reported that in patients with SAH, hyponatraemia is associated with a significantly greater risk of developing vasospasm and may precede vasospasm by at least one day, but Qureshi et al.[212] found that neither hypernatraemia nor hyponatraemia was associated with the risk of symptomatic vasospasm[37]. Zhang et al.,[302] using elemental and molecular mass spectrometry (MS) detection, size exclusion chromatography (SEC), inductively coupled plasma mass spectrometry (ICPMS), reverse phase (RP)-Chip and electrospray MS, found six protein families that could be the focus areas for possible biomarkers to predict vasospasm. Goddard et al.[74] reported that the treatment method (Clipping or coiling) had no influence on the incidence or duration of TCD detected vasospasm and there was no significant difference in outcome at discharge or follow-up between those patients who had surgery or endovascular management of their aneurysms. The effect of age on symptomatic vasospasm remains controversial. In a study, Magge et al.[155] showed that a younger age is associated with an increased incidence of angiographic and symptomatic vasospasm.

SITE OF OCCURRENCE

Vasospasm occurs only in arteries and is not seen in smaller arterioles or capillaries or veins because arteries have a well developed circumferential layer of smooth muscle, the tunica media. The perivascular sympathetic plexus is well developed and these sympathetic nerves arise in the superior cervical sympathetic ganglion. DuBoulay[48] reported on the distribution of spasm in the intracranial arteries after aneurysmal bleed. The middle cerebral artery is most frequently associated with vasospasm and this has been attributed to haematomas in the

Sylvian fissure being in close proximity with the course of the vessel. Bilateral spasm occurs with anterior communicating aneurysms and other aneurysms that are closer to the mid-sagittal line. In multiple aneurysms the spasm may be used to localise the site of the ruptured aneurysm. Internal carotid aneurysms are associated with wide spread and diffuse spasm which can extend to the opposite side.

CLASSIFICATION AND GRADING OF VASOSPASM

Vessel narrowing due to atherosclerosis or an arteritic process has to be differentiated from vasospasm. Congenital hypoplasia of vessels must be borne in mind and usually is easily differentiated from vasospasm. With hypoplasia the curvature of the internal carotid artery (ICA) and the contralateral A1 segment tends to be large.

Cerebral vasospasm can be classified variously according to location, severity and symptomatology.

One classification divides vasospasm into three types, namely—'subangiographic', 'angiographic' and 'clinical' vasospasm.

1. Subangiographic vasospasm is the type that affects small caliber vessels and is not seen on standard cerebral angiography. Clinical findings, cerebral blood flow studies and perfusion imaging pick up this subtype.
2. Angiographic vasospasm is vasospasm as seen on cerebral angiography. Many patients with significant narrowing may be asymptomatic. In vasospasm due to aneurysmal SAH the vasospastic arteries tend to be close to the site of the aneurysm rupture. Distant arteries can also be affected in a "diffuse" or "generalised" manner.
3. Clinical vasospasm is the type where the patient develops neurological signs and symptoms and these may not correlate with the radiological findings.

On conventional, angiography vasospasm can also be classified as 'local', 'diffuse' or 'segmental'.

1. Local—when the spasm is limited to one vessel.
2. Segmental vasospasm affects only a part of the vessel.
3. Extensive or generalised type is when there is spasm of at least two major vessels.

Sano and Saito[228] classified vasospasm into three types: Type 1—extensive diffuse; Type 2—multisegmental and Type 3—local. Type 1 was prognostically the worst, Type 3 was good and Type 2 was located between these two types.

Classification According to Size of Vessel

Small Vessel Spasm

There is impairment of vasodilatory capacity of small vessels distal to the vasospastic basal arteries after SAH and this concept of small vessel spasm is based on haemodynamic and histological evidence.

Large Vessel Spasm

Large vessels are involved by spasm and may include the carotid, vertebral, middle cerebral arteries (MCA), anterior cerebral arteries (ACA), posterior cerebral arteries (PCA) and other cranial arteries.

Grading According to Severity

As the diameter of arteries is reduced, the velocity of blood going through them increases. A progressive increase in this velocity indicates the severity of vasospasm. Vasospasm has been graded as moderate when the velocity is 120–200 cm/sec and severe when the velocity exceeds 200 cm/sec.

Vasospasm according to its severity is usually classified into three grades:

Grade I: The vessel still has 50% of luminal flow.

Grade II: There is more than 50% of reduction of the lumen.

Grade III: The vessels are barely visible on angiography.

Angiographic vasospasm was graded by Vora et al.[279] as none, mild (less than one-third artery luminal narrowing), moderate (one-third to one-half narrowing) or severe (more than one-half narrowing). Severe vasospasm is greater than 70% vessel narrowing.

Fisher Grading System

Fisher et al.[64] studied the amount of blood on the CT scan and risk of developing vasospasm in a landmark paper in 1980 and related the density of SAH on CT scans to the chance of developing vasospasm. Patients were grouped as low risk (Grades I and II) and high-risk (Grades III and IV) for developing vasospasm. Kistler et al.[128] reaffirmed that the extent and location of blood in the subarachnoid space determined the severity and location of vasospasm and the false-positive and false-negative cases could be explained by inadequate CT technique. Smith et al.[246] revisited the grading scale to determine its validity in the era of modern management, and found that angiographic vasospasm was associated with intraventricular blood but not with the Fisher grade. Fisher grade correlated with symptomatic vasospasm in only half the patients and they concluded that a new predictive CT grading scale for vasospasm may be necessary.

EXPERIMENTAL MODELS FOR STUDYING VASOSPASM

The phenomenon of vasospasm and its therapy is studied and developed using intracranial and extracranial vessels of *'in vivo'* and *'in vitro'* models in rats, rabbits, cats, pigs, dogs[96] and primates.[42,50,51,61,217] These models use pial vessels, circle of Willis, basilar artery or the peripheral vessels, e.g. rat femoral artery model. Sonebe et al.,[250] in their bibliography of experimental

vasospasm, highlighted the important landmarks in vasospasm experimental research. Megyesi et al.[168] in a review of *in vivo* models of cerebral vasospasm identified 57 models of SAH and vasospasm dating back to 1928. These models used one of three techniques to simulate SAH: (1) an artery was punctured allowing blood to escape and collect around the artery and its neighbours; (2) an artery was surgically exposed, and autologous blood obtained from another site was placed around the artery or (3) blood from another site was injected into the subarachnoid space and was allowed to collect around arteries. The majority of animal models of SAH and vasospasm use intracranial arteries; however, extracranial arteries (rat femoral artery model) have also been used in vasospasm experiments. These studies are easier to design and implement but the vasospasm in these vessels may not reflect the actual phenomenon of cerebral artery vasospasm. Echlin et al.[50,51] in an early study on monkeys showed arteriographic and other evidence that blood, in the absence of evident mechanical stimulation or injury to intradural arteries, when injected into the anterior cervical subarachnoid space through a catheter, consistently caused acute and chronic vasospasm of the intradural arteries. Evidence indicated that vasoconstrictor agents or factors in fresh blood caused the vasospasm, since similar subarachnoid injection of saline or clear serum did not cause vasoconstriction. Other circumstances involving mechanical or other factors, such as vessel injury, may also contribute to the length and severity of the spasm.

Two-Haemorrhage Model

The model of SAH and vasospasm used most frequently is the canine "two-haemorrhage" model,[96] obtained by injecting 0.5 ml/kg of autologous arterial blood into the cisterna magna of adult mongrel dogs on day 0 and day 2. Two injections of blood into the dog's basal cistern performed 48 hours apart, result in greater arterial vasoconstriction than that affected by a single injection of blood.

Perforation Model

In this model, the major intracranial vessels, like ICA, MCA, ACA and PCA, are punctured using filaments and endovascular techniques. Lee et al.[145] found that the perforation model produced more severe pathophysiological changes than the double blood injection, and it mimicked human SAH in having an injured blood vessel and a direct haemorrhagic brain lesion under arterial blood pressure, and concluded that endovascular perforation was more suitable for study of acute SAH sequelae.

Prechiasmatic SAH Model

The prechiasmatic SAH model seems to be suitable for study of the sequelae after SAH. It produces a significant decrease in cerebral blood flow (CBF), an acceptable mortality rate and substantial pathological lesions, with high reproducibility. The CBF reduction is predominantly dependent on the amount of subarachnoid blood as demonstrated by Prunell et al.[211]

Primate Model

The best model of vasospasm seems to be the primate model in which a blood clot is surgically placed around the large cerebral vessels at the base of the monkey's brain,[168] but the use is limited by cost and animal welfare constrains.

Cultured Cells

Cytoskeletal studies of cultured arterial endothelial and smooth muscle cells can be used to study the phenomenon of vasospasm and the cellular mechanisms of oxidant injury initiated by the breakdown products of haemoglobin.

Computational and Mathematical Models

Methods using 3-D patient-specific geometries, biofluid mechanics (shear and pressure), and the non-linear mechanics of the wall (properties, biaxial stress), including cell-mediated changes in wall structure are possible.

AETIOPATHOGENESIS OF VASOSPASM

Cooke et al.[35] in a recent publication reiterated that the pathophysiology of cerebral vasospasm is complex and poorly understood and that the ischaemia and inflammation incurred with SAH affects smaller vessels differently than larger ones. Cerebral vasospasm and early brain injury (EBI) are among other causes of subsequent morbidity and mortality.[282-284] The distribution of blood in the subarachnoid space, elevation of intracranial pressure, reduced cerebral perfusion and cerebral blood flow trigger the acute injury cascade leading to microvascular injury, plugging of vessels and release of vasoactive substances[193,287] by platelet aggregates, alterations in the nitric oxide (NO) and nitric oxide synthase (NOS) pathways and lipid peroxidation.

Is Vasospasm Protective?

Du Boulay[48] and Goel [75] hypothesise that vasospasm after aneurysmal rupture may have a protective role. This is borne by the incidence of re-bleed when the vasospasm abates[226] and the problem of treating vasospasm by various means in the presence of unsecured aneurysms.

BIOLOGY OF CEREBRAL BLOOD VESSELS

Khurana et al.[122] in their exhaustive chapter on the biology of cerebral vessels and blood flow described the topographic organisation and histology of cerebral arteries, cerebral blood flow physiology and pharmacology

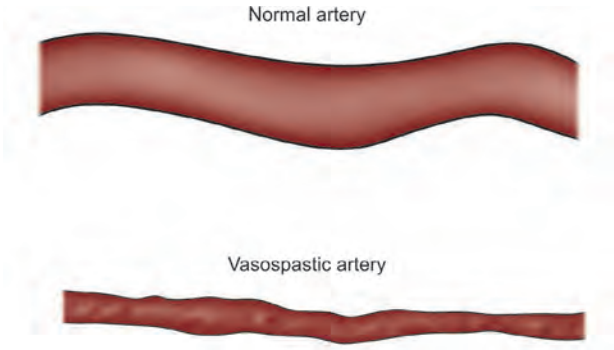


Fig. 1: Physiology of vasospasm showing the changes seen in the vessel wall following damage

especially those which are NO mediated and involved in cerebral autoregulation. Finally they present molecular biology developments leading to gene transfer technology for inhibition of angiographic vasospasm and vasospasm-associated vasculopathy. The cerebral blood vessels are characterised by a single elastic lamina, paucity of elastic fibres in the media and relatively little advential tissue.[35] The vascular smooth muscle and the endothelial cell are parts of an incompletely understood functional complex. Cerebral blood vessels are devoid of vasa vasorum. Zervas et al.[301] studied the micro-architecture of the adventitia of large feline cerebral vessels of the same size, in an effort to determine how the vessels are nourished. The cerebral vessels contain a rete vasorum in the adventitia that is permeable to large proteins and is in continuity with the subarachnoid space. This substructure may be analogous to the systemic vasa vasorum and may contribute to the nutrition of the cerebral arteries. The vasodilatory and vasoconstriction function of the vessel wall is modulated by neural, metabolic and hormonal factors and eventually by genetic factors.[123-126] The vasodilation is primarily mediated by NO and the vasoconstriction by endothelin. Peroxidative membrane damage in the arterial smooth muscle cell leads to prolonged arterial contraction that occurs during vasospasm (Fig. 1).

Genetics and Pathophysiology of Vasospasm at the Molecular Level

Genetic[49,126] and molecular changes[44,47,153] in the brain, the vascular endothelium and the vascular smooth muscle cells play an important role in the pathophysiology of vasospasm induced by SAH (Fig. 2). The SAH induces activation of immediate early genes and expression of stress proteins and heat shock proteins such as HSP70. Haeme present after SAH is metabolised by Haeme oxygenase to biliverdin and carbon monoxide. The SAH induces Haeme oxygenase-1 in the glia without affecting its isoform—Haeme oxygenase-2. Haeme oxygenase-1 is normally detectable in the neuronal populations but increases in response to oxidative stress. It is likely that Haeme itself, rather than ischaemia induced by vasospasm, plays a pivotal role in the expression of Haeme oxygenase-1. Haemolysate-induced Haeme oxygenase-1 and HSP70 expression may be used as markers for cell damage in infarcted brain associated with SAH and vasospasm.

Dietrich et al.[44] described recent developments in molecular biology to elucidate the mechanisms of SAH-induced vasospasm, and discuss the potential contribution of cerebral microcirculation regulation to the control of ischaemia. Recent findings of microvascular regulatory mechanisms and their failure after SAH suggest a role in the development and size of the ischaemia. Removal of NO produced by neuronal NO synthetase in the arterial adventitia may be important. Miyagi et al.[173] found mRNAs for Rho A and Rho kinases alpha and beta were expressed in the rat basilar artery and that they were significantly unregulated and reached their peaks on day 5. The mRNA upregulation of these proteins indicates that activation of Rho A/Rho kinase-related signal transduction pathways is involved in the development of long-lasting contraction of cerebral arteries after SAH. Peters et al.[198] stated that predisposition to intracranial aneurysm has a strong genetic component. Khurana et al.[124] indicated that endothelial NO synthetase gene polymorphisms predict susceptibility to aneurysmal haemorrhage and cerebral vasospasm.

Jayaraman et al.[99] showed that the pro-inflammatory cytokine tumour necrosis factor α and its proapoptotic downstream target, Fas-associated death domain protein, are increased in human aneurysms. In contrast, interleukin 10, which is secreted predominantly by T helper 2 cells, was absent in aneurysms. Increased tumour necrosis factor α and Fas-associated death domain protein may have deleterious primary and secondary effects on cerebral arteries by promoting inflammation and subsequent apoptosis in vascular and immune cells, thereby weakening vessel walls.

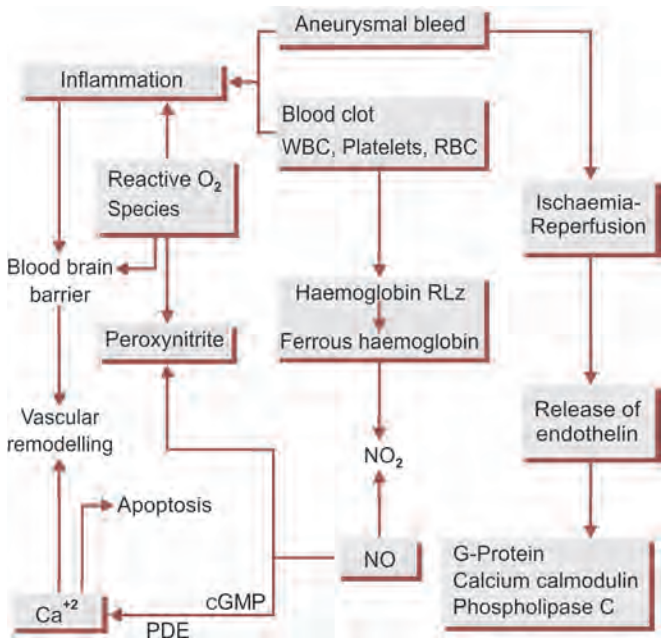


Fig. 2: Pathogenesis of vasospasm

Wang et al.[281] reported immediate early gene expression in vascular smooth-muscle cells synergistically induced by haemolysate components. Multiple high-molecular-weight components present in erythrocytes have synergistic effects on gene expression in smooth-muscle cells. The differences in patterns of gene induction suggest that multiple signalling pathways are activated. Ducruet et al.[49] presented a systematic review of 21 studies suggesting a genetic basis for clinical outcome after SAH, with a special emphasis on the pathogenesis of cerebral vasospasm and DCI. A study of genetic determinants of cerebral vasospasm, the predisposition to delayed cerebral injury, and the determinants of ensuing functional outcome after SAH has begun. The suspected genes are diverse and encompass multiple functional systems including fibrinolysis, inflammation, vascular reactivity and neuronal repair. Polymorphisms in the vasoregulatory molecule, endothelial nitric oxide synthase (eNOS), can increase susceptibility to cerebral vasospasm following brain aneurysm rupture. They highlight potential pitfalls in the interpretation of genetic association studies, and call for uniformity of design of larger multicentre studies in the future.

Red Blood Cells, Components and Other Spasmogens

The pathogenesis of delayed ischaemic neurological deficits (DINDs) after SAH has been related to products of haemolysis of the subarachnoid bood.[251,252] Fractionated plasma and white blood cells do not cause vasospasm, but even the washed erythrocytes can cause vasospasm. The breakdown of the erythrocyte is an important key event and the rate of dissolution determines the period or duration of vasospasm. Many factors are involved and the key component is haemoglobin and this acts along with a host of other factors as elaborated by Weir, MacDonald and Suzuki among others.[152,256,257,283] Vasospasm can be ameliorated by clot removal or reduction of its volume within 48 hours by surgery or by intra-cisternal t-PA and drainage. Oxyhaemoglobin is released from the 3rd day in incubated mixtures of blood and CSF and reaches peak levels after 7 days. This oxyhaemoglobin, derived from lysis of the red blood cells in the subarachnoid space, has been implicated in several cascades causing vasospasm. Pluta et al.[204] in a study provided *in vivo* evidence that the concentrations of oxyhaemoglobin and deoxyhaemoglobin increase in the cerebral subarachnoid perivascular space during the development of delayed cerebral vasospasm. Their results support the hypothesis that oxyhaemoglobin is involved in the pathogenesis of delayed cerebral vasospasm after SAH, and implicate deoxyhaemoglobin as a possible vasospastic agent. Topical brain superfusion of artificial cerebrospinal fluid (ACSF) containing the haemolysis products K^+ and haemoglobin (Hb), induces ischaemia in rats. Superimposed on a slow vasospastic reaction, the ischaemic events represent spreading depolarisations of the neuronal-glial network that trigger acute vasoconstriction as shown by Dreier et al.[47] Contraction of vessels also occurs in response to vasoactive substances released from the erythrocyte haemolysate, the key component being haemoglobin and other vasoactive factors, which include serotonin, norepinephrine, bradykinins, angiotensin, prostaglandin, thromboxanes and free radicals, or "reactive oxygen species", e.g. superoxide (O_2).[6,7] These toxic molecules damage endothelial cells, smooth muscle cells, adventitial fibroblasts and vessel wall nerve fibres. Other molecules implicated in the aetiology of cerebral vasospasm include the vasodilators NO and prostacyclin (PGI_2) which become underactive, and the vasoconstrictors endothelin-1 (ET-1) and thromboxane A_2 (TXA_2) which become overactive. Potassium channels are also thought to play an important role, as is the enzyme Haeme oxygenase. Endothelin-1 and transforming growth factor-beta increase collagen synthesis by smooth muscle cells, whereas NO and tissue necrosis factor-alpha decrease collagen synthesis. The delicate neurochemical mediated balance between vasodilatory and vasoconstrictors of the arterial wall muscle gets deranged due to some of these factors released from the red cell. These factors are usually secreted by the endothelium and include prostacyclins, NO endothelins and eicosanoids. 5-hydroxytryptamine (5-HT) and endothelin-1 (ET-1) cause constriction of cerebral arteries and upregulation of the ETB and 5-HT1B receptors is seen after SAH. Peerless and Griffiths[193] reported on release of plasma catecholamines following SAH. Sviri et al.[258] found that BNP plasma levels are elevated shortly after SAH, although they increase markedly during the 1st week in patients with symptomatic vasospasm. Their findings suggest that secretion of BNP after spontaneous SAH may exacerbate blood flow reduction due to arterial vasospasm.

Kim et al.[127] evaluated the status of thin (actin) and thick (myosin) filament regulation of smooth muscle contraction in the double-SAH canine model of cerebral vasospasm and to determine the effects of a kinase inhibitor reported to be effective in vasospasm, HA1077, on thin and thick filament regulation. Their data suggested that degradation of the thin filament-associated protein calponin plays a role in cerebral vasospasm and that the antivasospastic action of HA1077 is, at least in part, due to prevention of calponin degradation. Cytoskeletal changes in cultured vascular cells are sensitive indicators of oxidative injury. Cultured endothelial cells and smooth muscle cells showed a dose-related disruption of the cytoskeleton, particularly the F-actin and vimentin filaments, when exposed to oxyhaemoglobin. The cytoskeletal injury was prevented by the addition of deferoxamine or 1% albumin in experiments by Comair et al.[34]

Yamamoto et al.[298] examined the effects of intracarotid infusion of prostaglandins (PG) E_1 and F_{2a} on the circulation of the dog brain by fluorescein angiography, by measuring diameter changes in the epicerebral

vessels and by measuring microregional cerebral blood flow with ^{133}xenon and lithium-drift silicon detectors. Selective clipping of external and internal carotid arteries indicated that PGE_1 acts by constricting these vessels as well as the epicerebral arteries. Since prostaglandins are released from platelets as well as from stimulation of the cerebral cortex they should be considered as factors involved in the regulation of cerebral blood flow and in the mechanism of cerebral vasospasm.

It has been recognised that the endothelium plays an important role in the regulation of the cerebral vascular tone. In 1988, endothelin (ET)-1, a potent vasoconstrictor, was isolated from cultured porcine aortic endothelial cells.[302] ET-1 which is one of three distinct isoforms of ETs (ET-1, ET-2 and ET-3) has a more marked effect on cerebral arteries than do the other two isoforms. Elevated levels of ETs have been demonstrated in the CSF and plasma of patients after SAH and cerebral infarction. ETs act at least three different receptor subtypes, the ET_A receptor, which is localised in vascular smooth muscle cells and mediates vasoconstriction, and two different ET_B receptor subtypes. The ET_{B1} receptor subtype is present in vascular endothelial cells and mediates the endothelium-dependent vasodilation. The ET_{B2} receptor subtype is present in smooth muscle cells causing vasoconstriction. ET-1 acts from the adventitial but not from the luminal side of cerebral arteries. *In vivo* and *in vitro* ET-1 causes a dose-dependent and long-lasting vasoconstriction, similar to cerebral vasospasm after SAH. The vasoconstriction caused by ET-1 can be reversed by selective ETA receptor antagonists or combined ETA and ETB receptor antagonists.[302] Dehouck et al.[41] found that astrocytes can upregulate tight junction proteins and can play a critical role in blood-brain barrier (BBB) induction and maintenance. These endothelial pericyte interactions have Endothelin-1 as a mediator.

VASCULOPATHY

Inflammatory vasculopathy in response to haemorrhage has been extensively researched, but is incompletely understood and has strong genetic influences.[121,122,134] Krishna et al.[135] on studying vascular changes following experimental SAH in dogs found morphological changes in the arteries including subintimal proliferation and medial myonecrosis. It is clear that the greater the amount of subarachnoidal blood, the greater is the severity of the vasospasm. Peerless et al.[194] found structural changes in the human cerebral artery following SAH. Takemae et al.[264] found that intimal proliferation observed between 1 and 2 weeks after experimental subarachnoid blood injection to be an indicator of arterial injury. Poly (ADP-ribose) polymerase is important in modulating inflammation and inhibiting ADP-ribosylation attenuates cerebral vasospasm after SAH. The inflammatory reaction in the vessel wall causes destruction of the endothelial cells and adventitial nerve fibres, white cell infiltration, myoproliferation and eventual fibrosis leading to proliferative arteriopathy and prolonged vasospasm. Pluta et al.[206] found that cerebral vasospasm after SAH was not associated with the extent of proliferation of cells in the vessel wall, nor could the intensity of the limited proliferative changes have been responsible for narrowing of the vessel diameter.

TRAUMA OF MANIPULATION OF THE ARTERIES

Penfield et al.[197] in 1958 reported on manipulation hemiplegia—an untoward complication in surgery of focal epilepsy which they attributed to vasospasm. Harvey and Rasmussen observed general contraction of the middle cerebral arteries after manipulation and this was restricted to the vessels manipulated, but sometimes it spread to the ICA. Surgery in the presence of angiographic vasospasm was considered deleterious and leading to an increased incidence of post-operative cerebral ischaemia due to arterial narrowing exacerbated by surgical manipulation of vasospastic vessels during aneurysm dissection and clipping. Lindsay et al.[61] tested this theory in a primate model of cerebral vasospasm and found that the increased risk of post-operative cerebral ischaemia for surgery in the peak vasospasm period may be due to mechanisms other than increased arterial narrowing precipitated by surgical manipulation.

HYPOTHALAMUS

Wilson et al.[293] reported that vasospasm occurred after injection of hypothalamic extract in a dog model, hypothesising the role of hypothalamic injury in cases of vasospasm around the sellar region. Kamal et al.[106] in the experimental rat femoral artery model of vasospasm showed craniopharyngioma fluid to be vasospasmogenic.

SYMPATHETIC PLEXUS

The cerebral vessels, especially the pial vessels, are densely innervated by noradrenergic sympathetic nerves that arise in the superior cervical sympathetic ganglia and enter the intracranial cavity along the walls of the carotid artery. These cause constriction of the vessels and the interruption or temporary blockage of these causes relaxation and dilatation. The spinal arteries are also innervated by several systems that contribute to the control of spinal cord blood flow. The sensory fibres of the upper cervical nerves have a vasodilatory effect on the anterior spinal arteries (ASA). The SAH causes vasospasm by various neurochemical mechanisms. Kanat et al.[107] found the neuron density of C3DRG (Dorsal Root Ganglion) to be an important factor in the regulation of anterior spinal artery volume and spinal blood flow. They postulate that low density of C3DRG is an important factor in the pathogenesis of severe vasospasm in SAH and continuation of spinal cord blood flow. Suzuki et al.[256] were early proponents

of sympathectomy for vasospasm; many surgeons strip off the sympathetic plexus from the spastic vessels during surgery. Using minimally invasive techniques the superior cervical sympathetic ganglion can be blocked to relieve spasm.

Role of Nitric Oxide in Vasospasm

The reduction in the level of NO is a known mechanism of delayed vasospasm after SAH. Evidence for a causative role for NO includes the disappearance of NOS from the adventitia of vessels in spasm, the destruction of NO by haemoglobin released from the clot into the subarachnoid space, and reversal of vasospasm by intracarotid NO. Pluta et al.[205] sought to establish whether administration of L-arginine, the substrate of the NO-producing enzyme NOS, would reverse and/or prevent vasospasm in a primate model of SAH. Brief intracarotid and continuous intravenous infusion of L-arginine did not influence the incidence or degree of cerebral vasospasm but, after SAH, intracarotid infusion of L-arginine markedly increased rCBF in a primate model of SAH. Cerebrovascular tone is regulated by a dynamic balance of relaxing and contracting factors. Loss of the endothelium-derived relaxing factor—NO in the presence of oxyhaemoglobin and overproduction of endothelin-1 stimulated by oxyhaemoglobin have been postulated as causes of delayed cerebral vasospasm after SAH.[205] Perivascular concentrations of oxyhaemoglobin and deoxyhaemoglobin peaked on day 7 in the SAH group, at which time the concentrations in the dialysate were 100-fold higher than in any sample obtained from the control animals. Methaemoglobin levels increased only slightly, peaking between days 7 and 12, at which time the concentration in the dialysate was 10-fold higher than in samples from the control animals. Erythrocytes carry NO for release in vessels, whereas transfused erythrocytes may lack stored NO. Several converging lines of evidence also indicate that blood transfusion may exacerbate poor outcomes in some critically ill patients. Smith et al.[246] reported that development of angiographically confirmed vasospasm after SAH is associated with post-operative RBC transfusion and worse outcome is associated with intra-operative RBC transfusion. Before blood is transfused, patients with SAH should be carefully assessed to determine if they are symptomatic because of anaemia. Impairment of NO production and vasodilator function is an important mechanism associated with the pathogenesis of cerebral vasospasm, accompanied with decreased eNOS mRNA level, loss of neuronal NOS immunoreactivity and diminished cyclic guanosine monophosphate formation. Consequently, experimental vasospasm can be alleviated with NO or NO donors because of their potent relaxing function. Patients given blood transfusion during surgery for intracranial aneurysms have worse cerebral vasospasm. The explanation is that normally red blood cells deliver the NO required for vasodilatation of arteries, which is depleted in stored blood. Genetic studies have shown that eNOS gene promoter T-786C single nucleotide polymorphism (eNOS T-786C SNP) predicts susceptibility to post-SAH vasospasm. This information may be used in predicting vasospasm and developing methods for its prevention.

APOPTOSIS AND VASOSPASM

Apoptosis has been implicated in pathogenesis of aneurysmal SAH vasospasm and EBI. Following SAH causing vasospasm and resultant ischaemia, apoptosis occurs in the hippocampus, BBB and the vasculature, along with necrosis. Several apoptotic pathways are believed to be involved in SAH, including the death receptor pathway, caspase-dependent and caspase-independent pathways, and the mitochondrial pathway. Cahill et al.[24] found that p53 and associated apoptotic proteins were up-regulated after SAH and that downstream mediators of apoptosis were negatively influenced by the inhibition of p53 by Pifithrin-alpha. They found that apoptotic inhibition resulted in less cell death and an overall favourable outcome in the treated animals. There results suggest that apoptosis may be an important cause of cell death in the brain after SAH, and that p53 may play an orchestrating role regarding apoptosis in SAH. Apoptosis is important in the pathogenesis of secondary brain injury after SAH, and the apoptotic cascades present a number of potential therapeutic opportunities that may ameliorate secondary brain injury after SAH.

CASCADE OF EVENTS BEFORE AND AFTER VASOSPASM

The biology of cerebral blood vessels and blood flow is complex and genetic and molecular factors play a major role in the aetiology of SAH and vasospasm.[122-125] Immediately after SAH there is a decrease in cerebral blood flow, a CPP-independent fall in cerebral perfusion and loss of autoregulation, and this correlates with the degree of vasospasm which, when exceeds 50%, causes significant reduction of blood flow. Autoregulation is partially preserved when the flow is greater than 40% of basal flow but absent when the flow is less than 20%. Peerless[193,194] suggested that the progressive neurological deterioration was due to multiple factors including increased intracranial pressure, cerebral oedema, low perfusion pressure, low blood flow and impaired microcirculation and rheology. Following SAH, depolarisation of the vascular smooth muscle cells takes place due to depletion of energy metabolism and impaired potassium channel activity. Various agents acting on potassium channels can partially reverse vasospasm and activation of calcium channels can cause smooth muscle contraction and contribute to vasospasm. The rise of intracellular calcium observed after SAH is explained by oxyhaemoglobin-induced depletion of intracellular calcium; this leads to an influx of extracellular calcium through the voltage-dependent calcium channels. Protein kinase C is activated and may interact with other signalling

pathways such as myosin-light chain kinase, NO, intracellular calcium and protein tyrosine kinase. Takeuchi et al.[265] found impairment of autoregulation to be strongly affected by the development of cerebral vasospasm and that, in this state, a decrease in cerebral perfusion pressure easily depresses the electrical function of the brain.

EARLY BRAIN INJURY

Brain injury after SAH is a biphasic event with an acute ischaemic insult at the time of the initial bleed and secondary events such as cerebral vasospasm 3–7 days later. The EBI is a recently described term that describes the immediate injury to the brain after SAH.[11,12] The physiological and cellular events of EBI make significant contributions to patient outcomes and may even be a more significant factor than delayed cerebral vasospasm. A number of pathways have been recognised as having a role in the aetiology of EBI. Cerebral vasospasm and EBI after SAH are due to a combination of physiologic insults to the brain, resulting in global ischaemia, BBB breakdown, brain oedema and cellular death signalling. Atorvastatin ameliorated the vasospasm and EBI after experimental SAH. The underlying mechanisms may be related to its inhibition of the caspase-dependent proapoptosis pathway.[25,26] Sheba et al.[234] elaborate on the mechanisms of acute SAH-induced injury. Distribution of blood in the subarachnoid space, elevation of intracranial pressure, reduced cerebral perfusion and CBF and disturbed oxygen utilisation may be additional factors contributing to secondary brain damage after SAH,[286,287] initiating the cascades of acute injury.[232,233] Together they lead to direct microvascular injury, plugging of vessels and release of vasoactive substances by platelet aggregates, alterations in the NO/NOS pathways and lipid peroxidation. The pathophysiology of focal cerebral ischaemia is a multifactorial process[242,243] that involves the generation of free radicals, lipid peroxidation and activation of protein kinase C as well as phospholipase C and A2 with resultant accumulation of diacylglycerol and the release of endothelin-1. These events appear to create a positive feedback loop that, in turn, produces a tonic state of smooth muscle contraction and inhibition of endothelium-dependent relaxation. Serotonin, prostaglandins, catecholamines, histamine released from the breakdown of platelets and erythrocytes are also implicated as causative factors.

CLINICAL FEATURES OF VASOSPASM

Symptomatic vasospasm is the clinical syndrome of cerebral ischaemia associated with angiographically documented narrowing of a major cerebral territory.

Fox et al.[68] in an early study correlated computerised tomograms and angiograms with the clinical course. They suggested that delayed cerebral vasospasm may be preceded by relative vasodilation, or at least inhibition of vasoconstriction and concomitant increased vascular permeability of the parent vessels diagnosed by contrast enhanced computerised tomography. Schenk and Kricheffl[231] found infarcts in the brains of 65% of patients in whose angiograms vasospasm had been noted, while 82% of patients for whom vasospasm had not been reported also had infarcts. These figures suggested that there was no correlation between these two factors. However, since many of these reports were from the early days of cerebral angiography and represented the reading of many radiologists, it was felt that a more thorough study of this relationship was indicated to better assess the role of vasospasm in the production of cerebral infarcts in these patients.

Hemiparesis, hemihyperaesthesia, dysphasia, paraparesis, decreased sensorium, headache, low-grade fever and meningismus are the clinical features seen. Progressive impairment in level of consciousness or increase in focal neurologic deficit occurring after four days of any condition causing SAH should prompt investigation to rule out vasospasm and also other causes of neurological deterioration like electrolyte disturbance (hyponatraemia), infection (meningitis and sepsis), hydrocephalus and seizures (non-convulsive status). Patients can be asymptomatic despite angiographic vasospasm. The patients can present with progressive neurological signs involving cranial nerves, and ischaemic syndromes related to the arteries involved. Diffuse vasospasm may present with progressive deterioration in level of consciousness. Meningismus is also seen. The Hunt and Hess grade on admission correlates with risk of developing vasospasm. Chakravarti et al.[27] hypothesised the cerebral vasospasm in eclampsia, to be produced by a combination of reaction to hypertension, prostaglandin deficiency, defects in the e-NOS gene (coding for NOS) and endothelial damage. Vasospasm plays an important role, producing ischaemia and infarction in the brain tissue in this condition.

INVESTIGATIONS

After the history and clinical findings point towards vasospasm due to the various causes already mentioned, the clinician then has to decide on what would be the ideal set of investigations to diagnose and to treat the cause of vasospasm (e.g. aneurysmal rupture) or other rare causes of arterial spasm (e.g. tumour bleed). Once the patient has been evaluated with a haemogram, serum electrolytes, chest X-ray, USG abdomen, renal function, liver function and a complete coagulation profile is done. Angiography still remains the main modality of investigating and treating vasospasm (Figs 3A and B). Investigations to measure cerebral perfusion include cerebral blood flow studies, positron emission tomography (PET), single-photon emission computed tomography (SPECT), xenon CT and TCD among others.

Cerebral Blood Flow Studies

Various CSF flow studies are in clinical use and use radiolabelled H_2O, CO and O_2 with very short half-lives

for measurement of parameters like rCBF, cerebral metabolic rate of oxygen ($CMRO_2$) and oxygen extraction factor (OEF). The occurrence of irreversible ischaemia, penumbra, oligaemia, hyperperfusion and normal haemodynamics is investigated. In patients with vasospasm leading to ischaemic insult the regional oxygen extraction factor (rOEF) is elevated and in patients with a completed stroke the rOEF is normal. Yonas[299] emphasises that CBF technologies can help to determine whether new symptoms are caused by ischaemia, as well as define the often unpredictable manner in which ischaemia occurs in vasospasm. The CBF measurements may also help to identify the best time for surgical intervention following SAH. In addition, CBF studies may delineate when aggressive medical therapies are indicated and when they are potentially harmful. Despite the inherent limitations, as new technologies for CBF determination become more widely available, they should play an important role in the management of patients with aneurysmal SAH. Knuckey et al.[131] measured CBF during the 1st week of SAH in 46 patients who were in a good clinical grade and had a proven ruptured intracranial aneurysm. The mean initial CBF in patients who developed cerebral ischaemia was 42 ml/min/100 gm brain, which was significantly lower than in patients who did not develop cerebral ischaemia (49 ml/min/100 gm brain). This reduced CBF was not secondary to raised intracranial pressure or angiographic spasm. Patients with a reduced CBF (less than 50 ml/min/100 gm brain) and diffuse subarachnoid blood on computerised tomography had a very high incidence (78%) of cerebral ischaemia, despite a good clinical grade at the time of measurement. Serial CBF measurements are of value in monitoring the evolution of cerebral vasospasm. Yamakami et al.[297] used the xenon-133 inhalation method to clarify the relationship of vasospasm to the reduction of CBF and the DIND. Serial rCBF studies were conducted on 35 post-operative patients with ruptured intracranial aneurysms[78]. The CBF was calculated as an initial slope index (ISI) derived from the desaturation curve of each head probe, and the hemispheric mean value of the ISI (mean ISI) was calculated in both hemispheres. Their results suggest that severe vasospasm causes a reduction of CBF and that the reduced CBF brings about DIND.

Electroencephalography

Currently electroencephalography (EEG) is not commonly used, but a decline in the per cent of Alpha waves (6–14 Hz) predicts the onset of vasospasm and this is more sensitive than both angiography and TCD. A decline of EEG power or its amplitude was also a sensitive pointer to vasospasm development.

Transcranial Doppler

Introduced by Rune Aaslid in 1982, it has become an indispensable bedside test for vasospasm. Transcranial Doppler (TCD) uses the Doppler effect principle. Ultrasound signals are reflected off moving objects (RBCs in case of blood) and the frequency of the reflected signal changes in direct proportion to the velocity of the moving object. The main obstacle to ultrasound penetration of the skull is bone. Low frequencies, 1–2 MHz, reduce the attenuation of the ultrasound wave caused by bone. It is now an established method for diagnosing haemodynamically significant vasospasm in major intracranial arteries. It is safe, inexpensive and readily available. It is a cost effective, portable, non-invasive test that can be repeated as often as necessary. The TCD uses range-gated pulsed Doppler frequencies. The CBF can also be assessed with laser Doppler flowmetry (LDF) and LDF probes can be placed stereotactically over the cranial windows to allow online recording of cerebral blood flow. The utility of TCD in detecting and quantifying vasospasm has been extensively studied and correlated with angiography. In patients with moderate to large volume SAH, flow velocity (FV) rises between 3–10 days after ictus and reaches the peak between 11–20 days paralleling the natural course of vasospasm. The MCA velocity correlates best with vasospasm. The FV more than 140 cm/sec indicates angiographic narrowing and more than 200 cm/sec implies severe spasm. A rise in mean velocity by 50 cm/sec over 24 hours also indicates severe spasm. The TCD also provides the advantage of acoustic windows representing specific points of the skull where the bone is thin enough to allow ultrasound to penetrate. There are four acoustic windows: (1) transtemporal; (2) transorbital; (3) suboccipital and (4) retromandibular. Shekar et al.[236] reported that TCD examination has considerable potential in the early diagnosis of DIND (clinical vasospasm) in patients with SAH. Arslantas et al.[5] elaborated that TCD is a relatively recent advancement in imaging that enables measurement of blood FV in large intracranial arteries through temporal, occipital and orbital portions and transforamen magnum positions of insonation to check blood flow velocities (FVs) in cerebral vessels (windows where the bone is relatively thin) of the skull.

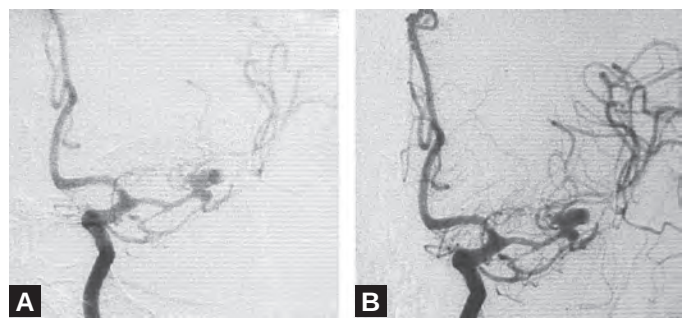
Lindegaard Index

The Lindegaard index (LI)[147] is defined by the ratio between the mean FV in the middle cerebral artery and the mean FV in the ICA. Criteria for diagnosis of a stenosis greater than 50% of an intracranial vessel with TCD include: (a) segmentary acceleration of FV; (b) drop in velocity below the stenotic segment; (c) asymmetry and (d) circumscribed flow disturbances (turbulence and musical murmur). The LI (VMCA/VICA) of more than three indicates vasospasm. Sensitivity and specificity of TCD in detecting vasospasm is high and is reported to be 84–85% and 89–98% respectively.[101]

In patients with a proven SAH, the clinical status, the amount of subarachnoid blood on a computerised tomography scan obtained within 5 days after SAH and the FVs in both MCAs measured by TCD sonography were correlated by Seiler et al.[235] All patients had pathological FVs over 80 cm/sec between day 4 and day 10 after SAH. The side of the ruptured aneurysm showed higher FVs than the unaffected side in cases of laterally localised aneurysms. Increase in FV preceded clinical manifestation of ischaemia. A steep early increase of FVs portended severe ischaemia and impending infarction. Maximum FVs in the range of 120–140 cm/sec were not critical and in no case led to brain infarction. Maximum FVs over 200 cm/sec were associated with a tendency for ischaemia, but the patients may remain clinically asymptomatic. In cases of no or only a little blood in the basal cisterns, mean FVs in both MCAs increased only moderately whereas, with thick clots of subarachnoid blood, there was a steeper and higher increase of mean FVs. Measurements of FV in defined segments of the basal cerebral arteries can be obtained through the intact adult skull using 2 MHz pulsed Doppler ultrasound. Lindegaard et al.[147] compared FV in these vessels with findings from 56 cerebral angiographies obtained in 51 patients from day 1 to day 21 after SAH. The median FV was 56 cm/sec, range 36–88 cm/sec (within normal limits). There was a clear inverse relationship between the MCA diameter and MCA flow velocity. Eleven of the 13 MCAs having diameter 1.5 mm or less showed FV in excess of 140 cm/sec. This seems a useful limit to diagnose pronounced MCA spasm (50% diameter reduction) with this method. Further clues to the severity of MCA spasm were obtained from the ratio calculated by dividing the MCA flow velocity by the FV in the ipsilateral, extracranial ICA, since spasm probably does not involve the neck vessels. This ratio was from 1.1 to 2.3, median 1.7 at day 1–2, but rose to over 10 in patients with the most severe MCA lumen narrowing. The PCA flow velocity was inversely related to the PCA diameter. Assessment of ACA spasm requires considering findings from both hemispheres combined, since the two proximal ACAs usually anastomose through the anterior communicating artery. Vora et al.[279] determined the correlation between TCD velocities and angiographic vasospasm after aneurysmal SAH.[1] For individual patients, only low or very high middle cerebral artery FVs (i.e. < 120 or ≥ 200 cm/sec) reliably predicted the absence or presence of clinically significant angiographic vasospasm. Intermediate velocities, which were observed for approximately one-half of the patients, were not dependable and should be interpreted with caution. Patients who develop clinical evidence of ischaemia from vasospasm often have mean velocities in the middle cerebral arteries of over 200 cm/sec. Daily increase of more than 50 cm/sec is a more sensitive indication of development of vasospasm. Intracranial hypertension can cause a false low mean middle cerebral velocity. Sloan et al.[245] reported TCD to be highly specific (100%), but a less sensitive (58.6%) test for the detection of angiographic vasospasm following SAH. Confirmatory angiography may be avoided if the TCD study is positive, but additional studies may be necessary if the clinical picture is suspicious and the TCD study is negative. Gonzalez et al.[76] found the use of TCD velocities, Lindegaard ratio and spasm index independently to be of limited value for the diagnosis of clinical and angiographic vasospasm.

Angiography

Angiography is still the main modality of investigation and offers the combined advantage of therapy, if necessary, in the form of mechanical (balloon angioplasty) and pharmacological angioplasty (Figs 3 to 6). Conventional four-vessel angiography is usually performed using the transfemoral route using Seldinger's technique and arterial spasm is seen as concentric narrowing of vessels, and this must be differentiated from other causes of arterial narrowing such as congenital arterial hypoplasia, pressure effect of the haematoma, hypertensive arteriosclerosis and narrowing due to increased intracranial pressure. The risk of vasospasm due to angiography is 1% and there is a 0.5–1% risk of an adverse vascular event. Spontaneous thrombosis of cerebral aneurysms demonstrated by angiography is infrequent. Kumar et al.[136] described angiographically documented spontaneous thrombosis of an intracranial aneurysm at the posterior cerebral-posterior communicating artery junction in a 40-year-old woman. The initial angiogram done on the 16th day after an episode of SAH showed a medium sized aneurysm. Subsequent angiograms done on the 30th, 40th and 60th day failed to demonstrate the aneurysm. The factors leading to this rare event remain obscure. Vasospasm can also cause the non-visualisation of a causative aneurysm and the angiogram must be repeated when such a possibility is suspected. Yamakami et al.[297] classified angiographic findings into the following five types: (1) diffuse, (2) peripheral, (3) proximal-severe, (4) proximal-mild and (5) no spasm. A retrospective analysis by Kivisaari et



Figs 3A and B: Angiogram showing vasospasm of the middle cerebral artery following aneurysm rupture. Saccular aneurysm can be seen arising from the middle cerebral artery

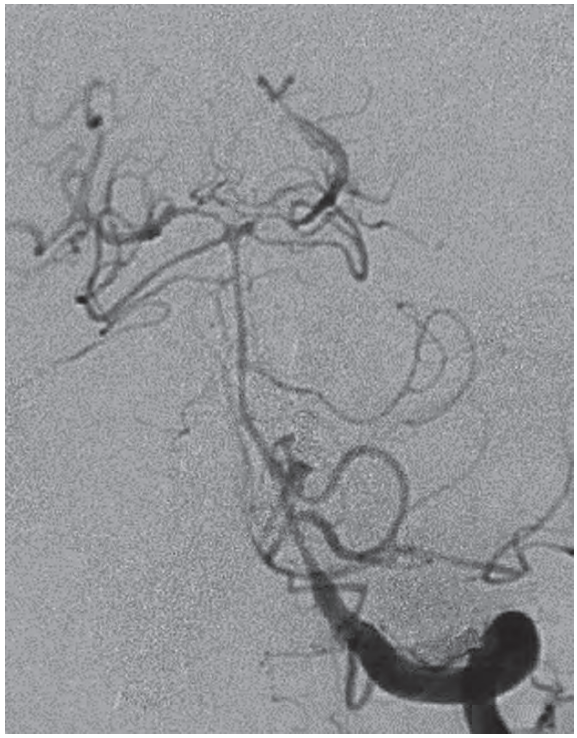


Fig. 4: Narrowing of the basilar artery seen after vertebral artery angiogram

al.[129,276] revealed that ruptured, posterior circulation and large/giant aneurysms are more prone to incomplete clipping. Therefore, these aneurysms require post-operative if not intra-operative evaluation with angiography. Chiang et al.[31] also found the use of routine intra-operative angiography to be safe and helpful in a significant number of cases, although it does not replace careful intra-operative inspection of the surgical field. Intra-operative angiography can be used to treat associated vasospasm. Le Roux et al.[144] explain the

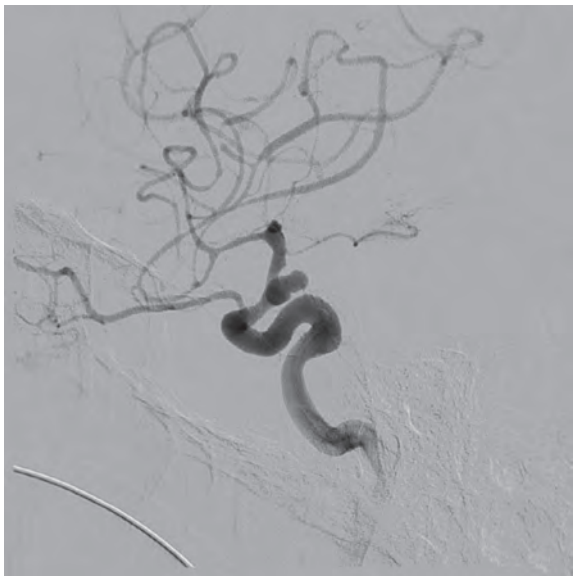
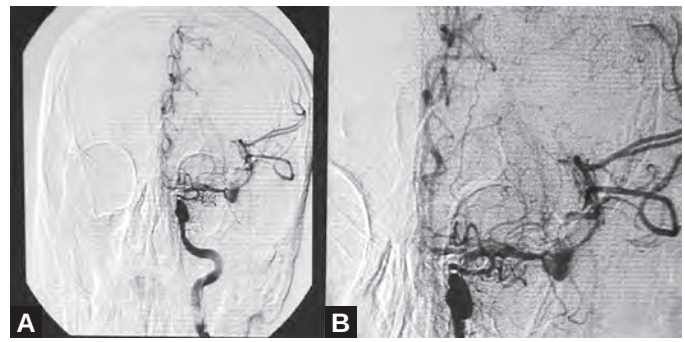


Fig. 5: Vasospasm after aneurysm rupture



Figs 6A and B: Vasospasm involving the left MCA and posterior circulation

role of immediate post-operative angiography in severe symptomatic vasospasm.

Computerised Tomography

The computerised tomography (CT) scan is the preliminary investigation after a thunderclap headache and can help in studying all causes of vasospasm. It is indispensable in the follow-up of these patients. When delayed neurological effects due to vasospasm and resultant infarction or haemorrhage appear, it is the primary investigation guiding treatment. It can be used to predict the occurrence of vasospasm depending upon the volume of blood seen on the initial scan as per Fisher et al.[64] The scan also gives valuable clues about the location and number of aneurysms, and other causes of SAH like arteriovenous malformations (AVMs). The CT scans are repeated to rule out hydrocephalus, re-bleed, infarction and haematomas which can be the cause of neurological deterioration other than vasospasm. Nabavi et al.[178] in a prospective study assessed the feasibility and diagnostic relevance of repetitive dynamic (contrast-enhanced) CT measurements of CBF, cerebral blood volume (CBV) and mean transit time (MTT) in the first 3 weeks after aneurysmal SAH. In 15 patients with SAH, 59 dynamic CT studies including 944 regions of interest were analysed. The results were correlated with the clinical course and time after the event and the occurrence of vasospasm. Significant differences in CBF and CBV were found between ROI in grey matter (GM) and white matter (WM), with time after the event, between patients with significant and absent or minor vasospasm, and between patients with and without a presumed vasospasm-related infarct. Simone et al.[244] aimed to clarify the convenience of CT perfusion for the assessment of cerebral vasospasm caused by SAH. Significant correlations between MTT and CBF values and neurovascular findings were obtained. The CT perfusion can be performed in a short time and on a regular basis, and it, therefore, has the potential to identify cerebral vasospasm because of SAH.

Computerised Tomography-Angiography

CT-angiography is a non-invasive and cost-effective investigation and is replacing conventional angiography.

Rapid technological advances and latest generation scanners provide better quality images and can be considered an adequate stand alone modality of investigation for vasospasm and its causative pathologies. Multislice CTA can detect angiographic vasospasm after SAH with accuracy similar to that of DSA. Multislice CTA is highly sensitive, specific and accurate in detecting mild and moderate cerebral vasospasm. It is less accurate for detecting no vasospasm and marked vasospasm. The limitation is its reduced reliability when more distal and intermediate degrees of spasm are encountered. Velthieus et al.[278] attempted to determine prospectively whether and to what extent CT angiography can serve as the sole imaging method for a pre-operative workup of patients with ruptured intracranial aneurysms. They concluded that CT angiography can replace DS angiography as the pre-operative neuroimaging technique in a substantial proportion of patients with ruptured intracranial aneurysms.

Single-Photon Emission Computed Tomography

The single-photon emission computed tomography (SPECT) uses CT with radioisotopes like inhaled intravenous xenon-133 or intravenous technetium 99-HM-PAO (Hexamethyl-propyleneamine oxime) to image topographically the blood flow in the superficial and deep regions of the cerebrum. The SPECT scan shows hypoperfusion in regions with angiographic vasospasm[95]. The SPECT cannot differentiate between infarcted and ischaemic regions and can miss a bilateral hypoperfusion state as it compares one hemisphere with another to detect hypoperfusion. The SPECT should be considered as the first test for the detection of clinically suspected vasospasm and may obviate the need for invasive studies before the onset of treatment. The SPECT may also help to prognosticate patients with a poor outcome. The SPECT brain perfusion studies can contribute to the diagnosis of vasospasm complicating SAH.

Xenon-Computed Tomography Scan

Xenon-CT scan (Xe-CT) imaging technique uses the ready diffusion capacity of inhaled xenon gas across vessel walls into brain parenchyma. The amount of the xenon then attenuates the CT rays and behaves like iodinated contrast material. The amount of xenon in the parenchyma is thus proportional to the blood flow. This rCBF data is then combined with a conventional anatomic scan creating a functional image. The xenon CT has better clinical correlation than the TCD. Xu et al.[295] investigated the association of TCD and Xe-CT with the characteristics of symptomatic vasospasm secondary to aneurysmal SAH in patients who underwent euvolemic treatment without sedation. No correlation was found between CBF and mean blood FV of the MCA territory. The differences between MCA velocity and lowest cortical CBF in patients with symptomatic vasospasm were significantly different from patients without symptoms. The TCD does not help to predict regional CBF in the MCA territory in patients with SAH on euvolemic treatment.

Perfusion Computed Tomography-Scan

Perfusion CT studies involve sequential acquisition of cerebral CT sections obtained in an axial mode during the IV administration of iodinated contrast material. The DCI is related to perfusion asymmetry on admission CT perfusion (CTP). The cerebral blood flow ratio (comparing contralateral regions of interest) seems the best prognosticator for development of DCI. Perfusion CT values of CBF have proved to be accurate in animals. Kanazawa et al.[108] clarify the convenience of CT perfusion technique for the assessment of cerebral vasospasm caused by SAH. The CTP can be performed in a short time and on a regular basis, and it, therefore, has the potential to identify cerebral vasospasm due to SAH. Significant correlations between CBF values and neurovascular findings were obtained by them. Linear regression analysis by Wintermark et al.[294] showed good correlation between perfusion CT and stable xenon CT. The CBF perfusion CT studies of CBF achieved with adequate acquisition parameters and processing lead to accurate and reliable results. Lefournier et al.[146] in a study, sought to identify the best perfusion parameters in perfusion-CT (PCT) which are able to predict vasospasm diagnosed by angiography after SAH. They found that PCT can accurately identify severe vasospasm and be used as a convenient non-invasive imaging modality to monitor patients with SAH.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is a very sensitive investigation and diffusion and perfusion weighted imaging and other MRI protocols are being used to pick up ischaemia due to vasospasm, which can lead to infarction if left untreated. Jadhav et al.[96] used MRI to examine the recently reported EBI after SAH. Double haemorrhage SAH model was obtained by injecting 0.5 ml/kg of autologous arterial blood into the cisterna magna of five adult mongrel dogs on day 0 and day 2, followed by imaging at day 2 and day 7 using a 4.7-Tesla (T) scanner. White matter (WM) showed a remarkable increase in T2 values at day 2 which resolved by day 7, whereas grey matter (GM) T2 values did not resolve. The apparent diffusion coefficient (ADC) values progressively increased in both WM and GM after SAH, suggestive of a transition from vasogenic to cytotoxic oedema. Ventricular volume also increased dramatically. Prominent neuronal injury with Nissl's staining was seen in the cortical GM and in the periventricular tissue. They concluded that multimodal MRI reveals acute changes in the brain after SAH and can be used to non-invasively study EBI and normal pressure hydrocephalus post-SAH. The MRI can also predict tissue histopathology and may be useful

for assessing pharmacological treatments designed to ameliorate SAH.

Magnetic Resonance-Angiography

MR-angiography (MRA) has been reported to have a sensitivity of only 46% and specificity of 70%, as there is the problem of motion artifact and difficulty in visualising distal vessels and branches. Technical hardware and software advances are rapidly increasing the role of MRA in the investigation and management of vasospasm. Ramdurg et al.[217] have used MRI and MRA for demonstration of SAH-induced vasospasm in a rat experimental model.

Positron Emission Tomography Scan

Positron emission tomography (PET) scans are available in all major cities in India, and rCBF and regional cerebral metabolic rate of oxygen ($rCMRO_2$) can be measured with PET in patients with SAH and hemiparesis due to cerebral vasospasm. Powers et al.[209] indicate that with PET studies it may be possible to prospectively differentiate patients with neurological deficits due to reversible ischaemia from patients with irreversible infarction. Frykholm et al.[70] investigated the occurrence of early haemodynamic and metabolic changes in the acute stage of SAH. Haemodynamic and metabolic disturbances proved to be common after SAH and oligaemia was the predominant pathophysiological pattern. These abnormalities probably reflect the primary brain injury caused by the initial haemorrhage. The impact of secondary insults such as acute hydrocephalus, brain oedema, vasospasm, seizures, hypotension and hypoxaemia are likely to be dependent on the degree of primary injury, which can be assessed by PET.

TREATMENT

Komotor et al.[132,133] in a recent review of advances in vasospasm treatment and prevention stated that, despite maximal medical therapy, up to 15% of patients surviving the ictus of SAH experience stroke or death from vasospasm. Causes of neurological deterioration and poor outcome after SAH, including delayed effects of acute global cerebral ischaemia, thromboembolism, microcirculatory dysfunction and cortical spreading depression, play a role. Cross et al.[36] provide compelling evidence that surviving an SAH is more likely, if the patient is admitted to a hospital with a high caseload of SAHs as multimodality treatment options, cumulative experience and technical infrastructure and personnel who are better exposed to the problem of vasospasm. Current management of vasospasm is still being defined and consists of medical therapy, including triple-H regimen and oral administration of calcium antagonists, cisternal clearance of blood after surgery or interventional procedures and endovascular balloon angioplasty and/or injection of vasodilatory agents for refractory cases. Wilkins[289-292,304] exhaustively reviewed the literature on the various approaches to the prevention and treatment of intracranial arterial spasm. Gianotta et al.[72] presented a series of 17 patients who developed severe neurologic deficit due to post-operative cerebral vasospasm. All underwent confirmatory post-operative cerebral angiography. Treatment included controlled hypertension, hyperventilation, over-transfusion of whole blood and colloids, and infusion of low-molecular weight dextran. Neurologic deficits were reversed promptly and completely in 12 patients and partially in three patients. The authors propose that methods designed to increase cerebral blood flow can reverse the ischaemic deficits of vasospasm.

Initial Intensive Care Unit Management

Patients with vasospasm are admitted to neurosurgical service and are managed within the neonatal intensive care unit (NICU). In critically ill patients or in those with compromised pulmonary function, a Swan-Ganz catheter should be in place and appropriate monitoring used to avoid circulatory overload and pulmonary oedema (PO), as well as to ensure the optimisation of cardiac output.[9,69,80,89,93,177,182,183] If vasospasm is suspected clinically or by TCD standard triple-H therapy is started after the offending aneurysm has been secured by clipping or neurointerventional methods. The patient is monitored by neurosurgeons preferably trained in both open microneurosurgery and neurovascular interventional methods. Periodically the patient is re-evaluated clinically and by TCD. Daily SPECT and digital subtraction angiography are done in a few tertiary centres when a new neurological deficit appears and other causes of deterioration like hyponatraemia have been excluded. Persisting deficit despite triple-H therapy, new or worsening vasospasm detected by TCD or SPECT[35] may require a change in the treatment modality or more aggressive methods. Gupta et al.[80] in a review on monitoring the injured brain in the intensive care unit focussed on the monitoring of intracranial pressure, blood flow to the brain (TCD), cerebral oxygenation using the methods of jugular bulb oximetry, near infrared spectroscopy and implantable sensors, and the monitoring of function using electrophysiological techniques. MacLaughin et al.[166] reported that PE occurs in 28.8% of patients after SAH, and most of the time it was delayed. Cardiac dysfunction, both systolic and diastolic, is commonly observed during SAH and could contribute to the genesis of PE after SAH. Thus all patients must be monitored by a team comprising a neurosurgeon, neurologist, intensivist, anaesthetist and cardiologist supported by excellent nursing and paramedical staff. The general measures of good intensive care, proper ventilation and provision of optimal nutrition promote faster recovery and helps in better outcome.

Triple-H Therapy

Induced Hypertension, Hypervolaemia, Haemodilution

Attempts to improve cerebral perfusion by volume expansion and induced hypertension are commonly

practiced.[196,222] This increases CBF and decreases the haematocrit. It is a safe and effective modality of treatment to prevent ischaemic neurological deterioration. Solomon et al.[249] suggested that immediate aneurysm surgery and aggressive post-operative prophylactic volume expansion in all patients can substantially reduce re-bleeding and DCI, potential causes of morbidity after aneurysmal SAH. Intensive care monitoring and close clinical supervision are indicated when patients are receiving inotropic agents such as dopamine or dobutamine with normalisation of the circulating blood volume with fluid administration or transfusion. Xenon blood flow studies have demonstrated that, rarely, patients with induced hypertension can have a reduction in rCBF. Walid and Zaytseva[280] reviewed the available evidence regarding the beneficial effects of hyperbaric oxygen (HBO) in preventing post-operative ischaemic complications due to vasospasm after surgery on ruptured cerebral aneurysms and the rationale for including HBO into the standards of care of these difficult patients. The authors' premise is that the oxygen-carrying capacity of the blood is lowered with hypervolaemic hypertensive haemodilutional (HHH) treatment and this side effect can theoretically be partially corrected using HBO therapy which appears to be the missing link in the above therapeutic regimen (Quadruple H therapy). Murthy et al.[177] state that the avoidance of hypovolaemia is perhaps more important than the institution of hypervolaemia. Individual haematocrit varies, and is maintained above 35% and haemoglobin is kept above 10 gm/dL to maintain the optimal oxygen carrying capacity. Crystalloid solutions are given to meet normal daily requirements. Glucose solutions are avoided. Human serum albumin can be used as a volume expander in a dose of 1 g/kg per day divided in 4–6 doses/day, each administered over 30–60 minutes. Gupta et al.[81] concluded that "triple-H therapy" is useful in treating vasospasm induced ischaemic deficits. The duration of "triple-H therapy" varied from 2–7 days with an average of 4.6 days and complications included hypokalaemia, haemorrhagic infarct and septicaemia which worsens brain oedema in the presence of acute infarcts and hence is contraindicated in such patients. In a study, Origitano et al.[192] utilised a protocol for prophylactic "triple-H therapy" in the treatment of SAH, and evaluated the response of CBF. The CBF remained elevated during 21 days after SAH, irrespective of neurological grade on admission, age, sex or angiographic arterial narrowing. They found a consistent method for establishing sustained improvement in CBF after SAH. The authors advocate that Triple-H therapy is a safe and effective modality for elevating and sustaining CBF after SAH. In combination with early aneurysm surgery, it can minimise DCI and lead to an improved overall outcome.

Shimoda et al.[241] investigated the frequency of various intracranial complications that may result from hypervolaemic therapy for a delayed ischaemic deficit (DID) following SAH. Around 28% developed an intracranial complication during hypervolaemic therapy—cerebral oedema was aggravated in 18, and a haemorrhagic infarction developed in 8. The authors suggested that hypervolaemic therapy is contraindicated in a patient who is found to have a massive abnormality on CT at the time when a DID is manifested, especially when it occurs within 6 days after the SAH. To avoid haemorrhagic infarction, it is important to discontinue hypervolaemic therapy as soon as the DID resolves. Demaraju et al.[38] in a validation study found that hyponatraemia with natriuresis in the neurosurgical setting responds to salt and fluid replacement guided by the patients' volume status as determined by the central venous pressure and that the syndrome of hyponatraemia with natriuresis is most often caused by "cerebral salt wasting" rather than by the syndrome of inappropriate secretion of antidiuretic hormone. The hyponatraemia post-SAH should be treated with fluids rather than fluid restriction as it is due to excessive sodium excretion and fluid restriction for hyponatraemia after SAH is associated with a worse outcome. Egge et al.[53] cite the paucity of information and important limitations in the design of the studies evaluating the efficacy of triple-H therapy.

Induced Hypertension

Kassel et al.[116] induced arterial hypertension in 58 patients with progressive neurological deterioration from angiographically confirmed cerebral vasospasm after spontaneous SAH in an attempt to improve their deficits. The most effective regimen consisted of intravascular volume expansion, blockade of the vagal depressor response, and the administration of antidiuretics and vasopressor agents. With this protocol, arterial blood pressure could be sustained at high levels for prolonged periods. Neurological deterioration was reversed in 47 patients, transiently in 4; permanent improvement occurred in 43. Complications experienced during therapy included PO, dilutional hyponatraemia, aneurysmal re-bleeding, coagulopathy, haemothorax and myocardial infarction. The presence of an untreated ruptured or intact aneurysm is a contraindication. The production of a hypervolaemic state by the use of colloid and crystalloid infusion accompanied by atropine blockade of the vagal depressor response and blunting of the diuresis with vasopressin enables arterial pressure to be elevated for longer than 1 week. Only if the aneurysm or cause of SAH has been tackled and the patient does not have cardiac contraindications like ischaemic and congestive cardiac disease, this option may be used and a systolic blood pressure of 200–220 mm may be maintained using dobutamine, or dopamine. If the patient does not respond within 60 minutes then phenylephrine or norepinephrine, or a combination of both is used. Fleischer et al.[66] successfully treated vasospasm, which resulted in cerebral ischaemia with a combination of aminophylline and isoproterenol.

PHARMACOLOGICAL PREVENTION OF VASOSPASM

The agents that have been tried include papaverine, procaine, cyclandelate, nitroglycerin, reserpine, kanamycin, platelet aggregation inhibitors, prostaglandin antagonists and serotonin antagonists among others. None of these have been found to be effective. In an experimental study on primates Sundt et al.[254] started using isoproterenol in the treatment of cerebral vasospasm. Isoproterenol acts by increasing the heart rate and cardiac output. It dilates the peripheral arterioles and decreases arterial pressure. It also increases venous return to the heart. The potential risk of cardiac arrhythmia is offset by the simultaneous use of lignocaine hydrochloride. Isoproterenol in a dose of 0.4–0.8 mg in 150 cc of 5% dextrose at the rate of 10–20 microdrops per minute is given, with simultaneous administration of lignocaine hydrochloride 2 g in 450 cc of 5% dextrose in 0.2% saline and 20 mg potassium chloride at the rate of 20 microdrops per minute. This regime was found to be effective, in treating patients with aneurysmal SAH, having symptomatic vasospasm. Brown et al.[23] advocated dopamine and mannitol. Dopamine in low doses (< 5 microgram/kg per minute) produces peripheral vascular dilatation, while in higher doses greater than 10 microgram/kg per minute produces peripheral vasoconstriction and an increase in arterial blood pressure. While using dopamine, monitoring fluid replacement and ECG and CVP is advisable.

Calcium Channel Blockers

Rinkel et al.[221] in a recent Cochrane review confirmed that calcium antagonists help to reduce spasm. The intracellular calcium ion is a key player in the development of muscle contraction of the vessel wall and calcium antagonists, like nimodipine, nicardipine and magnesium sulphate block, the slow channels of calcium which inhibit the contraction of smooth and cardiac muscles.[210] The skeletal muscles are not affected and these agents are very useful to prevent the onset of vasospasm and can help in its reversal. These agents are hypothesised to prevent brain injury by other mechanisms than blockage of slow calcium channels and also have a role in cerebral protection.

Nimodipine

Nimodipine is a calcium antagonist that has a selective CNS action and blocks the dihydropyridine sensitive (L-type) calcium channels. Other similar drugs used less commonly are nicardipine,[266] nifedipine and diltiazem. Oral nimodipine is given in dose of 60 mg four times a day and reduces infarcts and bad outcomes. Jan et al.[97] reported a 36% reduction in bad outcome in patients treated with nimodipine. Its clinical effectiveness was not based on its ability to prevent or reverse angiographically demonstrable vasospasm. Nimodipine can be used either orally or intravenously or intra-arterially. It is lipid soluble and crosses the BBB. Auer[8] demonstrated pial arterial vasodilatation by intravenous nimodipine in cats.

Although the large clinical studies have shown a beneficial effect, the mode of action is still debatable, as there is no significant reduction in angiographic vasospasm in these patients. The probable action may be protecting the nerve cells against the damaging influence of calcium.[98,121,190,200-202] Calcium channel blockers are thought to be more neuroprotective than counteractive to vasospasm itself. Their benefit may derive from their prevention of calcium entry into ischaemic cells, antiplatelet effect and ability to dilate leptomeningeal arteries. The calcium theory of neuronal damage has been recently adapted to SAH. It is proposed that haemorrhagic insult to the brain causes free radical mediated destructive reactions of membrane phospholipids, and the consequent decrease of phospholipid dependent enzymatic activities, such as Na^+-K^+ ATPase. Marazaitico et al.[156] found that nicardipine treatment reduced the TBRAS content and induced the recovery of Na^+-K^+ ATPase activity, exerting a brain protective role against the detrimental effects of the haemorrhage.

There was no significant difference in response using either two or three micrograms per hour infusion. Dorsch[46] used nimodipine infusion within 3 days of diagnosing an ischaemic deficit in 141 patients. Around 74% were in Glasgow Outcome Scale (GOS) I and 6% in II at the time of discharge, 11% died. Gilsbach et al.[73] in a European, multicentre, prospective, randomised, double-blind dose-comparison study on preventive therapy with intravenously administered nimodipine evaluated the efficacy and tolerability of two different doses: 2 and 3 mg/hr. All patients who were in Hunt and Hess grades I to III were operated upon—patients who had poor Hunt and Hess grades (IV-V) were operated upon on according to the surgeon's choice. This treatment regimen was associated with a low incidence of delayed neurological dysfunction with no significant difference between the two dosage groups: 3 patients (1.5%) remained severely disabled and 2 (1%) moderately disabled due to vasospasm with or without additional complications. Even among the patients in Hunt and Hess grades IV or V the long-term outcome was favourable (good-fair) in 40% and unfavourable in 60%. Among the patients in grades I to III, the long-term outcome was favourable in 89% and unfavourable in 11%. Mee et al.[167] found that nimodipine does not increase the cerebral blood flow or protect the heart after an SAH, but there were no side effects from nimodipine. Allen et al.[4] enrolled 125 neurologically normal patients with intracranial aneurysms in a multi-institution, prospective, double-blind, randomised, placebo-controlled trial within 96 hours of their SAH, to determine whether treatment with the calcium blocker nimodipine would prevent or reduce the severity of ischaemic neurologic deficits from arterial spasm. They concluded that nimodipine should be given to patients who are neurologically

normal after SAH in order to reduce the occurrence of severe neurologic deficits due to cerebral arterial spasm. Petruck et al.[199] concluded that nimodipine treatment in poor-grade patients with SAH results in an increase in the number of good outcomes and a reduction in the incidence of delayed neurological deterioration due to vasospasm. This effect occurs by a mechanism other than prevention of large-vessel spasm as visualised on angiography. Karinen et al.[110] in a randomised prospective clinical trial of nimodipine medication found that patients in the nimodipine group had an average of 3.46 years longer life expectancy (incremental effectiveness) than those in the placebo group. There was a significant difference in 3-month follow-up mortality and a slight difference in sickness pensions during the 10 years after SAH. Nimodipine treatment was associated with a significant decrease in mortality and its use in the management of patients with SAH seems economically justified because it increases patient life years at very low-incremental cost. Pillai et al.[203] reported that oral nimodipine given for 3 weeks did not improve outcome in patients with severe diffuse head injury even in the patients with SAH. In another double-blind placebo-controlled trial to determine the effect of intravenous nimodipine on delayed ischaemic deterioration and CT-visualised infarcts after SAH and surgery, Ohman et al.[188] found that nimodipine treatment was associated with a significantly lower incidence of deaths caused by DCI and significantly lower occurrence of cerebral infarcts visualised by CT scanning in the whole population, especially in patients without an associated intracerebral haemorrhage on admission CT scan. Hanggi et al.[85] for the first time demonstrated the feasibility and safety of intrathecal nimodipine lavage in patients with severe vasospasm resistant to the established medical and endovascular treatment strategies. Nimodipine 60 mg every 4 hours orally or via an NG tube for 21 days should be initiated within 4 days of haemorrhage as it has been shown to improve outcome in vasospasm. Patients should be monitored for renal failure, GI side effects, dependent oedema and PO, which are potential side effects of calcium channel blocker use.

Nicardipine

Flamm et al.[65] found nicardipine to be effective in a dose of 0.01–0.15 mg/kg/hr infusion. Nicardipine was found to induce the recovery of Na^+-K^+ ATPase activity, in experimental SAH thus exerting a brain protective role. High-dose intravenous nicardipine has been shown to reduce the incidence of angiographic and symptomatic vasospasm in patients with aneurysmal SAH, but treatment may be complicated by side effects, including hypotension or PO/azotaemia. Haley et al.[83,84] suggest that, from a clinical standpoint, the results of high-dose and low-dose nicardipine treatment are virtually equivalent, but administration of low-dose nicardipine is attended by fewer side effects. Nicardipine prolonged-release implants (NPRIs) have been used to prevent vasospasm in patients with SAH.[77] Kasuya et al.[118] reported on their use and NPRIs were applied principally to patients with thick clots (Fisher Group 3) through a frontotemporal or frontal craniotomy. The NPRIs were placed in the cisterns with thick clots where vasospasm was highly probable. Shibuya et al.[240] in a randomised prospective study found AT-877, a calcium channel blocker, to reduce symptomatic vasospasm.

Free Radical Scavengers

Free radicals reaction initiated by the lysis of clot has been implicated in the pathogenesis of vasospasm by Asano et al.[6] Oxyhaemoglobin has a direct effect on the vessel wall causing vasoconstriction and also causes injury due to the release of superoxide ion that injures the endothelial lining. Free radical induced lipid peroxidation has been identified as a potentially important contributor to both the arterial narrowing of vasospasm and the final cascade of ischaemic cell death.

Tirilazad mesylate[113,114,248] is a non-glucocorticoid 21-aminosteroid that exerts its anti-lipid peroxidation action through co-operative mechanisms—a radical scavenging action (i.e. chemical antioxidant effect) and a physicochemical interaction with the cell membrane that serves to decrease membrane fluidity (i.e. membrane stabilisation). It is a potent inhibitor of lipid peroxidation and also acts as a free radical scavenger. In experimental models of SAH and focal cerebral ischaemia tirilazad has been shown to ameliorate vasospasm and improve cerebral blood flow as well as reduce the size of cerebral infarction. In addition, preliminary studies with this drug have shown it to be safe and unassociated with side effects such as hypotension, mental status changes or glucocorticoid toxicities. Kassel et al.[113] found that there was a reduction in symptomatic vasospasm in the group that received the benefits of treatment with tirilazad which was predominantly in men rather than in women. Tirilazad was well tolerated at all three dose levels. These observations suggest that tirilazad mesylate at a dosage of 6 mg/kg per day is safe, and improves overall outcome in patients (especially in men) who have experienced an aneurysmal SAH. Phase III SAH clinical trials have shown a beneficial effect of tirilazad only in men. One explanation for the decreased efficacy in women is that women metabolise the drug up to 60% faster than men. However, it is also possible that other more subtle differences between the sexes alter the pharmacodynamic response of women to tirilazad. Recombinant human superoxide dismutase is supposed to act in prevention of vasospasm by blocking endothelial injury initiated by the superoxide ion.

Other drugs with similar mechanism of action are nicarven and ebselen. Asano et al.[7] reporting on hydroxyl radical scavenger synthetic nicarven found that it has no demonstrable vasoactive properties but scavenges hydroxyl radicals in aqueous environmental conditions at neutral pH. The usefulness of this therapy

for SAH was strongly indicated by the fact that the agent significantly ameliorated DINDs, leading to a marked improvement in the GOS scores at 1 month, as well as a reduction in the cumulative incidence of death by 3 months.

Endothelin

Endothelins are 21-amino acid vasoconstrictor peptides and are the most potent naturally occurring vasoconstrictors. They can be produced by the vascular endothelium and smooth muscle cells. Three endothelin genes have been identified and the proteins are called endothelin-1 to 3. Endothelin-1 is a powerful endogenous vasoconstrictor substance produced by endothelial cells, and causes significant and sustained vasospasm. Nilsson et al.[184] reported on the presence of contractile endothelin-A and dilatory endothelin-B receptors in human cerebral arteries. Endothelin receptor antagonists (TAK-044) cause prevention or reversal of vasospasm. In animal models, endothelin antagonists have been associated with reduced incidence of chronic vasospasm following clot placement. Such compounds have not yet gone to clinical trials. The NO has been tried with no conclusive results. Zimmermann and Seifertl,[303] in a review of the results of clinical and experimental investigations, support the hypothesis that ET-1 is a major cause of cerebral vasospasm after SAH. The SAH causes complex changes in the ET system and increased ET-1 levels after SAH; these are not solely responsible for the development of vasospasm but may occur after cerebral ischaemia. Endothelin receptor antagonists[269,274] (clazosentan) are still under investigation and may reduce both the frequency and the severity of vasospasm. Vajkoczy et al.[272,275] studied the safety and tolerability of the novel endothelin A (ETA) receptor antagonist clazosentan in patients with SAH and its potential to reduce the incidence and severity of cerebral vasospasm following surgical clipping of the aneurysm. In a Phase IIa multicentre, double-blind, randomised treatment with clazosentan resulted in a reduced incidence of angiographically evident cerebral vasospasm (40% compared with 88% of patients) and the severity of vasospasm was reduced in the clazosentan group ($p = 0.012$). In Part B of the study, in 50% of assessable patients who were initially treated with placebo, reversal of vasospasm was observed following the initiation of clazosentan therapy. The incidence of new infarctions was 15% in the clazosentan group and 44% in the placebo group. There was no adverse event pattern indicating a specific organ toxicity of clazosentan. Schubert et al.[232] found that prophylactic treatment with the ET receptor antagonist clazosentan prevented hypoperfusion, and has shown promise in phase 2 studies, and two randomised, double-blind, placebo-controlled phase 3 trials (CONSCIOUS-2 and CONSCIOUS-3) are underway to further investigate its impact on vasospasm-related outcome after an SAH.

Calcitonin gene related peptide, another potent vasodilator, has been used for patients with cerebral ischaemia following SAH[102]; however, adverse effects like hypotension are common. Its role in intra-cisternal administration has not yet been established.

Nitric Oxide

Vasoconstriction due to Deficiency of Endothelial Nitric Oxide

The NO donors like sodium nitroprusside and nitroglycerin are used. The NO is an extremely potent vasodilator and accounts entirely for the biological effect of endothelium-derived relaxing factor.[2,159,213] It acts through cyclic guanylic acid-dependent protein kinases and reduces the protein-dependent inflammatory response in the vessel wall in vasospasm. Intrathecal sodium nitroprusside was suggested as a treatment for cerebral ischaemia in patients with severe, medically refractory vasospasm after SAH (10–40 mg single dose and 2–8 mg/hr as infusion, 4 mg/ml,1–2 ml per dose up to three times daily for a week). Kumar et al.[136] found that intraventricular SNP therapy is effective in reversing the changes even in established cases of SAH-induced vasospasm. Intraventricular administration of nitroprusside has been shown to reduce severe vasospasm which was refractory to other therapy by Thomas and Rosenwasser.[268]

Recombinant Tissue Plasminogen Activator

It is well established, that the amount of blood in the basal cisterns has a correlation with the development of vasospasm.[255,257] Hence, continuous cisternal irrigation post-operatively to reduce the incidence of symptomatic vasospasm has been tried and an improved clinical outcome reported.[175] A single bolus of 10 mg of thromboplastin activator (TPA) injected into the basal cistern helps in clearing the subarachnoid clot post-operatively. However, the clearance of clots per se may not reduce the incidence of spasm as monitored by TCD. Intracisternal administration of TPA is also being used by some groups.[96,286,300] Usui et al.[273] reported the results of a retrospective review, between January 1986 and December 1991 of the results of early surgery and intrathecal thrombolytic therapy in 111 patients with aneurysmal SAH. Effects on clot lysis, angiographic and symptomatic vasospasm, cerebral infarction, and clinical outcome were compared in 60 patients treated with Urokinase (UK) 60,000 IU/dL for 7 days (UK group), 22 patients treated with 0.042–1 mg tissue plasminogen activator (tPA) every 6–8 hours for 5 days (tPA group), and 29 patients who did not receive treatment with either thrombolytic agent (no-treatment group). This study indicates that post-operative intrathecal thrombolytic therapies, especially with less than 4 mg/dL of tPA are effective in lysing subarachnoid clot and preventing

vasospasm and infarction safely. Findlay et al.[62] found that the intraventricular administration of recombinant tissue plasminogen activator (rtPA), in a dose of 3 mg every 24 hours, has been shown to be therapeutically efficient, significantly improving the outcome of patients with intraventricular haemorrhage. The use of rtPA also decreased the necessity for permanent VP shunt insertion in survivors. The intrathecal administration of rtPA[288] has been shown to dissolve subarachnoid clots, thereby preventing vasospasm in humans. The use of rtPA in human trials has reduced the severity of angiographic vasospasm and improved the clinical neurologic grade of the patients. Ramakrishna et al.[215] found that intraventricular tPA is a safe and effective treatment for reducing both angioplasty and shunting rates in patients with SAH in Hunt and Hess grades 3–5. Stolke and Serfant[253] in a prospective study of a single bolus injection of rtPA in patients with aneurysm rupture concluded that intrathecal thrombolysis is an effective and safe method for removal of intracisternal blood accumulations after SAH resulting in a significant reduction of symptomatic vasospasm and DID and conversion of a SAH Fisher grade III into a SAH Fisher grade II. It is sufficient for significant reduction of the incidence of post-haemorrhagic DID, avoiding the necessity of complete pharmacological blood clot evacuation and the use of higher concentrations of rtPA or continuous irrigation of the subarachnoid space. The other agents tried with varying results are streptokinase and urokinase.[229]

Papaverine

Papaverine (phosphodiesterase inhibitor) is an alkaloid and a powerful vasodilator. It acts directly on the smooth muscle cells of the arterial wall by trans-endothelial absorption. It is given in the dose of 200–300 mg over 30 minutes. Since the absorption is trans-endothelial, it is not surprising that the best results have been obtained with an infusion close to the site of spasm. Due to reported ocular complications, a supra-ophthalmic position should be used, if at all possible. An angiographic response is seen in 80–95% of cases. A clinical response is seen in 25–50% of cases. Given as intra-arterial infusion (12 mg/hr) by selective catheterisation, it was found to be effective,[105,157] without associated systemic complications.[104] Ramdurg et al.[217] compared the effects of single bolus doses of nitroglycerine and papaverine using magnetic resonance angiography in the rat model and found that papaverine is an effective drug for ameliorating SAH-induced vasospasm. Short-acting NO donors were not as effective in ameliorating vasospasm. Another endovascular treatment strategy for vasospasm is intra-arterial infusion of papaverine.[33]

Intra-arterial Papaverine

Intra-arterial infusion of papaverine is being used clinically as a vasodilator for spastic arteries after SAH, since *in vitro* experiments demonstrated that papaverine is one of the most potent vasodilators of human cerebral arteries following SAH. The proximal segment of the anterior cerebral artery, the posterior cerebral arteries and distal middle cerebral arteries are not amenable to balloon dilatation because of size or angle of take-off. The instillation over several hours of high concentrations of intra-arterial papaverine has been associated with reversal of spasm in some cases.[155] Milburn et al.[170] conducted a study to determine if there is a change in intracranial arterial diameters after papaverine infusion for vasospasm and to determine whether the change occurs in the proximal, intermediate or distal arteries. In all treatment groups an increase was found in the average arterial diameters ranging from 2.8% to 73.9%, with a mean increase of 26.5%. Increases in diameter were observed in proximal, intermediate and distal arteries. The timing of treatments ranged from day 3 to day 19 post-SAH, and there was no relationship between timing and arterial responsiveness ($r = -0.06$). There was a moderately good correlation between the degree of vasospasm in an artery and its responsiveness to papaverine. The effect of papaverine did not persist until the following day in patients who had repeat angiography performed. Kassel et al.[115] treated a series of 12 patients with intra-arterial papaverine. Arterial narrowing in the posterior circulation and middle cerebral artery distribution appeared to be more responsive to papaverine infusion than was spasm in the anterior cerebral arteries. The infusion of 300 mg of papaverine over 1 hour seemed to be an adequate and safe dose to effect these angiographic and clinical improvements.

Mathis et al.[160] describe three patients who experienced transient neurologic events associated with intra-arterial papaverine infusion in the vertebrobasilar system. Two of these involved respiratory depression and underscore the need for careful monitoring and, when required, cardiopulmonary support. Alternatively, the super-selective intra-arterial infusion of papaverine (2 mg over 10 s) has been shown to be effective in dilating spastic distal vessels not accessible to angioplasty techniques. Tsukahara et al.[270] described the successful treatment of cerebral vasospasm after SAH by intra-arterial infusion of papaverine hydrochloride and discuss the experimental background of this treatment. Livingstone et al.[148] reported that basilar artery vasospasm refractory to medical therapy in a 47-year-old man was successfully treated by the passage of a non-detachable balloon system and angioplasty after intra-arterial papaverine infusion.

The potential adverse effects of papaverine which have been reported include transient neurologic dysfunction, seizure, mydriasis, monocular blindness, drug precipitation, increased intracranial pressure and even aggravation of spasm.[160] Of these, by far the most common is elevation of the intracranial pressure.[161] Fortunately, this can usually be controlled (< 20 mm H_2O) with a mannitol infusion (25–50 gm); however, on occasion, the infusion must be either slowed or even stopped. Other complications which can occur with this form of

treatment include dissection and thromboembolism. The rate of serious complications is in the range of 5% or less. Rath et al.[219] found instillation of papaverine at the surgical site caused significant haemodynamic changes possibly because of stimulation of the hypothalamus in the third ventricle or vagal nuclei in the fourth ventricle, or even both. They recommend cautious use of intracisternal papaverine in such a scenario, especially when third ventriculostomy has been performed as an adjunct surgical procedure.

Statins

Lynch et al.[150] demonstrated that simvastatin reduces serum markers of brain injury and attenuates vasospasm after SAH. The use of simvastatin as prophylaxis against DCI after aneurysmal SAH is a safe and well-tolerated intervention. Its use attenuates serum markers associated with brain injury and decreases the incidence of radiographic vasospasm and DID. Currently pravastatin 40 mg daily orally or via NG tube for 21 days should be initiated within 4 days of haemorrhage as it has been shown to improve outcome in vasospasm.

However, McGirt et al.[165] found that the uniform introduction of simvastatin did not reduce the incidence of symptomatic cerebral vasospasm, death or poor outcome in patients with an SAH. Simvastatin was well tolerated, but its benefit may be less has been previously reported. Kramer et al.[134] reported that the addition of statins to standard care was not associated with any reduction in the development of vasospasm or improvement in outcomes after aneurysmal SAH. If there is a benefit to statin use, it may be smaller than suggested by previous studies. Further randomised controlled trials are awaited.

Miscellaneous

Fasudil is a calmodulin inhibitor and inhibits multiple kinases with maximal effect on Rho kinase, which results in inhibition of myosin light chain kinase and thus, causes smooth muscle relaxation through a Ca-independant pathway. It is given IV 30 mg thrice daily. Intra-arterial fasudil has been used. Colforsin daropate, a water-soluble forskolin derivative, is an adenyl cyclase activator with positive inotropic and vasodilatory effects. Intra-arterial injection of colforsin daropate hydrochloride (HCl) is capable of directly stimulating adenylate cyclase, which in turn causes vasorelaxation via elevated intracellular concentrations of cyclic adenosine monophosphate. Milrinone, a phosphodiesterase inhibitor, given intra-arterially, has vasodilating and inotropic properties similar to that of papaverine. Milrinone was effective and safe for the treatment of cerebral vasospasm after SAH and intra-arterial infusion with adjunctive intravenous infusion holds promise as a clinically advantageous treatment regimen. Erythropoietin has been cited to be neuroprotective by its anti-apoptotic action and systemic administration of r-Hu-EPO can significantly attenuate SAH-induced cerebral vasospasm and ischaemia. Prostaglandin E_1 (PGE1), known pharmaceutically as alprostadil—may be of value in the treatment of vasospasm.[79] Delgado-Zygamunt et al.[42] found intracisternal administration of the substance P (SP) antagonist spantide two hours and three days post-SAH significantly reduces the degree of late spasm and also decreases the degree of CBF reduction. The findings suggest that SP is involved in the development of both angiographic spasm and CBF changes post-SAH. Synthetic serine protease inhibitor FUT-175 (nafamostat mesylate) inhibits both complement pathways and the other plasma protease cascades (coagulation, fibrinolysis and the kinin system).

TIMING OF SURGERY IN RELATION TO VASOSPASM

Lawson et al.[143] found that coiling of ruptured aneurysms can be performed safely on patients who arrive on post-haemorrhage days 4–10 and treatment need not be delayed after day 10 as the results of the timing of aneurysm surgery studies initially suggested. De Ganz et al.[39] conducted a systematic review to compare early aneurysm surgery (days 0–3), intermediate surgery (days 4–7) and late surgery (> 7 days after SAH). Their meta-analysis suggested that both early and intermediate surgical treatments improve outcome after aneurysmal SAH, in particular for patients in good clinical condition at admission. Kassell and Torner[117] in a series of 2,265 patients admitted within 3 days of their first SAH found that the peak of re-bleeding occurred on the same day as the initial haemorrhage and there was no later peak. These data suggested that new management strategies for minimising re-bleeding must be considered for patients admitted soon after aneurysm rupture. Laidlaw and Siu[139] sought to determine whether the re-bleeding rate in poor-grade patients justified a period of supportive observation before selective treatment and whether unselected ultra early surgery would lead to acceptable results and the outcome results of ultra early surgery indicated that a non-selective policy did not lead to a large number of dependent survivors, even among elderly poor grade patients. The high ultra early re-bleeding rate indicated a need to urgently secure the ruptured aneurysm by performing surgery or coiling, and this indication is more pronounced for poor-grade patients than for good-grade patients. In earlier years Sundt et al.[254] and others recommended the delay of surgery till meningismus is gone. The international co-operative study on timing of aneurysm surgery had shown that patients who underwent surgery post-haemorrhage days 4–10 had worse outcomes than patients treated on days 0–3 and days 11–14 and many felt that patients who present on day 4–10 should have surgery delayed till day 10. But currently many surgeons feel that if the angiographically detected vasospasm has not produced any adverse effect on the clinical condition, its influence on the surgical outcome is not significant. Lawson

et al.[143] on analysing the effect of coiling on the clinical outcome found that coiling can be performed safely on patients who arrive on days 4–10 and endovascular treatment need not be delayed until after day 10. Sano and Saito[228] surveyed 443 cases of intracranial aneurysms operated upon within the first 3 days after SAH (the day of SAH being counted as the first day) and reported good results, minimal post-operative vasospasm and no mortality due to vasospasm. Cases operated upon 1 week after the SAH also showed good results, whereas fatal post-operative vasospasm was seen in cases operated upon on the 4–7th day after SAH. Cisternal, ventricular and epidural drainage are recommended after the clipping of aneurysms in the acute stage of SAH. Early surgery permits the mechanical removal of fresh blood clot by suction and irrigation.[246,247] Once the offending aneurysm has been secured by a clip, it is possible to place tissue plasminogen activator within the subarachnoid space, either at the time of surgery or subsequently through catheters, to facilitate early fibrinolysis of the clot, thus reducing the amount of decaying blood pressing against the arteries. This appears to be an effective way of preventing vasospasm. Gruber et al.[79] found the infarction rate was higher with endovascular treatment as opposed to surgery (37.7% vs 21.6%), as a result of a skewed Fisher Grade 4 infarction pattern in the endovascular treatment group versus the surgery treatment group (66.7% vs 24.5%). They suspected that unremoved subarachnoid/intracerebral clots contributed to the higher infarction rate with endovascular treatment. When patients with Fisher Grade 4 and Hunt and Hess Grade V were excluded from analysis, the difference in infarct incidence between the treatment groups no longer reached statistical significance. These fibrinolytic agents have a potential to cause bleeding by dissolving normal clot, so only patients at high risk of developing vasospasm should be chosen for this type of prophylaxis. Cisternal fibrinolysis using 10 mg rtPA intra-operatively and immediately following clipping using catheters was helpful in patients with thick clots. Cooke et al.[35] found that coiled patients had a greater degree of distal vasospasm than clipped patients and suggested that surgical clipping may reduce distal vasospasm as a result of direct evacuation of haemorrhage or indirectly via fenestration of the lamina terminalis, and the decompressive effect of craniotomy helps in reducing intracranial pressure and in turn reduces distal vasospasm. Varma et al.[265] have suggested that patients with aneurysmal SAH, in clinical grades I to III, should be operated upon as soon as possible irrespective of the time since ictus. Delay in definitive surgical treatment after admission to a neurosurgical unit can lead to death from re-bleeding in an additional 8.4% of patients who are in a stable neurological state. This additional mortality can be reduced if facilities for emergency cerebral angiogram, optimal theatre facilities and neuroanaesthesia backup are available, coupled with the surgeon's willingness, expertise and capability to give equally good results while operating on an aneurysm at odd hours.[277]

SURGERY

The debate on the ideal method of tackling the problems of aneurysmal bleed are unlikely to be resolved and probably clipping, coiling and angioplasty will all have indications and advantages in specific situations.[13,17,91,97,162-164,169,172,178,207,208] Fujii et al.[71] and Le Roux et al.[144] advocated immediate surgery followed by aggressive haemodynamic therapy and angioplasty in patients with an aneurysm and refractory vasospasm. Batjer and Samson[15] suggested that non-comatose patients with focal middle cerebral ischaemic deficits and secured aneurysms in whom medical management has failed or in whom these measures are contraindicated may benefit from extracranial-intracranial bypass. Patients with unsecured aneurysms remote from an ischaemic middle cerebral territory should probably be revascularised if cautious hypertension fails to improve their condition. Benzel and Kesterson[18] emphasised that extracranial-intracranial bypass surgery offers another alternative to the treatment of patients with vasospasm who have failed aggressive medical management.

Interventional Neurosurgery

Endovascular intervention is contemplated when symptomatic cerebral vasospasm is non-responsive to maximal medical management. Brisman et al.[20] reviewed the historical development and current status of endovascular techniques used in the treatment of symptomatic vasospasm following aneurysmal SAH. Neurointerventional treatment of vasospasm following aneurysmal haemorrhage has been proven to be a safe and successful technique for those patients suffering symptomatic vasospasm refractory to medical management. The techniques continue to undergo refinement as endovascular technology advances. Balloon angioplasty is better than intra-arterial antispasmodics due to the increased durability and long-lasting effects of the former and lower risk profile.[263] Schuknecht[233] summarised the indications, applications and limitations for microcatheter guided selective papaverine infusion and transluminal balloon angioplasty in patients who sustained cerebral vasospasm following SAH. They emphasised that structured neurointensive and endovascular treatment of imminent vasospasm integrating papaverine administration and balloon angioplasty are complimentary rather than alternative techniques. Percutaneous transluminal balloon angioplasty[21,22,32,56,57-59,72,92,143,218] is done with special balloon tipped catheters to dilate the proximal major cerebral arteries and must be done early when the other therapies fail to combat vasospasm. Due care must be taken to rule out cerebral infraction as a white infarct can be converted into a red one due to hyperperfusion. The PTA for high-grade symptomatic vasospasm after SAH is considered an effective treatment method for the patient who does not respond to medical therapy.[72] Immediate improvement of angiographic and clinical findings were frequently observed after PTA. Neurologic

improvement, defined as improvement in the Hunt and Hess neurologic grading scale has been shown in 60–80% of the patients so treated by Higashida et al.[86] Firlick et al.[63] studied the effects of transluminal angioplasty on CBF in the management of intractable vasospasm following aneurysmal (SAH) and reported that in the majority of patients with refractory vasospasm following SAH, angioplasty effectively dilated spastic arteries, reversed delayed neurological deficits and significantly improved CBF in areas of brain at risk of infarction. Transluminal balloon angioplasty[253] is effective in dilating larger proximal vessels, but its access for dilation of smaller distal vessels is limited and here intra-arterial vasodilating agents, including papaverine, nimodipine, nicardipine, verapamil, milrinone, fasudil and colforsin are used.

Angioplasty is performed via a femoral artery approach; usually with a 6 or 7 French sheath using wire silicone balloon microcatheter systems. Systemic heparinisation is used to minimise the risk of thromboembolic events. Brothers and Holgate[22] have described two modifications of the basic technique that have allowed increased selectivity and successful angioplasty of multiple branches, both proximal and distal, involved by vasospasm. The blind-ended, single-lumen balloon-dilatation catheter most widely used to date lacks steerability, limiting its application to unbranched stems and single branches at bifurcation or trifurcation points. Reported complications resulting from balloon angioplasty for cerebral vasospasm following SAH include perforation, aneurysm re-rupture, branch occlusion and haemorrhagic infarct. With most patients not able to co-operate, the procedure is best performed under general anaesthesia. Lakhani et al.[140,220,224,230,239] have emphasised the importance of airway safety. Le Roux et al.[144] in a subgroup of patients presenting with proven symptomatic vasospasm and an unclipped but ruptured aneurysm used urgent surgical obliteration of the aneurysm followed by immediate post-operative angioplasty and found it to be a safe and reasonable means to improve outcome. Kaku et al.[104] described the successful treatment of cerebral vasospasm after SAH with super selective intra-arterial infusion of papaverine hydrochloride. Percutaneous transluminal angioplasty was performed in two steps. First, a silicone balloon was used for dilation of the ICA and the proximal portions of the middle cerebral artery. A silicone leak balloon or Tracker-18 catheter was then introduced into or just proximal to the site of vasospasm not accessible to the angioplasty balloon catheter for superselective infusion of 0.2% papaverine. It is essential to infuse the papaverine just proximal to the spastic vessels in order to deliver sufficient concentration of drug, and infusion should be carried out as early as possible before the artery loses its ability to return to a normal luminal size. Yalamanchili et al.[296] retrospectively compared a group of 19 patients treated with craniotomy and aneurysmal clipping with a group of 18 patients who were treated via endovascular occlusion with Guglielmi detachable coils in regard to frequency and severity of cerebral vasospasm. In patients with similar Hunt and Hess grades and Fisher grades, preliminary data suggested that the frequency and severity of cerebral vasospasm may be reduced in those treated by endovascular occlusion of their aneurysm as compared with those treated by direct surgical clipping. Bejjani et al.[16] reported angioplasty to be a safe and effective treatment for symptomatic vasospasm that is refractory to hyperdynamic, hypervolaemic therapy. When used early (< 24 hour), it leads to significant clinical improvement. However the long-term outcome is good, even in cases of delayed angioplasty. The prevention of worsening of the cerebral ischaemia and its extension to other territories may be the reason. Elliot et al.[54] reported that balloon angioplasty is superior to papaverine infusion for the permanent treatment of proximal anterior circulation vasospasm following aneurysmal SAH.

Jaested et al.[100] found the frequency of infarction in the distribution of vessels undergoing TBA amounts to 7% and is significantly lower than in vessels not undergoing TBA. Nussbaum et al.[187] established the ability of intra-aortic balloon counterpulsation (IABC) to improve CBF significantly in a canine model of cerebral vasospasm. The IABC improves CBF in patients with vasospasm and is a rational treatment option in select patients with refractory cerebral vasospasm.

Cerebrospinal Fluid Drainage

Cisternal irrigation in meningitis has a role in protection of leptomeningeal and cortical structures as reported by Aydin et al.[10] They postulate that the irrigation procedure may decrease the percentage and severity of meningitic complications by way of the excretion of the inflamed purulent collection from the subarachnoid spaces. Ito et al.[94] performed enhanced cisternal drainage following early aneurysm surgery in patients with Hunt and Kosnik grades I–III, to effect continuous wash-out of subarachnoid blood clots and reduce symptomatic vasospasm.[130] Following extensive evacuation of the cisternal blood clots, Liliequist's membrane was opened extensively and a third ventriculostomy was affected by opening the lamina terminalis. They found that enhanced post-operative cisternal drainage can reduce the incidence of symptomatic vasospasm and be of benefit to the outcome of early aneurysm surgery. Usui et al.[273] in a retrospective review of the results of early surgery and intrathecal thrombolytic therapy in 111 patients with aneurysmal SAH found tPA therapy reduced the incidence of symptomatic vasospasm. This appears to be the result of the more rapid clearance of cisternal clot in the thrombolytic groups than the no-treatment group. This study indicates that post-operative intrathecal thrombolytic therapies, especially with less than 4 mg/dL of tPA, are effective in lysing subarachnoid clot and preventing vasospasm and infarction safely. Ohman et al.[189] reviewed patients receiving 3 mg,

10 mg or 13 mg of rtPA in a single intracisternal injection at the end of the operation. In all treatment groups a reduction was observed in the amount of blood seen on the post-operative CT scans compared to the pre-operative CT scans. Findlay et al.[60] administered rtPA directly into the basal subarachnoid cisterns after minimal surgical clot removal and aneurysm clipping. All patients except one demonstrated partial to complete cisternal clot clearance on CT scans within 24 hours after surgery. Intrathecal fibrinolytic treatment appears effective in clearing subarachnoid clot and reducing vasospasm, and may be associated with acceptable risks if given to patients with large-volume SAHs at high risk for severe vasospasm.

Inagawa et al.[90] studied the effect of continuous cisternal drainage on cerebral vasospasm using strict criteria in 140 patients with ruptured intracranial aneurysms. Angiographic vasospasm was less severe, the incidence of permanent symptomatic vasospasm and low-density area on computed tomography were lower, the mortality rate was lower and the rate of good recovery was higher.[137]

Cisternal irrigation therapy with urokinase is safe and effective for the prevention of symptomatic vasospasm after aneurysmal SAH. The efficacy and safety of cisternal irrigation therapy with urokinase to prevent symptomatic vasospasm was evaluated, and the optimal concentration of the drug was estimated by Sasaki et al.[229] After the aneurysm was clipped, irrigation tubes were placed in the Sylvian fissure (inlet) unilaterally and in the prepontine or chiasmatic cistern (outlet). Lactated Ringer's solution with UK (30, 60 or 120 IU/mL) was infused at a rate of 30 ml/hr. Analysis of the drainage fluid suggested that UK 120 IU/mL was effective. No abnormal changes were observed in the coagulative and fibrinolytic systems after UK irrigation.

OUTCOME

Outcome of patients with SAH and vasospasm continues to be poor, and cerebral vasospasm is still the most common cause of morbidity and mortality after aneurysmal SAH.[41] Vasospasm was the cause of 28% of all deaths and 39% of disability in the international co-operative study on the timing of aneurysm surgery. The patients with vasospasm had longer ICU stays and were more likely to be in poor grade. If the angiographically detected vasospasm did not produce any adverse effect on the clinical condition, its influence on surgical outcome was not significant. Kassel et al.[117] further elaborated that vasospasm and re-bleeding were the leading causes of morbidity and mortality in addition to the initial bleed. Predictors for mortality included the patient's decreased level of consciousness and increased age, thickness of the subarachnoid clot on computerised tomography, elevated blood pressure, pre-existing medical illnesses and basilar aneurysms. Hacket and Anderson[82] on evaluating 432 first-ever cases of SAH (76% due to confirmed cerebral aneurysm rupture) found only (56%) to be alive approximately 1 year later (mean time 1.2 years) and a high proportion of these long-term survivors of SAH experience ongoing deficits in high level (neuropsychological) functioning leading to impaired social roles. Juvela et al.[103] found that hyperglycaemia at admission seems to impair outcome, and excess weight and hypertension appear to elevate the risk of cerebral infarction after SAH and this was independent of the severity of bleeding. Rabenstein et al.[214] reported that patients with better clinical grades (WFNS Grades I–III) at hospital admission were less likely to suffer symptomatic vasospasm when treated by endovascular coil occlusion, compared with craniotomy and clip application. Nevertheless, they found no significant difference in overall outcome at the longest follow-up examination between the two treatment groups. Hoh et al.[87] found that there was no significant difference in total vasospasm or symptomatic vasospasm when patients who underwent clipping or craniotomy were compared with patients who underwent coiling. In patients with Hunt and Hess Grades I–III ("good grade"), clipping and craniotomy were associated with better outcome and less in-hospital mortality, but there was no difference in total vasospasm or symptomatic vasospasm versus coiling. In patients with Hunt and Hess Grade IV or V ("poor grade"), there was no difference in any outcome measure among the treatment groups. Niskanen et al.[186] stated that the modality of treatment of patients with SAH does not seem to affect resource use. Endovascular and surgical treatment are likely to require a similar amount of ICU resources in the year after initial treatment. Rabenstein et al.[214] found no significant difference in overall outcome at the longest follow-up examination between the two treatment groups, but patients with better clinical grades (WFNS Grades I–III) at hospital admission were less likely to suffer symptomatic vasospasm when treated by endovascular coil occlusion, compared with craniotomy and clip application. Dehdashti et al.[40] studied whether the incidence of symptomatic vasospasm and the overall clinical outcome differ between patients treated with surgical clipping compared with endovascular obliteration of aneurysms and found that symptomatic vasospasm and ischaemic infarction rate seemed comparable in both groups, even for patients with better clinical and radiological admission grades. There was no significant difference in the overall clinical outcome at long-term follow-up between both groups. Wermer et al.[285] found that only one-third of patients regain functional independence after aneurysmal SAH and despite this recovery, many of these patients experience psychosocial problems. The long-term psychosocial effects of SAH are considerable, even in patients who regain functional independence. Sengupta[237] found that there were personality changes associated with loss of interest, initiative and energy. Analysis of the different factors involved suggests that the outcome of surgery depends

mainly on pre-operative clinical condition which, in turn, reflects the severity of the haemorrhage. Lanzino et al.[141] reported no age-related differences in the overall incidence of angiographic vasospasm; however, symptomatic vasospasm was more frequently reported in the older age groups and there was a significant increased risk of poor outcome after the age of 60 years.

Lagares et al.[138] found that only the age, the level of consciousness defined by the WFNS scale and the presence of global brain hypodensity on the initial CT scan had a significant prognostic influence in the logistic regression model. Global brain hypodensity was strongly related to mortality. Salary et al.[227] reported no relation between aneurysm size and volume of subarachnoid blood. The volume of cisternal blood correlates with the Hunt and Hess grade but is not an independent determinant of outcome. Outcome is related to the following triad of well-established clinical factors: Hunt and Hess grade, age and clinical vasospasm.

Preventive Neurosurgery—The Future

Despite investigational, pharmacological, neurointerventional and surgical advances, the morbidity and mortality due to vasospasm is a huge unsolved problem. Vasospasm does not occur in all patients with SAH and obviously the aetiopathogenesis is multifactorial and incompletely understood.[120-124,126] Prevention of SAH would be the ideal step reducing its incidence, but mass screening of the population is impossible. Perhaps the high-risk patients could be imaged for prevention. The factors, like hyperglycaemia, hypertension, obesity and pre-existing medical illness, increase the risk of developing vasospasm[103,111] and these create possibilities on how the problem of vasospasm can be dealt with using principles of preventive neurosurgery. The close causal relationship between cigarette smoking and aneurysms, SAH and vasospasm[141] has been proved conclusively and lifestyle changes and health education can help to reduce the incidence of this devastating condition. Nakai et al.[180] reported that pretreatment with continuous wave ultraviolet (UV) light irradiation can lead to significantly reduced degree of vasospasm and this prophylactic effect of UV light on vasospasm was suggestive of involvement of apoptosis in the mechanism of this effect. Onoune et al.[191] studied the effect of recombinant eNOS gene expression on reactivity of canine basilar arteries to endothelin-1 (ET-1). Their results suggest that genetically modified adventitia can produce NO and cause relaxation in response to ET-1 via activation of ET_A receptors. This supports a novel concept that successful transfer and expression of recombinant eNOS gene can lead to a qualitative change in responsiveness to vasoconstrictor substances.

CONCLUSION

Mocco et al.[175] in an effort to help to clarify the current state of medical therapy for cerebral vasospasm reviewed the relevant literature on the established medical therapies used for cerebral vasospasm following aneurysmal SAH, and they discuss burgeoning areas of investigation. Despite advances in the treatment of aneurysmal SAH, cerebral vasospasm remains a common complication and has been correlated with a 1.5- to 3-fold increase in death during the first 2 weeks after haemorrhage. Weyer et al.[288] performed a systematic review of the literature on the treatment of cerebral vasospasm and made the following conclusions: nimodipine is indicated after SAH and tirilazad is not effective. More study of haemodynamic manoeuvres, the effectiveness of other calcium channel antagonists, such as nicardipine delivered by other routes (for example, intrathecally), magnesium, statin drugs, endothelin antagonists and intrathecal fibrinolytic therapy, is warranted. There is less enthusiasm for the study of steroid drugs and anticoagulant/antiplatelet agents because they entail more risks and investigations so far have shown little evidence of efficacy. The study of rescue therapy, such as balloon angioplasty and intra-arterial vasodilating agents, will be difficult. The quality of clinical trials should be improved.

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78 Cerebral Protection

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INTRODUCTION

The goal of every neurosurgical procedure is to achieve a preset objective whilst minimising the complications. This, however, is not the sole responsibility of the neurosurgeon. Modern neurosurgery requires a multi-disciplinary approach for a safe and successful outcome. This is where the concept of cerebral protection comes in. Cerebral protection can be described as any manoeuvre used to prevent the occurrence of a neurological deficit, or any other complication following a neurological insult. This is the responsibility of the neurosurgeon as well as the rest of the "team". The "Team" includes the neuroanaesthetist as well as the intra-operative monitoring team. This responsibility extends to the team managing the ICU since neuroprotection is equally, if not more necessary, during the post-operative or post-insult period. Protection implies improved outcome as evidenced by electrophysiologic, metabolic or histologic indices of recovery and ultimately by improved clinical neurological recovery.

In order to understand the various nuances of cerebral protection, it is essential to understand the pathophysiological processes involved in neuronal damage. This chapter has been divided for the sake of simplicity into two parts; the first half deals with the pathophysiology of cell damage, the latter half details the various modalities of cerebral protection being practiced worldwide.

PATHOPHYSIOLOGY OF INJURY TO THE CENTRAL NERVOUS SYSTEM

Neuronal cell damage in a neurosurgical setting occurs commonly intra-operatively with a varying degree of insult based on many factors. However, the pathophysiological processes in intra-operative injury are similar to those involved in other forms of injury to the central nervous system (CNS) such as stroke and trauma. Major advances in neurobiological research have outlined a cascade of cellular events that occur in injured tissue. This cascade of events involves neuronal depolarisation, excessive activation of excitatory amino acid receptors, energy depletion with ionic refluxes, and activation of catabolic enzymes and subsequent lipid peroxidation and free radical formation. These processes perpetuate the initial insult. At the same time, brain ischaemia causes the proliferation of neural stem cells/neural progenitor cells (NSCs/NPCs) in both the subventricular zone (SVZ) and the subgranular zone (SGZ) of the brain. A NSC/NPC-conditioned medium showed neuroprotective effects *in vitro*. NSC/NPC-released brain-derived neurotrophic factor (BDNF) and vascular endothelial growth factor (VEGF) are required for NSC/NPC-conditioned medium-induced neuroprotection. These data suggest that NSC/NPC-generated trophic factors are neuroprotective and that brain ischaemia-triggered NSC/NPC proliferation is crucial for brain protection.[49] Nerve growth factor (NGF) was recently characterised as an angiogenic factor inducing proliferation, migration and capillary sprouting in endothelial cells (ECs) of different vascular beds.[48] These processes lead to oedema, which compromises local perfusion and triggers further activation of the injury cascade. It is necessary to understand these events well, as they have a bearing on the multiple pharmacological strategies aimed at preventing or attenuating CNS injury.[2]

The main events leading to neuronal cell damage can be studied lucidly under the following headings.

Intracellular Calcium Accumulation

There is considerable evidence that excessive intracellular calcium is a fundamental mediator of cell death. Numerous studies have demonstrated intracellular calcium accumulation prior to ischaemic neuronal death.[76,83,85] Removal of extracellular calcium prevents hypoxic neuronal death in cell culture models.[16,36] Increases in intracellular neuronal calcium concentrations can occur from many sources including multiple membrane channels as well as intracellular storage sites. Some of these sources are unique to neurons explaining the extreme sensitivity of neurons to ischaemic and traumatic injury. The role of intracellular calcium in neuronal injury can be understood better in Figure 1.

Excessive Activation of Excitatory Amino Acid Receptors

Glutamate and aspartate are the major excitatory neurotransmitters in the brain; ironically they are also potent neurotoxins. Excitatory amino acids are present throughout the grey matter of the CNS. These amino acids are packaged inside synaptic terminals and are

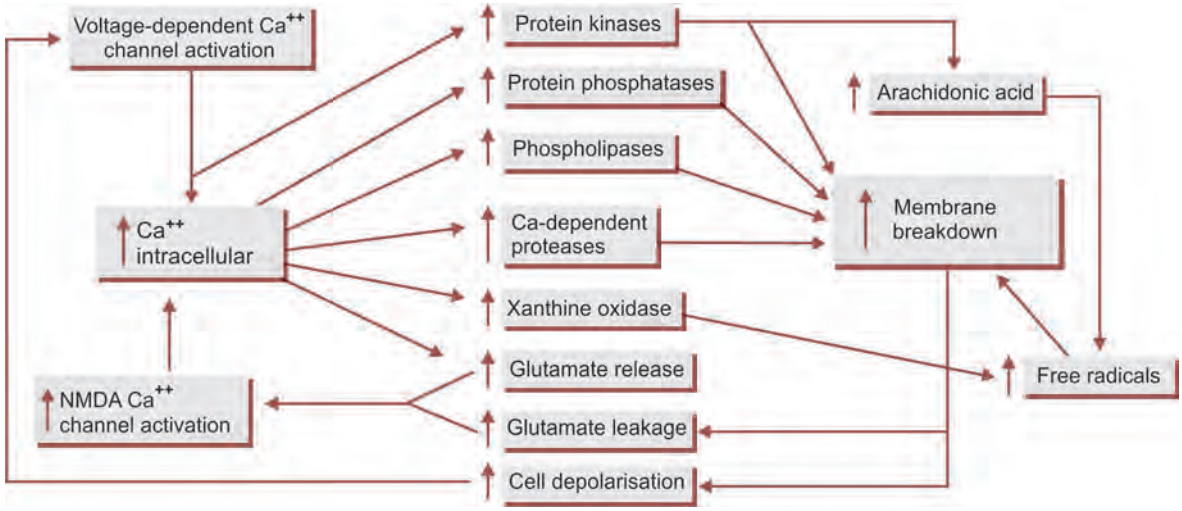

Fig. 1: Role of intracellular calcium in neuronal injury

released into the extracellular environment for synaptic transmission. Following their release into the synaptic cleft, they activate post-synaptic receptors to facilitate excitatory neurotransmission. They are then rapidly cleared from the extracellular space by energy dependent cellular uptake mechanisms.

These uptake mechanisms fail when there is hypoxia-ischaemia, leading to toxic accumulation of excitatory amino acids in the extracellular space. This accumulation has been proven to destroy neurons in cell culture (Fig. 2), and the injury thus caused appears to be mediated by excessive activation of excitatory amino acid receptors that are linked to ion channels with a high permeability to calcium. Three major families of receptor subtypes have been identified:

1. N-methyl-D-aspartate (NMDA)
2. AMPA/Kainate (also referred to as "non-NMDA")
3. Metabotropic receptors

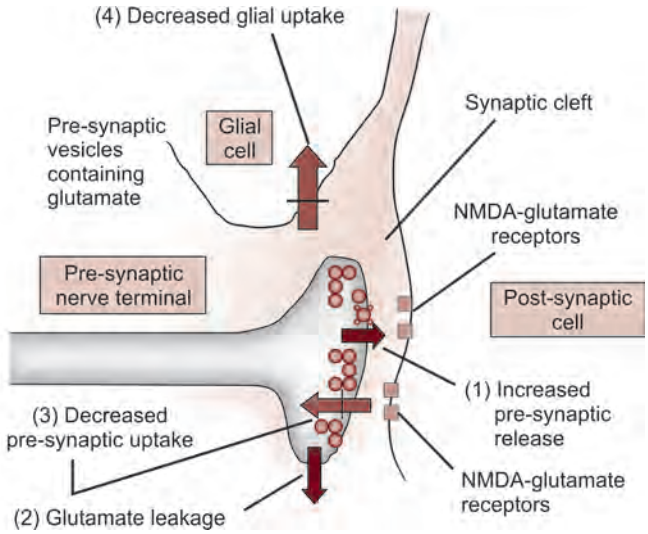

Fig. 2: Four mechanisms of increased extracellular glutamate during trauma: (1) Increased pre-synaptic vesicular release (2) Increased leakage of neurotransmitter (3) Decreased pre-synaptic neurotransmitter uptake (4) Decreased glial uptake
NMDA = N-methyl-D-aspartate

Numerous experimental studies have shown that NMDA antagonists can significantly reduce brain injury from focal ischaemia or trauma. These antagonists are also sufficient to inhibit early swelling and delayed cell death. This suggests that the NMDA-associated ion channels are of critical importance for both sodium and calcium influx into the hypoxic neuron.[16,25,41]

Voltage-Gated Calcium Channels

Voltage-Gated Calcium Channels (VGCCs) are an additional avenue for calcium to enter neurons. These channels are involved in the release of glutamate into the synaptic cleft. Hence, inhibition of these VGCCs may provide neuroprotection indirectly by decreasing excitatory aminoacid-mediated neurotoxicity.

Other Sources of Intracellular Calcium

There are numerous additional sources of intracellular calcium such as:

a. Energy depletion results in reverse operation of the sodium/calcium exchanger, leading to further increases in intracellular calcium.
b. Release of calcium from intracellular storage sites during acute injury.
c. Non-specific leakage of toxic excitatory aminoacids into the extracellular space leading to activation of receptors on neighbouring neurons and culminating in propagation of the brain injury.

Lipid Peroxidation

Excessive levels of intracellular calcium mentioned above trigger an array of neurochemical changes that eventually lead to neuronal injury. Modulators, such as calpain and protein C and intracellular proteases, are activated leading to damage of the cellular proteins. Moreover, phospholipases trigger lipid peroxidation and the generation of free radicals. Lipid peroxidation is one of the most damaging consequences of elevated intracellular calcium. This progressive process can rapidly

propagate through cell membranes leading to membrane destruction. Free radicals formed during the process of membrane destruction also attack nearby glial cells and vasculature, which causes additional injury. Brain tissue has very limited defences against these free radicals because cerebral neurons have low levels of endogenous antioxidants. This "neuronal injury" cascade following trauma, ischaemia or due to hypoxia involving the CNS, ultimately leads to cell death.

Role of Oxygen-Free Radicals

Oxygen is both a life-sustaining and a life-threatening inhalant. A free radical is defined as an atom of a molecule in a particular state with an unpaired electron in its outer orbit.[37] It is now well recognised that oxygen-free radicals are formed during the metabolism of all aerobic cells. There are several pathways in aerobic cells that lead to the production of oxygen-free radicals. The discovery of superoxide dismutase (SOD) by McCord and Fridovich[56] showed the way to research on oxygen-free radicals. Evidence supporting the deleterious effects of oxygen-free radicals in many pathological processes has grown considerably.[10,11,14,31,32,40,80,89]

The current major candidates for a source of oxygen-free radicals are,[37,54] (Fig. 3):

- Accumulation of reduced metabolites
- Xanthine oxidase
- Mitochondria
- Activated neutrophils
- Arachidonic acid metabolism
- Catecholamine oxidation

The fact that oxygen-free radicals are one of the factors responsible for cell damage is well documented in:

- Traumatic brain injury[22,29,43]
- Cerebral ischaemia-reperfusion injury
- Subarachnoid haemorrhage and vasospasm
- Peritumoral brain oedema

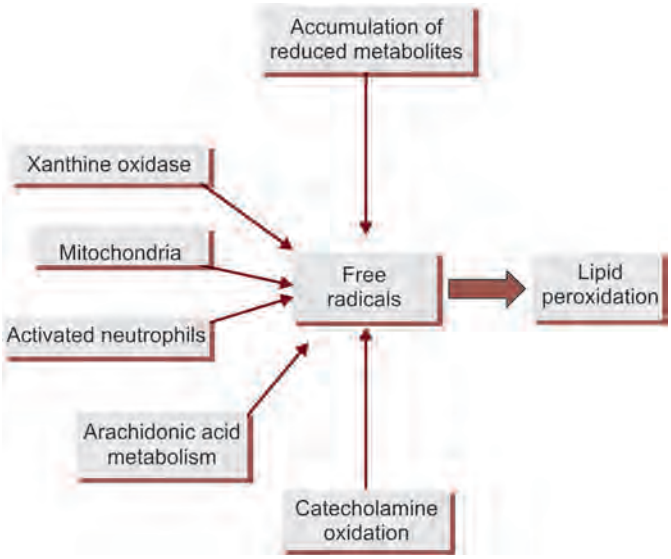

Fig. 3: Sources of free-radical release and lipid peroxidation

PROTECTIVE MECHANISM AGAINST OXYGEN-FREE RADICALS

A variety of enzymatic mechanisms have evolved which provide protection against oxygen-free radicals. SOD scavanges the superoxide, which is formed during the process of reduction of oxygen by aerobic cells. Two other enzyme systems also help in the scavenging of hydrogen peroxide; these are catalase and glutathione peroxidase.[77] Another endogenous defence exists in hydrophilic and hydrophobic regions. In hydrophilic regions, ascorbic acid, cysteine, ceruloplasmin and transferrin are the antioxidant compounds. In hydrophobic regions, several fatty acids and vitamin E are the antioxidant compounds. More details regarding protective mechanisms in a clinical setting have been discussed in the later parts of this chapter.

MODALITIES OF CEREBRAL PROTECTION

The various modalities of cerebral protection available for therapeutic use are shown in Table 1.

PHARMACOLOGICAL THERAPIES

Barbiturates

Barbiturates produce a dose related decrease in neuronal function that is accompanied by a dose related decrease in cerebral metabolism.[63] Barbiturates interfere with synaptic transmission and multineuronal networks, can exert a local anaesthetic effect on membranes, and can enhance presynaptic inhibition by facilitating

Table 1: Modalities of cerebral protection

A.	Pharmacological therapies:
1.	Barbiturates
2.	Isoflurane
3.	Etomidate
4.	Local anaesthetics
5.	Calcium entry blockers[5]
a.	Flunarizine
b.	Lidoflazine
c.	Nimodipine
6.	Diuretics
a.	Mannitol
b.	Furosemide
7.	Corticosteroids
8.	Diphenyl hydantoin
9.	Perfluorochemical blood substitutes
10.	Antioxidants/free radical scavengers
B.	Non-pharmacological therapies:
1.	Hyperventilation
2.	Hypervolaemia
3.	Haemodilution
4.	Induced hypothermia
5.	Induced hypertension
6.	Induced hypotension

the binding of gamma-aminobutyric acid. The parallel decrease in cerebral oxygen consumption accompanying the decrease in neuronal function reaches a plateau when neuronal function is abolished as evidenced by isoelectricity on the EEG.

The proposed mechanism of action of barbiturates can be outlined as follows:

- Decrease in cerebral metabolic requirements
- Improvement in distribution of CBF
- Suppression of seizures
- Suppression of catecholamine induced hyperactivity
- Anaesthesia, deafferentation, immobilisation
- Loss of thermoregulation
- Decrease in ICP
- Decrease in cerebral oedema
- Decrease in CSF secretion
- Scavenging free radicals
- Stabilisation of membranes
- Blocking calcium channels
- Alteration in fatty acid metabolism

Barbiturates help in protecting against temporary focal ischaemia. Prophylactic barbiturate treatment has been recommended for brain protection during periods of focal ischaemia when temporary clamping of a major cerebral vessel is necessary as during carotid endarterectomy,[27,33,58,92] aneurysm clipping[12,21,34] or extracranial to intracranial bypass procedures.[47,52,91] Relatively small, single doses of barbiturates have been recommended due to concern about cardiovascular compromise. Drug induced coma produced by larger doses of barbiturates may delay examination of neurological functions postoperatively.

Normal anaesthetising doses of thiopental (3–5 mg/kg) will produce burst suppression on the EEG lasting less than 5–10 min. Larger doses of thiopental (10–25 mg/kg) produce burst suppression on the EEG lasting about 10 min. Ideally, the occluded vessel should briefly be opened every 5–10 min to allow subsequent small doses of thiopental (1–2 mg/kg) to reach the ischaemic area. If this cannot be done, a continuous infusion of thiopental (3–5 mg/kg/hr) should be administered to maintain burst suppression throughout the period of ischaemia. Ideally, the EEG should be monitored to determine the correct dosage of thiopental required to produce burst suppression in each patient. Blood pressure should be maintained within normal limits. If there is need for profound hypotension during aneurysm clipping, a larger dose of thiopental (6–8 mg/kg) decreases both arterial blood pressure and cerebral metabolism.[62]

Barbiturates have two major undesirable effects. First they may decrease Mean Arterial Blood Pressure (MABP), especially in patients who are hypertensive or hypovolaemic for any reason. They are known to decrease cardiac output with either no change or an increase in heart rate. At high doses, they decrease cardiac contractility, which may lead to a need for vasopressors. A second undesirable side effect of high dose barbiturate is delayed awakening and prolonged time to extubation.

The one clear contraindication to the use of barbiturates is the patient with either acute intermittent porphyria or variegate porphyria. In these patients, the increase in porphyrin synthesis that can be provoked by barbiturates can precipitate an acute attack with widespread demyelination leading to pain, weakness and possible paralysis.

Isoflurane

While barbiturates remain the prototype for cerebral protection during focal ischaemia, it is presumed that any anaesthetic drug that decreases neuronal function with an accompanying decrease in cerebral metabolism might provide cerebral protection during focal or incomplete global ischaemia to the extent that it provides metabolic suppression without disrupting systemic haemodynamics.

Isoflurane is unique among the volatile anaesthetics in that two MAC isoflurane (2.4%) can induce a level of anaesthesia in man that is characterised by an isoelectrical EEG and haemodynamic stability.

Isoflurane increases the tolerance of the brain to low blood flows. It has the ability to lower cerebral metabolism significantly more than the other volatile anaesthetics (halothane, enflurane, innovar) at the clinical concentrations (0.5–1 MAC) used, thereby maintaining the oxygen supply-demand ratio.[57,60] In addition, isoflurane provides protection by suppression of seizures, reduction of catecholamine induced hypermetabolism and immobilisation, deafferentation and anaesthesia. It has not been demonstrated whether isoflurane can favourably redistribute rCBF.

Etomidate

Etomidate is another anaesthetic capable of producing a dose dependent decrease in neuronal function with a parallel decrease in cerebral metabolism.[64] In addition, it is a direct cerebral vasoconstrictor with the ability to significantly decrease CBF. Other mechanisms that may contribute to protection against ischaemia include redistribution of CBF,[97] reduction in intracranial blood volume, decrease in ICP,[64] membrane stabilisation and attenuation of FFA liberation.[81] Etomidate has two advantages over the barbiturates if used as a protective agent. Even large doses of etomidate, sufficient to produce maximal suppression of neuronal function and cerebral metabolism, do not produce cardiovascular depression, hence eliminating the need for isotropic or vasopressor support.[19,20,26] Due to its shorter half-life, etomidate may allow a more rapid awakening time than high doses of thiopental. Etomidate has the disadvantage of suppressing the usual adrenocortical response to stress. Etomidate in a dose of 0.4–0.5 mg/kg achieves burst suppression in 2–3 min.

Calcium Entry Blockers

Calcium entry blockers form a heterogeneous group of drugs; they block the influx of calcium into the cell[95]

and can block the intracellular flux of calcium into the mitochondria.[4,82]

Classification of Calcium Entry Blockers

A. Myocardial, electrophysiologic and vascular effects:
   - Verapamil
   - Tiapanil
   - Diltiazem

B. Predominantly vascular effects (Dehydropyridine derivatives):
   - Nifedipine
   - Nimodipine
   - Nisoldipine
   - Nitrendipine

C. Only vascular effects:
   - Cinnarizine
   - Flunarizine

D. Complex effects:
   - Lidoflazine.
   - Perhexilene

Primarily, four Ca^{+2} entry blockers have been studied for a possible role in brain protection. They were chosen for study because they produced vasodilatation in cerebral vessels *in vitro*.

Mechanism of Protection by Calcium Entry Blockers

A. Cerebral blood flow phenomena:
   - Improve ischaemic flow
   - Attenuate post-ischaemic hypoperfusion
   - Prevent vasospasm
   - Improve rheological properties

B. Cellular changes phenomena:
   - Prevent enhanced proteolysis
   - Prevent formation of FFA and free radicals
   - Antioxidation

Nimodipine: The calcium entry blocker most extensively studied for its protective effects against cerebral ischaemia is nimodipine. There are three prospective randomised double blind, placebo-controlled studies on the use of nimodipine in patients with vasospasm after SAH.[6,73,74] All patients treated with nimodipine orally for 21 days after SAH had a significantly lower incidence of delayed ischaemic deficits or death and had significantly better neurological outcome than those patients given placebo. Although a similar number of patients in each group developed vasospasm as determined by angiography, nimodipine seemed to attenuate the extent and severity of the vasospasm. Nimodipine acts through its effects on neurons by preventing Ca^{+2} entry into the cells, Ca^{+2} sequestration by mitochondria and the alterations in FFA metabolism and the arachidonic acid cascade or by free radical scavenging.

Nimodipine has also been studied for a possible protective effect in animal models of complete cerebral ischaemia. Treatment with nimodipine before or after complete cerebral ischaemia significantly ameliorates post-ischaemic hypoperfusion.[39,65,93,94] It has been demonstrated that this flow enhancement is regionally heterogeneous, but tends to redistribute blood flow such that areas of low flow receive a greater increase in rCBF than areas of high flow.[86]

Flunarizine: Studies of flunarizine have focused on possible prevention of neurological damage after complete global ischaemia. However, inconsistent results are seen in ameliorating post-ischaemic hypoperfusion or improving neurological outcome. In addition, flunarizine precipitates in the lungs producing severe pulmonary oedema. It is not likely to be useful clinically.

Lidoflazine: This has only been investigated for its use in the prevention of neurological damage after complete global ischaemia in animal models of cardiac arrest. Until definite results in the clinical trials emerge, its role in cerebral protection is not clear.

Nicardipine: Experimental studies in animal models of global ischaemia showed no neurological improvement.

Diuretics

Diuretics have been used as adjunctive therapy in brain protection primarily for their role in decreasing cerebral oedema or in decreasing ICP. The two common agents for neuro-protection are mannitol and furosemide.

Mannitol

The use of mannitol in neurosurgery has been studied for over 30 years. In spite of being widely used in neurosurgical operations involving patients with cerebral oedema, the indications and the optimum dose schedule for mannitol remains to be established.[8,15,70] Some of mannitol's beneficial effects include osmotic diuresis, decreased blood viscosity and free radical scavenging.

Mannitol has been shown to increase CBF in experimental and clinical situations. Maximum reduction in blood viscosity occurs during the first 30–60 min after rapid infusion of mannitol; however, this is largely resolved within 4 hours.[70] Decrease of ICP following mannitol administration in an experimental cat model has been shown to be similar to that of decreased viscosity. The maximum white water content reduction in the control hemisphere was at 60 min, whereas no reduction was seen in the lesioned, oedematous hemisphere.

Mannitol also effects serum sodium and potassium acutely. These changes may be of significance intra-operatively for patients with severe cardiac or renal disease, particularly in any procedure in which mannitol is given in high doses. 20% w/v mannitol (0.5–2 g/kg) given over 30 min effects osmotic diuresis. In case of aneurysmal surgery, a total dose of 2 g/kg is given when temporary artery occlusion is planned. Its action begins within 4–5 min and peaks in about 30–45 min. The classic mechanism is believed to be movement of intracellular water into the intravascular volume along the osmotic gradient (the osmolarity of 20% mannitol is 1098 osm/L); some evidence also exists that the rapid action of mannitol can be mediated by decreased production of CSF.

Lastly, despite mannitol's ability to improve CBF in ischaemic regions, it has not been shown to preserve brain or spinal cord electrical activity in ischaemia. Hence, the administration of mannitol should not be considered a substitute for appropriate electrophysiological monitoring.

Furosemide

Furosemide is the diuretic most commonly used intra-operatively in neurosurgery. It is a potent loop diuretic that decreases ICP by venodilatation and by decreasing total intravascular blood volume, and causes the diffusion of oedematous fluid into the vasculature. Furosemide selectively dehydrates abnormal ischaemic or traumatised cerebral tissue and, therefore, may act synergistically with mannitol. Large doses of furosemide also decrease CSF production. The recommended dose ranges 0.1–1 mg/kg followed by 0.3 mg/kg every 4 hours. Given its relative safety and effectiveness, furosemide should be considered intra-operatively whenever ICP reduction or fluid volume reduction is indicated.

Steroids

Corticosteroids are commonly used pre-, intra- as well as post-operatively by neurosurgeons. Although several mechanisms have been suggested for the neuroprotective effects of corticosteroids, its major action is probably inhibition of lipid peroxidation. The efficacy of steroids in reducing vasogenic peritumoral oedema is well documented, but whether corticosteroids have the same efficacy in intra-operative ischaemic cerebral oedema is uncertain. Other mechanisms by which steroids prove helpful is in scavenging of free radicals, reduction of CSF production and increasing the seizure threshold.[71,79,83] The side effects of steroids have been frequently cited as a reason for avoiding their usage. Gastrointestinal bleeding and infections are two major complications with steroids. Exacerbation of hyperglycaemia and subsequent increase of brain injury, especially in an ischaemic situation, is another problem with steroids.[51,75] In conclusion, the use of steroids remains controversial for intra-operative neuroprotection while they are effective in vasogenic peritumoral oedema. Hence, judicious usage of steroids is warranted.

A new class of steroids, 21 aminosteroids or lazaroids, have been developed that inhibit lipid peroxidation of membranes, but lack the glucocorticoid side effects.[55] When free radical destruction of membranes via lipid peroxidation contributes significantly to irreversible cell damage after ischaemia, lazaroids may provide protection from these secondary consequences of ischaemia. However, further animal studies are needed to establish the efficacy of lazaroids in preventing neurological injury after focal and complete global cerebral ischaemia.

Phenytoin

Phenytoin has been shown to stabilise membranes and slow the release of K^+ from ischaemic neurons. Increase in extracellular K^+ concentration causes contraction of vascular smooth muscle, thereby further reducing CBF and increasing glial water content resulting in cytotoxic oedema. Phenytoin has also been shown to attenuate FFA accumulation during complete global ischaemia, thereby preventing the arachidonic acid cascade leading to the production of endoperoxides, prostaglandins and free radicals, and the potential detrimental effects these could have in ischaemic cells.

Perfluorochemical Blood Substitutes

These are small biologically inert particle fluorocarbons (perfluorodecalin and perfluorotripropylamine) emulsified and suspended in an iso-osmolar mixture of intralipid, glycerol and fatty acids. The total surface area for gas exchange per unit volume is approximately 100–170 times that of blood so that gas exchange occurs twice as fast as with haemoglobin. It has been reported that treatment with one such perfluorocarbon blood substrate, Fluosol DA immediately after the onset of permanent focal ischaemia in cats resulted in significantly less neuronal damage than that in saline treated control animals.[72] Suggested mechanisms of protection include increasing oxygen availability to the tissues, decreasing blood viscosity, preventing narrowing of the vascular lumen and increasing flow to the ischaemic areas via collateral circulation because of the small particle size.

Sendai Cocktail

Suzuki[66] advocated a combination of mannitol (500 ml of 20% solution or 100 gm), Vit. E (500 mg) and dexamethasone 50 mg, often referred to as Sendai cocktail, for protection during temporary arterial occlusion. Up to 60 or more minutes of temporary arterial occlusion were possible by this regime without apparent post-operative neurological deficits.

Excitotoxic Antagonists

A major role for excitatory neurotransmitters, notably glutamate, in ischaemic cerebral injury has been well documented. The relationship between excitatory neurotransmitters and increased intracellular calcium has been established. Excitotoxic injury appears to be the result of activation of several receptors: (a) N-methyl-D-aspartate (NMDA) receptor; (b) amino-3-hydroxy-5-methyl-4-isoazole propionic acid receptor and (c) additional receptors.[17]

Although many excitatory antagonists have been studied, few have proven suitable for human trials.[3] The ones in use are dextromethorphan, its primary metabolite dextrorphan and CGS-19755. The limiting factors for the clinical trials to date are significant side effects and unproven efficacy. Continuing research in this area holds promise that an agent truly suitable for intra-operative use will be developed in the relatively near future.

Antioxidants/Free Radical Scavengers

Given that the three primary mechanisms of ischaemic brain injury are loss of calcium homeostasis, acidosis

and increased free radical production, it is not surprising that antioxidants or free radical scavengers should be a part of pharmacological neuroprotection. An oxygen-free radical scavanger is a compound that removes free radical species. A list of known oxygen-free radical scavangers that have been demonstrated to be useful in animal models[11,37,78] is shown in Table 2. Although multiple approaches to inhibit lipid peroxidation and free radical formation have been attempted, substantial clinical benefits have not been clearly documented in human trials with these agents.

Vitamins C and E have a very slow onset of action, while deferoxamine does not cross the blood-brain barrier. Only two agents are likely to be candidates for intra-operative use primarily as antioxidants in the near future, SOD and tirilazad mesylate (TM). SOD has been shown to be effective in treating the vascular changes and increased ICP that occur in several types of brain injury, such as fluid-percussion injury and cold injury.[44,69]

Since SOD has a biological half-life of only 5 min, it has been conjugated with polyethylene glycol (PEG-SOD) for human trials. In a phase II trial of PEG-SOD in patients with severe head injury, treatment was a single bolus intravenous administration, with a mean time from injury to treatment of approximately 4 hours.[69] The percentage of time the ICP was above 20 mmHg and the amount of mannitol required to control ICP were less in the moderate dose PEG-SOD (5,000 U/kg) and in the high dose PEG-SOD (10,000 U/kg) treated patients than in controls. Given these results, it is possible that PEG-SOD or a similar form of SOD may prove to be an important component of a "cocktail" to minimise free radical induced ischaemia-reperfusion injury.[30,85]

TM is an L1-aminosteroid that was developed specifically to maximise the inhibition of lipid peroxidation by glucocorticoids, such as methylprednisolone, but eliminates the unwanted glucocorticoid effects. TM is effective in both focal and global ischaemia with reperfusion.[52] It has also improved outcome in an animal model of spinal cord injury when given 30 min post injury. Its mechanism of action appears to be cell membrane preservation by inhibition of lipid peroxidation.[7] TM was well tolerated when given intravenously up to 6 mg/kg/day (in divided doses every 6 hours); it is expected that doses considerably higher may be feasible and more effective. It is also likely to be a strong candidate for intra-operative use in the near future.

Recent studies have suggested possible roles for pyruvate in protecting CNS neurons from excitotoxic and metabolic insults. Pyruvate can induce glia to up-regulate the synthesis of glutathione (GSH), an antioxidant that protects cells from toxins such as free radicals.[61]

Two well-studied protective proteins, heat shock protein 72 (Hsp72) and SOD2 were genetically targeted for expression in astrocytes using the astrocyte-specific human glial fibrillary acidic protein (GFAP) promoter. This neuroprotection was associated with significantly better preservation of astrocyte glutamate transporter-1 immunoreactivity at 5-h reperfusion and reduced oxidative stress and improving the resistance of astrocytes to ischaemic stress by targeting either the cytosolic or the mitochondrial compartment.[100]

Table 2: Oxygen-free radical scavengers

A. *Enzymatic*:
a. Superoxide dismutase
b. Catalase
c. Allopurinol, oxypurinol (xanthine oxidase inhibitor)
B. *Non-enzymatic*:
a. Dimethyl sulfoxide (DMSO)
b. Dimethylthiourea (DMTU)
c. Deforoxamine
d. Mannitol
C. *Hydrophilic*:
a. Ascorbic acid (vitamin C)
b. Glutathione peroxide
c. L-methionine
D. *Hydrophobic*:
a. Vitamin E
b. Barbiturates

NON-PHARMACOLOGICAL THERAPIES

Hypothermia

Conditions of metabolic inhibition that reduce O_2 and glucose consumption may provide protection for the ischaemic brain owing to the diminished gap between demand and supply.

Mechanism of Protection by Hypothermia

- Reduction in cerebral metabolism: Activation metabolism (neuronal function) and residual metabolism (cellular integrity).
- Membrane stabilising effect: sodium channels restriction and reduction in Na^+ and K^+ flux.
- Reduction in cerebral oedema.
- Reduction in ICP.

The therapeutic benefit of deep hypothermia against cerebral ischaemic injury is largely as a result of reduced metabolic demand and decreased cerebral metabolic rate of oxygen consumption. O_2 consumption is reduced approximately 6–9% per degree drop in temperature. On the basis of animal studies and clinical studies, it is estimated that CMRO2 is decreased 50% at 30°C, 75% at 25°C, 85% at 20°C and 90% at 15°C.

The duration of cerebral ischaemia that can be tolerated is related to the magnitude of temperature reduction and, hence, to the magnitude of metabolic suppression. Deep hypothermia of less than 27°C requires cardiopulmonary bypass, with surgery, general anaesthesia and complex equipment to provide support of the circulation since the heart commonly fibrillates at a temperature below 26–28°C. Mechanical ventilation is required

because hypothermia decreases or abolishes spontaneous respiration depending on the depth of hypothermia. Metabolic acidosis may result from decreased perfusion due to inadequate blood flow and temperature gradients between the core and the periphery. Aggregation or sludging of RBCs due to hypothermia may contribute to poor peripheral circulation.

From clinical trials and animal studies, it is clear that hypothermia alone will not provide complete protection or stimulate the repair that is necessary for normal neurodevelopmental outcome. Other agents such as xenon, N-acetylcysteine, erythropoietin, melatonin and cannabinoids are discussed as future potential therapeutic agents that might augment protection from hypothermia.[18]

Recommended Limits of Total Circulatory Arrest under Deep Hypothermia

	Circulatory arrest time	*Core temperature*
Adult neurosurgical procedures	45–60 min	15–18°C
Paediatric cardiovascular operations	60–90 min	18–20°C

Systemic Effects of Deep Hypothermia

A. Clotting defects:
   - Heparinisation with inadequate reversal
   - Thrombocytopaenia
   - Abnormal platelet function
   - Inhibition and deficiencies of factor I, II, V, VII, X and XII
B. Altered delivery, metabolism and effects of anaesthetic agents
C. Decreased O_2 availability
D. Disturbed acid/base balance
E. Decreased hepatic and renal function
F. Decreased carbohydrate metabolism
G. Reduced cerebral blood flow, increased cerebrovascular resistance
H. Increased blood viscosity
I. Cardiac arrhythmia
J. Shivering

Complications of deep hypothermia include myocardial depression, arrythmias, hypotension and tissue injury due to inadequate or inhomogeneous tissue perfusion.

Hyperventilation

Controlled hyperventilation producing hypocapnia is an effective short-term means of reducing ICP by decreasing CBF and cerebral blood volume when $PaCO_2$ decreases. Cerebral vessels vasoconstrict until the limit of vasoconstriction is reached, which occurs at a $PaCO_2$ of approximately 20 mmHg. If $PaCO_2$ decreases below 18–20 mmHg, ischaemia may occur.[84]

It is hypothesised that hyperventilation might exert a protective effect in focal cerebral ischaemia by vasoconstricting normal cerebral vessels, thereby shunting blood from the normal tissue to the ischaemic area (Robin Hood Steal phenomenon).[46] Hyperventilation begun before experimental focal ischaemia has been shown to decrease the incidence of cerebral infarction;[88] however, it has no effect if begun after ischaemia.[87] Conversely, it has been reported that increased $PaCO_2$ improved CBF in areas of ischaemia.[42] Due to these conflicting reports, hyperventilation is rarely used as a method for improving outcome from focal cerebral ischaemia unless increased ICP is present. Cerebral ischaemia-reperfusion injury (IRI) is a complex process resulting in cellular damage and death. Several recent studies confirmed that repeated hyperbaric oxygen preconditioning (HBO-PC) prior to cerebral ischaemia or spinal cord ischaemia can provide neuroprotection.[96]

Hypertension, Hypervolaemia and Haemodilution (Triple H Therapy)

Hypertension

Cerebral vasospasm occurring as a consequence of SAH is usually accompanied by ischaemia and disturbed auto regulation. Several studies have demonstrated that both CBF and abnormalities in neurological function resulting from this focal ischaemia secondary to vasospasm can be improved by increasing the arterial pressure.[13,23,38,45,67,68]

Induced hypertension may be effective in reversing the effects of focal ischaemia only if CPP is raised before the endothelial cells and the BBB have been damaged by the ischaemia.[35] If raised after damage to these structures, the raised cerebral arterial pressure may cause extravasation of blood and fluid into ischaemic tissue, which would result in intracerebral haemorrhage, increased cerebral swelling, intracranial hypertension and an excaberation of ischaemia.[35]

Hypervolaemia

Although there is little evidence to substantiate a direct relationship between intravascular volume and CBF,[50,98] expansion of intravascular volume by colloid infusion has been commonly used to treat focal cerebral ischaemia.[24,53]

Haemodilution

Blood viscosity varies inversely with the shear rate of the fluid and is, therefore, greater at lower flow rates. During and after cerebral ischaemia, blood viscosity increases as a result of shift in electrolytes and water from plasma to tissue. Haemodilution would decrease blood viscosity and improve cerebral perfusion during and after ischaemia. There are three major types of haemodilution depending on the amount of volume expansion. Hypovolaemic haemodilution is produced by phlebotomy and less fluid replacement. Isovolaemic

haemodilution is produced by exchanging fluid for blood. Hypervolaemic haemodilution is produced by infusion of fluid (colloid or crystalloid) into the circulation. Hypervolaemic haemodilution has been commonly used in patients with focal ischaemia and has been shown to improve cerebral perfusion of ischaemic brain and decrease neurological deficits.[1,28,38,99]

Agents for Volume Expansion

Crystalloids
a. Normal saline
b. Ringer's lactate
c. Hypertonic saline
d. Hypertonic Ringer's lactate
e. Dextrose solution

Colloids
a. Blood
b. Albumin
c. Dextran
d. Hetastarch
e. Perfluorocarbons

Induced Hypotension

Over the MABP range (50–150 mmHg), the cerebral blood flow (CBF) remains constant or nearly constant in the intact brain (Fig. 4). To be truly effective, induced hypotension or hypertension would need to exceed these values to affect CBF, i.e. drop below 50 mmHg or rise above 150 mmHg. In actual intra-operative practice, cerebral auto regulation for blood pressure is not fully intact in many circumstances and, thus, the relationship between MABP and CBF more closely resembles the dashed line in the figure. In regions of severe ischaemia, cerebral oedema or infarction, auto regulation may be completely lost.

Induced hypotension is employed to reduce blood loss. It is necessary to distinguish prolonged induced hypotension during procedures in which blood loss is virtually continuous (extensive spinal fusions or the resection of large vascular tumours), from temporary induced hypotension to facilitate control of unexpected profuse bleeding (premature rupture of aneurysm or AVM). In the former situation, the induced hypotension is elective and is undertaken with maintenance of adequate perfusion of neural tissue as an essential goal. In the latter situation, the induced hypotension is emergent and is undertaken at the risk of ischaemic injury to neural tissue.

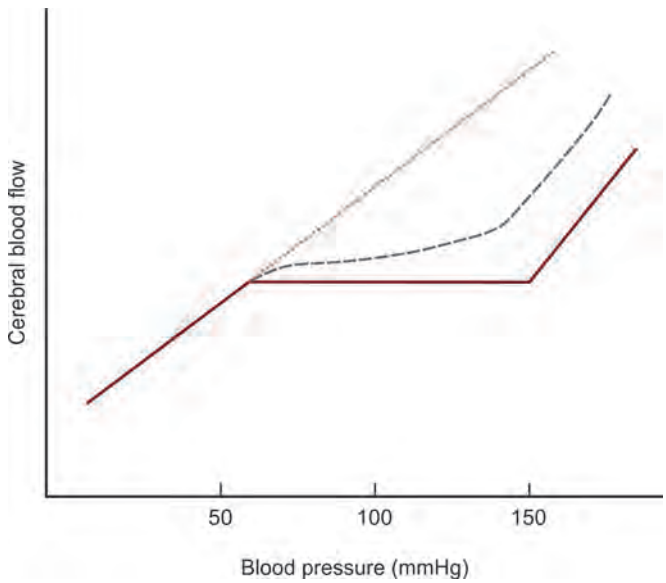

Fig. 4: Cerebral blood flow auto-regulation (solid black line); partial autoregulation of CBF to changing MABP, realistic in many clinical situations, e.g. cerebral oedema (dashed blue line); complete loss of auto-regulation of CBF to changing MABP, i.e. CBF fluctuates with fluctuations in MABP (dotted red line)

Relative Contraindications to Induced Hypotension

- Ischaemic cerebrovascular disease
- Ischaemic coronary artery disease
- Chronic hypertension
- Hypovolaemia
- High (> 45) or low (< 30) haematocrit
- Extremes of age.

Complications of Induced Hypotension

- Stroke
- Cardiac arrest or myocardial infarctions
- Hepatic failure
- Renal failure or renal artery thrombosis
- Retinal artery thrombosis.

Agents for Induced Hypotension[90]

- Inhalation anaesthetic (increased isoflurane)
- Intravenous anaesthetic (propofol, thiopental, etomidate)
- Vasodilator (sodium nitroprusside, nitroglycerine, hydralazine)
- Sympathetic blocker (esmolol, labetalol)
- Ganglionic blocker (trimethapan)
- Narcotic (sufentanyl)
- Adenosine (less commonly used at present).

Nitroglycerine would preserve brain tissue oxygenation better than sodium nitroprusside due to its venous dilating properties. Sodium nitroprusside is a peripheral arterial bed dilator (rather than a venous bed) and, thus, may produce increased peripheral vascular resistance. Following discontinuation of induced hypotension with these agents, increased CBF (hyperaemia) can be seen. With respect to the duration of sodium nitroprusside induced hypotension that can be safely tolerated, a well-established primate model of temporary middle cerebral artery occlusion provides relevant data. Hypotension from a MAP of 60 through 65 mmHg to 48 through 50 mmHg for 15 min was well tolerated, but neurological deficits occurred with 30 min or longer of occlusion plus hypotension.

Electrophysiological Monitoring

Electrophysiological monitoring, such as EEG and evoked potentials (EPs), may allow intra-operative detection of cerebral ischaemia, leading to a change in surgical technique that improves perfusion. However, they are not routinely used because their changes are

not always specific and the recording sites not always accessible.

EEG monitoring may be indicated when temporary occlusion is planned, either to determine the duration of tolerance or for titration of anaesthetic agents when burst suppression is desired.[9,59]

Somatosensory evoked potential (SSEP) has been investigated for use during procedures on both anterior and posterior circulation aneurysms, whereas brainstem auditory evoked potential (BAEP) has been primarily investigated for use during procedures on vertebral-basilar aneurysms. EPs can be recorded even when EEG is suppressed with high dose barbiturates and, therefore, the only electrophysiological monitor available when maximal pharmacological metabolic suppression is used.

Spontaneous breathing has been used in the past as an indicator of brainstem function, particularly when extreme hypotension is used. It is seldom used today, because optimal brain relaxation is difficult and extreme hypotension is no longer used. However, with aneurysms of the lower basilar artery and vertebral artery, where temporary or permanent occlusion of the feeding vessel is contemplated, spontaneous breathing may provide additional and more specific information than cardiovascular monitoring.

Cerebral protection implies providing an environment in which there is scope for maximising recovery for the damaged neuronal cells and minimising the side effects of the various therapeutic manoeuvres involved. Neuronal cell damage can follow ischaemia, hypoxia and even cerebral trauma. Many of the pathological processes, e.g. free radical release are still poorly understood and more research needs to be done in order to make rational choices about therapy either for prevention of cerebral ischaemia/hypoxia or for treatment to prevent irreversible cell damage once the pathological processes are set in motion. Lastly, as neurosurgical operations become more complex and newer technologies are introduced into the field, the need to have a team approach is very evident in order to have an optimum outcome.

Editors note: For more detailed information reference may be made to a monograph: VK Khosla and VK Kak (Eds). Brain Protection and Neural Trauma. New Delhi: Narosa Publishing House; 2000.

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79 Paraclinoid Aneurysms

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INTRODUCTION

Paraclinoid aneurysms arise from the internal carotid artery (ICA) distal to the cavernous sinus but proximal to the posterior communicating artery.[6,9,14,24] Five to ten per cent of all intracranial aneurysms arise from this segment of the ICA.[16,24,26] Satisfactory clipping of paraclinoid aneurysms, while preserving the ophthalmic artery and maintaining the patency of the ICA, is technically challenging. A number of these aneurysms are giant and are difficult to clip due to splaying of branch vessels at the neck of the aneurysm and atherosclerosis and calcification at the neck and dome of the aneurysm. Advances in skull base techniques and endovascular procedures and their combinations have greatly improved surgical outcome. In this chapter, we review the neuroanatomy of the paraclinoid region and discuss the operative nuances involved in the surgery of paraclinoid aneurysms.

NEUROANATOMY

Paraclinoid Internal Carotid Artery

The modification of Fischer's classification proposed by Bouthillier and colleagues[4,16] classifies segments of the ICA in an anterograde sequence (Fig. 1). The cavernous segment of ICA is designated the C4 segment. After exiting from the cavernous sinus, the ICA bends twice to form the anterior loop and reverses its course by 180 degrees. Here, it is surrounded by the anterior clinoid process laterally, the optic strut anteriorly and the carotid sulcus medially.[16,26]

The intracavernous ICA is separated from the intradural space by two layers of the cavernous sinus dura, an inner membranous layer and the outer dura propria. These layers split at the anterior clinoid process (Figs 2A to C).

The inner membranous layer forms the periosteum covering the inferior surface of the anterior clinoid process. At the point at which the ICA comes in close contact with the inferior surface of the clinoid process, the inner layer encircles the ICA, forms the proximal dural ring and then further wraps the clinoidal segment of the ICA in a dural sleeve (known as the carotid collar).[24,37] The proximal dural ring does not fuse with the adventita of the ICA and can easily be separated from it. The dural sleeve fuses with the distal dural ring at the point where the ICA enters the intradural space after emerging from the cavernous sinus (Figs 2B and C).

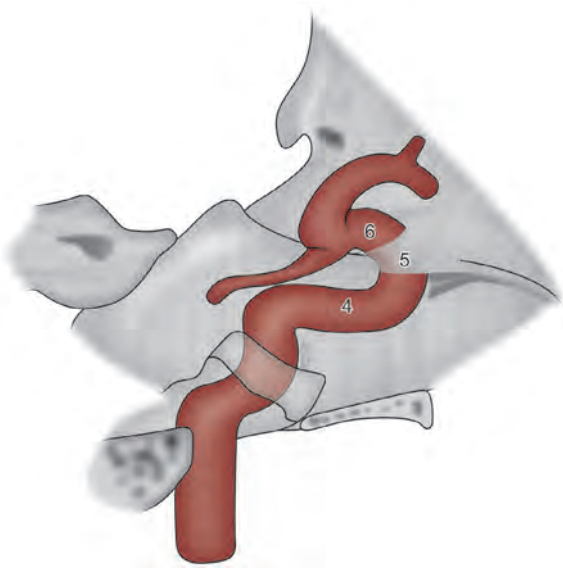


Fig. 1: Lateral view of the ICA showing the segments described by Bouthillier et al. C4 corresponds to the cavernous ICA, C5 to the clinoidal ICA and C6 to the ophthalmic ICA

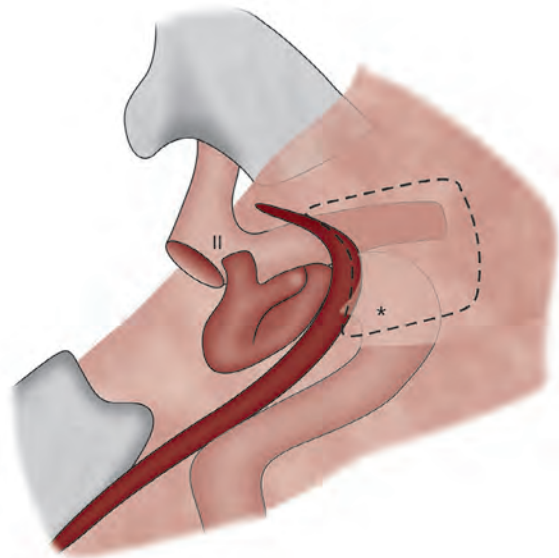


Fig. 2A: Lateral view of the left paraclinoid region showing the dura covering the anterior clinoid (*). The drilling of the anterior clinoid in order to expose the clinoidal ICA requires the reflection of the dura overlying it. The optic nerves and the chiasma are represented by II

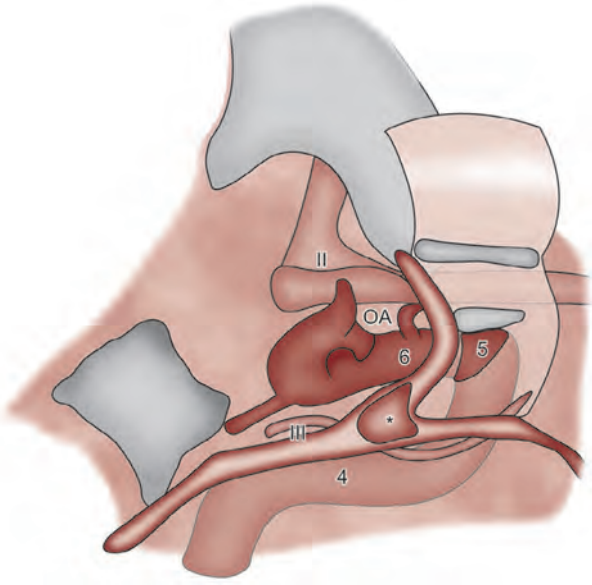


Fig. 2B: The drilling of the anterior clinoid (*) exposes the clinoidal ICA (5) between the proximal and the distal dural rings. The ophthalmic artery (OA) arises from the ophthalmic segment of the ICA (C6) just distal to the distal dural ring. The third nerve (III) is seen entering the cavernous sinus

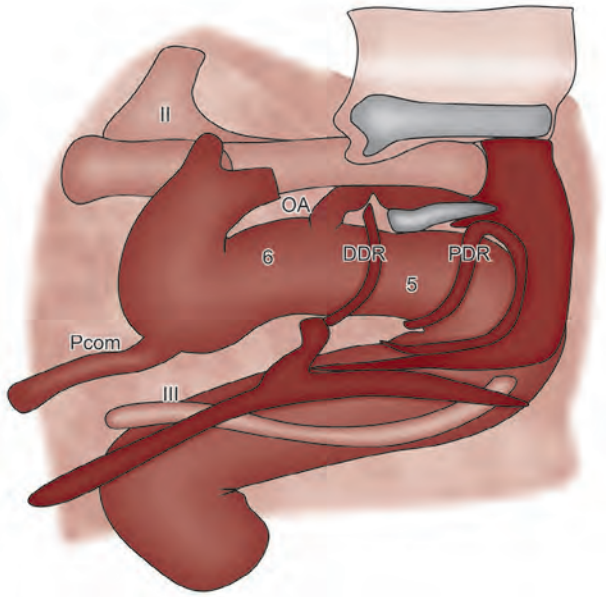


Fig. 2C: The anterior clinoid has been completely removed exposing the proximal and distal dural rings. The cavernous (C4), clinoid (C5) and ophthalmic (C6) segments of the ICA and the ophthalmic artery (OA) can be seen. The clinoid (C5) segment, situated between the proximal and the distal dural rings; and, the ophthalmic (C6) segment, situated between the distal dural ring and the origin of the posterior communicating artery together constitute the paraclinoid region of the ICA. The inner dural layer of the roof of the cavernous sinus forms a sheath over the oculomotor nerve (III) and then encircles the ICA as the proximal dural ring (PDR). It forms the carotid collar around the clinoid segment of the ICA and fuses with the distal dural ring (DDR). After removal of the anterior clinoid process, a space exists between the inner and the outer dural layer known as the clinoid space

Posteriorly, the inner dural layer forms the dural sheath of the oculomotor nerve and continues as the inner layer of the lateral wall of the cavernous sinus. The portion of the proximal ring that separates the clinoid ICA from the oculomotor nerve is termed the carotico-oculomotor membrane and is the surgical landmark for encountering the clinoidal ICA through the roof of the cavernous sinus.[24]

The clinoidal (C5) segment of the ICA is the part of the ICA from the proximal to the distal dural ring (Figs 2B and C). This part of the ICA is regarded as extracavernous and extradural. Aneurysms located proximal to the distal dural ring do not cause subarachnoid haemorrhage (SAH) and, therefore, do not produce the same morbidity as do aneurysms arising from the intradural space. The veins of the cavernous sinus may extend through the incompetent proximal dural ring up to the distal dural ring through the space between the dural rings and the ICA.[24,37]

The outer dural layer or the dura propria of the cavernous sinus forms the periosteum covering the superior surface of the anterior clinoid process, the planum sphenoidale and the tuberculum sellae. It also continues as the diaphragma sellae and the falciform ligament (the dural sheath of the optic nerve), and fuses with the adventitia of the ICA to form the distal dural ring (Figs 2B and C).[24]

The distal dural ring forms the boundary between the extradural and the intradural spaces and marks the end of the clinoid (C5) segment and the beginning of the ophthalmic (C6) segment of the ICA. The distal dural ring is adherent to the adventitia of the ICA so a blunt rather than a sharp dissection of the distal dural ring from the ICA may tear the adventitial layer of the ICA.[16,24] The distal dural ring is reinforced on its lateral aspect by the anterior petroclinoid ligament that extends from the petrous apex to the anterior clinoid process.

A small subarachnoid pouch exists at the medial aspect of the ICA at the distal dural ring known as the carotid cave.[27] This cave points towards the cavernous sinus. The apex of the cave contains connective tissue, which, if breached, communicates this space with the clinoid venous plexus. Thus, large aneurysms in this location may be both intradural and extradural. Since the cave contains the subarachnoid space, carotid cave aneurysmal rupture may cause SAH. Thus, carotid cave aneurysms, despite being located proximal to the distal dural ring, are intradural.[24]

The clinoid space is the potential space between the outer and the inner dural layers and is occupied by the anterior clinoid process. It is a potential space, since it is only created after an anterior clinoidectomy.[32,33]

The proximal ophthalmic (C6) segment of the ICA lies under the anterior clinoid process beyond the distal dural ring. The ophthalmic artery arises distal to the distal dural ring from the rostromedial aspect of the C6 segment of the ICA. It travels through the optic foramen lying inferior and lateral to the optic nerve. In 2–16% of

cases, it may also arise proximal to the distal dural ring either from the C5 or from the C4 segment.[16]

The superior hypophyseal arteries arise from the posteromedial wall of the proximal C6 segment, vary from 1–5 in number and cross over the diaphragma sellae. Occasionally, they may originate near the distal dural ring, within the carotid cave or may even be intracavernous.

The paraclinoid segment of the ICA, therefore, extends from the proximal dural ring to the origin of the posterior communicating artery and encompasses both the clinoid (C5) and the ophthalmic (C6) segments.[16,24,26]

Review of Classification Schemes

Drake et al. had described carotid-ophthalmic aneurysms as a distinct entity in 1968, but did not propose any classification.[9] In 1971, Kothandaram et al. first classified these aneurysms according to their relationship with the optic chiasma into subchiasmal, suprachiasmal and parachiasmal aneurysms.[28] In 1976, Almeida et al. divided them into lateral optochiasmatic and suboptochiasmatic[1] to which Thurel, in 1976, added the suprachiasmatic and global groups.[41] Based on arteries of origin, Day, in 1990, classified them into ophthalmic artery, superior hypophyseal-paraclinoid and superior hypophyseal-suprasellar aneurysms.[6] In 1993, Al-Rodhan et al. classified them based on the projection of the neck and dome of the aneurysm into supraophthalmic, ophthalmic, infraophthalmic/supracavernous, transitional and cavernous groups.[2] In 1994, Batjer et al. classified these aneurysms into ophthalmic artery, superior hypophyseal artery and proximal posterior wall aneurysms,[3] to which, in 1997, Fries et al. added "partially intracavernous aneurysms.[14] In 1997, Kumon et al. classified these aneurysms into five groups: the subchaismatic; lateral chiasmatic; suprachiasmatic; carotid cave and paraclinoid.[29] In 1999, De Jesus et al. divided them into four groups: clinoid; ophthalmic; superior hypophyseal and posterior paraclinoid.[7] In 2003, Barami et al. reclassified them again as per their location in relation to the ICA segments.[5]

Classification of Paraclinoid Aneurysms

This is based upon the site of origin of the aneurysm on the C5 and C6 segments of the ICA and the direction of projection of these aneurysms, and was primarily proposed by Barami et al. in 2003 (Figs 3A to D)[2,5,16,24,38] (Table 1).

Carotico-ophthalmic Aneurysms

These aneurysms arise from the origin of the ophthalmic artery (Fig. 3A).[6] They usually arise from the dorsal surface of the C6 segment, project superiorly into the subarachnoid space and displace the optic nerve superiorly and medially. Their neck as well as their dome is intradural (Ia). Occasionally, the ophthalmic artery arises from the C5 segment of the ICA proximal to the distal dural ring in which case the neck and the dome are extradural. These lesions either present with SAH, or if

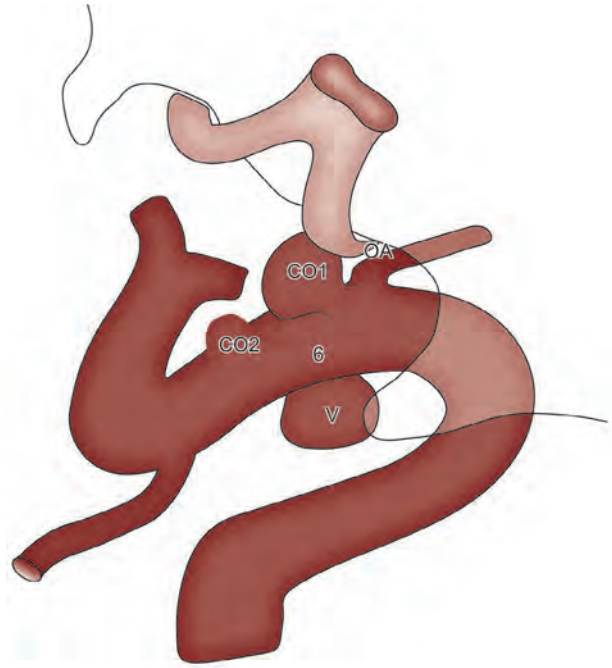


Fig. 3A: Lateral view of the ICA showing a carotico-ophthalmic aneurysm (CO1) arising from the origin of the ophthalmic artery; a blister aneurysm (CO2) arising from the dorsal wall of the ophthalmic segment of the ICA; and a ventral wall aneurysm (v) arising from the ventral surface of the ICA

they grow to a large size cause optic nerve or chiasmal compression. One variant of this aneurysm arises from the dorsal and the superior surface of the ICA, a few millimetres distal to the origin of the ophthalmic artery. The latter aneurysms are broad based, sessile and project superiorly (Ib) (Fig. 3A).[18,19,25]

Ventral or Posterior Wall Aneurysms

They originate between the ophthalmic and the posterior communicating arteries and project into the cavernous sinus (Fig. 3A).[13,32,33] The neck lies 180 degrees opposite

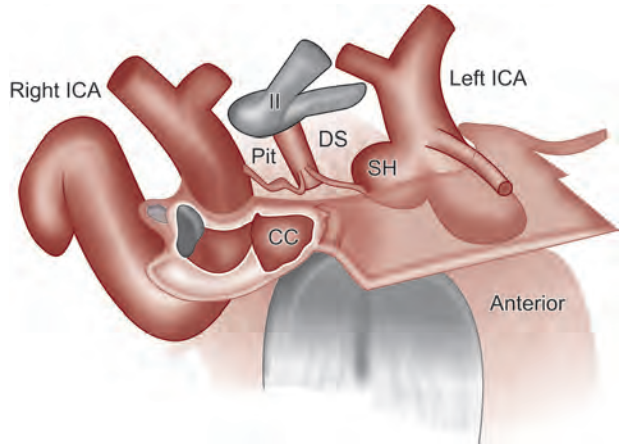


Fig. 3B: Anteroposterior view of the right and left ICA. The left ICA is showing a superior hypophyseal artery aneurysm (sh) while the right ICA is showing the sub-diaphragmatic (carotid cave) variant of a superior hypophyseal artery aneurysm (CC). The pituitary stalk (Pit) is seen entering the diaphragma sellae (DS)

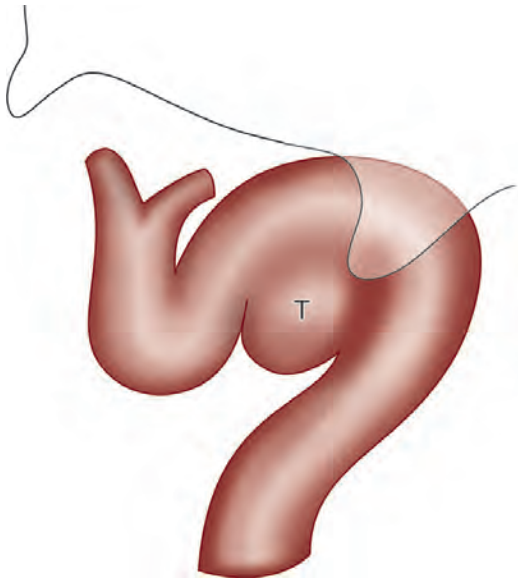


Fig. 3C: A transitional aneurysm (T) takes origin from the cavernous, clinoidal and ophthalmic segments of the ICA

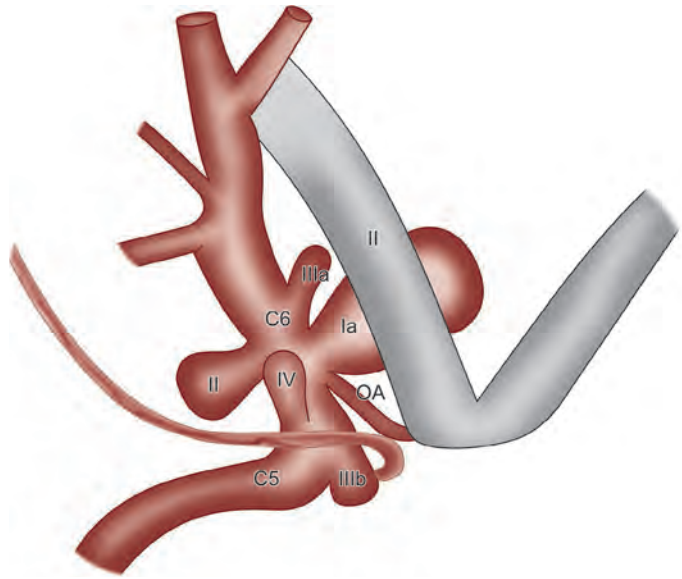


Fig. 3D: Overview of the location of paraclinoidal aneurysms

Table 1: Paraclinoid aneurysms

Classification	*Origin from ICA*	*Origin from surface of ICA*	*Relation to branch of ICA*	*Other relations*
(Ia) Ophthalmic artery aneurysm	Ophthalmic segment of ICA (C6)	Dorsal	Ophthalmic	Medial or lateral to II nerve
(Ib) Ophthalmic artery aneurysm	Ophthalmic segment of ICA (C6)	Dorsal	None	Lateral to optic nerve
(II) Ventral wall or posterior carotid wall aneurysm	Ophthalmic segment of ICA (C6)	Ventral	None	Aneurysm dome may project into cavernous sinus roof. Arise from ventral wall right opposite and just distal to origin of ophthalmic artery
(IIIa) Superior hypophyseal artery aneurysm	Ophthalmic segment of ICA (C6)	Medial	Superior hypophyseal artery	Arise distal to ophthalmic artery and are above the diaphragma sellae
(IIIb) Carotid cave aneurysms	Clinoidal segment of ICA (C5)	Medial	Superior hypophyseal artery	Arise at or below the dural ring around the ICA as it enters the subarachnoid space. They are below the diaphragm sella and may project into the sella
(IV) Transitional aneurysms	Clinoidal (C5), ophthalmic (C6) and often also the cavernous segments of ICA (C4)	Ventral	None	Often giant aneurysms extend from the cavernous sinus proximally to the subarachnoid space distally, widening the dural rings

to the origin of the ophthalmic artery. They are not associated with an arterial branch. Although they look and behave like other saccular aneurysms, they are often blister-like with a relatively thin wall and a broad base, and are extremely fragile. Therefore, during the post-subarachnoid haemorrhage period, their surgical treatment carries a high morbidity rate. The dome may project towards the roof of the cavernous sinus and involve the III nerve. Thus, large aneurysms of this type occupy both the intradural and the extradural spaces.[18,19]

Superior Hypophyseal Aneurysms

They arise from the medial surface of the proximal C6 ICA closely related to the origin of the superior hypophyseal artery distal to the ophthalmic artery (Fig. 3B).[6] The neck as well as the dome are intradural and they project medially above the diaphragma sellae (IIIa). A variant of this aneurysm arises from the carotid cave,[27] with its neck and fundus being intradural and projects inferomedially along the medial aspect of the distal dural ring. This may project below the diaphragma sellae and may be assumed to be a sellar mass on CT imaging (IIIb). It arises at or below the dural ring around the ICA as it enters the subarachnoid space (Fig. 3B).[18,19]

Siphon or Transitional Aneurysms

These giant aneurysms have a base extending from the distal cavernous to the ophthalmic segments (Fig. 3C).[8] The dome may elevate the roof of the cavernous sinus, enlarge the proximal and distal dural rings, and also extend intradurally.[2]

Clinical Presentation

These aneurysms may present as SAH with sudden severe headache, decreased visual acuity, field deficits, changes in colour vision, diplopia or retro-orbital pain.[6,12,23] Occasionally, transient ischaemic attack or stroke, dizziness, facial pain or numbness, audible bruit, panhypopituitarism and epistaxis have been described. As per the series of Hoh et al. 32% had multiple aneurysms and 10% had aneurysms in a paraclinoid location. 26% of their paraclinoid aneurysms were incidental and detected with other ruptured or unruptured aneurysms, AVMs, family screening and accompanied with other syndromic disorders such as Marfan's syndrome.[20]

SPECIAL RADIOLOGICAL CONSIDERATIONS

On CT, in patients with SAH, the extent of haemorrhage is graded using Fischer's classification. Thin section CT of the clinoidal region with bone windows determines the position of the ICA, aneurysmal calcification and clinoidal erosion. An aneurysmal calcification with clinoidal erosion may predispose to an inadvertent tearing of the aneurysm during clinoid drilling.[16]

On cerebral angiography, carotid-ophthalmic, ventral wall and transitional aneurysms are better visualised on the lateral projection; superior hypophyseal and carotid cave aneurysms are better seen on anteroposterior and submentovertical projections.[16]

Since the position of the distal dural ring determines the intradural and extradural segments of the ICA (the aneurysms located proximal to the distal dural ring, being extradural, do not cause SAH), an angiographic determination of the distal dural ring may help in planning the surgical approach. Punt proposed that the origin of the ophthalmic artery may be used as a marker for the intradural ICA,[35] but the ophthalmic artery may occasionally be situated proximal to the distal dural ring. Taptas stated that the base of the anterior clinoid process on lateral views may mark the intradural ICA.[39] Oikawa et al. stated that the medial aspect of the ring was at the level of the tuberculum sellae and its lateral aspect at the level of the clinoid process.[34] However, carotid cave aneurysms may be observed below the level of the tuberculum sellae or the anterior clinoid process. Therefore, at present, there is no reliable angiographic method to determine the precise level of the distal dural ring and, therefore, the point of transition of the extradural and the intradural ICA. However, Murayama and colleagues, using three dimensional CT angiography of the paraclinoid region, have found a concavity corresponding to the distal dural ring on the paraclinoid segment of the ICA.[30]

Carotid cave aneurysms[27] and ventral wall aneurysms[32,33] are located close to each other, so it is angiographically difficult to differentiate the two from each other. A ventral wall aneurysm originates at a nonbranching point of the ICA just distal to and opposite to the ophthalmic artery origin, while a carotid cave aneurysm arises proximal to the origin of the ophthalmic artery, next to the distal dural ring and grows ventromedially into the carotid cave. According to Zhang et al. the main differentiation between the two is the finding of an angiographic axillary space between the axilla of the ICA and the anterior or anteroinferior surface of a ventral aneurysm in the lateral projection, since the neck of a ventral aneurysm arises more distally than that of a carotid cave aneurysm. This finding was absent in all carotid cave aneurysms due to their inferoposterior projection from the genu towards the axilla of the ICA.[44] Another differentiating point is that since the carotid cave lies in the 1–6 o'clock position medial to the ICA, a carotid cave aneurysm has a prominent medial projection in the AP view when compared to a ventral aneurysm.[27,44]

Differentiating between the two is important since ventral wall aneurysms can be clipped after removal of the anterior clinoid process;[32,33] while carotid cave aneurysms can only be clipped after removal of the anterior clinoid process as well as separation from the distal dural ring, mobilisation of the ophthalmic artery and dissection of the genu and axilla of the ICA.[27,44]

Intra-operative angiography has been a useful adjunct during direct surgery for paraclinoid segment aneurysms. It may reveal either a residual portion of the aneurysm after clipping or compromise of the patency of the ICA that was not easily apparent under direct microscopic vision. Thus, clip repositioning with intra-operative angiography has improved the radiological efficacy of direct surgery.

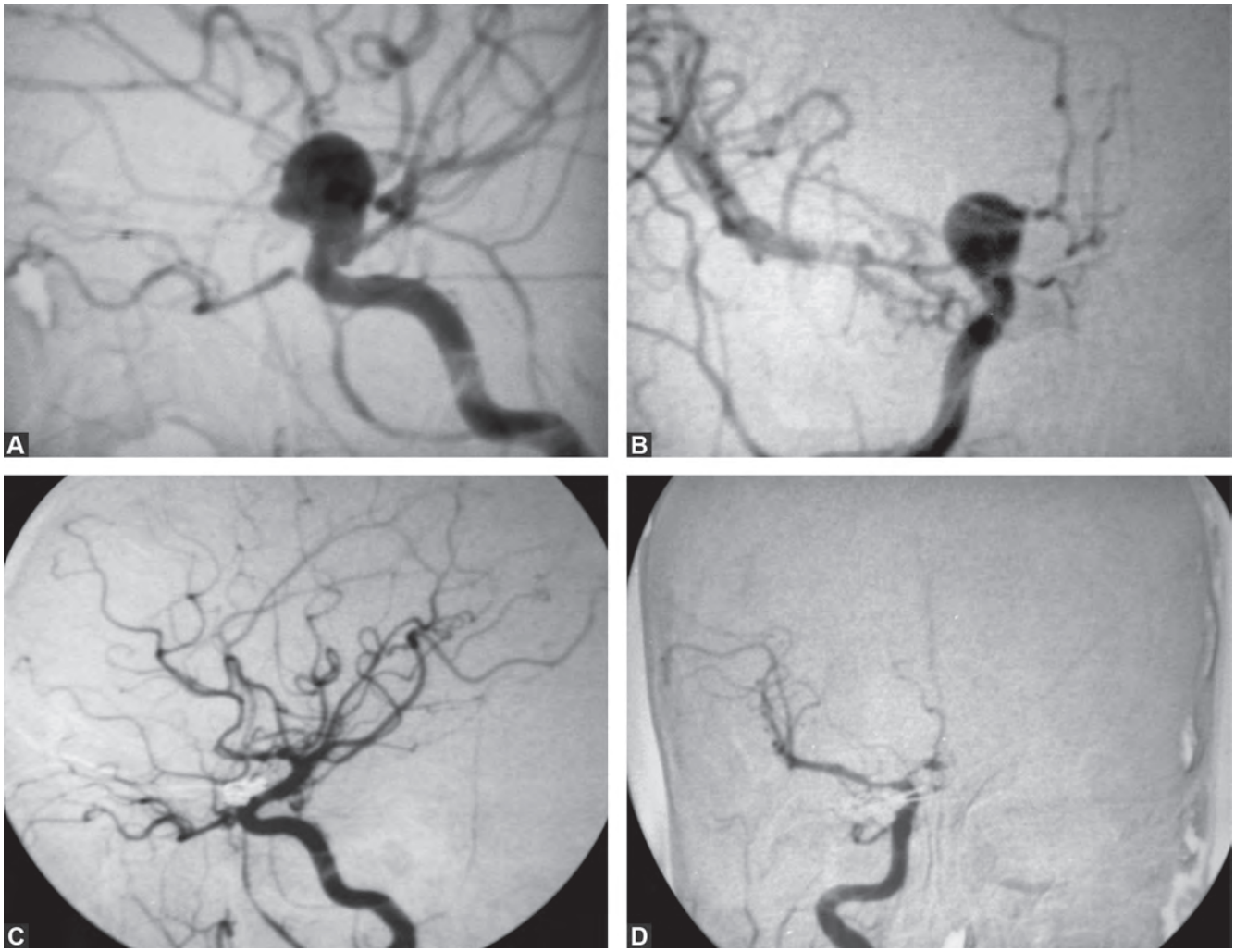
On MR imaging, the precise dimensions of an aneurysm with a thrombus may be determined. The coronal images delineate superior hypophyseal and carotid cave aneurysms. The infradiaphragmatic location of the latter is also determined on MR studies since these aneurysms can only be accessed by dividing the diaphragma sellae.[16]

Testing for collateral flow in patients with a large broad necked aneurysm before either surgery or endovascular therapy where ICA occlusion is a possible outcome: In large or giant aneurysms, the suitability of permanent ICA occlusion is determined by the balloon test occlusion (BTO) accompanied by a clinical examination that does not suggest any asymmetry of clinical signs; angiographic criterion, in which symmetry of flow in both hemispheres or in the anterior and posterior circulation throughout all phases of flow, is determined; a single photon emission computed tomography (SPECT) study, in which a decrease in perfusion during a hypotensive challenge with a mean BP 20% below the baseline is determined; and xenon computed tomography in which the symmetry of perfusion is determined.[40] In case the BTO with SPECT is well-tolerated, the ICA may be trapped. In case it is not tolerated and perfusion defects are seen on SPECT, a vascular bypass using superficial temporal to middle cerebral artery anastomosis may be required.[20,21,40]

THERAPEUTIC OPTIONS

Clip Alone

This is the ideal method of treatment since it provides a direct obliteration of the aneurysm with preservation of the carotid and ophthalmic arteries and a simultaneous decompression of the optic apparatus. Even aneurysms with a broad neck may be dealt with using a clip (Figs 4A to D, 5A to E and 6).



Figs 4A to D: (A) Lateral. (B) Anteroposterior ICA angiogram showing a carotico-opthalmic aneurysm. (C) Post-operative lateral. (D) Anteroposterior ICA angiogram showing successful aneurysm clipping

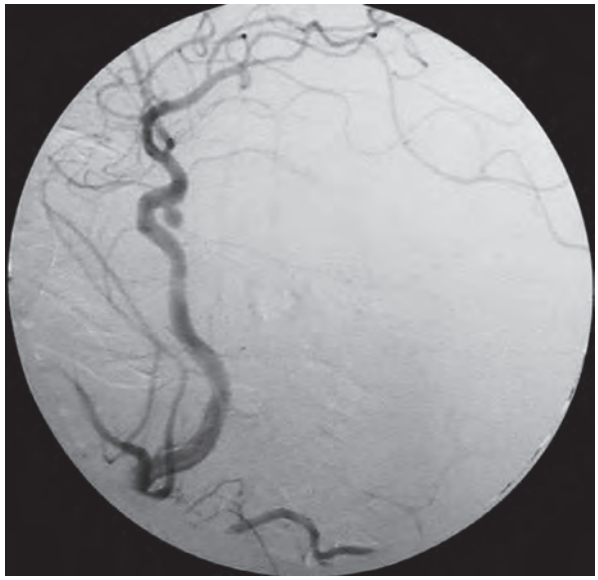


Fig. 5A: Right carotid angiogram showing a type II, ventral wall aneurysm situated opposite to the ophthalmic artery with no branch relations

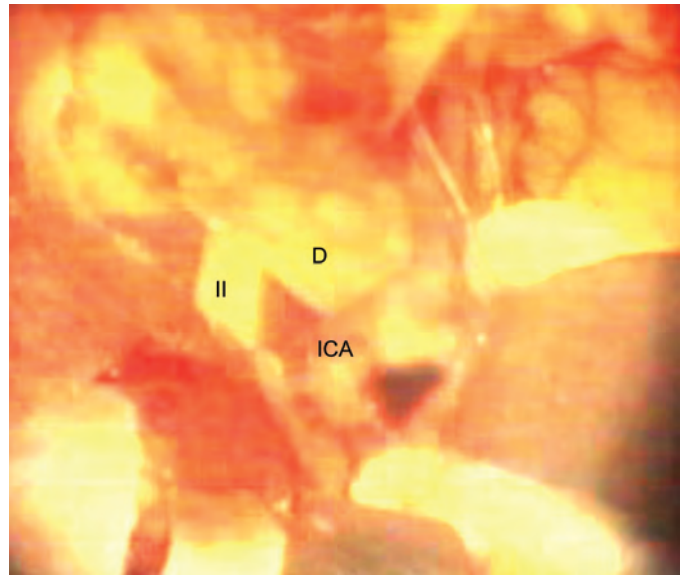


Fig. 5C: The last part of the anterior clinoid process is removed with dissectors exposing the dura (D) over the clinoidal segment of the carotid artery (ICA) and the optic nerve (II)

Ligature and Clip

The purpose of the ligature is to narrow a broad neck sufficiently to allow an easier application of the clip, but not to narrow the neck so much as to kink the parent ICA.[12]

Trapping of the ICA with or without Extracranial-Intracranial Bypass

This takes care of aneurysms with a large neck, especially involving the cavernous and clinoid carotid artery (Figs 7A to G). It is not the preferred method of treatment since cerebral ischaemia may occur after trapping of the ICA, despite a successful pre-operative BTO.

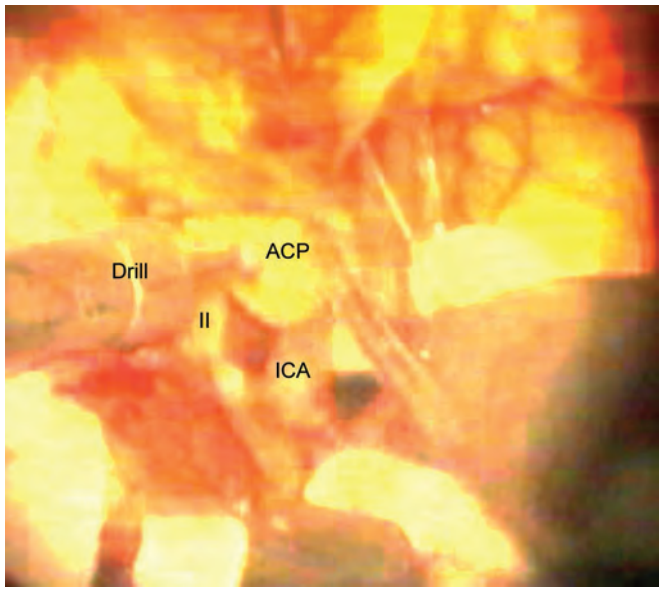


Fig. 5B: An intra-operative view showing the anterior clinoid process (ACP) being drilled. The optic nerve (II) and internal carotid artery (ICA) are exposed in the suprasellar cisterns after Sylvian fissure splitting

Circumferential Wrapping

Occasionally, in blister like aneurysms with no neck and a fragile dome, a circumferential clip graft may be applied.[12]

Cardiopulmonary Bypass with Profound Hypothermia and Circulatory Arrest

This serves as a useful adjunct to both clipping and trapping as the aneurysm neck may be identified and the fundus dissected with minimal bleeding.[12,20,21]

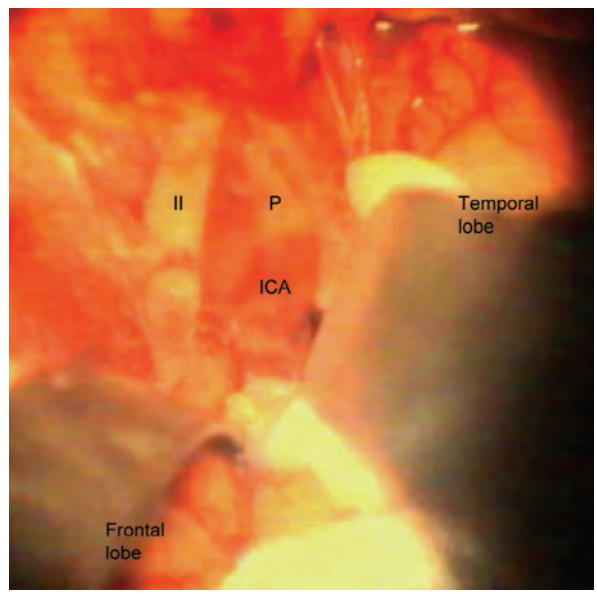


Fig. 5D: The distal dural ring and carotid collar are removed exposing the paraclinoid segment of the internal carotid artery. This was utilised both for proximal control and for achieving adequate space for the clip blades. The unroofing of the optic canal also exposes the distal optic nerve

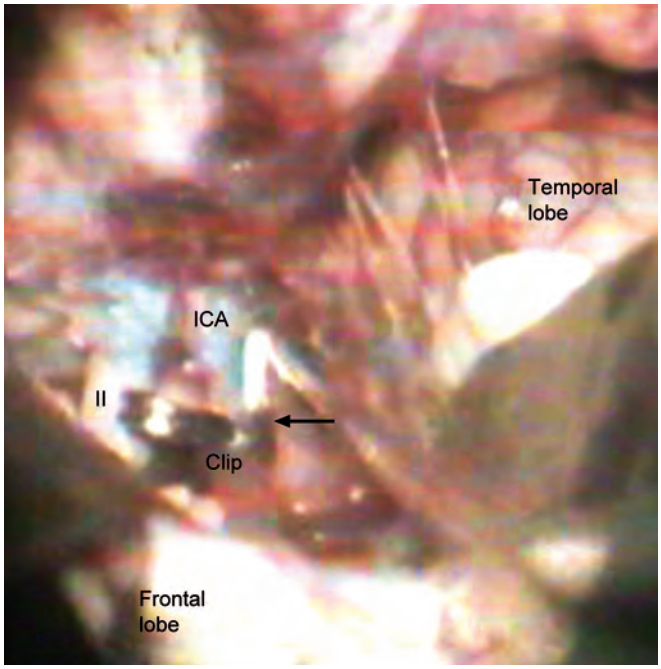


Fig. 5E: A right angled fenestrated clip applied to the aneurysm. The fenestration of the clip is looping around the clinoidal segment of the internal carotid artery

Endovascular Treatment

Since paraclinoid aneurysms are more difficult to treat surgically and have a higher surgical morbidity, endovascular treatment may have a more prominent role in their obliteration. This includes: coiling of the aneurysms with Guglielmi detachable coils while preserving the parent artery; intravascular stenting; balloons to remodel coils at the neck of the aneurysm and permanent balloon occlusion of the ICA.[20,40,42] As an adjunct to surgery for the clipping of paraclinoid aneurysms, a novel endovascular method utilised a balloon catheter with a coaxial lumen inserted via the transfemoral route as a means of proximal control, along with the provision for a simultaneous suction decompression and intra-operative angiography.[31]

Batjer and Samson have described a technique of retrograde suction decompression in clipping of large and giant paraclinoid aneurysms.[3]

Thornton et al. have estimated the amount of occlusion of the aneurysm, in terms of percentage, on follow-up angiograms after endovascular treatment as: 100%: dense coil packing with no contrast filling the aneurysm; > 95%: contrast fills a very small portion ("dog ear") at one side of the neck or within the interstices between the coils at the level of the neck only; < 95%: coil packing is less dense, contrast fills at least a small portion of the neck and there is minimal contrast filling within the interstices between the coils. Any additional filling of the aneurysm with contrast is also included in this group. Unsuccessful: no coils placed in the aneurysm.

Progression of Thrombosis

Any decrease in the amount of contrast filling at follow-up angiography.

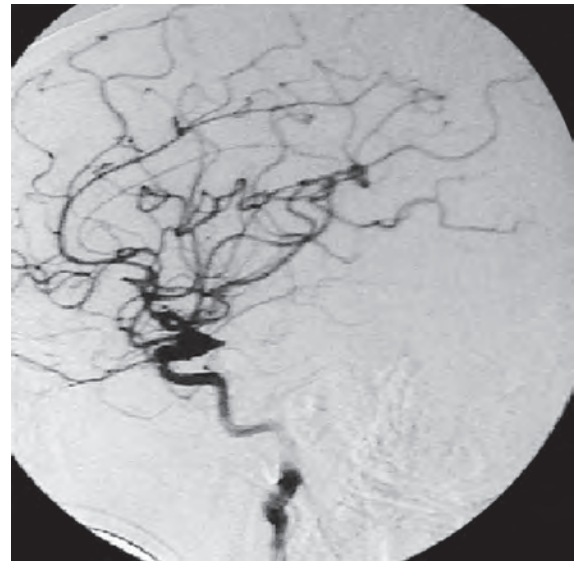


Fig. 6: Lateral carotid angiogram showing another ventral wall aneurysm with a wide neck

Refilling

Any increase in the amount of contrast filling at follow-up angiography.[40]

The main complications of endovascular coiling include coil compaction leading to refilling of the aneurysm, blockage of parent vessel, progression of aneurysm thrombosis to parent vessel or its subsequent embolisation and aneurysm rupture during the procedure.[17,22,42]

Surgical Considerations

Craniotomy

The pterional craniotomy is the standard craniotomy for paraclinoid aneurysms. A larger craniotomy, especially extending towards the midline, provides greater manoeuvrability for clip application and suction. The Sylvian fissure should be opened widely to visualise the carotid bifurcation and the proximal middle cerebral artery. However, to approach the paraclinoid area, the other craniotomies which may be considered include the ipsilateral supraorbital, subfrontal and ipsilateral frontobasal. Occasionally, contralateral approaches may be useful.[14]

Proximal Control

For proximal control of the ICA, there are several alternative strategies: (A) The common and internal carotid arteries may be exposed in the neck. However, if there is extensive collateral flow to the aneurysm, this strategy may not work; (B) The portion of the ICA between the proximal and the distal dural rings may be exposed by dividing the distal dural ring circumferentially around the ICA after the ophthalmic artery has been dissected free.[15,16] The disadvantages of this method are that it is technically demanding since the drilling and manipulation are very close to the aneurysm sac. The carotid artery is thin and within bony confines and, therefore, is difficult to occlude. There may be substantial cavernous

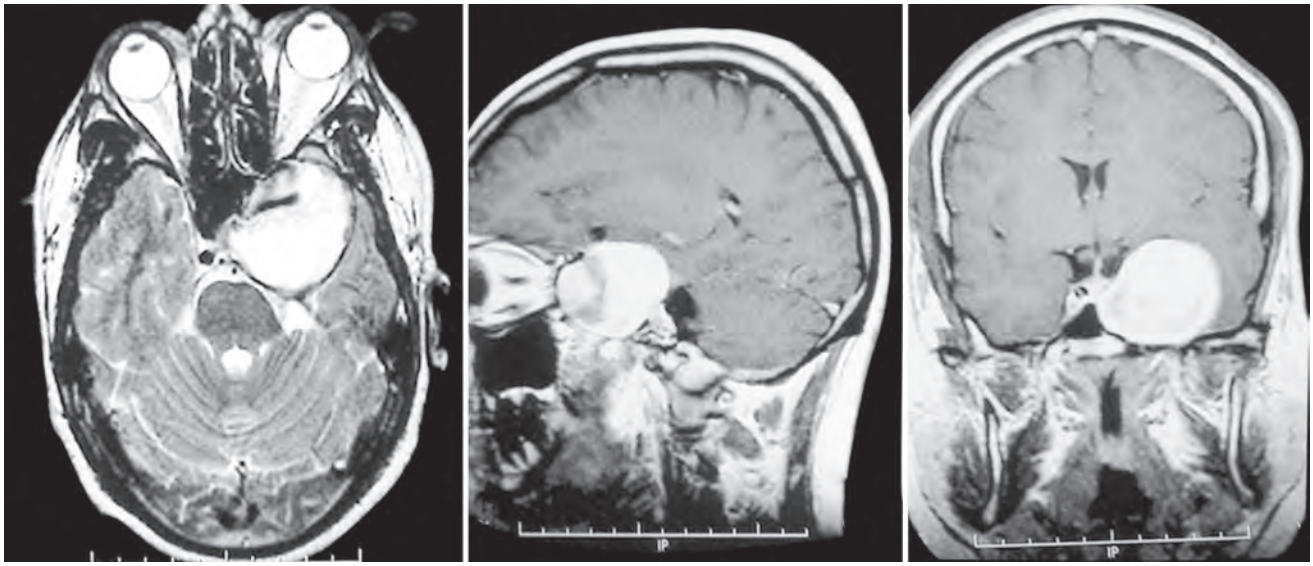


Fig. 7A: Axial T2 and sagittal and coronal T1-weighted MR images showing a giant cavernous and paraclinoid transitional aneurysm

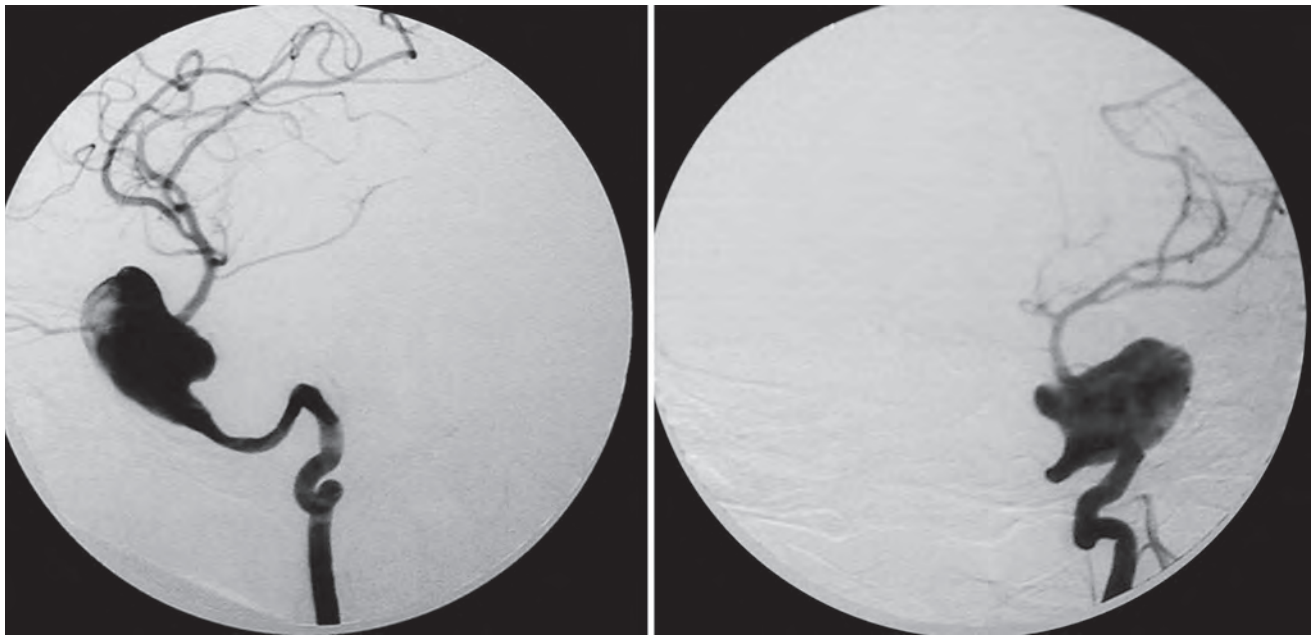


Fig. 7B: Lateral and oblique views of a left carotid angiogram showing a giant aneurysm that is occupying the cavernous, clinoidal and supraclinoidal segments of the internal carotid artery. The origin of the ophthalmic artery is from the dome of the aneurysm

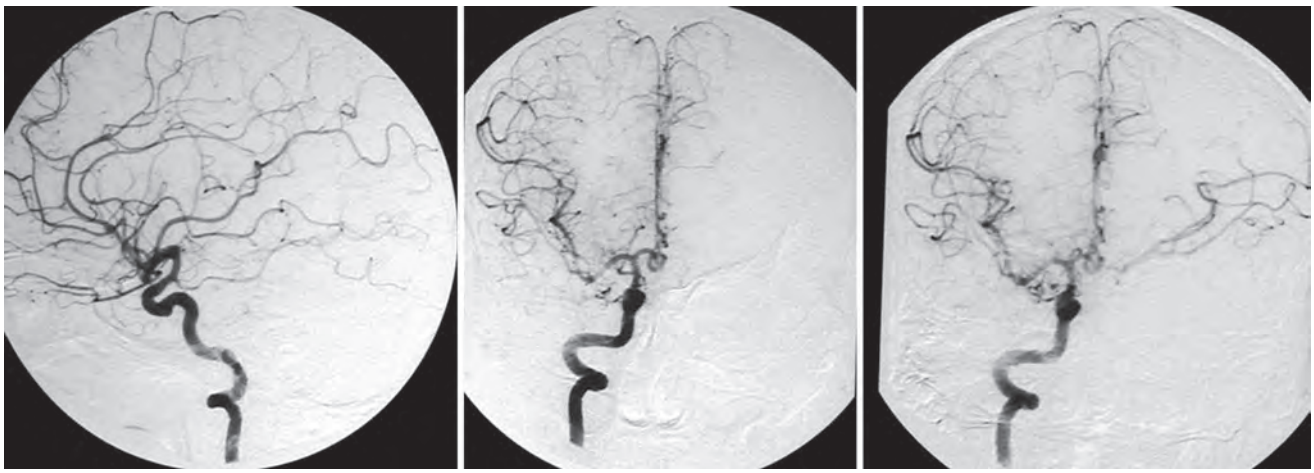


Fig. 7C: Lateral, anteroposterior and cross-compression studies showing a good cross-flow of circulation from the right to the left side. The patient also withstood 20 minutes of balloon test occlusion of the left internal carotid artery

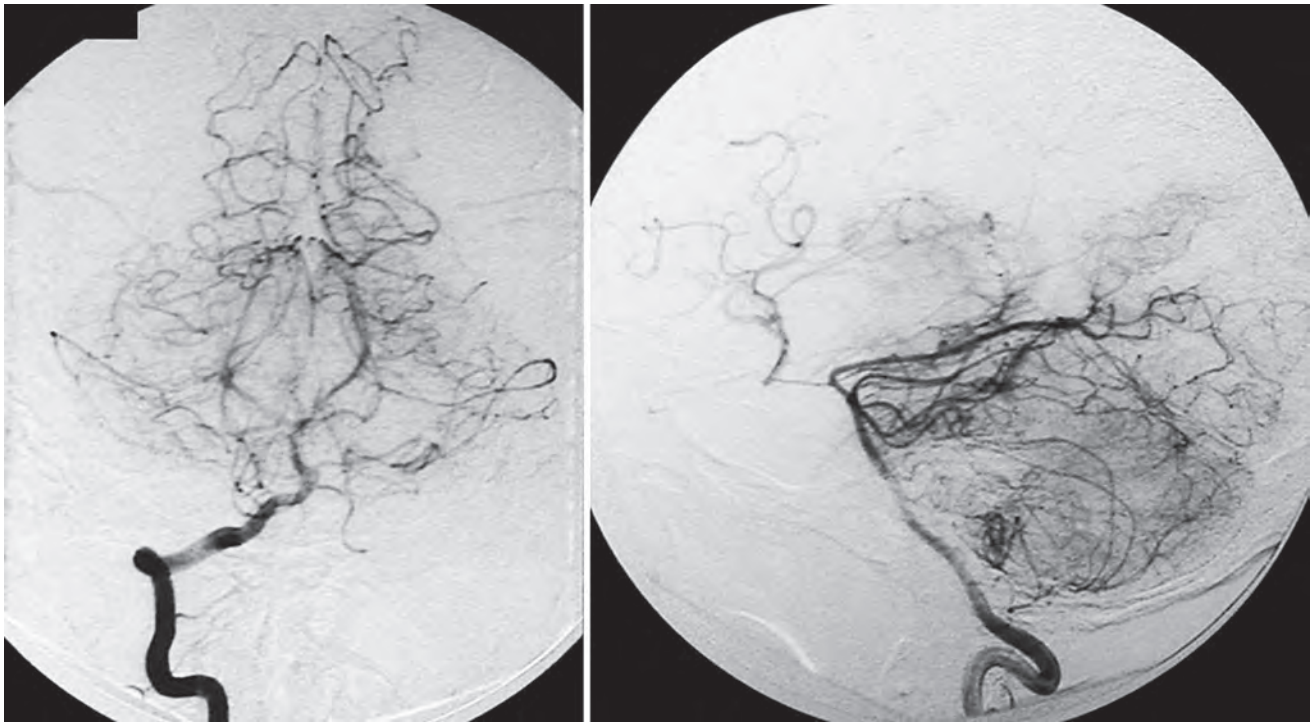


Fig. 7D: The verterbral angiogram also shows a good cross-flow to the anterior circulation through the posterior communicating artery

sinus bleeding; (C) The cavernous carotid artery may be exposed by retracting the temporal lobe laterally and incising the dural sleeve medially from the point of entry of the oculomotor nerve into the cavernous sinus up to the superior orbital fissure. The cavernous sinus is opened to extend the exposure of the ICA from the distal dural ring to the posterior clinoid process. The cavernous sinus bleeding is controlled by packing with surgicel. Within the cavernous sinus, injury to the VI nerve is prevented by remaining close to the artery, especially on its lateral aspect;[15,16] (D) Retrograde suction decompression either by the endovascular route by passing a non-detachable balloon transfemorally into the distal ICA to temporarily occlude its lumen; or, by exposing the carotid bifurcation in the neck, occluding the common and external carotid artery and applying a retrograde suction through the catheterised ICA.[11,20,31] However, in large aneurysms, the dome of the aneurysm does not collapse until it has been dissected from the surrounding structures and, (E) The petrous carotid artery may also be used for proximal control. This is located extradurally deep to Glasscock's triangle in the middle cranial fossa. The boundaries of this triangle are the groove of the greater superficial petrosal nerve coursing in an anteromedial direction in the floor of the middle cranial fossa; the mandibular nerve exiting through the foramen ovale; and, the line joining the foramen spinosum to the arcuate eminence. Exposure of the petrous ICA starts 5 mm medial to the foramen spinosum, deep and just medial to the location of the divided greater superficial

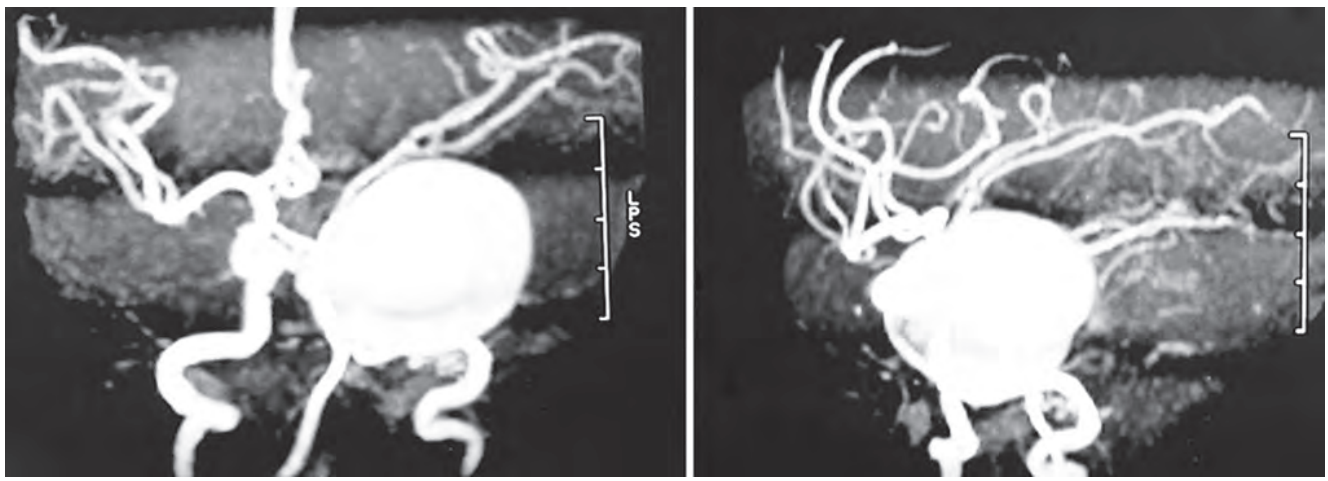


Fig. 7E: Anteroposterior and lateral images of magnetic resonance angiography (MRA) showing the giant aneurysm

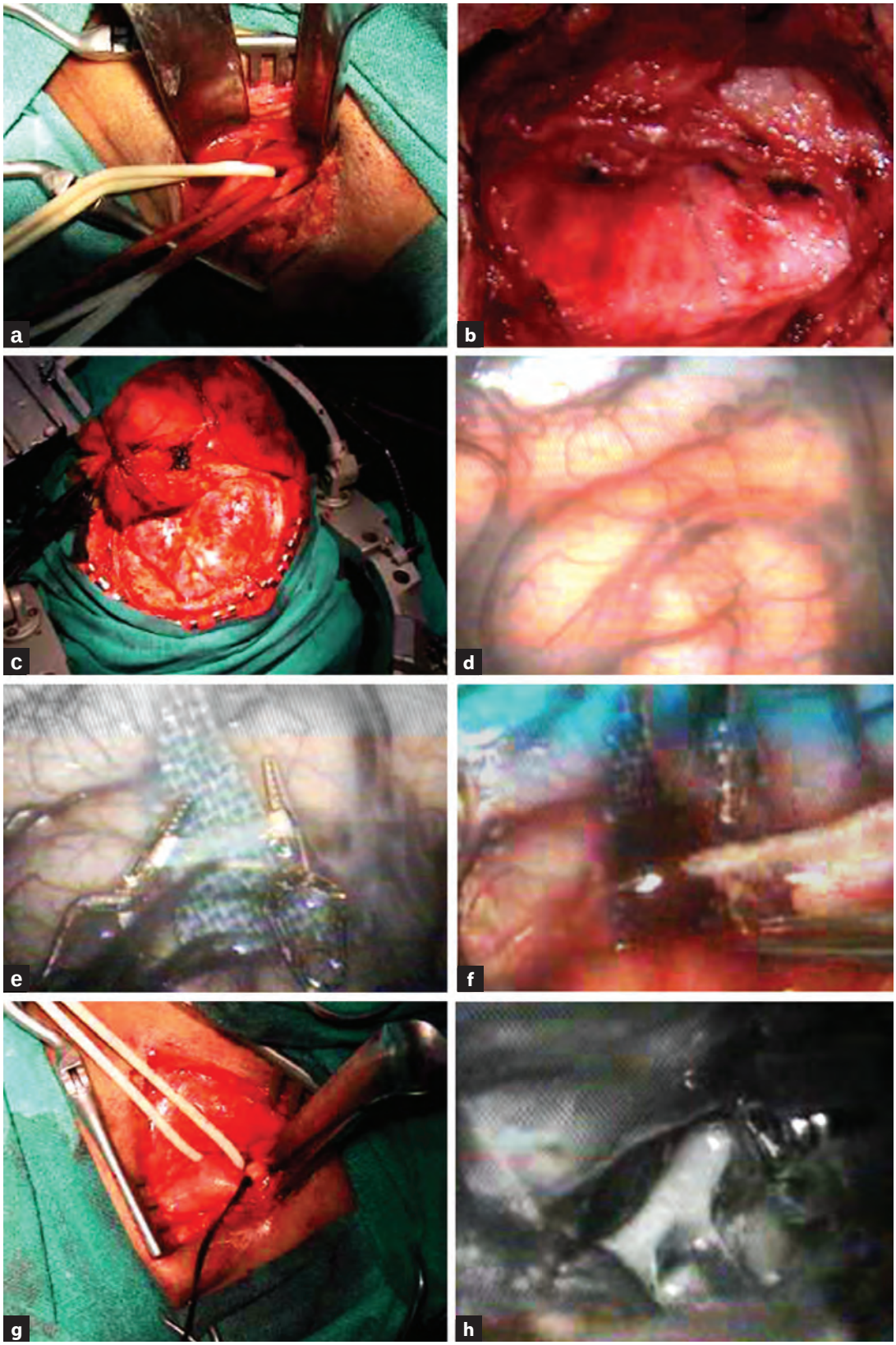


Fig. 7F (a to h): Despite a very good cross-flow to the left internal carotid artery, additional flow was also established by a superficial temporal to middle cerebral artery (STA-MCA) bypass. The operative steps of the STA-MCA bypass and left internal carotid artery trapping are shown: (a) Proximal control of the internal carotid artery in the neck; (b) Harvesting of the superficial temporal artery; (c) Performing the frontotemporal craniotomy and exposing the frontal and temporal lobes; (d) Harvesting the opercular branch of the middle cerebral artery; (e) Clamping of this artery using temporary clips, keeping it patent with heparinised saline and opening it on its side; (f) End-to-side anastomosis of this vessel with the frontal branch of the superficial temporal artery; (g) Ligating the internal carotid artery in the neck, and (h) Trapping the internal carotid artery proximal to the anterior communicating artery

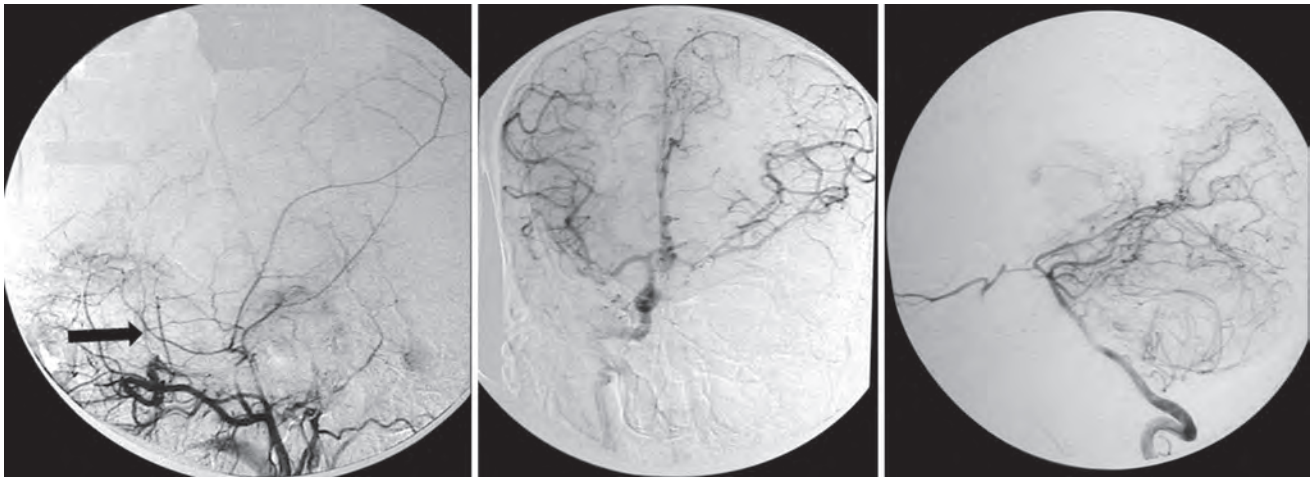


Fig. 7G: The post-operative left external carotid angiogram, anteroposterior images of right carotid angiogram and vertebral angiograms showing the supply from the external carotid artery through the bypass, and the maintenance of a good cross-flow

petrosal nerve. An extra-arterial Fogarty balloon catheter may be inflated in the carotid canal for proximal control. However, traction on the superficial petrosal nerve may cause VII nerve paresis; injury to the petrous ICA may occur, if its bony covering is not adequate; and, hearing may be lost if the drilling proceeds posteriorly towards the arcuate eminence (Fig. 8).[43]

If, despite proximal control, the sac of the aneurysm still remains turgid, then it may reflect a substantial inflow from the posterior communicating artery which requires a separate temporary clip; or, it may represent a retrograde flow to the aneurysm from the ophthalmic artery via its extensive external carotid anastomosis that may require an additional temporary occlusion of the external carotid artery. However, this occlusion, if prolonged, increases the risk of retinal ischaemia.[15]

Untethering of the Optic Nerve

One crucial feature of the approach is the unroofing of the optic canal and mobilisation of the optic nerve at its entrance to the optic canal. The dura propria over the optic nerve is incised in the centre along the long axis of the optic nerve with a hook knife; then both flaps of the falciform ligament are mobilised laterally and medially to provide an additional length of 3–10 mm of untethered optic nerve; finally, further deroofing of the optic nerve is carried out by drilling the osseous optic canal, the anterior clinoid process and occasionally parts of the tuberculum sellae (the latter procedure is applicable for a medially directed aneurysm or for a contralateral approach to carotid-ophthalmic aneurysms).[14,20]

Anterior Clinoidectomy

Removal of the anterior clinoid process along with the roof of the optic canal provides decompression of the optic nerve, provision for proximal carotid artery control and ensures that the tips of the aneurysm clips extend past the aneurysm to ensure complete obliteration of the aneurysm neck.[2,10,16] For large aneurysms and, especially

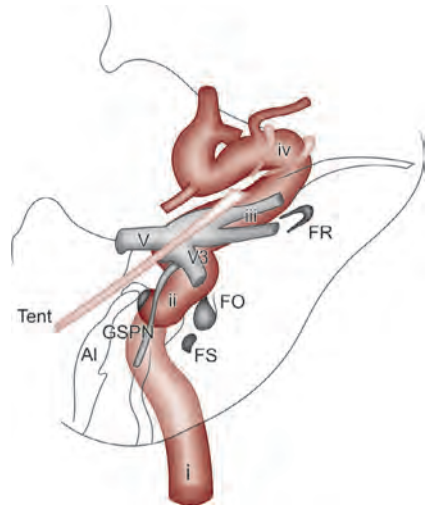


Fig. 8: Proximal control of the ICA may be obtained in the neck; (i) in the Glasscock's triangle (ii) the boundaries of which are formed by the groove of the greater superficial petrosal nerve (GSPN), the mandibular nerve (V3), and the line joining the foramen spinosum (FS) to the arcuate eminence (AE); in the cavernous sinus (iii) by retracting the temporal lobe laterally and incising the dural sleeve medially from the point of entry of the oculomotor nerve into the cavernous sinus up to the superior orbital fissure; and in the portion of the ICA between the proximal and the distal dural rings (iv). The foramen ovale and rotundum are represented as FO and FR, respectively

carotico-ophthalmic aneurysms that point dorsally, an intradural rather than extradural drilling of the anterior clinoid process is safer since it permits direct observation of the position of the aneurysm and the optic nerve during the drilling. Removal of the anterior clinoid process allows for at least 6 mm more exposure of the proximal ICA without entering the true cavernous sinus (see Figs 2A to C, 5A to F).[15,16,26]

Before starting the drilling, the anterior clinoid process is palpated with a dissector to determine whether or not it has been eroded, and also to assess the proximity of the optic nerve. The contents of the superior orbital

fissure are on the inferolateral aspect of the anterior clinoid process; the genu of the ICA is underneath and the optic nerve is medial to the anterior clinoid. The dura over the anterior clinoid process can be turned down as a flap prior to drilling or the flap can be completely coagulated to leave the bone exposed. A diamond burr is used to core out the centre of the anterior clinoid, to expose the optic nerve dural sheath and to resect the optic strut. Then a dissector is utilised to dissect out the residual shell of the anterior clinoid from the carotid artery and the cavernous sinus.[15] Bleeding from the bone can be controlled with bone wax. Removal of the anterior clinoid process may cause post-operative CSF leak, especially when the anterior clinoid is well-pneumatised and communicates with the ethmoidal sinuses. Bone wax should be applied to the open sinuses to obliterate any potential opening in them.[10,15,16]

Dural Ring Division

After removal of the clinoid process, the dural collar around the ICA is opened by slitting the lateral edge of the optic nerve dural sleeve using sharp dissection. This exposes the cave portion of the carotid artery and facilitates negotiation of the distal tips of the aneurysm clips beyond the neck of the aneurysm in order to ensure a proper clipping (see Fig. 2C).[15,36]

Dissection

Dissection of the aneurysm should not be done till the clinoid process has been removed and the distal dural ring has been opened. After the clinoidectomy, the arachnoidal dissection around the aneurysm and the branches of the ICA is performed and the ophthalmic artery identified. The ICA branches and the perforators in close proximity to the aneurysm are dissected away from it. This may be facilitated by a gentle temporary deflection of the aneurysm sac. In unruptured aneurysms, the dome of the aneurysm may be dissected from the surrounding adhesions to promote its collapse. In order to avoid traction of the optic apparatus, the aneurysm sac is dissected off from the optic nerve and chiasma before it is completely collapsed.[15,16]

Clipping

For clipping these aneurysms, the clip blades must assume a path parallel to the parent vessel. Long straight, side angled or angled fenestrated clips may be required to secure these aneurysms (with the carotid artery placed within the clip fenestration). The clip should be long enough to completely cover the neck but not to impinge upon the ophthalmic, superior hypophyseal, posterior communicating or anterior choroidal arteries.[6,14,15,16]

For aneurysms with a large neck, clips may have to be applied in a tandem fashion (Fig. 9). If the sac is large, the closing force of the clips may not be sufficient to keep the neck of the aneurysm obliterated. This may require fenestrated straight clips placed perpendicular to the tandem clips and the long axis of the ICA. In case of a long neck, neck shortening may be performed using bipolar coagulation with constant irrigation. When multiple tandem clips are being used, care should be taken that the pulsations of the sac do not force the clips down against the parent vessel, thus obliterating its lumen. Care should also be taken to see that the optic nerve is not deflected after clip placement.[15,16,36] In heavily calcified or atherosclerotic aneurysms, the clip should be placed slightly away from the neck and closer to the fundus in order to prevent rupture of the vessel wall.[16]

Accessing Bilateral Carotico-ophthalmic Aneurysms via the Same Approach

If bilateral carotico-ophthalmic aneurysms are present, after clipping the ipsilateral aneurysm, consideration for securing the contralateral aneurysm may be given only if: (1) the contralateral aneurysm is unruptured, since to obtain proximal control from the contralateral approach is difficult; (2) the aneurysm is superiorly or medially directed so that it can be accessed under the contralateral optic nerve; (3) during its expansion, the aneurysm displaces the optic nerve superolaterally and the chiasma superiorly; (4) the aneurysm is small so that only minimal dissection is required and, (5) some drilling of the tuberculum sellae is performed to completely expose the aneurysm.[14,20]

The limitations of the contralateral approach include the danger of visual apparatus damage while working through the narrow corridor between the optic nerves; the danger of opening the sphenoid sinus during drilling of the tuberculum sellae; the difficulty in opening of the optic canal and in the removal of the optic strut from the contralateral side; and the lack of proximal control of the ICA by the contralateral approach.

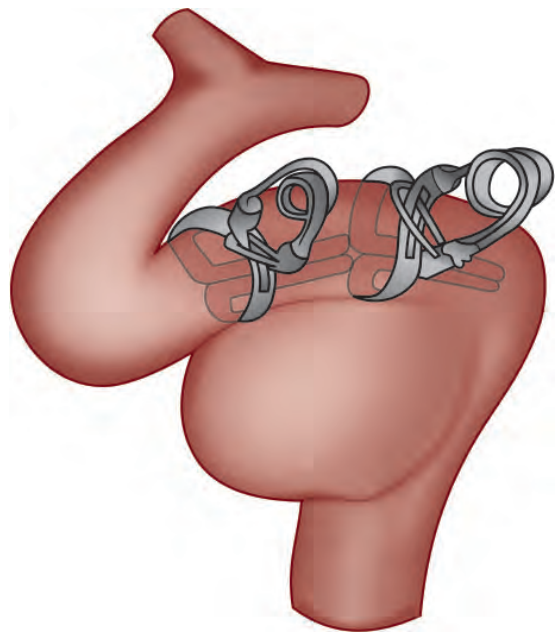


Fig. 9: Clipping of a transitional aneurysm using multiple fenestrated clips in tandem

Precautions during Surgery

Prevention of Optic Nerve Injury

While unroofing the optic canal, the dura covering the optic nerve must not be disrupted by the drill. The field is continuously irrigated using saline in order to avoid thermal injury to the optic nerve. The artery may be retracted laterally after its complete exposure and extensive mobilisation in order to access the carotid-optic space, and a medial exposure of the optic nerve must be avoided. Before incising the distal dural ring, the ophthalmic artery must be clearly identified. The microvasculature of the optic nerve must be meticulously preserved by keeping its pial covering intact during the opening of the dura propria.[16]

Avoidance of Cerebrospinal Fluid Rhinorrhoea

The frontal sinus may be opened during the craniotomy. The sphenoidal and posterior ethmoidal sinuses may be opened during the anterior clinoid resection. Both must be properly sealed using bone wax.[10,32,33]

Avoidance of Arterial Lumen Compromise during Aneurysm Clipping

While placing the clips tangential to the ICA, care should be taken to see that the lumen of the vessel or one of its main branches or perforators is not compromised. A Doppler ultrasound or intra-operative angiography may be used to ensure the patency of vessels and the requirement for readjustment of clips.[15] In case ICA trapping is done, a saphenous vein or superficial temporal to middle cerebral bypass may be performed to prevent brain ischaemia.

Outcome

During the management of paraclinoid aneurysms, the surgical complications associated with permanent morbidity include visual deficits (approximately 3%), ICA occlusion (approximately 2%) and embolic stroke (approximately 1%). The endovascular procedures are associated with an embolic stroke rate of approximately 2.5%, and an overall immediate morbidity rate related to the GDC procedure of approximately 9% (aneurysm perforation, unintentional parent artery occlusion and embolic stroke). The overwhelming cause of morbidity and mortality in both the surgical and the endovascular groups is vasospasm-related ischaemia in patients with SAH, which may be managed with Triple H therapy, intra-arterial papavarine infusion and angioplasty.[17,22,42]

For successful management of paraclinoid aneurysms, the following are essential requirements:

- An understanding of the three dimensional anatomy of the paraclinoid region and the radiological assessment of the ICA and the aneurysm and the surrounding structures.
- The acquisition of the surgical skills for high speed drilling close to the aneurysm, drilling the anterior clinoid process, controlling the proximal ICA, mobilisation of the optic nerve, dissection of the perforating vessels, application of various complex clip configurations and the utilisation of adjunctive measures like cerebral protection and proximal ICA control.
- The development of the capability for alternative therapeutic strategies, like endovascular procedures, that can preserve the arterial lumen and provide a lasting repair, using stents, coils or both.

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80 Internal Carotid Bifurcation Aneurysms

Mathuriya SN

INTRODUCTION

Non-traumatic subarachnoid haemorrhage (SAH) accounts for 5–10% of all strokes. The overall worldwide incidence of SAH is 1.1–96/100,000 population, the average being 10.5 as reported in various studies. The lowest incidence is in the Middle East, and the highest in Scandinavian countries, more so in Finland.[2] In the Indian population it is somewhere in between. A very low incidence was reported in India in the earlier years.[11,28] There is a female preponderance of 1.3–1.6. The incidence of aneurysms increases with age, and it plateaus by the fourth decade. Internal carotid bifurcation aneurysms (ICBA) constitute the main group in children (26–29.5%).[20] A familial association of SAH with intracranial aneurysms has been described. Internal carotid artery (ICA) aneurysms can be classified into seven groups based on the site of origin, wall morphology, and clinical and surgical behaviour: (a) ICA extracranial, (b) ICA petrous and ICA cavernous, (c) ICA ophthalmic, (d) ICA wall, (e) ICA-PCoA (f) ICA-AChA and (g) ICA bifurcation.[18]

Arterial bifurcations are sites of maximal haemodynamic stress, where cerebral aneurysms commonly develop. In ICBA, the neck may not necessarily exist exactly at the ICA bifurcation and it often deviates slightly to the M1 or A1 side.[27]

Most of the aneurysmal necks deviate to the side of the anterior cerebral artery (ACA). Aneurysms tend to arise at the junction of the ICA and the A1 segment of the ACA rather than at the junction of the ICA and the M1.[27]

ICB aneurysms constitute 5% (2–9%)[18] of all intracranial aneurysms. This forms 7.9% in our series. There is a male predominance.[18,20] The ICA bifurcation is the commonest site in children, and they have a better outcome than their adult counterparts. ICBA represented 18% of all ruptured intracranial aneurysms before the age of 30 years.[18]

Amongst ruptured ICA aneurysms, in the author's series, 16% were at the bifurcation of the ICA. These are relatively uncommon and frequently rupture at a younger age compared to others.[14,38] Around half of these aneurysms rupture, of which 50% are smaller than 7 mm.[18] These have an embryogenetic factor responsible for their origin.[27] Mean age of presentation at the time of rupture is 41 years. In the younger age group (less than 20 years of age) these constitute more than 40% of all intracranial aneurysms. The probable risk factor could be arterial wall defects and wider angle of the ICA bifurcation. Around 7% of ICA bifurcation aneurysms are giant. Multiple aneurysms are seen in 43% of patients and the most frequent site of another aneurysm is on the MCA. Bilateral ICA bifurcation aneurysms occur in 6%.[28] Rebleeding occurs in 30–33% before clipping. Angiographic vasospasm is present in 33–63% of ICBA.[14,16,24,25,29,35]

No clinical symptomatology is specific for ICBA. SAH is seen in the anterior cisterns in 92% of patients on CT scan.[9] There may be an intracerebral haematoma (ICH) in the orbitofrontal gyrus (9.5–20%).[16,18,25,35] Fluid attenuated inversion recovery (FLAIR) sequence of MRI has recently been shown to be effective for detecting SAH in the subacute period when CT sensitivity decreases. Lumbar puncture (LP) detects blood in 98% of SAH patients. Uncommonly, when the aneurysm grows to a large size, it can cause pressure on the medial temporal lobe leading on to seizures. Sometimes, if the aneurysm is totally medially directed, it can compress the anterior third ventricle leading to hydrocephalus. ICBA are of median size of 8 mm (range 2–60 mm) in 52% and are associated with ICH in 15–19% and SDH 1–2%.[28] The ICH, when present, is located in the frontal lobe in 73%. Intraventricular haemorrhage leads to a dismal prognosis.

Digital subtraction angiography (DSA) confirms or excludes an aneurysm. Around 2–5% of aneurysms which are missed on the initial study due to vasospasm are detected on repeat DSA. Magnetic resonance angiography (MRA) can effectively demonstrate large aneurysms. CT angiography (CTA) reveals most aneurysms larger than 2–3 mm. This has a high diagnostic accuracy with false negative results in very small aneurysms. Around 99% of ruptured aneurysms of 3–4 mm can be recognised by CTA.[6,32]

The CTA also visualises the neck from all sides and the exact relation of branches to the neck and fundus.[20] It delineates details of the fundus, neck and relations to the branches and, sometimes, this proves a better investigation than DSA in large/giant complex aneurysms (as far as visualisation of large branching vessels is concerned, but not the perforators). The CTA lacks visualisation of

dynamicity of the circulation and visualisation of perforators.[32] It is mandatory to preserve flow in all the perforators surrounding or adherent to the aneurysm dome. A detailed pre-operative knowledge of the presence and extent of atherosclerotic plaques in the parent artery, the aneurysm base and presence of associated aneurysms is required. A mental spatial view of the angioarchitecture of the ICA bifurcation and its relation to the surrounding structures is formulated, which is necessary for proper orientation during the microsurgical dissection. CTA does miss small incidental aneurysms. CTA, being a non-dynamic study, provides no information regarding collateral circulation, hence, on many occasions it may not be used as the only imaging modality for ICBA (Figs 1 and 2).

Conventional four vessel angiography, DSA or 3D DSA are the diagnostic imaging methods. Many projections and angles, e.g. anteroposterior, lateral, forward oblique, reverse oblique and basal views, are used. These are to delineate the aneurysm sac, its direction, projection, neck size configuration and straddling on to initial M1/A1, perforators and their relation to neck/sac, status of vasospasm, extent of cross circulation and any other associated aneurysms.[33] The 3D DSA provides not only 3D visualisation of the endoluminal image, but also provides most precise correlation between rotational images and actual findings at surgery (Figs 3 and 4).[33] For intra-operative navigation, 3D CTA and/or DSA should be rotated to illustrate (a) the angioarchitecture of the ICA bifurcation and its relation to the skull base, (b) projection of the ICBA dome and its relationship to the A1 and M1 segments and (c) the probable site of rupture. Sometimes, in giant complex partially thrombosed aneurysms, it may not be possible to obtain all the details particularly involvement/take off of M1 and A1 and these may be from the aneurysm sac itself. For this purpose 3D CTA may be a useful modality particularly the angioscopic views.[32]

ANATOMY

The ICA, after emerging from the cavernous sinus, traverses in the carotid cistern and gives off the ophthalmic (Oph. A.), superior hypophyseal (SHAs.), posterior communicating (P.com) and anterior choroidal (Ach) branches. The P.com can be absent altogether in up to 14% of cases. The Ach may arise as a single trunk or as multiple vessels from the posterolateral surface of the ICA. Preservation of the Ach during different steps of dissection for ICBA or temporary clipping is

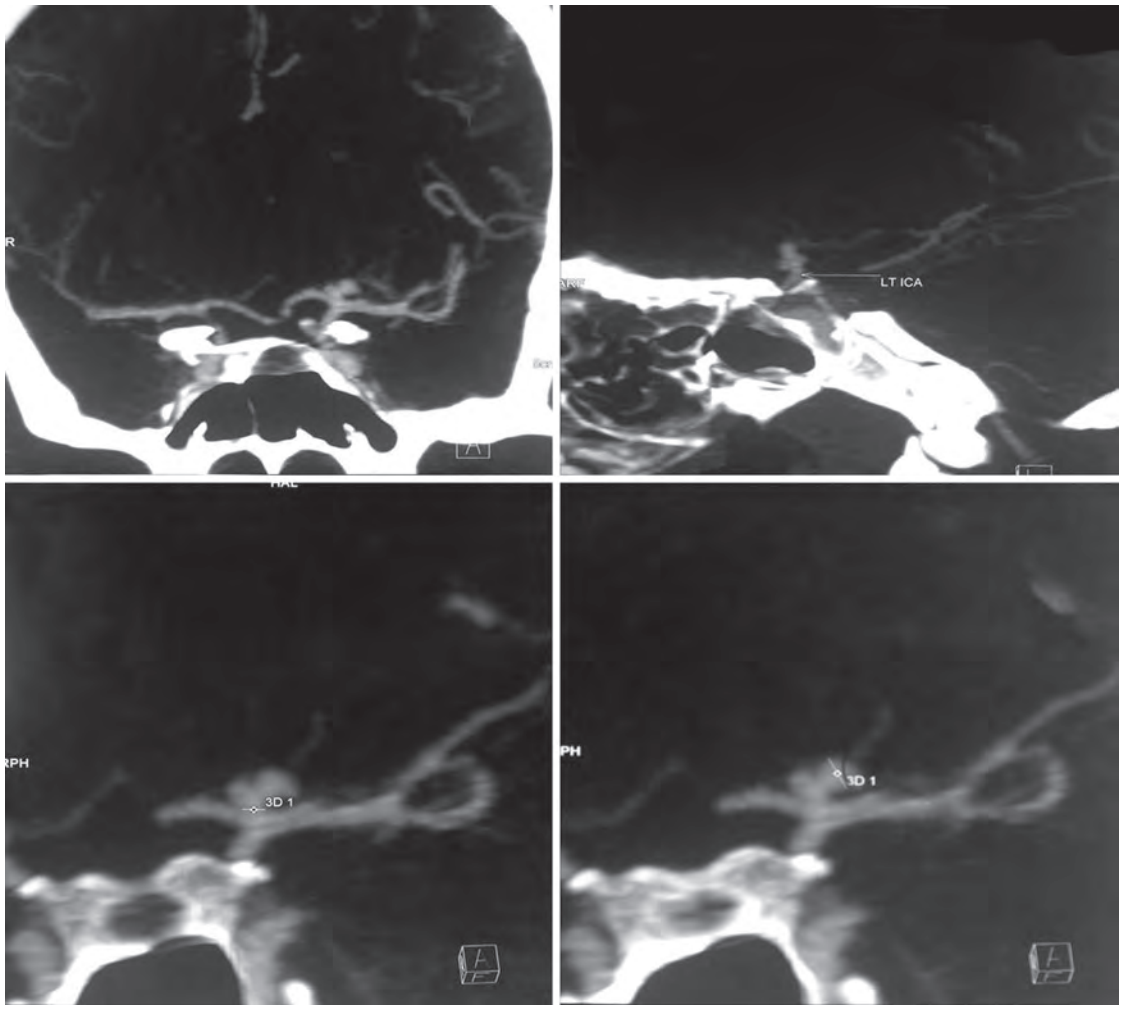

Fig. 1: CTA showing bilobed ICBA

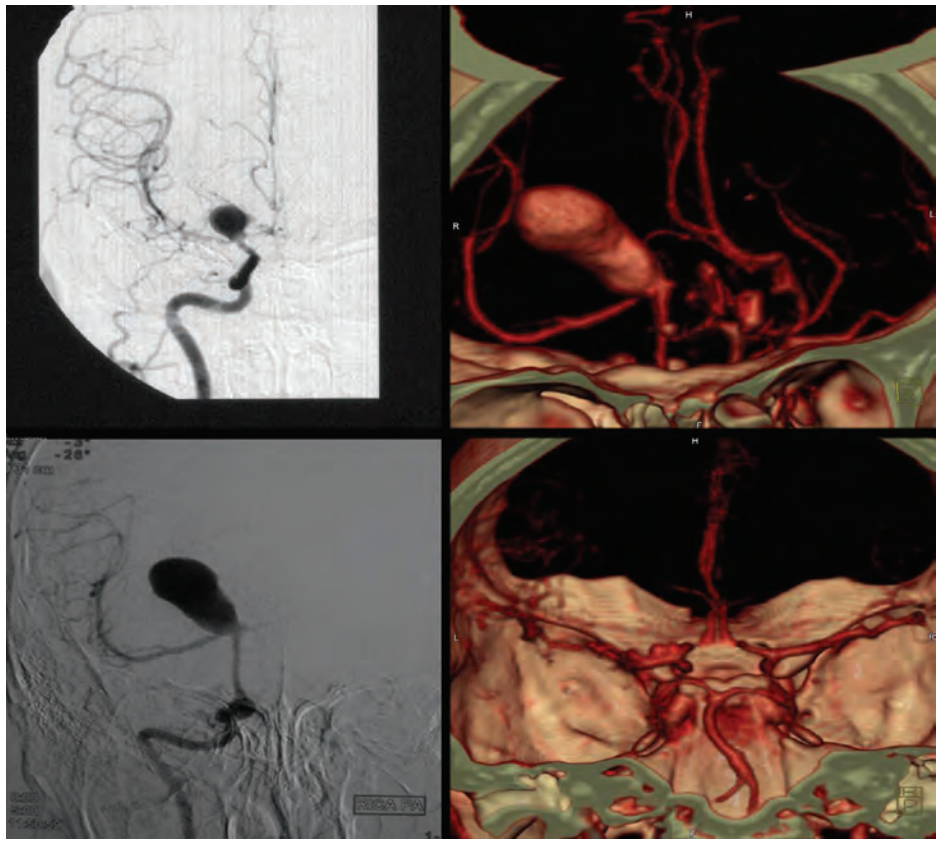

Fig. 2: CTA and DSA showing a large left ICBA

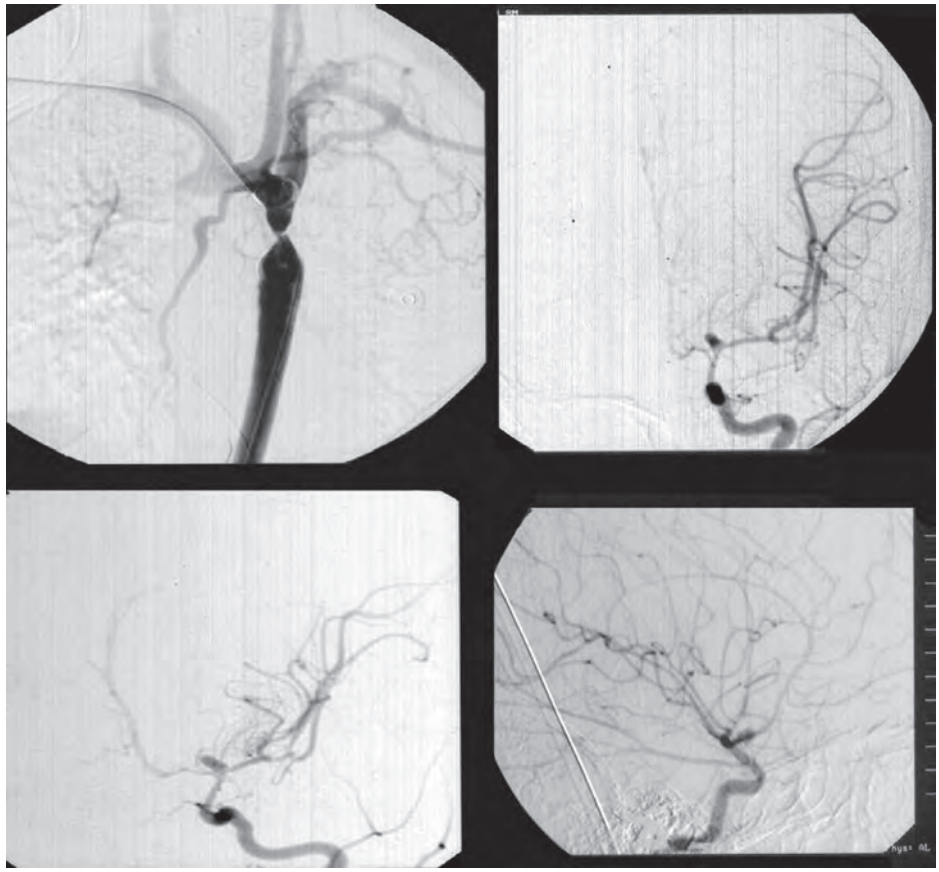

Fig. 3: DSA showing coarctation of aorta and left ICBA

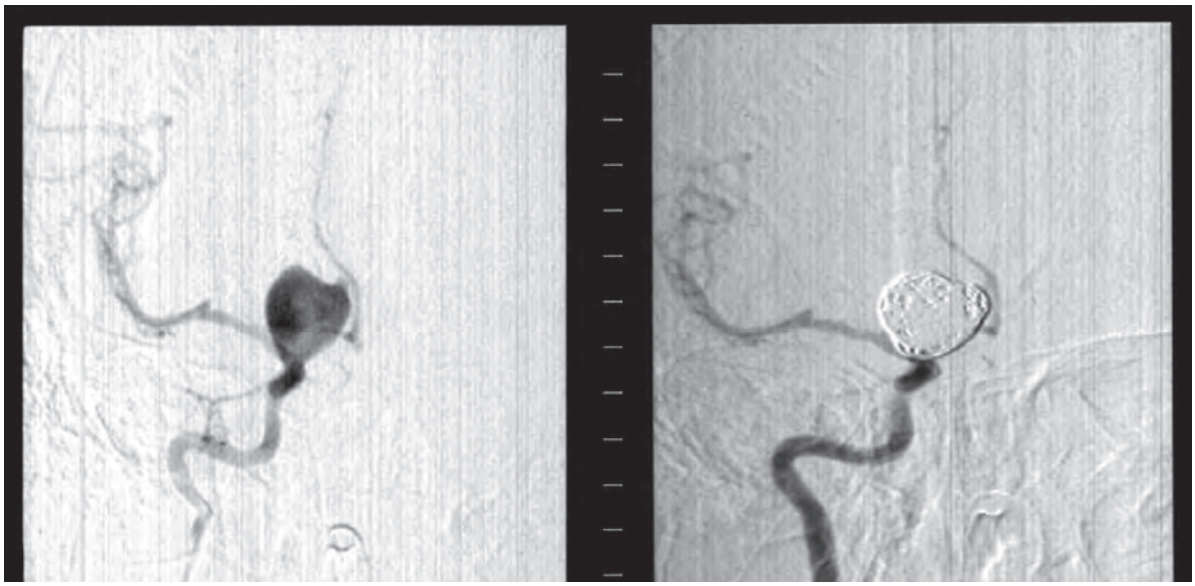

Fig. 4: DSA—large right ICBA—coiled

of paramount importance. After its origin in the carotid cistern, the Ach enters the crural cistern with a postero-medial course and is often found behind the ICA bifurcation. The Ach traverses lateral and inferior to the optic tract, passes through the wing of the ambient cistern to enter the choroidal fissure. Uncal arteries usually originate distal to the Ach, from the very proximal part of the MCA, from the anterior wall of the ICA 3–5 mm proximal to its bifurcation or rarely from the proximal A1 segment. Infrequently, up to 3 small perforators arise from the posterior wall of the ICA and pass to: (a) the optic tract, (b) the premammillary part of the floor of the third ventricle, (c) the optic chiasm and (d) the infundibulum. They rarely enter the anterior/posterior perforated substance (APS/PPS). The perforating branches of the choroidal segment (average, 4; range, 1–9) arise from the posterior half of the ICA wall, pass upward and terminate in: (a) the APS, (b) the optic tract and (c) the uncus. Some of these perforators may also arise from the ICA bifurcation. For temporary clipping in ICBA, a comprehensive knowledge of the possible sites of origin and trajectories of these small branches and perforators is of great utility and safety.[28,37] The vessel then passes postero–supero-laterally and bifurcates. The calibre, direction and tortuosity of the vessel vary, as also the length. The bifurcation can be comparatively anterior or deep. The ICB is the deepest portion of the anterior part of the circle of Willis. This usually lies lateral to the optic chiasm, inferior to the APS and at the medial most end of the Sylvian fissure. ICBAs point upwards in the direction of the long axis of the prebifurcation segment of the ICA towards the APS.[8] In case of a long ICA, the ICB may lie in the Sylvian cistern. The APS is bounded by the olfactory trigone, optic tract and uncus. This triangular field of grey matter is studded with entry sites of perforating vessels. These vessels are known to arise from M1, A1, recurrent artery of Heubner (RAH), P.com and Ach.[8] The ICB lies at the convergence of the cisterns of the anterior and middle cranial fossa.[8,20]

Arteries related to the ICB area are ICA, ACA, MCA, perforators from A1, M1 (medial and lateral striate), RAH, Ach, diencephalic branches of P.com and temporal branches of MCA.[38] There are a large number of perforating branches with their course behind the ICA bifurcation. These arise from: (a) the choroidal segment of the ICA, (b) the Ach, (c) the RAH, (d) the medial lenticulostriate arteries (MLAs) and (e) the lateral lenticulostriate arteries (LLAs).[28] Relation of the ICA and the optic nerve can vary from a parallel course of the artery and the nerve to a concave or convex course in relation to the nerve.

Anatomical variations of ICA, M1 and A1 may affect intraoperative orientation during dissection of ICBA: (a) hypoplastic ICA, (b) absent ICA, (c) ICA trifurcation, or (d) persistence of foetal remnants. A hypoplastic ICA diminishes in calibre at or shortly distal to its origin. In these cases, the petrous and sellar segments may also be absent. Hypoplasia or aplasia of the ICA occurs in less than 0.01% and only 100 cases have been described in the literature.[18]

Three major patterns of collateral circulation have been described in hypoplasia/absence of the ICA.[30] Carotid trifurcation is a unique and unusual anatomical variant where three arterial branches arise from the carotid termination.[13] This may result either from anomalies of the carotid termination itself, from accessory origins of the Ach at the ICA termination or from absent M1 portion of the MCA. When the M1 segment is absent, the MCA bifurcation is located at the ICA termination and both the frontal and the temporal M2 branches arise at the ICA termination itself. The frontal M2 may even be hypertrophied like a normal M1. The branches include the ACA and the two M2 portions of the MCA. The P.com and Ach originate at their usual

location. The other variant includes an accessory MCA arising at the carotid termination which is a residual congenital remnant of the foetal MCA. The most proximal segment of the primary cranial division of the foetal internal carotid gives off the Ach first, the second collateral is the MCA and the next segment is the stem of the ACA.

The embryonic origins of a duplicated MCA and accessory MCA are still not clear. Theoretically an aneurysm located at the carotid trifurcation may arise between any two branches arising at the trifurcation. Depending on the location and the size of the aneurysm, the perforators, especially the MLAs, may course along or wrap over the body of the aneurysm arising between the ACA and the MCA like any other standard ICBA. The perforators arising from the distal carotid, medial ACA and even the RAH may be in close relation to the aneurysm.

When the aneurysm arises between the two M2 vessels originating at the carotid termination, the MLA perforators may be in close proximity and need to be protected during dissection and clipping. These anatomical variations should be identified pre-operatively and displayed during surgery before clipping is attempted.[13]

Anterior cerebral and Sylvian veins converge in the area of ICB and reach the sphenoparietal and cavernous sinus. The deep venous system includes anterior cerebral, deep middle cerebral and basal vein of Rosenthal, and these are located inferior to the ICB.[38] The supraclinoid ICA, origins of its branches, and the fronto-orbital veins draining into the sphenoparietal sinus are all within the carotid cistern.

Aneurysms in this location vary from 3 mm to giant aneurysms. This is a common site for giant aneurysms to occur. These aneurysms are broad based and the neck extends on to the A1 or M1 side from the ICB. The relationship of the aneurysmal sac to the structures around depends on the direction and projection of the fundus, which could be superior, posterior or inferior.[4] Projection of the fundus is superior in 56%, posterior in 18%, anterior in 20% and inferior in 6%. A detailed knowledge of the ICBA which includes projection of the dome (anterior, superior, posterior), anatomy of the perforators, relation and calibre of main vessels is important for planning the approach. The anteriorly projecting ones arise from the anterior aspect to project into the lateral orbitofrontal gyrus or the base of the olfactory tract. The superiorly projecting originates from the superior aspect of the ICA bifurcation with its dome projecting into the APS, the lateral portion of the lamina terminalis cistern, or the Sylvian cistern. Posteriorly projecting ICBAs originate from the posterior aspect of the ICA bifurcation with their dome projecting into the carotid, interpeduncular or even the ambient and crural cisterns.

These aneurysms are covered by arachnoid from the carotid, olfactory, lamina terminalis and Sylvian cisterns. When the aneurysm grows, it occupies the Sylvian cistern and cistern of the lamina terminalis and compresses the M1, A1 and the perforators which are displaced around the aneurysm. Disposition of arterial branches around will depend on the direction of the fundus and its projection. A postero-inferior projection is into the IPC and crural cistern and is related to diencephalic branches of the Ach and P.com. An enlarging aneurysm widens the crotch of the ICB and may displace the A1 and M1 inferiorly or laterally depending on the direction and growth of the fundus. The dome may get buried into the surrounding brain parenchyma, and is surrounded by a large number of perforators from A1, M1, RAH, Ach and P.com. These perforators lie posterior to the aneurysm sac, but their proximity and adherence will depend on the extent and projection of the fundus. These are more bound in posteriorly directed lesions. Sometimes, the temporal arteries are also pushed and are adherent to the aneurysm wall in giant aneurysms.[31]

PRE-OPERATIVE EVALUATION

Clinical evaluation, investigations and medical management are the same as for all other patients with aneurysmal SAH in other locations. Blood pressure is maintained. CSF drainage, if necessary (through lumbar or ventricular route), is performed to lower the intracranial pressure (ICP). This is the same protocol as in patients with aneurysmal SAH in other locations. An acceptably lax brain is mandatory as the location of ICB is deep as compared to most of the other aneurysm locations.

Position and Skin Incision

The patient is positioned supine with the vertex tilted 10–15 degrees below the horizontal plane. The head is rotated from the midline by 30–60 degrees depending on the projection of the aneurysm to allow proximal control and optimal exposure of A1 and M1. As already described, these aneurysms typically point in one of the three directions: (1) superiorly; (2) posteriorly or inferiorly and (3) anteriorly.[26] In case of supero-medial projecting aneurysms along A1, the head is turned 60 degrees from the vertical plane. Posteriorly directed aneurysms accompany the MCA and occupy the Sylvian cistern and, hence, the head needs to be turned 30–45 degrees. Inferiorly directed aneurysms drape down over the posteromedial aspect of the ICA and may enter the IPC and the head tilt should be the same as for posteriorly directed ones. Anteriorly directed aneurysms are less common and are along the ICA; hence a tilt of 30 degrees is adequate.[4,18,20,23] The malar eminence is at the highest level with the lesser wing of the sphenoid perpendicular to the floor.[28] Extent of craniotomy depends on the surgeon's experience, the projection of the ICBA, and the presence of ICH.

A frontotemporal (FT) semicoronal incision is made beginning at the superior border of the zygomatic arch close to the tragus and anterior to the superficial temporal artery (STA), which should be preserved. The incision proceeds superiorly and posteriorly, curving anteriorly

to end just behind the hairline in the frontal region.[9,32,33] In 1984, Yasargil[38] described the standard pterional craniotomy and subsequently reported a modified procedure for reconstruction of the temporalis muscle avoiding facial nerve injury.[36] In the 1990s, several modified techniques were proposed. The aim of the approach is maximum surface exposure and minimum brain retraction. Facial palsy and post-operative temporalis muscle atrophy along with discomfort/pain should be avoided. A musculocutaneous flap avoids facial nerve injury, but a thick pad of temporalis is a hindrance to the basal approach. Hence, an interfascial dissection is mandatory. The interfascial approach and removal of a part of the orbital roof and sphenoid wing greatly increases the exposed area at the base of the surgical pyramid. The frontotemporal branch of the facial nerve overlies the temporalis muscle. The temporal fascia is present from the origin of the temporal muscle along the superior temporal line (where it is continuous with the galea) to the zygomatic arch. The facial nerve, after emerging from the stylomastoid foramen, courses anterolaterally over the ramus of the mandible into the substance of the parotid gland where it divides into five main branches. The frontotemporal (FT) branch can be injured during pterional craniotomy. The three twigs exit the parotid gland to run in the subcutaneous tissue. The posterior branch has a very short course. The middle and anterior branches continue in the subcutaneous tissue 1 cm anterior to the STA. The middle branch courses anterocephalad to innervate the frontalis muscle. The anterior branch courses anteriorly and 1–2 cm above the zygoma to innervate the orbicularis oculi and corrugator muscles. An attempt should be made to maximally retract the temporalis muscle from the temporal fossa without injuring the FT branch of the facial nerve. The skin incision is not extended too deep, rather continues superiorly to the temporal crest then curves sharply anteriorly. The galea is then separated from the pericranium and the temporal fascia is exposed within 4 cm of the orbital rim. At this level the anterior part of the temporal fascia divides into two layers separated by a 5–6 mm thick sickle shaped pad of fat. The two layers of fascia are attached to the outer and inner border of the zygomatic arch. The fat layer is dissected apart carefully with a knife and reflected with the superficial layer and the skin flap; hence the FT nerve coursing superficially along the fascial layer is protected. The temporal fascial attachment to the medial surface of the zygomatic arch is incised and carried anterosuperiorly along the superior temporal line releasing the temporal fascia and aponeurotica muscle periosteum. The temporalis muscle is then reflected and rotated inferoposteriorly.[36] An additional fascia periosteal cuff is made along the superior temporal line to facilitate subsequent muscle closure.[20]

The author raises a slightly larger scalp flap and further retracts posteriorly, so as to handle a very thin portion of temporalis posteriorly. A small cut is made in the temporalis lateral to the key burr hole and then raising an osteoplastic flap. This causes less handling of the temporalis and utilises the advantages of an osteoplastic flap. The key burr hole is properly centred (just inferior to the convergence of the inferior frontal bone, greater wing of sphenoid and frontal process of the zygomatic bone). The anterior cut should be flush with the supraorbital margin. In addition to the pterional flap, the temporal squama and the lateral 2/3 of the lesser wing of the sphenoid are drilled/nibbled. These manoeuvres are necessary to facilitate the opening of the anterior Sylvian fissure and minimise brain retraction. The exposure required is comparatively more for these aneurysms located in the deepest portion of the anterior portion of circle of Willis.

Brain relaxation is obtained by proper head positioning, venous drainage, normal ventilation and administration of mannitol and furosemide at the time of the last cut in the skull flap. In case the brain is not slack, the IPC and lamina terminalis are opened to release CSF. Intraoperative ventricular puncture is rarely required. The CSF can also be drained through a lumbar catheter. An adequately lax brain is mandatory to avoid excessive brain retraction.

To achieve a safe exposure, dissection and clipping the following points must be adhered to:

- Specific microsurgical approach dictated by the direction and projection of the aneurysm and length of the supraclinoid ICA.
- Wide exposure of the Sylvian fissure, parent artery, main arteries and perforators.
- The arachnoid over the Sylvian fissure is stretched with the help of a fine suction tip. This is placed on the inferior frontal gyrus on the right side and the superior temporal temporal gyrus (STG) on the left side. The Sylvian fissure may be full of blood clots or may be collapsed due to oedema. The superficial layers of the arachnoid are cut medial to the superficial Sylvian vein.
- Arachnoid is separated and cut.

The dissection in the Sylvain fissure is performed with the help of suction tip, ballpoint dissector and microscissors. The main dissection and separation is performed with the help of fine tipped bayonet or bipolar forceps. A few small bleeding points on adjoining cortical surfaces need to be coagulated. The major Sylvian veins and tributaries, even the superficial ones, are not sacrificed. There are two small veins one at the middle of the posterior limb and another at the medial end of the Sylvian fissure which cross through the Sylvian fissure. These may be coagulated and cut to obtain proper exposure of the Sylvian cistern. As an initial step, dissection of the Sylvian fissure is performed only superficially. The remaining part of the Sylvian cistern dissection, whether prior to or after carotid cistern dissection, will depend on the projection of the aneurysm fundus and length of the supraclinoid carotid.

When the ICA is short, the dissection is performed from proximal to distal (carotid cistern). This is contrary

to when the ICA is long or the aneurysm is large/giant complex and anteriorly projecting when the Sylvian fissure must be widely opened in a retrograde manner to avoid excessive retraction in exposing the ICB.

The incision in the arachnoid at the basifrontal region (between ON and frontal lobe) is now extended medially to the lamina terminalis to avoid strangulation of A1 by arachnoid bands on retraction of the frontal lobe. The Sylvian fissure is widely opened incising the arachnoid trabeculae in the Sylvian cistern. However, the MCA is not skeletonised. Thick clots in these cisterns are removed by flushing with saline. Clot removal necessary for dissecting the vessels should be picked up and removed by sharp dissection (microscissors). The laterobasal frontal lobe is elevated. A small artery from the ICA to the dura over the anterior clinoid is coagulated and cut and the carotid cistern is opened. A careful dissection of trabeculated arachnoid bands within the carotid cistern is mandatory for mobilisation of the supraclinoid origin of the P.com which may be adherent to the dura overlying the posterior clinoid.

The ICA bifurcation complex is dissected and mobilised. After dissecting the ICA, the course of the P.com and Ach arteries is determined and the relationship of their branches while dissecting the fundus is noted. Dissection is done along the antero-inferior surface of the A1 and M1 and the extent is determined by the size and exact direction of the fundus. The A1 remains often hidden behind the aneurysm dome at this stage. In posteriorly, superiorly or inferiorly projecting ICBAs or in large and giant aneurysms, the risk of premature rupture of the aneurysm is a real challenge (Fig. 5).

The temporopolar and anterior temporal arteries are mobilised for a few millimetres to avoid retraction stretch/trauma. Wide dissection of the lamina terminalis cistern, Sylvian and carotid cisterns will help in proper delineation and tracing of adjoining arteries (A1, M1, P.com, Ach) and their branches from the origin (Ach, RAH and perforators from A1, M1, P.com and Ach).

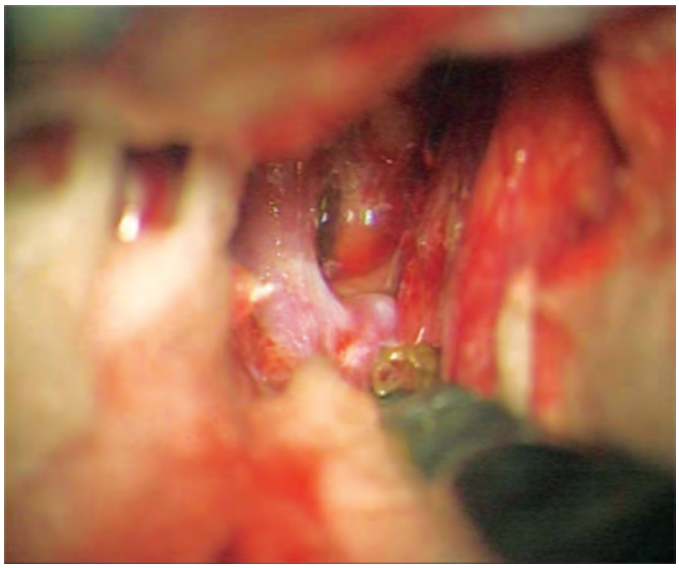

Fig. 5: Operative photograph showing a bilobed ICBA

The recurrent artery of Heubner may loop beneath the A1 and is hidden behind the aneurysm. The M1 perforators (lateral, proximal and distal striate vessels) and A1 perforators (medial, proximal and distal) must be preserved. These originate from the inferior surface of M1 and can be identified by retracting the M1. These supply the substantia innominata, lateral portion of the anterior commissure, most of the putamen, lateral part of globus pallidus, superior half of the internal capsule, adjacent corona radiata, and body and head of the caudate nucleus. Perforators also arise from the posteroinferior surface of A1 (2–5 mm away from ICB). These supply the septum pellucidum, medial portion of the anterior commissure, pillars of the fornix, optic chiasm, paraolfactory area, anterior limb of the internal capsule, anteroinferior part of the striatum and the anterior hypothalamus.[15]

The subfrontal exposure is used for posteriorly or inferiorly directed aneurysms and is subsequently followed by temporal lobe mobilisation after coagulating and dividing temporal tip veins. The superficial Sylvian vein should be preserved, although its occlusion is tolerated without any serious consequences. However, the basal vein of Rosenthal and its tributary the medial Sylvian vein must be preserved to avoid venous infarction. These are located in relation to the ICBA.

Standard microsurgical techniques are used to prepare the aneurysm for clipping the aneurysm fundus projecting in different directions. The final step of dissection involves isolation of the aneurysm neck and separation of the perforators. Mostly the sac of these aneurysms is adjacent to perforating vessels and in many instances these perforators are adherent to the sac.[32] The aneurysm base, with the adjacent arterial branches, should be visualised before clipping. Superiorly projecting aneurysms are buried in the orbitofrontal gyrus or the base of the olfactory tract and these cases require slightly more elevation of the frontal lobe. Perforators are related to the posterior and lateral walls and the base can be approached relatively safely and controlled before dissecting the entire dome free. In such cases temporal retraction is required initially, after sacrificing temporal veins. In posteriorly projecting aneurysms into the APS or lateral portion of lamina terminalis, and also in inferiorly projecting aneurysms into the IPC or ambient cisterns both frontal and temporal retraction is required. These latter are the most challenging ICBA, but fortunately are the least frequent ones. The dome is obstructed by the ICA and so proper visualisation of the perforators is particularly difficult even in small aneurysms. These are embedded in the perforators, posing the greatest risk of their injury. These may be adherent to the dome and may be severed during retraction, dissection, coagulation, kinking, compression for haemostasis, temporary occlusion or final clipping. Identification is essential as the deficit produced may be severe. Hence, this demands an astute microneurosurgical technique, skilled, painstaking and patient dissection on and around the aneurysm. Temporary clipping as and when required under full cover of neuroprotection needs to be used.

When there is an associated ICH, a small cortical incision is made depending on the location, avoiding Broca's area, and some haematoma is evacuated to gain space. The ICH in the immediate vicinity of the aneurysm should be left in place until proximal and distal control has been obtained. Finally, more ICH can be removed at the end of operation. One should be cautious in dealing with anteriorly projecting aneurysms as retraction of the frontal lobe may risk rupture, hence, this should be avoided until proximal control of the ICA has been established. Large anteriorly projecting ICBA may initially obstruct the view towards the A1 trunk, preventing temporary clipping of the A1. The pilot clip is inserted with the temporary clips on. The aneurysm sac is then opened and eventually reshaping with bipolar coagulation is performed and the final clip is inserted. If the aneurysm dome is obstructing and hiding the visualisation of perforators it may be desirable to first place a pilot clip at the aneurysm base and proceed with dissection of their details.

The aneurysm neck is dissected free of branches of P.com, Ach, perforators from the recurrent artery, A1 and M1 with the help of small cotton pledgets and guarded microsuction compression. The microscope is angled from the frontal side and the table is tilted laterally to visualise the perforators on the temporal side and vice versa. The fundus of the aneurysm is left undisturbed.

Appropriate cleavage around the neck is created so as to clear the clip passage free from the perforators' adherence. Arachnoid adhesions between the aneurysm neck and A1 are opened. The optic tract may abut the aneurysm fundus and this should be separated from the wall of the aneurysm and A1. Sometimes the sac may be partially or fully buried in the orbitofrontal cortex. Subpial tissue resection is performed through a pial opening around the sac. This is to free the aneurysm from the fronto-orbital region and release tension, which can be precipitated by frontal lobe retraction which is kept at a minimum before this dissection. If there is a haematoma in the orbitofrontal region the same should be evacuated, at least partially.

The site for proximal control should be prepared just above the origin of the Ach. Temporary clips, if needed, should be placed at this site safeguarding the perforators. If the aneurysm neck is broad, then a straight clip can cause a kink in one of the vessels or a patent dog-ear in the aneurysm. In such a situation, a curved or fenestrated angled clip can be placed in the axis of A1 and M1 to exactly reconstitute the ICB. All venous ooze close to the base should preferably be controlled with surgicel to avoid perforator insult by bipolar coagulation. While removing the temporary clips, even the slightest resistance noted should be taken as a caution as there may be a possibility that a small branch is attached to the clip or applicator.

During clipping there are certain recommendations to be followed. Ideally the bifurcation should be reconstructed without jeopardising supply to A1 and M1. The clip is best introduced across the neck of the aneurysm along the M1 trunk, slowly wiggling the blades between the neck of the aneurysm and the ACA and the MCA as well as their branches to avoid crimping of the parent artery or "dog earing" of the aneurysm. The clip is closed slowly. However, the A1 may be sacrificed if mandatory in desperate situations (when the ipsilateral A2 is perfused from the contralateral side). The size of the clip should be slightly larger or of the size of the neck of the aneurysm. The lie of the clip for wide neck aneurysms should always be parallel to A1 and M1. In case of any resistance during clip application the area is inspected to avoid injury to vessels, perforators, neck or hidden fundus. In rare cases, bipolar coagulation at low intensity by light squeeze-release manoeuvre is performed under saline irrigation. After clip placement, inspection is made to confirm the preservation of perforators and the patency of main vessels by microvascular Doppler (IMD).[10,19] Intra-operative angiography or indocyanine green angiography (ICG, if facility is available) is performed. The distal end of the clip is visualised free from any vessels or a part of it. After the clipping, the aneurysm dome is punctured and the collapsed sac can be mobilised, coagulated, transected and removed.

Inferiorly directed aneurysms need a special mention as these are embedded amongst the perforators and are pointing into the IPC or even to the ambient and crural cisterns. The clips usually required are straight or curved fenestrated ones. The final clip should preferably be small, appropriate, properly angled for neck occlusion avoiding compromise or kinking of the main vessel lumen, branches and perforators. If bipolar reshaping is not considered, then the blade of a single occluding clip should be one and a half times the width of the base as suggested by Drake. Sugita clips have a wider opening and blunt tips in comparison to Yasargil ones so one should tailor the clip as per aneurysm architecture and status noted at dissection.

Multiple clipping using two or more clips is occasionally required for wide-neck aneurysms. Previously coiled aneurysms pose additional difficulties for adequate clip placement as there may not be an adequately free base for safe application of the clip. One has to consider removing some or all of the coils under temporary clipping to provide extra room for the clip at the base.[22]

INTRA-OPERATIVE RUPTURE

Intra-operative rupture (IOR)[1] can occur during craniotomy, after dural opening, during dissection or while clipping. Morbidity and mortality is around 30% in IOR. Earlier in the surgery the rupture takes place the worse is the prognosis. Blunt dissection causes large and irregular tears extending close or may be on to the neck whereas, most of the microtears/micropunctures are small and are at a specific site, hence can be successfully tackled without ischaemia or vessel sacrifice.

In case of rebleed during craniotomy (before bone flap removal) the procedure is postponed. If the IOR

occurs just before/soon after dural opening then continuance with the aim to clip the aneurysm will add to the trauma caused by the fresh insult. Hence, the dura is opened and a large pericranial or fascial patch is sutured to reduce ICP. The bone flap is placed in the abdominal wall. In case a large ICH in the frontal lobe is detected on intra-operative ultrasound, CT or MRI then one can go ahead with haematoma evacuation, clipping of aneurysm, decompressive craniotomy, duroplasty and post-operative ventilation.

The two most common causes of intra-operative rupture soon after initiation of the procedure are retraction of the frontal lobe and dislocation of the ICA while the aneurysm dome is still adherent to the frontal lobe. The risk is highest for anteriorly projecting aneurysms. Control is obtained via suction and compression of the bleeding site with cottonoids. Short and sudden hypotension by cardiac arrest, induced by intravenous adenosine can be used to facilitate quick dissection and application of a pilot clip in case of uncontrolled bleeding. If the rupture takes place before completing the dissection, temporary clips must be applied to the parent vessels proximally and distally, and the aneurysm is prepared for pilot clipping under local flow arrest. A small and thin-walled ICBA may rupture at its neck during dissection. In such a case, under temporary clipping, reconstruction of the base by including a small part of the parent artery inside the clip should be attempted. In case the same is not effective, a clip on a mini cotton wrap can be applied. In case the rupture takes place after starting dissection (opening of Sylvian cisterns/basal cisterns) a part of the frontal/temporal lobe is excised (depending on the direction of fundus projection). The feeding artery is reached for temporary clipping with immediate institution of neuroprotective measures. Subsequent dissection is the same, though more focussed and is to be carried out in a limited time frame.

The IOR during dissection is managed by temporary clipping under cover of already administered neuroprotectants. A small hole can be managed by suction on cotton. In case of a large hole temporary clipping and dissection is performed which are followed by permanent occlusion of the neck. In case the bleeding aperture is exposed/dissected, a tentative clip can be applied on the aneurysm just proximal to the rent in the aneurysm. Tentative clipping can either be a temporary clip or a permanent clip (mostly permanent clip) depending on the force required/extent of dissection completed at the tentative clip site. Rupture at clipping could be avoided by dissection of the neck to its total extent. Status of the neck and adjacent vessels is kept in consideration in view of plaque/severe atheromatous changes. The clip ends are never forced through any resistance. If bleeding is at the time of clip closure, the clip is removed as the application will result in increase of the size of the rent in the aneurysm. The remaining steps are the same as for IOR during dissection. After successful clipping of the aneurysm, the dome is punctured and the collapsed sac is mobilised to visualise the perforators, distal end of the clip and remaining neck if any (particularly in inferiorly directed sacs). Gradually the remaining wall of the aneurysm is moved in the clip by readjustment under temporary occlusion of the proximal artery.

TEMPORARY CLIPPING[3,12,21,23,34]

(See Chapter 83 "Middle Cerebral Artery Aneurysms")

GIANT ANEURYSMS[17,31]

Giant ICBA comprise 7% of all ICBA. The dome of a giant ICBA is usually at least partially covered by the frontal lobe and extends also into the Sylvian fissure. Perforating arteries frequently follow and/or arise from the base of these aneurysms and it may be very difficult, even impossible, to dissect them free. The large size, distorted anatomy, origins of the perforating arteries and other arterial branches originating directly from the aneurysm, calcifications at the base, and intraluminal thrombus, make microneurosurgical management of giant ICBA an extremely difficult task. Proximal occlusion or trapping is difficult even if bypass is done. Comprehensive pre-operative imaging by CTA, DSA and MRI is mandatory. The 3D reconstructions of the CTA and rotational DSA help to show the aneurysm orientation with relation to the bony landmarks and to identify calcifications, thrombus, organised thrombus and their location in the aneurysm. DSA provides important information about the flow dynamics of the ICA bifurcation complex.

Direct clip occlusion remains the most effective treatment for giant aneurysms as well. The perforators are often draped over the aneurysm neck and dome. The neck is broad most of the time, and thick walled, incorporating the origins of A1 and M1. Hence, the angioscopic views of 3D CTA are quite informative for pre-operative decision making of the extent of safe clipping. However, proximal ICA occlusion is often ineffective for ICA and other aneurysms distal to the ophthalmic artery origin. Still these patients should have a balloon test occlusion (BTO) done and, in case the aneurysm is unclippable or high risk, then a bypass procedure needs to be performed. This acts either as a prerequisite for intra-operative temporary clipping of ICA or for proximal ICA occlusion directly or endovascularly to induce thrombosis of the aneurysm.[4,17] This procedure should soon follow the confirmation of graft patency. This is to obviate any risk of aneurysm rupture due to hyperdynamic circulation following bypass and stump emboli due to delaying anticoagulation.

In addition to obtaining detailed radiological work up of giant ICBA the points to be considered are:

- A comparatively larger craniotomy flap
- Extremely lax brain
- Wide roomy exposure of the Sylvian cistern
- Satisfactory exposure of ICA, M1, A1 and P.com for temporary occlusion

- A stepwise dissection and clipping of the aneurysm dome/body using a tentative clip and then proceeding towards the base to achieve the desired complete occlusion
- Assessment of size of the neck and its contents
- Relation of the neck to the origin of the M1 and A1 so as to exactly assess the safe clippable portion of the aneurysm sac. Intraluminal thrombus can be removed and a temporary clip is applied at the patent portion of the aneurysm
- Working out the location of organised clots/plaques in relation to the aneurysm neck on MRI, CT/CTA+DSA
- Disposition of vessels around are visualised at surgery and are cautiously dissected.

In addition to all neuroprotective measures, intraoperative evoked potential monitoring and IMD/ICG to assess patency of vessels after clipping are needed.

Utmost care is needed not to damage the surrounding perforators. Once the dome is decompressed and if the aneurysm wall is not heavily calcified, it is usually reduced by bipolar coagulation to allow for final dissection of the neck, before deciding how to perform the final clipping. Giant ICBA often require complex clip reconstruction. Multiple clips are applied to ensure complete occlusion of the neck preserving all the perforators and branches originating from the neck. With the neck clipped, one must ensure that there is no kinking in the A1, M1, and the terminal ICA is open.

In aneurysms which significantly involve the perforators, direct surgical clipping or trapping may not be feasible. Parent vessel sacrifice with distal revascularisation by high-flow bypass may be the only treatment option in these cases.

Subsequent to confirmation of the previously mentioned requirements, the aneurysm is isolated by temporary occlusion of ICA, M1, A1, P.com and Ach. If the aneurysm does not contain organised clots/plaques, especially near the neck, then intermittent suction decompression with a scalp vein cannula attached to the suction with intermittent trapping of aneurysm for dissection is adequate for clipping. In case the aneurysm contains clots/organised clots/plaques, more so close to the neck, then the aneurysm is to be opened away from the probable site of permanent clip and parallel to the bifurcation (the neck). The contents are peeled through the cleavage between organised clots and aneurysm wall. Sometimes, these are too tough to be removed by suction, dissector and tumour forceps. The CUSA at a lower setting is useful in this situation. The wide neck is clipped with the help of both fenestrated and nonfenestrated clips. Usually this works if organised clot has been removed off the wall at the neck. If not possible, then a Sundt booster clip can be used as the amount of pressure generated across clip jaws by giant aneurysms is incredible. A small portion of the neck is maintained patent. This is recommended to maintain a small neck proximal to the clip so as to avoid compromising the diameter of the lumen of the parent vessel incorporated during growth of giant aneurysms. In case of non-availability of a booster clip, a 2.0 suture is passed under the ICA and then around the neck after safeguarding the perforators and other branches. This is tied to oppose the wall at the neck because, a tight knot will jeopardise circulation by occlusion/kink of main artery/branches. The gentle tie is reinforced by a fenestrated/nonfenestrated clip. Ligature should be used only when really necessary as extensive dissection of the aneurysm is a prerequisite for this procedure. Chances of vessel occlusion, infection and dissolution of suture are subsequent problems. Post clip IMD to see the patency of the vessels is essential and an intra-operative angiogram/ICG is recommended. Wrapping of a giant aneurysm produces dense scar around the base but has very little effect on the dome.

Unruptured ICBA with the dome projecting anteriorly or superiorly can also be approached from the contralateral side provided that the ICA bifurcation is not too high and there are no large venous structures obstructing the view. In posterior projecting and large superiorly projecting ICBA, proper visualisation of the perforators attached to the posterior wall of the aneurysm would be very difficult from the contralateral side and would lead to perforator injury. The contralateral approach requires more retraction/lifting of the frontal lobe, and we do not recommend it in acute SAH and brain swelling. The lateral supraorbital craniotomy (LSO) is a more direct and simple approach for ICBA.[5] The LSO craniotomy is a more subfrontal and less invasive modification of the pterional approach for anterior circulation aneurysms.[25] The angle of approach towards an ICBA is a little less lateral than that provided by the pterional approach. Fusiform ICBA are extremely rare. Wrapping, trapping, excision and bypass surgery can be considered for these lesions.

COMPLICATIONS

Intra-operative non-progressive soft brain bulge in which a haematoma is not likely needs to be managed by duraplasty, avoidance of muscle closure, post-operative decongestant therapy and removal of bone flap (if required). Immediate post-operative motor deficit could result from marked ischaemia due to temporary clipping for a prolonged period in the absence of good collateral flow. All attempts must be made to enhance perfusion by Triple H therapy, antivasospastic measures, vasodilators and others. Dense deficit could result from perforator injury.

Delayed deficits can develop due to subdural/epidural/intracerebral haematoma which could result from a little lapse in haemostasis/coagulopathy. The latter needs proper investigations, CT, complete coagulogram, diagnosis and appropriate therapeutic measures. The other causes of deterioration could be hydrocephalus and vasospasm. Hence, a detailed close monitoring, leucocyte count, CT along with transcranial Doppler is mandatory to arrive at a proper diagnosis and then

institute treatment accordingly. Deterioration can also take place due to meningitis, electrolyte disturbances and seizures. Medical problems like chest infection/myocardial ischaemia/pulmonary ischaemia can lead to depressed respiration, hypoxia, hypercarbia and perfusion insults.[26]

Endovascular Treatment

Recanalisation and coil compaction remain a major limitation of embolisation therapy. A higher tendency for aneurysmal recanalisation and regrowth occurs in incompletely occluded aneurysms at initial treatment. Those at the bifurcation or wide-necked aneurysms are at higher risk. Hydrocoils consisting of a carrier platinum coil coated with a layer of hydrogel polymer have been shown to possess a potential to achieve higher rates of volumetric occlusion as a result of expansion of the hydrogel after contact with blood. High rates of delayed progressive occlusion and significantly better neointima formation at the aneurysm neck have been reported in two different animal models. Aneurysms are packed as densely as possible until angiographically complete occlusion is achieved and/or the last coil cannot be introduced into the sac.

Volumetric occlusion has been found to be significantly greater with Hydrocoils than with bare platinum coils (about 70% vs 20–30%) immediately after embolisation. A recent study comparing Hydrocoils with Matrix and platinum coils has been reported. Basilar and ICA aneurysms are subject to constant arterial pulsations, the so-called "water-hammer" effect, which may play an important role in recanalisation of these aneurysms, especially following incomplete occlusion. The regrowth rate of ICA bifurcation aneurysms is around 22%. Procedural mortality and morbidity are 2.2% each. Death or permanent neurological deficit due to thromboembolism can occur. The overall thromboembolic complication rate in the Hydrocoil is 8.1–12%.[7]

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81 Anterior Communicating Artery Aneurysms

RP Sengupta, Anil Pande

INTRODUCTION

The anterior communicating artery (ACoA) complex is the most frequent site of intracranial aneurysms, and an anterior communicating artery aneurysm (ACoAA) is the commonest aneurysm a neurosurgeon tackles.[34,43,52,68,77,91,105] The anatomy of the ACoA is complex with frequent associated congenital vascular anomalies. These aneurysms are located posteriorly between the frontal lobes and their close proximity to the hypothalamus, optic nerves, chiasm and their blood supply makes surgery of these aneurysms difficult.[34,43,85] The anterior communicating artery aneurysms (ACoAAs) have a varied morphology. Saccular, fusiform,[93] blister,[8,51] multiple including kissing ACoA[12,47,113] and giant types[21,42,59,70] have been described. Hernesniemi et al.[43] analysed a database of 3,005 patients with 4,253 aneurysms, 1,145 patients (38%) had altogether 1,179 anterior cerebral artery (ACA) aneurysms; of them, 898 patients harboured 921 (78%) ACoAAs. In their series, 715 patients (80%) presented with ruptured ACoAAs with the median diameter of 7 mm. Giant ACoAAs were present in 15 (2%), whereas only 3 (0.3%) were classified as fusiform. The ACoAAs present frequently with subarachnoid haemorrhage (SAH) when of small size and luckily giant ACoAAs are rare.[43,70]

INCIDENCE

The ACoAAs form 30–37% of all aneurysms and comprise the largest percentage of ruptured aneurysms.[34,43] They are found to be more common in men with a male:female ratio of 2.3:1. These aneurysms are seen in the middle aged with a peak in the late forties.[45] The ACoAAs are very rare in children. Jain and Mehta[49] reported an ACoAA in a 3-year-old girl, who presented with subarachnoid haemorrhage. Multiple aneurysms are seen in 4.1–18.2%[47,52,79,113] of patients who present with an ACoA aneurysmal bleed. Inci and Ozgen[47] found an incidence of 4.1%. Kissing ACoAAs are variants of multiple aneurysms.[12] The inheritable connective tissue disorders like polycystic kidney disease, Ehler-Danlos syndrome, Marfan's syndrome, neurofibromatosis type 1 and alpha 1 antitrypsin deficiency may be associated. Rarely, familial occurrence of intracranial aneurysms is seen. Maramottom[72] reported the management of ACoAA in a patient with Takayasu's arteritis, a rare type of vasculitis which affects predominantly young females and involves the aorta, its large branches and the pulmonary arteries. Bulsara et al.[19] reported on the coexistence of pituitary adenoma and ACoAAs.

AETIOLOGY

Aneurysmal formation has multifactorial aetiopathogenesis with genetic, molecular, structural and flow dynamics being among the many factors involved. The genesis and increase in size of ACoAAs is due to loss of normal balance between vascular vectors, flow rheology and arterial wall characteristics. The progressive thinning and weakening of the wall finally result in aneurysmal rupture and SAH. This aetiological march is well seen in patients with ACoAAs. Aneurysms of the ACoA complex commonly have asymmetric A1 segments with one side being atretic or hypoplastic and the major flow is from the dominant A1 segment.[100] The ACoAAs have been produced in hypertensive rat models by ligation of the common carotid artery on one side and the contralateral internal carotid artery (ICA). The cross-circulation from the right ACA and hyperdynamic flow through the ACoA have been implicated in aneurysm formation. The direction of the aneurysm is determined by the direction of dominant flow. Castro et al.[22] in a study, analysed the flow dynamics in 26 ACoAAs by using image-based computational fluid dynamics methods. They found that aneurysms with small impaction zones, higher flow rates into the aneurysm and elevated maximum wall shear stress were more likely to be ruptured. The angles of the arteries at bifurcations, as well as the blood flow cause haemodynamic stress on the apical region, leading to aneurysm formation. Kasuya et al.[54] determined the angles between A1 and A2 segments of the ACA of the ACoA complex associated with aneurysms using images obtained with three-dimensional (3D) computed tomographic angiography. They found that ACoAAs are associated with the smaller A1-A2 angle junction of the ACoA complex, where higher haemodynamic stress occurs in patients with normoplastic A1 segments.

SURGICAL MILESTONES IN THE MANAGEMENT OF ANTERIOR COMMUNICATING ARTERY ANEURYSMS

In 1936, Wilhelm Tönnis[34] used a midline surgical approach to directly reach the ACoAA by splitting the genu of the corpus callosum. In 1938, Walter Dandy[26]

described the pterional (PT) craniotomy and his approach to the skull base has withstood the test of time. Hamby and Falconer[32] used the unilateral subfrontal approach to reach ACoAAs. In 1956, Vincent Logue[69] used proximal occlusion of the A1 and Hamby proposed the exposure of both carotid arteries in the neck for temporary occlusion to prevent a premature rupture. Williamson and Brackett[34] suggested temporary occlusion of the proximal anterior cerebral arteries and Pool[88] used the midline bifrontal approach with temporary occlusion of both A1 arteries. In 1962, Lyle French[35] described resection of the anteromedial part of the frontal lobe to prevent premature rupture of ACoAAs. Kempe,[57] in 1968, and Vander Ark,[56] in 1971, described the gyrus rectus approach to these aneurysms and highlighted the importance of the direction of projection of the aneurysm in the operative approach (Fig. 1). They further classified aneurysms of the ACoA into three basic categories depending upon the orientation of the dome, and based the approach on the principal of leaving the fundus of the aneurysm alone.[57] Those which pointed downwards were approached from above, anteriorly projecting aneurysms were tackled from above and behind, superiorly and posteriorly pointing aneurysms were to be approached from below. In 1964, Adams and Whitt[1] reported on the use of the operating microscope in the surgery of aneurysms and, in 1966, Pool and Colton[87] stressed the advantage of the microscope in intracranial vascular surgery. In 1969, Yasargil et al.[116] introduced concepts of microneurosurgery. The microsurgical corridor using the PT approach to ACoAAs was popularised by Yasargil[115] and Fox.[34] Sengupta[100] researched the circulatory patterns, anomalies and morphological aspects of ACoAAs and used a modified subfrontal, gyrus rectus approach. In 1986, Hakuba et al.[40] described the orbitozygomatic-infratemporal approach increasing bone removal to reduce need for brain retraction. In 1989, Smith et al.[104] described the orbitocranial approach which involved the removal of the orbital rim and roof, and the sphenoid bone. In 1991, Guglielmi et al.[39] reported on the electrothrombosis of saccular aneurysms via the endovascular approach. The use of the endoscope to assist the microsurgical clipping of cerebral aneurysm was first reported by Fischer and Mustafa in 1994. In 1982, Jane et al.[50] described the supraorbital approach for suprasellar lesions and ACoAAs and thereafter the use of Keyhole concept in aneurysm surgery has been developed and modified by many authors.[24,25,27,53,67,102] Image guided approach to these aneurysms has been described.[102]

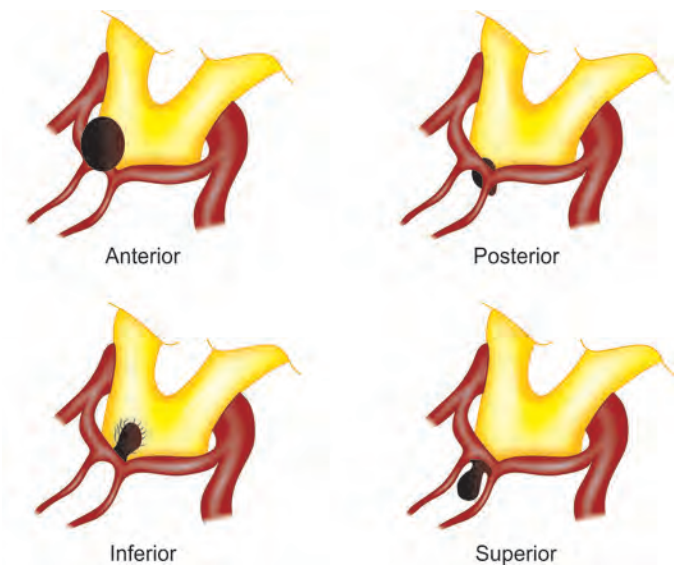


Fig. 1: Illustration showing the various directions of the ACoAA

MICROSURGICAL ANATOMY OF ANTERIOR COMMUNICATING ARTERY COMPLEX

Anterior Cerebral Artery

This artery arises as one of the two terminal branches of the ICA at the medial end of the Sylvian fissure. It runs anteriorly and medially above the chiasm (70% of cases) or optic nerve and enters the interhemispheric fissure.[86] Arteries from both sides are joined together by the ACoA at the beginning of the interhemispheric fissure. These two arteries then ascend in front of the lamina terminalis to pass into the interhemispheric fissure. The arteries make a smooth curve around the genu of the corpus callosum and pass backwards in the pericallosal cistern. The pericallosal artery continues backwards along the splenium to anastomose with splenial branches of the posterior cerebral artery. The ACA is divided into three segments.

1. The segment from the bifurcation of the ICA to the point of origin of the ACoA is known as A1 segment. This is also known as the horizontal part of the ACA.
2. The segment distal to the ACoA up to the point of origin of the callosomarginal artery is known as the A2 segment.
3. The part distal to the origin of the callosomarginal is termed pericallosal artery.

The A1 segment of the ACA runs forward and medially from the bifurcation of the internal carotid. Small perforating branches originate from this segment to supply the genu, the posterior limb of the internal capsule and the rostral thalamus. Proximal branches supply the anterior limb of the internal capsule. It also supplies the optic chiasm, hypothalamus and anterior commissure.

Proximal A1 segment aneurysms constitute less than 1% of all aneurysms. These can also give rise to bleeding into the septum pellucidum and the pre-operative computerised tomography (CT) scan can be misleading. They can be associated with fenestration of the A1 segment. Depending upon the site of origin, they are divided into the following five groups:[108]

1. Junction of the A1 segment and a perforating artery
2. A1 segment directly
3. Proximal end of A1 fenestration
4. A1 segment and cortical branch
5. Fusiform dilatation of A1 segment

The recurrent artery of Heubner arises from the A2 segment in about 80% of cases.[85,86] It then runs laterally and passes in close relationship to the superolateral aspect of the proximal ACA or A1 segment. It turns upwards and backwards to enter the anterior perforated substance.

ANTERIOR COMMUNICATING ARTERY COMPLEX

The ACoA overlies the optic chiasm at the level of lamina terminalis. The average length of this artery is 4 mm (0.3–7 mm) and it consists of a single or multiple channels. Three to four branches arise from the posterior/inferior aspect of the ACoA and supply the fornix and septal region.[92] Pai et al.[85] studied the anatomy of the ACA-ACoA complex in Indian subjects. They found variations were more in the ACoA and DACA segments rather than the A1 segments. The diameter of the ACoA (anteroposterior) ranged from 1 to 3.5 mm with a mean of 2.1 mm. The length of the ACoA ranged from 1 mm to 4 mm with a mean of 2.45 mm. All the ACoAs in their study gave rise to perforators. These ranged from 1 to 5 in number with a mean of 3. These arose from the posterosuperior surface of the ACoA and coursed superiorly. They may arise as a large stem vessel or multiple thin small vessels. In one case the ACoA gave rise to the pericallosal artery which coursed directly anterosuperiorly over the genu and then posteriorly over the corpus callosum. Rosner et al.[92] studied the microsurgical anatomy of the anterior perforating arteries, the group of arteries that enter the brain through the anterior perforated substance and observed that the ACA branches arose from the A1 segment and from the recurrent artery. Intrasellar aneurysms originating from the ACoA are located above the chiasm or optic nerves. The A1 courses above the optic chiasm or nerves to join the ACoA. The junction of the ACoA with the right and the left A1 is usually above the chiasm (70% of brains) rather than above the optic nerves (30%). Of the arteries traversing above the optic nerves, most traverse above the nerve near the chiasm rather than distally. The arteries with a more forward course are often tortuous and elongated and some of them rest on the tuberculum sellae or planum sphenoidale. The length of A1 varies 7.2–18.0 mm (average 12.7 mm). Camuscu et al.[20] describe the microanatomy of the perforating arteries arising from the ACoA complex (distal 5 mm of the A1 segment, the ACoA and the proximal 5 mm of the A2 segment). As important perforating arteries arise both from the A1 segment and the ACoA, dissection in this area should be careful while isolating the neck of the aneurysm. Vascular anomalies are common in the region of the ACoA.[6,11,60,63,71,100] These include, accessory ACA, azgous anterior cerebral, occasionally hypoplastic anterior communicating and fenestration of anterior communicating and A1 segment.[6,13,63] Avici et al.[11] studied the anterior communicating complex in 25 cadaver specimens obtained at routine autopsy. In 15 specimens (60%), an anomalous ACoA was found. The most common anomaly identified was a multi-channelled ACoA. The first channel was always the smallest channel, and all of the perforators arose from this smallest channel 45% of the time. All other anomalous anterior communicating arteries presented with concomitant anomalous perforator anatomy. In clinical practice the difference in the reported incidence depends upon the surgical approach used.[80] These anomalies are visualised better with the interhemispheric approach.[84] The pre-operative vigilance and delineation of these anomalies is necessary to avoid accidental occlusion of these vessels, especially the median artery of the corpus callosum or third distal ACA, with a poor or fatal outcome.[37] Fenestration of the A1 segment,[73] and asymmetry of the ACA[71] are commonly associated with aneurysms in this region. Kwak et al.[63] observed fenestration in the ACoA or the presence of more than two anterior communicating arteries in 17 cases (5.7%). As the anomaly was duplicated in some of these cases, the total number of cases with anomalies of the ACoA was 26 (8.8%) out of 296 cases. Perlmutter and Rhoton[86] found the origin of the recurrent artery of Heubner at the A2 segment in 78%, A1 in 14% and at the ACoA in 8%. Variations in the circle of Willis are often seen in patients with intracranial aneurysms.[60,114] Norlen and Barnum[82] described different patterns of circulation through the anterior part of the circle of Willis (Figs 2A to D). In an analysis of 100 patients with anterior communicating aneurysms, Sengupta et al.[100] found the following four types of collateral circulation:

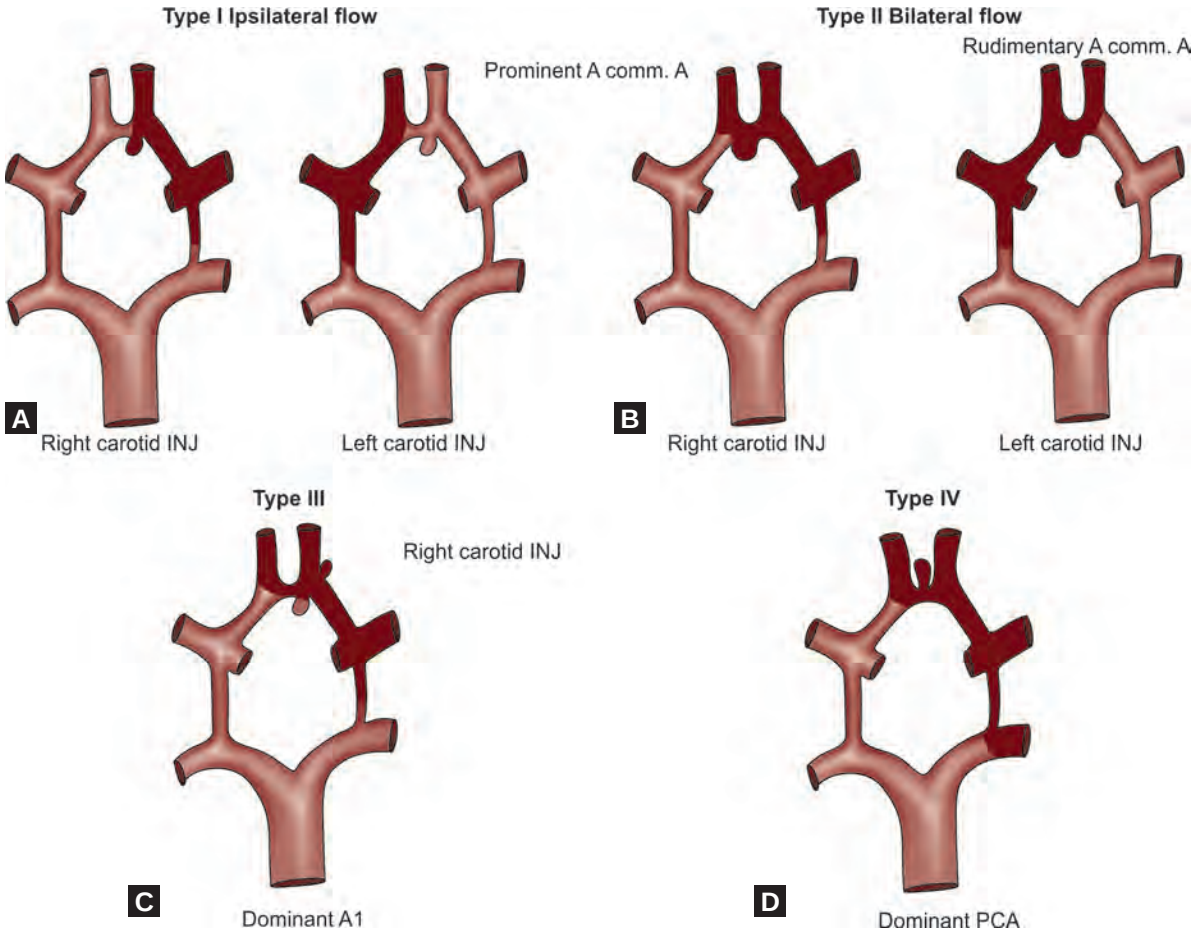
Type I: Ipsilateral (66%). In this type the aneurysm and the distal ACA fill from one proximal ACA.

Type II: Bilateral (14%). The aneurysm and both the ACAs fill from both carotid injections.

Type III: Dominant ACA (12%). The aneurysm arises from the axilla of the two anterior cerebral arteries, both of which fill from one anterior cerebral. The contralateral A1 segment is hypoplastic.

Type IV: Dominant ACA with foetal posterior cerebral artery (8%).

Murai et al.[78] reported a patient with a heterogeneously enhancing, partially calcified intrasellar mass on Magnetic resonance imaging (MRI) and the normal pituitary gland was identified at the bottom of the sella, and the optic chiasm was located superior to the aneurysm. Digital subtraction angiography (DSA) and 3D computed tomography angiography demonstrated the mass to be a partially thrombosed ACoAA. Intrasellar aneurysms originating from the ACoA are likely to present difficulty in dissecting the neck of the aneurysm from the bilateral optic nerves and pituitary stalk, impeding direct aneurysm clipping. Kawashima et al.[55] report an unusual variant of a ruptured ACoAA located on the planum sphenoidale where the course of both the A1s were not tortuous, but were rather straight. The left A1 was 20.5 mm in length.



Figs 2A to D: Patterns of circulation through the anterior part of the circle of Willis. (A) Type I circulation showing ipsilateral filling of the ACA on carotid injection. (B) Type II circulation showing bilateral filling of ACA from either carotid injection. (C) Type III circulation (dominant) with the opposite Alhypoplastic and with poor collateral circulation. (D) Type IV circulation (dominant with foetal PCA) with very poor circulation

Supreme Anterior Communicating Artery

Albert et al.[3] reported on a rare case of a ruptured pericallosal aneurysm originating from an atypical communicating segment between both distal A2 arteries, called the 'supreme ACoA'. The neurosurgeon should be aware of this rare vascular anomaly that might be angiographically occult and raise unexpected intra-operative difficulties. Rarely, an anomalous ACA can arise from the ICA at the bifurcation.[28] The aberrant artery coursed anteriorly along the ipsilateral olfactory tract and made a hairpin turn posterior to the olfactory bulb, supplying the circulation of the ACA. Persistence of the primitive olfactory artery is suggested as the embryological origin of this vascular anomaly.

CLINICAL FEATURES

Most ACoAAs present with a bleed causing the classical "thunder clap" headache described commonly by patients as the "worst headache of their life". Not taking cognisance or failing to take this history can lead to the diagnosis being missed with disastrous consequences. These aneurysms can present with loss of consciousness, seizures, anosmia, oculomotor nerve paresis,[90,94] diabetes insipidus or hypothalamic dysfunction. The aneurysm can cause a large frontal haematoma or intraventricular bleed. Acute and chronic hydrocephalus can be the cause of neurological deterioration in these patients.

The "ACoA Syndrome"

Patients with ACoAAs may present with memory disturbance,[4] confabulation, paraparesis and personality changes. This has been characterised as the "ACoA syndrome". Greene et al.[38] in a clinicopathologic evaluation of patients with lower extremity weakness following rupture and repair of ACoAAs found angiographic vasospasm in the ACA distribution in all their cases, and this paraparesis persisted beyond the angiographic resolution of vasospasm. All their patients had evidence of frontal lobe dysfunction throughout their post-operative course and deep venous thrombosis and pulmonary emboli were common causes of morbidity and mortality. Their autopsy data supported regional microvascular ischaemia within the ACA distribution as the aetiology of these motor deficits. The combination of vasospasm in the ACA distribution and lower extremity weakness associated with cognitive and affective impairment that resolves with time is common in patients with ACoAAs. They propose that this constellation of clinical,

radiographic and pathologic findings be referred to as the "ACoAA paraparesis syndrome". Sensory disturbances are also seen. Gait apraxia is defined as the loss of ability to walk in the absence of weakness. Extrapyramidal symptoms and incontinence result due to injury involving the anterior cingulate gyrus, medial superior frontal gyrus or the superolateral frontal gyrus. Altered states of sensorium similar to akinetic mutism are seen along with abulia, a decrease in spontaneous speech with increased response latency and decreased capacity to persist while doing an activity.

Vascular injury to the corpus callosum causes a type of disconnection syndrome with ideomotor apraxia, agraphia and tactile anomia restricted to the left hand. Pathological grasp phenomena or alien hand syndrome can be an associated finding. Vascular injury to the frontal lobe or basal ganglia has been linked to the pathological grasp reflex seen in these patients.

Neuropsychological Symptoms

Neuropsychological examination must be detailed and performed in all patients with a suspected ACoAA both before and after surgery. These include Mini Mental Scale Examination (MMSE), the Micro Cognitive Test, Computerised Assessment of Cognitive Function (CACF), Wisconsin Card Sort, Trail-making Test, Rey's Complex Figure Test and Recall and portions of the Wechsler Memory Scale 3 among others. Beeckmans et al.[15] correlated the neuropsychological performance of five patients with an ACoA syndrome (amnesia, confabulation and personality changes) with neuroimaging techniques and found basal forebrain and frontal lobe pathology in all patients, and all patients displayed a profound amnesic syndrome. Retrograde amnesia characterised by a temporal gradient was seen with normal short-term memory. Böttger et al.[17] hypothesised that lesions of the medial septum and nucleus of the diagonal band of Broca were closely associated with memory deficits and prefrontal lesions were associated with attentional, executive and psychopathological dysfunctions. Bilateral lesions were associated with severe disturbances. The type and severity of these deficits were independent of the side of lesion in unilateral cases of gyrus rectus resection, and of the Hunt and Hess grading system according to them. Alexander et al.[4] studied 11 patients with amnesia and personality change after surgical repair of ruptured ACoAA. The CT and clinical evidence suggested that infarction in the territory of the ACoA was responsible for amnesia and personality change. The medial septal nuclei, the paraventricular nucleus of the anterior hypothalamus and the medial forebrain bundle were the probable regions involved. Gross infarction in the frontal lobes was not a requirement for the syndrome. Diamond et al.[29] explain that in these patients amnesia is seen despite traditional cerebral areas implicated in memory disturbances not being damaged. Mavaddat et al.[74,75] support the dual lesion hypothesis (damage to both frontal lobes and basal frontal lobes) to have the ACoA syndrome. They also feel that involvement of basal frontal cholinergic and the medial temporal circuit accounts for the amnesia.

Visual Symptoms

The ACoAAs can cause visual symptoms by direct chiasmal and optic nerve pressure or due to indirect ischaemic aetiology. Chan et al.[23] described six cases of leaking anterior communicating aneurysms that caused acute monocular blindness. They explained that as the aneurysm enlarges, the down-pointing dome compresses the optic nerve from above and adheres to it. When the aneurysm ruptures through the adherent dome, it bleeds directly into the optic nerve, resulting in severe headache and monocular blindness. Direct optic nerve compression by the aneurysm is also possible. Umredkar et al.[110] reported that monocular blindness can result due to the direction of the growth of fundus of large ACoAAs and compression of the optic nerve, and also due to the haemorrhage into the optic nerve. Distortion or traction, and indirect pressure on the optic nerves at the margins of the optic foramina also play an important role. Another factor cited by them is the interference with the blood supply of the optic nerve or chiasma either by occlusion or distortion of the perforating arteries. In large ACoAAs, the intra-aneurysmal thrombus may occlude the origins of the branch vessels supplying the optic nerves and chiasm, thus causing ischaemia. An adherent optic nerve to the fundus of the ACoAA may be damaged from direct haemorrhage.

Endocrinological Symptoms

The syndrome of inappropriate secretion of antidiuretic hormone (SIADH), cerebral salt wasting syndrome and diabetes insipidus are seen in these patients and they need to be differentiated as the treatment modalities differ significantly. Sayama et al.[95] studied the incidence and timing of hyponatraemia (Na < 135 mEq l-1) after subarachnoid haemorrhage with special reference to ruptured ACoAAs. The ACoAA group had a significantly higher incidence of mild hyponatraemia and severe hyponatraemia than other groups. Among ACoA cases, hyponatraemia occurred significantly more often in grade III and IV cases, in cases with vasospasm, and in cases with hydrocephalus. Respective days of onset for symptomatic vasospasm and for hyponatraemia were day 7.6 ± 4.4 and day 10.6 ± 5.8 following SAH, representing a 3-day delay for hyponatraemia. In most patients hyponatraemia resolved within 28 days following SAH. Hyponatraemia occurred more often with ACoAAs, possibly due to vasospasm around the ACoA or hydrocephalus causing hypothalamic dysfunction. Since hypervolemic therapy can cause hyponatraemia, particularly careful observation is required during such therapy in patients with ACoAA. Panhypopituitarism is also seen and Nukta and Taylor et al.[83] reported that the panhypopituitarism could be due to injury to the anterior pituitary or the hypothalamus.

Hydrocephalus

Cerebrospinal fluid (CSF) diversion procedures are often required in patients with an ACoAA.[9,62,103,118] These aneurysms are close to the third ventricle and lamina terminalis and often the aneurysmal bleed extends into the ventricle and can cause acute hydrocephalus causing rapid clinical deterioration within 24–48 hours after SAH. Hydrocephalus requiring shunt placement is a common complication after aneurysmal subarachnoid haemorrhage (aSAH). Komotor et al.[62] found fenestration of the lamina terminalis appears to be associated with a decreased incidence of shunt-dependent hydrocephalus of more than 80% after aSAH.

INVESTIGATIONS

Once the history or clinical features are suggestive of an ACoAA presenting as a bleed or with the varied symptoms described above the patient must be rapidly shifted to a neurosurgery centre where all investigations are carried out on an emergency basis and appropriate therapy is instituted as early as feasible to avoid the risk and devastating consequences of rebleed. Patients undergo routine haemogram, liver and renal parameters are checked along with complete coagulation profile. A physician, cardiologist and anaesthetist urgently evaluate and clear the patient followed by the neurosurgeon who decides on how to investigate further and manage the case.

Conventional Angiography

Multiple angiographic views (standard, oblique, submental vertex views) are usually required to visualise these aneurysms. Oblique views with the ACoA artery projected into the centre of the left and the right orbits are essential pre-operative studies. A basal view is helpful. These angiograms must be studied carefully for multiple aneurysms. Individual aneurysms are studied for their morphology, direction, flow features and associated vasospasm. In a few cases the aneurysm may not be visualised in the angiogram. The angiogram reveals whether the aneurysm fills from one or both sides and cross compression verifies whether collateral flow is present. In analysing the angiogram attention is paid to see if the ICA is long or short, as a long ICA makes the visualisation of the ICA bifurcation difficult and to follow the A1 to the ACoAA brain excessive retraction may be required. DSA, a 3D rotational angiogram or 4D angiogram are routine (Fig. 3). Anterior communicating aneurysms rarely arise from the ACoA itself. From a careful study of the angiograms the position of the neck of the aneurysm can be ascertained in the majority of cases. The aneurysm is usually to one side of the ACoA in relation to one of the major vessels. An understanding of this is important for successful occlusion of the neck without compromise of other vessels. The anatomical variations of the ACoA complex occasionally allow the inclusion of one half of the ACoA in the clip

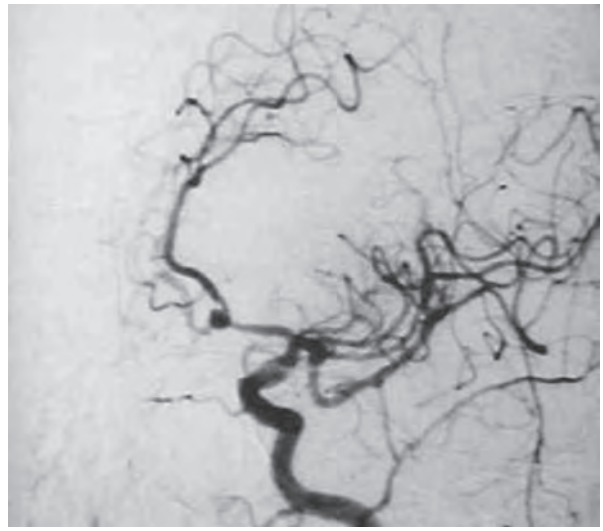


Fig. 3: Four vessel DSA showing ACoAA

without any untoward effects.[100] The small perforating vessels which arise from the ACoA (3–4 in number) will be perfused from the opposite ACA in such occasions. Jha et al.[52] reported a series of 44 consecutive patients with aneurysms of the ACoA during an 8 years period; these formed 55% of all aneurysms operated during this period. Eight patients (18.2%) had multiple aneurysms. Twenty-seven ACoA aneurysms (61.4%) were directed antero-inferiorly, 8 (18.2%) postero-superiorly, 6 (13.6%) superiorly and 3 to the side (Fig. 2). Twenty-nine (65.9%) arose at the dominant A1-ACoA junction.

Computerised Tomography

Computerised tomography (CT) of the brain is generally the first investigation ordered after a thunderclap headache. The CT shows characteristic anterior interhemispheric fissure SAH and a frontal intracerebral haematoma should raise the suspicion of a bleed due to an ACoAA. Diffuse and extensive SAH is often seen and attention is then paid to look for the usually globular hyperdense aneurysm in the ACoA region (Fig. 4). Flame shaped intraparenchymal haematomas

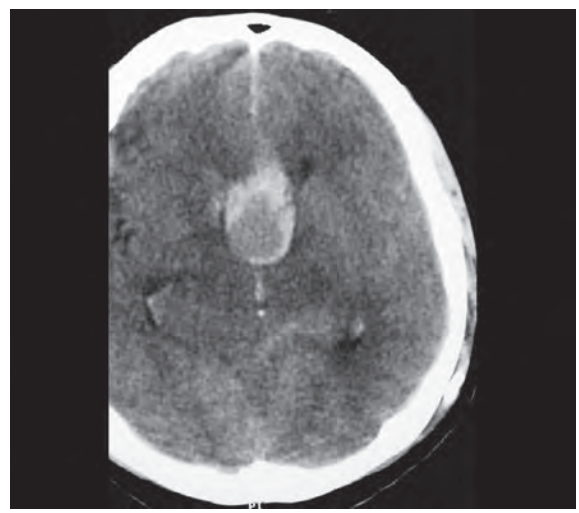


Fig. 4: The CT scan brain showing large globular ACoAA

in the gyrus rectus are characteristic of ACoA aneurysmal bleed. Yock et al.[118] analysed the CT findings in 19 cases of ruptured ACoAAs and compared these with the angiographic appearance. They observed: (a) occasional negative scans, (b) visualisation of non-giant aneurysms on infused axial scans, (c) common asymmetric subarachnoid haemorrhage, (d) involvement of the anterior interhemispheric fissure whenever subarachnoid haemorrhage is visualised, (e) "typical" septal haematoma in a minority of cases, (f) frequent infarction, particularly in the ACA distribution, (g) "meningeal hyperaemia" seen on post-contrast scans and (h) little correlation between angiographic aneurysm orientation and the location of haemorrhage on CT scan. Calcified aneurysm and atherosclerotic walls may be seen in giant aneurysms. Hydrocephalus was seen in 25% of their cases. Frontal lobe infarcts were seen in 20% of cases and bilateral anterior infarcts were seen due to associated vasospasm. A normal CT scan should be looked at with caution and if the history and clinical features are pointing to an ACoA aneurysmal bleed a lumbar puncture should be done to look for crenated RBCs and evidence of SAH.

3D Computerised Tomography Angiography

The 3D-4D CT angiography can be done in the emergency situation and provides a very good 3D idea of these complex aneurysms and adjacent structures and vessels (Figs 5 and 6). Villablanca et al.[112] evaluated the utility of volume-rendered helical CT angiography in patients with intracranial aneurysms. The CT angiography was reported to be superior to both DSA and MR angiography in the evaluation of the arterial branching pattern at the aneurysm neck, aneurysm neck geometry, arterial branch incorporation, mural thrombus and mural calcification. For surgical cases, CT angiography had a significant impact on treatment. Beck et al.[14] reported about accurate size and location of a consecutive series of ruptured and un-ruptured aneurysms taking the complex 3D anatomy and parent vessel morphology into consideration by using the newly developed 3D rotational angiography (3D-RA).

Anduluz et al.[8] reported that DSA failed to reveal an aneurysm in three patients, which were eventually diagnosed by CT angiography. 3D-CTA is a superior imaging modality to magnetic resonance angiography (MRA)

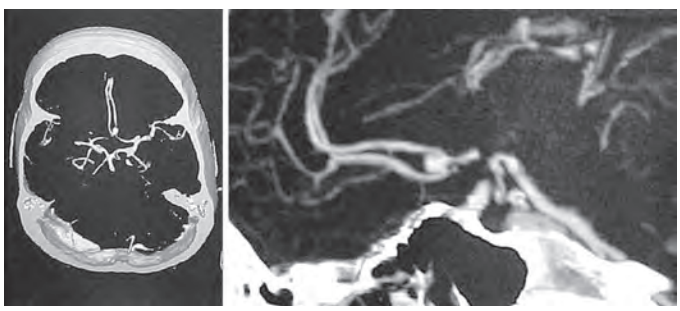


Fig. 5: Reconstruction CT angiogram appearance of the ACoAA

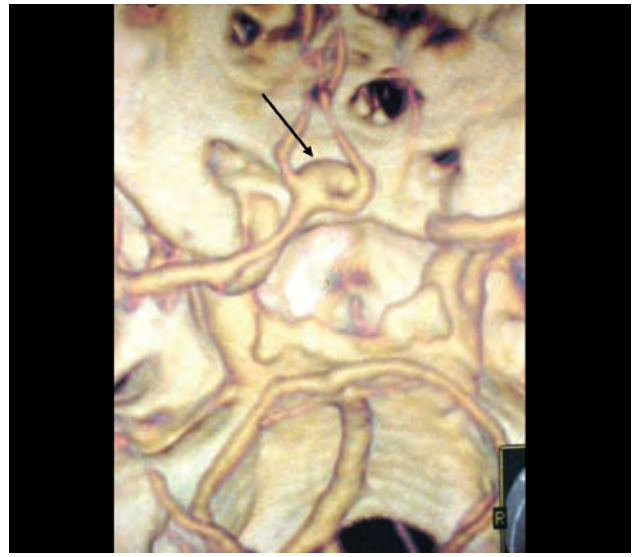


Fig. 6: 3D reconstruction of the CT angiogram showing ACoAA

and DSA in understanding the relationship between the aneurysm and surrounding structures in spite of the bony artifacts. The CT angiogram shows the regional anatomy around the ACoAA and patient specific variations in the skull shape and bony landmarks should be studied to plan the surgical corridor and manoeuvres to clip the aneurysm. In two cases, the authors found that aneurysms were initially misdiagnosed as a single complex aneurysm based on routine cerebral angiograms, but special angiographic views demonstrated double aneurysms. In one case, multiple ACoAAs could be identified using 3D-CT angiography. Double fenestration of the ACoA complex associated with an aneurysm is a very rare finding and is usually caused by ACoA duplication and the presence of a median artery of the corpus callosum. De Oliveira et al.[28] reported a patient, in whom double fenestration was not associated with ACoA duplication, representing, therefore, a previously unreported anatomic variation. The DSA images missed the double fenestration which was disclosed by 3D-RA, indicating the importance of 3D-RA in the diagnosis and surgical planning of intracranial aneurysms. Presence of bi-lobed or multilobed ACoAAs should raise the suspicion of kissing aneurysms.[12,79,113] Shekar et al.[98] found that the technique of 3D-CT angiography was useful in delineating the vascular anatomy and its relation to the cranial base structures. This helped the surgeon to plan the appropriate approach to the aneurysm. Inci and Ozgen[47] studied 146 patients with ACoAAs. Six (4.1%) of these patients harboured multiple aneurysms of the ACoA. The size of the ACoAAs ranged from 3 to 12 mm (mean 5.3 mm). In bilobular ACoAAs, special angiographic projections and 3D-CT angiography or 3D DSA should also be performed to obtain a correct diagnosis. The differentiation of two aneurysms from a bilobular aneurysm during the pre-operative period is important for surgical planning.

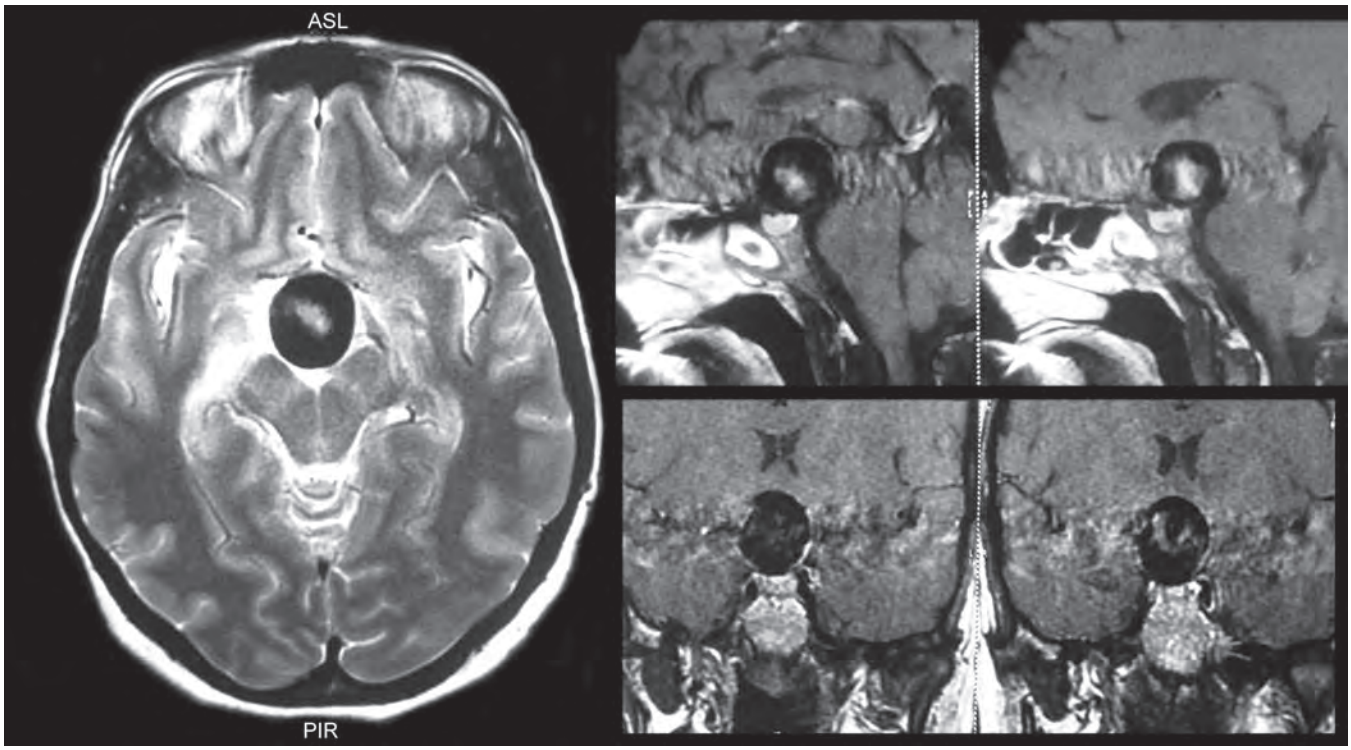


Fig. 7: MRI scan of the brain showing large ACoAA in the suprasellar region with an intramural thrombus

Magnetic Resonance Imaging and Magnetic Resonance Angiography

The MRI shows these aneurysms and the regional neuroanatomy very well. This is the best modality to visualise the infarcts and regions of ischaemia. Aneurysms missed on conventional angiography can be seen sometimes. The morphology, configuration of aneurysm and fundus direction are well observed. The MRI is indispensible in the evaluation of giant ACoAAs as angiography can underestimate the true size of the aneurysm due to a large thrombus (Figs 7 and 8). In a significant number of patients with SAH angiography can be normal.

Fig. 8: MR angiogram showing the ACoAA of the patient as in Figure 7

Currently, repeat cerebral angiography is done after 1–8 weeks, during which time a number of these patients can rebleed with considerable morbidity and mortality. Vassilouthis et al.[111] suggest that MR angiography, guided by the CT findings, probably has a place in the management of these patients with SAH of "unknown aetiology" before repeat catheter angiography is undertaken.

CLIPPING AND COILING DEBATE IN THE MANAGEMENT OF ANTERIOR COMMUNICATING ARTERY ANEURYSMS

The ACoAAs are least amenable to interventional methods of treatment due to multiple factors.[16,31,77] The endovascular techniques to treat aneurysms require that the intimal proliferation occurs over the platinum coils and the thrombus forms to obliterate the aneurysm. In ACoAAs due to the aneurysm being in the direct line of flow this intimal proliferation may be less optimal than in side wall aneurysms.[16] The ACoAAs are smaller and their sac may be too small for coil placement. Other factors complicating the treatment were when the aneurysmal neck was not clearly distinct from the adjacent or parent vessels or because the aneurysm sac was too small and treatment may be difficult due to atheroma of the cervical and intracranial vessels. The rarer variants of ACoAAs including the giant,[21,42,48,59,70] fusiform,[43,93] kissing[12,113] and blister aneurysms[8,51] require complex decision making and evaluation. Giant ACoAAs are less amenable for treatment by coiling and tend to have significant residual lumens and tendency to recanalise post coiling and these may require special

types of stents. The contention that microsurgical clip application should be the preferred option in the treatment of ACoAAs with anteriorly directed fundi and that endovascular packing is selected for those lesions with posteriorly directed fundi, depending on morphological criteria is currently followed.[16,31,77]

SURGICAL TECHNIQUE

The majority of the aneurysms in this area point anteriorly and inferiorly, and are safely clippable. The posterior and superiorly pointing aneurysms are fraught with more risks due to the proximity and involvement of ACoA perforators, recurrent artery of Heubner and A2 segments.[85] Pai et al.[85] in their study of ACoA in Indians found that the anterior border of the A1 segment was devoid of any perforators and dissection carried along this border in approaching the ACoA is advisable. The postero-superior perforators are frequently more in the lateral A1 segment than the medial portion. Hence Pai et al.[85] also advocated that during surgery the temporary clip should be placed as medially as possible to avoid perforator ischaemia.

Hernesniemi et al.[43] review the practical microsurgical anatomy, importance of pre-operative imaging in surgical planning and microneurosurgical steps in dissection and clipping of ACoAAs. As ACoAAs have a higher tendency to rupture, incidental unruptured aneurysms in size between 5 mm and 25 mm can be safely operated upon by experienced neurosurgeons with low morbidity and mortality in young and healthy patients. These authors feel that patients who are elderly and with associated co-morbidity may not benefit from elective clipping of an unruptured aneurysm. Great skills and experience are required in the surgical management of the ACoAAs due to the disproportionate fundus to neck ratio. A broad based neck which incorporates the parent vessel and mass effect that can totally alter regional anatomy may make clipping impossible at times. The ACoAAs present frequently with SAH when they are small.[43] Furthermore, unruptured ACoAAs may have increased risk of rupture regardless of size; also they may be associated with other aneurysms. The aim in microneurosurgical management of an ACoAA is total occlusion of the aneurysm sac with preservation of flow in all branching and perforating arteries. Shanno et al.[102] advocated the use of image guidance in ACoAA surgery. The surgical trajectory should provide optimal visualisation of the ACoA complex without unnecessary brain retraction. Temporary clips, pilot clips and a wide selection of fenestrated and normal clips along with a good surgical and radiological pre-planning are required in complex giant aneurysms. Cranial base approaches[98] are routinely used and give more exposure with minimal retraction. Figueiredo et al.[33] compare the angles of approach and area of exposure to the ACoAAs associated with pterional (PT), orbitopterional (OPT) and orbitozygomatic (OZ) craniotomies before and after gyrus rectus resection. The vertical and horizontal angles of approach to the ACoAA complex were significantly larger for the OPT and OZ approaches compared with the PT approach. Use of the OZ approach may decrease the need for frontal lobe retraction and resection of the gyrus rectus according to them.

PRE-OPERATIVE MEASURES

All patients with a ruptured ACoAA should be immediately admitted in a neurosurgical intensive care unit and standard guidelines[76] are useful to decide on patient management. The patient is monitored closely to treat haemodynamic and neurological deterioration. Anticonvulsants, steroids and calcium channel blockers are used as indicated. Close watch is maintained to pick up vasospasm which may require aggressive treatment. Without definitive therapy surgery 4% bleed on the first day, thereafter for two weeks the daily risk is 1.5%, and 25% bleed within 6 months and thereafter have a yearly bleed rate of 3% per year. The functional survival rate is a dismal 18% at 10 years. Early surgery is therefore commonly practiced.

Nathal et al.[80] compared the intra-operative anatomical findings of the ACoA complex in 46 patients with anatomical variations to those in an equal number of patients without variations in order to determine the visualisation of the elements of the vascular complex. Visualisation of the vascular elements was similar in patients with or without anatomical variations. The differences observed were dependent on the surgical approach selected and on the projection of the aneurysm. It was found that, even when the intra-operative anatomical field and the number of vascular elements visualised are different from those obtained in autopsy studies, the vascular microanatomical characteristics can be confirmed with each surgical approach to the extent necessary to ensure safe clipping of aneurysms in patients both with and without anatomical variations.

APPROACHES TO ANTERIOR COMMUNICATING ARTERY ANEURYSMS

The approaches to ACoAAs are: anterior, lateral and skull base approaches. The anterior approaches include the anterior interhemispheric, basal interhemispheric and the midline trephine approach.

Side of Approach

These are usually approached from the right side to prevent injury to the dominant hemisphere and because it is easier for a right-handed surgeon to approach from the right side. However, these aneurysms being in the midline are approached from the left or right side depending upon the side of the dominant A1, haematoma, direction of the fundus, pre-existant anterior cerebral territory infarct and radiographic characteristics seen on angiogram and CT angiograms. The dominant A1 is used for

achieving proximal control and also because the dome of the aneurysm is generally pointing towards the direction of main thrust of flow and away from the direction of the dominant A1. If there is a large frontal haematoma then it is advisable to operate from that side allowing for evacuation of haematoma and also preventing the possibility of bifrontal injury. Similarly, a large infarct on one side may warrant an approach from the same side.

The Subfrontal Modified Gyrus Rectus Approach

Kempe and his colleagues[56,57] popularised the original idea of Falconer[32] to approach the ACoA complex through the gyrus rectus. Gyrus rectus dissection does not cause any effect on the outcome.[46] The patient is placed supine on the table with the chest piece elevated 30 degrees and the head piece is lowered 15 degrees. During the early part of the operation the head piece can, however, be kept elevated for convenience of performing the craniotomy. The head is turned 45 degrees to the opposite side and placed on a ring to allow change of angle during surgery, if necessary. The ipsilateral shoulder is raised on a sandbag to avoid traction on the brachial plexus and facilitate venous drainage. The aim is to allow the pterion to face directly upwards. This allows the frontal lobe to fall away from the floor of the anterior cranial fossa when the arachnoid dissection is complete and the optic nerve can be seen with a little retraction.

The skin incision runs along a line starting in front of the tragus, gently curving behind the hairline medially and anteriorly to the midline and gently backwards up to the point in the plane of the mid-point of the opposite pupil. This ¾ coronal scalp flap meets all the requirements. If a cosmetic scar is not of paramount importance, a short incision curving forwards to a point about 1.5 cm in front of the hairline at the level of the ipsilateral pupil will be quicker. While incising the scalp care is taken to avoid injury to the main stem of the superficial temporal artery and the temporalis muscle. The scalp flap is reflected over the brow. While elevating the scalp flap it is wise to mark the midline for orientation during placement of burr holes. The supraorbital and supratrochlear nerves are carefully separated from the periosteum and stay with the scalp flap. Placement of the craniotomy is crucial. The bone flap should be generous and extend as close to the floor of the anterior cranial fossa as possible, and the medial limb should be in the plane of the ipsilateral pupil. If the frontal sinus is opened the mucosa should be removed and the sinus sealed with bone chips and pericranium before opening the dura. The crucial burr hole is the one above the zygomatic process which should expose the frontal and temporal fossa. Although the use of craniotome and power drills are common multiple burr holes connected with Gigli saw are also an option. Craniotomy should expose the Sylvian fissure well. The lateral half of the sphenoid wing must be removed and the bony margins waxed. In elderly persons the dura is often adherent to the bone and great care is necessary to prevent laceration of the dura and the underlying brain. The bone flap with the attached temporalis muscle is now reflected laterally and held in position with fish hooks. The dura is hinged against the bone margins with hitch sutures to prevent extradural bleeding.

On palpating the exposed dura, the brain tension can be assessed. If there is any tension, CSF is removed via a lumbar drain if already in place. When the ventricles are enlarged on the CT, the frontal horn of the lateral ventricle is cannulated and a ventricular catheter is introduced to remove CSF. The CSF should not be drained excessively as this makes subsequent arachnoid dissection difficult. Once the dura is slack a linear incision is made 1 cm above the anterior margin of the bony opening along the entire length of the exposed dura. After opening the dura, the headpiece of the table is lowered to allow maximum extension of the head, making sure the head is resting comfortably on the ring and the endotracheal tube is not disturbed. A 1.5 cm wide hand-held retractor is used to retract the orbital surface of the frontal lobe. If the optic nerve can be visualised with minimal frontal lobe retraction, the position of the head is ideal. It must be appreciated that undue retraction of the brain can cause oedema resulting in decreased blood flow.[10,41,96] The retractor is now attached to the Leyla (Aesculap) self-retaining retractor system mounted on the left side of the operating table.

The operating microscope with 300 mm objective is now brought into the operating field. The paraoptic cisterns are opened with a sharp 22 gauge needle bent 90 degree at the tip and mounted on a suitable handle. This is the cheapest and finest arachnoid knife that is available in any operating theatre. As the CSF starts to flow it is sucked out. The arachnoid is divided with scissors from the pre-chiasmatic cistern medially to the lateral limit of the exposure. The arachnoid over the medial end of the Sylvian fissure is very thick. With careful division of this thick band the frontal lobe will fall back without any tension on the temporal lobe. While dissecting the arachnoid medial to the optic nerve, care must be taken not to disturb the anteriorly projecting aneurysm or the blood clots in the pre-chiasmatic cistern. If the angiogram suggests a backward or inferiorly projecting aneurysm the arachnoid over the opposite optic nerve and A1 is divided. During these early stages, the retraction over the frontal lobe should be kept over the lateral aspect of its orbital surface to avoid any tension on the aneurysm complex. Once the proximal part of the internal carotid and the olfactory tract are exposed, this stage of the operation is complete (exposure of ICA bifurcation and A1 segment are avoided in this approach).

The brain retractor is now replaced over the medial aspect of the orbital surface of the frontal lobe just above the olfactory tract without any tension on the interhemispheric fissure. A site below (medial) the olfactory tract is now selected for corticectomy in the gyrus rectus. A 1.5 cm incision is made over the cortex with bipolar

coagulating forceps. Cortical tissue 1 cm^3 in volume is removed in such a way as to enable the interhemispheric fissure to be reached. The suction pressure is crucial at this time, as the arachnoid in the interhemispheric fissure over the aneurysm complex should not be disturbed at all. If the frontopolar or orbitofrontal arteries come in the way, they should be sacrificed. After removal of this cortical tissue, a suitable size retractor can be placed over the olfactory tract deep into the cavity created by corticectomy and the frontal lobe retracted further without any tension on the aneurysm complex.

The next stage of dissection is crucial. The risk of premature bleeding is highest at this stage. The blood pressure should be allowed to fall gradually to 80 mm systolic in a normotensive patient. Magnification is increased to a comfortable level. A second suction is kept ready and so also a temporary clip. The surgeon should be mentally prepared to tackle bleeding from the aneurysm. In spite of all pre-operative planning, the anatomy of the aneurysm complex may appear confusing at the beginning. The pia-arachnoid in the interhemispheric fissure is generously dissected using suction and bipolar forceps. This will expose the A2 or the ACoA region. The dissection is kept on the outer side, to avoid the aneurysm and the perforating vessels. If the aneurysm is found to be tense at this stage, the proximal part of A1 is cleared of arachnoid and a site free of perforators is chosen for temporary clip application. If the configuration of the circle is normal, enough blood will perfuse the brain supplied by the occluded A1. However, if a temporary clip is applied on both A1 arteries, the blood pressure should be elevated to 100 mm.

In this approach, the vasculature ipsilateral to the aneurysm complex and the adjacent ACA will be seen. Contralateral vessels remain obscured by the aneurysm itself. An attempt is made to pass a fine hook to the free border of the aneurysmal neck before dissecting the adherent side. If this should fail, coagulation of part of the sac with a broad tip bipolar forceps will shrink the aneurysm sufficiently to discover or create a cleavage for the passage of the clip. If one of the cortical vessels gets in the way at this stage, it is coagulated and divided but not separated from the sac. The Heubner's artery is always away from the sac and is not seen unless looked for. Perforating vessels from the ACoA are also not looked for, as these get separated (segregated) when the neck is shrunk all around at the final stages of dissection. After clearing the neck on the opposite side, attention is drawn to the ipsilateral side with the adjacent A2. Again, gentle coagulation of the adjacent part of the sac under hypotension will expose the potential space which is further dissected free with micro scissors. If the aneurysm is projecting laterally underneath the A2, separation of the vessel is done with a temporary clip on A1. With the sac being slack, careful coagulation of the sac will expose the ipsilateral borders of the neck. If there is a leak from the aneurysm, gentle pressure on the cottonoid with the left hand sucker will allow continued dissection or coagulation of the rent. Using bipolar coagulation, it is possible to render a broad neck small. Once the neck has been isolated all around, a crucial decision must be made as to which size and shape of clip is appropriate to obliterate the aneurysm. The length of the clip is usually 1.5 times the diameter of the neck of the aneurysm, i.e. a 10 mm neck needs a 15 mm clip to occlude it. The tip should be advanced gradually beyond the neck and released gradually to avoid a tear in the neck. Distortion of the clip by the overlying frontal lobe should be avoided. Pieces of muslin are placed around the clipped neck. Papaverine 2.5% solution is instilled over the exposed vessels.

The dura is not closed in acute cases of ruptured aneurysms. If necessary, dural graft is used to provide space for brain swelling. Ventricular drainage is continued if the ventricles are large. The bone flap is secured loosely to the pericranium and muscles. Post-operatively the pupillary size is noted. Papaverine can cause pupillary dilatation.

Pterional Craniotomy

A fronto-temporo-sphenoidal craniotomy of Dandy[26] as modified by Yasargil[115] is the most commonly used approach to ACoAAs and is especially preferred for inferiorly projecting aneurysms. This approach is also optimised by using a tailored resection of the gyrus rectus to expose the ACoAA.

The medial aspect of the Sylvian fissure is opened and the carotid bifurcation defined. The cisterns are opened to let out the CSF. The arachnoid fibres running between the olfactory tract and the optic nerve are divided to allow the frontal lobe to be retracted. The ACA (A1 segment) is exposed by opening the cistern of the lamina terminalis on the antero-superior aspect of the vessel. To avoid spasm of the perforating vessels the A1 is not exposed in its entire course. By following the lamina terminalis cistern medially, the surgeon will come to the ACoA complex. Further dissection depends upon the direction of the aneurysm, superiorly (84%) or forwards (16%). If the aneurysm is directed superiorly, the left ACA is identified and dissected medially, towards the A1 complex. This step should be postponed if the aneurysm is directed forwards. Occasionally, 1 cm of the gyrus rectus has to be resected to define the anatomy clearly, before application of the clip on the neck. A careful search should be made for the presence of a third A2 segment. In this procedure both A1 and A2 segments bilaterally, Heubner's artery and the hypothalamic perforators are identified.

Anterior Interhemispheric Approach

This is used in cases where the ACoA is located more than 12–14 mm above the anterior clinoid process and when the aneurysm projects posteriorly in between the frontal lobes. The anterior interhemispheric approach[107] is via a bifrontal craniotomy and the dura is opened in

a W-shaped manner and turned anteriorly. After ligation of the superior sagittal sinus anteriorly, the anterior interhemispheric fissure is entered to identify A2 and this is followed up to the ACoA. Frontal lobe retraction is then done to expose the A1.

Coagulation of the bridging veins may be necessary in the interhemispheric approach to ACoAAs. Most people do not develop any infarct. However, in the acute stage of subarachnoid haemorrhage, patients do not tolerate coagulation of the bridging veins and venous infarcts develop. This is more frequently seen in poor grade and elderly patients.[109]

The Basal Interhemispheric Approach

This involves the removal of more bone, and the midsection of the base of the anterior cranial fossa is resected. This extension downwards into the frontal sinus and nasal bone region provides greater exposure and limits brain retraction. In the basal interhemispheric approach[117] there is no anosmia which is a frequent complication with the interhemispheric approach.

Midline Trephine Approach

The anterior interhemispheric approach through a midline trephine has been advocated by Keogh et al.[58] This approach uses a limited forehead incision, low midline trephine, unilateral dural opening up to the interhemispheric fissure, dissection of the interhemispheric region up to the genu and basal region and then to approach the aneurysm after defining the anatomy. The sectioning of superior sagittal sinus or cutting the falx in the anterior interhemispheric region is avoided.

Other Skull Base Approaches

Shekar et al.[98] emphasise that cranial base approaches, used selectively, can provide improved exposure of deep-seated aneurysms and large or giant aneurysms, while minimising brain retraction. In the orbitozygomatic approach[40] and modified orbitozygomatic approach removal of the orbital rim and the zygomatic arch can be combined with a fronto-temporal craniotomy to gain additional space, so as to decrease cerebral retraction. As shown by Alaywan and Sindon[2] by incorporating orbitozygomatic removal the field view angle was increased by 75% in the sub-frontal approach, 46% in the PT approach and 86% in the sub-temporal approach. In patients with increased intracranial pressure, giant ACoAAs and those projecting superiorly these approaches are useful. Schwartz et al.[97] showed that area of exposure provided by the fronto-temporal transsylvian approach was increased by 26–39% by adding orbital rim osteotomy and an additional 13–22% with removal of the zygomatic arch. Significant and consistent increases in surgical exposure were obtained by using orbital osteotomy, whereas zygomatic arch removal produced less consistent gains. Both manoeuvres may be expected to improve surgical access. However, since larger and more consistent gains were afforded by orbital rim removal, the threshold for removal of this portion of the orbitozygomatic complex should be lower according to them.[97]

Orbitopterional Approach

The orbitopterional (OPT) approach is an anterior skull base extension of the PT approach that provides greater exposure to the anterior cranial fossa, supra and parasellar regions and ACoA complex. With use of the OPT approach, resection of the zygomatic arch is not needed and extension of the temporal craniotomy is considerably less.

Andaluz et al.[7] explain the better outcomes in the OPT approach to ACoAAs to be due to the following three factors:

1. Avoidance of dissection of the Sylvian fissure decreases the risk of temporal lobe injury.
2. Decreased retraction on the basal frontal lobe as significant space is gained from the removal of the sphenoid ridge and superior and lateral orbital rim.
3. Better basal access allows a better cisternal toilette which, complemented by fenestration of the lamina terminalis during ruptured ACoAA surgery, can decrease the incidence of cerebral vasospasm and post-SAH hydrocephalus, in addition to providing improved relaxation of the brain during surgery. Benefits of the OPT approach versus the PT approach in terms of exposure of the ACoA complex were corroborated by Figueiredo et al.[33] The vertical and horizontal angles of approach to the ACoAA complex were significantly larger for the OPT and OZ approaches compared with the PT approach. The authors feel the use of the OZ approach may decrease the need for frontal lobe retraction and resection of the gyrus rectus.

Orbitocranial Approach

Fujitsu et al.[36] described an orbito-fronto-temporo-basal craniotomy technique that allows excellent access to ACoAAs. This orbitocraniobasal approach is particularly useful for the surgical treatment of ruptured aneurysms in the acute stage of subarachnoid haemorrhage, when retraction of the brain needs to be kept to a minimum. With this approach, retraction of the orbital contents decreases the amount of retraction of the brain to such an extent that a brain retractor is not necessary to access to the ACoA complex.[104]

Supraorbital Keyhole Minicraniotomy

The supraorbital minicraniotomy using the eyebrow incision can be used for the management of these aneurysms.[17,19,35,50,77,81,85] Jane[50] described the supraorbital approach to approach ACoAAs in a technical note in 1982 and AL-Mefty[5] elaborated on the supraorbital-pterional surgical approach. Deep lesions can be handled via subfrontal, transsylvian or subtemporal routes

during the same operation with minimal brain retraction. Czirják and Szeifert[25] reported the frontolateral keyhole craniotomy, together with the advent of modern neuroanaesthesia, cerebrospinal fluid drainage and microsurgical techniques, to be a safe approach for an experienced neurosurgeon to use in the treatment of supratentorial aneurysms or tumours of the anterior fossa and sellar regions. Jho[53] described the steps of this approach. A small (4–5 cm) long eyebrow incision is made and the pericranium is separated. Thereafter a small basal orbital roof craniotomy (measuring 2 cm by 3 cm), including the supraorbital arch, is made as a single piece bone flap using a craniotome. The orbital roof is then opened up to the supraorbital fissure and to the optic canal by additional removal of bone in the orbital roof. This will expose the globe and the orbitofrontal dura mater. When the dural incision is made at the orbital portion of the dura mater, the orbital contents are retracted by tack-up sutures. The surgery is carried out utilising the orbital space rather than the intracranial space. The direct eyebrow incision provides an additional vital working space with a width of more than 1 cm at the skull base by eliminating the scalp flap which a coronal incision employs.[53] Dare et al.[27] reported on the successful use of this procedure in elective surgery of 10 aneurysms of the anterior circulation. The mean aneurysm size was 5.9 mm, with a range of 4–10 mm. They highlight the advantages of this approach that include minimal disruption and exposure of normal brain tissue, reduced frontal lobe retraction, and an excellent post-operative cosmetic result. The authors found that the neuroendoscope was helpful at times but was not essential and no special instruments or intra-operative image guidance was required. According to them relative contraindications include the presence of a large frontal sinus, severe brain oedema and recent subarachnoid haemorrhage. In addition, this approach was not used for the treatment of giant intracranial aneurysms.

Cheng et al.[24] have developed a small pterion keyhole approach as an alternative access to treat anterior circulation aneurysms. An oblique skin incision about 3–5 cm in length was made just from 1 cm anterior to the superficial temporal artery at the level of the zygomatic arch, curved just below the temporal line to the forehead, and stopped at the hairline over the Sylvian fissure. Then a small craniotomy (2–3 cm) was made just over the Sylvian fissure and the aneurysm was exposed through the lateral cerebral fissure.

Steiger et al.[106] describe the technique of transorbital keyhole approach to ACoAAs. This approach did not necessitate resection of the gyrus rectus and provided more ventral access than the supraorbital approaches and the ACoA complex can be controlled by splitting the basal aspect of the interhemispheric fissure.

Endoscopic Assisted Microneurosurgery

Profeta et al.[89] emphasise that, among the aneurysms of the anterior circulation, the endoscope is particularly useful in those of the internal carotid and the anterior communicating arteries. In their 3 years experience they found that endoscopes can carry out a supportive role in planning surgical manoeuvres and in verifying clip position. They feel that the endoscope has now become almost indispensable for the "difficult" aneurysms, including the large and giant ones before and after clipping. Thus, the endoscope should be kept ready for use in the operating theatre for any eventuality.

GIANT ANTERIOR COMMUNICATING ARTERY ANEURYSMS

A giant intracranial aneurysm is defined as one larger than 2.5 cm in diameter. These represent about 5–8% of all intracranial aneurysms.[68] Hauck et al.[42] emphasised that patients with very large or giant unruptured intracranial aneurysms present with ischaemic stroke and progressive disability. The aneurysm rupture risk in these patients is up to 50% in 5 years. The ACoAAs rarely grow to giant size as they rupture much earlier and only 10% of giant aneurysms occur in the ACoA.

Patients with a giant aneurysm present with mass effect that causes visual symptoms due to pressure on the optic nerves and chiasm, cranial nerve dysfunction, hemiparesis, seizure or headache. Hydrocephalus is due to pressure on the anterior third ventricle. Lownie et al.[70] reviewed their 20-year experience with giant ACoAAs and found on analysis that at least 3.5 cm of aneurysm mass effect was required to produce dementia in the patients. Dementia was usually caused by direct brain compression by the aneurysm rather than by hydrocephalus and optic apparatus compression occurred with smaller aneurysms (2.7–3.2 cm) when they pointed inferiorly. Aneurysm neck clipping was possible in half of their cases and special techniques, including temporary clipping, evacuation of intraluminal thrombus, tandem and/or fenestrated clipping, and clip reconstruction were often required. Occlusion of or injury to the ACA was the main cause of poor outcome or death. Proximal ACA occlusion, even of dominant A1 segments with small or no contralateral A1 artery, was an effective treatment alternative and was well tolerated as a result of excellent leptomeningeal collateral circulation.

Sometimes it may not be possible to safely clip these aneurysms due to multiple factors like, the neck is too small or very wide, arteries of the ACoA complex or multiple perforators being closely positioned to the aneurysm or a turgid large aneurysm over which the clip keeps slipping and there is risk of kinking and occluding the parent vessel. Appropriate clip selection and proper sequencing of multiple clips are important. Straight clips with short blades are preferred to avoid hindrance of the surgeon's operative field and interference between the clips. Multiple and fenestrated clips may be required to reconstruct the vascular anatomy. These aneurysms can be trapped, opened and the thrombus removed using a cavitron ultrasonic surgical

aspirator (CUSA) and then the reconstruction is done using various clips. Vascular clamps[81] may be required in some cases followed by definitive clipping. Cantore et al.[21] reiterate that the "gold standard" for the treatment of giant aneurysms remains surgical clipping. When direct surgical clipping or endovascular repair is contraindicated, the high-flow EC-IC bypass is a viable surgical option. Kim et al.[59] describe a giant aneurysm of the ACoA which was treated with a STA-RA graft-A3 bonnet bypass and A3-A3 side-to-side anastomosis. Inoue et al.[48] cite a case where revascularisation of the ACA was done with an A3-A3 anastomosis and a superficial temporal artery bypass using an A3-radial artery graft to trap a giant ACoAA.

Zada et al.[119] show that the fenestrated aneurysm clip can be a simple and practical tool in the operative management of ACoAAs. The ACoAAs pointing in a superior direction are more likely to require clip fenestration around the A2 vessel, whereas those pointing in an inferior direction are more likely to require clip fenestration around the A1 vessel. The parallel approximation of the fenestrated clip blades makes them especially useful in the treatment of large or giant aneurysms. Drake et al.[30] reported that Hunterian proximal artery occlusion was used in the treatment of 160 of 335 patients harbouring giant aneurysms of the anterior circulation with 90% satisfactory outcomes. They found that the ACA had very good leptomeningeal collateral flow that prevented infarction even without cross flow.

FUSIFORM ANTERIOR COMMUNICATING ARTERY ANEURYSMS

Fusiform ACoAAs are rare, and a series of five fusiform aneurysms has been reported by Sampat et al.[93] They advise a thorough review of angiograms and 3D CT angiography reconstruction images to identify the complex and fusiform entity of ACoAA. They emphasise the importance of experience in operative techniques and thorough knowledge of the ACoA anatomy in tackling these rare forms and maintain flow in all vessels while surgically recreating an ACoA of normal calibre.

BLISTER-LIKE ANTERIOR COMMUNICATING ARTERY ANEURYSMS

Blister aneurysms are rare lesions characterised by a hemispherical shape and fragile walls.[9,51,101] Blister-like aneurysms constitute technically challenging lesions that may occur at the ACoA. Andulez and Zuccarello[8] reported on a series of five patients with blister-like aneurysms of the ACoA. Usually, blister-like aneurysms have been reported to occur at non-branching sites of the dorsomedial ICA. The CT angiography is valuable in diagnosis. Blister-like aneurysms should be suspected when DSA is negative for subarachnoid haemorrhage. These aneurysms arose from the horizontal portion of the ACoA without any involvement of the branches of the ACA. All such aneurysms were thin-walled and lacked a surgical neck. On dissection, two of the lesions were ruptured. All lesions were treated with straight fenestrated clips through the A1-ACoA junction, thus remodelling the ACoA.

KISSING ANTERIOR COMMUNICATING ARTERY ANEURYSMS

The term "kissing aneurysms" refers to two anatomically adjacent aneurysms with different origins and partially adherent walls.[12,113] These require careful preoperative planning and surgical techniques like gyrus rectus resection, applying temporary clips on the A1 segment, coagulation and shrinkage of one aneurysmal sac, appropriate clip selection and sequencing. Kissing ACoAAs can be successfully clipped.[12]

COMPLICATIONS

Hydrocephalus, perforator and arterial occlusion, vasospasm, parenchymal brain injury, neuropsychological sequelae and electrolyte disturbance are common complications after aSAH from ACoAAs.

Intra-Operative Rupture

The ACoA is associated with higher intra-operative rupture risks than other aneurysmal locations in the anterior circulation. This can be partly attributed to increased dissection and retraction that is used to expose these aneurysm and the associated perforators. Most intra-operative ruptures occur during the dissection to expose the neck and clip application stage. A good mental 3D image and cautious, sharp dissection, proper magnification and illumination, keeping the surgical area wet, microsurgical technique and use of sharp instruments are essential to avoid intra-operative rupture of the aneurysm.

Injury to Arterial Branches and Perforators

Baldawa et al.[12] point out the difficult and deep surgical anatomy of these aneurysms, especially their intimate relationship to 11 crucial arteries and their perforators—paired A1 segments, paired A2 segments, two recurrent arteries of Heubner, two orbitofrontal arteries, two frontopolar arteries and the ACoA—any of which may be injured or inadvertently clipped during surgery. Pai et al.[85] found that perforators arose from the posterior and the superior surface in 90% of the cases. Occlusion of these perforators with the aneurysm clip is a major cause of morbidity and mortality in patients with ACoAAs pointing posteriorly or superiorly. They observed that a clear view of the ACoA was usually hindered by the overhanging gyrus rectus. Profeta et al.[89] reported fatal outcome of a patient with giant ACoAA due to cerebral infarction due to post-clipping stenosis of one distal cerebral artery in which it was not possible to re-position the clip correctly due to the presence of an arteriosclerotic calcific plaque near the aneurysm neck.

More commonly vasospasm can complicate the picture. The injury to the recurrent artery of Heubner results in upper limb and facial weakness with speech difficulty. Injury to the ACA commonly manifests as paraparesis. The ACoA syndrome comprises of abulia, Korsakoff-like syndrome, hypokinesis, visual field defects, affective disorders and diabetes insipidus. Gibbons et al.[37] emphasise pre-operative and intra-operative vigilance in determining the presence of anomalies prior to clip placement to avoid clip occlusion of a third distal ACA segment which can occur during the treatment of ACoAAs.

Hydrocephalus

These aneurysms are located close to the lamina terminalis and the bleed can extend into the 3rd ventricle leading to hydrocephalus. Rarely, giant ACoAAs can cause obstruction by mass effect. Sindou,[103] analysing a series of 197 consecutive cases of ruptured intracranial aneurysms, reported that opening of the lamina terminalis and Lilliequist's membrane facilitates CSF circulation in the basal cisterns and favourably influences the outcome in patients with ruptured intracranial aneurysms. Andaluz and Zuccarello[9] suggested that fenestration of the lamina terminalis is a valuable adjunct in ACoAA surgery and this was associated with statistically significant decreases in shunting rates, incidence of vasospasm and better outcomes. They recommend its routine use in patients with Fisher grade 3 ACoA aSAH.

Electrolyte Disturbance

The ACoAA management is frequently complicated by electrolyte and fluid disturbance. Hyponatraemia, hypernatraemia, SIADH, DI and cerebral salt wasting syndrome have been reported. Hyponatraemia is more common than hypernatraemia and post-SAH hyponatraemia is commonly due to cerebral salt wasting syndrome rather than SIADH. The cerebral salt wasting syndrome is due to the kidneys being unable to conserve sodium loss and this leads to hyponatraemia and fluid loss.

Brain Retraction Injury

Many complications and subsequent poor outcome in ACoAA surgery are due to excessive retraction[61] of the frontal and temporal lobes and splitting the Sylvian fissure. Andrews and Brings[10] reviewed the literature on brain retraction injury, with particular attention to the use of intermittent retraction, intra-operative monitoring techniques (brain electrical activity), cerebral blood flow and brain retraction pressure. They concluded that through a combination of judicious retraction, appropriate anaesthetic and pharmacological management, and aggressive intra-operative monitoring, brain retraction should become a much less common source of morbidity in the future.

Schaller et al.[96] emphasise that the transsylvian approach is "minimally invasive" but not "atraumatic". They used SPECT scans to demonstrate ipsilateral regions of hypoperfusion in 100% of the cases and contralateral hypoperfusion in 80%. Cerebrovascular reactivity was found to be impaired in 83.3% of the cases ipsilaterally and in 33.3% contralaterally. Thus, a significant proportion of patients who undergo microneurosurgical procedures develop bilateral alterations of their cerebral circulation. There are elevations in mean blood flow volume values caused by cerebral vasospasm. Since these changes remain asymptomatic in the majority of patients, the transsylvian approach can be considered "minimally invasive" but not "atraumatic". The authors suggest alternative surgical routes and alternative treatment modalities should be investigated in a similar manner.

Neuropsychological Sequelae

These aneurysms are associated with highest incidence of neuropsychological deficits which can be seen before and after rupture of these aneurysms or after surgical clipping due to iatrogenic injury or vasospasm of perforators. Nearly 40% of patients will have these complications. The ACoA syndrome with severe memory deficits, confabulation and personality changes, like abulia, lack of motivation and poor cognition with relative sparing of intelligence, is seen in a few patients. Cognitive impairment after surgery for ruptured and unruptured aneurysm can be due to many factors as emphasised by Hillis et al.[44] including subarachnoid haemorrhage, general effects of neurosurgery, peri-operative management. Finally, some of the post-operative deficits may be a reflection of premorbid states.

Others

Post-operative haematomas, optic nerve and chiasmal injuries and rarely optic chiasm arachnoiditis due to wrapping of the aneurysm by material, like muslin, are seen.

OUTCOMES

The outcomes in ACoAAs continue to improve due to better imaging, improvements in critical-care techniques, better management of vasospasm and newer treatment options.[16,43,64] The assessment of the outcomes after aneurysm surgery is not easy and many factors have to be taken into account. Buchanan et al.[18] point out a well known fact that despite the neurosurgeon's classification of patients as having a "good recovery" or "moderate disability", the majority of patients surgically treated for SAH reported psychosocial and neurobehavioural changes that were disabling for them and burdensome to their family. The ACoAAs have the worst surgical outcomes among all anterior circulation aneurysms. The clinical grade of the patient as measured by the Hunt and Hess or WFNS scale is still the primary factor that determines the final outcome in patients with an ACoAA after SAH. In patients with good grade the mortality is

less than 5% and most patients have a good outcome. Outcome scores, like Glasgow outcome score, Modified-Rankin scores and Disability Rating Scale (DRS), are used to access outcomes and these are evaluated by independent observers. Andaluz et al.[7] evaluated the short- and long-term follow-up of 75 patients with ACoAAs who underwent surgical treatment through the OPT approach and found overall outcomes at discharge using the modified Rankin Scale to be good in 52 (69.4%) patients, fair in 13 (17.3%) and poor in 10 (13.3%). Sengupta et al.[99] described a series of 32 patients and in 28, the aneurysms were treated by direct surgery with no deaths; 26 of these patients were studied psychometrically from 4 to 33 months after operation. There was no evidence of post-operative intellectual impairment; however, there were personality changes associated with loss of interest, initiative and energy. Analysis of the different factors involved suggests to the authors that the outcome of surgery depends mainly on the pre-operative clinical condition which, in turn, reflects the severity of the haemorrhage. Mavaddat et al.[74,75] reported that after open surgery for ruptured ACoAAs, patients who have achieved a favourable neurological outcome still exhibit significant cognitive deficits, primarily in tests sensitive to temporal lobe dysfunction. However, early surgery did not carry a higher risk of neuropsychological disability. The direction of the aneurysm at the ACA-ACoA and its bearing on surgical outcome was stressed by Jha et al.[52] and they observed that most of the posterosuperior pointing aneurysms presented in poorer grades and outcome was unsatisfactory. In comparison most of the antero-inferiorly pointing aneurysms presented in a better grade and the results were satisfactory. Le Roux et al.[65,66] found that predicting outcome based only on clinical and diagnostic criteria present at admission may have resulted in withholding treatment from 30% of the patients who subsequently experienced favourable outcomes. They emphasised that aggressive management including surgical obliteration of the aneurysm can benefit patients with poor neurological grades and should not be denied solely on the basis of the neurological condition on admission. Andaluz and Zuccarello,[9] on analysing 106 patients affected by ACoAAs, with hydrocephalus requiring shunt to be 4.25% in patients who underwent fenestration of the lamina terminalis (FLT) and 13.9% in patients who did not. Clinical cerebral vasospasm occurred in 29.6% of patients who underwent FLT and in 54.7% of patients who did not. Frontobasal hypodensity was identified post-operatively in 0% of patients who underwent FLT and in 5% of patients who did not. Good outcome was reported in 69.81% of patients who underwent FLT and in 33.96% of patients who did not. Poor outcome was associated with higher Hunt and Hess grades, need for ventricular drainage, elevated intracranial pressure and multiple interventional vasospasm therapies. No complications were linked to FLT. Hauk et al.[42] reported that patients presenting with a TIA, a poor baseline condition, an aneurysm greater than or equal to 25 mm, and/or an age greater than or equal to 50 years are at increased risk for a poor outcome. The most important predictor of outcome was a post-operative stroke. About 75% of poor outcomes were due to a major ischaemic stroke. Solomon et al.[105] also found stroke to be the most significant complication accounting for 50% of poor outcomes.

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82 Distal Anterior Cerebral Artery Aneurysm

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INTRODUCTION

Distal anterior cerebral artery (DACA) aneurysms, located distal to the anterior communicating (ACom) artery on the A2-A5 segment of the anterior cerebral artery (ACA) are less common and account for 3.1–9.2% of all intracranial aneurysms.[3] The characteristics of the aneurysm arising from distal accessory ACA are considered similar to those of distal ACA aneurysms.[5] In 1948 Sugar and Tinsley reported the first attempt to treat a distal ACA aneurysm surgically.

MICROSURGICAL ANATOMY

Most DACA aneurysms arise at the pericallosal-callosomarginal artery (PerA-CMA) junction, which is usually located in the A3 segment of the ACA around the genu of the corpus callosum. The aneurysms can rarely arise at the origin of the frontopolar artery more distally.

Aneurysms in the PerA-CMA junction are divided into two types according to their location:[4]

1. Supracallosal
2. Infracallosal

Infracallosal distal ACA aneurysms are defined as those located in the lower-half of the A3 segment, which makes it more difficult to gain proximal control.

CLINICAL CHARACTERISTICS

The average age at presentation is 50 years with a slight female preponderance.

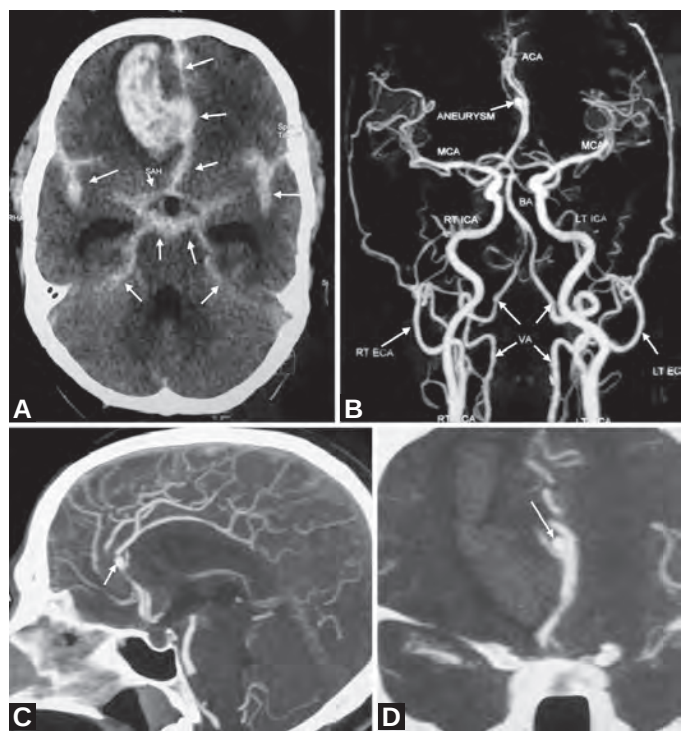
Patients with ruptured DACA aneurysms present with symptoms and signs typical of subarachnoid haemorrhage (SAH) with occasional monoparesis of a lower extremity. A hemispheric disconnection syndrome may occur if there has been a significant intracallosal haemorrhage. Intracerebral haemorrhage is a common (50%) complication of ruptured DACA aneurysms. DACA aneurysms are commonly associated with other intracranial aneurysms and may be identified in patients investigated for SAH from aneurysms at other sites.

INVESTIGATIONS

The computerised tomography (CT) findings are similar to those seen with ACom aneurysms. Hyperdense areas are seen in the interhemispheric fissure, cingulate sulcus, pericallosal cistern and cistern of the lamina terminalis in ruptured aneurysms. A four-vessel digital subtraction angiography (DSA) is the investigation of choice for evaluation of SAH from DACA aneurysms. For determining the laterality of the aneurysm a unilateral injection of contrast is done. CT angiography is also useful to detect these aneurysms (Figs 1A to D).

SURGICAL CONSIDERATIONS

As the two anterior cerebral arteries are side by side, the effect of SAH, haematoma and surgical manipulation may involve both the vessels. At surgery, if the callosomarginal artery is mistaken for the pericallosal artery, the surgery will be difficult. This happens when there is subfalcine herniation of the cingulate gyrus.



Figs 1A to D: Imaging of a patient with distal anterior cerebral artery (DACA) aneurysm. (A) Computerised tomography. (CT) scan showing subarachnoid haemorrhage and intracerebral haematoma in the right frontal lobe. (B) CT reconstructive angiogram in anterior view showing the DACA aneurysm. (C) CT angiogam in sagittal section showing DACA aneurysm. (D) CT angiogram in coronal section showing DACA aneurysm

With the patient in the supine position, a craniotomy flap is raised, with the medial limb over the sagittal sinus. Identification of the aneurysm at operation becomes easier if the bone flap is planned using some guidelines from the angiogram. A line is drawn on the lateral view of the angiogram from the nasion to the aneurysm. From the end of the line, a perpendicular is drawn to meet the vault of the skull. The point where the second line meets the vault should be the midpoint of the medial limb of the bone flap. A search for the aneurysm should be made along the imaginary perpendicular line. While retracting the medial frontal lobe, the bridging veins should be preserved as far as possible. The callosomarginal and pericallosal arteries are closely related to the neck and the fundus of the aneurysm and care should be taken to preserve the continuity of the vessels while applying the clip. Proximal control of the feeding artery is not easily possible in this approach. Resection of a portion of the corpus callosum helps in providing excellent exposure of the proximal A2 segment. No untoward effects of resection of the corpus callosum have been noticed.[1,6] Occasionally, a transfalcine approach through the side opposite to the lesion by cutting the falx, will help direct visualisation of the lesion and clipping of the aneurysm.[2]

Endovascular treatment by coiling, including parent vessel occlusion using coils or coils combined with n-butyl-2-cyanoacrylate is safe and effective.[3]

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83 Middle Cerebral Artery Aneurysms

Mathuriya SN, Pathak A, Gupta Vivek, Grover VK

Aneurysms of the middle cerebral artery (MCA) pose a significant challenge to neurosurgeons. They constitute around 20% of all cerebral aneurysms. MCA aneurysms constituted 25.3% of 2,588 intracranial aneurysms operated upon by the author at PGIMER, Chandigarh, during an 18-year period. The commonest location is MCA bifurcation both in the ruptured and unruptured group. They constitute 89% of all ruptured and 30% of all unruptured aneurysms.[10] Mirror MCA bifurcation aneurysms are seen in 14% of patients. Around 45% of ruptured MCA bifurcation aneurysms caused an intracerebral haematoma (ICH).[1,54] Around 96% of aneurysms were saccular, 10–15% were located at M1 and 5–7% in the distal MCA segment.[10]

The majority of MCA bifurcation aneurysms are located between two or three M2 branches as a lateral extension of the M1 segment and they project laterally. Aneurysms in this location, more frequently than other locations, produce ICH, but have a lesser incidence of hydrocephalus. Around 24% of aneurysms have been reported to be large and 9% giant. Around 47% were located on the left side and 53% on the right.[10] They may be associated with aneurysms in other locations.[10,31,59] The size of the neck has been reported to be narrow or wide in an equal number of cases in some studies, whereas a few report that a large number usually have a comparatively wider neck which involves the origin of M2 branches. Aneurysms of the M1 segment arise at the origin of the temporopolar or anterior temporal arteries (lateral wall) or in relation to the lenticulostriate arteries [(medial wall) 10–15%].[2,4,11,20,69]

CLINICAL FEATURES

Middle cerebral artery aneurysm rupture leads to a symptom complex which is indistinguishable from subarachnoid haemorrhage (SAH) due to bleed of an aneurysm in any other location.[8] More than half of the patients with a ruptured MCA aneurysm lose consciousness, which is more than in aneurysms in other locations. Severe headache is the most prominent symptom of SAH which is usually diffuse, but one-third of patients with MCA aneurysms have unilateral headache.

Eighty per cent of patients with ruptured MCA aneurysms had focal neurological deficit at presentation in the form of hemiparesis, aphasia, visual field defects and facial weakness. These are noticed in only 34% of aneurysms in other locations and only 7% had severe deficits. Headache and vomiting were seen in 90% and 66% respectively. Seizures occur in 10% of patients. It is far less common in other locations. A patient with SAH, who is conscious with gross hemiparesis on presentation, is most likely to have an aneurysm in the MCA. Giant aneurysms are commoner in the MCA than in other locations, except the paraclinoid region.[10] These can grow to a massive size without producing deficits. Large and giant MCA aneurysms without rupture produce mass effect and can, in rare instances, lead to raised intracranial pressure (ICP). A rare presentation in these aneurysms is temporal lobe epilepsy, which is exceptional in aneurysms in other locations. These seizures result from damage and gliosis of the medial temporal lobe due to compression or repeated subclinical haemorrhages.[33] Giant aneurysms may, rarely, lead to cranial nerve compression. Ischaemic symptoms, such as TIA and stroke, are comparatively uncommon presentations of aneurysms, but these are more common with MCA aneurysms than others. Exceptionally, a major stroke can result from occlusion of the MCA or its major branches due to aneurysmal expansion and spontaneous thrombosis.

Aneurysms in the paediatric age group are uncommon (0.5–4.6%) and still more infrequent in neonates.[30] The ultimate outcome is poor due to delayed diagnosis. Clinical features include irritability, vomiting, seizures SAH and coma. SAH is the most common presentation. Mortality in patients who are not treated surgically is high. The important diagnostic modalities are cranial ultrasound and MRA.[23,30]

Aneurysms can occur at the site of arterial bypass and it depends on a disproportion between the donor and recipient vessels and the number of sutures inserted. These aneurysms result from increased haemodynamic forces and intra-operative disruption of the intima and media at the anastomotic site. These patients need periodic follow-up, specifically patients with an unusual ICH at the site. These aneurysms are relatively large, project into the frontal lobe in the direction of flow and usually present after a short interval of bypass surgery.[38]

Intracerebral Haematoma

Around 30% of ruptured MCA aneurysms present with intracerebral haematoma (ICH) (Figs 1 and 2). A

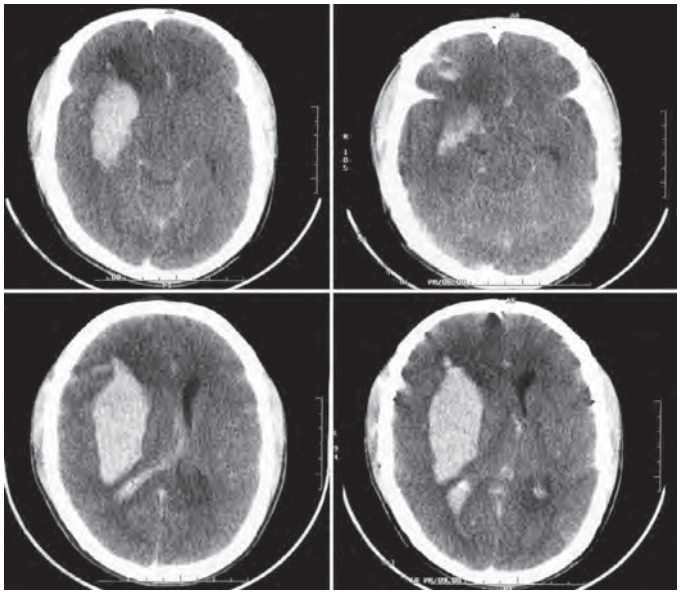

Fig. 1: CT showing Rt. frontotemporal ICH (deep) with IVH

haematoma extending into the frontal operculum and the temporal operculum, bridging the sphenoid ridge, is virtually pathognomonic of a ruptured MCA aneurysm. Computed tomography (CT) is mandatory to diagnose SAH, IVH and ICH. The location of the ICH, its size, extension and associated ischaemic areas and infarcts in the temporal/frontal lobe or associated intra-Sylvian haematoma (ISH) also help in diagnosing the site of aneurysm rupture. Management of ISH needs appropriate and precise judgement as it involves a large number of perforators in the Sylvian cistern with their variations and adhesion to the haematoma. Patients with temporal ICH are usually in poor grade or they may deteriorate fast. Hence, definitive investigations (angiogram/CTA) are required to visualise the details of the pathology.

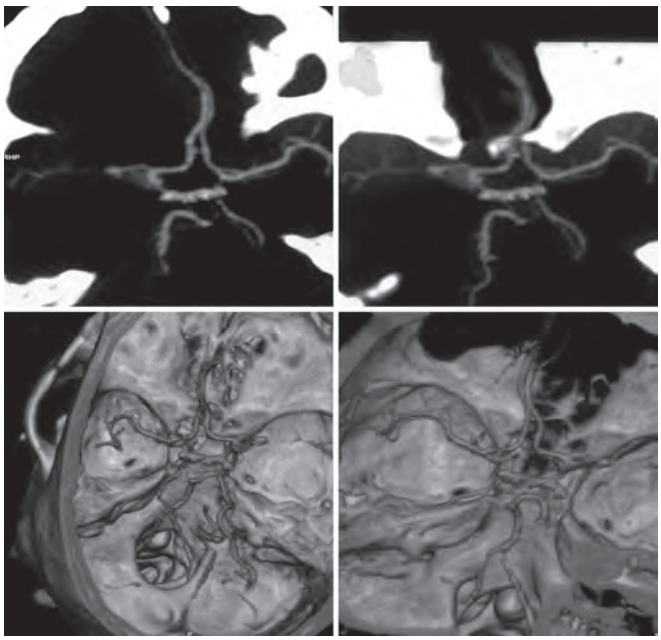

Fig. 2: CTA showing Rt. M1 aneurysm

ICH occurs maximally in laterally directed MCA bifurcation aneurysms.[1,10,39,48,54]

INVESTIGATIONS

After CT has confirmed SAH, an angiogram/CTA is performed on an urgent basis after confirming fitness for the same, mainly after assessing hydration and renal parameters. This can differentiate an ISH from a temporal ICH in which there will be elevation of M1 and increased distance between the M2 branches and the inner table of the skull.[34] Aneurysms originating at the early temporal branches project into the temporal lobe and those from the lenticulostriate arteries into the lateral frontal side.

MCA bifurcation aneurysms have three main projections: (1) anterosuperior; (2) posterior and (3) inferior.[73] These aneurysms are classified into five types: (1) Intertruncal—These have a superiorly and posteriorly directed dome and the base is usually towards the M2, and the M2 is commonly involved in the base. (2) Inferior MCA bifurcation aneurysms project inferiorly and anteriorly towards the sphenoid ridge. (3) Lateral aneurysms project in line with the long axis of M1. (4) Insular MCA bifurcation aneurysms project towards the insula in the coronal plane and medially in the axial plane. Types 2 and 4 are not intertruncal and do not involve the M2. (5) Complex MCA bifurcation aneurysms.[10]

In some dysmorphic and giant aneurysms the growth may be multidirectional in relation with M1 and M2. A detailed anatomical study, not only of the aneurysm complex (neck size, fundus, lobes, rupture site) but also the vessel of origin, branching, perforators close to the neck and fundus and their adherence, and any branches originating from the fundus/just close to the neck, origin of other vessels, type of circulation, displacement of vessels, vasospasm, any other aneurysms and any more lesions is essential for planning treatment. Information about dynamic flow is important when DSA or 4D CTA is done. All these details are useful for planning the type of treatment, type of approach, exposure of vessels, temporary clipping and dissection around the neck. The 3D DSA provides most of the information required. All angiographic studies underestimate the size of the neck as compared to what is seen at surgery, but 3D DSA is relatively accurate. This being an endoluminal contrast study it under represents all intraluminal contents (plaques, calcification, etc.).[51]

Distal MCA aneurysms arising from the second bifurcation are still in the Sylvian fissure, but not those arising beyond the M3. Almost all MCA aneurysms have a neck except fusiform, serpentine and dissecting ones. Branches usually arise close to or at some distance from the neck but, rarely, they may arise from the dome.

The CTA being a non-invasive, short procedure, not requiring much of the patients' co-operation can be used as a definitive diagnostic modality for MCA aneurysm diagnosis (Figs 3 to 10). One can construct and generate a surgeon's view on the console, rotate the image 360

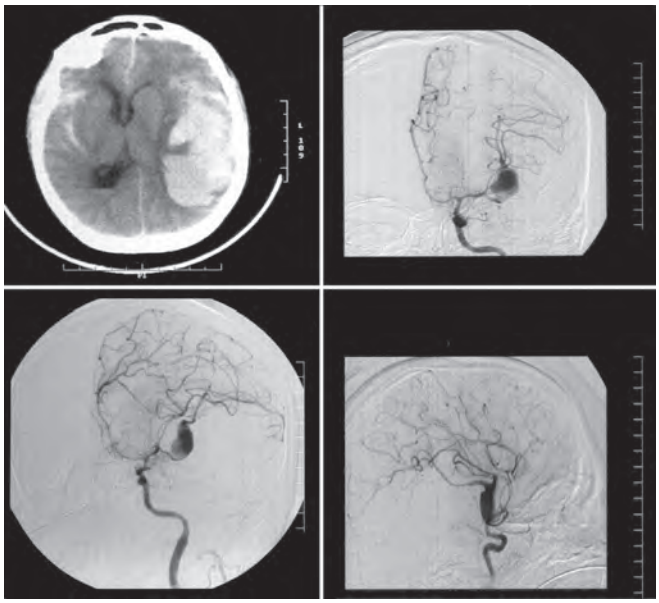

Fig. 3: CT and DSA—large Lt. temporoparietal ICH and partially thrombosed large MCA bifurcation aneurysm

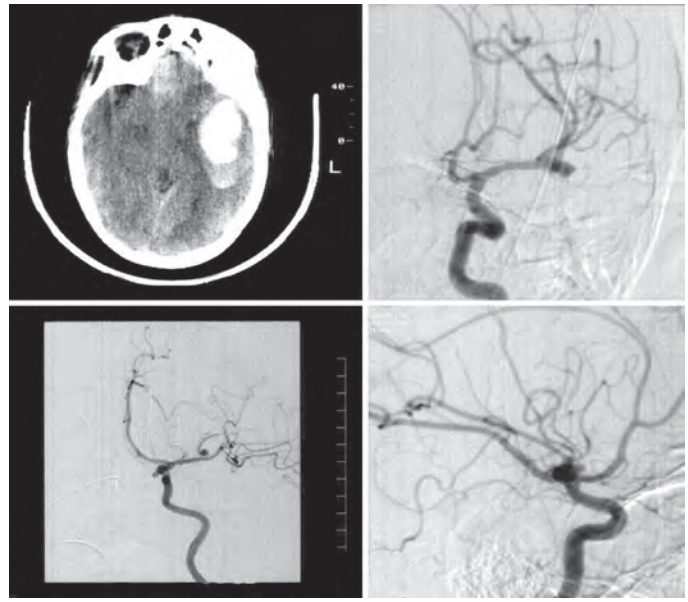

Fig. 4: CT and DSA—Lt. temporal ICH and MCA bifurcation aneurysm

degrees and visualise the aneurysm, vessels and their relation on all surfaces of an aneurysm. The operative technique: splitting of Sylvian fissure, sequence of vessel exposure and aneurysm dissection can be well planned so as to avoid premature rupture at exposure and dissection. The 2D CTA allows identification of the clot and its detailed configuration and CTA can predict a probable rupture point (3D and 2D CTA fused). An irregular aneurysmal shape or aneurysmal bleb on 3D CTA and adjacent thick high density areas on 2D CTA indicate the haematoma and clot on the dome in areas of likely rupture. Many MCA aneurysms are bulbous and broad necked. The CTA can provide information to pre-operatively decide on the size and shape of clips required, and also the need for multiple clips. The direction of the dome and its relationship to the M1 and M2 branches can be visualised in all views and on rotation, thereby helping in deciding on the approach. On CTA it can be seen whether the M1 is anterior or posterior to the aneurysm. In superiorly directed aneurysms M1 is exposed first, and the M2 in inferiorly and laterally directed aneurysms.[7,30,56]

Early branches typically arise at right angles to the main trunk of the MCA, whereas the true post-bifurcation trunks run nearly parallel, diverging only minimally before they reach the genu of the MCA. The lateral lenticulostriate arteries usually arise proximal to the bifurcation, but in 17–23% of patients, they originate from the post-bifurcation part of the MCA.[15]

The CTA is a non-dynamic study, hence, has an inherent pitfall of not providing information about collateral circulation and flow contribution from the various

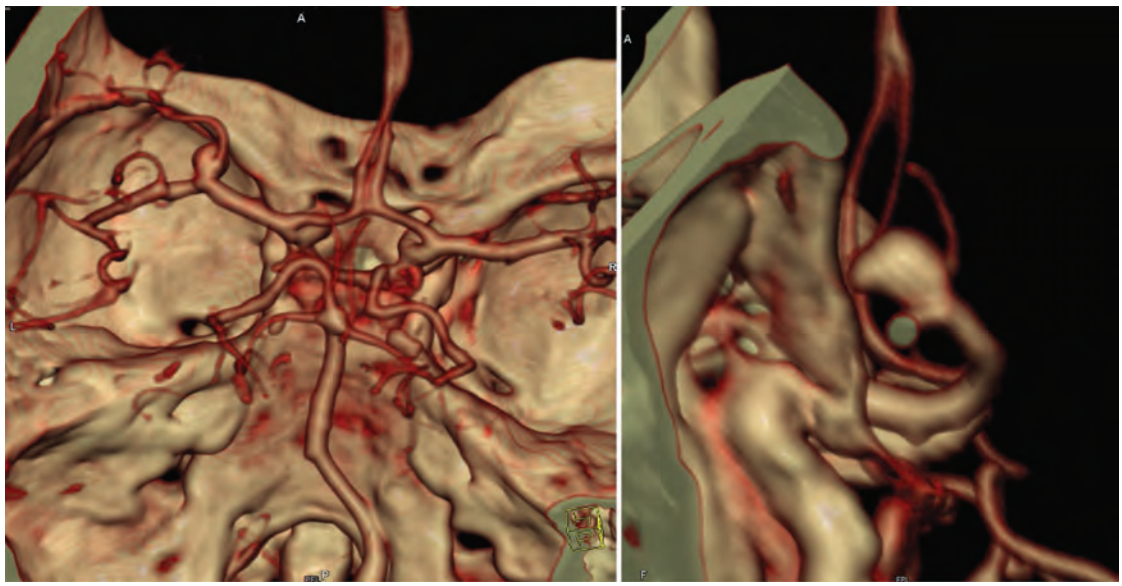

Fig. 5: CTA—Rt. MCA bifurcation aneurysm

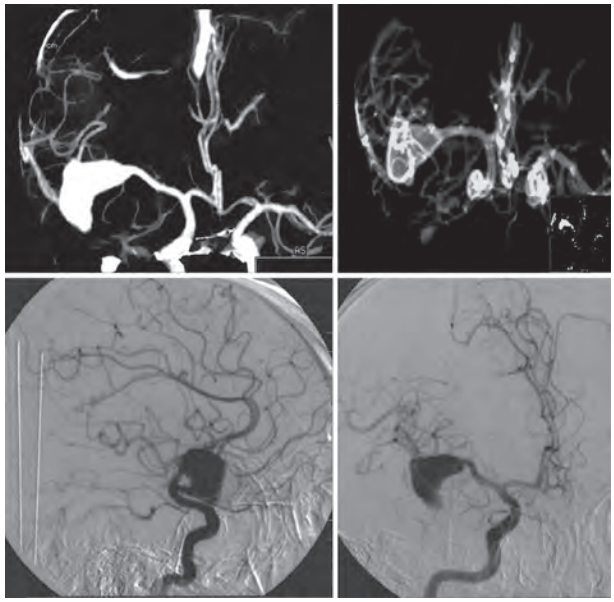

Fig. 6: CTA and DSA—Rt. MCA fusiform aneurysm

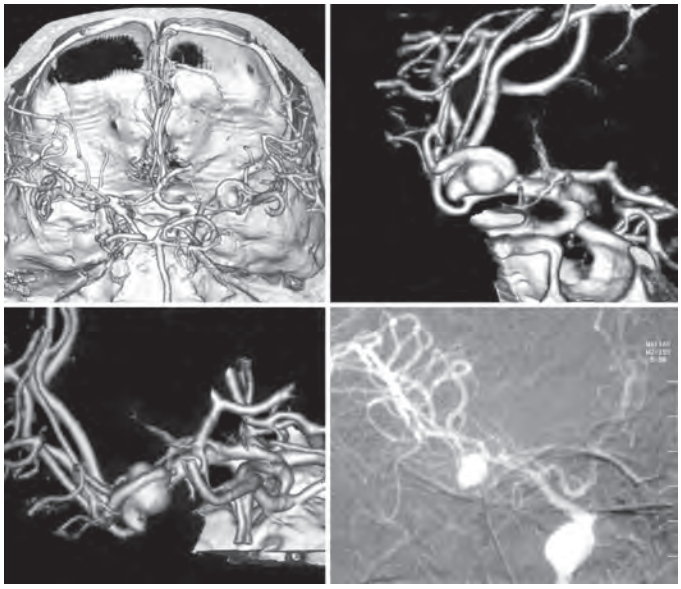

Fig. 7: CTA and DSA—MCA bifurcation aneurysm. Showing one M2 branch behind the aneurysm

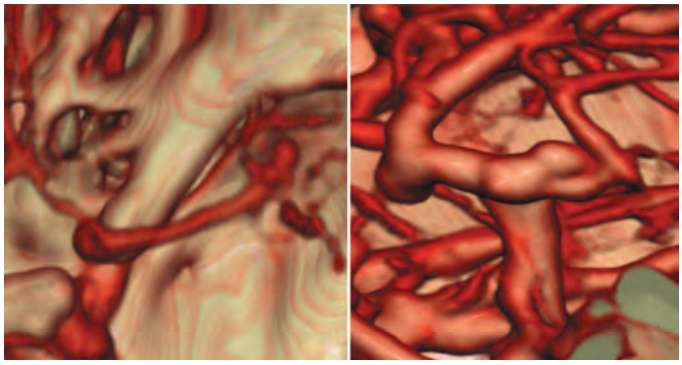

Fig. 8: CTA showing MCA bifurcation aneurysm with a ruptured bleb

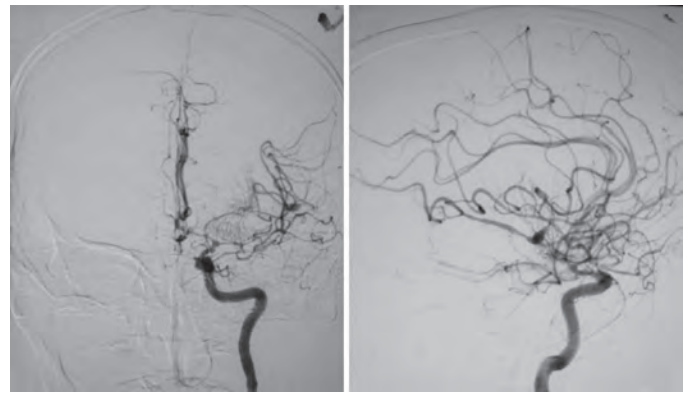

Fig. 9: DSA—Lt. distal MCA aneurysm

vascular territories, which is required for temporary clipping. The CTA cannot image definitely aneurysms less than 2 mm in size, and perforators and other very small vessels less than 1 mm diameter.[22] There are a few more drawbacks, e.g. kissing vessel artifact, wherein the exact site of origin of branching vessels originating at the neck of the aneurysm may not be visualised and may give an erroneous impression of a broad neck. A superimposed Sylvian vein and venous confluence may wrongly be interpreted as aneurysm. It may not be possible to differentiate a crooked infundibular dilatation from an aneurysm and vessel adherence to the aneurysm.[26,44] Vasospasm and its grade and extent cannot be made out. In post-operative follow-up, CTA is not an alternative to DSA due to metal artifacts of clips in the usual software, but the artifacts can be obviated by use of software for their removal.[6,63]

4D Computed Tomography Angiography

It provides details of aneurysm wall dynamics, e.g. dome pulsation, blebs and growth of aneurysm. It entails CTA with a retrospective electrocardiography-gated reconstruction algorithm by use of technology that

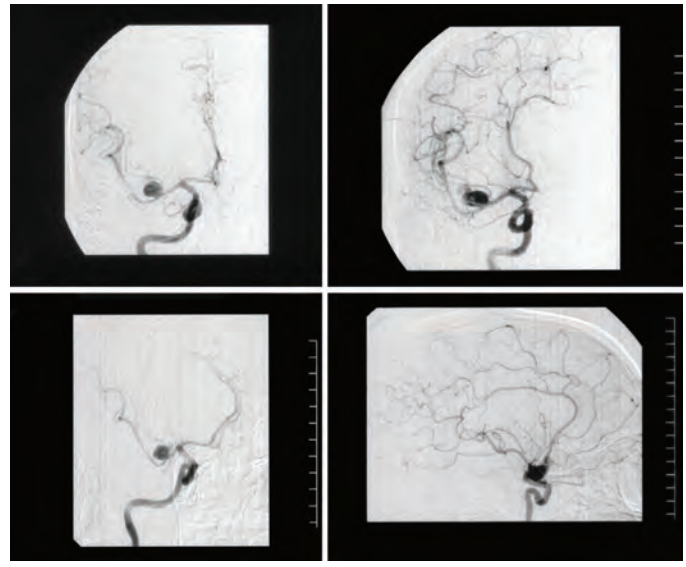

Fig. 10: DSA showing MCA bifurcation aneurysm Rt

was developed initially to examine coronary arteries. Pulsating blebs are seen in 32% of saccular aneurysms and 50% enhancement of volume difference between systole and diastole.[19] These contractions may indicate the site of rupture. The rupture points are seen in 40% of cases. This visualisation of the aneurysm wall in 3D cannot be made out even on DSA. It shows both the entrance and the exit points in dissecting aneurysms and also subacute and chronic intramural haematoma.

TREATMENT

Direct microsurgical repair is the most accepted, common, effective, and safe modality to treat MCA aneurysms, specifically with a wide neck and major branches arising at the initial portion of the dome/base. This is an accepted method even at institutions where coiling is a technique used for most locations.[46] The peripheral location and comparatively well known anatomy and characteristics are more suitable and acceptable for microsurgery. Anatomical variations are seen, but usually are well known and described. This awareness avoids untoward problems. In spite of all these positive characteristics, these aneurysms do not have that good an outcome in spite of a safe and non-complicated clipping technique. The responsible factors are: initial poor clinical grade; hemiparesis/hemiplegia; dense SAH; ISH; large temporal/sometimes frontal ICH and raised ICP. Dense SAH and ISH cause vasospasm also. Many a time a large temporal ICH demands an emergency evacuation and clipping of aneurysm/EVT.[10,22,31]

Anatomy[15,31,43,47,68,73]

These aneurysms can be classified location wise as: (1) M1 segment—(a) at lenticulostriate arteries takeoff, (b) at temporal arteries take off, (c) at frontal arteries take off; (2) MCA bifurcation or trifurcation and (3) Distal sites on M2, M3 and M4 segments. Most studies indicate that MCA bifurcation aneurysms are the commonest (80–90%).[15,31,73] Many a times proximal early branch aneurysms resemble MCA bifurcation aneurysms.

The MCA, after its origin from the ICA lateral to the optic chiasm, traverses underneath the anterior perforated substance (APS) and 1 cm posterior to the lesser wing of the sphenoid. In the Sylvian cistern, it makes a posterosuperior turn (genu) at the limen to lie on the surface of the insula. At the periphery of the insula, the branches of the MCA lie on the medial surface of the frontal, temporal and parietal opercula.

Sylvian Fissure[15,73]

This is a longitudinal cleft and has a superficial portion visible on the surface, a stem and three rami. The deep portion is hidden in the cleft between the frontal and parietal opercula above and the temporal operculum below. Laterally, the Sylvian cistern contains the MCA complex, the deep Sylvian vein and its tributaries. The sphenoid ridge projects into the stem separating the frontal and temporal lobes. The posterior ramus extends between the frontal and parietal lobes above and the temporal lobe below. The two anterior rami divide the inferior frontal gyrus into the pars orbitalis, triangularis and opercularis.

The anterior portion of the Sylvian cistern is called the sphenoidal compartment and the posterior part is called the operculo-insular compartment. Thick arachnoid bands cover the origin of the MCA and it appears like a tunnel. Many arachnoid trabeculae cross over the MCA from the frontal to the temporal lobe. These are numerous and thick on many occasions, and should be cut with sharp instruments to expose and dissect the MCA complex. The Sylvian cistern narrows down superiorly as the frontal and temporal lobes come close to each other. The width on the surface is around 5–10 mm. This is classified into four catagories:[10,73] (1) Large and voluminous with transparent and fragile arachnoid bands; (2) A small cistern with thin and fragile arachnoid bands; (3) Large cistern with thick and tough arachnoid and (4) Small cistern with thickened and tough arachnoid. The arachnoid trabeculae may be toughened by adhesions that occur after a SAH or meningitis, making dissection of the Sylvian cistern more difficult. In some patients, the frontal lobe may indent the temporal lobe within the fissure or vice versa, further complicating dissection.

Middle Cerebral Artery[10,15,31,47]

The MCA is classically divided into four segments. These are: (1) the M1 or sphenoidal segment; (2) the M2 or insular segment; (3) the M3 or opercular segment and (4) the M4 or cortical segment. The M4 segment is the parasylvian segment while the M5 segment is the terminal segment.[10,47]

The M1 extends from the origin of the MCA to the genu, which lies on the limen insulae and lies in the deep part of the Sylvian fissure. In 57–86% the bifurcation occurs proximal to the genu[10,15,31,47] and in 27% is distal to the genu. The M1 segment can be divided into pre-bifurcation and post-bifurcation segments.

Two sets of branches arise from the M1 trunk. Those from the superolateral surface supply the temporal lobe. They may include the uncal artery (usually arises from the ICA), the temporopolar artery and the anterior temporal artery. Often, the temporopolar artery is absent, with a commensurate increase in the size of the anterior temporal artery. The second group of arteries arises from the inferomedial surface of the middle cerebral trunk and consist of a variable number of striate arteries. The striate vessels can be divided into proximal, middle and distal groups. Their number ranges from 1 to 15. The lenticulostriate arteries (LSAs), particularly the more lateral vessels, are recurrent arteries forming vascular loops as they turn medially to enter the lateral two thirds of the APS. The substantia innominata, the lateral anterior commissure, the putamen, the lateral globus pallidus,

the superior half of the internal capsule, corona radiata and the body and head of the caudate nucleus are supplied by the LSAs. In rare circumstances, LSAs arise from M2 branches.[3,15,22,47]

The "early branches", include the temporopolar and anterior temporal arteries from the inferior trunk and the fronto-orbital artery from the superior trunk. These arteries supply the anterior part of the temporal lobe and orbital part of the frontal lobe. Thirty per cent of the time, the uncal artery may arise from the M1 segment instead of the ICA and proximal to the temporal branches.[73] Sometimes (5%), two temporal arteries take off as a single large-stem artery, giving the impression of an early bifurcation. This condition was coined as a "false bifurcation" by Yasargil.[73] In some cases, the temporopolar and anterior temporal arteries are hypoplastic or absent and a single temporal branch coming from the M2 segment may take over the cortical areas supplied by them. The LSAs arise from the posteromedial aspect of M1. These arteries may also arise from the M2 segment or from a large fronto-orbital artery taking off from the superior trunk of the MCA. Three patterns of origin of these vessels have been observed: (1) all LSAs arise from a single artery (40%); (2) two large arteries originate from the M1 and then divide into a number of small arteries (30%) and (3) a number of small twigs of LSAs arise from the M1 (30%).[3,15]

The M2 (insular) segment begins at the genu and terminates at the circular (peri-insular) sulcus. The MCA divides into superior and inferior trunks at the level of the limen insulae, and these trunks course over the insula as M2 segments. The superior and inferior trunks may be equal in diameter, or one of them may be larger than the other.[15,22,43,47]

According to Umansky,[68] there are four types of branching patterns: (1) cortical branches arise as collateral vessels from a single trunk that terminates in the angular artery (6%); (2) the MCA divides into the superior (frontal) and inferior (temporal) trunks (64%); (3) the MCA divides into the superior, middle and inferior trunks (29%) and (4) the MCA divides into four trunks (1%).

In a study reported by Gibo et al.,[15] 78% of the MCAs divided as a bifurcation, 12% as a trifurcation and 10% divided into multiple trunks. In contrast to these studies, Yasargil[73] stated that, when a large branch arises from the superior or inferior trunk just after the bifurcation, a false impression or "pseudotrifurcation" or "pseudoquadrification" takes place. The M2 segment gives off approximately 10 branches that arise mainly from the superior trunk. Some of these arteries constitute the main blood supply to the insula. The prefrontal, precentral, and central arteries, and sometimes the anterior and posterior parietal arteries, fan out over the insula from the superior trunk. Once they reach the superior peri-insular (circular) sulcus, these arteries make a sharp angle to become the M3 segment. Due to this sharp angle, these arteries are called "candelabra arteries". An important anatomical landmark for the central artery in the region of the insula is that it courses along the central sulcus of the insula. The inferior trunk gives rise to the middle temporal artery, posterior temporal artery and angular artery. The M3 (opercular) segment begins at the circular (peri-insular) sulcus of the insula and terminates at the surface of the Sylvian fissure. The M3 segment passes over the insula parallel to the M2 segment, but in the opposite direction. The M4 (parasylvian) segment begins at the surface of the Sylvian fissure and M5 is the terminal segment.[10]

Branches for ECIC Bypass

A cortical artery with appropriate cortical length and at least 4 mm diameter is the temporo-occipital artery. The central sulcal artery is the largest branch to the frontal lobe, the angular artery is the largest branch to the parietal lobe and the temporo-occipital and posterior temporal arteries are the largest branches to the temporal lobe. The angular, posterior parietal and temporo-occipital have the longest segment on the cortical surface.[31] A 4 cm diameter craniotomy centred 6 cm above the external auditory canal is appropriate for the same.

Variants

Duplication of the MCA has been reported in 1–3% of cases. Duplication of the MCA should especially be differentiated from early branching of the MCA, which is a more common variant. Accessory MCAs have also been associated along with aneurysms.[34,35]

Surgical Techniques [3-5,8-10,14,17,25,31,32,40,45-47,50,58,60-62,66,70-73]

Despite good technical results, these patients have surprisingly poor outcomes, primarily because a rupture often produces both SAH and ICH/ISH. The general principles are an adequate exposure and no brain retraction. These are the keys to successful aneurysm surgery.[10,61,62] Excessive retraction leads to unsatisfactory results. The critical elements of aneurysm surgery are: (1) head positioning and fixation determined by the origin of the aneurysm and direction of the fundus; (2) extent of bony exposure; (3) relaxation of the brain via drainage of cerebrospinal fluid (CSF), evacuation of haematoma or by other means like normoventilation and cerebral decongestants in acceptable doses and (4) dissection should routinely be limited within the subarachnoid space (SAS).

Three basic approaches have been described.[3,8,10,31,40,45,50,58,60,61,70,72]

1. Proximal Trans-Sylvian—Splitting the Sylvian fissure medially and following the MCA trunk distally.
2. Distal Trans-Sylvian—Following the major divisions proximally to the aneurysm by opening the fissure peripherally/distally.
3. Superior Temporal Gyrus (STG) Approach[3,17,40]—Making a small corticectomy in the STG and then

subsequently entering the distal portion of the Sylvian fissure and following the M2 branches to the aneurysm.

Skeletal fixation is painful and may cause transient hypertension even in an anaesthetised patient. In patients with a recent SAH, we prefer to inject a local anaesthetic into the anticipated pin sites before securing the device to the cranium. The head is rotated to the contralateral side so that the Sylvian fissure and sphenoid ridge are oriented vertically in the operative field. This rotation usually requires approximately a maximum 30-degree turn of the patient's head and places the malar eminence near the apex of the operative field. Excessive rotation will lead to the temporal lobe obscuring the operative field, thereby needing more retraction to obtain a required exposure. It also leads to obscuration of the medial MCA branches behind the aneurysm dome, especially in large or giant aneurysms. This in turn complicates the dissection and aneurysm clipping. The head is extended (vertex down), allowing the surgeon to see up into the Sylvian fissure. This varies by approximately 20 degrees, depending on the aneurysm's location and its depth in the Sylvian fissure and the course of the MCA. More extension is used for aneurysms deep in the fissure than for those in more superficial locations. Finally, the head and neck are elevated to improve venous drainage before the fixation device is secured.

Proximal Trans-Sylvian Approach[8,10,14,31,40,72]

The basic pterional approach[50,72,73] elaborated by Yasargil is used. For a free bone flap, the flap of skin and muscle are turned together by opening the fascia and muscle along the same line of the skin incision posteriorly and then detaching the muscle from the bone by subperiosteal dissection and leaving it attached to the skin flap. Cutting the anterior (frontal) attachments of the muscle fibres from within facilitates retraction of the muscle backward and downward towards the temporal fossa with barbless fishhooks or sutures attached to strong rubber bands. This is done to suture the muscle properly anteriorly during closure and also to avoid a cosmetically unpleasant depression over the pterional region. Injury to the frontalis nerve is prevented by starting the incision at the level of the zygoma just in front of the tragus as opposed to 1 cm or 1.5 cm in front of the tragus. By starting the incision just in front of the tragus, one spares not only the frontal branch of the facial nerve but also the superficial temporal artery. The authors prefer to raise an osteoplastic flap. It is important to expose 1–2 cm of the temporal lobe to provide access to the Sylvian fissure. The craniotomy should extend along the floor of the frontal fossa just above the supraorbital rim, exposing 3–4 cm of the frontal lobe. The lesser wing of the sphenoid is drilled medially as far as possible to make the anterior and middle cranial fossa floor flat. This helps in avoiding excessive brain retraction.

After adequate relaxation is obtained, the surgeon decides whether the exposure should proceed from medial to lateral or vice versa. In the former case, the carotid cistern is opened by sharp arachnoidal dissection, and the medial aspect of the Sylvian fissure is then opened, preferably on the frontal side of the Sylvian veins. One may have to coagulate a venous tributary at the medial end, but quite often the vein can be spared by dissection and lengthening. Whether coagulating a vein can lead to problems may be determined by applying a temporary clip on the vein and observing the flow on indocyanine green angiography (ICG). The exact location of the fissure medially is not always apparent and the fissure does not always "open" in a clean arachnoidal plane. Use of retractors at the initial part of the procedure should be avoided as the brain is usually lax with decongestants, ventilation and CSF drainage. The arachnoid is opened sharply and CSF is released from the optic and carotid cisterns. Wide opening of all the medial cisterns and separation of the frontal lobe from the optic nerves, chiasm, and lamina terminalis fenestration minimises the need for brain retraction. The Sylvian fissure usually underlies the indentation in the brain made by the sphenoid wing. The Sylvian vein generally hugs the temporal edge of the fissure. Occasionally, neither the sphenoid indentation nor the Sylvian vein will lead to the location of the fissure. Cortical middle cerebral branches are more difficult to see on the surface, but consistently mark the location of the fissure as they emerge from the depths of the fissure and travel over the surface of both the frontal and the temporal lobes. The arachnoid is best dissected sharply when it is held taut. It is safe and less traumatic to use intermittent suction retraction on a small cottonoid to accomplish this task and reserve mechanical brain retraction for the final stages of dissection. By spreading and dissecting with the fine tip bayonet and cutting with microscissors, the arachnoid of the Sylvian fissure is opened from the lateral to the medial side. One or more veins bridging the Sylvian fissure may be encountered, and these may be sacrificed. As the fissure is opened progressively, retraction can be applied immediately adjacent to the area of dissection, always keeping the arachnoid under some tension. The superficial arachnoid layer is divided before carrying the dissection deeper into the fissure. As the fissure is split, the frontal lobe can be mobilised and retracted progressively with the suction tip. The microscope view is more from the frontal lobe towards the medial temporal lobe as the opening in the fissure deepens. If the surgeon gets lost in the subpial plane, following the middle cerebral branches will lead to the fissure and the MCA. When dissection in the fissure is impossible, the surgeon should orient the dissection towards the temporal lobe and perform subpial dissection in the STG. The MCA is followed along its anteroinferior aspect, away from the perforators.

One or two temporal or frontotemporal branches will be seen before the aneurysm is reached. When the aneurysm arises from the M1 segment in relation to a perforating branch, it is necessary to achieve a limited separation of the perforators from the neck which is enough to pass a clip. Care is taken to preserve the LSAs. These aneurysms

usually are not too large and point straight upward into the frontal lobe; it is not necessary to dissect the dome completely. In some patients, the dome of the aneurysm is embedded in the temporal lobe; thus, care should be taken when applying the retractor. A potential site should be selected for placement of temporary clips avoiding the portion of the vessel harbouring the LSAs and provide enough space for deployment of the permanent clips. Dissection is begun at the aneurysm base because the body and dome of the aneurysm are invariably more fragile and one should try and keep away from the initial rupture site till the terminal step of dissection. The site of rupture is determined on CTA + 2D CT fusion and, at surgery, by adherence of the aneurysm to the arachnoid or the cortex.

MCA bifurcation aneurysms pose particular surgical challenges. In aneurysms of the bifurcation (or rarely the trifurcation) of the MCA a complete dissection of the aneurysmal complex is usually preferable. The main problems encountered are: a broad neck, calcification or atherosclerosis in the neck and adhesion of major divisions and sometimes smaller perforating vessels to the neck. When the neck is broad, it is not infrequent to have kinking following clip application. The LSAs exit mainly proximal to the bifurcation; however, some may arise distal to the bifurcation. The surgeon must ensure that they are not adherent to the aneurysm and included inadvertently in the clip. Sometimes, a third division that arises either from the bifurcation or shortly thereafter from one of the other major divisions, or a perforating vessel that arises either before or after the bifurcation and was not evident during initial and preliminary preparation of the neck may surprise the surgeon. Another advantage of dissection of the entire aneurysm complex including the dome is the increased freedom for clip application or modification in clip application. When a recently ruptured aneurysm dome is adherent to the brain, the surgeon should not hesitate to develop a subpial plane, leaving a small amount of adherent clot and brain with the dome. If felt necessary, a tentative clip may be placed proximal to the rupture point to facilitate complete dissection without the need for a temporary clip. The relation of the divisions to the dome is then worked out, and usually, at least one division must be separated carefully from the base of the aneurysm by sharp dissection to define the true neck. Care must be taken to spare the important recurrent perforators, at least one of which is usually found adherent to the aneurysm. Attempts should be made to dissect it sharply off the neck and also a deep vein invariably located there. In those cases, we score the connective tissue that binds the aneurysm to the artery by using a small, sharp knife/needle knife under high magnification. It is frequently necessary to replace the clip several times to avoid kinking of the divisions or "slippage" of the clip proximally onto the MCA. The dissection is begun to separate the divisions more proximally down to a narrower neck. The surgeon can retract the vessel gently away from the aneurysm to stretch the arachnoid bands. These must be sharply divided to separate the vessel from the aneurysm. Usually, one can control bleeding by placing a small cotton patty over the perforation in the aneurysm and applying gentle pressure with the sucker. Bleeding often stops after a few minutes of pressure. When this fails, temporary clips/trapping controls the bleeding. Deformation of the aneurysm by using the sucker, bipolar or dissector allows identification and dissection of the MCA branches hidden behind the aneurysm. In multilobulated or bulbous aneurysms with broad necks, a flawless clipping without prior shaping of the base may be difficult/not possible on many occasions. Bipolar coagulation is used to prepare these aneurysms for clipping. The current is at a low setting. The cleaned bipolar tips are held a few millimetres apart and applied to the aneurysm. This procedure eliminates some of these small blisters and makes the wall look relatively "normal".

How far to proceed in separating the adherent division from the base of the aneurysm is a matter of exquisite surgical judgment of sharply separating the divisions from the neck of the aneurysm only after the aneurysmal complex is completely exposed and a temporary clip is applied. At this juncture, a tiny puncture hole generated can be controlled readily. Due to the complex anatomy of these aneurysms, a full array of aneurysm clips must be available. Fenestrated clips are frequently beneficial to leave a division in the fenestration when the division cannot be separated fully from the base.

Distal Trans-Sylvian Approach[40,45]

This surgical technique minimises retraction injury to the brain and preparation of broad-based MCA aneurysms for clipping is better. It is preferable to open the Sylvian fissure peripherally, find the distal divisions, and dissect proximally towards the aneurysm. This approach has the advantage of facilitating exposure of the distal anatomy of the aneurysm complex, which is usually the difficult part of the dissection. An M2 branch is identified and is followed proximally on to the proximal side of the aneurysm projection until the genu and the bifurcation are exposed. Proximal control is established just proximal to the neck of the aneurysm bypassing the aneurysm complex to avoid any intra-operative aneurysm rupture (IOAR) before gaining proximal control. Then the aneurysm complex is dissected, and the aneurysm is clipped. Yasargil advocates exposure of the MCA to achieve proximal control and then moving laterally. The distal trans-Sylvian approach is associated with less risk of injury to the LSAs. Leaving the proximal MCA unexposed, the risk of exacerbating vasospasm is also minimised.

Superior Temporal Gyrus Approach[17,40]

When the distal fissure cannot be opened atraumatically, occasionally, with a recent haemorrhage or when there is a large temporal ICH, a variant of the lateral Sylvian approach, the STG approach, is considered. This

approach allows the surgeon to enter the fissure distally by subpial dissection without disturbing the Sylvian veins and the superficial portion of the frontal operculum.The only difference is that the surgeon enters the fissure not at the surface but at a depth of 1.5–2 cm from the surface through a cortisectomy in the anterior aspect of the STG. The cortisectomy is extended medially into the vertical segment of the Sylvian fissure over the insula, the arachnoid is then opened, and the fissure is entered. Peripheral branches of the MCA are identified and followed medially. From this point, dissection and clipping proceeds in the same way as done in the distal Sylvian approach. This approach offers the advantage of reducing brain retraction and manipulation of the middle cerebral trunk and its perforators. Its advantages are preservation of the Sylvian veins, minimal retraction even with a large temporal ICH and a swollen brain. A rapid procedure is performed. Its main disadvantage is its violation of brain tissue and theoretical increase in the risk of epilepsy.

For this approach, the skin incision is started at the level of the zygoma, just in front of the tragus. The incision curves slightly backward above the ear before starting to swing forward to the hairline. The cut is extended farther back on to the temporal bone to expose more of the temporal lobe. The pterion and lateral aspect of the sphenoid ridge are drilled. This step is important because it exposes the anterior aspect of the Sylvian fissure, which allows dissection of the aneurysm and clip application from an anterolateral direction as well as from a posterior direction. The exposure is obtained by suction of non-eloquent brain tissue or by removal of any existing temporal haematoma. A 1.5–2 cm incision is made in the STG beginning just behind the front of the Sylvian fissure and continuing posteriorly in a direction parallel to the fissure. The haematoma is evacuated sufficiently to achieve good relaxation, but staying away from the aneurysm. The subpial dissection is then extended medially into the vertical segment of the Sylvian fissure over the insula. Then, one may convert a STG approach to a distal trans-Sylvian approach (Fig. 11). Sometimes, it is difficult to appreciate the anatomy of the MCA, its branches and the aneurysm when approaching the aneurysm through the temporal lobe. Enough of the distal trunk of the MCA is exposed to allow the application of a temporary clip; should this become desirable. Once the distal part of the trunk of the MCA and the origin of the main divisions have been identified then one can proceed with dissection of the entire aneurysm complex. One should take the precaution of leaving adherent brain tissue and clot on the dome in the area of likely rupture (may be secured with a tentative clip). A temporary clip is used for these final stages of dissection. Most MCA bifurcation aneurysms project laterally as a direct continuation of the MCA; less commonly, they project caudally or rostrally.

In an aneurysm projecting backward over the insula, the dome of the aneurysm is in the way when the aneurysm is approached from a distal direction. Many prefer to approach such aneurysms from a medial direction by splitting the medial aspect of the Sylvian fissure first. The distal-to-proximal approach is not suited for aneurysms of the main trunk of the MCA, proximal to the bifurcation, and to those aneurysms that arise from the MCA at the point of origin of an early temporal branch. This is also not suitable for patients in whom the main trunk of the MCA is short, in aneurysms arising from an early bifurcation before the genu and those arising from the horizontal segment of the MCA beneath the insula. In these locations nothing is gained by following the M2 branches from the distal direction. The medial trans-Sylvian approach is ideal for these locations. For giant and complex aneurysms combined approaches are suitable.

Intra-Operative Rupture

Intra-operative aneurysm rupture (IOAR)[5] can occur during craniotomy or after dural opening, but usually it occurs during the final stage of dissection and clipping. Morbidity and mortality is around 30% in IOAR. Earlier in the surgery the rupture takes place, the worse is the prognosis. Blunt dissection causes large and irregular tears extending close or may be on to the neck, whereas most of microtears/micropunctures are small and are at a specific site, hence, can be successfully tackled without ischaemia or vessel sacrifice (Figs 12 to 14).

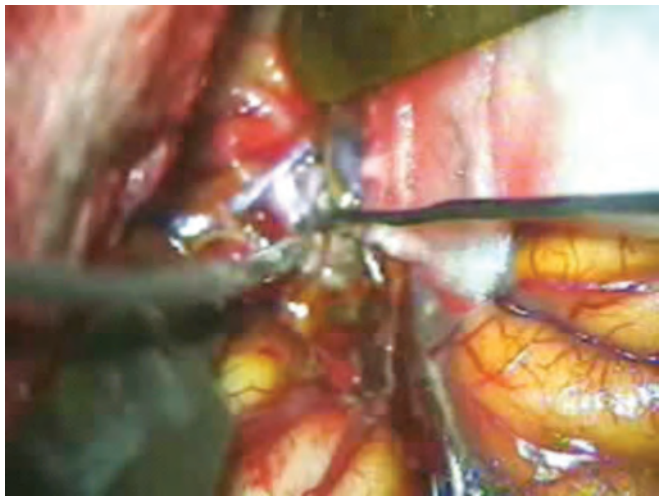

Fig. 11: Operative photo—distal trans-Sylvian approach

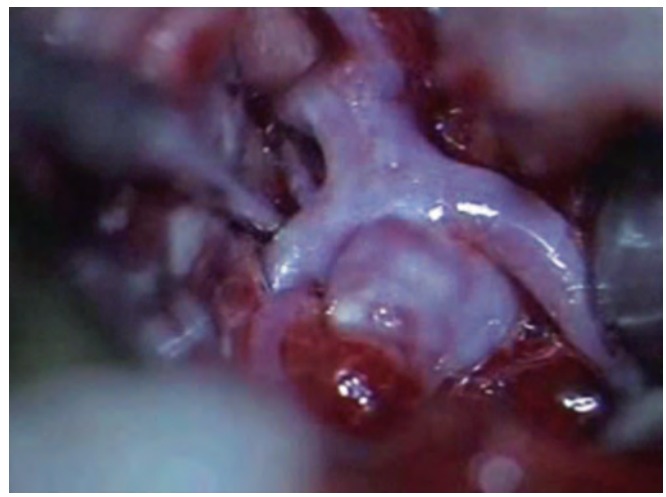

Fig. 12: Operative photo—large MCA bifurcation aneurysm

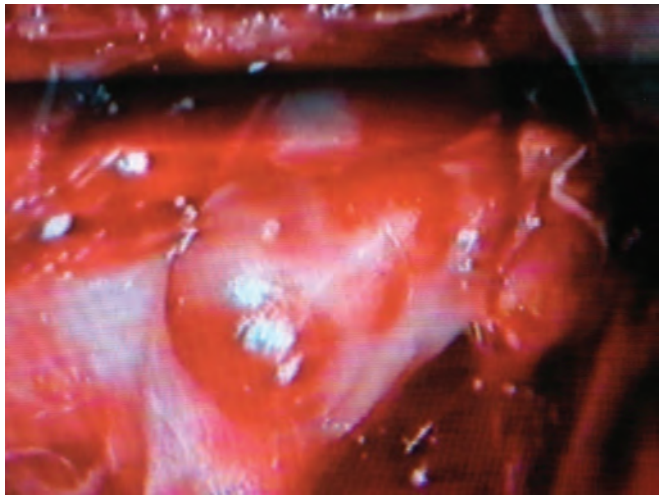

Fig. 13: Operative photo—MCA bifurcation aneurysm

- In case of rebleed during craniotomy (before bone flap removal), the procedure is postponed. If IOAR occurs just before/soon after dural opening, then continuing the surgery with the aim to clip the aneurysm will add to brain trauma caused by the fresh insult. Hence, the dura is opened and a large pericranium or fascia patch is sutured to reduce ICP. The bone flap is placed in the abdominal wall. In case of rupture after starting dissection (opening of Sylvian cisterns/basal cisterns), a part of the frontal/temporal pole can be excised, if needed, and the feeding artery is reached for temporary clipping with institution of immediate neuroprotection measures. Subsequent dissection is as described earlier, but has to be carried out in a limited time frame. IOAR during dissection is managed by temporary clipping and already administered neuroprotectants. A small hole can be managed by cotton and suction. In case of a large hole temporary clipping and dissection is followed by permanent occlusion of the neck. In case the bleeding aperture is exposed/dissected, a tentative clip can be applied on the aneurysm just proximal to the rent. Tentative clipping can either be with a temporary clip or permanent clip (mostly permanent clip) depending on the force required to occlude the ruptured site/extent of dissection completed at the tentative clip site.
- Rupture at clipping can be avoided by dissecting the full extent of the neck. The status of the neck and adjacent vessel should be considered when there are severe atheromatous changes or plaque. The clip ends are never forced through any resistance. If bleeding occurs at the time of clip closure, the clip is removed as the application will result in increase of the size of rent in the aneurysm. After successful clipping of the aneurysm, the dome is punctured and the collapsed sac is mobilised to visualise perforators, the distal end of the clip and the remaining neck if any (particularly in inferiorly directed sacs). Gradually, the remaining wall of the aneurysm is moved into the clip by readjustment under temporary occlusion of the proximal artery.

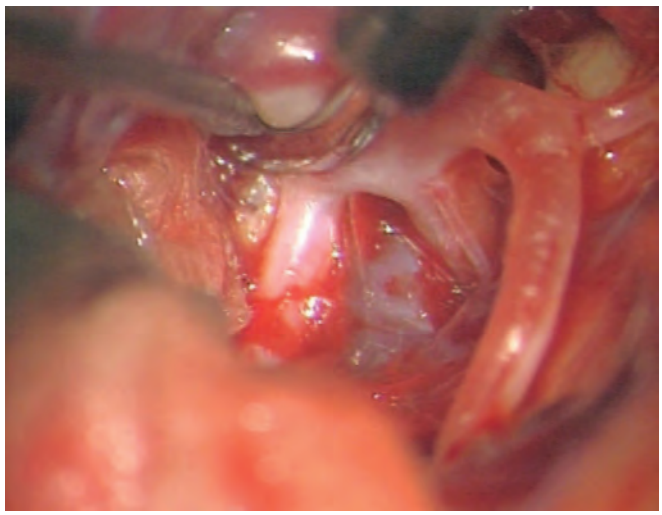

Fig. 14: Operative photo showing MCA bifurcation aneurysm

Single-Stage Approach for Bilateral Middle Cerebral Artery Aneurysms[32]

The patient's head is fixed in the supine position, not rotated but extended enough to minimise (frontal lobe) retraction. The operation table can be tilted to either side according to the requirement. The amount of tilt necessary for an approach to either side is less than 10 degrees and the head can be rotated as necessary on either side just by loosening a single screw from below in a four pin head clamp.

A bifrontal scalp flap is turned down to expose the pterional areas bilaterally. The ruptured aneurysm is approached first. The operating table can be tilted to the opposite side. A similar craniotomy is done on the opposite side and the aneurysm is clipped. This bifrontal scalp incision is symmetrical and better shaped as compared with two separate fronto-temporal scalp incisions. It carries an inherent risk of causing anosmia. This subfrontal approach with the head in almost the neutral position takes more time than for a unilateral MCA aneurysm, but this obviates the troublesome worry about the rupture of the untreated aneurysm during the peri-operative period.

Clipping of a contralateral unruptured aneurysm from an ipsilateral craniotomy can also be performed by experienced surgeons. The proximal ICA bifurcation to M1 is dissected and the aneurysm complex is located at the bifurcation area. The contralateral proximal and distal parent vessel can be exposed adequately for temporary control in case of rupture of the contralateral aneurysm. To obtain the additional working space needed to gain adequate contralateral exposure, a low fronto-orbital extension is necessary. With the Sylvian fissure opened wide, egress of CSF from the SAS allows relaxation of the brain and provides an adequate corridor into the basal cisterns containing the circle of Willis. This minimises the need for retraction of the frontal lobe and provides maximal working space at the depth of

the dissection. After clipping the ipsilateral aneurysm, dissection of the contralateral spaces is continued.[54] The unilateral approach is not always suitable, e.g. for peripherally located MCA aneurysms, a long M1 segment, or in case of large or complex MCA aneurysms. Careful study of the MRA/angiogram/CTA will always reveal if such a unilateral approach will be feasible or not.

Intra-Operative Microvascular Doppler

Intra-operative microvascular Doppler (IMD)[29] is useful in preventing incorrect placement of the clip more so in MCA bifurcation aneurysms due to the need for confirming the patency of three and, sometimes, four vessels. Mechanical arterial spasm is treated by topical sodium nitroprusside (SNP) and its efficacy is verified by IMD. This is a feasible, safe, and very reliable technique in aneurysm surgery. Compared to other procedures such as intra-operative angiography, the cost and efficiency of IMD is favourable. In complex and large aneurysms, a suspected residual neck could be detected by the typical turbulent flow. A 20-MHz 1-mm vascular probe is an appropriate module for direct insonation of the afferent and efferent vessels and the aneurysm sac before and following surgical clipping.

Indocyanine Green Chorioangiography Angiography

It is an extremely useful non-invasive technique to help in dissection to obtain a proper orientation, visualisation of perforators, wall thickness and plaques. This is a great help in delineating the remaining aneurysm neck and any vessel compromise due to the clip, the placement of which can be modified accordingly.

Giant Aneurysms[10,49,59,60]

Only about 5% of intracranial aneurysms are giant (an adequate understanding of these lesions, including the nuances of blood flow dynamics, natural history, and potential therapeutic options, is necessary when one is managing such aneurysms). The most common clinical presentations are SAH and ICH or, both. The poor natural history of these lesions is related to their mass effect on the surrounding brain tissue, to emboli that can dislodge to the downstream vascular territory, and to their high risk for rupture compared with that of other aneurysms. Detailed pre-operative planning includes MRI, CTA, angiography and balloon test occlusion (BTO) of the parent vessel. These can often provide additional valuable information for surgical planning. The treatment of complex aneurysms should be based on a balance between the risks associated with each treatment and its benefit to the patient. The procedures are direct clipping, wrapping and potential bypass. The CT is useful for evaluation of calcification. The MRI is ideal to visualise an intraluminal thrombus and its type, perilesional oedema and associated infarcts, if any. Sometimes, asymptomatic lesions may be incidentally detected on non-invasive imaging. Rotational angiography with 3D reconstruction delineates the anatomy of the aneurysm in relation to the surrounding structures and real time rotation, hence, is important for treatment planning. If BTO is tolerated, there may not be a need for a bypass or only a superficial temporal artery STA-MCA bypass is indicated. If, however, temporary occlusion evokes neurological deficits, a high-calibre conduit is needed to replace the target vessel flow with less complex lesions. Giant aneurysms have a higher rate of arterial wall calcifications, atherosclerotic plaque, and intraluminal organised thrombus along with a wide neck, incorporated branches and dysmorphic structure. These features complicate direct clip reconstruction. Occasionally, adjunctive treatment techniques, including profound hypothermia and circulatory arrest, may have to be adopted.

Direct aneurysm exposure and clip reconstruction of the parent vessel with multiple clip technique is recommended.[49] Total control of the aneurysm anatomy is necessary. With large and giant aneurysms, a small self-retaining soft and pliable retractor with very low tension is applied on the aneurysm itself. A small Rhoton-type dissector and self-retaining retractor can be used for this purpose. Temporary clips must be used in each of the divisions and on the main trunk. Closing a residual pouch sometimes results in a significant aneurysmal base remnant. Proximal anastomosis can be achieved to the external carotid artery or to the common carotid artery, depending on the anatomy in a given patient. The distal anastomosis usually is achieved to an M2 branch.

A certain degree of surgical experience is required to choose between the various options possible for dealing with giant aneurysms: (i) clipping using extra large, fenestrated or multiple clips; (ii) excision with or without interposition graft; (iii) proximal and distal vessel occlusion.

In giant aneurysms a good dissection of the ICA, A1, proximal M1, distal M1 and MCA bifurcation is required. Intra-operative angiogram and availability of endovascular help is extremely beneficial. The thrombus is removed and the aneurysm is clamped between the neck and the incision for decompression of intra-aneurysmal contents. The vascular clamp softens the aneurysm and prevents slippage of thrombus into the M1. In case the clip slides on to the vessel then several clips are used to avoid this problem.

Large, giant or globular aneurysms have thick walls that prevent the tips of the aneurysm clip from closing. In these situations one can safely use Drake's tandem-clipping technique with use of a fenestrated clip proximally; to seal the proximal portion of the aneurysm that is missed by the fenestration, a non-fenestrated proximal clip is applied. In extreme uncontrolled situations in giant aneurysms with organised thrombus and a thick wall, De Bakey's vascular clamp may have to be utilised as a rescue measure.[36] The sclerotic, calcific portion (if easily possible), and organised thrombus (with

a CUSA) are removed, followed by primary clipping, without a long duration of trapping and vessel compromise. Finally, the MCA trunk and branches are assessed with IMD, which is mandatory in large/giant/complex aneurysms.

When the amount of calcification is extensive, the only solution is to perform an aneurysmorrhaphy or to abandon efforts to clip the aneurysm and consider either endovascular occlusion if the anatomy is suitable or, sometimes (particularly in older patients), simply wrapping of the aneurysm. In general, wrapping has been proven to confer no long-term protective value in giant aneurysms.

A bypass is required when attempts to clip are unsafe/not possible. Combined endovascular therapy and revascularisation is a newer solution in these cases. Approximately 25–30% of giant MCA aneurysms simply cannot be clipped, the only possible treatment (other than no treatment) is occlusion of the afferent artery with a high-flow vein/arterial graft.

Advances in endovascular technology (EVT), such as modified stents (covered, partially covered or low porosity) and new embolic agents, will probably improve therapeutic options for these complex lesions. Newer stent technology, such as the "pipeline stent", will have a major impact on the treatment of giant aneurysms. The most important task is to choose the most appropriate management strategy for a specific patient.

Neuroprotection[13,37]

In addition to the routinely used intravenous brain protectants (IVBP, mannitol, antioxidants), the brain-protecting anaesthetic agents include propofol, etomidate, pentobarbital and isoflurane. These are administered individually or in combination. Overall infarction rate is reported to be 22.4% in the IVBP group versus 45.5% in the non-brain protected (NBP) group.

As a general guideline, temporary occlusion of the MCA up to 10 minutes is considered safe. The mean temporary clip time for patients free from infarction was significantly longer in the IVBP group than in the NBP group. Intermittent temporary clip application with periods of reperfusion had significantly less chance of developing an infarction than those who underwent one continuous episode of long occlusion. Propofol and etomidate have been shown to decrease the cerebral metabolic rate for oxygen ($CMRO_2$) and have the ability to produce a burst-suppression pattern on EEG monitoring with conclusive evidence of reduced neuronal damage following experimental ischaemia. Five minutes of reperfusion after every 10 minutes of ischaemia produced by intraluminal occlusion of the MCA in rats resulted in significantly smaller infarction volumes as compared with animals undergoing continuous ischaemia. Studies show that mild hypothermia too salvages penumbral tissue by intermittent reperfusion during iatrogenic ischaemia.

Temporary Clipping[21,53,64,65]

The safety and value of temporary clipping of the MCA are matters of considerable controversy. As per some authors, there is a 45% infarction rate associated with temporary clipping of the MCA.[33] Others have indicated that temporary clipping does not contribute significantly to peri-operative complications.[1,3,7,43]

- Temporary clipping helps in dissection of awkward necks, providing clarity of vision, reducing tension in the sac, capacity to open the sac and evacuation of clot. These render complete/near complete occlusion possible. Pentothal is administered in a loading dose of 10 mg/kg body weight (BW) 5 minutes before temporary occlusion and a maintenance dose of 5–10 mg/kg BW to produce burst suppression pattern on electrocorticography (ECOG).
- Pentothal can also be introduced as 3–5 mg/kg BW intravenously (IV) which is repeated every 15–20 minutes, if occlusion extends beyond that time. 100 gm mannitol, 20–30 minutes prior to temporary clipping, is protective. 1 gm methyl prednisolone, 50 ml/hr, low molecular weight dextran and IV vitamin E or C have also been recommended for neuroprotection.
- Hypertension is maintained at 150 mmHg systolic. Mild hypothermia of 33–34 degrees centigrade has also been found to be effective in a few isolated studies.
- The clip blades used should be of low force, the maximum being 70–80 gm (Sugita, Yasargil). Higher force, longer duration and repeated application at the same site may lead to partial endothelial damage to total desquamation and fragmentation, thereby exposing the subendothelial layers. This is followed by proliferation of smooth muscle cells, accumulation of connective tissue and lipid deposition. The changes in the smooth muscle cause changes in the adjacent nerve fascicles impairing neurogenic innervation and autoregulatory function.
- The vascular occlusion force is determined by four variables. These are vessel diameter, blood pressure, clip blade contact area and vessel elasticity.
- A few moments after MCA occlusion, the blood flow falls to 10 ml/100 gm/min in primates (normal 50 ml/100 gm/min), which is sufficient to induce infarction within 6 hours. This is sufficient to abolish electrical activity of the cortex, but reperfusion within 15 minutes restores the activity. Ischaemia induced in humans by temporary clipping depends on collateral circulation, area containing deep perforators (with poor collateral flow) and blood supply to major deep nuclei (6 min – 15 min).
- Clinical/radiographic strokes take place when occlusion lasts greater than 20 minutes. When hypertension and mild hypothermia are used, temporary occlusion is tolerated better.
- Temporary occlusion under somatosensory evoked potential (SEP) and motor evoked potential (MEP) monitoring indicate that gradual attenuation of SEPs/

MEPs takes place after temporary vascular occlusion. This does not cause ischaemic brain damage if recirculation is established within about 10 minutes of the disappearance of the potentials. These have been observed in ICA and MCA temporary occlusion.

- Observations to be made after clipping are—ensure ample room for adequate blood flow to all distal vessels from the bifurcation area and full patency of distal branches from the bifurcation. Distal tip of the clip is off any branches/perforators. Sometimes, branches originate from the sac or even the dome. Multiple clips to safeguard these branches are really mandatory. Infrequently, if it is not possible then a bypass is the answer or relying on the collaterals.

Outcome

The overall mortality and morbidity of surgery for MCA aneurysms are 6% and 11%, respectively. The presence of an ICH usually does not increase the morbidity much, but patients with ISH have a worse outcome. Patients developing vasospasm have a significantly poorer outcome, around five times more than usual. The size (not the large/giant), site and shape of the aneurysm *per se* do not have any effect on the development of vasospasm. Multinodular and multilobulated aneurysms have a poorer outcome due to therapeutic problems. In large aneurysms with an ICH, a poorer outcome has been reported in some studies. The outcome is significantly better if the surgery is undertaken within 0–3 days of the ictus as compared to the group that had late surgery. This helps in more aggressive management of vasospasm. Post-operative vasospasm is basically related to pre-operative clinical grade, patient's age, artery size and severity of SAH, rather than to the timing of surgery. Evaluation of cognitive functional outcome is an extremely important parameter in assessing the recovery.

Giant MCA aneurysms need to be opened, thrombectomy is performed and then the neck is clipped. Around 18% of the patients had poor outcome and there is a 12% morality. Yasargil[72] noted a higher incidence of hemiparesis in proximal MCA aneurysms and attributed it to the technical difficulties associated with clipping of proximal MCA aneurysms, leading to occlusion of the anterior temporal artery or lenticulostriate perforators.

M1 Segment Aneurysms[2,10,11,16,18,20,52,69]

The usual length of the M1 segment is 12.7 to 20.2 mm. Aneurysms arising along the M1 segment proximal to the MCA bifurcation from early frontal and early temporal branches have distinct anatomic features. M1 segment aneurysms make up less than 10% of the total number of MCA aneurysms. They are often small and thin walled, which makes their clipping a tedious task. They are often wide necked and are in intimate relation to important branches. Preservation of these branches is of paramount importance. These aneurysms usually project superiorly and towards the frontal lobe in contrast to MCA bifurcation aneurysms which usually project towards the temporal lobe in the axis of the Sylvian fissure. Frontal lobe retraction should be avoided as that could result in premature rupture as the projection of the dome is to the frontal lobe. The average distance of a typical MCA bifurcation aneurysm is 20.2 mm from the ICA bifurcation, for early frontal branch aneurysms 13.1 mm and for early temporal branch aneurysms 12.7 mm. After peripheral splitting of the Sylvian fissure till the limen insulae, the M1 is dissected avoiding the superior surface. Enough M1 segment is exposed to allow temporary clipping before any frontal lobe retraction that might be required to complete the dissection of the medial fissure is attempted. A cautious dissection of the neck is required as this is critical. Early frontal branch and LSAs course inferiorly en route to the APS and lie deep to the aneurysm neck and dome. These aneurysms may be hidden under the insula, sometimes burrowing into the limen. Adequate head rotation facilitates the exposure. Slightly less rotation is required for MCA bifurcation aneurysms.

Early frontal branch, early temporal branch, lenticulostriate and short M1 segment bifurcation aneurysms all arise in the sphenoidal portion of the MCA and project superiorly towards the frontal lobe in the anteroposterior (AP) view. The arachnoid adhesions between cortical branches, LSAs and small pial arteries limit mobilisation and dissection of M1.

Associated ICH may prove a hindrance in the management of these lesions. These haematomas may be located in the frontal lobe, temporal lobe, insula or putamen and have to be differentiated from hypertensive bleeds. Early frontal branch aneurysms are not uncommon. These aneurysms may sometimes be mistaken as MCA bifurcation aneurysms, which may put the M1 at risk during surgery. When giant M1 aneurysms project towards the frontal lobe or have a massively calcified wall, parent artery occlusion with pre-operative bypass is recommended.

Complete 3D visualisation of the neck, dome and branches around is necessary by whatever methods available. In giant and fusiform aneurysms a good resolution MRI is required to show a thin aneurysm wall and thrombus separately.

Mini-Craniotomy Approaches[9,12,28]

With the aid of navigation, it is possible to easily locate MCA aneurysms and perform minimally invasive surgeries such as mini-craniotomies, tailored Sylvian dissection and successful clipping of unruptured MCA aneurysms.

Navigation systems incorporate almost real-time localisation, orientation and guidance that facilitate minimally invasive techniques and enable surgeons to achieve the desired results with accuracy and safety. Minimally invasive techniques are contraindicated for giant aneurysms and are not generally accepted for recently ruptured aneurysms.

The head is rotated 30 degrees to the contralateral side so that the Sylvian fissure is oriented vertically in the surgical field and the M1 segment would appear less vertical from the surgeon's perspective. A nearly linear skin incision (approximately 4–5 cm long) is made 1 cm behind the hairline to do the craniotomy for the trans-Sylvian approach for anterior circulation aneurysms. Subsequently, a sphenoid ridge keyhole approach was also described. These two approaches are applicable to anterior circulation aneurysms, including MCA aneurysms, as minimally invasive techniques. The lateral supraorbital approach is also used by many experienced surgeons even for surgery within 24–48 hours. However, a lax brain has to be ensured by expert anaesthetic techniques, CSF drainage and neuroprotection. A basic additional prerequisite for using this approach is ensuring that the skills and adequate experience are available to dissect the Sylvian fissure and treat recently ruptured cerebral aneurysms.

The lateral supraorbital approach is more subfrontal and the head is rotated 15–20 degrees with a little tilt to optimally visualise the M1, the branches, and the neck and dome of the aneurysm at a comfortable working angle. When there is an associated ICH, an incision is made in the temporal or frontal cortex depending on the location of the haematoma, safeguarding the eloquent speech area. On many occasions, there are calcific plaques in M1 hence, a wider splitting of the Sylvian fissure and more exposure of M1 is necessary to avoid placing a temporary clip in the plaque area. The arachnoid is dissected and cut on the frontal side of the superficial Sylvian vein. The arachnoid is cut with scissors and closed scissors can be used as a sharp microdissector. Small cottonoids can be used to expand the cisternal space by dissection. The dissection is usually done on the anteroinferior surface so as to avoid dissection in relation to the origin of the perforators. In aneurysms on the frontal side, the dissection usually starts at the ICA bifurcation. Sharp dissection of the branches around the neck is crucial. The dissection of these thin walled, broad necked aneurysms which are adherent to LSAs should be painstaking and delicate to safe guard all these structures individually. In the event of rupture of these aneurysms under proximal control, a final dissection is attempted with the application a tentative clip after control of the bleeding by cotton and suction. If this fails, short time temporary clipping or trapping by small clips is attempted. Sometimes, these aneurysms are too small to clip specifically following rupture and then 8 or 10 zero suture or clip with small portion of the vessel wall in the clip or clip on wrap (in extreme situations) is attempted.

Dissecting Aneurysms[27,41,42]

These are comparatively less common intracranially, and their natural history is not clear. These are predominantly seen in the younger age group. These usually occur in the vertebrobasilar circulation and are seen in the proximal vessels in the anterior circulation. The arterial pressure is weaker in the distal branches than in the proximal branches, but dissecting aneurysms may occur in the distal branches intracranially. In distal locations they occur due to head trauma, vasculitis, atherosclerosis, neoplastic emboli, bacterial infection, and are associated with endocarditis. These are known to be related to such diseases as migraine, fibromuscular dysplasia, mixed connective tissue disease, trauma, periarteritis nodosa, syphilitic angiopathy, moyamoya disease and Guillain-Barre syndrome. They present as thrombotic and haemodynamic ischaemia correlated with atherosclerosis. It is advisable to include this possibility in the differential diagnosis of occlusive vascular disease, especially in young patients. Dissecting aneurysm of the MCA has been known to cause cerebral infarcts in young individuals. The plane of dissection is mainly in the subintimal layer. A dissecting aneurysm should be considered as a diagnosis when a saccular intracranial aneurysm is excluded in patients having haemorrhage around the MCA.

There is no specific and definite causative factor identified for intracranial dissecting aneurysms in the MCA. These are relatively rare in the MCA with only 26 reported cases. Histological studies have indicated that these may be produced by penetration of the circulating blood into the vascular wall with subsequent extensions of the effused blood for a varying distance between the layers of the vessel. These have been classified based on the condition of the internal elastic lamina (IEL) and the state of the intima as follows: type 1 has acute widespread disruption of the IEL without intimal thickening; type 2 shows extended and/or fragmented IEL with intimal thickening and type 3 manifests fragmentation of the IEL, multiple dissections of the thickened intima, and organised thrombus in the lumen.[13] The classification as per the different planes of the dissecting laminae of the arterial wall, in which type 1 (submedial dissection) is likely to cause cerebral infarction and type 2 (subadventitial dissection) causes SAH as it communicates with the true lumen through the disrupted portion of the IEL.

Angiographic characteristics of dissecting aneurysms include the pearl and string sign, narrowing, fusiform dilatation and occlusion, but these are not diagnostic. The pathognomonic sign for dissecting aneurysm may be double lumen, but this is infrequently found. MRA can substitute for intra-arterial angiography when repeated studies are necessary. Infarcts were observed not only in the territory of the MCA branches, but also in the territory of the LSAs originating from M1. Surgery, including bypass surgery, does not therefore seem likely to be effective, since it cannot improve flow through these perforating arteries.[55] The optimal surgical procedure is yet to be established, however, there is some consensus that surgical treatment such as wrapping or trapping with arterial reconstruction may be appropriate in the presence of SAH, since subsequent bleeding often leads to

poor outcomes in dissecting MCA aneurysms presenting with SAH. Most of the patients treated surgically had good outcomes. Surgery should be done promptly to prevent critical rerupture and SAH. The natural history of intracranial dissection is obscure, so surgery should be performed in patients with recurrent SAH, but may be unadvisable in neurologically stable patients without recurrent SAH.[2] The surgical methods, such as trapping with or without bypass surgery, ligation or wrapping for ruptured MCA dissecting aneurysm, have been reported.[51] The routine surgical treatment for dissecting aneurysms of the M1 portion is bleb clipping and wrapping due to the presence of perforating arteries, whereas that for aneurysms of the M2 or M3 portion is resection or trapping of the dissecting aneurysm, and if possible STA-MCA anastomosis to maintain MCA flow distal to the lesion. Despite the risk of haemorrhage, the endovascular technique may be considered in high-risk patients.

Distal Middle Cerebral Artery Aneurysms[1,24,35,57]

Intracranial aneurysms mostly occur at the main trunks of the circle of Willis. Distal MCA aneurysms are the least common of all MCA aneurysms. They constitute around 1–6% of MCA aneurysms. These are usually associated with aneurysms in other locations (56%). Their treatment is a great challenge due to location, small distal arteries, terminal branches, type of aneurysm (embolic and fusiform), wide neck, tight Sylvian fissure, and these aneurysms have more chances of rebleed. Lack of collateral circulation in these arteries may mandate bypass and revascularisation. These present as ICH in addition to SAH in 50–60% of patients, which is one of the factors for poor outcome in them. The clinical features include small diameter aneurysm (usual 7–9 mm) with wide neck and fusiform shape in more than half. These can originate just distal to the bifurcation at M2-3 or beyond. These are hidden deep in the distal Sylvian cistern amongst the distal branches of MCA. The location could be M2, M2-3 and M3. Radiology shows SAH with moderate to large ICH with increased incidence of rebleed in 50% of cases. The M3 opercular segment commences at the peri-insular sulcus, M4 at the parasylvian surface and the distal most branches are designated as M5. The distal Sylvian fissure as such is narrow and previous SAH produces adhesions and makes it tough as well. The usual aetiological factors for aneurysms in this location are infective endocarditis, neoplastic emboli, inflammation and trauma. These are located mostly on cisternal branches and are rarely seen on perforating or penetrating branches. The bleed and rebleed are determined not only by size at rupture, but more so by the thickness of the wall and diameter of the artery of origin. The smaller aneurysms have higher arterial pressure than larger ones and if the growth rate exceeds the capacity of wall repair the thinness of the wall results in early rupture.

The DSA and CTA (aneurysms larger than 2 mm diameter) have a comparable sensitivity in diagnosing these aneurysms. The CTA can help by providing a surgeon's view and one can measure the length of M1 and distance of the aneurysm from the MCA bifurcation. The T2 coronal and axial MRI are also useful for pre-operative planning in these aneurysms. The aneurysms of M2 can be approached through the same approach as for MCA bifurcation aneurysms and more distal ones need more occipital exposure over the Sylvian fissure. Patients with a large ICH present in a poor clinical state and there may even be a life threatening situation. Therefore, on many occasions these need to be operated upon immediately after CT angiography. More distal aneurysms are not only problematic to treat but even more tedious to locate, more so in the presence of ICH (responsible for swollen and even tight brain). Therefore, neuronavinagation is of great help. Intra-operative DSA, colour Doppler or 3D intra-operative ultrasound are of use in localisation and management.[54,67,68] A fifth of patients have hydrocephalus needing ventricular drainage. The pre-operative measurement of distances of M1 segment and the onward distance is beneficial to get a guide for opening the arachnoid in the Sylvian fissure, locate the aneurysm and orient the extremely complicated arterial tree in the distal Sylvian fissure. After proper localisation, the dissection may be performed under frequent, short clipping, maximally for 5 minutes at one time. Usually the required clips are small or mini clips (one and a half times the size of the neck). As the anatomy is complex in the region with small branches being present, it is better that a post clip ICG is performed to confirm complete occlusion and complete patency of vessel lumen. The haemodynamic stress is less in the distal MCA as compared to M1 and MCA bifurcation; hence, these aneurysms occasionally grow to a giant size. Fusiform aneurysms with beer belly can be tangentially clipped. In fusiform aneurysms with retrograde flow confirmed on IMD after temporary clip, it may be possible to clip the parent artery without a bypass.

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84 Posterior Circulation Aneurysms

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INTRODUCTION

Aneurysms of the posterior circulation are relatively uncommon lesions, which account for about 15% of all intracranial aneurysms. These aneurysms are technically difficult to tackle as they require manipulation in the confined space in front of the brainstem and cerebellum. In 1946, Schwartz was the first surgeon who successfully clipped an aneurysm in the posterior fossa without the aid of magnification.[45] In 1965, Drake reported his experience with aneurysms of the basilar bifurcation and attributed the high mortality and morbidity in his series to injury to the perforators arising from the proximal posterior cerebral arteries.[10]

Advances in micro-neurosurgical instrumentation, development of different skull base approaches, pharmacological brain protection, modern neuroimaging and development of precise scientific neuroanaesthesia have all contributed to advancement in surgical management of posterior circulation aneurysms. Interventional neuroradiology has developed as a separate scientific discipline and has undergone recent technological advancement leading to more and more patients with posterior circulation aneurysms being treated by endovascular methods,[33] though its long-term efficacy is yet to be established.

In this chapter, we discuss the relevant microsurgical anatomy, incidence, clinical presentation, diagnostic imaging and available treatment options, surgical as well as non-surgical, for the management of posterior circulation aneurysms.

MICROSURGICAL ANATOMY

The anatomy of the posterior circulation and its relationship to adjacent neural structures can conveniently be divided into the following three neurovascular complexes (Fig. 1):

1. *The basilar apex*: Basilar artery (BA) bifurcation, posterior cerebral artery (PCA), superior cerebellar artery (SCA), BA-SCA junction, upper basilar artery.
2. *The basilar trunk*: Midbasilar artery, anterior inferior cerebellar artery (AICA).

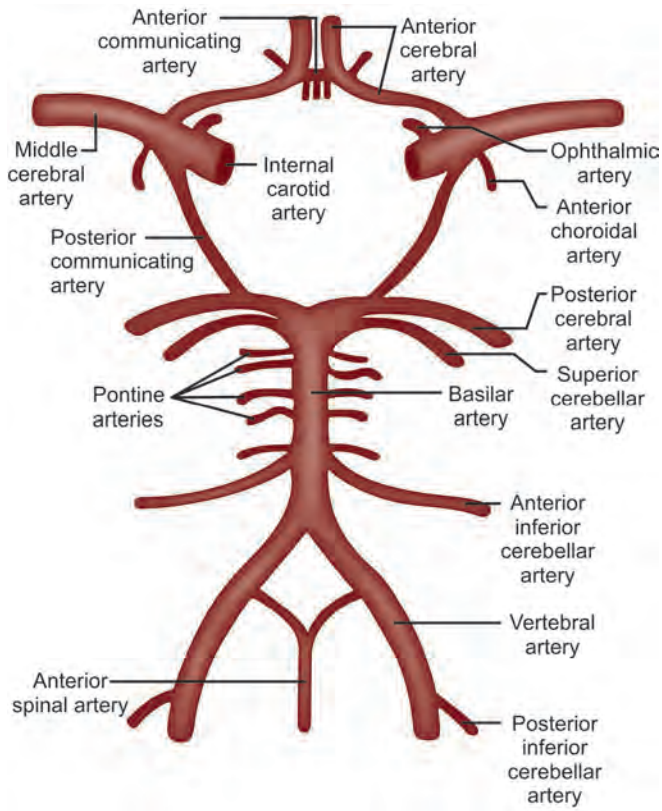

Fig. 1: Diagrammatic representation of circle of Willis showing both anterior and posterior circulation

3. *The vertebral trunk*: Vertebral artery (VA), posterior inferior cerebellar artery (PICA), VA-PICA junction, vertebrobasilar junction (VBJ).

Vertebral Artery (VA)[42]

After its exit from the subclavian artery, the VA traverses through the foramina transversaria of the lower six cervical vertebrae, arches over the posterior arch of the atlas and penetrates the dura at the level of the foramen magnum behind the occipital condyles to become intradural and intracranial.[6,7] The vertebral arteries are frequently asymmetrical in size, the left being dominant in 90%. The extradural branches are the muscular branches and the posterior meningeal artery. The intradural branches are the posterior spinal artery, the PICA, the medullary perforating arteries and the anterior spinal artery. The

vertebral trunk is the intradural portion of the artery from its dural ring to the VBJ.

Posterior Inferior Cerebellar Artery (PICA)[19,28]

The PICA represents the largest and most clinically significant intracranial branch of the vertebral artery. It arises at the level of the olive (10 mm above the foramen magnum) in around 92%. The PICA can be considered as having four segments which are defined by their relationship to adjacent cranial nerves. The anterior medullary segment begins at the origin of the PICA, lies anterior to the medulla and extends posteriorly past the hypoglossal rootlets at the medial edge of the inferior olive. The second, the lateral medullary segment, extends from the olive along the lateral surface of the medulla to the rootlets of the IX, X and XI cranial nerves at the lateral edge of the olive. The third, the tonsillomedullary segment, passes under or between the rootlets of the CN IX, X, XI triad and around the cerebellar tonsil, then it makes an inferomedial turn called the caudal (infratonsillar) loop. The fourth segment of the PICA, the telovelotonsillar segment, passes along the medial surface of the tonsil, ascends towards the roof of the IVth ventricle and curves downwards again forming a cranial loop (supratonsillar loop). The peak of the cranial loop is called the 'choroidal point' and is closely related to the floor of the IVth ventricle. The PICA may be absent in about 26% unilaterally and in 2% bilaterally. In 16%, it is hypoplastic. The PICA and AICA have an inverse relationship in size. Aneurysms in this region arise at the PICA-VA junction, but rarely from the distal PICA.

Basilar Artery[36]

This originates at the junction of the vertebral arteries at the level of the pontomedullary sulcus, runs upwards anterior to the pons to terminate at the level of the pontomesencephalic junction into two PCAs. At the bifurcation point, it is closely related to both the oculomotor nerves. The bifurcation is typically within 1 cm of the dorsum sellae in 90%. This configuration means that the BA can bifurcate as far as caudally as 10 mm below the pontomesencephalic junction or as far rostrally as the mammillary bodies. The location of the basilar bifurcation in relation to the dorsum sellae and the posterior clinoid process is important in selecting the surgical approach to clip an aneurysm. The branches of the basilar artery include the pontomedullary artery, the long lateral pontine artery, AICA, SCA, the posterolateral artery, PCA and the caudal, middle and rostral perforators. Perforating branches arise from the posterior and the lateral surfaces of the basilar artery and not from its anterior surface.

Posterior Cerebral Artery (PCA)[56]

This is the terminal branch of the basilar artery. The basilar apex, along with its bifurcation into two PCAs, constitutes the posterior portions of the circle of Willis. The PCAs can be subdivided into three segments. The P1 segment (basilar bifurcation to origin of posterior communicating artery) gives rise to the thalamoperforating arteries and long and short circumflex arteries. The P2 segment (starts at the PCA-PCom junction and extends to the posterior aspect of the midbrain) courses through the crural and ambient cisterns giving origin to the anterior temporal, hippocampal, medial posterior choroidal and posterior temporal arteries from the anterior part; and middle, posterior and common temporal arteries and lateral posterior choroidal arteries from the posterior part. The P3 branch courses through the lateral part of the quadrigeminal cistern towards the calcarine fissure and terminates into calcarine and parieto-occipital arteries which supply the occipital and posterior temporal lobes.

Superior Cerebellar Artery (SCA)[23]

The SCA arises from the basilar trunk just before its bifurcation and encircles the midbrain in the pontomesencephalic sulcus. In 20%, it may arise directly from the PCA. Cranial nerve III separates the SCA and PCA. The SCA passes between CN III and V into the cerebellomesencephalic sulcus and gives off the superior vermian and lateral hemispheric branches.

Anterior Inferior Cerebellar Artery (AICA)[20]

The AICA arises from the lower third of the basilar artery, courses around the anterior and the lateral surface of the pons below and between abducens fascicles and runs laterally towards the flocculus. It has premeatal, meatal and postmeatal parts. It gives origin to the internal auditory, subarcuate and recurrent perforating arteries. Along its course, it also sends branches to the upper anterolateral medulla, CN VII and VIII, middle cerebellar peduncle and petrous surface of the cerebellum.

Perforating Vessels[29]

The basilar apex and PCAs give rise to a large number of essential perforating arteries. These perforators can be divided into three categories.

1. The first group arises from the apex of the basilar artery itself, typically from the terminal 2–3 mm of the artery and supply the posterior perforated substance, cerebral peduncles and lateral pons.
2. The second group of perforators arises from the posterior and the superior aspects of the P1 segments of the PCA, along with long and short circumflex arteries. Together, they supply the medial and the lateral geniculate bodies (posterior thalamoperforating arteries), interpeduncular fossa, mammillary bodies, cerebral peduncles and posterior mesencephalon.
3. The third group arises from the superior and the lateral surfaces of the PCom, supplies the hypothalamus and posterior optic chiasm anteriorly or perfuses the

posterior perforated substance and the thalamus posteriorly (posterior thalamoperfoarating arteries).

INCIDENCE

Aneurysms of the posterior circulation account for around 15% of all intracranial aneurysms.[12,31,38,52] Morphologically, they can be saccular, fusiform or dissecting. Saccular aneurysms of the posterior circulation most often occur at the basilar apex (45–55%), followed by the origin of SCA (15–24%), PICA and PICA-VA junction (7–21%), PCA (10–14.5%), and lower third basilar artery, VBJ and AICA (3–4%).[14,15] Saccular aneurysms of the AICA are the least common. The frequency of coexistent multiple aneurysms range between 24% and 36%.[11,39] They most commonly present in the fifth and sixth decades of life, most often in females.

Dissecting and fusiform aneurysms are more common in the posterior circulation compared to the anterior circulation. Fusiform aneurysms account for 9% of all posterior circulation aneurysms. Fusiform aneurysms of the vertebrobasilar system frequently occur in the setting of intracranial atherosclerosis.[38] Dissecting aneurysms account for 31% of vertebral artery lesions and are found in young males.[52] Dolichoectatic aneurysms of the vertebral and basilar arteries may result from dissections that produce fusiform degeneration of the artery, progressive enlargement and luminal thrombosis.[1,34]

Giant aneurysms (>25 mm in diameter) occur in the posterior circulation as frequently as in the anterior circulation and follow the same anatomic distribution as the smaller aneurysms. Posterior circulation aneurysms appear to be less frequent in paediatric and geriatric age groups.[30,32]

Anatomic variations and vascular abnormalities associated with posterior circulation aneurysms include hypoplastic or foetal PCAs, persistent carotid-to-basilar anastomosis and arteriovenous malformation in the occipital lobes or cerebellum.[23,38,45,52,55] Connective tissue disorders (e.g. polycystic kidney disease, Marfan's syndrome, Ehlers-Danlos syndrome) can increase the likelihood of aneurysms in the posterior circulation as they do in the anterior circulation.

CLINICAL PRESENTATION

The clinical presentation of posterior circulation aneurysms depends upon whether the aneurysm has ruptured or not. Almost 80% of posterior circulation saccular aneurysms present with signs and symptoms of acute subarachnoid haemorrhage (SAH)[3,38,52] almost always without features localising the source of bleeding. Headache, nuchal pain and rigidity, nausea, vomiting and altered mental status are the most common manifestations of rupture. Intraparenchymal bleeding is rarely associated with rupture of posterior circulation aneurysms[11,38,52] due to the tough pial envelope of the brainstem. Superiorly, pointing basilar tip aneurysms, however, often rupture through the floor of the IIIrd ventricle causing intraventricular haemorrhage and obstructive hydrocephalus. Likewise, a ruptured PICA aneurysm can present with IVth ventricular bleed with hydrocephalus. Occasionally, a cranial nerve deficit points to the origin of a particular aneurysm;—oculomotor paresis (aneurysms of basilar apex, upper basilar artery and superior cerebellar artery); abducens dysfunction (aneurysms of VBJ and lower basilar trunk); VII and VIII cranial nerve involvement (AICA); IX, X, XI (PICA); XII nerve involvement (PICA and vertebral artery aneurysm).

Unruptured giant aneurysms of the vertebrobasilar system usually present with mass effect on the adjacent cranial nerves and brainstem.[3,38,52] These signs can range from isolated cranial neuropathies to brainstem compression syndromes that mimic posterior fossa tumours. These include hydrocephalus (due to obstruction of CSF flow through the cerebral aqueduct or IVth ventricle); contralateral haemiparesis with ipsilateral IIIrd nerve palsy (due to compression of the cerebral peduncle by a basilar tip or SCA aneurysm); dysphagia, dysarthria, cerebellar symptoms (by compression of lower cranial nerves and cerebellum by a giant vertebral artery aneurysm).[51,53]

Dissecting aneurysms present with occipitocervical headache, SAH, non-haemorrhagic infarction of the thalamus, brainstem, cerebellum or other signs of cerebral thrombosis, oculomotor palsy, Horner's syndrome or a mass lesion.[39]

DIAGNOSTIC STUDIES

The initial evaluation of a patient with suspected SAH invariably involves computed tomography (CT), which clinches the diagnosis; allows visualisation of accompanying infarcts, cisternal clot, hydrocephalus and a giant aneurysm. The location of the SAH can sometimes provide a clue to the location of an aneurysm, though it is not always a reliable indicator. Basilar tip aneurysms can cause a large amount of clot in the interpeduncular cistern.[13] PICA aneurysm rupture can cause IV ventricular bleed (Figs 2A to C). CT angiography may reveal a posterior circulation aneurysm with a three dimensional external morphology and its relationship to the bony anatomy of the skull base.

Magnetic resonance imaging (MRI) can be a helpful adjunct in the evaluation of giant aneurysms of the posterior circulation and its relation to the brainstem and cranial nerves.[3,52] MRI is not routinely used for the assessment of most saccular aneurysms. Magnetic resonance angiography (MRA) has superseded MRI in that respect (Fig. 3A).

High quality four-vessel digital subtraction angiography (DSA) in multiple projections (anteroposterior, lateral, oblique, submentovertical) remains the gold standard for diagnosis and surgical planning (Fig. 3B). Pre-operative angiographic studies determine the following important features:

- Aneurysm's vessel of origin.
- Aneurysm's shape, size and relationship to parent and adjacent arteries.

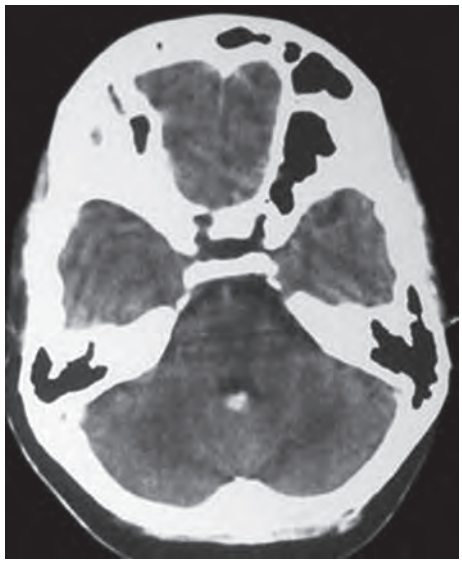

Fig. 2A: NCCT head showing IVth ventricular bleed in case of PICA aneurysm

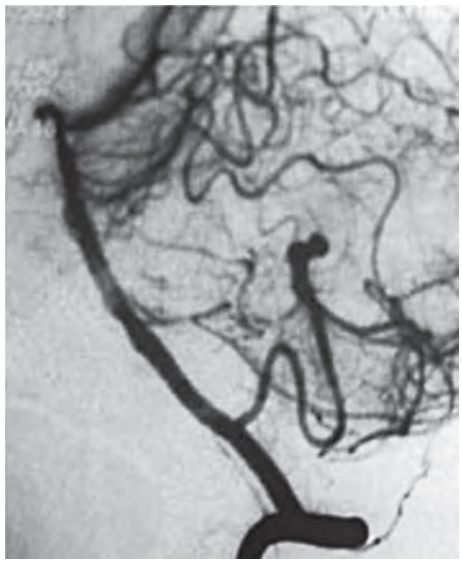

Fig. 2B: IADSA showing left PICA aneurysm

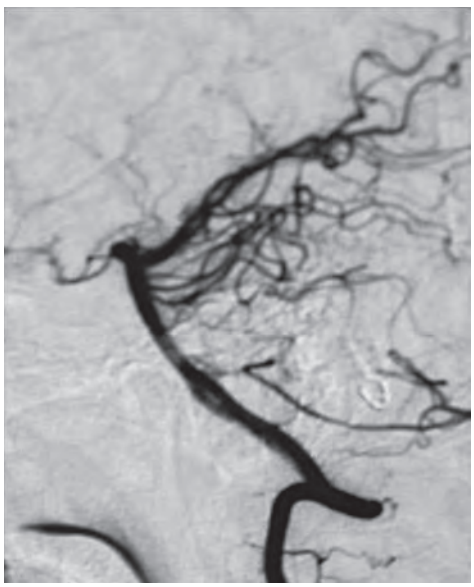

Fig. 2C: IADSA of the same patient showing well-clipped left PICA aneurysm

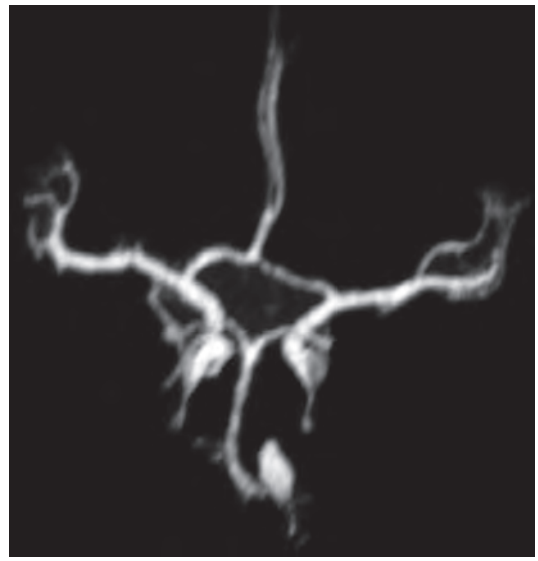

Fig. 3A: MR angiography showing left VA-PICA junction aneurysm

- The presence and location of vasospasm.
- The displacement of adjacent vessels, suggesting mass effect from haematoma or partial thrombosis of an aneurysmal sac whose dimensions are much larger than that seen on angiography.
- The presence of associated multiple aneurysms or vascular abnormalities.

Four-vessel angiography also delineates features of the underlying circulatory supply to the posterior fossa that may affect surgical strategy, e.g. foetal PCA, dominant vertebral artery, etc. DSA is also essential to assess the adequacy of filling of both vertebral arteries as well as possible collateral circulation via the posterior communicating arteries (Alcock Test). Dissecting aneurysms, more common in the vertebral circulation, can be recognised as a double lumen (diagnostic hallmark), a narrow tapered lumen (string sign) or an irregular post-stenotic dilated segment (pearl sign).[33]

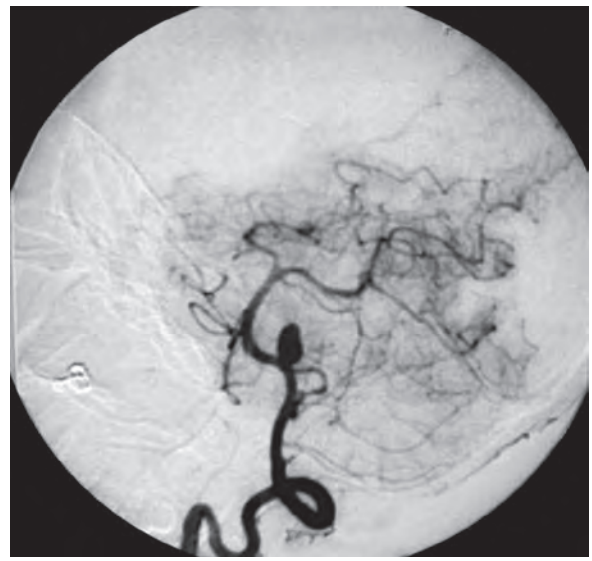

Fig. 3B: IADSA of the same patient showing left VA-PICA junction aneurysm

Table 1: Surgical approaches for posterior circulation aneurysms

Aneurysms	*Trajectory*	*Approach*
Basilar top, PCA, SCA, Upper basilar artery	Anterosuperior	Subtemporal (Peerless and Drake)[11,39] Pterional transsylvian (Yasargil),[54] Transsylvian temporopolar (Sano),[44] Modified pterional transcavernous transsellar (Dolenc),[8] Middle subtemporal transtentorial (Sugita)[50] Orbitozygomatic, Orbitozygomatic infratemporal,[16] *Extended orbitozygomatic approach*
Midbasilar artery, AICA	Lateral	*Transpetrosal* (Kawase),[22] Transtemporal (Sekhar),[47] Retrolabyrinthine transsigmoid (Gianotta and Marceri),[14] *Combined supratentorial and infratentorial approaches* (Kadson and Stein),[21] Transoral transclival approach (Saito),[43] Transoral transclival with Le Fort I maxillotomy (Archer),[2] Extended middle fossa approach
VA, PICA, VBJ	Posteroinferior	Midline suboccipital, Paramedian suboccipital, *Far-lateral approach* (Heros),[17] Extended far-lateral approach

(*Italic letters* indicate the preferred approach)

It is beyond the scope of this chapter to describe the operative steps of each surgical approach in detail. Still, an attempt has been made to acquaint the reader with common approaches used for management of posterior circulation aneurysms.

SURGICAL MANAGEMENT

Principles of surgery for posterior circulation aneurysms are essentially similar to those followed for aneurysms of the anterior circulation;—shortest trajectory to the aneurysm, bone removal in lieu of brain retraction and maximum dissection of the arachnoid from brain, vessels and nerves. Several surgical approaches, viz. infratentorial, supratentorial, combined supratentorial/infratentorial and transbasal have been used for successful treatment of posterior circulation aneurysms.

The choice of surgical approach depends on the anatomical location, size and projection of the aneurysm, relationship of the aneurysm to the foramen magnum and midline, level of basilar bifurcation and the shortest possible distance from the cranial surface to the aneurysm (Table 1) (Fig. 4).

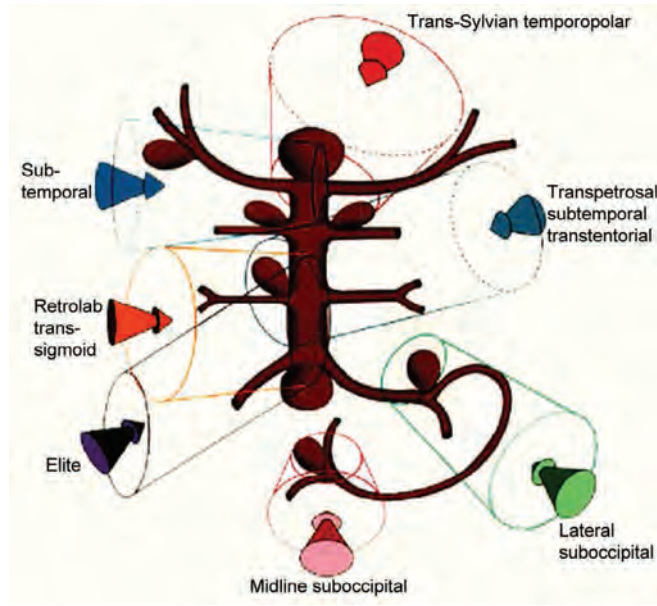

Fig. 4: Diagrammatic representation of various surgical approaches to posterior circulation aneurysms

SUBTEMPORAL APPROACH

The subtemporal approach, developed by Peerless and Drake,[9,11,39] employs a lateral trajectory with elevation of the temporal lobe. The patient is placed in the supine position with the head semi-extended and turned to the opposite side. A question-mark shaped incision is made just anterior to the tragus. A temporal craniotomy is made flush with the floor of the middle cranial fossa to minimise temporal lobe retraction. If required, the zygomatic arch may be removed, especially if the basilar bifurcation is high. The dura is opened based inferiorly. A self-retaining retractor is placed to expose the tentorial edge and the ambient cistern. The arachnoid is opened and CSF is drained; the tentorial edge is cut and the cut ends are hooked by a stitch. The arachnoid is widely opened. The membrane of Liliequist is opened and CN IVth is carefully visualised; tracing the IIIrd CN proximally permits the identification of PCA and SCA. The PCA is traced proximally to reach the basilar bifurcation. In many cases, the subtemporal trajectory parallels the

long axis of the aneurysm's neck, which is the optimal direction for placing a clip on these aneurysms. The posterior perforating arteries, whose preservation is perhaps the most crucial aspect of the procedure, can also be visualised best from this trajectory. The neck of a posteriorly projecting aneurysm has to be separated from the perforators and the opposite PCA. In technically difficult cases, cardiopulmonary bypass and hypothermic circulatory arrest can be used.

PTERIONAL-TRANS-SYLVIAN APPROACH

This approach, popularised by Yasargil,[54] is an excellent approach for basilar apex aneurysms. This approach is also a familiar approach to most neurosurgeons as it is the standard approach for most anterior circulation aneurysms. The patient is in the supine position with the head rotated approximately 30 degrees to the opposite side and extended approximately 20 degrees. Exposure of the basilar apex through this approach requires splitting the Sylvian fissure, widely opening the cisterns around CN IInd and the carotid artery, and gently retracting the frontal and the temporal lobes (Figs 5A and B). The PCom is followed posteriorly through Liliequist's membrane to the PCA, which is then followed medially to the basilar apex.

ORBITOZYGOMATIC AND EXTENDED ORBITOZYGOMATIC APPROACH

The orbitozygomatic approach is an extension of the pterional approach in which the superior and the lateral portions of the orbit are removed, thereby creating more space in the operative corridor and providing an extended upwards view of the basilar apex. The fulcrum of the trajectory drops lower across the orbit, resulting in a higher view of the basilar apex above the posterior clinoid process. Consequently, it is one of the preferred approaches for a basilar apex aneurysm. Several modifications to the orbitozygomatic approach enable an extended exposure to facilitate the surgical management of giant posterior circulation aneurysms, particularly those located below the basilar artery apex.[25] Additional inferior exposure is gained by removing three intradural bony obstacles, viz. the anterior clinoid process, the posterior clinoid process and the dorsum sellae. Removal of the upper clivus opens a window to the anterior surface of the basilar artery through which the aneurysm can be dissected (extended orbitozygomatic approach). While drilling the clivus, it is important to preserve the medial dural wall of the cavernous sinus to avoid entry into the cavernous sinus.

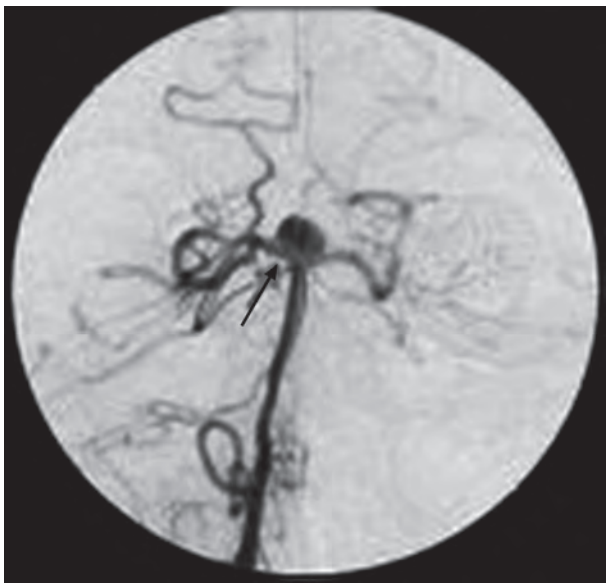

Fig. 5A: IADSA showing basilar top aneurysm

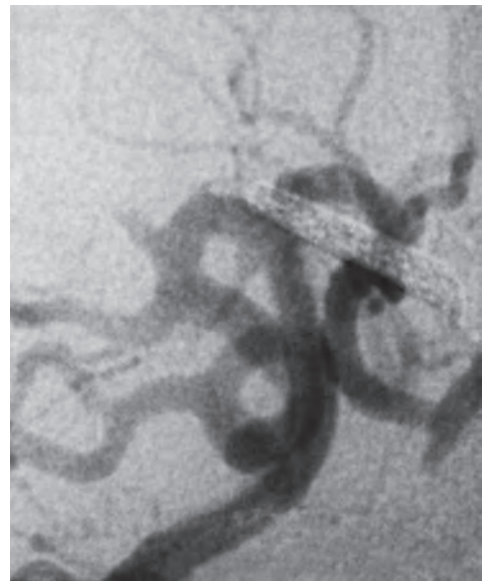

Fig. 5B: IADSA of the same patient showing well-clipped basilar top aneurysm

TRANSPETROSAL APPROACH

The transpetrosal approaches have three variations, viz. retrolabyrinthine, translabyrinthine and transcochlear.[24] The three types of temporal bone dissection represent a graduated increase in the amount of petrous bone resected with a corresponding increase in anterior exposure. Any one of these approaches can be used to access an aneurysm in the middle zone of the basilar artery.

FAR LATERAL APPROACH

[Synonyms—lateral suboccipital approach, extreme lateral approach, extreme lateral inferior transcondylar exposure (ELITE) (Fig. 6)].

The far lateral approach is the most common approach to aneurysms of the vertebral trunk.[17,48] For aneurysms in this location, the authors use a modified suboccipital craniectomy. The patient is positioned in the lateral position in three point fixation with flexion in the anteroposterior plane, rotation 45 degree away from the side of the lesion and lateral flexion of 30 degree down towards the floor. A hockey-stick incision is made in the

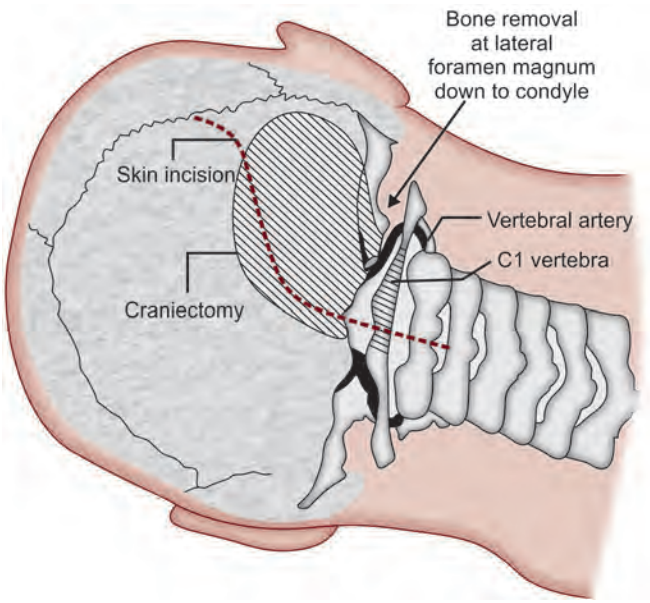

Fig. 6: Diagrammatic representation of skin incision and extent of craniectomy in Heros far lateral approach. [Courtesy: Heros RC. J Neurosurg. 1986;64(4):559-61)]

beginning of cervical midline over the C5 spinous process. It extends cephalad to the inion, courses laterally along the superior nuchal line to the mastoid bone, and finishes inferiorly at the mastoid tip. Bony removal consists of three parts: a C1 laminotomy, a lateral occipital craniotomy and a partial condylectomy. The posterior arch of C1 is also removed. Exposure is made superiorly till the transverse sinus, laterally till the sigmoid sinus, medially till the midline and inferiorly right up to the level of the jugular foramen. The dura is opened. After the arachnoid of the cisterna magna is widely opened and CSF drained, the cerebellum is retracted superomedially. The vertebral artery is identified and traced distally in front of the lower cranial nerves. The arachnoid is further cut widely from the brain, nerves and blood vessels.

ALTERNATIVE SURGICAL STRATEGIES

- Parent artery occlusion/proximal ligation/Hunterian ligation[49]—The principle of this technique introduced by John Hunter about 200 years ago for giant aneurysms is to remove the forceful flow of blood through the artery to the aneurysm and to depend upon collateral circulation to nourish the part deprived of direct blood flow. Proximal ligation is technically easy to perform; reduces the pressure in the aneurysm and subsequently the incidence of rupture and encourages thrombus formation. However, unpredictable haemodynamic complications ranging from ischaemia to thrombus formation and later, migration from the stump can occur.
- Wrapping[49]—Muscle and various substances, such as methyl methacrylate, silicone, polyvinyl and temporalis fascia, are used to wrap the aneurysms. The purpose of wrapping is to induce fibrosis in the wall of the aneurysm, thereby, decreasing the risk of rupture and rebleeding. However, the mass effect of the aneurysm is not removed by wrapping. The aneurysm can continue to grow and erode even the coating of methacrylate and rupture.
- Trapping[49]—Trapping the aneurysm involves isolating the aneurysm from the circulation. Trapping of distal aneurysms is certainly possible, e.g. distal PICA aneurysms. Proximal trapping of PICA aneurysms may be possible, but should be followed by some form of revascularisation if the vessel must be trapped proximal to the choroidal point.
- Revascularisation—If sufficient collateral flow is present, one can go for parent artery ligation. However, if revascularisation is needed, aneurysm excision with primary reanastomosis of the artery may be possible.[34] Alternatively, bypass from the extracranial circulation (superficial temporal artery or occipital artery) to the posterior circulation (SCA or PICA), or an interposition radial artery or saphenous vein bypass from the external carotid artery (ECA) to SCA or PCA, may be useful.[26,35,41,46]
- Cardiac bypass with hypothermic circulatory arrest[27]—Hypothermic circulatory arrest is a useful technique for giant and complex posterior circulation aneurysms that cannot be treated by conventional surgical and endovascular approaches. With 24 degree celsius core cooling, the brain will be protected for 1 hour of complete circulatory arrest. Draining the cerebral circulation allows the aneurysm to collapse and permits the surgeon to dissect the perforators and branches away from it. However, it is associated with significant morbidity and mortality rates related to systemic heparinisation, cardiopulmonary bypass, cardiac arrest and prolonged ischaemia. Hence, it should be used with extreme caution.

ENDOVASCULAR MANAGEMENT

The advent of endovascular techniques, particularly detachable coil embolisation of aneurysms, has added a new treatment strategy in the management of intracranial aneurysms.

Indications of endovascular treatment include aneurysms in surgically difficult locations;—basilar bifurcation, lower basilar trunk and VBJ; previous unsuccessful neurosurgical exploration and patients in whom the surgical risk is unacceptably high, or in a medically unstable patient.

ENDOVASCULAR OBLITERATION

- *Intravascular obliteration of the aneurysm along with parent artery/flow modification—*

A. Detachable balloons:
   - Silicone balloons filled with iso-osmolar contrast medium (Iohexol) or solidification agent like HEMA (Hydroxymethyl methacrylate).
   - Latex balloons filled with iohexol or silicone.

B. Flow modification techniques:
   - Extracranial-intracranial bypass excluding the aneurysm.
   - Parent artery obliteration proximal to the aneurysm with good collateral flow.

Complications of balloon embolisation include intraprocedural aneurysm rupture,[18] incomplete occlusion of sac, distal propulsion of balloon and migration of thrombus from the neck of the aneurysm.

- *Intraluminal obliteration of the aneurysm—detachable coils—*
  A. Free pushable coils (Cook).
  B. MDC—Mechanically Detachable Coils (Balt, France).
  C. IDC—Interlocking Detachable Coils (Japan).
  D. GDC—Guglielmi Electrically Detachable Coils (USA).

The most successful of all these and the one currently used by the majority of interventional neuroradiologists is the Guglielmi Detachable Coils (GDC), introduced by Guglielmi et al.[15]

The GDC coil is 0.01 inch in diameter and contains three parts, the proximal part (175 cm) is made of stainless steel wire, then the intermediate portion (3 cm in length) is made up of very soft stainless steel coil and the distal component varies from 4–40 cm in length and is made up of platinum with helical memory. Platinum is not affected by electrolysis and is radio-opaque, biocompatible and thrombogenic. When the coil is in place, electrothrombosis is generated by applying low voltage (0.5–2 millivolts) positive direct current to the proximal end of the stainless steel guide wire using battery operated current generation. The negatively charged blood particles are attracted and thus electrothrombosis is caused. By the time the thrombosis occurs, the current also dissolves the uninsulated stainless steel coil closest to the platinum coil by electrolysis. This detaches the coil from the main catheter. The number of coils required depends upon the size of the aneurysm. Coils probably provide immediate protection against re-haemorrhage by reducing blood flow within the aneurysm sac, buffering arterial pulsations within the fundus and sealing the weak portion of the wall. Eventually, organised thrombus forms within the aneurysm and the aneurysm is excluded from the parent vessel by the formation of an endothelialised layer of connective tissue that covers the neck's ostium.

Factors that limit successful endovascular aneurysm occlusion include dome-to-neck ratio less than 2, neck width greater than 4 mm, inadequate endovascular access, unstable intraluminal thrombus and if any arterial branch is incorporated in the neck.

Those aneurysms with a dome-to-neck ratio that did not favour endovascular therapy can be made more suitable for the procedure with the use of a stent.

Stents can also be used to cover the orifice of the aneurysm and to serve as a buttress to keep coils within the aneurysms from herniating into the lumen of the parent artery.[40] (Figs 7A to D and 8) Complications of coiling of aneurysms include aneurysm perforation, parent artery narrowing, parent artery occlusion, embolisation, coil migration and post-embolisation aneurysmal haemorrhage.

Although endovascular therapy is an effective modality of treatment in the short term, there are very few studies regarding its long-term effectiveness. The main challenge with endovascular treatment continues to be unacceptable rates of recurrence and the associated risks. Pandey et al.[37] in one of the largest series regarding endovascular management of posterior circulation aneurysms, have reported a 24.5% incidence of clinically significant recurrence at 3 years follow-up. Further areas of research in this regard include development of new

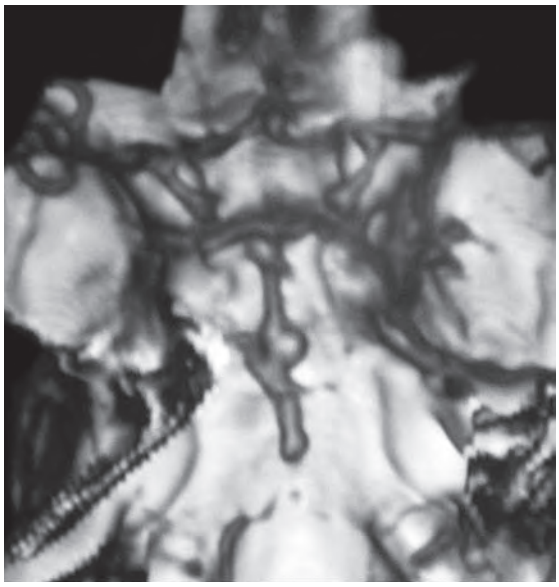

Fig. 7A: CT angiography with three-dimensional reconstruction showing mid-basilar artery aneurysm

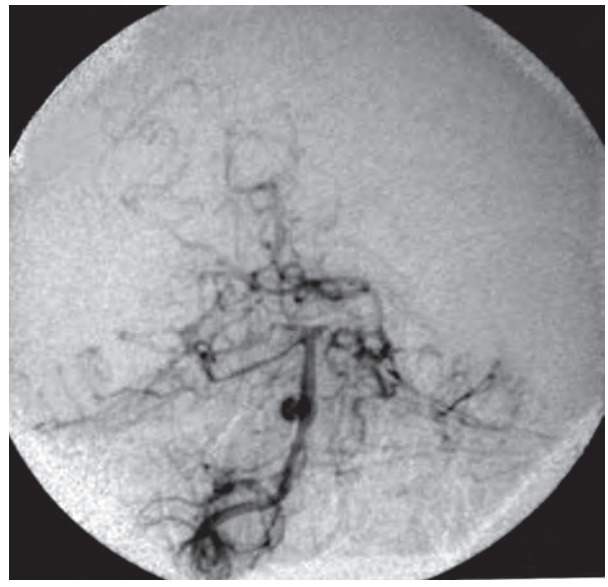

Fig. 7B: IADSA of the same patient showing mid-basilar artery aneurysm

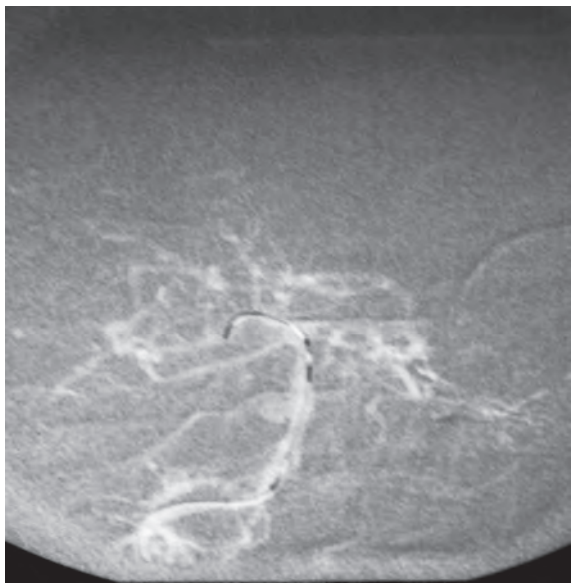

Fig. 7C: IADSA showing roadmap for stent-assisted coiling of mid-basilar artery aneurysm

Fig. 8: CT head with sagittal three-dimensional reconstruction showing stent in basilar artery (stent-assisted coiling of mid-basilar artery aneurysm)

bioactive coil technology towards the goal of permanent occlusion of the aneurysm and the elimination of recurrences and all associated risks.

Multi-modality strategies, such as a surgical bypass with subsequent endovascular occlusion of the aneurysm, can also be designed for optimal management of posterior circulation aneurysms. A poor grade patient can be treated by partially coiling the aneurysm, obliterating its dome to protect against re-haemorrhage and leaving the neck for definitive clipping later. Alternatively, broad-necked aneurysms[4] that cannot be clipped completely might be clipped partially to create a narrower neck that would be more amenable to coiling. Although endovascular technology is promising, the management of patients with posterior circulation aneurysms can be improved by strategies that combine surgical and endovascular techniques.[5]

MANAGEMENT OF GIANT POSTERIOR CIRCULATION ANEURYSMS (FIGS 9A TO C AND 10A TO C)

A giant aneurysm is defined as one larger than 2.5 cm in diameter. Treatment of giant aneurysms has traditionally been associated with the higher morbidity and mortality than smaller lesions. Giant aneurysms represent around 5–8% of all intracranial aneurysms. Fifteen percent of these giant lesions occur at the top of the basilar artery, and approximately 5% arise from the vertebral artery.

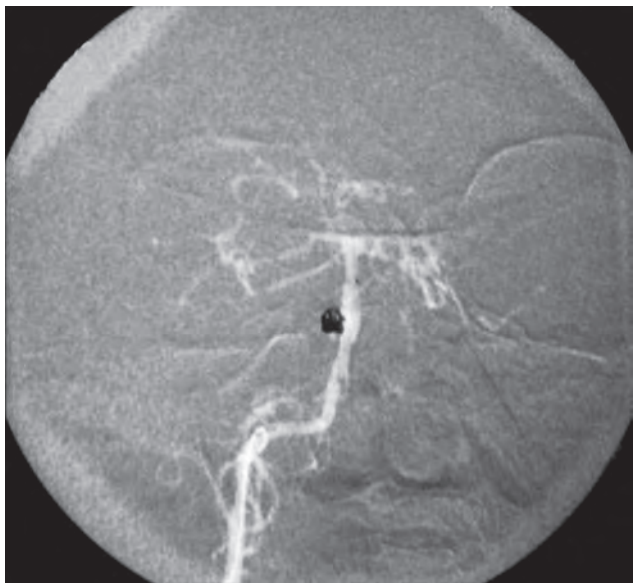

Fig. 7D: IADSA showing stent in basilar artery with well-coiled mid-basilar artery aneurysm

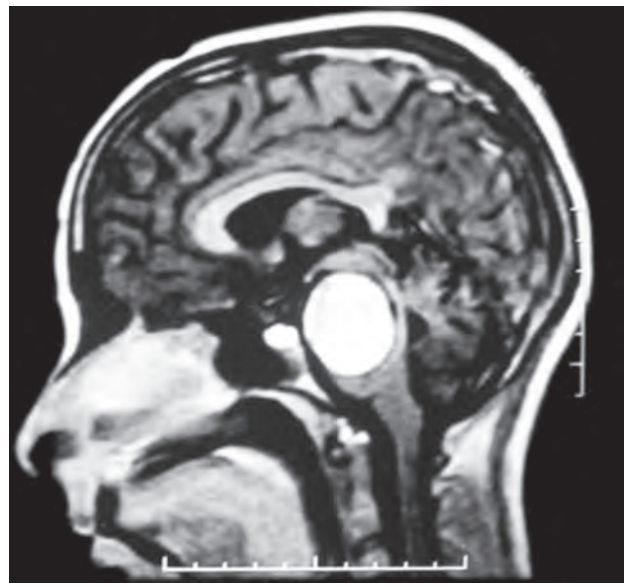

Fig. 9A: Contrast enhanced MRI of brain showing giant distal basilar artery aneurysm

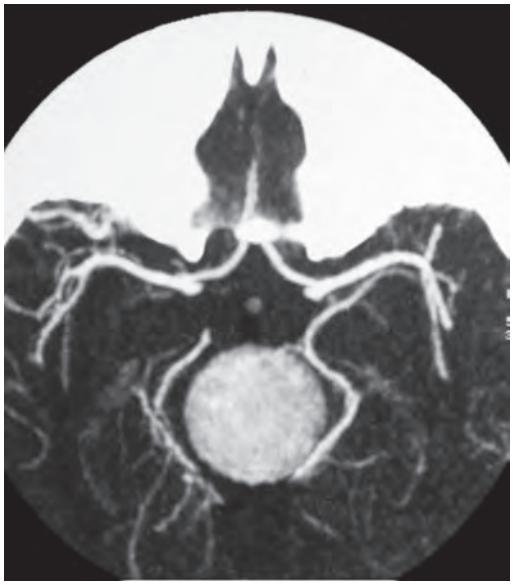

Fig. 9B: CT angiography of the same patient showing giant distal basilar artery aneurysm

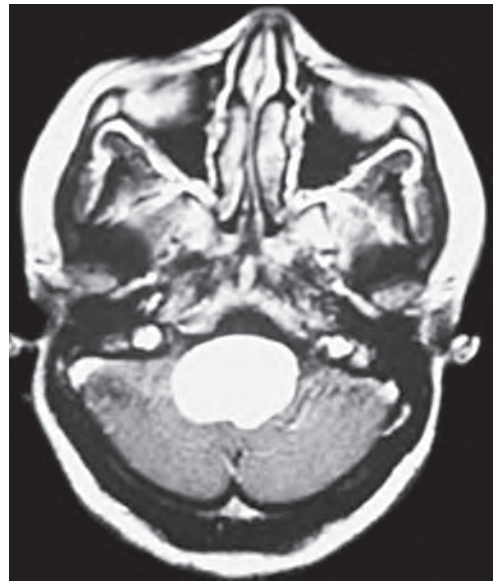

Fig. 10A: Contrast enhanced MRI of brain showing giant right vertebral artery aneurysm

Several different strategies are currently available to manage giant posterior circulation aneurysms. This stems from the fact that no single technique is absolutely effective in dealing with all giant aneurysms. Current treatment options for these lesions include direct surgical techniques, endovascular techniques and combined approaches. Regarding surgery, the aneurysm can be attacked directly with clipping and resection of the mass lesion, or aneurysmorrhaphy with vessel wall reconstruction. Indirect surgical techniques include proximal occlusion and trapping of the aneurysm using clips and ligatures above and below the lesion, parent vessel occlusion or an extracranial to intracranial bypass procedure. Endovascular management includes occlusion of giant posterior circulation aneurysm using GDC coils.

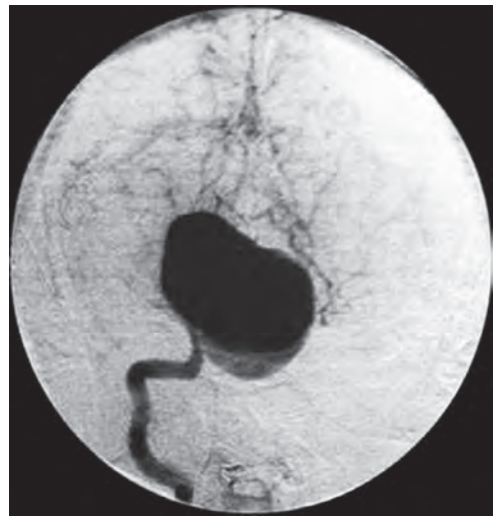

Fig. 10B: IADSA of the same patient showing giant right vertebral artery aneurysm

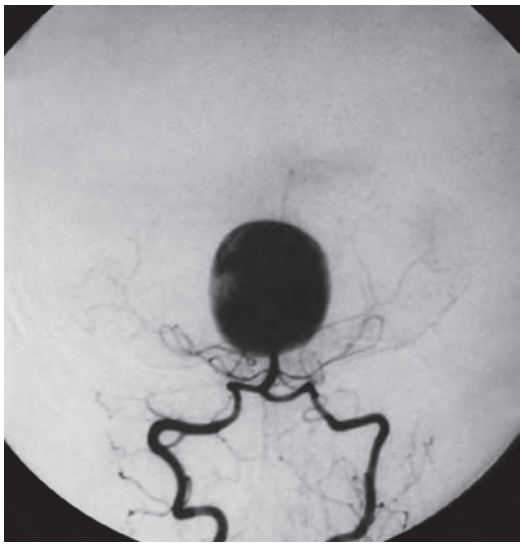

Fig. 9C: IADSA of the same patient showing giant distal basilar artery aneurysm

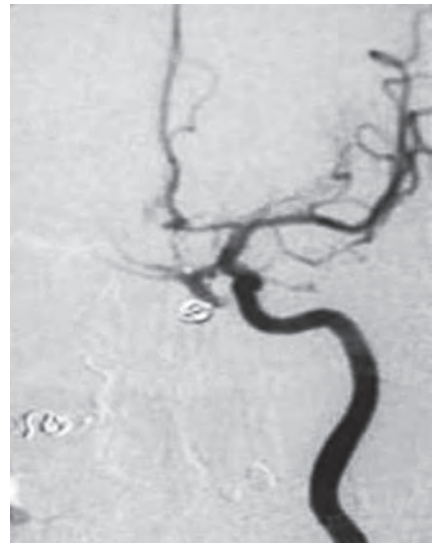

Fig. 10C: Check IADSA of the same patient showing well-coiled right vertebral artery

Other treatment options for giant posterior circulation aneurysms include combined techniques. In this approach, a surgical procedure, such as an intracranial to extracranial bypass, can be performed prior to endovascular occlusion of the parent vessel. Alternatively, bypass techniques can be combined with endovascular trapping of certain giant aneurysms or intra-aneurysmal endovascular techniques.

CONCLUSION

Posterior circulation aneurysms, due to their rarity, deep location, intimacy with cranial nerves and small vascular perforators, can be among the most difficult cerebrovascular anomalies to treat. The advent of endovascular treatment in the management of posterior circulation aneurysms has added another treatment option, which has immense potential. The challenge for vascular neurosurgeons is to embrace and integrate endovascular techniques into the management of posterior circulation aneurysms while still maintaining technical proficiency in all skull base approaches.

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85 Giant Aneurysms

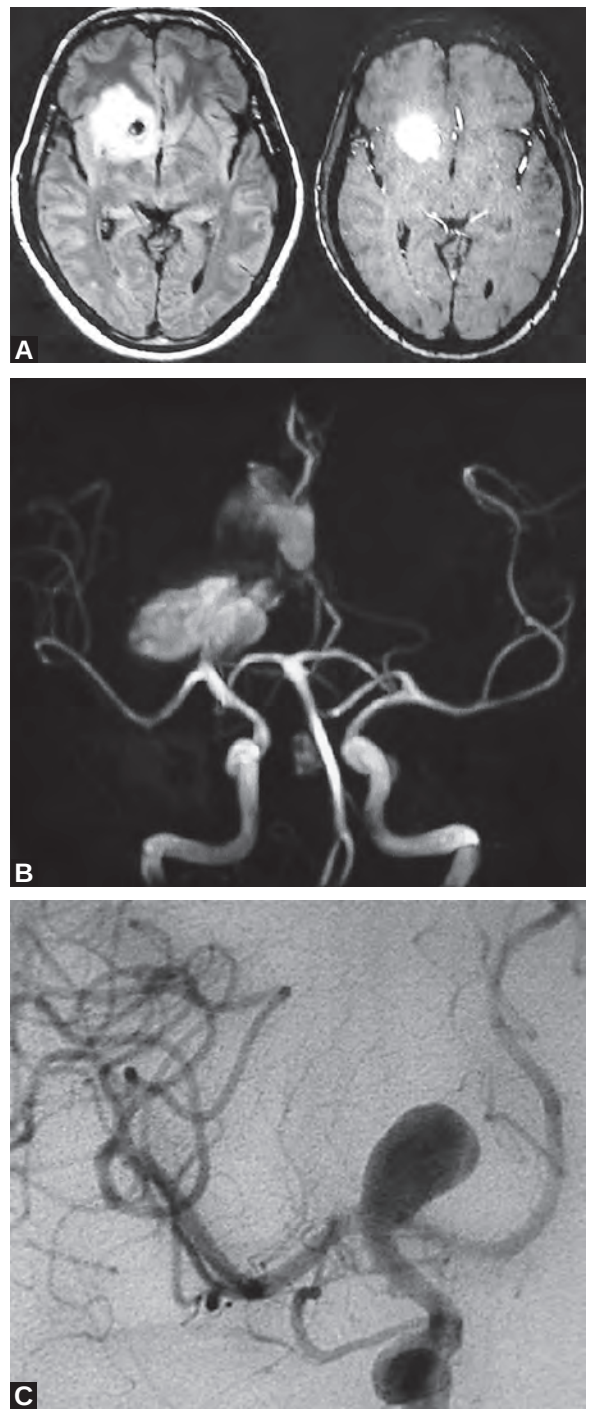
Sanjay Behari, Rabi Narayan Sahu, Rupant K Das, Vijendra Kumar Jain

INTRODUCTION

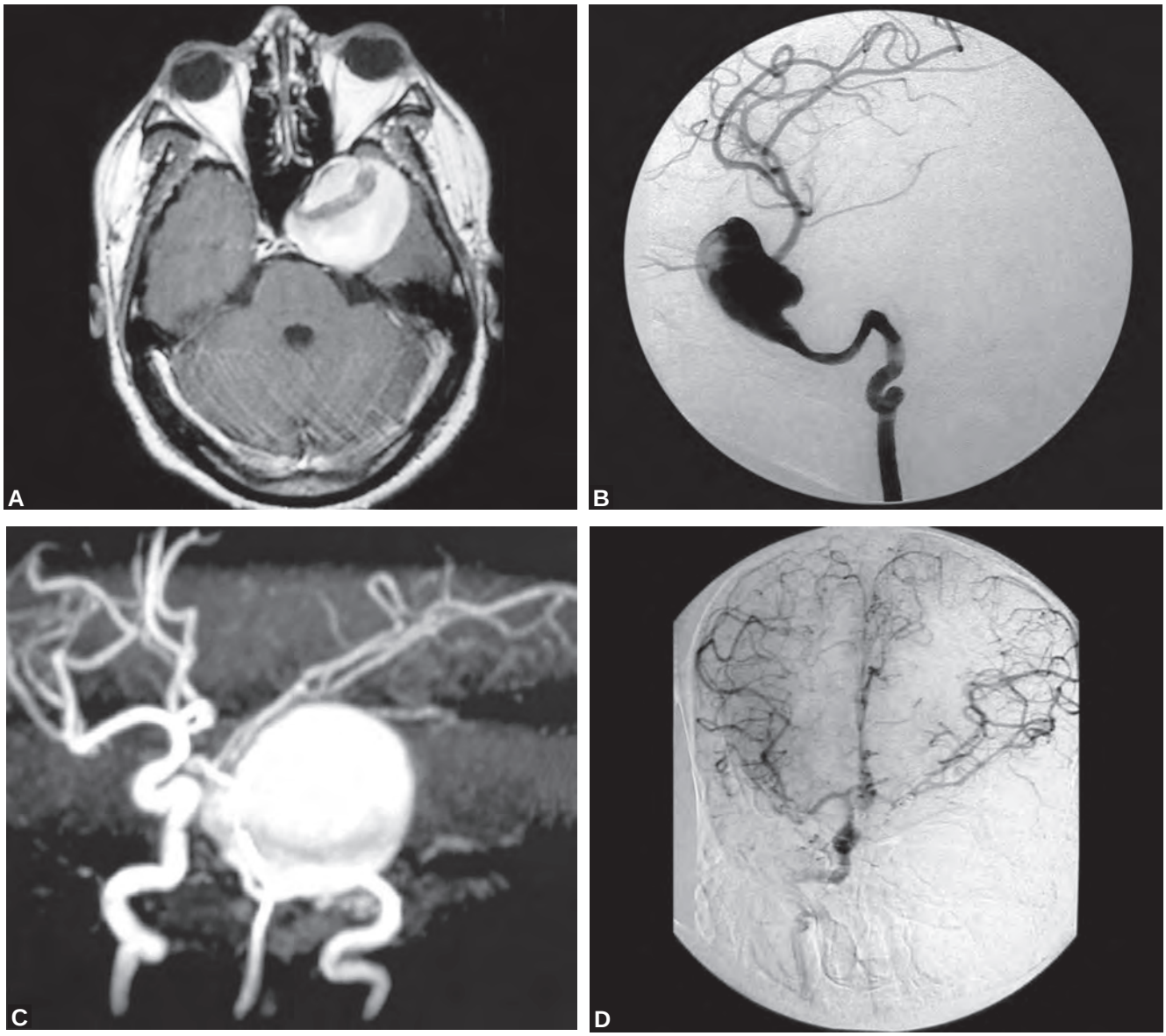
Giant aneurysms are aneurysms that are 2.5 cm or larger in size. They represent approximately 5% of all intracranial aneurysms. They most often present either in the 6th decade (in approximately 35% patients, i.e. one decade later than the smaller aneurysms) or in the paediatric age group (5–10%). Approximately 60% of giant aneurysms are seen in the anterior circulation, especially on the internal carotid artery.[18] Giant posterior circulation aneurysms comprise 1–2% of aneurysms seen in clinical practice and are often associated with much poorer outcomes than anterior circulation aneurysms.[18] In the anterior circulation, the frequently encountered giant intracranial aneurysms include intracavernous and petrous carotid aneurysms, ophthalmic segment aneurysms, posterior communicating artery aneurysms, carotid bifurcation aneurysms, anterior communicating artery aneurysms and middle cerebral artery aneurysms.[10,11,15,16,18] Giant posterior circulation aneurysms have a predilection for the basilar bifurcation, the vertebral artery at the origin of the anterior and the posterior inferior cerebellar arteries and the vertebrobasilar junction.[14,17] With growth, these aneurysms may incorporate the origin of major arterial branches as well as vital perforators. In 1875, Hutchinson performed the first proximal ligation for a middle fossa giant intracranial aneurysm.[18] Direct surgical treatment with a good outcome in nearly 80% patients and especially the need for proximal vessel ligation when direct clipping was impossible, was advocated in two classical series by Drake in 1979[7] and Sundt et al. in 1991.[16]

PATHOLOGY

Giant aneurysms may be saccular (Figs 1 to 5) or fusiform (Figs 6 and 7). Saccular aneurysms may arise from gradual expansion of berry aneurysms. Their fundus and neck grow both by growth of their wall as well as its thinning and distension. Due to the large volume within the aneurysm and resultant flow stasis, intra-aneurysmal thrombosis and distal embolisation are frequent. The turbulence of blood leading to endothelial damage within the aneurysm may also lead to thromboembolic phenomena. A thrombosed giant aneurysm may still bleed due to its thin walls. Fusiform aneurysms result from weak vessel walls or from arterial dissections (Fig. 7).



Figs 1A to C: (A) Axial MR image. (B) MR angiography. (C) Internal carotid artery DSA showing a giant middle cerebral artery aneurysm



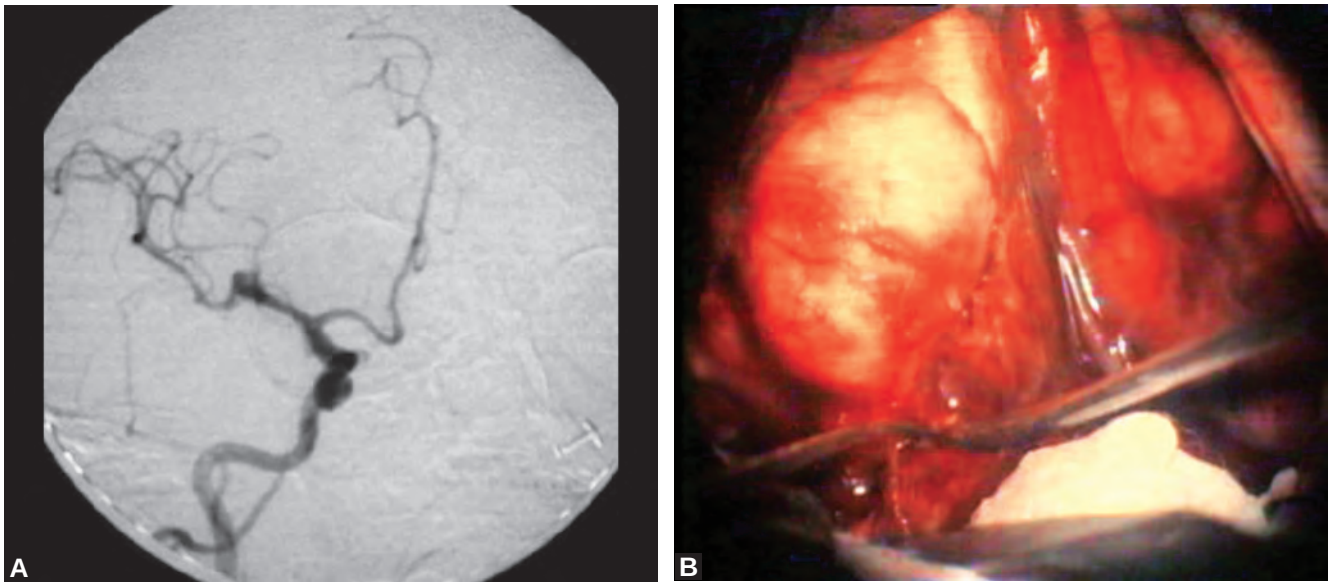
Figs 2A to D: (A) Contrast enhanced MR image. (B) Lateral view of internal carotid DSA. (C) AP MR angiogram showing a giant transitional cavernous and paraclinoid internal carotid artery aneurysm. (D) Post-operative AP internal carotid artery DSA image following trapping of the aneurysm showing a good cross flow across the anterior communicating artery

Atherosclerosis and collagen vascular disease may be the predisposing causes. The atherosclerotic plaque extending from the parent vessel to the fundus of the aneurysm may compromise the ostia of perforating vessels resulting in ischaemia of the surrounding brain.[6,18]

CLINICAL PRESENTATION

Fifty to sixty percent of giant intracranial aneurysms are either found incidentally or produce mass effect. The commonly found aneurysms produce symptoms depending upon their regional anatomy.[18] Cavernous internal carotid artery aneurysms present with retro-orbital pain, diplopia, facial hypoaesthesia, ocular nerves palsies, hypopituitarism or epistaxis.[11] Ophthalmic segment aneurysms present with retro-orbital or frontal headache, decreased visual acuity or field defects. Carotid bifurcation aneurysms present with homonymous hemianopia and other visual field defects, seizures and hemiparesis. Middle cerebral artery aneurysms may also present with hemiparesis, speech disturbances, hemianopia and seizures. Anterior communicating artery aneurysms may obstruct the foramen of Monro and cause hydrocephalus, cognitive disturbances due to bifrontal mass effect, decreased visual acuity or field defects such as bitemporal hemianopia. Posterior communicating artery aneurysms may cause IIIrd nerve palsy and trigeminal neuralgia.

Thirty to forty percent of giant aneurysms present with subarachnoid haemorrhage; 3–5% present with cerebral ischaemia due to thromboembolic phenomena, especially those in the middle cerebral artery and the internal carotid artery. Occlusion of the ostia of perforating vessels by thrombus or an atherosclerotic plaque may contribute to ischaemia. Parent vessel occlusion may also cause infarction.



Figs 3A and B: (A) Internal carotid artery DSA showing the patent part of a partially thrombosed giant aneurysm. (B) Intra-operative photograph showing the partially thrombosed giant internal carotid artery aneurysm

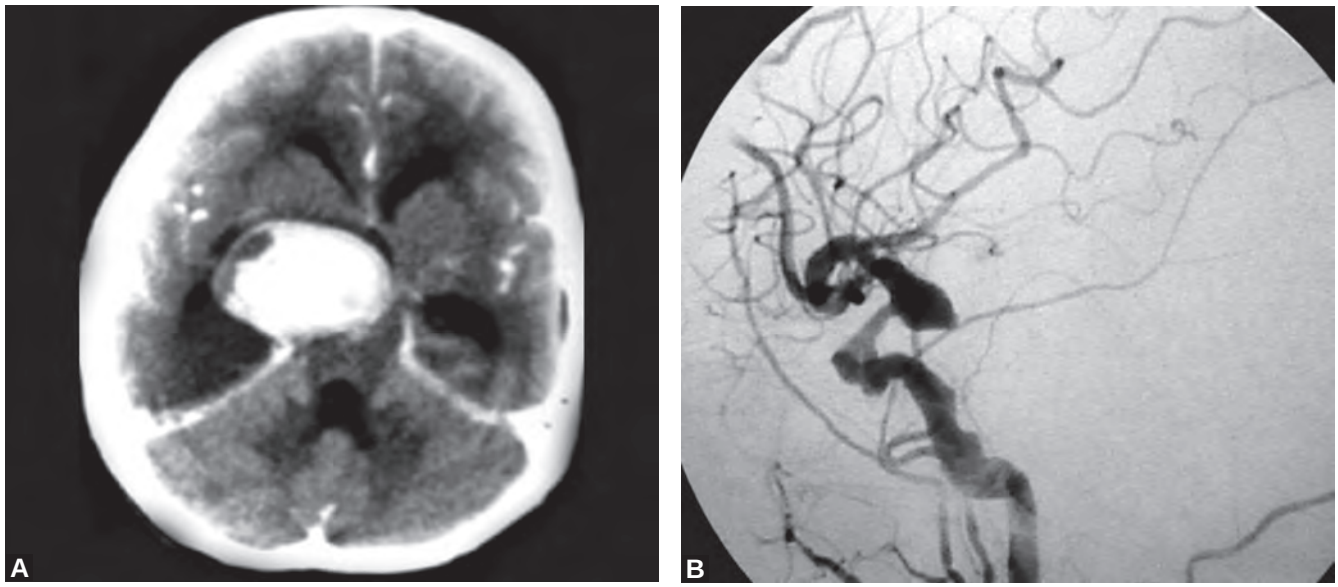
Nearly 80% of patients with giant aneurysms presenting with subarachnoid haemorrhage or mass effect die or develop severe morbidity within 5 years if the aneurysm is left untreated.[18] Ophthalmoplegia or visual deficits may lead to visual impairment in the involved eye.

Thirty to forty percent of posterior fossa aneurysms present with subarachnoid haemorrhage. The most common presentation of these lesions is mass effect compressing the mesencephalon and diencephalon. Basilar apex aneurysms may compromise the IIIrd and VIth cranial nerves; midbasilar aneurysms may compromise Vth, VIth, VIIth and VIIIth cranial nerves and vertebral aneurysms may compromise the lower cranial nerves. Territory infarction and brainstem syndromes may occur if the perforators get stretched and thrombosed by the pressure of giant aneurysms. Besides subarachnoid haemorrhage, severe headache may also be due to intra-luminal thrombosis or dissection within the walls of the aneurysm.[6,7,14,17]

RADIOLOGICAL EVALUATION

Skull Radiographs and Bone Windows of Computed Tomographic (CT) Scans

A ring calcification, bony erosion of sella or skull base (Fig. 5), erosion of anterior or posterior clinoid process or sellar enlargement may be found, but these are not



Figs 4A and B: (A) A contrast enhanced axial CT scan showing a giant intracranial aneurysm. (B) Lateral internal carotid angiogram showing that the aneurysm is completely thrombosed and, therefore, not visualised. The ICA is stretched in the region. [Reprinted from the article: Wani AA, Behari S, Sahu RN, Jain VK. Pediatric aneurysms: A review. Journal of Pediatric Neurosciences. 2006;1(Suppl 2):11-5, with permission]

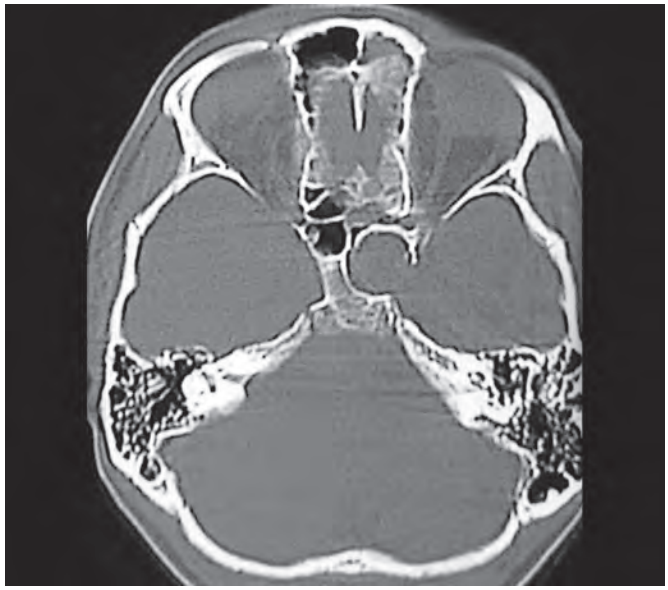


Fig. 5: Bone windows of axial CT scan showing the bony changes due to a giant cavernous sinus aneurysm

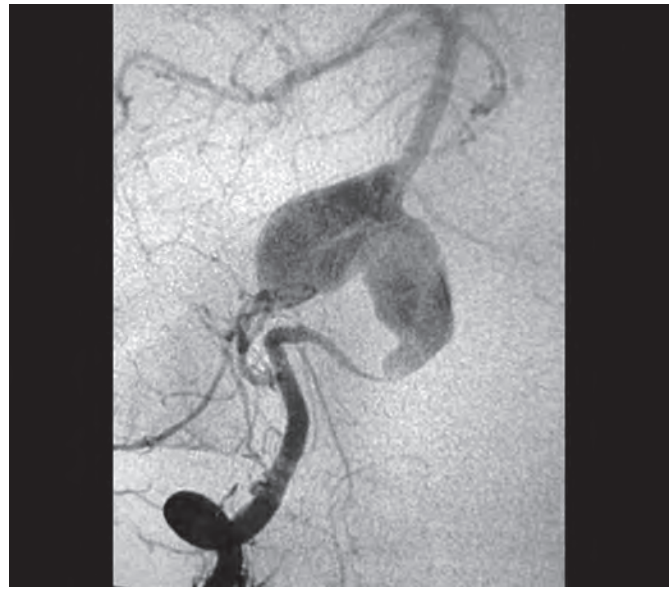
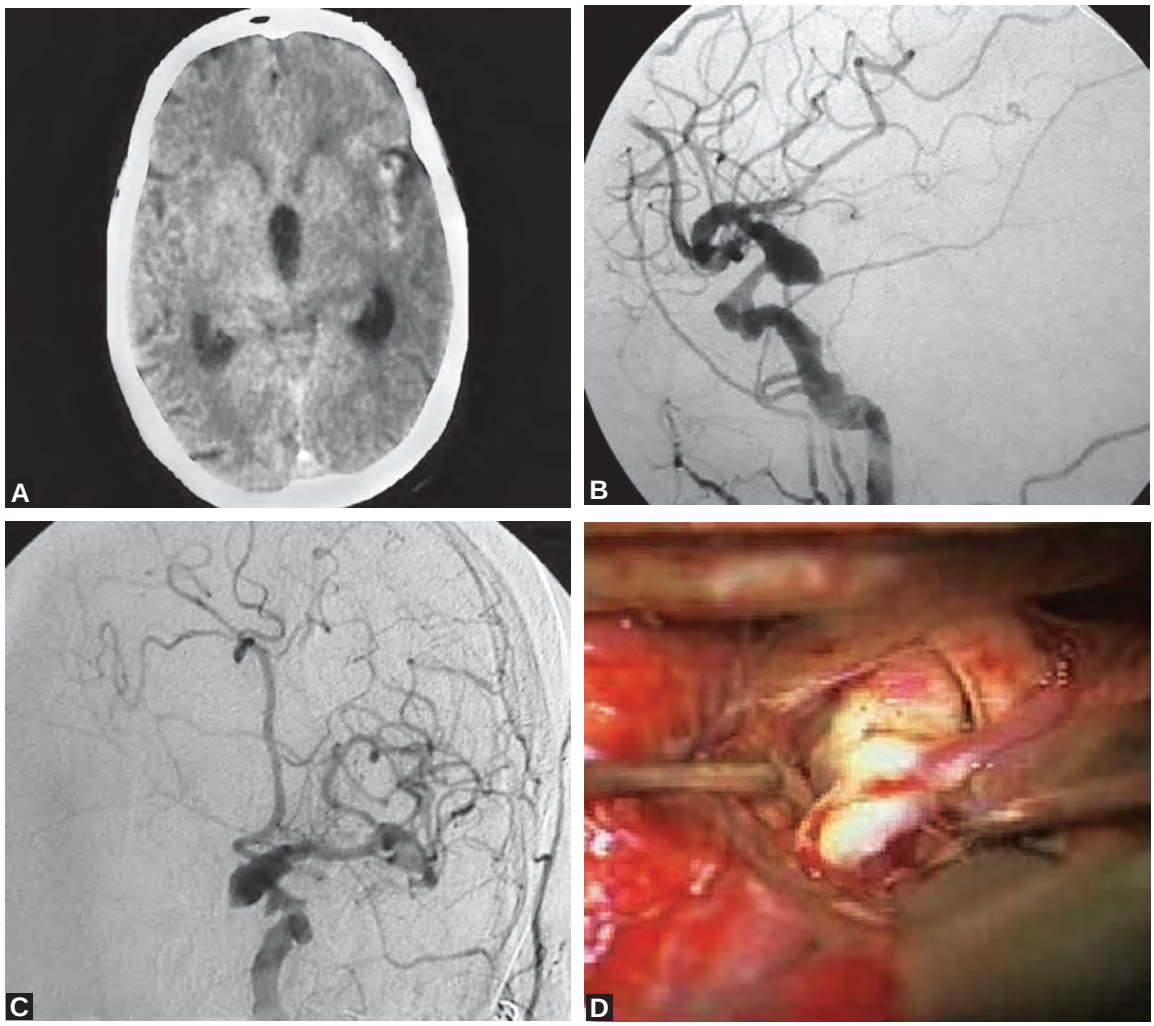


Fig. 6: A vertebral angiogram AP view showing fusiform giant aneurysms on both vertebral arteries [Reprinted from the article: Wani AA, Behari S, Sahu RN, Jain VK. Pediatric aneurysms: A review. Journal of Pediatric Neurosciences. 2006;1(Suppl 2):11-5, with permission]



Figs 7A to D: (A) Axial CT scan showing subarachnoid haemorrhage in the Sylvian fissure. (B) Lateral angiogram. (C) AP angiogram. (D) Operative view showing a fusiform aneurysm of the internal carotid artery. The subarachnoid haemorrhage was due to bleeding from a thin walled bleb from the atherosclerotic segment. The entire segment was wrapped during surgery

characteristic of giant aneurysms and are more commonly seen in other lesions.

Computed Tomography

Non-thrombosed aneurysms are hyperdense and enhance uniformly after contrast injection. They are often round in configuration and are in close proximity to the parent vessel. Perianeurysmal oedema is rare. In partially thrombosed aneurysms, a "target" sign may be seen. This may present as a central or eccentric densely enhancing area representing the flowing blood. The peripheral thrombus may show a halo and heterogeneous or no enhancement due to the presence of various stages of blood products. The outermost rim of enhancement may be due to the vascularity of the vasa vasorum. A completely thrombosed aneurysm may be hypodense to hyperdense depending upon the age of the clot. There may be ring or intra-aneurysmal calcification. Three dimensional CT angiogram helps in defining the neck, perforators and anatomy of the skull base and may be helpful in planning clipping techniques.[18]

Magnetic Resonance Imaging (MRI)

MRI may show a thrombosed giant aneurysm where only a small part of the lumen was being filled up on angiography. The laminated thrombus may give a heterogeneous intensity on T1- and T2-weighted images. The sagittal, coronal, axial and MR angiographic images help in completely defining the aneurysm. Gradient echo flow imaging may differentiate flow voids from bony structures, calcification from thrombus and CSF pulsation induced artefacts from pulsating vessels from actual aneurysms. Thromboembolism may also be picked up on various MR sequences.[6,9,18]

Digital Subtraction Angiography (DSA)

DSA is essential to visualise the shape and size of the giant aneurysm, define the neck-fundus ratio and identify the taking up of the parent vessel by the aneurysm. Cross compression studies involve compression of the proximal portion of the internal carotid artery harbouring the aneurysm while the opposite carotid artery or the vertebral artery is injected with dye to assess the collateral circulation to the brain on the side ipsilateral to the aneurysm. The balloon test occlusion (BTO) helps in defining whether the patient will tolerate proximal vessel control or ligation during aneurysm surgery. The external carotid angiogram evaluates the status of the external carotid system for a possible superficial temporal-middle cerebral artery or an occipital artery-posterior inferior cerebellar artery bypass, if needed. Superselective angiography helps in defining the neck of the aneurysm by guiding the microcatheters to the aneurysm. With a partially thrombosed giant aneurysm, the angiographic filling of the lumen may not be a true estimate of the aneurysm size and may require CT or MR reconstructed images to precisely define the size of the aneurysm.[9,10]

Intra-operative angiography permits assessment of completeness of aneurysm occlusion and patency of parent vessel during surgery. It also serves as an adjunct to the surgical procedure since suction decompression of the aneurysm or proximal control of the parent vessel may be secured through the endovascular route; any residual neck of the aneurysm may also be coiled under the same anaesthesia and permanent proximal vessel coiling may be done after patency in the bypass graft has been ensured. To perform intra-operative angiography, the femoral sheaths are placed pre-operatively and a radiolucent operating table and head frame are used.[3,6,19,20]

AIM OF SURGICAL TREATMENT[18]

- To exclude the giant aneurysm from the circulation to prevent its rupture, while maintaining the patency of the parent vessel.
- To alleviate the mass effect caused by the aneurysm.
- To prevent thromboembolic events.

SURGICAL TREATMENT

Special Considerations for Giant Aneurysms

- *Assessment of cross flow*: In large or giant aneurysms, the suitability of a permanent ICA occlusion is determined by the BTO accompanied by a clinical examination that does not suggest any asymmetry of clinical signs; angiographic criterion, in which symmetry of flow in both hemispheres or in the anterior and the posterior circulation throughout all phases of flow, as well as a good angiographic cross flow through the anterior communicating artery (from the contralateral anterior circulation) and through the posterior communicating artery (from the posterior circulation) is maintained; a single photon emission computed tomography (SPECT) study, in which a decrease in perfusion during a hypotensive challenge with a mean blood pressure 20% below the baseline is determined and xenon computed tomography, in which the symmetry of perfusion is determined. In case the BTO with SPECT is well tolerated, the internal carotid artery may be trapped, if required. In case the BTO is not tolerated and perfusion defects are seen on SPECT, a vascular bypass using the superficial temporal to middle cerebral artery anastomosis may be required.
- *Reduction of mass effect*: Corticosteroids and various dehydrants, such as furosemide and mannitol, may be administered to alleviate the mass effect. A ventricular drain or lumbar drain may decrease the brain swelling and facilitate lobar retraction.
- *Neuro-protection during temporary clipping*: Barbiturate neuro-protection during temporary vessel occlusion involves using thiopental sodium in a dose titrated to maintain burst suppression on EEG. good hydration, oxygenation, mild hypertension, hypothermia (33–35

degrees), mannitol supplementation and calcium channel blockers have all been used as neuroprotective agents during temporary clipping. Following clipping, in cases of subarachnoid haemorrhage, hypervolaemic, hypertensive, haemodilutional therapy may be used.[3,8]

- *Proximal control*: For proximal control of the internal carotid artery, there are several strategies: (a) The common and internal carotid arteries may be exposed in the neck. (b) The portion of the ICA between the proximal and distal dural rings may be exposed by dividing the distal dural ring circumferentially around the ICA after the ophthalmic artery has been dissected free. (c) The petrous carotid artery may also be used for proximal control. This is located extradurally deep to Glasscock's triangle in the middle cranial fossa. The boundaries of this triangle are the groove of the greater superficial petrosal nerve coursing in an anteromedial direction in the floor of the middle cranial fossa; the mandibular nerve exiting through the foramen ovale and the line joining the foramen spinosum to the arcuate eminence.
- *Intra-operative assessment of patency of parent vessel and completeness of aneurysm clipping*: Intra-operative angiography and Doppler studies give information regarding patency of the parent vessel after successful clipping of the aneurysm. In case intra-operative trapping of the main artery is possible, the Doppler helps in localising the superficial temporal artery for a possible superficial-middle cerebral artery bypass.[3,5,6]

Surgical Technique

- *Exposure*: A giant aneurysm requires wide exposure often requiring skull base approaches. Wide Sylvian fissure dissection, opening of the basal cisterns to release the cerebrospinal fluid and relax the brain, use of diuretics and ventricular catheters all help in gaining a wide exposure.
- *Considerations during clipping*: In clipping of a giant aneurysm, occasionally, the neck may be very wide and not completely visualised. With the help of dissectors, it must be made sure that the clip blades are free from any perforators and arachnoidal bands. Atherosclerosis may make the aneurysm wall extremely thin and prone to rupture. An aneurysm harbouring a thrombus at the neck may be difficult to occlude unless proximal vessel temporary occlusion and opening of the aneurysm to strip the thrombus from the aneurysm wall is resorted to. A number of different clip sizes and shapes may be required for adequate clip placement. The clip may slide down and cause parent vessel occlusion unless a series of stacked clips are used for full deflation of the aneurysm prior to clip placement. Angled fenestrated clips with loops that go around the vessel wall and right angled blades that clip the neck of the aneurysm and reconstruct the vessel wall are often very useful. Booster clips and extra long clips may also be required. After clip placement, the aneurysm has to be observed for sometime to ensure that the vessel has not twisted around occluding its lumen, the aneurysm is not filling due to inadequate closing force of the clips and the clip is not sliding towards the parent vessel.[7,11,15,18]

Adjuvant Techniques

- *Temporary clipping*: Proximal and distal clipping is useful during aneurysm dissection, in case of aneurysm rupture during dissection, to deflate the fundus of the giant aneurysm prior to clipping or arterial wall reconstruction and to remove the thrombus from its neck to facilitate permanent clipping. Neuroprotective agents, induced hypertension, mild hypothermia and bypass grafts may help in increasing the ischaemia time. Distal occlusion also decreases the risk of embolisation of the thrombus.[8,18]
- *Wrapping*: This technique may be used for fusiform, thin walled aneurysms or when a perforating vessel is originating from a part of the fundus of the aneurysm that cannot be included in the clip. This, however, is ineffective unless the entire aneurysm can be exposed.
- *Suction aspiration*: After temporary clipping, the dome of the fundus may be aspirated to shrink it prior to clipping of the neck. Endovascular proximal vessel balloon occlusion followed by suction aspiration of the aneurysm also facilitates its clipping.[4,5]
- *Bypass*: The low flow superficial temporal artery-middle cerebral artery bypass or the high flow saphenous vein interposition graft are placed. The bypass may be done from the cervical internal or external carotid artery to the M2 branch of the middle cerebral artery in the anterior circulation and the occipital-PICA anastomosis or superficial temporal-P2/3 bypass in the posterior circulation. These techniques are especially helpful in case aneurysm trapping is being planned or prolonged temporary occlusion of the parent artery is anticipated considering its difficult location or large size.[18]
- *Proximal vessel ligation*: This may be associated with nearly 30–50% incidence of ischaemic complications without bypass. Its effectiveness depends upon the adequacy of the collateral circulation. Intracavernous and petrous internal carotid artery aneurysms have a 90% occlusion rate; paraclinoid segment (with collaterals from ophthalmic artery) have a 75% occlusion rate and supraclinoid aneurysms (with collaterals from anterior and posterior communicating and anterior choroidal artery) have only a 50% occlusion rate.[6,18]
- *Deep hypothermic circulatory arrest*: If the brain is cooled to 18 degrees centigrade even the brainstem can tolerate ischaemia up to one hour. At about 29 degrees centigrade, however, ventricular fibrillations are precipitated necessitating the need to bypass the heart to perfuse the brain and other vital organs while

hypothermia is continuing. Once the body temperature reaches 18 degrees centigrade, the bypass pump may be switched off for about an hour. Using circulatory arrest, the giant aneurysm may be decompressed by draining a part of the blood volume into a storage reservoir to facilitate clipping. The disadvantages of this procedure are: Perforators may look like arachnoidal bands and be inadvertently injured; ruptured perforators may bleed when the pump is restarted; the aneurysm may fill up again due to insufficient strength of the applied clips or heparinisation and platelet depletion by the pump circuit may lead to persistent oozing.[2,3]

- *Skull base approaches*: For adequate exposure, especially in posterior circulation aneurysms, these approaches have been developed.[1,6,7,22] The important ones are as follows: (A) For giant paraclinoid/caroticoophthalmic aneurysms, a frontotemporal craniotomy and orbitozygomatic osteotomy and anterior clinoidectomy provides access to the paraclinoid segment of the internal carotid artery. Removal of the orbital rim also provides access to the anterior cranial fossa base for a subfrontal clipping of giant anterior communicating artery aneurysms. Retraction of the temporal lobe posteriorly and drilling of the posterior clinoid after this approach provides access to a high basilar artery bifurcation.[15,22] (B) The transcavernous approaches are extensions of the trans-Sylvian or subtemporal approaches and provide access to the cavernous sinus, the tentorial edge and the posterior fossa giving a good view of the pons, midbrain, middle fossa and upper clivus. In Dolenc's approach, after a frontotemporal craniotomy and extradural and intradural anterior and posterior clinoidectomy, the cavernous sinus is entered into laterally along the IIIrd nerve. In the extradural temporopolar approach, an extradural resection of the anterior clinoid during a frontotemporal craniotomy and orbitozygomatic osteotomy is performed. With a trans-Sylvian exposure and retraction of the temporal lobe posteriorly, the paraclinoid segment of the carotid artery is mobilised laterally dividing the dural ring. The orbital roof is also drilled exposing the IInd nerve medially. Thus, a wide exposure to the posterior fossa may be gained via a considerably widened carotico-optic space. Access to the posterior fossa may also be gained by working lateral to the IIIrd nerve and mobilising it medially. Kawase's approach involves a subtemporal or frontotemporal craniotomy, anterior petrosectomy from the middle fossa base and opening the tentorium and lateral cavernous sinus wall to gain access to the posterior fossa at the level of the lower midbrain and pons. (C) The transpetrosal or presigmoid approaches involve removal of the petros bone in addition to temporal or retrosigmoid bone removal. This provides access to the mid pons, upper medulla, lower basilar trunk, vertebrobasilar junction and distal vertebral arteries. (D) The far or extreme lateral approaches involve drilling of the posteromedial aspect of the occipital condyle after a standard retromastoid suboccipital craniectomy to change a predominantly posterior approach to the brainstem to a more lateral one. They provide access to the lateral and ventral pons and medulla and 7–12th cranial nerves. They also provide access to the vertebral artery from its intradural entry to the vertebrobasilar junction.[6,14,17,22]
- *Endovascular techniques*: Primary endovascular treatment for giant intracranial aneurysms involves:[19] (A) Stenting of the vessel with sheathed stents to exclude the aneurysms. These ideally should exclude the aneurysm from the circulation while blood flow in the branching and perforating vessels is maintained, and be flexible and self expanding to automatically conform to the vessel lumen. (B) Endosaccular occlusion involves placement of thrombogenic metal wires or coils, such as the Guglielmi detachable coils, to totally occlude the aneurysm.[1] Liquid material, such as N-butyl cyanoacrylate, that becomes solid by precipitation or polymerisation, onyx whose solvent dimethylsufoxide is washed away in blood leaving a precipitate within the aneurysm, or neurocryl have been used.[19] (C) Proximal vessel occlusion using coils, balloons or N-butyl cyanoacrylate for aneurysms proximal to the circle of Willis which decreases the flow within the aneurysm and induces thrombosis. (D) Taking proximal control of the parent vessel intra-operatively during aneurysm clipping, the site of occlusion may be chosen based on the collateral flow distribution; a prior BTO also ensures the patient's ability to undergo proximal vessel occlusion. (E) Intra-operative endovascular suction decompression of the aneurysm to make it smaller and more amenable to surgical clipping. (F) In poor grade patients after subarachnoid haemorrhage, with a broad-based aneurysm in a location that requires a difficult exposure, partial coiling reduces the immediate danger of rebleeding. (G) Flow reversal technique: In giant fusiform aneurysms of the proximal basilar artery, proximal occlusion of both vertebral arteries reverses flow through the basilar artery and decreases the intraluminal pressure within the aneurysm leading to its thrombosis and shrinkage.[5,19,20]

Endovascular embolisation is often not the primary choice of treatment in giant aneurysms. Giant aneurysms usually have a wide neck. Total occlusion requires dense packing of the sac. The wide neck predisposes to coil herniation and compromise of the parent artery. Intrasaccular thrombus increases the risk of recurrence due to migration of coils into the thrombus. The mass effect of the aneurysm is not alleviated and GDC does not protect against thromboembolic events. The coils may rotate, compact or remodel permitting re-entry of blood into the aneurysm.[1,5,19,20]

Long-Term Outcome

The most important risk factors associated with a poor outcome of unruptured aneurysms are giant aneurysms

(>2.5 cm) and location in the posterior circulation. Giant aneurysms rupture in more than 50% of cases and the mortality is greater than 60% within 2 years. The International Study of Unruptured Intracranial Aneurysms Part 2 found that the annual rupture rates for giant aneurysms were 8% in the anterior circulation and 10% in the posterior circulation.[21] A meta-analysis on the clipping of all unruptured aneurysms found an overall mortality and morbidity of 0.8% and 1.9%, respectively; in patients with giant aneurysms of the anterior circulation, however, the mortality and morbidity were 7.4 and 26.9%, respectively; and, of the posterior circulation, the mortality and morbidity rates were 9.6 and 37.9%, respectively.[13] Nakase et al.[12] investigated the long-term outcome of patients with unruptured giant aneurysms and found that surgery significantly reduced the mortality (from 31 to 4%) but increased the morbidity (from 8 to 19%) as compared with conservatively treated patients. Thus, giant intracranial aneurysms have a poor prognosis if left untreated, but the treatment goals are also difficult to achieve with the presently available options.

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86 Incidental Intracranial Aneurysms

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The morbidity and mortality associated with aneurysmal subarachnoid haemorrhage remain distressingly high despite advances in microneurosurgery, interventional radiology, neuroanaesthesia and critical care. Although intracranial aneurysms are common affecting 5% of the population,[59] the incidence of subarachnoid haemorrhage is relatively low (approximately 1 case per 10,000 persons per year),[16] especially in patients with small (<10 mm in diameter) aneurysms, suggesting that most aneurysms do not rupture. A great number of unruptured and often incidental intracranial aneurysms are being diagnosed today because of the increasing age of the population and improvement in imaging techniques. Patients harbouring an unruptured intracranial aneurysm (UIA) are potentially at high-risk of dying from subarachnoid haemorrhage (SAH). Prevention of this rupture with surgical or endovascular treatment is believed to be the most effective strategy to prevent mortality and morbidity. However, all current treatments carry some risks and, therefore, the natural history of UIAs must be considered carefully before formulating treatment recommendations. The decision to treat or not to treat is important because treatment related complications usually occur at or around the time of the procedure. Therefore, the cumulative lifetime risk for rupture of an untreated aneurysm needs to be evaluated to make a judgement of what is best for the patient. Also one should know the factors associated with risk of intracranial aneurysm formation and subarachnoid haemorrhage and identify the subset of people who can be screened for incidental aneurysms. With a thirty-day mortality rate following rupture reaching 50% with nearly half the survivors having irreversible brain damage,[30,65] it is understandable that discovery of UIAs should prompt a decision for expeditious treatment.

There are many growing controversies about incidental aneurysms:

1. Should we screen for incidental intracranial aneurysms in people at risk of harbouring them?
2. When is it appropriate to secure an incidental anenurysm?
3. What are the risks of rupture if the aneurysm is not treated?
4. If treatment is pursued, what treatment modality should be used?

To answer the above questions and to obtain a rationale for management of UIAs, one should have an idea of its formation.

The majority of aneurysms are saccular in shape and result from a combination of factors including degeneration and weakening of the internal elastic lamina and collagen fibres of the arterial wall, as well as the haemodynamic effects of fluid pulsations. Factors associated with the risk of intracranial aneurysm formation and subarachnoid haemorrhage can be classified as modifiable and non-modifiable. The major identified modifiable risk factors include active smoking, hypertension, excessive alcohol consumption and possibly the use of oestrogens.[1,4,6,27,28,41,58] Some case control studies also found increased risk with intake of coffee and use of cocaine.[9] The most important unchangeable risk factors are familial occurrence of SAH and autosomal dominant polycystic kidney disease (ADPKD).[8,46] Aneurysms have also been associated with connective tissue diseases, such as Ehlers-Danlos syndrome type IV, neurofibromatosis and Marfan disease, but these disorders are rare and therefore the number of patients with SAH related to them is small.[53]

POPULATION AT RISK

A family history of subarachnoid haemorrhage is the strongest risk factor and is defined as having at least one first-degree relative (parent, sibling or child) with SAH. However, because such a family history is not common, screening of people who have a family history of SAH will not have a large effect on the incidence of SAH.[47] The chance of having an aneurysm and the lifetime risk of SAH depend on the number of affected first-degree relatives.[8,46] The lifetime risk of SAH in individuals with two or more affected first-degree relatives is unknown, since there are few families with this history and because those that exist tend to seek screening for aneurysms and treatment of those detected. The chance of harbouring an aneurysm depends not only on the number of affected relatives but also on the relationships. If the affected relatives are siblings, the risk of having an aneurysm is higher than if they are parents or children.[8,46] Aneurysms are more commonly large and multiple in familial than in sporadic SAH.[50] However, since only 10% of cases of SAH are associated with a family history,

large and multiple aneurysms are more commonly seen in sporadic than in familial SAH. Patients with familial SAH tend to be younger than sporadic cases and, in families with two generations affected, the age at onset is earlier in the younger than in the older generation.[7,8,55] Risk of intracranial aneurysms and of SAH according to the number of affected first-degree relatives shows that individuals with one affected relative have a 5.5 times greater lifetime risk of SAH than the general population, but the risk of finding an aneurysm with screening in an individual with one affected relative is only 1.7 times higher than in the general population.[8,46] This suggests that familial intracranial aneurysms have a higher risk of rupture and the rate of development of new aneurysms is quicker in relatives with familial occurrence of SAH than in individuals without familial occurrence. People with two or more affected relatives and with a negative magnetic resonance angiography have a 7% risk of developing an aneurysm within 5 years of screening.[64]

Although SAH is common in patients with ADPKD, less than 1% of cases of SAH are attributable to ADPKD because the disease is rare.[14] Intracranial aneurysms are found in about 10% of patients with ADPKD.[46] Apart from a positive family history for SAH, no clinical characteristics have been identified that are associated with increased risk of aneurysm in patients with ADPKD. The position of the mutation in PKD1 is predictive of development of aneurysms, but mutation detection is not yet used in clinical practice. As for people with a positive family history of intracranial aneurysms, people with ADPKD are at risk of developing new aneurysms.

Patients who have been successfully treated for an aneurysm are at risk of developing new aneurysms. There are only few series, all with short follow-up, which have reported the risk of development of de novo aneurysms. In these reports the rate of development of new aneurysms was between 0.4% and 2.2% per year.[12,21,61] Apart from development of new aneurysms, an occluded aneurysm might reopen or a new aneurysm could develop at the site of a treated aneurysm. The rate of growth of aneurysms after clipping was about 0.5% per year in two series with high rates of follow-up angiography.[18,19] In two follow-up studies, the risk of recurrent SAH after clipping was estimated to be 2% in 10 years, and about 9% in 20 years, which is about 30–50 times higher than the risk in the general population.[12,21] A higher proportion of patients with two episodes of SAH had a positive family history of the disorder (30%) than those with SAH in general (10%).[8] Patients with recurrence of SAH were also younger at onset than those with the disorder in general. The mean time between the first and second episodes was 7.8 years, ranging 2.8–14 years for SAH from *de novo* aneurysm.[33,62] The lower limit of about 3 years for a new episode from a *de novo* aneurysm accord with other studies on rupture of *de novo* aneurysms. A new aneurysm seems to take some time to develop, although some case reports have described rupture of new aneurysms within 2–6 months after initial SAH.[33,69]

ISUIA STUDY AND CONTROVERSIES

Asymptomatic unruptured aneurysms, which constitute between 17% and 37% of all unruptured aneurysms, are less prone to bleeding than symptomatic unruptured aneurysms.[59,60,69] Their annual bleeding rate has been the subject of much controversy. Most of this controversy stems from the results of the International Study of Unruptured Intracranial Aneurysms (ISUIA) which was first published in 1998.[59] The ISUIA had two objectives. The first was to evaluate the natural history of UIA, and the second was to establish the risk of treatment. The study consisted of retrospective and prospective components. In the retrospective component, the natural history of UIAs was evaluated and in the prospective component, the morbidity and mortality related to treatment were evaluated. A total of 1,449 patients with 1,937 UIAs were included in the retrospective cohort. They were divided into two groups: 727 patients of group 1 who had no prior history of SAH and 722 patients of group 2 who had history of SAH. The mean duration of follow-up was 8.3 years. Of the 1,449 patients, 32 had documented aneurysmal rupture. In group 1, the cumulative rate of rupture was 0.05% per year for aneurysms less than 10 mm in diameter and about 1% in those over 10 mm in diameter. Aneurysms larger than 25 mm had a 6% rupture rate in the first year. In group 2, the cumulative rate of rupture was about 0.5% per year for lesions smaller than 10 mm and about 1% for those larger than 10 mm in diameter. In group 1, in addition to size, location was related to haemorrhage risk, with basilar top, vertebrobasilar, posterior cerebral and posterior communicating artery aneurysms having a higher risk of rupture. In group 2, only location (i.e. basilar tip) and increasing age predicted an increased risk of haemorrhage. The risks quoted in the ISUIA study, however, was lower than previous studies had suggested.[17,21,31] Jane and co-authors estimated that the long-term risk of rupture for an incidentally discovered cerebral aneurysm was between 1% and 2% per year.[17] Similarly, Juvela et al. found the annual rupture risk to be 1.4% per year among 181 untreated aneurysms followed in 132 Finnish patients over a 30 years period. The annual risk to patients was 2.1% because some patients had more than one aneurysm.[20,21] Results of the initial report of the ISUIA have created much controversy, and the study has been criticised based on the select nature of the retrospective cohort and the comparison between the prospectively gained morbidity data and the very low rupture rate for patients in the historical cohort who had been selected for non-operative intervention. It was suggested that the retrospective group had excluded patients with the highest risk of rupture and introduced data-collection bias, artificially lowering the estimated annual haemorrhage rate and those patients enrolled in ISUIA were pre-selected for low natural history risk and these low-risk patients represented only about 2% of the patients seen in practice.[13,22,38] This combined

retrospective/prospective ISUIA report did not make a clear distinction between the risks of symptomatic and truly incidental unruptured aneurysms and did not determine the influence of genetic factors, smoking history or concurrent diseases such as ADPKD. Subsequently, in a population based study by Juvela et al. 142 unselected patients from a defined geographic area were observed for an average of 20 years. The risk of haemorrhage was 1.3% and each millimetre increase in aneurysm size was associated with an increase of 1.11 in the relative risk of haemorrhage.[20] In addition, active cigarette smoking was found to be an important predictor of aneurysm rupture. This study, along with another study from Japan,[60] suggests that risk of rupture from asymptomatic aneurysms is probably closer to 1% than 0.1% per year and this risk is highly dependent on age, smoking, lesion size and lesion location. Surgical series show that multiple aneurysms represent about a third of unruptured aneurysms. The annual risk of bleeding of an unruptured aneurysm discovered during angiography performed for a ruptured aneurysm in another location is greater than the risk for an isolated asymptomatic lesion.[15,67] In the ISUIA, prior SAH was associated with an 11-fold increase in rupture for small (<10 mm) aneurysms.[24] No additional risk was observed for larger aneurysms. The exact additional risk of rupture from an asymptomatic aneurysm when there is a history of SAH is not certain.

There is considerable evidence in literature that the majority of ruptured aneurysms are smaller than 10 mm. In the Co-operative Aneurysm Study angiographic studies revealed a mean maximal diameter of 8.2+/–3.9 mm and a median diameter of 7 mm.[23] Seventy-one per cent of the sacs were smaller than 10 mm and 13% were less than 5 mm in diameter. The relationship between aneurysm size and haemorrhage from unruptured aneurysm is not fully elucidated. According to ISUIA, in patients with no history of subarachnoid haemorrhage, the five-year cumulative rate of rupture of aneurysms located in the internal carotid artery, anterior communicating artery, anterior cerebral artery or middle cerebral artery is zero for aneurysms under 7 mm, 2.6% for 7–12 mm, 14.5% for 13–24 mm, and 40% for 25 mm or more.[67] This rate is in contrast to rupture rates of 2.5%, 14.5%, 18.4% and 50%, respectively, for the same sizes of aneurysms in the posterior circulation and posterior communicating artery. Some authors suggest that unruptured aneurysms less than 10 mm in diameter do not bleed even though the average size of ruptured aneurysm from the same group was 7.5 mm.[37,66] Yasui et al. followed 25 unruptured aneurysms including 66% that were less than 5 mm at the time of detection. Twenty-five per cent of the aneurysms were still less than 5 mm when SAH occurred.[70] In a prospective population based study an association between increased aneurysm size and bleeding was observed.[21] The median diameter of unruptured aneurysms that subsequently bled was no different from the median diameter of those that did not rupture (4 mm). In the same study, aneurysm growth on serial examination was associated with an increased risk of bleeding. The available data suggests that, whereas increased aneurysm size is associated with increased risk of rupture, small aneurysms certainly bleed and in some patients this risk of bleeding may be predicted by aneurysm growth.

Results of a continuation of the prospective arm of ISUIA have recently been published.[67] Compared with rupture rates in the retrospective cohort, rupture rates were higher in patients from group 1 (no prior SAH) of the prospective cohort who had unruptured aneurysms at least 7 mm in diameter, and this difference was most pronounced for aneurysms 7–9 mm in diameter. Size had little predictive value in patients with history of SAH from a different aneurysm (group 2). On multivariate analysis age greater than 50 years, aneurysm size greater than 12 mm, posterior circulation location, previous ischaemic cerebrovascular disease and aneurysm symptoms other than rupture were predictive of poor outcome after craniotomy while, in patients treated endovascularly, only size greater than 12 mm and posterior circulation location were associated with poor outcome. Comparison between the surgical and endovascular groups is not possible due to the unbalanced distribution of patients in the treatment groups of this nonrandomised study. There was a high rate of incomplete aneurysm obliteration in patients who underwent endovascular therapy, although the overall treatment related morbidity and mortality at one year was lower in the endovascular group.

SHOULD WE SCREEN FOR INCIDENTAL ANEURYSMS

The benefits of screening for asymptomatic intracranial aneurysms have never been quantified. No clinical trials have been done on screening for aneurysms in patients at increased risk and presumably such trials will not be done because the follow-up needs to be 20 years or longer. The goal of screening is not to detect or to treat an aneurysm, but to increase the number of quality years of life.[3] Decisions therefore must be made from calculations and assumptions about perceived quality of life.[47] Definitely the patient gets a reassurance with a negative screening result, but it can also cause anxiety if a 3 mm aneurysm is found and left untreated or if an unrelated abnormality is found.[63] Also one has to bear in mind that even screening, repeated screening and preventive treatment cannot prevent all episodes of SAH because, in rare instances, aneurysms can develop and rupture within the regular screening interval of 5 years.[52] Conventional angiography, however, is not useful for screening high-risk groups because a single negative angiogram does not exclude the possibility of a de novo lesion developing in future. MRA is at present the most satisfactory technique for screening high-risk groups. The number of false negatives may be reduced by the simultaneous use of CT angiography. Screening should be done in individuals with two or more affected first-degree relatives, and

in patients with ADPKD. With this screening strategy, approximately 10% of individuals are found to have an intracranial aneurysm.[9,42,48,49,51] In approximately a third of these patients, the aneurysms are larger than 5 mm in diameter.[48] Since aneurysms are very rare before the age of 20 years, screening is started after this age. If a first screening is negative, repeated screening should be advised, because the risk of finding an aneurysm 5 years after the initial screening is about 7%.[64] Screening should not be advised if the life expectancy of the patient is short because of advanced age or comorbid illness and the maximum age for screening is 60–70 years depending on the individual's health status.[47] Screening should also be done in identical twins if SAH has occurred in one of the twins. In many pairs, the aneurysms are at the same site and SAH tends to occur at around the same age.[35,40] In individuals with only one affected first-degree relative, screening is not very efficient or effective as relatives of index SAH cases have only a 4% risk of harbouring an intracranial aneurysm and this low incidence may not make screening cost-effective.[43,71] To prevent one episode of fatal SAH, 300 at risk people must be screened.[47] The general advice is not to screen individuals with only one affected relative. Patients with Ehlers-Danlos syndrome type IV are advised against screening because of the fragility of the vessel wall which substantially increases risk of treatment.[34] There is no indication for screening patients with neurofibromatosis or Marfan disease, because an increased risk of SAH has not been confirmed in these groups.[47] Patients who have had an aneurysmal SAH are at increased risk for development of a new aneurysm some time after the initial aneurysm has been discovered. Each year, new aneurysms develop in at least 2% of patients with previously ruptured aneurysms and in this group of patients, the incidence of aneurysmal rupture is approximately 6 per 10,000 per year, which is substantially higher than the incidence of aneurysmal SAH in the general population.[21] Follow-up screening for aneurysms in this group might be beneficial, but evidence to advise on follow-up screening in such patients is insufficient.

MANAGEMENT ISSUES

We know that the rate of rupture of UIA is affected by factors such as aneurysm size, aneurysm location, multiplicity of aneurysms, aneurysmal growth, symptomatic aneurysms and patient factors such as age, gender and history of hypertension and smoking. The presence of severe progressive symptoms from an aneurysm within the subarachnoid space is an indication for treatment regardless of the size of the unruptured aneurysm. Symptomatic unruptured aneurysms often require treatment because of headaches, cranial nerve deficit, seizures, embolic stroke or hemiparesis. The risk of bleeding is also greater in symptomatic unruptured than asymptomatic unruptured aneurysms.[67] Symptomatic lesions represent about a third of all unruptured lesions, but account for three quarters of the cases that bleed during observation. Overall, the risk of complications from treatment is around 5% for death or persisting impairment in activities of daily living, and 10% for persisting cognitive deficits or reduced quality of life.[67] The risks are higher for neurosurgical clipping than for endovascular coiling, especially in patients older than 50 years.[5,44,45,67]

The complication rates are probably lower for aneurysms detected by screening, because they are mostly small, and risks of complication from treatment increase with the size of aneurysms.[54] In a meta-analysis by Raaymakers and co-workers, in which the treatment of 2,568 unruptured aneurysms in 2,460 patients was examined, surgical morbidity was 10.9% and mortality 2.6%.[44] Similarly, in the prospective arm of the ISUIA, among 996 patients undergoing surgery, 1 year mortality was 2% in patients with previous SAH and 3.8% in patients without prior history of SAH.[67] The morbidity for both groups was approximately 12% and much of this morbidity included subclinical neuropsychological defects that had limited functional impact. The meta-analysis of Raaymakers et al. had several caveats because of studies with varied inclusion criteria, inconsistent outcome measures, unclear information about neurosurgeon's experience and a relatively high percentage (37%) of symptomatic unruptured aneurysms were included in the analysis. In addition, a relatively large number of giant and posterior circulation aneurysms, which both have particularly poor surgical outcomes, were included in the study. When these two groups of patients were analysed separately, Raaymakers and co-workers found that the surgical mortality and morbidity among other aneurysms were 0.8% and 1.9%, respectively. To date, the most selective meta-analysis of unruptured aneurysm surgery was performed by King and associates, who observed an overall mortality rate of 1% and morbidity of 4.1%. This study, unlike the meta-analysis by Raaymakers included more aneurysms less than 10 mm in diameter (72% vs 54%) and more aneurysms located in the anterior circulation (94% vs 70%).[26]

FACTORS ASSOCIATED WITH SURGICAL OUTCOME

Increased aneurysm size is the most important factor associated with surgical complications and poor outcome. Aneurysms larger than 25 mm in diameter have a fourfold increased risk compared with 5 mm aneurysms.[25] Wirth et al. showed operative morbidity following surgery to be 2% for aneurysms smaller than 5 mm, 7% for aneurysms 6–15 mm and 14% for aneurysms 16–25 mm.[68] Among 92 unruptured giant aneurysms operated at Columbia Presbyterian Hospital, morbidity occurred in 25% and, overall, 83% experienced a good or excellent outcome, while for lesions less than 10 mm, 99% had good or excellent outcome.[54] Ninety-nine per cent of non-giant and 90% of the giant aneurysm patients returned to work. Aneurysm size was also related with

technical results with only 60% of giant lesions undergoing clip occlusion while it was 85% for lesions less than 10 mm diameter.[11] The association between increased aneurysm size and poor outcome may be explained in part by the aneurysm's intimate association with small perforators, broad aneurysm neck, intraluminal thrombosis, or atherosclerosis in the aneurysm neck or dome. In the series of Wirth et al.[68] aneurysm location affected outcome in anterior circulation aneurysms; morbidity was 5% for posterior communicating aneurysms, 8% for middle cerebral aneurysms, 12% for ophthalmic lesions, 16% for anterior communicating lesions and 17% for internal carotid bifurcation lesions. A similar relationship between anterior circulation aneurysm location and outcome was not observed by the Columbia Presbyterian hospital group.[60] In their observation basilar bifurcation lesions were associated with poor outcome and worse angiographic result with only 66% having angiographic occlusion but 81% experienced a good or excellent outcome in this group.

Even though advanced age is recognised as a poor prognostic indicator for surgery, many surgeons have reported good surgical results in patients older than 60 years.[11,54,68] Wide aneurysm neck reduces the success of endovascular procedures, but generally play a less significant role in surgery. Calcification in the aneurysm neck is associated with increased surgical difficulty and is also associated with an increased incidence of cerebral embolism and intra-operative bleeding from the aneurysm neck. Patient related factors include advanced age, ischaemic cerebrovascular disease, and medical conditions, such as diabetes mellitus, also increase the risk of unruptured aneurysm surgery.

ENDOVASCULAR TREATMENT

In some patients endovascular coil occlusion is a valuable alternative to surgery in the treatment of unruptured aneurysms, even though the long-term effect on natural history remains uncertain. Also there are difficulties in evaluating coil embolisation technology, because the procedure is constantly being refined and additional experience gained. Procedural morbidity with this technique is between 6% and 19% in the older series with overall favourable outcome in 82% and a mortality of 10%.[10,29,39] Endovascular procedures appear to be less successful than surgical procedures in occluding unruptured aneurysms with only 50% achieving complete occlusion.[29,39] A second limitation to an endovascular procedure is aneurysm recurrence, which is between 16% and 32%.[11] The results of GDC embolisation for incidentally discovered, unruptured aneurysms were assessed in a series of 120 patients by Murayama and colleagues.[32] Thirty-nine percent of the aneurysms were ophthalmic segment aneurysms and 18% were located at the basilar bifurcation. Complete GDC occlusion could be achieved in only 63% of cases and procedure related morbidity was 5.2%. Follow-up angiograms were available in only 77 patients of the original 120 patient cohort. After the original embolisation, complete occlusion was observed in 52 aneurysms, and a small neck remnant was visualised in 22 aneurysms. At follow-up angiography, none of the 52 completely occluded aneurysms had recanalised. In the 22 aneurysms with small neck remnants, 8 (36%) showed aneurysmal recanalisation due to coil compaction. A comparative study by Johnston and coworkers in a cohort of patients treated at 60 University Hospitals from January 1994 through June 1997, using the University Health System Consortium database, looked at the outcome between coil embolisation and surgical clipping for both symptomatic and incidental unruptured aneurysms.[18] Adverse outcomes were significantly more common in surgical cases (18.5%) than in endovascular cases (10.6%). In another study Johnston and colleagues compared 130 cases ideal for either technique that underwent surgery or coil embolisation during a 10 years period. Surgical complications were threefold greater than endovascular complications, probably because the surgical team did not have a dedicated cerebrovascular surgeon and low volume surgical centres were compared with high volume endovascular centres.[18]

MANAGEMENT GUIDELINES FOR INCIDENTAL ANEURYSMS

Whether or not to treat a truly incidental (asymptomatic) aneurysm remains controversial. It is clear that size of the aneurysm is important; however, it is also clear that there is no cut-off size below which rupture is not possible. Small aneurysms have a risk of haemorrhage even though this risk may be less than that of larger aneurysms. In general, the risk that small aneurysms (<7 mm) will rupture is low, particularly if they are on the anterior circulation. Small aneurysms might therefore best be left untreated.[38] However, this approach is not appropriate for patients who have two or more relatives who died from SAH. Several studies have found a higher risk of rupture for familial than for sporadic aneurysms.[46] Patients with unruptured aneurysms, whose relatives have died from SAH, know that the haemorrhages occurred from small aneurysms. A patient with a small aneurysm but a positive family history is difficult to reassure with general statements that small aneurysms have a low-risk of rupture. In patients with small aneurysms (<7 mm), the decision on whether or not to treat depends on the age of the patient, site of the aneurysm, accessibility of the aneurysm for coiling in older patients, whether or not a previous SAH has occurred and the ability to cope with the knowledge of having an untreated aneurysm.[47] In patients with very small aneurysms (3 mm or less), follow-up assessment to check whether or not the aneurysm is increasing over time seems to be a reasonable approach. The optimum period between follow-up assessments and the duration of follow-up are not known. At the University of Miami School of Medicine, each case of incidental aneurysm is considered individually and treatment offered

accordingly.[2] They recommend treatment of incidental aneurysms that are more than 7 mm in diameter if the patient is relatively young and without major co-morbidities. If the patient is very young or has a family history of aneurysms or has had a SAH from another aneurysm, they recommend treatment even for aneurysms of a significantly smaller size. With larger aneurysms, they stretch the indications for treatment and treat even patients who are older, but in relatively good medical health or younger patients with some co-morbidities who are still likely to tolerate general anaesthesia. Due to location and configuration, the decision making becomes more problematic for truly incidental large and giant aneurysms, where risk of treatment is very high. In such cases they consider age an important factor and tend to take a risk in a younger patient and to observe an older patient with periodic imaging. A more aggressive approach is pursued if prominent growth of the aneurysm is seen on follow-up imaging. They also address the issue of treating an incidental aneurysm with open microsurgery or endovascular occlusion. With unruptured aneurysms one does not have the problem of swollen, hyperaemic and friable brain that may be injured by retraction at surgery and also there is no problem of vasospasm that may be exacerbated by surgery. Therefore, they tend to lean more towards open microsurgery under equal circumstances with unruptured incidental aneurysms because of the uncertainty about the long-term durability of coiling as opposed to microsurgical clipping in experienced hands. They recommend open microsurgical clipping for most aneurysms of the anterior circulation and for vertebral artery including origin of PICA or distal PICA or distal AICA aneurysms and aneurysms at the origin of the superior cerebellar artery. For most basilar aneurysms they recommend endovascular treatment. As suggested by this group, it is very important to emphasise that the evaluation of "risk versus benefit" is an ongoing process that continues until an aneurysm is secured by either coiling or clipping. If one finds, during surgery, unexpected circumstances that clearly increase the risk of treatment, one should not hesitate to back off as may be seen during open surgery when the aneurysm neck is found calcified or if the surgeon finds vital perforators that cannot be saved. Under such circumstances the authors' advice is to back off and either treat the patient conservatively or recommend endovascular therapy.

THE AMERICAN HEART ASSOCIATION GUIDELINES

Members of the Stroke Council[63] recommended that incidental aneurysms smaller than 10 mm in patients without a previous SAH should be observed rather than treated unless the patient is young, there is a daughter aneurysm or if there are unique haemodynamic features. Patients with a family history of aneurysmal SAH also deserve special consideration for treatment. Aneurysms larger than 10 mm should be considered for treatment depending on age, health and aneurysm risk factors.

ADVANCES

Recent advances in molecular genetics have made linkage studies possible to map the chromosomal locus of a putative intracranial aneurysm gene mutation. One approach is to screen the human genome for intracranial aneurysm genes by testing linkage of a large number of distinct highly polymorphic genetic markers. Another method for studying linkage is to analyse variations in the sharing of marker alleles among affected sibling pairs only. Polymorphisms of several genes have now been investigated in patients with intracranial aneurysms. Certain polymorphisms of the angiotensin I converting enzyme, matrix metalloproteinases and endoglin genes may be associated with an increased risk for aneurysm development.[56-58,72] Olson and colleagues[36] performed a sibling-pair linkage analysis in Finnish patients with intracranial aneurysms and identified a susceptibility locus at 19q13.1-13.3.

CONCLUSION

The advent of reliable non-invasive imaging and efficacy of treatment for incidental cerebral aneurysm has aroused an interest in the medical fraternity in the management of these patients. The numbers of incidental aneurysms will continue to increase as the age of the population increases. The treating physician must understand the natural history to assess the effectiveness of treatment options. Whether or not it is proper to screen for incidental aneurysms is based on an understanding of aneurysm formation and rupture. If aneurysms develop over a brief time frame and are most prone to rupture during this period, aneurysm screening programs will identify only stable aneurysms and miss the unstable ones that require treatment. If the long-term risk of haemorrhage from an incidentally detected aneurysm is as low as that reported by ISUIA, treatment in its current form may pose a greater risk to patients than does the disease itself. Treatment of incidental aneurysms will continue to evolve. The development of intravascular stents and flow redirectors may improve the result of endovascular procedures. Less invasive surgical approaches, better neuroprotection that permits longer temporary occlusion times, and endoscopic instruments designed to identify perforators will similarly improve surgical results. The patients should have a management plan that is individualised and should consider the age of the person, life expectancy, co-morbidities and characteristics of the aneurysm.

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87 Multiple Intracranial Aneurysms

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INCIDENCE

Based on observations from autopsy studies, nearly 10–15 million people in the United States are largely believed to have, or will develop, cerebral aneurysms in their lifetime.[16,17] Winn and colleagues from the University of Virginia retrospectively reviewed 3,684 cerebral angiograms not related to subarachnoid haemorrhage (SAH) or known aneurysms and found only 24 (0.65%) asymptomatic unruptured aneurysms.[45] Interestingly, no case of multiple aneurysms was noted. Complex management issues arise when a patient with multiple cerebral aneurysms is encountered, especially with SAH following a rupture of one of the aneurysms.[21] The overall incidence of this entity has been reported to vary from 7 to 30% among patients with intracranial aneurysms (Table 1), although there is a study reporting an incidence as high as 45% based on angiographic findings.

A review of 23 studies revealed a prevalence of 16.6% with 3,189 multiple aneurysms among 19,268 patients. There is not a significant difference noted among various types of studies. A single meta-analysis of asymptomatic, (unruptured) intracranial aneurysms using a MEDLINE search from 1966 to 1992 revealed an incidence of 39.8%.[20] Two autopsy studies showed between 9% and 19% of deaths resulted from ruptured intracranial aneurysms.[10,13] The reported incidence among

Table 1: Incidence of multiple intracranial aneurysms[9,24,30,40,41]

Author (Year)	*Study type*	*Incidence (%)/ Duration*	*Multiple aneurysms*	*Total aneurysms*
Kaminogo (2003)	Population/Co-operative	17.7/9	361	2037
Juvela (2000)	Population	30	80	266
Lee (1998)	Population	7.3/1	32	439
Sim (1998)	Population	10.7	306	2863
Rinne (1994)	Population	22/14.5	266	1200
Nishimoto (1985)	Population/Co-operative	13/2	626	4750
Rinne (1994)	Prospective/Angiogram	34/1	39	114
Phan (2002)	Retrospective/Angiogram	32/9	18	57
Ellamushi (2001)	Retrospective/Angiogram	28/12	108	392
Khamlichi (2001)	Retrospective/Angiogram	9/16	18	200
Hino (2000)	Retrospective/Angiogram	20/12	93	462
Qureshi (1998)	Retrospective/Angiogram	30/7.5	127	419
Orz (1996)	Retrospective/Angiogram	14.2/6.7	221	1562
Wilson (1989)	Retrospective/Angiogram	44.9/3	114	254
Sakoda (1989)	Retrospective	13/13	28	215
Nehls (1985)	Retrospective/Angiogram	33.5/4.3	69	205
Ostergaard (1985)	Retrospective	17.8/12	133	748
Kojima (1984)	Retrospective	17/6.3	59	356
Andrews (1979)	Retrospective	29/13	62	212
Paterson (1973)	Retrospective	9.6/12	168	1686
Gonsoulin (2002)	Autopsy	9.1/20	22	219
Inagawa (1990)	Autopsy/Population	19/36	16	84
King (1994)	Meta-analysis	39.8	292	733
Total		**16.6**	**3189**	**19268**

thirteen retrospective studies with angiograms ranged from 9 to 44.9%.

It may not be feasible to determine the exact incidence of multiple intracranial aneurysms in the population; however, a literature review of various studies over the years done around the globe appears to indicate that the overall incidence is about 17%.

The difference between reported incidences in literature depends on the nature of the study, patient selection and time of study.

The incidence of multiple aneurysms is higher in women than men (20.2% vs 12.4%).[4] The cause of this higher incidence of multiple aneurysms in women is unknown. The menopausal state and high prevalence of collagen diseases may play a role in the formation of multiple aneurysms.

The correlation between increased age and multiple aneurysms is controversial.

RISK FACTORS FOR MULTIPLE INTRACRANIAL ANEURYSMS

Hypertension

Historically, the presence of chronic hypertension was a major risk factor for SAH. Some recent studies have shown a correlation of hypertension as a risk factor for multiple aneurysms.[1,18,33] The findings were significant among people less than 55 years old with post-operative hypertension and carrying more than two intracranial aneurysms. Ellamushi and co-workers found among their 400 patients with SAH to have odds ratio of 1.9 for hypertension and multiple aneurysms.[8] Some other studies have failed to find a correlation between hypertension and multiple aneurysms, and the authors hypothesised that the higher prevalence of antihypertensive therapy in their study group compared to the others may have an effect.[38] The presence of hypertension delays synthesis of collagen and elastin and causes degeneration of the internal elastic lamina to develop in the arterial wall. Subsequently, weakened walls begin to bulge under added haemodynamic stress caused by hypertension.[15]

Gender

A higher incidence of intracranial aneurysm formation has been observed in the female population, especially among post-menopausal women. Although there is controversy about the presumed mechanism for the role of female hormones in the aetiology of aneurysms, observations from a number of studies have shown that there are changes in patient characteristics once menopause takes place. Decrease in oestrogen levels has a negative effect on collagen production. In turn, this decline in collagen will cause the cerebral blood vessels to get weaker and predispose them to develop aneurysms. In one study, the difference between males and females was 17.6% versus 32.4% in multiple intracranial aneurysms.[22] Others have also observed that being a female increase the risk of developing multiple intracranial aneurysms.[8,18,38]

Arteriovenous Malformation

The association of intracranial aneurysms and arterio venous malformation (AVM) has been described for several decades. Thompson et al.[42] found 7.5% of patients with AVM had associated intracranial aneurysms. The majority of these patients had multiple aneurysms (51%), most of the aneurysms being located on the feeding vessel of the AVM (85%). The risk of haemorrhage is higher in patients with AVM and associated aneurysms than for patients with AVM alone. One hypothesis to explain association of aneurysms with AVM is that haemodynamic stress on the feeding vessel leads to aneurysm formation. It has been shown that increased blood flow leads to degeneration of arterial walls. Because of the high-risk of intracranial haemorrhage in these patients, aggressive treatment is necessary.[42] The treatment of these patients with complex vascular anomalies is challenging and needs to be individualised. Most authors agree that the aneurysms on the feeding arteries should be treated before initiating definitive treatment of AVM.[42]

Familial Aneurysms

An ongoing series of 30 patients with familial intracranial aneurysms from thirteen families in Canada has determined an incidence of 17% for multiple intracranial aneurysms in this group. Each family has been questioned and found to have 2 or more individuals with intracranial aneurysms.[23] Other authors have reported a higher incidence of around 50%.[27,31] With only a limited number of families available for study, it is difficult to conclude that there is a higher incidence of multiple intracranial aneurysms among these family members. Patients with familial aneurysms and multiple aneurysms tend to be younger, and there is a higher incidence of middle cerebral and internal carotid aneurysms.

Connective Tissue Disease and Congenital Disorders

Rare cases of hereditary connective tissue diseases, such as polycystic kidney disease, Ehlers-Danlos syndrome, pseudoxanthoma elasticum and Marfan syndrome, have been known to be associated with multiple intracranial aneurysms.[5] It has been proposed that an embryological endothelial defect in one or two embryonic segments of the neural crest or mesoderm leading to dysfunctional vessel wall remodelling in the presence of repeated or long-lasting triggers is responsible for this. Eighty-eight patients with polycystic kidney disease were screened for intracranial aneurysms. Three out of four (75%) patients with aneurysms had more than one intracranial aneurysm.[6] Although small in size, this number is significant given the rarity of the disease. Multiple aneurysms are also reported to be associated with moyamoya

disease, fibromuscular dysplasia, aortic coarctation and tuberous sclerosis.[26]

Sickle Cell Disease

The endothelium is interrupted following repeated injury from adhesion of the sickled erythrocytes to the endothelial cells. This cascade may disrupt the supply of oxygen and other nutrients throughout the entire vascular system and, in turn, the formation of an aneurysm may be initiated at multiple locations. The overall incidence of intracranial aneurysm among sickle cell disease patients is low compared to the overall population as there are only a small number of reported cases since a seven-year-old boy was diagnosed at autopsy to have the first documented case of SAH with sickle cell disease in 1930.[2,7] Oyesiku et al. reported 9 cases (60%) of multiple aneurysms in their fifteen patient series.[34] The same authors also combined their data with previously published cases and found 14 (47%) out of 30 published cases of sickle cell disease had multiple aneurysms. There were 44 cases of intracranial aneurysms among sickle cell disease patients reported more recently.[36] Fifty-seven per cent of them had more than one aneurysm, and aneurysms from patients with multiple aneurysms comprised nearly 80% of the total number of aneurysms.

Smoking

A presumed molecular mechanism for negative risk factors of cigarette smoking on aneurysm formation is based on a serum elastase/α1-antitrypsin imbalance or increased elastase activity.[3] Repetitive transient increases of systemic blood pressure have been observed for about three hours following cigarette smoking.[25] Thus, it is plausible that long-term smoking can weaken the cerebral blood vessels by promoting degradation of elastin in the blood vessel walls to initiate formation of aneurysm at anatomic sites of maximum turbulence under the load produced by hypertension. Juvela et al.[18] analysed 266 consecutive patients with SAH and found that regular smoking at any time is a significant risk factor for the presence of multiple intracranial aneurysms when adjusted for age, sex and hypertension in patients aged less than or equal to 60 years. Qureshi et al.[38] reported an estimated odds ratio of 1.7 for smoking at any time with the presence of multiple intracranial aneurysms among 419 patients. A retrospective study of 392 SAH patients between 1985 and 1997 at Queen's Square Hospital, London, showed a statistically significant correlation of multiplicity of aneurysms to smoking ($p < 0.001$).[8]

ANEURYSM DISTRIBUTION

The distribution of multiple aneurysms as reported by several studies is displayed in Table 2. The most common site for multiple aneurysms is different from patients with a single aneurysm. In patients with multiple aneurysms, the most common sites are the internal carotid artery (ICA) and the middle cerebral artery (MCA). However, in patients with a single aneurysm, the anterior communicating artery (ACoA) is the most common site. In a retrospective study by Roganovic, the incidence of ACoA aneurysms in patients with multiple and single aneurysms was 17.8% and 37.4%, respectively.

INSTITUTIONAL EXPERIENCE

Over 300 aneurysms have been treated at our institution, which has functioned as the regional tertiary referral centre for complex vascular and skull base lesions since the early 1990s. The incidence of multiple aneurysms was around 12% among the patients treated. The presence of multiple aneurysms was more common among female patients (male to female ratio of 1:4). The median age was around 51 years. Most patients had two aneurysms, and they were clipped at a single sitting, if they were on the same side. Otherwise, the second stage of the operation for the contralateral side was planned after a few weeks of the first operation. Posterior communicating artery was the most common site of aneurysms in these patients.

ILLUSTRATIVE CASE

A 60-year-old female with a history of heavy smoking and hypertension presented with the worst headache of her life to an outside hospital. She was neurologically intact except for mild confusion (Hunt and Hess Grade III). CT scan of the brain showed diffuse SAH with extension mostly into the left Sylvian fissure (Fisher Grade III) (Fig. 1). Four-vessel cerebral angiogram revealed multiple aneurysms on both sides: bilateral MCA, bilateral ophthalmic and left PCom (Fig. 2). Although the aneurysm on the right MCA was the biggest in size and suspicious for the rupture, her initial presentation of left-side periorbital headache and more concentrated SAH on the left-side confused the matter of localisation

Table 2: Distribution (%) of multiple aneurysms

Author (Ref.)	*PCoA*	*MCA*	*ACoA*	*ICA*	*VBA*
Nehls et al.[28]	22	21.5	12	–	15
Rinne et al.[39]	16	47	16	25	5
Proust et al.[37]	–	42	15	25.5	–
Langawa et al.[14]	–	28	17	44	6

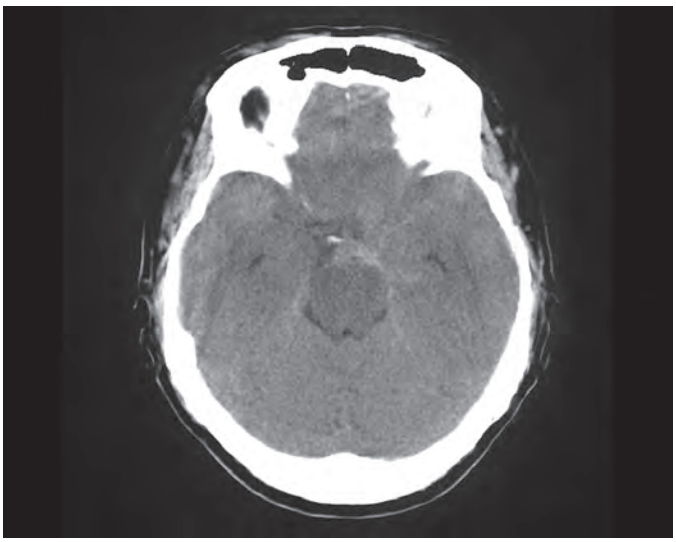

Fig. 1: There is diffuse SAH along the basal cisterns with extension into the left Sylvian fissure

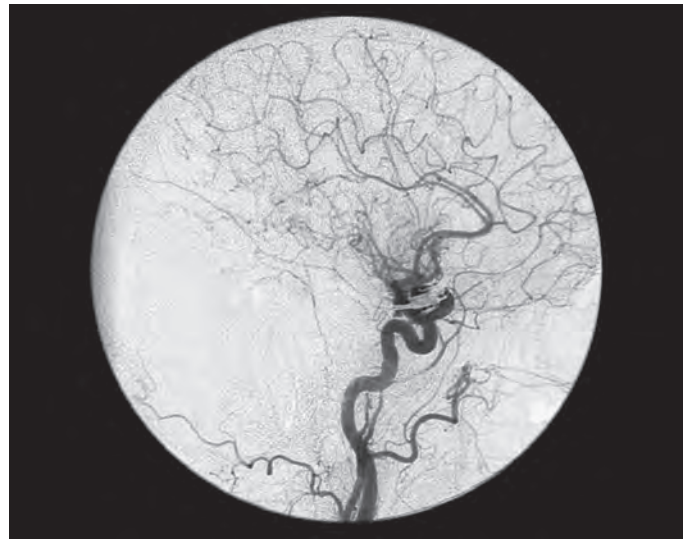

Fig. 3: Right side selective lateral view of the carotid shows presence of multiple aneurysm clips with complete obliteration of the aneurysms and preservation of the major vessels following the second stage of the operative plan

of the rupture site. A slight bulging area on the dome of the left PCom along with the above mentioned factors persuaded the senior author to clip the left sided aneurysms first. Intra-operatively, most of the blood was found around the left PCom, and a total of eight clips were applied to clip all three aneurysms without any complications (Fig. 3). She did well following the operation and the rest of the aneurysms were clipped 3 months after the initial operation (Fig. 4).

PREDICTION OF RUPTURE SITE

The most common site of rupture in patients with multiple aneurysms as compared to patients with a single aneurysm is ACoA.[28] In patients with SAH and multiple aneurysms, the ruptured aneurysm must correctly be identified, especially in cases where complete aneurysm clipping cannot be accomplished in a single operation. False localisation of the ruptured site may result in disastrous post-operative haemorrhage from the unprotected ruptured aneurysm.[12]

With clinical signs, computed tomography (CT) and angiographic findings, the site of ruptured aneurysm usually can be identified with a high degree of certainty (Hino et al. 91%; Nehls et al. 98%).[12,28] Other methods for predicting the rupture site are magnetic resonance imaging (MRI) and electroencephalography (EEG).[12,26]

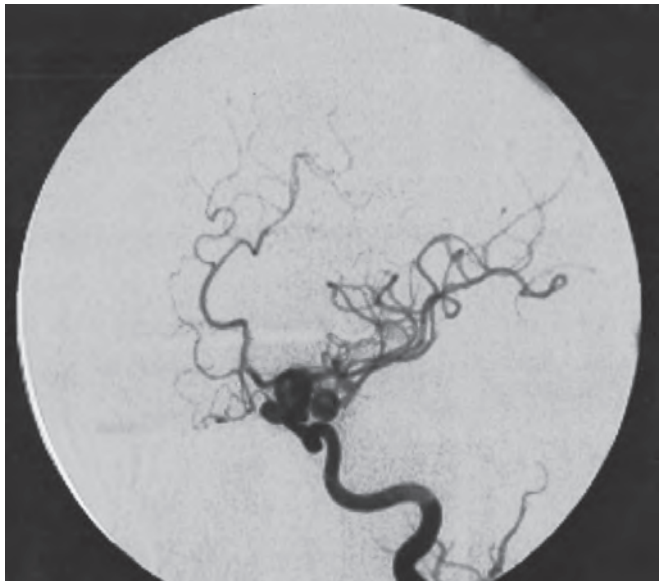

Fig. 2: AP and lateral views of carotid angiogram show the presence of bilateral MCA, bilateral ophthalmic and left PCom aneurysms. There is a slight bulging on the dome of the left PCom, which is highly suspicious for being the possible rupture site. There are no obvious signs of vasospasm on these views

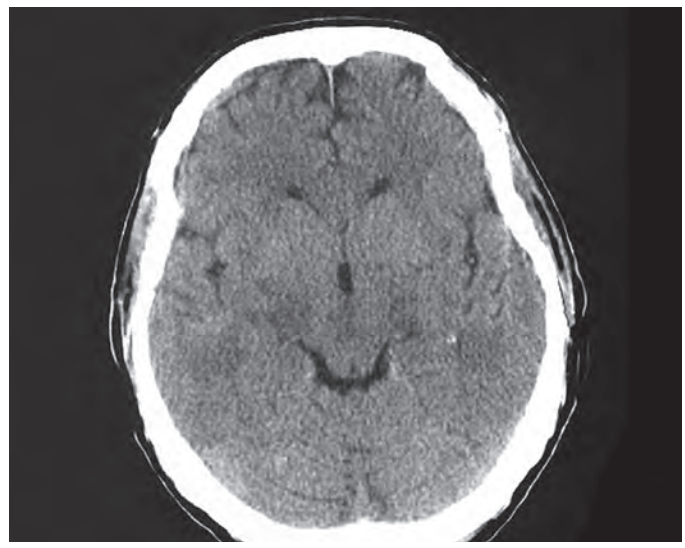

Fig. 4: CT of the brain without contrast shows no signs of infarction or hydrocephalus following the second operation

In some patients with cranial nerve palsy, the neurological examination will help in identifying the site of rupture. However, some other finding, such as hemiparesis, can be misleading. In the majority of patients with multiple aneurysms, clinical signs are not helpful for localisation of the ruptured aneurysm. In the study conducted by Zderkiewicz et al. it was helpful only in 7.6% of cases.[45]

CT plays a significant role in localising the ruptured site. The haemorrhage site in CT can provide very important information, such as focal blood collection in the specific cistern (suprasellar, perimesencephalic clot in posterior communicating artery aneurysms), interhemispheric fissure haematoma (in ACoA), intracerebral haematoma (in the temporal or frontal lobes in MCA aneurysms), and the area of intraventricular haemorrhage (isolated fourth ventricular haemorrhage in PICA aneurysm).[26]

The angiographic signs that can help in localising the ruptured aneurysm are as follows:

- Aneurysm bleb
- Irregular aneurysm contour
- Focal vasospasm
- Size of aneurysm
- Focal mass effect from blood clot
- Extravasation of contrast (rare cases)
- Changing aneurysm shape in serial angiograms.

In patients that have MRI, focal oedema or increased signal adjacent to one aneurysm may indicate a recent haemorrhage.[26] In some cases, EEG findings may help in identifying a ruptured aneurysm. To determine the site of ruptured aneurysm, one should use all the possible information from clinical presentation, CT, angiography and, in some patients, MRI and EEG.[12,26]

TREATMENT

The treatment criteria for incidental multiple intracranial aneurysms are similar to incidental aneurysms in general.[26] Studies have shown that the morbidity and mortality of patients with multiple aneurysms with SAH related to ruptured aneurysms, as well as the rebleeding, was from a ruptured aneurysm.[12] Most authors suggest treatment of multiple aneurysms using a one stage operation early post-SAH period.[43] This can be accomplished with a standard or modified approach. In some series, early surgery and one stage operations have been associated with less surgical morbidity and mortality. The favourable results with one stage operations compared to multi-stage operations may be related to easier access to aneurysms.

In SAH patients with multiple aneurysms, the symptomatic aneurysm should be treated first. The remaining aneurysms will be clipped from deep to more superficial aneurysms. In these cases, clipping the symptomatic aneurysm may obscure the view of deeper aneurysms or interfere with the clipping of the deeper aneurysms. There are three options for a successful completion: (1) clip the deeper aneurysm first with care not to disturb the ruptured aneurysm; (2) clip and aspirate the symptomatic aneurysm to allow clipping deeper aneurysms, and (3) treat the symptomatic aneurysm first and treat the deeper aneurysm through a different approach.[26]

The advantage of a one stage operation is to eliminate the need for a second surgery, to be sure that the ruptured aneurysm has been clipped, and to aggressively treat vasospasm with induced hypertension and hypervolaemia without the risk of aneurysmal rupture.[43] On the other hand, in the two stage operation, the exposure and clipping is technically easier when the subarachnoid blood has been cleared and the brain is less swollen.

Most authors suggest clipping all aneurysms in a one stage operation, if they are easily accessible and clipping the ruptured aneurysm has been completed smoothly. Otherwise, some or all asymptomatic aneurysms should be treated in second operations 6–12 weeks later. The other therapeutic option in patients with multiple aneurysms is an endovascular approach. In some cases, a combination of an endovascular approach and open surgery is a valuable option.

OUTCOME

The prognosis of SAH patients with multiple aneurysms is less favourable than in SAH patients with a single aneurysm, especially in elderly patients. In patients with multiple aneurysms, surgical complication is significantly more than that of single aneurysms.[32] Makio et al.[19] reported surgical complications of 12.1% in patients with multiple aneurysms versus 6.0% in patients with a single aneurysm. The factors that affect the outcome in patients with multiple intracranial aneurysms include: (1) misdiagnosing the site of the ruptured aneurysm; (2) failing to treat multiple aneurysms with multiple surgical approaches and (3) associated complications of surgical treatment of unruptured aneurysms.[11,29] As the number of aneurysms increases, the surgical results become more unsatisfactory.[8] In the study reported by Rinne et al.[8] there was no difference in outcome between patients having unilateral and bilateral aneurysms. Delayed neurological deficit has a major influence on the outcome of patients with multiple aneurysms. Furthermore, patients with vertebrobasilar aneurysms have a poorer outcome.[8]

CONCLUSION

Multiple aneurysms occur in about one-third of patients with aneurysms. They are more common in women and also in cases of familial aneurysms.[23,38] Other conditions associated with multiple aneurysms include connective tissue diseases and congenital disorders. The site of rupture can be determined with high accuracy using clinical signs, CT and angiographic signs.[12,26] If it is feasible, the symptomatic and asymptomatic aneurysms should be treated in a one stage operation (with a standard or modified approach). In some cases, the treatment of asymptomatic aneurysms could be done in a second surgery a few weeks later. Recently, one stage operations have become more frequent. In most series, it has been demonstrated that the prognosis and surgical outcome are worse in patients with multiple aneurysms.[19]

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88 Infectious Intracranial Aneurysms

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HISTORY

Virchow, in 1847, and Osler, in 1885, discovered that bacterial endocarditis may lead to vascular disruption and aneurysmal development.[22] In 1869, Church first described an infectious aneurysm in a 13-year-old boy with mitral valve endocarditis. "Mycotic aneurysms" was the term coined by Osler for all infectious aneurysms.[21] Bohmfalk et al. recommended that those aneurysms resulting from bacterial infections be designated "bacterial intracranial aneurysms" and the term "mycotic aneurysms" be reserved for those resulting from fungal infections.[5] Ojemann recommended that all types of aneurysms resulting from infection be termed "infectious intracranial aneurysms".[21] Infectious aneurysms form about 0.5–6.2% of intracranial aneurysms, occur more frequently in the anterior circulation and may be multiple.[6,7,9,20,21,24] They clinically manifest in 2% of cases of bacterial endocarditis and 5–15% of cases are detected at autopsy.

AETIOPATHOGENESIS

In intracranial arteries, contrary to the systemic blood vessels, the internal elastic membrane provides strength to the vascular wall. The external elastic lamina is absent, the muscularis layer is thin and there is no external support in the subarachnoid space. Infection affects the internal elastic membrane leading to its damage. Hydrostatic pulsations against a weakened wall lead to aneurysmal dilatation.

Haematogenous spread occurs via large calibre blood vessels to the tiny nutrient vessels supplying the intracranial vessels, the vasa vasora. Due to the small size of these vessels, the septic emboli cannot travel any further and, therefore, block it establishing a local infection of the outer adventitial layer of the blood vessel of the brain. This leads to ischaemic necrosis and the local infection also spreads to the subarachnoid spaces via the Virchow-Robin spaces. The blood vessel progressively weakens due to establishment of infection in a centripetal fashion in the vessel wall. The hydrostatic pulsations of blood in the blood vessels cause progressive dilatation of the vessel wall. Occasionally, turbulence, atherosclerosis or trauma to the vessels may lead to stasis of flow or endothelial damage causing direct implantation of the septic emboli through the damaged endothelial surface. Direct blood vessel invasion occurs due to the presence of endogenous central nervous system infection. A paranasal sinus infection may produce a contiguous spread to the cavernous sinus or meningitis may involve the basal cisterns. The blood vessels within the basal cisterns are surrounded by the infective process leading to local invasion of the adventitia.[17] This, especially, is the pathogenetic mechanism in immunocompromised patients and patients undergoing immunosuppressive therapy following organ transplants. The transmitted blood pulsations on the luminal aspect of the weakened wall lead to its progressive dilatation.[2,9,15,19]

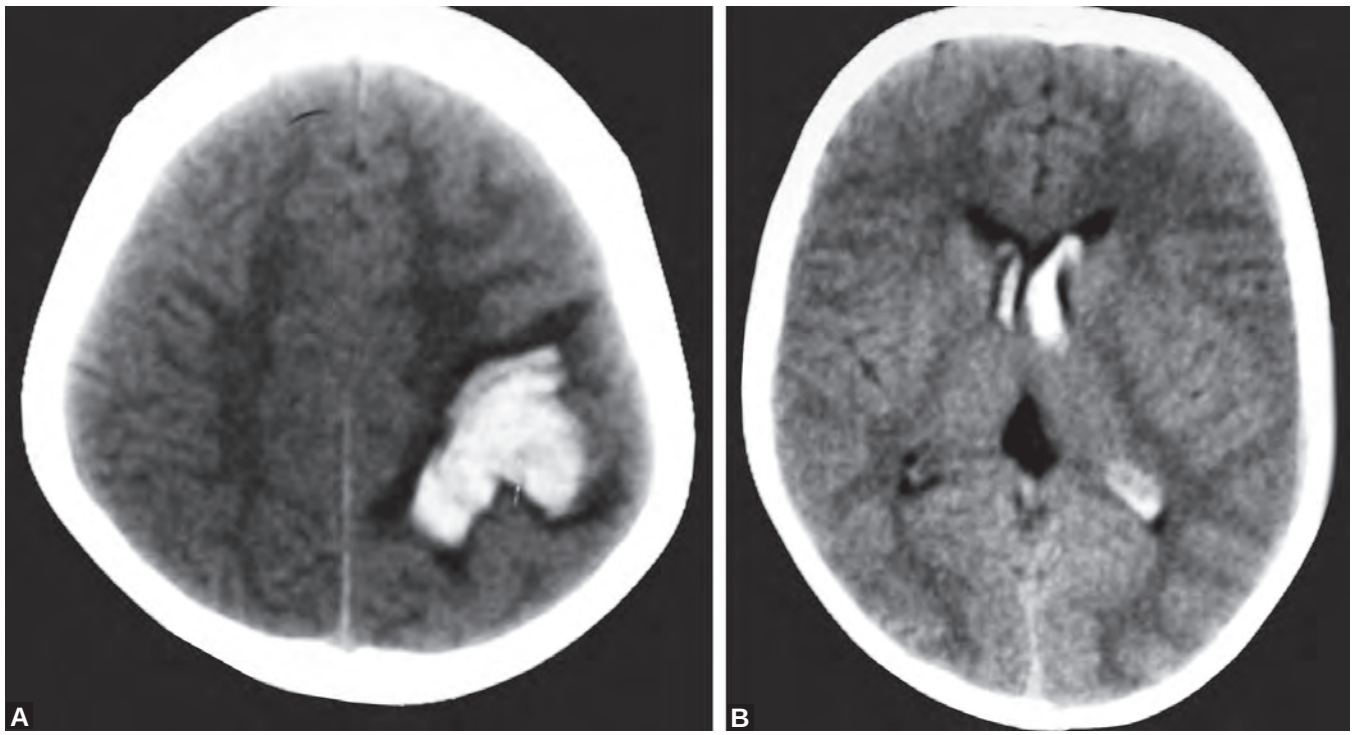
Patients with HIV infections, diabetes mellitus and immunocompromise are more likely to have fungal infections, while patients having a septic picture and multiple or distal aneurysms are more likely to be harbouring a bacterial aneurysm.[9]

CLINICAL FEATURES

The clinical profile of these patients varies. If unruptured septic intracranial aneurysms are present, then the patients may have a clinical symptomatology of sepsis without any signs pertaining to the central nervous system. In cases of spontaneous thrombosis or intracerebral haemorrhage, there may be focal signs based on territorial infarction. Subarachnoid haemorrhage may lead to sudden severe headache, neck stiffness or even obtunded sensorium. Early sentinel signs may often lead to an early identification of these lesions provided a high index of suspicion is maintained. Approximately 5% of patients with subacute bacterial endocarditis will develop an intracranial lesion, so any neurological changes warrant cerebrospinal fluid studies and CT/MR. These investigations may help in detecting a central nervous system infection, but are relatively insensitive for detecting infective aneurysms. Any abnormality in these studies in patients with neurological symptoms thus warrants angiography.

RADIOLOGICAL FEATURES

On digital subtraction angiography, the infective aneurysms may be single or multiple. The anterior circulation is involved more often than the posterior circulation. In the series by Chun et al., the commonest site was the distal middle cerebral artery (at or beyond



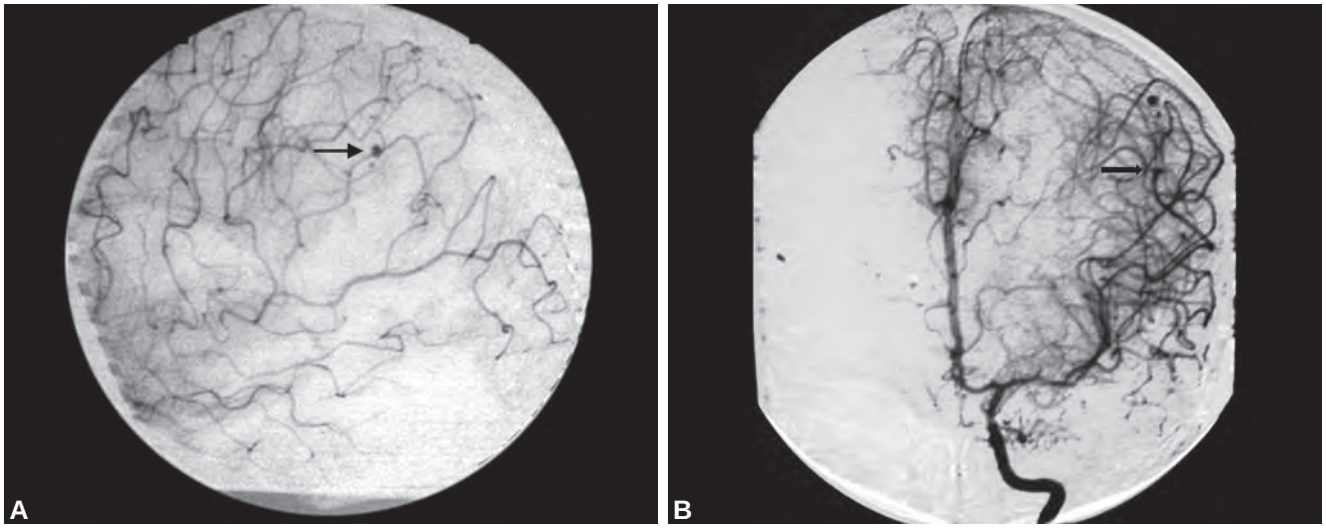
Figs 1A and B: Plain axial CT scan showing a left parietal haematoma with intraventricular haemorrhage in an 11-year-old child with rheumatic heart disease

the trifurcation), followed by the M1 segment and the distal anterior cerebral artery.[6]

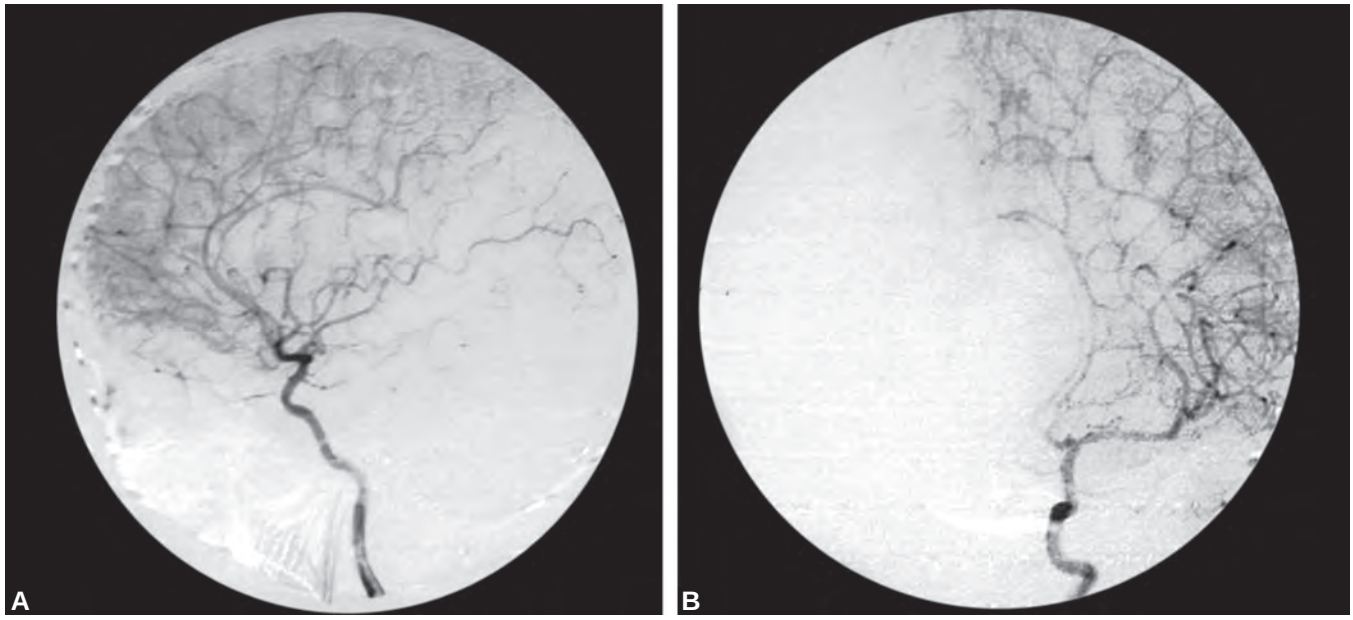
These aneurysms are typically fusiform and irregular, without the neck that characterises saccular aneurysms (Figs 1 to 4).[4,10] The diagnosis of an infectious aneurysm is fairly straightforward in the cases when endocarditis is associated with distal aneurysms. When evaluating proximal aneurysms, a combination of radiological findings may help in diagnosing an infectious aneurysm. These include arterial stenosis or occlusion close to the aneurysm, the presence of multiple aneurysms and rapid morphological changes within the aneurysm. CT angiography may be a less invasive and quicker technique to serially follow-up the infectious aneurysm.[1]

MANAGEMENT ALGORITHM

Suspecting the diagnosis helps in initiating early treatment but may be difficult in patients without endocarditis. Chun et al.,[6] Dowd and Awasthi[9] and Phuong et al.[23] have given the management algorithm for management of infective intracranial aneurysms (Flow chart 1). The clinical decision making is based upon whether the aneurysm has ruptured; whether there is a haematoma

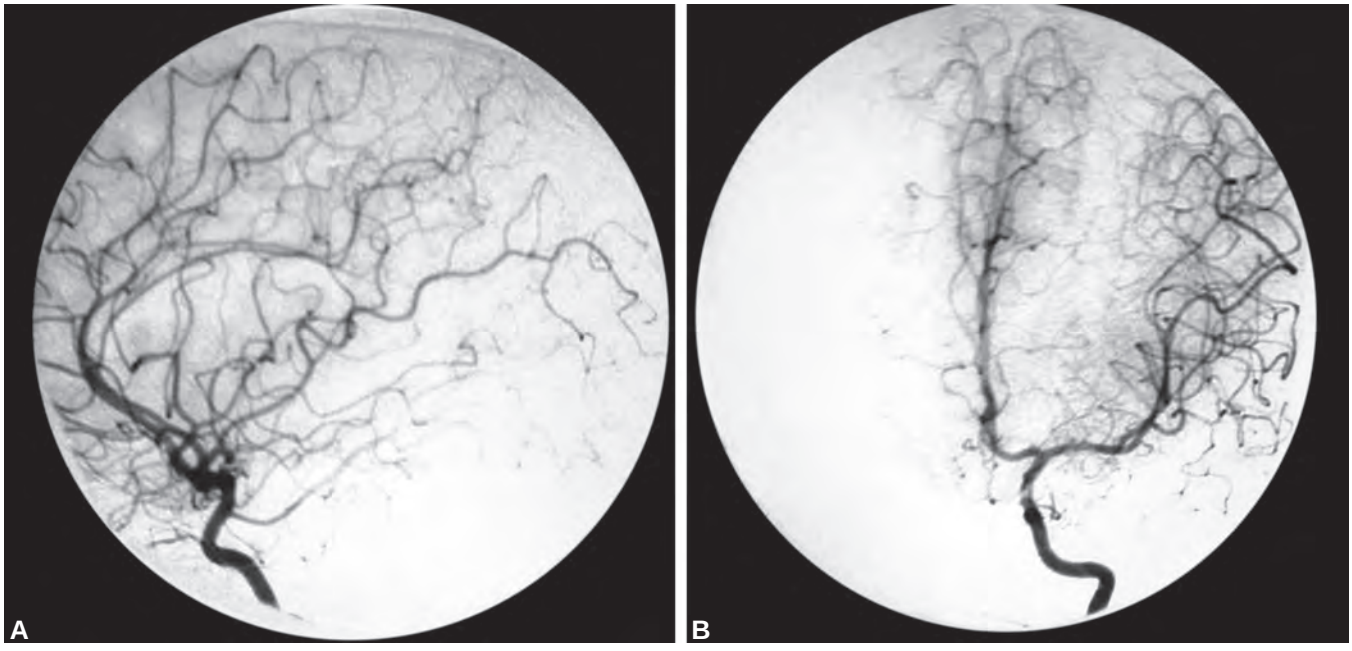


Figs 2A and B: (A) Lateral. (B) anteroposterior images of internal carotid artery angiogram showing an infected aneurysm arising from the posterior parietal branch of MCA. The aneurysm is small, sessile and situated on a peripheral vessel trunk without a branching vessel



Figs 3A and B: The angiogram after 6 weeks showing complete resolution of the aneurysm on antibiotic therapy

producing mass effect or increased intracranial pressure and whether the parent artery is supplying eloquent brain tissue. Serial angiograms are necessary in patients being treated medically after aneurysm detection, since the characteristics of infected aneurysms may change leading to six scenarios: (1) spontaneous resolution with preservation of the parent artery; (2) spontaneous resolution with thrombosis of the parent artery; (3) increase in size; (4) decrease in size; (5) unchanged size with the same morphological features (stable) or (6) unchanged size with different morphological features (unstable).[6] Thus, if there are neurological symptoms with bacterial endocarditis or sepsis (especially with the background of immunocompromise) then a contrast enhanced MR or CT scan with CSF studies is required. If it shows a positive intracranial finding, four-vessel angiography is performed to detect an intracranial aneurysm. If the angiography is negative, then medical treatment may be continued. If the angiography is positive for an infective aneurysm, but the patient has an unstable medical condition, such as severe sepsis or congestive cardiac failure rendering him unfit for surgery; or, there is no evidence of intracranial haemorrhage or neurological worsening, then he may be treated with antibiotics. In both the above scenarios, angiography should be repeated after 2–4 weeks. A patient harbouring an infectious aneurysm should be placed on appropriate antibiotics that achieve therapeutic levels in the central nervous system.



Figs 4A and B: The angiogram after 4.5 months showing that the infected aneurysm had not recurred

Flow chart 1: The algorithm for management of infectious intracerebral aneurysms
(Adopted from: Chun et al.,[6] Dowd and Awasthi[9] and Phuong et al.[23])

The correction of the cardiac disorder is also important in patients with infective endocarditis. The resolution of the aneurysm may occur on appropriate antibiotics often with preservation of the parent artery. Therefore, if an aneurysm is unruptured, or is in a difficult area to approach surgically or there are multiple aneurysms, then a trial of antibiotic therapy alone may be appropriate.[9]

Medically treated patients with enlarging or dynamic unruptured aneurysms; ruptured aneurysms in stable patients in surgically accessible areas especially in the presence of haemorrhage and mass effect causing neurological worsening are eligible candidates for surgical intervention or endovascular treatment.[4,6]

The choice of intervention between surgery and endovascular treatment may be decided by the algorithm suggested by Chun et al.[6] According to them, patients with ruptured aneurysms that are not associated with haematomas and that do not involve eloquent vascular territory are treated endovascularly. In patients who also require continuous heparinisation for their prosthetic cardiac valves, and those patients with compromised haemodynamic status, especially with acute endocarditis, endovascular intervention, is desirable. Patients are treated surgically when there is a haematoma or the risk of ischaemic complications in an eloquent territory. Therefore, endovascular therapy is the first choice for patients in stable condition with ruptured aneurysms; surgical therapy is the first option for patients in unstable condition with ruptured aneurysms and the second option for patients in stable condition who experience failure of endovascular therapy. Medically treated patients with enlarging or morphologically changing unruptured aneurysms also require direct surgical or endovascular intervention.

The aims of surgery are to eliminate the infectious aneurysms from the circulation, prevent ischaemic complications from arterial sacrifice and evacuate any associated haematoma. The surgical options available include trapping and resection of the aneurysm, trapping and bypass to the distal parent artery, direct clipping and wrapping of the aneurysm.[20,23,25] In contrast to primary aneurysms, surgery for these aneurysms is more difficult as these aneurysms are situated more often on peripheral blood vessel branches, the surrounding brain may be inflamed and oedematous (both due to the presence of infection and the haemorrhage) and the blood vessel wall is often friable. The aneurysm is often sessile and may be arising directly from the blood vessel wall without a neck. Attempted clipping of an acute, friable infected aneurysm can lead to clip erosion of the vascular wall as well as catastrophic peri-operative rupture. Occasionally, the only option left with the neurosurgeon for aneurysm exclusion from the parent vessel may be

trapping or excision of the parent blood vessel.[3] A bypass procedure may be mandatory in case the parent vessel is supplying an eloquent area of the brain. Endovascular management may also involve parent vessel occlusion after a test occlusion has negated the possibility of neurological deficits developing after the procedure. Harris et al. have described a special MRI technique to accurately localise the flow-related signal of a small infectious aneurysm masked by short T1 value/bright signal of the methaemoglobin in the intraparenchymal and extraparenchymal blood. This was done by mathematically subtracting a three-dimensional unenhanced MR angiogram from an identical < 30 seconds gadolinium bolus administered three-dimensional MR angiographic sequence. The subtraction angiographic MR image removed the high signal from the obscuring haemorrhagic components thus delineating the peripherally situated small mycotic aneurysm. With this technique, frameless stereotaxy was a useful adjunct in managing the infectious aneurysm.[12] Often, due to the small size of the infected aneurysm and the remoteness of the blood vessel that harbours it, frameless stereotactic navigation may not be helpful. In such cases, frame-based angiographic stereotactic localisation for distal aneurysms that cannot be treated endovascularly may be a useful technique.[8]

There has been a steady progress in the endovascular treatment and parent vessel occlusion is not always necessary. Improved microwires, microcatheters, stents and balloons have facilitated access to the distal circulation. Thus, balloon or stent assisted coil embolisation procedures may be used to maintain parent vessel integrity, although with some risk of rupture, given the fragility of the diseased parent vessels.[11,26]

The timing of intervention in infected aneurysms is vital. The patients harbouring these aneurysms may be systemically ill and anaesthesia may pose an increased risk; antibiotic treatment helps to reduce systemic infection as well as local inflammation in the arterial wall and facilitates clipping or coiling of the aneurysm.

BACTERIAL ANEURYSMS

In the series by Ojemann, the causative organism in bacterial aneurysms was *Streptococcus* in 51%, *Staphylococcus* in 21% and *Pseudomonas* in 3% of cases. Six per cent had multiple aneurysms and 14% had no growth.[21] Bacterial endocarditis, meningitis and cavernous thrombophlebitis have all been implicated in their causation.[4,17,23,25]

Therapy

The antibiotic therapy must be tailored to the culture and sensitivity profile of the patient's infection and the considerations of blood-brain barrier penetration of various antibiotic regimens. It should be administered for a minimum of 6 weeks.

Approximately 30–50% of infective aneurysms resolve with antibiotic therapy alone due to spontaneous thrombosis of the involved vessel. Ten to thirty per cent of patients may have a new aneurysm developing or the pre-existing aneurysm enlarging despite antibiotic therapy. Therefore, repeat angiography after 2–4 weeks is recommended to rule out new aneurysms. The risk of rupture and its consequent morbidity should be weighed against the chances of spontaneous resolution. Since the mortality from aneurysmal rupture varies between 60% and 90%,[11,23] in case an unruptured aneurysm is surgically accessible and the patient does not have septicaemia, a pre-emptive surgery or therapeutic embolisation should be considered. Patients who have clinical deterioration or in whom the angiogram shows progression of the aneurysm should also be treated surgically. Attention should also be focussed on the cardiac cause of the septic focus. A combined staged repair of the cardiac and neurological lesions with the timing based on which one is the more stable lesion often leads to a successful outcome.

FUNGAL INFECTIONS

Fungal infections are rarer and usually spread by contiguity from basal meningitis, following a surgical procedure or from paranasal infections. Therefore, they are found on more proximal intracranial vessels compared to the bacterial aneurysms. Diabetics, patients with widespread prolonged sepsis, intravenous drug abusers or immunocompromised patients are particularly susceptible to develop these lesions.[1] Embolisation from bacterial endocarditis may also occur. Finally, "a primary or cryptogenic mycotic aneurysm" occurring in the absence of an obvious inflammatory reaction may also occur. The common organisms were *Aspergillus*, *Phycomycetes* and *Candida*.[9,13,14,16,18] The antifungal therapy must be tailored to the organism identified and the considerations of blood-brain penetration. The prognosis is grave due to widespread disease or aneurysm rupture. In stable patients, surgery may be considered for taking care of accessible aneurysms, expanding lesions or those that fail to resolve with follow-up imaging and for those that demonstrate evidence of haemorrhage or mass effect.

VIRAL INFECTIONS

There is no conclusive evidence that viral infections cause aneurysm formation. However, the increasing frequency of aneurysm formation with age, the seasonal incidence of aneurysm rupture and increased incidence of aneurysm detection in children with HIV, especially during the periods of increased viral load, may point towards the implication of viral infections in aneurysm formation.[9,27] Furthermore, HIV may produce large vessel coagulopathy and intimal invasion with HIV containing mononuclear cells.

To conclude, an algorithm for the management of infective intracranial aneurysms is given. A high index

of suspicion in susceptible cases facilitates their earlier detection with early institution of antibiotic and surgical/endovascular therapy and thus prevents morbidity. Given the often changing nature of the aneurysm, repeat angiograms are mandatory during their management.

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89 Intracavernous Aneurysms

BS Sharma, VS Mehta

INTRODUCTION

Intracavernous aneurysms constitute about 5% of all intracranial aneurysms. Middle aged females are affected five times more commonly than males. These aneurysms may be true or false. The true aneurysms may be purely within the cavernous sinus or transitional. In true intracavernous aneurysms, the neck and dome of the aneurysm are contained within the cavernous sinus.[1] Rupture of true intracavernous aneurysms may cause spontaneous carotico-cavernous fistula (CCF).[28] False aneurysms are secondary to head injury or following internal carotid artery (ICA) injury during trans-sphenoidal or cavernous sinus surgery.[4,10] In the transitional variety, the aneurysm extends into the subarachnoid space. Intracavernous aneurysms may be saccular or fistulous. Fistulous aneurysms may be spontaneous or traumatic. About 15–20% is bilateral and 15–20% have associated aneurysms. Intracavernous aneurysms enlarge insidiously and are frequently of giant size. Management of these aneurysms is difficult and pose a major challenge due to their intracavernous location, giant size, presence of atherosclerosis/thrombosis/calcification, broad neck and incorporation or origin of a major branch or perforator from the neck of the aneurysm.

CLINICAL FEATURES

Intracavernous aneurysms present with the clinical features as mentioned below.

Cranial Neuropathy

Cranial nerve deficit from II to VI alone or in combination occurs due to mass effect causing progressive visual loss, decreased visual acuity, field defects, diplopia, blepharoptosis and/or ophthalmoplegia. Proptosis, chemosis and bruit occur in spontaneous CCF. Parasellar syndromes[9] which consist of pain in V1 and V2 and paresis of one or two extraocular muscles are also due to mass effect. Rarely, they may present with bilateral VI cranial nerve paresis,[5] and as Tolosa-Hunt syndrome, with recurrent intolerable retro-orbital pain, ptosis and diplopia due to oculomotor nerve and abducent nerve involvement.[31] Bilateral intracavernous segment ICA aneurysm simulating pituitary apoplexy has been reported.[25]

Pain

Causes of the pain associated with intracavernous aneurysms are:

- Headache is caused by local irritation of the dura
- Retro-orbital pain which is caused by trigeminal nerve compression by aneurysm mass
- Facial pain is caused by episodes of distension or enlargement of the aneurysm and involvement of the trigeminal nerve. It may be severe, intractable and episodic.

Subarachnoid Haemorrhage

Subarachnoid haemorrhage (SAH) occurs in transitional cavernous aneurysm.

Epistaxis[13,22,24]

In false aneurysms secondary to trauma, massive, delayed and life-threatening epistaxis is a leading symptom. In the presence of blindness or blurring of vision, recurrent epistaxis and fracture of the skull base following trauma, early angiography should be performed.

Transient Ischaemic Attacks

These are caused by thromboembolism.

INVESTIGATIONS

In addition to conventional angiography, three-dimensional (3D) computed tomography angiography (CTA), slow injection angiography, aneurysmography and balloon test occlusion (BTO) are useful in determining the method of treatment. At angiography size of the aneurysm, width of the neck, origin of a branch or perforator from the neck, presence of thrombus and other aneurysms, presence of waist deformation and collateral circulation should be studied (Fig. 1). Waisting seen at angiography indicates extension of the aneurysm into the subarachnoid space,[29] either through the dural ring or eroded dural roof of the cavernous sinus. The waist indicates that rupture would be life-threatening. Deformation of the aneurysm may be due to compression against the optic nerve or anterior clinoid process (ACP) with an intact dura. Computerised tomography (CT) scan is useful in detecting bony erosion, SAH and

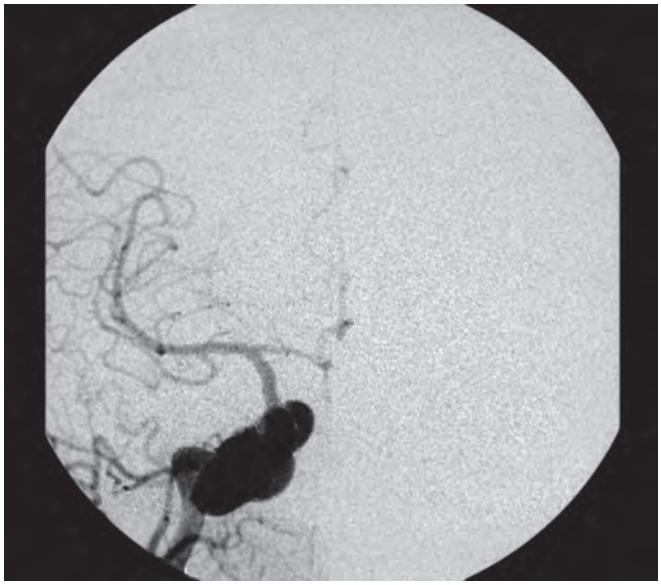

Fig. 1: Digital subtraction angiography showing intracavernous aneurysm

calcification. Magnetic resonance (MR) (Fig. 2) detects the presence of thrombus. Krings et al.[11] described a patient with an intracavernous aneurysm in whom the area of increased aneurysm pulsatility as demonstrated by high-temporal resolution dynamic CT angiogram using a 320-detector row CT, was identical to the area of aneurysm growth on follow-up. They hypothesise that this technique may predict aneurysm growth and may, therefore, be helpful in the non-invasive *in vivo* assessment of individual aneurysm features such as dome and bleb pulsations in both unruptured and ruptured aneurysms.

TREATMENT

Indications for Treatment

The indications for treatment are:

- Diminution of vision
- Severe intractable facial pain

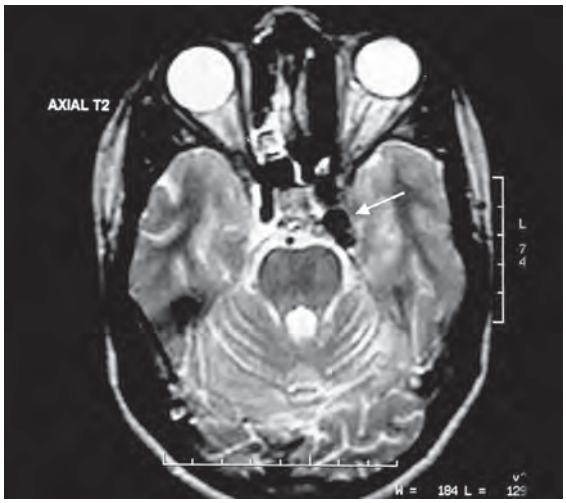

Fig. 2: Magnetic resonance imaging showing intracavernous aneurysm

- Progressive ophthalmoplegia
- Evidence of enlargement of aneurysm
- Transient ischaemic attacks
- Presence of waist in angiogram
- Risk or presence of SAH
- Risk or presence of epistaxis.

Asymptomatic or minimal symptoms of compression can be observed, especially in elderly patients.

METHODS OF TREATMENT

The aim of treatment is exclusion of the aneurysm from the circulation and preservation of efferent flow. This can be achieved by endovascular techniques or surgery. Bavinzski et al.[3] in their study divided 48 patients with cavernous carotid aneurysms into two subgroups by location. Morphological features in both groups correlated well with differences in clinical presentation and also influenced therapy.

1. Group I—In this group, aneurysms arose from the C3 portion, were small and saccular, with an epidural partly intracavernous location. This group was well-suited for endovascular obliteration.
2. Group II—In this group, aneurysms arose from the C4-5 segment, were usually large or giant and often fusiform with a true intracavernous location. These can be treated with direct or indirect surgery, or endovascular methods. Stiebel Kalish et al.[21] reported a large cohort of carotid cavernous aneurysms (CCA), comparing the neuro-ophthalmic presentation, complications and outcome with and without endovascular treatment. The results of 185 patients with 206 CCA were reviewed. Seventy-four CCA underwent treatment [endovascular, 67 (91%); surgical treatment, 6 (9%)], and 115 were followed for an average of 4 years, two of whom required treatment later. Statistical examination revealed that the treated group had a higher proportion of neurological and visual complications than people who were not treated. They concluded that endovascular treatment of CCA leads to a significantly higher rate of pain resolution compared with untreated patients, even after adjusting for initial pain severity. Diplopia may not resolve after treatment. The results of their study underscores our approach indicating treatment only in cases of debilitating pain, visual loss from compression, or diplopia in primary gaze or in patients with risk factors for major complications such as pre-existing coagulopathy or sphenoid sinus erosion. Vasconcellos et al.[27] analysed a group of patients with internal carotid aneurysms in the intracavernous segment. Patients were divided into two stratified groups, one with 19 patients who underwent interventional treatment, and another with 21 patients who were conservatively treated. Their study demonstrated that intervention is significantly correlated with a better prognosis considering evolution of pain symptoms secondary to neurovascular compression (p = 0,002).

Regarding neurological deficits, an interventionist approach was also significantly correlated with better outcome in comparison with initial presentation (p = 0,008). Their results indicate that interventional treatment determines improvement or resolution of pain symptoms in comparison with patients conservatively treated, as well as stabilisation or partial improvement of neuro-ophthalmological deficits.

Endovascular Technique[3,4,26]

Selective endovascular occlusion[28] with detachable balloon or Guglielmi detachable coils via the arterial route or electrothrombosis by detachment of platinum coils via the transvenous approach can achieve the objective. Proximal segment cavernous ICA aneurysms (C3 position) with a definable and narrow neck are better suited for endovascular treatment.[3]

Endovascular treatment of giant and large aneurysms by using a combination of stent placement and liquid polymer injection has been successful.[12] The metallic stent is first placed across the neck of the aneurysm to reconstruct a tubular arterial lumen, followed by obliteration of the fundus with ethyl vinyl alcohol polymer. This excludes the aneurysm from the circulation with preservation of the parent artery. Kadyrov et al.[10] treated an intracavernous ICA pseudoaneurysm following trans-sphenoidal surgery with stent assisted coil embolisation. Appelboom et al.[2] reported a unique case of wide-necked mycotic intracavernous large aneurysm treated with a new generation of intracranial flow-diverting, endoluminal implant placed across the aneurysm neck without coiling. Angiographic controls showed complete thrombosis of the aneurysmal sac with dramatic improvement of symptoms. Follow-up magnetic resonance imaging (MRI) and digital subtraction angiography 3 months after the procedure, confirmed total occlusion of the aneurysm with normal circulation in the parent vessel.

Surgical Treatment

Surgical treatment of aneurysms can be done in two ways:

A. Direct surgical methods
B. Indirect surgical methods

Direct Surgical Methods

These include clipping or resection followed by ICA wall reconstruction. Direct clipping is recommended in aneurysms with a definable neck arising from the anterior genu segment and in the transitional variety. The cavernous sinus can be approached intradurally or extradurally (ED). The ED approach[6] provides complete exposure and good proximal control of the ICA.

Pre-operatively, good cross-circulation through the anterior communicating artery and retrograde filling of the ICA through the posterior communicating artery is desirable, so that temporary occlusion of the ICA can be tolerated. However, this operation should not be contemplated in poor risk or elderly patients.

The cavernous sinus is approached directly using a combination of three different techniques:

1. Pterional exposure of the ICA
2. Subtemporal exposure of the ICA
3. Extradural petrosal exposure of the ICA

The sphenoid wing is removed to the ACP. The ACP, optic canal (superior and lateral aspect) and optic strut are drilled. The intrapetrous segment of the ICA is exposed in Glasscock's triangle bounded by the middle meningeal artery, the arcuate eminence and the greater superficial petrosal nerve. The middle meningeal artery is coagulated and ligated. The greater superficial petrosal nerve is interrupted and the bone over the ICA between these three landmarks is removed with a diamond burr, unroofing the anterior and superior aspect of the ICA. The bony canal of the Eustachian tube, located lateral to the ICA, is opened and its soft components are left intact. The entire circumference of the ICA inside the petrous bone is exposed for a possible temporary clipping.

The dural incision is made along the sphenoid wing and continued down to the clinoid process and extended to the optic nerve and to the foramen spinosum along the outer margin to the cavernous sinus. The temporal lobe is retracted and the tentorial edge is exposed from the clinoid process to the entrance of the IV nerve. The III and IV nerves are separated from the tentorial edge at the point where they enter the lateral dural wall of the cavernous sinus and followed to the superior orbital fissure. The outer layer of the lateral dural wall of the cavernous is dissected from the III, IV and V nerves and turned in one piece. The incision of the dura of the lateral wall of the cavernous sinus is started at the entrance point of the IV nerve, continued forward along the tentorial edge to the entrance point of the III nerve and is extended along the superior orbital fissure and inner aspect of the lateral margin of the lateral wall of the cavernous sinus to the foramen ovale. The V nerve is dissected from the Gasserian ganglion by lifting the posterior part of the dural layer consisting of the outer layer of the lateral wall of the cavernous sinus. The first division of the V nerve is followed to the supraorbital fissure, the second division to the foramen rotundum and the motor branch and third division to the foramen ovale. The ICA is dissected from the ophthalmic artery backwards along the sella turcica by packing the cavernous sinus with surgicel along the medial aspect of the ICA. Dissection of the horizontal part of the intracavernous ICA is carried out meticulously using Glasscock's techniques. This provides complete exposure of the ICA from the petrous bone to the supraclinoid portion. The neck of the aneurysm is defined and clipped. Multiple fenestrated clips are particularly useful or the aneurysm may be resected and the ICA reconstructed using sutures. The parent ICA lumen must be kept patent. The cavernous sinus is covered with the dural flap which

is sewn down along the previous incision. The bony canal of the Eustachian tube is packed with bone wax and the intrapetrous part of the ICA is covered with a muscle flap taken from the temporalis muscle. Romani et al. reported a case of intraoperative rupture of an intracavernous carotid aneurysm caused by clinoidectomy, which was repaired by using a single-clamp applicator, i.e. anastoclip vessel closure system, 1.4 mm.[15]

Indirect Surgical Methods

Proximal parent vessel occlusion or trapping is indicated in aneurysms with a poorly definable neck, origin from the proximal cavernous segment of the ICA, traumatic aetiology, fusiform aneurysms and when direct surgery is not feasible or carries a high-risk.

Before the ICA can be sacrificed, it is necessary to assess collateral flow by angiographic BTO of the ICA. This may be supplemented with electroencephalography (EEG), transcranial Doppler (TCD), cerebral blood flow (CBF) studies using direct intracarotid injection of Xenon, distal ICA pressure measurements and single photon emission computerised tomography (SPECT) studies. The BTO is performed under light sedation. The BTO is deemed successful when there is good clinical tolerance and there is adequate angiographic collateral circulation in the arterial, parenchymal and venous phases with symmetric filling of both hemispheres (Fig. 3). Additional criteria include no change in EEG, CBF of greater than 35 ml/100 gm/min, distal carotid pressure greater than 60 mmHg and symmetric perfusion in SPECT. If collateral flow is inadequate, suggested by development of neurological deficit, poor filling in angiography, changes in EEG, CBF less than 20 ml/100 gm/min and asymmetric perfusion on SPECT, an external carotid-internal carotid (EC-IC) bypass procedure is needed.

Carotid ligation is also contraindicated in patients with recent SAH, poor Hunt and Hess SAH grade, hypovolaemia, cerebral vasospasm and/or intracerebral haematoma. Relative contraindications include presence of atherosclerosis or aneurysms in the contralateral ICA.[1]

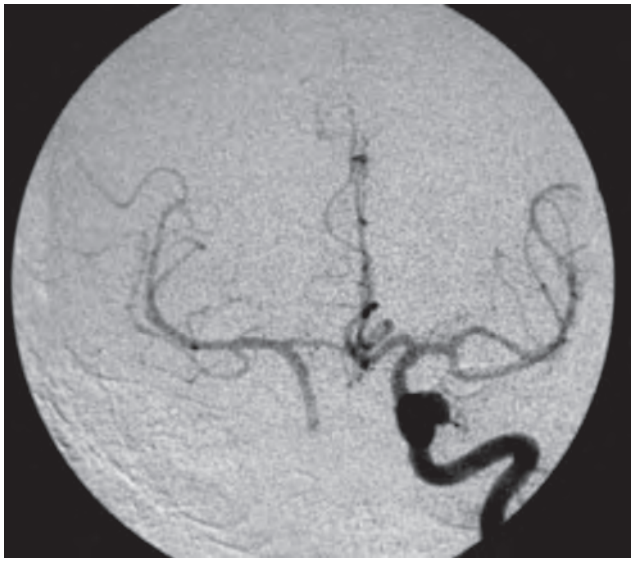

Fig. 3: Digital subtraction angiography showing good cross-circulation

Proximal Internal Carotid Artery Occlusion

Occlusion of the proximal internal carotid artery by balloon or ligation in the neck is the simple traditional method. Gradual ICA occlusion in the neck is performed with a Silverstone clamp. Adequate hydration is ensured. Aspirin is started to prevent thromboembolism. The angiogram is repeated after 3 months. If the aneurysm fills, trapping is performed. It is not a preferred method, but may be used in patients in advanced age, high medical risk and proven adequate collateral flow. After ICA occlusion, induced hypertension, anticoagulants and increase of circulating blood volume to minimise the risk of delayed thromboembolism is advocated. Common carotid artery (CCA) ligation preserves some ICA flow through the external carotid system and so the risk of ischaemia is less as compared to ICA ligation. ICA ligation provides a better reduction of aneurysm pressure and high rate of aneurysm thrombosis as compared to CCA ligation.

Trapping

ICA occlusion by balloon or ligation proximally in the neck, and distally proximal to the ophthalmic artery may be performed in patients presenting with haemorrhage or mass effect. This allows emptying of the aneurysm to reduce the mass, and minimises the risk of ischaemia caused by thromboembolism by reducing the dead space.

Immediate symptomatic relief is obtained by loss of aneurysm pulsations and pressure. Aneurysm thrombosis occurs in the first post-operative week, but retraction is maximal after several months and can be monitored by MR angiography.

External Carotid-Internal Carotid Bypass[16-30]

Indications

- In patients treated by ligation or trapping who have inadequate collateral circulation, i.e. failed BTO
- In patients with unclippable aneurysms, who have long-life expectancy or are young, hypertensive, and/or have bilateral or associated aneurysms. The EC-IC bypass preserves ipsilateral cerebral vascular reserve
- Failure of endovascular or clipping treatment
- Interposition high flow saphenous vein graft (SVG) from the proximal ICA or external carotid artery (ECA) in the neck to the middle carotid artery (MCA) bifurcation is the preferred procedure. Petrous ICA to supraclinoid ICA bypass requires temporary occlusion of the ICA during the anastomosis for 90–120 minutes and is not preferred.[18-20] Radial artery graft (RAG) from the carotid to the MCA may be used,[8] but two grafts to major MCA branches are required. Superficial temporal artery to middle cerebral artery

(STA-MCA) anastomosis itself may not be sufficient, but can supplement the already present collateral flow.

PRE-OPERATIVE EVALUATION

Cardiac functions, cerebrovascular disease, hypercoagulable states and coagulation parameters are evaluated. Angiography with cervical compression or balloon occlusion is performed to assess vascular anatomic features and collateral circulation to know the tolerance to temporary occlusion.

ANAESTHESIA

The brain should be lax. Prior to clamping the recipient vessel 2000 units of heparin, mannitol, phenytoin, methyl prednisolone, fentanyl and propofol are given. During occlusion the blood pressure is raised 20% above the baseline and mild hypothermia of 34°C is maintained.

SUPERFICIAL TEMPORAL ARTERY TO MIDDLE CEREBRAL ARTERY ANASTOMOSIS

Patients should be properly selected and careful attention should be given to peri-operative details to minimise complications.[7]

Technique

Donor (Superficial Temporal Artery Dissection)

The donor vessels should be of greater than 1 mm lumen diameter. Anterior or posterior branches of the STA are identified by palpation and Doppler ultrasonography and are externally marked. A linear incision is made directly over the distal artery. The initial cut passes through the skin and dermal fat. The edges of the wound are retracted and elevated with skin hooks and the dissection is continued proximally exposing the external surface of the STA in its entire length. A 1 cm pedicle of supporting tissue is prepared along with the artery. The pedicle is elevated from the temporalis fascia. The proximal and distal ends are left *in situ* to allow continued flow of blood. The artery is bathed in 3% papaverine saline until it is used for anastomosis.

Intracranial Exposure

Through the same skin incision used for STA dissection, the temporalis muscle and fascia are divided into anterior and posterior leaflets. A free bone flap of 5–6 cm size is raised. The proximal Sylvian fissure is exposed and split. An accessible 15 mm segment of the MCA which is free of branches is isolated over a latex dam.

A temporary clip is placed on the proximal STA pedicle and the distal end is sectioned. The entire pedicle is rotated to the recipient MCA site. An extra 1 cm length of STA is mobilised to compensate for brain displacement when cerebrospinal fluid is let out. The distal end of the STA is dissected off all the supporting tissue. A fresh cut is made across the distal end of the artery and its patency is checked by releasing the proximal STA clamp transiently. After irrigation with heparinised saline, the free end of the STA is fish mouthed to approximately twice the diameter of the vessel.

The dissected MCA segment is isolated between two temporary clips. A linear arteriotomy (two times STA diameter) is made and is irrigated with heparinised saline through a venflon. With 10-zero nylon on a BV-6 needle microsuture, the base of the fish mouth is sewn to the distal end of the MCA incision. The apex of the oblique cut end of the STA is sutured to the proximal end of the MCA arteriotomy. This directs flow towards the proximal portion of the MCA. About six to eight independent microsutures are taken through the arterial walls. Posterior wall suturing is difficult, so it is performed first. After placement of all sutures, each suture is tied with four knots. Before tying the last suture the STA clip is transiently released to allow residual debris to be dislodged through gaps in the anastomosis. The clips are removed individually to allow back bleeding of each end into the anastomosis site. Significant leaks are closed with isolated microsutures. A small amount of bleeding from the anastomosis can be controlled with surgicel or gelfoam. If the patency of the anastomosis is in doubt, a few sutures are removed and the clips are released for direct inspection of back bleeding and the fault is corrected. The STA-MCA bypass alone may be inadequate to prevent a stroke after acute ICA occlusion in patients with poor collateral circulation.

Internal Carotid Artery or External Carotid Artery-Middle Cerebral Artery Bypass Using a Graft

Saphenous Vein Graft Harvesting

The technical aspects of harvesting and preparation are crucial to long-term success. The saphenous vein may be harvested from the leg or thigh depending upon the calibre of graft required. It is harvested from the leg due to a better match for the vertebral artery (VA), posterior cerebral artery (PCA) and MCA. The lower limb is positioned externally rotated at the hip and flexed at the knee. The incision is made 1 cm anterior to the medial malleolus. In the groin, used for carotid circulation grafts, the skin is incised directly over the vein. The vein is found medial to the femoral pulse near the fossa ovalis two finger breadths lateral and inferior to the public tubercle, up to the adductor tubercle. The delicate layer of areolar tissue under the skin is incised sharply 5 mm from the wall of the vein. This leaves stumps of branches for ligation with 4-0 ligatures. Holes in the graft are repaired with 7-0 prolene mattress stitches. Prior to ligation of the branches and mobilisation, 5-0 prolene or marking pencil is used for Garrett orientation line to avoid twisting and kinking. The vein is dissected and mobilised, but left *in situ* covered with cottonoid soaked in 3% papaverine until extraction. The vein should not be grasped with forceps. After extraction, the lumen is flushed with heparinised solution and distended to

fracture of the wall. The flow rate in SVG is high and creates turbulence. Veins greater than 1 cm are more prone to thrombosis due to slow flow (Poisellile's law).[14]

Radial Artery Graft Harvesting

The arm is extended and supinated. An incision is made just lateral to the biceps tendon in the cubital fossa skirting the belly of the brachioradialis up to just lateral to the flexor carpi radialis tendon. Dissection is started at the wrist first, proceeding proximally between the muscle layers up to the bifurcation of the brachial artery. Venae comitantes are preserved except 2 cm at either end. The branches are ligated, clipped or cauterised. The artery is left *in situ* covered with moist packs of papaverine until extraction. Before extraction, a temporary clip is placed on the artery and a Doppler probe is placed on the palmar arch to confirm adequate flow. After extraction a blunt needle is introduced into the lumen of the artery and is distended with pressure using heparin solution until the artery visibly pops and distends. The artery is then plicated over a blunt needle and the procedure is repeated from the other end.

The superficial temporal, occipital and superior thyroid artery may also be extracted for interposition grafting. The VA can be used as a donor when it is of sufficient size and can be occluded for 30 minutes and the other VA is not hypoplastic or absent.[17]

The RAGs do not undergo denudation as SVG do because it has arterial endothelium. Arteries do not have valves, so remain open even at low flow rates. This low flow rate can be an advantage to avoid hyperaemia in ischaemic brain, but may not prevent stroke after acute occlusion. Flow through RAG is less (40–70 ml/minute) than through SVG (70–140 ml/minute) so a single RAG is not sufficient to prevent stroke in patients with no collaterals and in such cases two RAGs (one from ECA and other from ICA) to each major branch of MCA or SVG is required. Best diameter ratio of donor/recipient is 1.6:1 for patency. This is best matched between the posterior inferior cerebellar artery and STA. Due to a thicker wall, RAG is easier to perform. The RAG is easier to keep open compared to SVG because the arterial endothelium does not undergo denudation and can support the slower flow through them and less turbulence is created. Spasm is the most important problem responsible for failure, which can be prevented by calcium channel blocker prophylaxis and "pressure distension technique" and can be treated by angioplasty. The radial artery is a good thickness and diameter match for MCA/PCA. When the recipient artery is less than 2.5 mm, a RAG is best.

Anastomosis

Distal anastomosis is performed first because blood in the graft makes it more difficult, if proximal anastomosis is performed first. A frontotemporal craniotomy is performed and the Sylvian fissure is split. The main trunk of the MCA and its major branches are isolated. The arteries are coated with papaverine soaked cotton. A rubber dam is placed under the arteries. The MCA bifurcation is the ideal location for anastomosis because it orients blood flow along the axis of the MCA reducing turbulence. The proximal end of the vein or distal end of the RAG is obliquely divided. The main trunk of the MCA is occluded distal to the lenticulostriate perforators and its branches are also occluded. A 5 mm arteriotomy is done at the bifurcation. The lumen is flushed with heparinised saline. The vein graft or artery is anchored to the arteriotomy at both ends with 8-0 prolene/nylon sutures. During suturing only the adventitia should be held. About six to eight interrupted sutures are passed through approximating the vessel walls. Interrupted sutures take more time, but provide better approximation without leak or stenosis at the suture line. The loops are left long and tightened at the end of the procedure, allowing better inspection of the edges of the arteriotomy and venotomy. The graft is flipped over and sutures are applied through the other wall. Before the sutures are tied, the graft and arterial segment are flushed with heparinised saline.

Temporary clips on the MCA are released to allow back bleeding into the anastomosis and the suture line is inspected for leaks. Large leaks require additional sutures, whereas small leaks are controlled with gel foam. The graft is temporarily occluded close to the recipient artery and flow through the recipient artery is resumed after the distal anastomosis.

Since the pre-auricular tunnel takes a sharp turn, a post-auricular tunnel is preferred and the subcutaneous tunnel is made with Mayo's scissors. The graft is passed through the tunnel via a small diameter chest tube.[17]

Proximal anastomosis is performed with 7-0 prolene. The ECA or ICA is dissected in the carotid triangle in the neck. The ECA should be exposed at least 2 cm from the common carotid bifurcation and the ICA for at least 3 cm from the bifurcation or up to the XII cranial nerve which lies below the belly of the digastric muscle and superficial to the ECA. The ECA is used as the donor in patients with no or poor collaterals. The ICA is used as the donor, if there are at least some collaterals and the ICA can be safely occluded temporarily.

The carotid is isolated and arteriotomy performed. An oblique tear drop shaped 8 mm arteriotomy or venotomy in the free end of the graft is made by bevelling and fish mouthing. In case of size discrepancy, the graft is anastomosed to the carotid end to side to reduce turbulence. This anastomosis is performed under slight tension because the vein expands after resumption of arterial flow. The proximal clamp on the artery and the temporary clip on the graft are released. The carotid distal to the graft is occluded with a clip or ligated. If the vein graft is attached to the ECA, the ICA must be occluded or artificially narrowed by placing a tie and clamp to reduce the flow through the vessel to maintain patency of the graft. The ICA then can be occluded permanently with endovascular technique or ligated. Intraoperative assessment of flow through the graft is

done by TCD. Intraoperative angiography is performed after dural closure and the speed of flow is assessed, which must be faster through the graft than through the ECA.

If flow through the graft is poor, the graft is incised 2 cm proximal to the distal anastomosis and flow through the graft is assessed from both ends. If flow from the distal end is poor, the anastomasis must be revised.

Cervical to supraclinoid ICA bypass is performed when the MCA is not suitable for anastomosis. The ICA is occluded proximal to the ophthalmic artery and is sectioned. The cut vessel is sutured shut with 7-0 prolene. One clip is applied to the posterior communicating artery. The cut end of the ICA is fish mouthed. The vein is anastomosed end to end with 7-0 prolene. The needle should pass through both the intima and media to avoid dissection. A temporary clip is placed on the graft and the vein graft is brought out through a wide dural opening into the clinoidal space. A pexy of the graft may be required to prevent kinking.

The C5-C3 bypass for cavernous ICA is the shortest possible length and is a large calibre high flow venous graft entirely within the skull avoiding pressure on the venous graft during movement of the head. The distal anastomosis is in the ICA between the ophthalmic and posterior communicating arteries. Proximally the petrous portion of the ICA is exposed just posterior to the foramen ovale and medial to the foramen spinosum. This technique has the advantage that it is a high flow graft from one large artery to another. Trapping of the cavernous ICA is immediately adjacent to the proximal and distal ends eliminating vascular dead space, which may encourage thrombus formation leading to delayed complications. However, 90–120 minutes of temporary occlusion of the ICA is required for both proximal and distal anastomosis and is a major disadvantage.[18,19]

Closure

A cruciate dural incision is made for entry of the graft to prevent occlusion. Fibrin glue is used for a watertight seal. Careful epidural haemostasis is performed with bipolar diathermy, dural hitch sutures, gelfoam or surgicel, because considerable oozing can occur after heparinisation. The adventitia of the graft can be sutured to the dural edges. Graft flow is assessed along the tunnel after closure using a Doppler probe. The site of the tunnel is marked for further assessment.

POST-OPERATIVE MANAGEMENT

Normovolaemia is maintained. Heparin (5,000 units) is given subcutaneously for 7 days and then aspirin 325 mg orally for 1 month in RAG and for life in SVG. Graft patency is assessed by palpation with a finger behind the mastoid, TCD, MRI and MRA. Follow-up angiogram is performed within 1 week after surgery. 3D CTA and/or arteriography are advised at 3 months and then yearly (Fig. 4). Phase contrast MR is useful in evaluation of cerebral circulation in the area supplied by the bypass. In high flow grafts, mild hypotension is used to avoid breakthrough bleeding in the first 24 hours. Intraoperative angiography allows immediate recognition and correction (salvage procedures) of graft related problems.

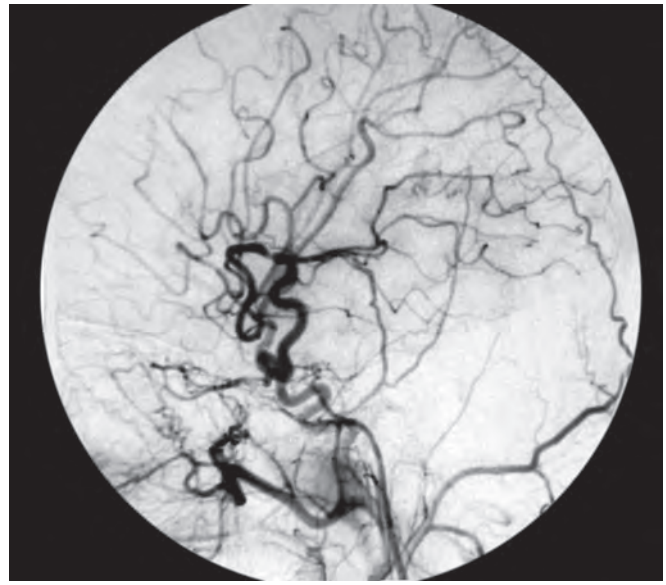

Fig. 4: Digital subtraction angiography showing functional superficial temporal artery to middle cerebral artery anastomosis

COMPLICATIONS

Epidural, subdural or intracerebral haematoma may occur due to the use of intraoperative heparin. Infarcts may be deep-perforator related from temporary occlusion or hemispheric due to hypoperfusion, embolism, graft occlusion, vasospasm or meningitis in patients with poor collateral, inadequate protection during surgery or protracted vascular occlusion. Poor outcome or ischaemic complications are highest in the posterior circulation.

GRAFT PROBLEMS[17,23]

Shortest possible length of the graft and end to end anastomosis at both ends are preferred to reduce the turbulent flow. Annual occlusion rate is 1–1.5%. The RAGs have better long-term patency rates.

Use of the operating microscope, improved perioperative treatment, brain protection agents, intra-operative angiography and improved micro-surgical techniques of harvesting, meticulous, atraumatic and perfect anastomosis have produced excellent patency results of 80–98% for bypass surgery.[17–19]

Graft Failure[23]

Early Graft Occlusion

It is most often due to thrombosis promoted by loss of native intima, slow graft flow and hypercoagulable states. Intimal desquamation or endothelial cell loss due to exposure to a high-flow high-pressure arterial

environment is accelerated by trauma during harvesting. Most problems that cause early graft occlusion are technical. Trauma during harvesting can be avoided by using delicate, non-crushing vascular clamps and forceps, grasping only the adventitia and by avoiding stretching the vein longitudinally. Meticulous atraumatic techniques of harvesting, preparation and anastomosis minimise internal damage and graft flow turbulence. The graft patency is also related to distal atherosclerotic disease, number of vessels available for run off, length of the graft, kinking and size discrepancy between the graft and recipient.

Subacute Graft Occlusion

A vein graft undergoes structural changes in response to arterial haemodynamics and the trauma of harvesting. Subintimal fibrosis (arterilisation) occurs by the end of the 1st month and so vein graft occlusions are common during this time. Steroids protect venous endothelisation. Subacute changes that threaten patency of the graft are:

- Internal hyperplasia and medial fibrosis are due to ischaemia of the media caused by interruption of the vasa vasorum. It is most prominent in the floor of the recipient artery and heel of the graft. Factors contributing to this include mismatch of mechanical properties of the donor and recipient and local turbulence. Aspirin decreases the incidence
- *Valve fibrosis*: Most valves lie flat posing no threat to patency, but fibrotic change makes them impinge on the vascular lumen generating turbulence. This is why some people advocate valvotomy
- Aneurysmal dilatation of the graft at the anastomotic site
- Clamp stenosis may occur. Delicate clamps have to be used to prevent this
- Suture stenosis.

Delayed or Late Graft Occlusion

This occurs due to atherosclerotic changes. It occurs usually 4 years after the surgery leading to late occlusion of the graft. Diabetics are at special risk. Control of serum cholesterol and low-density lipoprotein may improve graft survival. Aspirin prevents lipid accumulation in the graft. This is a progressive disease causing graft occlusion in 13% of cases in the first 5 years and an additional 26% occlude in the next 5 years. Patients with slow flow experience delayed graft occlusion.

Treatment of Graft Occlusion

- *General*: A hypercoagulable state is corrected by hydration. Slow flow is corrected by occlusion, narrowing or artificial stenosis to obtain adequate graft flow, e.g. ICA, proximal VA. Spasm is treated with 3% papaverine local application
- Proximal anastomosis end problems affect flow into the graft. It may be caused by suture line stenosis which requires revision. An anastomotic kink can be corrected by pexy
- Tunnel compression is caused by narrowing of the tunnel which requires surgical opening and dilatation
- Distal end problems occur due to a stitch applied through both walls and it requires revision.

The authors have treated 16 cases of intracavernous aneurysm in the last 3 years using various methods, i.e. ICA ligation without EC-IC bypass,[10] ICA ligation with external carotid-middle cerebral artery high flow SVG bypass[3] or RAG bypass,[1] STA-MCA bypass[1] and endovascular obliteration.[1] One patient with ECA-MCA bypass died of mismatched transfusion and acute renal failure. Two patients developed hemiparesis which improved later at follow-up. One patient each had bypass block and subdural haematoma with no neurological consequences.

SUMMARY

Intracavernous aneurysms constitute 5% of all aneurysms and predominantly affect females in their middle age. The common clinical presentation includes cranial nerve neuropathy (II to VI), pain and SAH. They are frequently giant and broad-necked. The best treatment is clipping using Dolenc's extradural approach whenever possible. Endovascular obliteration with preservation of efferent flow is useful in proximal aneurysms with a definable neck. Internal carotid ligation or trapping with or without extracranial-intracranial bypass is a viable alternative in unclippable aneurysms, failure of surgery or endovascular obliteration.

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90 Contemporary Endovascular Treatment of Intracranial Aneurysms

Uday Limaye, Anand S

INTRODUCTION AND HISTORICAL BACKGROUND

Endovascular treatment of intracranial aneurysms is gaining more acceptance and is now more commonly available in India. Over the last decade, catheter technology and technical advances have taken it to a higher level of competence.

Neurosurgical clipping has been the gold standard in treatment for intracranial aneurysms since 1937, when Walter Dandy started clipping aneurysms.[20]

Fedor Serbinenko, a Russian neurosurgeon, first described endovascular treatment of intracranial aneurysms in the early 1970s. He used detachable latex balloons to treat aneurysms, either by depositing the balloon directly into the aneurysm lumen or by occluding the artery from which the aneurysm was arising.[29,30] Then came the use of free coils which did not offer any significant advantage. Detachable coils revolutionised endovascular treatment. In 1991, Guido Guglielmi was the first to describe the technique of embolising aneurysms using an endovascular approach with electrolytically detachable platinum coils, termed Guglielmi detachable coils (GDC).[12]

Endovascular treatment has been practised in India once the GDC coils became available in 1997. As the endovascular horizon widened, the management of wide neck aneurysms was tackled with the bioactive coils, stents and balloon-assisted techniques.

Recanalisation of aneurysms after coiling is still an issue, despite the low risk of rebleeding (<1% per year).[7,31] The disadvantage of coiling in our country is the high cost of the material. The equipment and expertise too are limited to a few centres in major cities.

The International Subarachnoid Haemorrhage Trial (ISAT) gave a much-needed boost to endovascular treatment of intracranial aneurysms all over the world and it has made a visible impact even in India. The results were so compelling, that recruitment was stopped after 2,143 cases. In this trial, aneurysm cases deemed suitable for treatment by both neurosurgical and endovascular techniques were enrolled. The results showed that the risk was 22.6% higher with neurosurgical technique than by endovascular means. The other advantages were the hospital stay, which was two times longer with surgery, and new deficits were four times more common with neurosurgical clipping.[21,22]

Intracranial aneurysms are common, with a prevalence of 0.5–6% in adults, according to angiography and autopsy studies. The majority of intracranial aneurysms are asymptomatic. They are diagnosed once they have ruptured and caused subarachnoid haemorrhage, a devastating type of stroke associated with 32–67% case fatality and 10–20% long-term dependence in survivors due to brain damage. For ruptured aneurysms, early treatment within 72 hours has been recommended because the risk of re-rupture is high, with approximately 20% risk of rebleed in the first 2 weeks after first subarachnoid haemorrhage and 60% by 6 months. The mortality from a rebleed is around 50%. With the availability of newer imaging, more unruptured aneurysms are being diagnosed. This is leading to the treatment of more and more unruptured aneurysms.[6,13,25,32,33,35]

INDICATIONS FOR ANEURYSM COILING[4,19,23,26]

- Posterior circulation aneurysms
- Multiple aneurysms
- Paraclinoid aneurysms
- Aneurysms with severe vasospasm
- Patients in extremes of age
- Giant/serpentine, fusiform, dissecting, mycotic and pseudoaneurysms
- Blood-blister like aneurysms (Ogawa aneurysms)
- Aneurysms with brain AVM
- ISAT supports offering coiling when there is high likelihood of success.

LIMITATIONS OF ENDOVASCULAR TREATMENT

- Tortuosity of neck vessels (Stability of arterial access is the primary step for endovascular treatment)
- Renal failure
- Non-availability of modern DSA facility
- High cost of material
- Aneurysms with large parenchymal clot may require surgical evacuation and clipping done in the same sitting.

STEPS OF ENDOVASCULAR COILING

- All procedures are done under general anaesthesia
- Transfemoral access is secured and adequate heparin is given

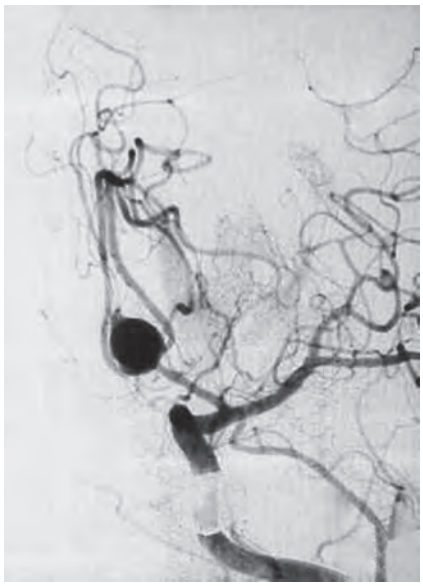


Fig. 1A: Lt ICA angiogram showing a large, wide neck anterior communicating artery aneurysm (ACoA)

- The guiding catheter is placed in the appropriate artery [Cervical internal carotid artery (ICA) or vertebral artery]
- Microcatheter over microwire is navigated into the aneurysm carefully under road map guidance
- Aneurysm coiling is carried out with detachable platinum coils of suitable sizes
- Depending on an individual case balloon or stent assisted coiling is done (Figs 1A and B).

POST-PROCEDURE MANAGEMENT

- All patients post coiling are admitted in the ICU
- Continuous monitoring of vital signs and neurological examination at regular intervals are done
- Triple H therapy and calcium channel blockers are used for treatment of vasospasm
- Patients with post-SAH hydrocephalus and intraventricular haemorrhage may require external-ventricular drainage
- Antiplatelets and low molecular weight heparin are used when indicated.

FOLLOW-UP

- Patients are clinically followed up at regular intervals
- Angiographic follow-up is done at 3–6 months, 18 months, 3 years and 5 years interval with DSA, CT angiography or MR angiography.

EQUIPMENT AND DISPOSABLE MATERIAL

- A fully equipped DSA catheter lab adds invaluable support in the endovascular technique. Biplane imaging, rotational angiograms, 3D-reconstruction techniques, flat panel and digital zooming and CT like cross-sectional images can now be obtained on high end DSA systems. Advanced imaging techniques help us understand and treat the disease better. Good quality fluoroscopy with magnification and road map facilities are basic necessities for endovascular treatment (Figs 2A and B).
- *Guiding catheters-5F to 8F lumen*:
  a. Envoy (J & J Cordis)
  b. Guider (Boston Scientific)
- *Microcatheters*:
  a. Eschelon (EV3)
  b. Excelsior (Boston Scientific)
- *Microwires*:
  a. Transend 14 (Boston Scientific)
- *Detachable platinum coils:*
  a. 2D, 3D, 360, complex coils (Compass-Microvention, 360-Boston Scientific, Orbit-Cordis and Morpheus-EV3)
  b. Ultrasoft and hypersoft coils

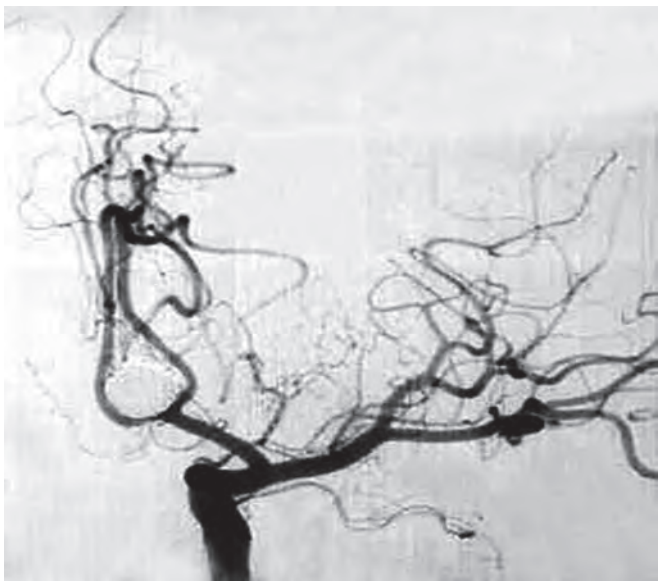


Fig. 1B: Complete occlusion on post-coiling angiogram

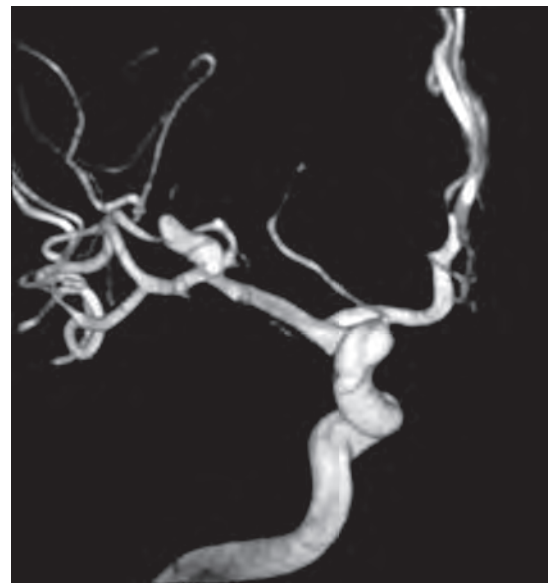


Fig. 2A: Right internal carotid artery (ICA) angiogram (3DRA) showing MCA trifurcation aneurysm

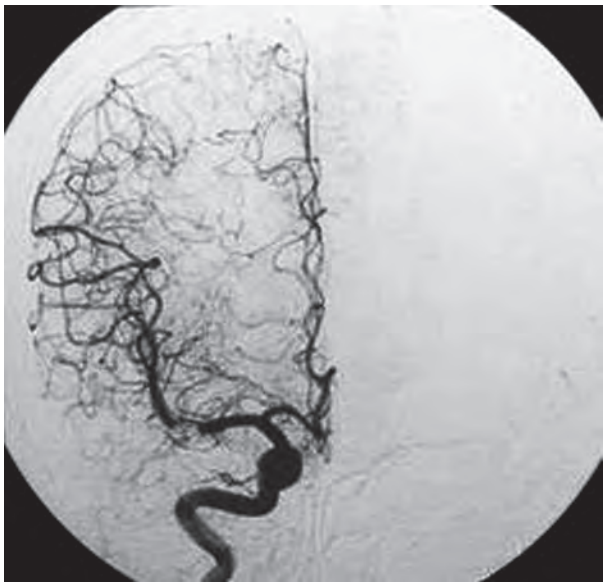


Fig. 2B: Post-coiling

c. Bioactive coils (Matrix, Boston Scientific)
d. Coated coils (Hydrocoils-Microvention)

- *Balloon remodelling catheters*:
  a. Hyperform (EV3)
  b. Hyperglide (EV3)
- *Self expanding intracranial stents*:
  a. Neuroform (Boston Scientific)
  b. Enterprise (J & J Cordis)
- *Stentgrafts*:
  a. Graft master (Jomed)
- *Liquid embolic agent*:
  a. Oynx (EV3)
  b. NBCA glue (Histoacryl, B Braun).

DRUGS USED DURING THE PROCEDURE

- Heparin
- Protamine sulphate for reversal of heparin, if required
- Contrast media (Nonionic Ultravist, German Remedies).

DRUGS USED IN ADVERSE EVENTS

- Mannitol
- Anticonvulsants
- Abciximab
- Right-PA

TREATMENT OF VASOSPASM

- *Chemical angioplasty*: Intra-arterial nimodipine therapy (3–4 mg/arterial territory)[3,28]
- *Balloon angioplasty*: Focal spasms are treated with cerebral angioplasty balloons.[9]

SPECIAL CONSIDERATIONS IN ENDOVASCULAR ANEURYSM TREATMENT

Dissecting Aneurysms

Dissecting aneurysms are commonly seen in the vertebrobasilar circulation. All dissecting aneurysms are treated with endovascular technique. Embolising the aneurysm with coils with parent vessel sacrifice is important to prevent recurrence. If this is not feasible, stents will have to be used.[1]

Giant Aneurysms

The commonest location is the cavernous ICA followed by the vertebro-basilar circulation. Cavernous ICA aneurysms are treated with proximal parent vessel occlusion; which is done after a successful Balloon Test occlusion of the artery (Figs 3A to C). Basilar giant aneurysms may be treated by flow reversal techniques with occlusion of one or both vertebral arteries. This requires the presence of prominent posterior communicating arteries.[8]

Mycotic (Infective) Aneurysms

Mycotic (Infective) aneurysms are seen more commonly with infective endocarditis. They are treated with antibiotics. Ruptured mycotic aneurysms are treated with coils or glue with embolisation of the parent branch vessel.[23]

BALLOON REMODELLING CATHETERS

The balloon remodelling catheters are commonly used to protect the neck of the aneurysm while coiling large wide neck aneurysms. They are also used to seal the neck of the aneurysm during embolisation of aneurysm with Oynx. These balloons, on temporary inflation, occlude the neck keeping the coils inside the aneurysm. The balloon catheters available are: (a) hyperform and (b) hyperglide (EV3), which can be used depending on the type and location of the aneurysm (Figs 4A to C).

Large, wide neck and giant aneurysms can also be treated with stent assisted coiling. Generally, the stent will be deployed across the neck of the aneurysm. This is followed by cannulation of the aneurysm through the

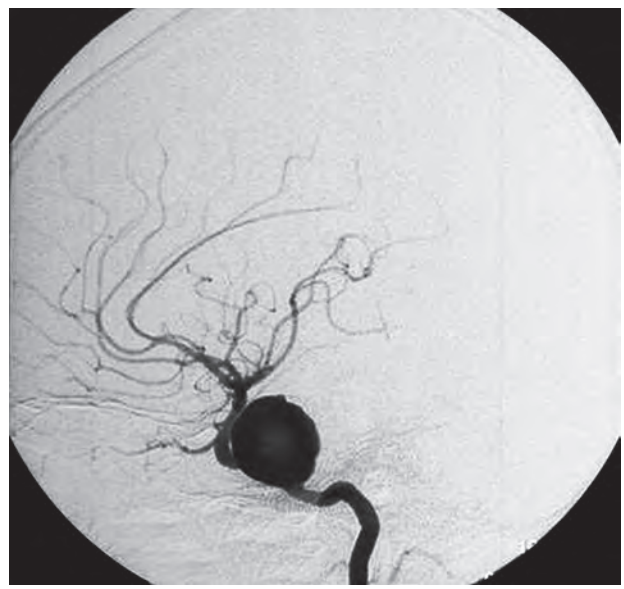
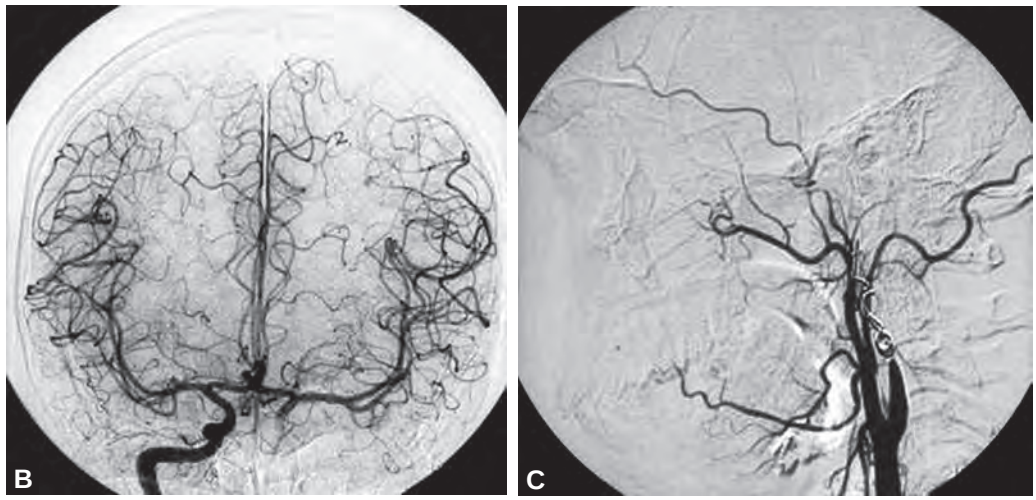
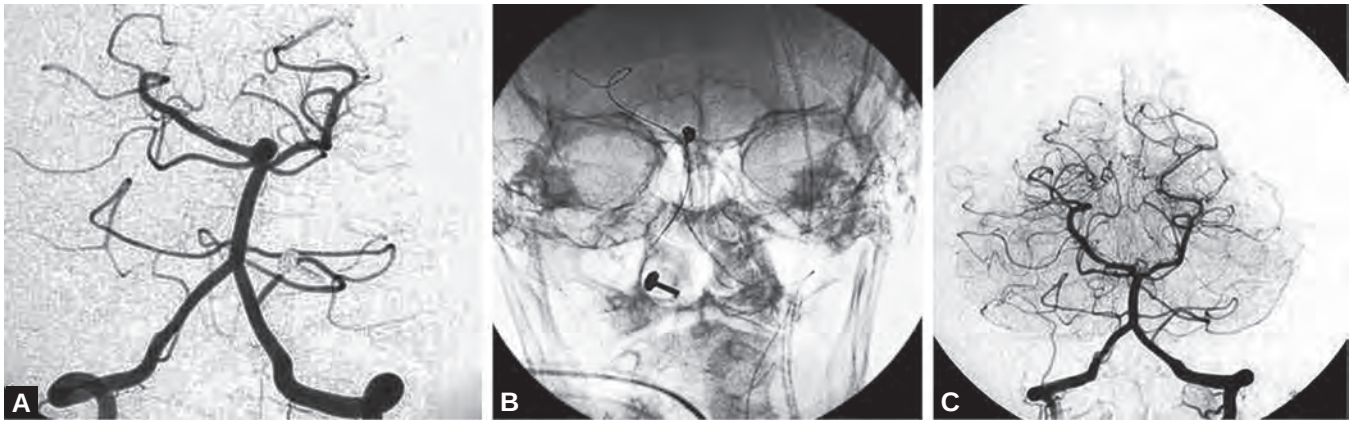


Fig. 3A: Left ICA angiogram showing giant cavernous ICA aneurysm

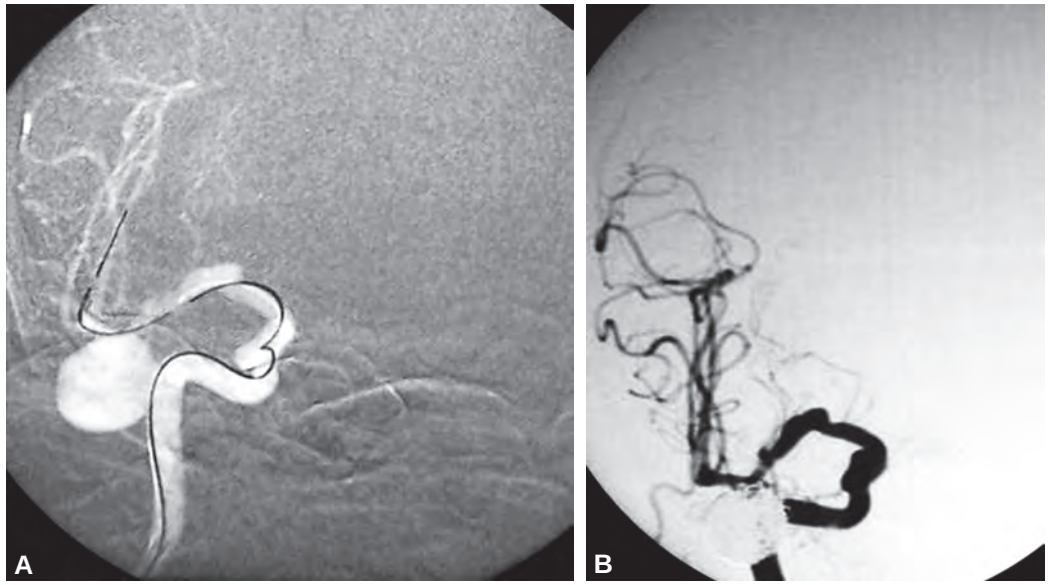


Figs 3B and C: Parent vessel (Left ICA) occlusion. Right ICA angiogram showing good cross flow across ACoA. Left ICA has been occluded



Figs 4A to C: (A) Basilar top aneurysm. (B) Balloon remodelling with hyperglide balloon. (C) Post-coiling angiogram shows complete occlusion of the aneurysm with the patent posterior cerebral arteries

stent strut for coiling. The self-expanding nitinol stents available for intracranial use are (a) Neuroform (Boston Scientific) and (b) Enterprise (J & J, Cordis). The newer stents are highly flexible and help in easy navigation into the intracranial circulation. These are preferentially used in unruptured aneurysms, taking into consideration the antiplatelet agents required to be given before, during and after the procedure (Figs 5A and B).



Figs 5A and B: (A) Giant MCA trifurcation aneurysm. Self-expanding stent has been deployed. (B) Post-stent assisted coiling, complete exclusion of the aneurysm and good patency of all MCA branches is seen

COATED/BIOACTIVE COILS

Matrix

Matrix detachable coils are platinum coils covered with a bioabsorbable polymer (90% polyglycolide, 10% polylactide) and attached to a stainless steel delivery wire. The coil consists of 70% polymer and 30% platinum.[36]

Hydrocoils

This device consists of a carrier platinum coil coupled to an expandable hydrogel material, which undergoes a ninefold increase in volume when placed into a physiological environment.

There is no concrete evidence in favour of these coils that they improve long-term occlusion or significantly prevent recanalisation.

NEWER ADVANCES

Stent Grafts

Coronary stent grafts have been used infrequently in endovascular treatment of giant or pseudoaneurysms.

They constitute a promising alternative for endovascular treatment. They have mainly been used in the carotid circulation. The stent graft seals the neck of the aneurysm. Long-term patency of the graft is an issue. A case where the arterial curvature is acceptable, side branches are absent or can be sacrificed, stent graft is an option for treatment. Their use is limited due to lack of flexibility and free availability.[15]

Oynx

Oynx (Micro Therapeutics, Inc, Irvine, CA) has been used to treat selected cases of aneurysms. It is an ethylene vinyl alcohol copolymer dissolved in the organic solvent dimethyl sulfoxide (DMSO). Oynx HD 500 has been used in selected cases of giant or large wide neck aneurysms that are not suitable for coil treatment or in whom previous treatment has failed to occlude the aneurysm.[2]

COMPLICATIONS

- Perforation
- Thromboembolism

Procedure-related morbidity and mortality rates as reported in most published series are between 1.5% and 4%. A few series report a very low mortality of 0.8% and permanent morbidity of 2.5% in ruptured aneurysms. In patients with unruptured aneurysms the morbidity is below 2% in most series. Lowest reported is 0% mortality and permanent morbidity of 1%. Complications although these cannot be avoided, are inversely proportional to the expertise and experience of the operating endovascular specialist.[2,10,11,18,21,22,34]

Perforation

During coiling the microwire/microcatheter/coil may inadvertently perforate the wall of the aneurysm. This leads to SAH, which may increase the mortality/morbidity if not rapidly controlled. Heparin is reversed and the aneurysm is rapidly packed with coils. Use of a remodelling balloon catheter for urgent tamponade is life saving. Aneurysmal rupture is depicted by the issue of the tip of the coil or the microcatheter outside the limit of the aneurysmal sac and/or extravasation of contrast media during angiography. Aneurysm rupture may also lead to large parenchymal haematomas which require surgical evacuation. Rupture of the aneurysm into the ventricle may require an external ventricular drainage to treat hydrocephalus.

Thromboembolism

It is a feared complication during the procedure leading to cerebral infarction. Clinically relevant thromboembolic complications are reported in 3.3–6% in different series. The occurrence of a thromboembolic event is dependant on several factors such as the technique used to treat the aneurysm or the medication administered before, during and after treatment. Treatment of thromboembolic complications is tailored to the specific situation of each patient. Medical treatment is modified during the procedure with an increase of the systemic heparinisation, IIb/IIIa antagonist or intra-arterial fibrinolysis with rt-PA (Figs 6A and B).

Device Related Issues

Malfunctioning of devices, rarely, may occur. Stretching of coil, non-detachment of coil, coil or stent migration, and microcatheter/balloon rupture may rarely complicate a procedure.

RECANALISATION/RECURRENCE

The long-term stability of aneurysmal occlusion obtained with coils remains the most significant limitation.

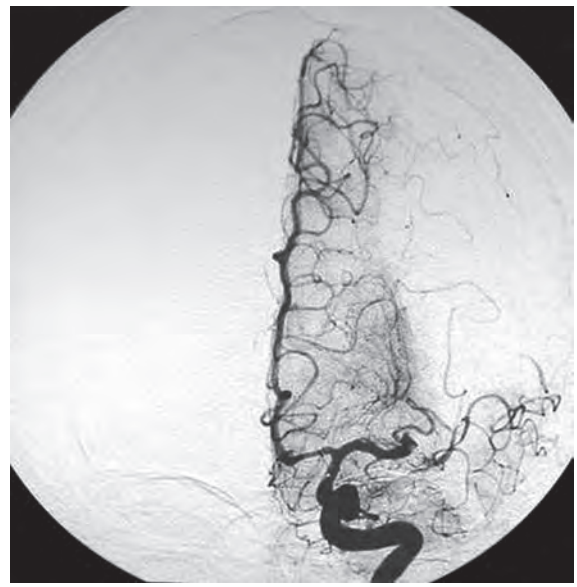


Fig. 6A: Thromboembolism during left MCA trifurcation coiling

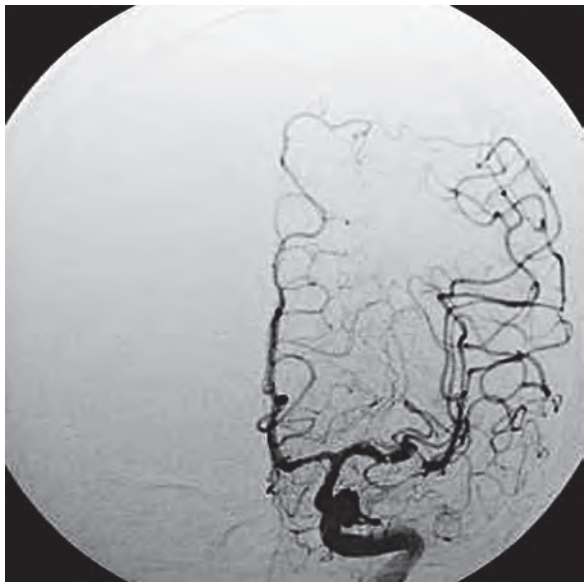


Fig. 6B: Complete recanalisation after the use of abciximab

According to the largest published series, the rate of recanalisation after selective endovascular treatment of intracranial aneurysms is between 13% and 34%. Recanalisation is commonly seen with large wide neck aneurysms or giant aneurysms. It depends on the initial packing or coil density at the time of first treatment. Recanalisation occurs due to coil compaction, incomplete packing or neck residue. Recurrence of aneurysm at the same site or at other sites is also reported. Repeated check angiograms are done to look for recanalisation or recurrence of aneurysms. The risk of rupture of these aneurysms is negligible (<1% per year). If there is significant recanalisation/recurrence of aneurysm then recoiling or a neurosurgical clipping is selected.[5,14,16,17,24,27,31]

CONCLUSION

Endovascular techniques used are constantly undergoing improvisations and modifications. With wider acceptance and newer advances in endovascular technique, most aneurysms are now amenable to endovascular treatment. Complete occlusion of aneurysms and use of a stent when indicated have improved long-term and stable angiographic cures.

Objective selection of the safest and most effective treatment option should be done for each patient. However, the issues of recanalisation and regrowth cannot be ignored. Further advances to minimise these are desirable.

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91 Vascular Malformations of the Brain

Ravi Ramamurthi, Amit Kapoor

INTRODUCTION

Vascular malformations of the brain, hitherto commonly known as angiomas, are defined as congenital non-neoplastic lesions which arise from faulty embryologic resolution of primitive vascular networks. Krayenbuhl and Yasargil[143] found evidence in the literature that Egyptians had recognised the existence of cerebral vascular malformations as early as 1500 BC. However, Luschka (1854) and Virchow (1863) are credited for their pioneering efforts to describe the morphological features of these lesions. The first clinical diagnosis of cerebral arteriovenous malformation (AVM) was made by Steinhill in 1895. The earliest surgical exposure of cerebral AVMs was done by Giordano in 1890 and Krause in 1908. Following the introduction of cerebral angiography in 1927, by Egaz Moniz, the first angiographic diagnosis of cerebral AVM was reported by Bergstrand et al. in 1936.[8] Since the first successful total extirpation of a cerebral AVM by Olivecrona in 1932,[85] a number of monographs, based on large series of cases, have been published.[47,67,86,110,128] With better understanding of the natural history of cerebral AVMs, and with the application of the recent advances in diagnostic and therapeutic neuroradiology, neuroanaesthesia and microsurgical techniques, the management of cerebral AVMs has become much easier than in the past. However, it still remains one of the major surgical challenges.

CLASSIFICATION

The term "arteriovenous malformation" is commonly used to describe all types of vascular malformations of the brain. Though numerous classifications have been proposed by various authors, the widely accepted classification is that propounded by McCormick in 1966[65] and is based on the morphology of the component vessels, the existence of intervening neural elements and the biological behaviour of the lesion. This classification, subsequently modified by him in 1978, is as follows:[66]

- AVM
- Cavernous angiomas
- Venous angiomas
- Capillary telangiectasia
- Transitional forms

AVMs are the commonest of these lesions in surgical series, whereas, venous angioma is the most common type in large autopsy series.[114]

ARTERIOVENOUS MALFORMATIONS

Aetiopathogenesis

Although the definite aetiopathogenesis of these developmental vascular malformations is still unknown, a genetic factor has been considered. Familial or hereditary cases with various neurocutaneous syndromes are often associated with such lesions.[3,68,122]

Early development of the cerebral circulation has been divided into five chronological stages. AVMs of the brain are congenital lesions which develop during the late somite stage, between the 4th week and the 8th week of embryonic life. Cells (angioblasts) differentiate from the mesoderm during the 3rd week of embryonic life forming small syncytial islands. These syncytial cells develop tiny sprouts which interconnect them and form a syncytial plexus. Intercellular clefts now appear in this syncytial plexus and they later fuse to form the primitive vascular lumen. The syncytial cells enveloping these clefts become the endothelium of the vessels and these later proliferate linking the vascular lumina into an irregular endothelial vascular meshwork over the surface of the developing brain. The more superficial portion of this primordial vascular plexus forms the arteries and veins, and the deeper portion resolves into the capillary component.

The exact pathogenesis of AVMs is unknown. Capillary agenesis during the second stage was postulated as the predominant feature of congenital AVM by Olivecrona and Ladenheim.[86] However, Tonnis and Lange-Cosak,[128] thought that the developmental arrest took place during the fifth stage. Kaplan et al.[43] felt that, originally, many plexiform anastomoses exist between arteries and veins which later get reabsorbed and disappear. Arrest of development at this phase will lead to persistence of abnormal arteriovenous (AV) communications. The fact that AVMs are of congenital origin is substantiated by the absence of a history of trauma, stress and other potential causes of a vascular fistula, their development and increase in size by displacement of the maturing brain at its margin with preservation of neurological function, failure of attempts at production of an experimental model, as well as lack of evident growth of an AVM by any neoplastic process.

Incidence

In the absence of an epidemiological study, the true incidence of intracranial AVMs is difficult to provide.

Varying figures have been mentioned based on the type of material examined. Cerebral AVMs rank second to aneurysms among the intracranial vascular lesions that produce subarachnoid haemorrhage (SAH). They occur with one-tenth[22] to one-fourth[68,142] the frequency of intracranial aneurysms. The incidence of AVMs in the co-operative study[94] was one-seventh of that of intracranial aneurysms. The majority of patients present in the third decade. Earlier reports from India suggested a higher incidence of AVMs compared to saccular aneurysms.[41] However, further studies have refuted this observation. The Indian Council of Medical Research collaborative study established that the relative incidence of these two lesions in Indian patients with SAH was the same as reported from the rest of the world (Aneurysm:AVM is 5:1). With wider use of complete sequential angiography, computerised tomography (CT) and magnetic resonance (MR), AVMs may be detected more frequently. A male preponderance is reported by almost all authors. Average annual AVM detection rate of 1.34 per 100,000 person years has been reported with the incidence of first ever AVM haemorrhage of 0.51–0.55 per 100,000 person years. Estimated prevalence of AVM haemorrhage is about 0.68 per 100,000 person years. Mean age of presentation is 33 ± 18 years with no sex predisposition. Approximately half of the patients with AVM may suffer intracranial haemorrhage (ICH) during life time.[29,57] Familial occurrence is rare, but described in text.[73]

Location

Most of the medium and large AVMs extend over two or more anatomical vascular territories. Hemispheric AVMs situated in the watershed areas are usually supplied by more than one arterial pedicle. Mingrino[68] in a review of 1012 cases collected from six large series found the distribution to be supratentorial in 86% and infratentorial in 14%. The parietal lobe is the commonest region involved in supratentorial lesions. There is no significant hemispheric preference. In the series of Rout,[106] the lesions were superficial in 51.4% cases and deep in 48.6%. The majority of deep AVMs were located in the medial paratrigonal region[77] Bilateral hemispheric malformation was encountered in only one case. Vascular malformation in the internal auditory canal has been reported by Saleh et al.[112] Anterior cavernous malformation and those malformations involving the superior petrosal, transverse and sigmoid sinus region are readily recognised and diagnosed as compared to those involving basal sinuses, prominent cortical venous drainage and other drainage patterns.[1,101,102] AVMs were in eloquent location in 71% of cases and 55% cases had deep venous drainage.[65]

Pathology

Hemispheric AVMs are located in the middle cerebral, posterior cerebral and anterior cerebral territories in declining frequencies. These may derive arterial supply either from one or a combination of epicerebral (perforators arising from pial vessels), transcerebral (major parenchymal arteries and their branches) or subependymal vessels (choroidal arteries). The malformations supplied by the epicerebral vessels are confined to the cortex and are drained by cortical veins. The AVMs fed predominantly by the transcerebral vessels usually assume the shape of a wedge, based on the surface with its apex often reaching the ventricular wall. These drain into both the superficial and deep venous systems (Fig. 1). The centrally located AVMs mostly receive feeders from the anterior as well as the posterior circulation (Fig. 2). Malformations located in the watershed areas are always fed by more than one major artery. Depending upon the size, the malformation may involve one or several adjacent lobes, the entire cerebral hemisphere or, rarely, the whole brain.[3]

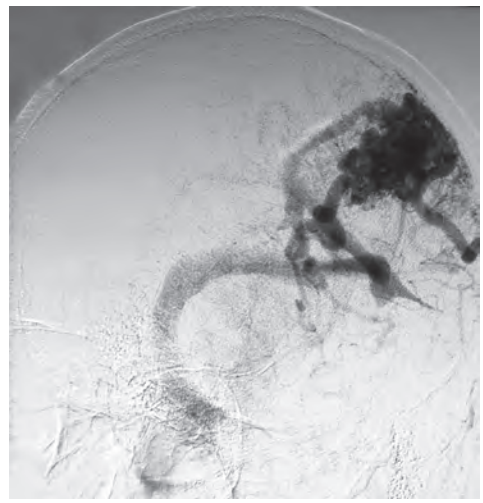


Fig. 1: Digital subtraction angiography study showing arteriovenous malformations draining into both superficial and deep venous systems

An AVM is a cluster of congenital AV communications without an intervening capillary bed (Fig. 3). Both the feeding arteries and the draining veins are tortuous and dilated. As the draining veins are arterialised, they are disproportionately enlarged and often look like arterial feeders at operation. The number of fistulous communications

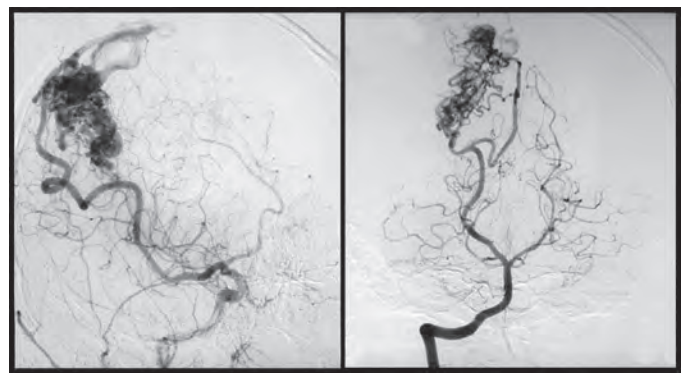


Fig. 2: Arteriovenous malformations receiving feeders from the anterior as well as the posterior circulation

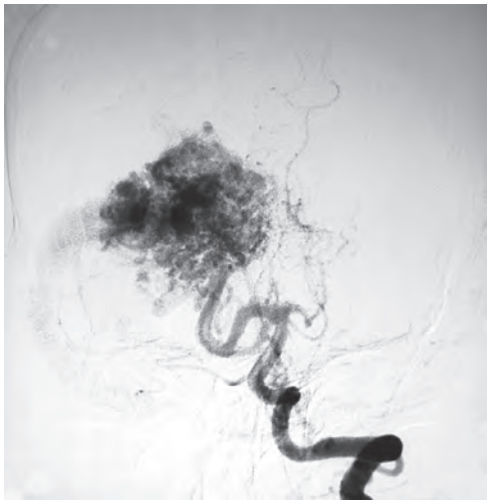


Fig. 3: Arteriovenous communications without an intervening capillary bed

probably remains constant, but may enlarge in size with the passage of time due to high flow dynamics through the malformation.[21] The growth of the malformation proceeds apace with the growth of the brain. However, in exceptional circumstances, dramatic enlargement has been observed.[119] In the absence of an interposed capillary bed with diminished resistance of blood flow and deficient vasomotor control in the shunt, an increased amount of blood passes through the malformation unutilised. The malformation becomes a "parasite on the cerebral circulation", depriving the adjacent brain of normal perfusion. Increasing "shunt flow" may even embarrass the cardiac output in neonates.[124]

In the presence of large cortical draining veins, the arterial feeders are often submerged within the brain parenchyma. Large AVMs with associated varices do behave as space occupying lesions producing neurological deficits either due to mass effect or because of intracerebral steal (Fig. 4). The leptomeninges covering

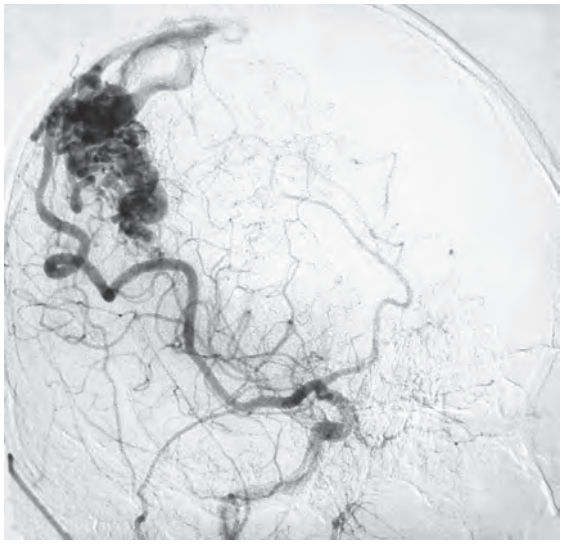


Fig. 4: Digital subtraction angiography study for arteriovenous malformations showing evidence of steal from the right anterior cerebral artery

the malformation are often thickened and opacified giving it a milky white appearance. Some AVMs, rarely, may be so compact that they even resemble a cavernous angioma in gross appearance. Most AVMs demonstrate a gliotic core associated with the nidus and a gliotic wall around the malformation forming a "pseudo capsule" which helps in surgical dissection for total extirpation. Hyaline degeneration causes collagenous replacement of the normal smooth muscle component of the media in the main arterial feeders adjacent to the malformation.[30] Smooth muscle and intimal nodules often project into the lumen of large arterialised draining veins and their walls may reveal amyloid like material. In between the component vessels, gliotic parenchyma and foci of haemosiderin laden macrophages are often encountered. Spontaneous thrombosis of component vessels with inflammatory changes leading to disappearance of the AVM is rarely seen. Calcification of the vessel in an AVM is not uncommon.

Expression of modulation of various molecules, receptors and mediators has been implicated in the pathogenesis of AVM. The IL-6 genotype is associated with increased expression of IL-6 in AVM with increased angiogenesis and increased incidence of intracerebral haemorrhage. RASA 1 defects and phosphorylated extra cellular signal regulated kinase promote abnormal vascular remodelling, thus promoting AVM pathogenesis. Similarly, VERF–VEGF receptor and integrin alphabeta I have been indicated in promoting growth of AVM. Smoothelin expression is reduced in large AVMs and has associated loss of contractile property associated with the homodynamic stress. Tie-2 expression has also been implicated in a similar manner. Smooth muscle cell specific protein marker SM2 is absent in normal vascular structures and is expressed strongly in AVM. The SAH induced vasospasm is mediated by endothelin 1 whose levels are elevated in endothelial cells from ruptured AVM.[8,11,12,47,49,50,62]

Moyamoya disease, sickle cell disease, Marfan's syndrome, Turcot syndrome, hereditary haemorrhagic telangiectasia (HHT), Beckwith-Wiedemann syndrome, high grade glioma, angioma, other vascular formations, persistent trigeminal artery and metaplasia have been associated with AVM.[4,11,28,68,79,81]

The HHT is autosomal dominant and associated with cerebral malformation ranging from AV fistula (AVF), small nidus type AVM or micro-AVM with nidus less than 1 cm in size.[7,64]

Immediate perinidal brain tissue may show dilated capillaries with severe congestion. These vessels are sometimes called "giant bed capillaries" and are associated with significant ischaemia in the surrounding brain matter.[30]

Developmental venous anomalies with an AV shunt are a risk factor for aggressive clinical behaviour rending the lesions to complications similar to AVM.[55] Cerebral AVM classified into AVFs and plexiform types, essentially exhibit similar morphology with the plexiform

type being a conglomeration of AVFs.[76] Reperfusion into unprotected capillaries of severely hypoxic cortical areas results in "break through" and vasoparalysis does not appear to be the underlying cause.[77]

Natural History

There are several long term studies reported in the literature, addressing the issues of the natural history of AVMs.[5,15,31,38,59,88,94,133,140] The onset of symptoms is maximal in the second and third decades, although these lesions are present since birth. This latency in the onset of symptoms is probably due to progressive maturation and growth of the lesion and gradual changes in the adjacent neural parenchyma. Haemodynamic factors eventually lead, either to a weakening of the vessel wall resulting in haemorrhage, or to irritation and gliosis of the surrounding neural tissue causing seizures. Growth of AVMs occurs in about 20% due to repeated haemorrhages, gradual dilatation of the vessels, expansion of feeders, and recruitment of new supply.[21,77] AVMs in the elderly may at times diminish in size,[58] especially small AVMs with a single feeder. Occasionally, an AVM may disappear spontaneously as demonstrated angiographically.[23,113]

In their extensive study of the natural history of AVMs Ondra et al.,[88] found that in an unruptured AVM, the incidence of first bleed is 4% per year. The annual re-bleed rate continues to be the same, i.e. 4% per year. This is at variance with the earlier studies of Graf[31] and the co-operative study[94] where it was mentioned that the incidence of re-bleed in the 1st year after the initial bleed goes up to 6% and drops to 2–3% from the 2nd year onwards. Kitamura[46] has stated that AVMs bleed probably more than what we expect. Ondra et al.[88] have also determined that the annual mortality rate due to an AVM is 1%, with the mortality at the initial or first bleed being 10%. Morbidity with each bleed occurs in 20–30% per episode of bleed, with long term morbidity being 2.7% per year. The mean interval between haemorrhages was 7.7 years in their study and mortality with recurrent bleeds also remained the same as that of the first bleed, i.e. 10%. A higher mortality rate of 13% for the second haemorrhagic event and 20% for the subsequent episodes has been reported.[21,31,100,140] Forster[28] had reported that in a patient presenting with seizures, there was a 25% chance of the first bleed within 15 years, whereas in patients presenting with a bleed, the possibility of a second bleed was 25% in the next 4 years, and that of a third bleed was 25% within 1 year of the second episode.

Ondra et al.[88] observed that contrary to the earlier belief, there is no change in the risk of suffering a haemorrhagic ictus in a patient manifesting for the first time with seizures or any symptom other than a bleed. The co-operative study[94] revealed that on long term follow-up, only 34% of patients harbouring an AVM remained symptom free. About 26% became minimally symptomatic, 26% were partially disabled, 11% were severely disabled and 3% were severely incapacitated. While there is a chance of a decline in the incidence of haemorrhage from an AVM after the age of 40 years,[58] there is only a 50% chance of leading a normal life after the age of 55 years. Untreated posterior fossa AVM carries a poorer prognosis.[57]

Celli et al.[12] observed that the risk of bleeding in children, as compared to adults, was approximately three times greater by 10 years and about 2.5 times greater by 25 years of age. In their series, the incidence of parenchymal or intraventricular haematoma was greater in children as compared to adults.[127] Wilkins[140] found that the risk of haemorrhage from an AVM in a child is threefold compared to adults and the incidence of re-bleed is seven times more. The size of the haematoma is larger in children, causing more focal neurological deficits and the risk of death is higher. However, in the series of Rout, the only factor that was significantly different between the paediatric and adult age groups was the initial mode of presentation, with bleed (90%) outnumbering other symptoms in children. There was no significant difference in the re-bleed rate, size of AVMs and the incidence of pre-operative or post-operative deficits.[79]

Only 18–20% of cerebral AVM are diagnosed during infancy and childhood. ICH is a presenting feature in 75–80% of cases and is associated with higher morbidity and mortality. The natural history of untreated cerebral AVM is worse in children with longer life expectancy than in adults, higher annual risk of AVM bleed [3.2% vs 2.2%] and a higher incidence of posterior fossa and basal ganglia AVM, most of which present with massive haemorrhage.[74] Spontaneous occlusion of AVM and *de novo* occurrence and growth of AVM, though rare, have been reported.[3,10,28,32,38,40,45,51,78] Haemorrhage either at original presentation or during follow-up of an untreated AVM appears to carry a lower morbidity than ICH from other causes.[5] Haemorrhage risk of grade IV and grade V AVM appear to be lower than grade I through grade III.[33] Deep seated large AVM are more prone to haemorrhage.[39]

Intracerebral haemorrhage in the paediatric age group differs from the adult and is mainly due to vein related causes.[48,52]

Clinical Features

An AVM may present with ICH, seizures, headaches, focal neurological deficits, dementia, raised intracranial pressure, congestive heart failure (especially in neonates) or unusual symptoms like trigeminal neuralgia or hemifacial spasm. In the series of Rout, 73% of patients harbouring an AVM presented with bleed, 37.6% had seizures and 57% had neurological deficits at admission.[106] The incidence of various clinical features has been reported variously as haemorrhage (43–51%), headache (14–24.9%), seizures 17.3% (generalised 75%, focal 25%), persistent neurological deficits (7%) and progressive neurological deficits in 45% of cases.[18,65]

Symptoms occur due to cortical venous hypertension, venous stasis and ischaemia.[35,41,42,53,59]

Haemorrhage

In most of the reported large series, ICH was the common-most mode of presentation of AVMs, with the majority having bled before the age of 40 years. It is the initial presenting symptom in 65–79% of cases. The peak incidence of haemorrhage is between 11 years and 35 years of age. There is no gender preference for the propensity to bleed. Although it is conventionally believed that AVMs tend to rupture more frequently during pregnancy, there is no convincing evidence to substantiate such a belief.[75] Haemorrhage may be intraparenchymal, intraventricular, subarachnoid or subdural. Spontaneous SAH due to AVMs has been reported in 2–10%.[91,94] Some authors have observed that haemorrhage from AVMs occurs more frequently during sleep, as compared to strenuous activities. Bleed from an AVM is unrelated to stress, activity, trauma or hypertension.

Patients with ruptured AVM tend to have more deficits at presentation and generally better post-operative prognosis than with unruptured AVM.[14] In comparison to ICH due to other causes AVM related ICH occurs more frequently in younger individuals, female, non-smoker, people with lower blood pressure, cholesterol and WBC counts.[31]

Predictors for a high-risk of AVM rupture are:

- *Age*: There is a higher propensity for AVM to rupture in children. Crawford[15] and Celli et al.[12] have shown that the risk of bleed from an AVM progressively declines after the age of 40 years. Increasing age increased the risk of ICH. Higher age shows higher fraction of AVM haemorrhage and these patients are more likely to harbour additional risk factors such as intranidal arterial aneurysms and small AVM diameter.[6,26]
- *Size*: Small AVMs have an increased likelihood of bleeding because of the higher pressures in the feeding artery. Small AVMs commonly present with a massive intraparenchymal bleed (Fig. 5). Micro AVM presents with large haemorrhages and significant neurological deficits.[69]
- *Location*: AVMs located in the posterior fossa have a higher risk of rupture and also have a poorer outcome. Periventricular AVMs also show a greater propensity to bleed. Infratentorial location is an independent risk factor of haemorrhagic presentation.[24,125] Choroid plexus AVMs present with intraventicular haemorrhage.[34] Border zone location is an independent determinant of lower risk of AVM haemorrhage.[63]
- *Past history of bleed*: In the study by Forester,[28] as well as in the co-operative study,[95] it is mentioned that an incidence of bleed is followed by a higher risk of second bleed in the 1st year. Forester[28] also mentions that re-bleed is inversely proportional to the neurological status at the first bleed, but both these observations have not been substantiated by any other large series. An initial haemorrhagic presentation is associated with increased incidence of re-bleeding with an annual re-bleeding rate of 2–4%.[20]
- *Intranidal aneurysm*: Demonstration of an associated intranidal aneurysm suggests a high possibility of bleed. Pedicle aneurysms on feeding vessels are frequently associated with haemorrhage. About 40–96% of aneurysms are situated on the feeding artery and 23% at an arterial bifurcation. About 9.9% of AVMs are associated with an aneurysm. Intranidal aneurysms have higher re-bleeding rates.[66,67,71]
- *Venous drainage*: Miyasaka et al.[70] observed that the venous drainage pattern is an important determinant of haemorrhage from an AVM. There is a high risk of bleed in the presence of only one draining vein (89%), deep drainage (94%) and demonstration of venous obstruction (94%). The deep drainage pattern may be associated with stenosis of the vein of Galen which increases their propensity to bleed; or else, the arterial pedicles of the deep seated central AVMs being smaller, result in high flow and pressure within the nidus, thus predisposing to their rupture. Deep venous drainage is an independent risk factor of haemorrhagic presentation.[24,39] The risk of rupture of an AVM is less in cases of peripheral or mixed venous drainage and in the presence of an angiomatous change, because this results in dilatation of cortical or leptomeningeal vessels recruited by large AVMs which have a low perfusion pressure within them.[63,105,107]

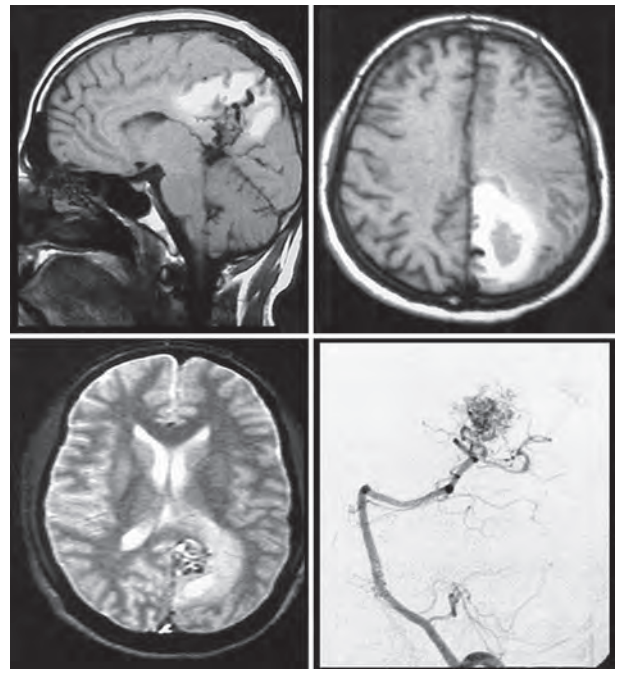


Fig. 5: Arteriovenous malformations presenting with bleed

Pathogenesis of haemorrhage: Venous obstruction resulting from either a mechanical cause like venous stenosis or a relative haemodynamic venous obstruction due to

increased venous outflow results in rupture of the thin-walled venous end, more so at the nidus-venous junction. Haemorrhage may also result from rupture of an associated intranidal aneurysm. The intranidal aneurysm occurs as a consequence of mechanical or haemodynamic venous outflow obstruction. Rarely, an aneurysm of the feeder artery, as a result of high flow through the vessel, may rupture and cause haemorrhage. Draining vein pressure and feeding artery pressure (Pfed) are significantly higher in AVM with haemorrhage.[75,108,116,118]

The Pfed is lower in distally located AVMs, large lesions and in AVMs with multiple draining veins.[9] The number of draining veins, the mean transit time (MTT) of the feeding artery and the ratio of MTT of the draining to the feeding vessels determine the incidence of ICH.[72]

Seizures

The second most common manifestation of AVMs is seizures, its incidence being 10–50% in different series. With the advent of non-invasive diagnostic modalities, more such cases are being reported. The average age of onset of seizures is 25 years. Seizures may be associated with a subclinical bleed in 6.5% of cases, as observed on MR scans as areas of haemosiderin deposits or during surgery as xanthochromic staining of the tissues. About 12% of patients presenting with features of intracerebral haematoma may have associated seizures. Seizures are more common with large, superficial, high flow malformations. In the elderly, epilepsy is less frequent with an increased incidence of infratentorial lesions.[21,93,145]

Pathogenesis of seizures: Although an AVM is a congenital lesion, the irritation and gliosis produced in the surrounding brain tissue with maturation of the lesion, may result in a seizure disorder. An epileptogenic focus may also be caused by associated cerebral ischaemia due to steal in a high flow AVM. Haemosiderin deposits and areas of intervening gliosis result from the pressure of dilated vessels and/or decreased tissue perfusion due to venous hypertension. Mass effect, due to venous ectasia or pouches and retrograde dural sinus hypertension resulting in hydrocephalus or raised intracranial pressure, may also cause seizures. Rarely, a secondary epileptogenic focus may occur in the temporal lobe.[144]

Focal Neurological Deficits

AVMs can present with focal deficits alone in 4–12% or in combination with haemorrhage or seizures in 25% of cases. Neurological deficits and mental changes are the result of arterial steal, venous hypertension causing hypoperfusion of the surrounding brain parenchyma, mass effect of the AVM or hydrocephalus. Most of the strokes in AVM are haemorrhagic.[17] Selective retrograde amnesia occurs in patients with AVMs in mediobasal and diencephalic regions.[27,43,46]

Other Features

Large AVMs produce changes in the scalp and the skull. The scalp veins may enlarge and also increase in number. In some a thrill may be palpable over the neck vessels, associated with a bruit. Bruit is more common when the malformation has connections with the external carotid system. Papilloedema and fundus changes, when seen, are mostly secondary to SAH or a haematoma. Retinal angiomas may be associated in a small percentage of cases. Intermittent exophthalmos may occur in anterior AV malformations associated with orbital varices. Posterior fossa angiomas may cause trigeminal neuralgia.[42] Mental changes are also common in posterior fossa malformation, when all the blood vessels take part in the supply to the malformation. Orbital congestion may present as chiasmal syndrome, headache or without visual symptoms.[70]

Cardiovascular Effects

In very large AVMs with enlargement of the feeding vessels, and increased blood flow, there is an associated change in the pulse pressure giving rise to a water hammer pulse. There is a proportionate increase in the cardiac output and cardiomegaly results, especially in children.[136] This may be the first sign of a cerebrovascular anomaly. In the late stages, high output cardiac failure may result. This complication is rare, except in infants with an AVM involving the vein of Galen. Cerebellar haemorrhage has been associated with neurogenic pulmonary oedema.[19]

Haematological Effects

Some AVMs have a tendency to trap platelets which adhere to the poorly formed endothelium of the malformation. This may result in thrombocytopaenia and a bleeding diathesis.

HAEMODYNAMICS OF ARTERIOVENOUS MALFORMATION

An AVM is typically an abnormality comprising direct AV shunts, characterised by the absence of the intervening capillary bed. The absence of these resistance vessels, therefore, causes a low perfusion shunt flow which adversely affects the brain parenchyma, either by altering the blood flow pattern in the neighbouring areas causing "intracerebral steal", or, by affecting the metabolism in the adjacent normal tissue which shows evidence of decreased glucose utilisation.[120] Feeding artery pressures in the AVM are an important determinant of the haemodynamic events related to the lesion. The pressure in the feeding arterial pedicle is determined by:

- *Size of the AVM*: The smaller the size of the AVM, the higher will be the feeding artery pressure
- *Length of the feeding artery*: The smaller the feeding arterial segment, the higher will be the pressure within that vessel
- *Number of nutrient arteries to the adjacent parenchyma*: The more the number of nutrient branches, the less will be the pressure head feeding the AVM

Shunt flow velocity within the AVM nidus is an important determinant of the clinical manifestations and can be measured non-invasively by using transcranial Doppler ultrasound.[55,82,83,87]

INVESTIGATIONS

Plain X-ray may occasionally show evidence of calcification and/or abnormal vascular markings on the skull, but this is not an important investigative tool in the diagnostic armamentarium available today.

The CT scan is valuable in diagnosis. In the hyperacute and acute stages, CT visualises the intracerebral haematoma and brain oedema better than MR. A plain CT scan may show an area of hypodensity within the haematoma. This is a useful guide to the location of the nidus of the AVM and was described by Wakai[134] as the "nidus sparing sign". In the presence of an acute haematoma, a contrast-enhanced CT may or may not reveal the AVM, but after resolution of the haematoma, the AVM may be visualised as a serpiginous enhancing lesion with an early draining vein (Fig. 6). The presence of associated calcification is easily seen. There may be evidence of "steal" phenomenon and hypoperfusion of the surrounding brain in the form of perilesional hypodensity, grey matter changes, disturbances of grey-white interface or cortical atrophy. Intrinsic hypodense areas within the AVM may be visualised in a high resolution scan, corresponding to the areas of gliosis or old haemorrhage.

Magnetic resonance imaging (MRI) will show areas of serpiginous flow void on T1-weighted and T2-weighted images (Fig. 7). The signal intensity of the AVM may be paradoxically increased if there is slow flow, stagnation or thrombosis within the vessels. Areas of associated haemorrhage are revealed and old subclinical haemorrhages, which are difficult to diagnose on a CT scan, can be easily visualised. The exact location of the AVM nidus, feeders and draining veins is easily established in relation to the eloquent areas of the brain because of the ease of multiplanar imaging. Areas of cortical atrophy are also easily visualised. Serial MR imaging is useful in diagnosis and management of occult AVM.[56,103,109]

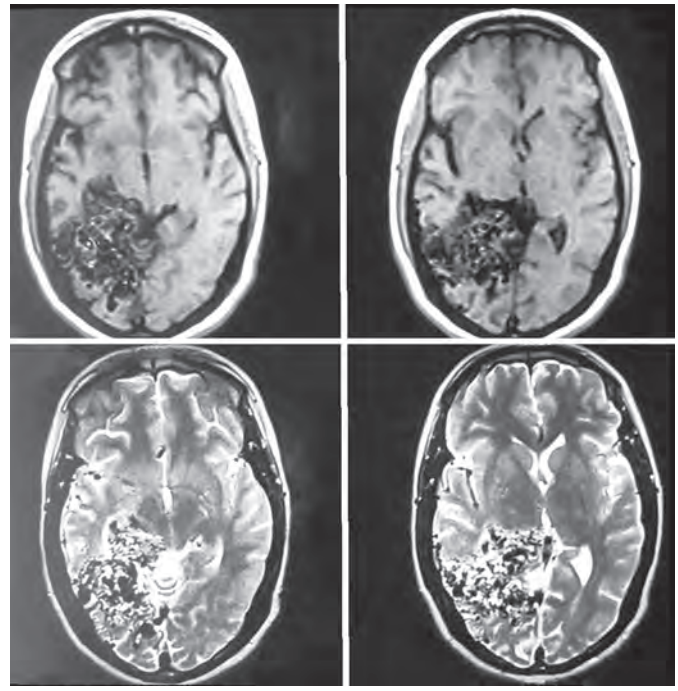


Fig. 7: Magnetic resonance imaging will show areas of serpiginous flow void on T1-weighted and T2-weighted images

Functional MRI (fMRI) is useful in identifying language activation patterns and the relative location of an AVM.[22,23,36] Brain plasticity in relation to structural abnormalities like AVM can be demonstrated by fMRI.[44] MR tractography is useful in assessing the relationship between the AVM, sensory motor fibres and tracts.[15] Magnetoencephalogram is useful in estimating an interictal paroxysmal activity source in patients with AVM.[60]

MR angiography (MRA) gives an excellent outline of the AVM with detailed information on the arterial pedicles and venous drainage pattern (Fig. 8). However, as of today, it has neither replaced nor supplanted digital subtraction angiography (DSA) which is still considered the "gold standard" in the imaging of an AVM.

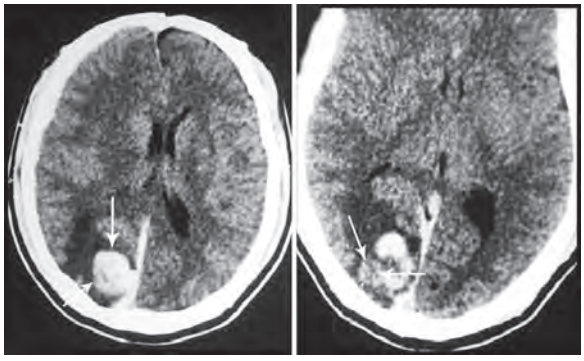


Fig. 6: Contrast computerised tomography scan showing serpiginous arteriovenous malformations after resolution of haematoma

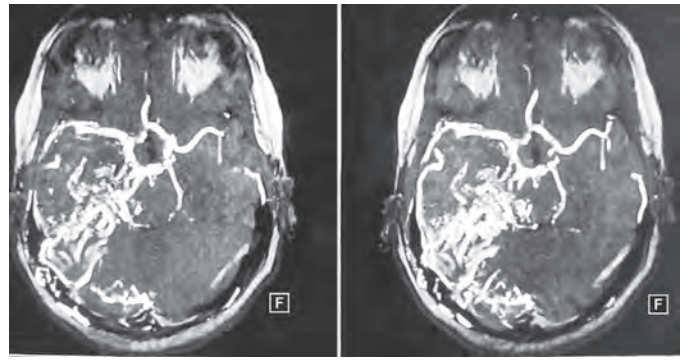


Fig. 8: Magnetic resonance angiography showing an excellent outline of the arteriovenous malformations with detailed information on the arterial pedicles and venous drainage pattern

The MRA is a beneficial supplement of DSA in patients with cerebral AVM at both initial diagnosis and at follow-up after therapy. The MRA can be performed using various techniques.[2] Volume rendered three-dimensional (3D) time-of-flight MRA helps in assessing the relationship between the components of the AVM and that of AVM with an associated haematoma. Surface anatomy scanning of the brain in a superficial AVM can non-invasively demonstrate the superficial AVM along with the brain surface and provide information useful for planning surgery.[25,37] Magnetic resonance venography may be of importance in detection and assessment of small AVMs which are difficult to diagnose with other MR methods.[54]

Conventional angiographic evaluation of an AVM, utilising subtraction and magnification techniques, should be routinely used. The angiographic definition is definitely enhanced by using super-selective techniques and stereo angiographic 3D display, though it is not really necessary for pre-operative planning. Super-selective catheterisation is certainly helpful in a pre-embolisation study.[98,99,131,132,139] Complete angiographic evaluation of an AVM consists of studying the characteristics of the arterial feeders, the nidus and the draining veins (Figs 9A and B).

The features to be noted in the feeding arterial pedicles are:

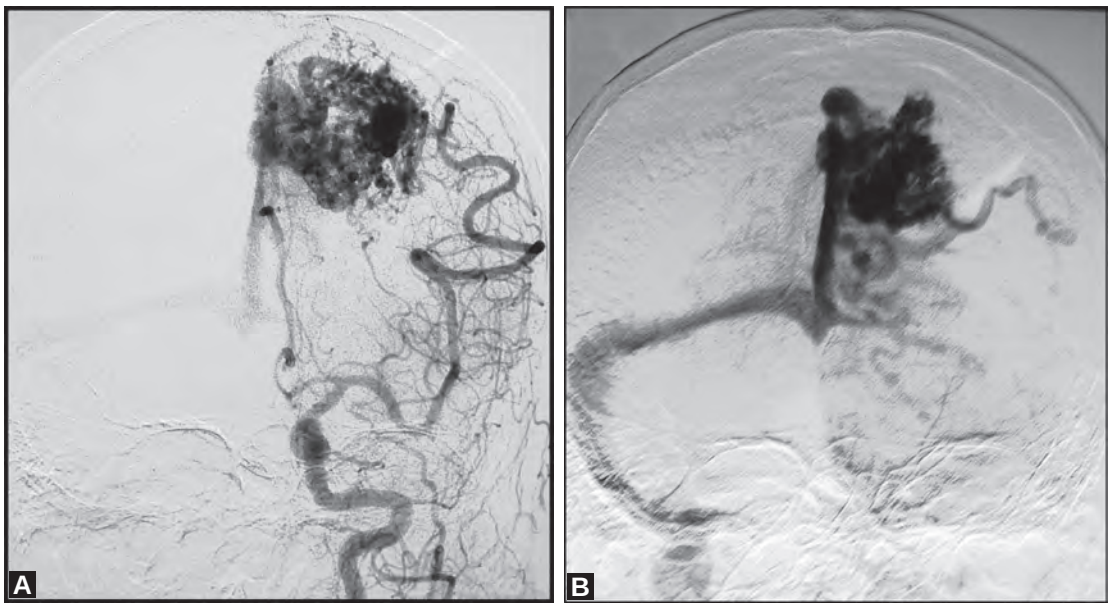
- Whether it is a direct or an indirect feeder
- Presence of stenotic segments in the arteries
- Presence of any dural supply
- Associated angiographic variations of the arteries
- Presence of associated aneurysms which may be either dysplastic or flow related
- Presence of angiographic spasm (which is uncommon in this condition).

A study of the nidus should be undertaken to evaluate:

- The type of nidus, whether it is compact or diffuse. A compact nidus should be further categorised as to whether it is single, multifocal or multicompartmental
- The size of the nidus
- The presence of AV communications and flow characteristics: whether a high flow or a low flow AVM. A high flow AVM is characterised by the presence of a large nidus, usually larger than 4 cm, a few large feeders, high shunt flow within the nidus, decreased circulation or dilated arteries in the adjacent brain parenchyma and evidence of steal from adjacent vascular territories
- Venous pouches
- Intranidal aneurysms
- Careful observation of the venous drainage pattern is mandatory to note:
- *Drainage*: Whether central, cortical or mixed
- Variations in venous anatomy
- Stenosis, thrombosis or kinking of the veins
- Ectatic dilatations of the draining veins

Studies necessary for pre-surgical planning include:

- A good subtracted and magnified angiogram showing the above mentioned features
- The relevant frames to delineate the nidus of the AVM in relation to bony landmarks like the coronal suture, external occipital protuberance and external auditory meatus
- Delineation of the cortical draining veins of both the hemispheres, when an interhemispheric approach to the AVM is planned.



Figs 9A and B: Complete angiographic evaluation of a arteriovenous malformations consists of studying the characteristics of the arterial feeders, the nidus and the draining veins

CAUSES FOR ANGIOGRAPHICALLY OCCULT ARTERIOVENOUS MALFORMATIONS

AVMs that are not visualised on angiography are termed angiographically occult vascular malformations.[84] These may be either truly occult or may not be visualised due to the various factors enumerated below:

- Truly occult AVMs such as cavernoma, telangiectasia, thrombosed AVM
- Transiently occult AVMs due to destruction or compression by haematoma and/or oedema
- Micro AVM
- Intraluminal thrombosis because of stagnation or turbulent flow
- Changes in blood vessels, e.g. fibrosis, spasm, placation or dysplastic changes
- Variable filling of the AVM during angiography.[97]

The CT or MR scan may be helpful in revealing the lesion. In case of angiographically negative AVMs, delayed angiography or surgical exploration has been reported by various authors to be positive in as high as 27–53% of cases.

CT angiography with spiral/helical CT and maximum intensity projection can be used to display vascular images in a 3D format with excellent delineation of the anatomical features. It has a lower acquisition time as compared to MRA. It may become available in the near future as a minimally invasive, low cost screening tool, especially for follow-up examination.[13,81] Volume rendered 3D CTA allows for accurate differentiation of AVM from haemangiomas and other lesions. Precise volumetric definition of an AVM is helpful in radio surgical treatment and planning.[13]

Transcranial Doppler is useful in the study of intracranial vascular malformations in neonates and children to evaluate the malformation as well as the ICH. Colour Doppler imaging can be used in pre-natal diagnosis of foetal brain malformations. It can be utilised to monitor the shunt flow velocity and the status of perfusion of the surrounding parenchyma in pre-operative as well as post-operative evaluation.[27,55] Ultrasound assessment of the volume flow in the extracranial internal carotid artery is useful to evaluate perfusion states of the brain in the presence of an AVM pre-operatively and post-operatively.[16] Transcranial Doppler can be used to demonstrate the size and shape of an AVM which may not be detected on emergency CT in the presence of massive haemorrhage.[61]

Single-photon emission computerised tomography and functional positron emission tomography (PET) scanning are useful for assessment of the extent of hypoperfusion.[54] PET activation studies are also useful in precise location of cortical functions of patients with an AVM to guide management as cortical functions may undergo translocation when a huge AVM involves eloquent areas.[58]

Scanning electromicroscopy shows shunting arterioles (150–250 microns) which can be selectively sectioned to interrupt arteriolar blood supply of the AVM in functional areas of the brain.[80]

GRADING OF ARTERIOVENOUS MALFORMATIONS

Total surgical resection of an AVM is determined by many factors:

- Age and neurological status of the patient
- Size (small, medium, large, giant)
- Location, especially with respect to eloquent areas of the brain
- Configuration of the nidus (compact or diffuse)
- Number, size, type and source of arterial feeders
- Nature of venous drainage (superficial, deep or mixed) and number of draining veins
- Haemodynamics of the AVM (shunt flow, degree of steal from the surrounding parenchyma, feeding artery pressure and participation of perforators)

Various authors have tried to evolve a grading system, which would incorporate the above mentioned factors in order to prognosticate the difficulties of surgical resection and the neurological outcome after surgery. Earliest grading systems were based only on the size of the AVMs.[21,57,58,92,95,104,111,115,123,126,129,130,135,137,138,141] Garretson in 1979[30] proposed a system based on the age of the patient and the arterial feeders. These systems, though easy to apply, did not take into account the eloquent areas of the brain or the relation of the draining vein. Parkinson and Bachers[89] divided AVMs into five types, depending on the arterial feeders and venous drainage patterns. A comprehensive grading system was prepared by Shi and Chen[117] in 1986, but the major drawback of this system was that it failed to determine precisely the eloquence of the area of the brain involved. Spetzler and Martin,[121] in 1986, proposed a system based on the size of the AVM, the venous drainage and the eloquence of the involved brain. This system is simple and easy to remember and has been found to correlate well with surgical difficulty and the post-operative deficits. However, this system ignores the arterial feeders and also makes no mention of the number of draining veins. Pertuiset[96] devised a score system for evaluation of operability and surgical strategy based on anatomic, haemodynamic and clinical factors. Pasqualin[90,91] also proposed a system for grading of AVMs based on the size (volume) of the nidus, the pattern of venous drainage, shunt flow and the arterial feeders. Comparing all these available systems, it is obvious that there is no single grading system that addresses all the important variables affecting the ultimate prognosis in a given case; therefore, they all remain far from ideal. All these systems are only applicable to surgical cases. An ideal system should be simple, uniformly applicable, able to predict operative difficulty as well as outcome, and should enable comparison and evaluation of all treatment modalities.

A simple and easily applicable grading system is described below. The Spetzler and Martin grading system takes into consideration the size, the venous drainage and the eloquence of the adjacent brain.[121] Points are assigned for each factor as follows:

1. Size of AVM:
   - Small (< 3 cm) 1 point
   - Medium (3–6 cm) 2 point
   - Large (> 6 cm) 3 point
2. Eloquence of adjacent brain:
   - Non-eloquent 0 point
   - Eloquent 1 point
3. Pattern of venous drainage
   - Superficial only 0 point
   - Deep 1 point

The grades are I to V and this is arrived at by adding the scores. Grade I, i.e. a small AVM in a non-eloquent area with a superficial drainage has the best prognosis; and grade V, i.e. a large AVM in an eloquent area with deep venous drainage has the worst prognosis. Inoperable lesions are in Grade VI and diffusely involve the brainstem or hypothalamus.

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92 Surgical Management of Cerebral AVMS

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The management of an AVM can be a simple matter or a most challenging neurosurgical exercise. The following varieties of procedures that have been used for dealing with this condition are:

1. Excisional surgery,
2. Endovascular treatment,
3. Radiosurgery,
4. Combination of the above.

The criterion for cure of an AVM is the complete obliteration and non-visualisation of the AVM on follow-up angiography.

CONSIDERATIONS IN THE TREATMENT OF AVM

Important considerations in the treatment of an AVM are:

- Factors related to the patient—age, general condition, neurological state, occupation and psychological attitude
- Factors related to the AVM—natural history of the AVM, its mode of presentation, and anatomic and haemodynamic characteristics of the AVM
- Experience of the neurosurgical team and the available facilities.

Factors Related to the Patient

Age is an important determinant of surgical therapy. Young patients have a high-risk of bleeding from an AVM and the cumulative morbidity due to haemorrhage or seizures is very high. While confronted with an older patient, the risk: benefit ratio for the individual patient should be considered, keeping in mind the life span of the patient and also the fact that the risk of bleeding may actually decrease after middle age. A patient with a poor performance on the Karnofsky scale is unlikely to have a good outcome. Occupation of the patient and the psychological motivation are important considerations, especially in relation to the post-operative morbidity.

Factors Related to the AVM

(a) The natural history of cerebral AVMs leaves no doubt that the long-term prognosis for patients with untreated malformations is grim. The natural risk associated with most of the AVMs far exceeds the risks related to treatment.[28,29,61]

(b) *Mode of presentation:* There is no argument as far as the treatment of AVMs presenting with haemorrhage is concerned. They undoubtedly merit definitive treatment. With increasing understanding of the natural history it is becoming evident that AVMs presenting with non-haemorrhagic manifestations also deserve aggressive management. Surgery is being increasingly advocated for AVMs presenting with seizures.[11,56,76] Heikkinen et al.[27] employed radiosurgery for AVMs presenting with seizures and reported a good outcome as regards to seizure control. Patients with intractable headache alone, progressive neurological deficits or hemifacial spasm, all need to be considered for definitive treatment based on the individual merits of the case. A fixed neurological deficit from a past haemorrhage does not improve following surgical excision, but such patients, if young, are offered definitive treatment in order to prevent recurrent bleeds and further increase in morbidity. An asymptomatic AVM in a young patient definitely deserves aggressive management, whereas, in an elderly patient it may be left alone.

(c) *Anatomic and haemodynamic factors:* These are important determinants of the mode of therapy to be chosen for a specific case. While the majority of the AVMs can be surgically excised, it may be difficult to operate on certain small AVMs in deep, inaccessible or eloquent areas. The same applies to very large, diffuse AVMs occupying almost an entire hemisphere. The relative merits of radiosurgery, embolisation or any of the combinations of the available modalities need careful consideration.

Experience of the Neurosurgical Team

As each AVM is different from the other, the feasibility and the risk of surgical excision is best judged by the surgeon based on his individual experience. In addition, the availability of competent neuroanaesthetists and neuroradiologists, especially trained in interventional techniques, is helpful in the total management of difficult and challenging malformations.

SURGERY

Total surgical excision remains the gold standard in the treatment of AVM. The aims of surgical excision are to interrupt the natural history of the disease, and prevent

future haemorrhage, decrease cerebral steal, improve neurological deficits and to achieve seizure control.

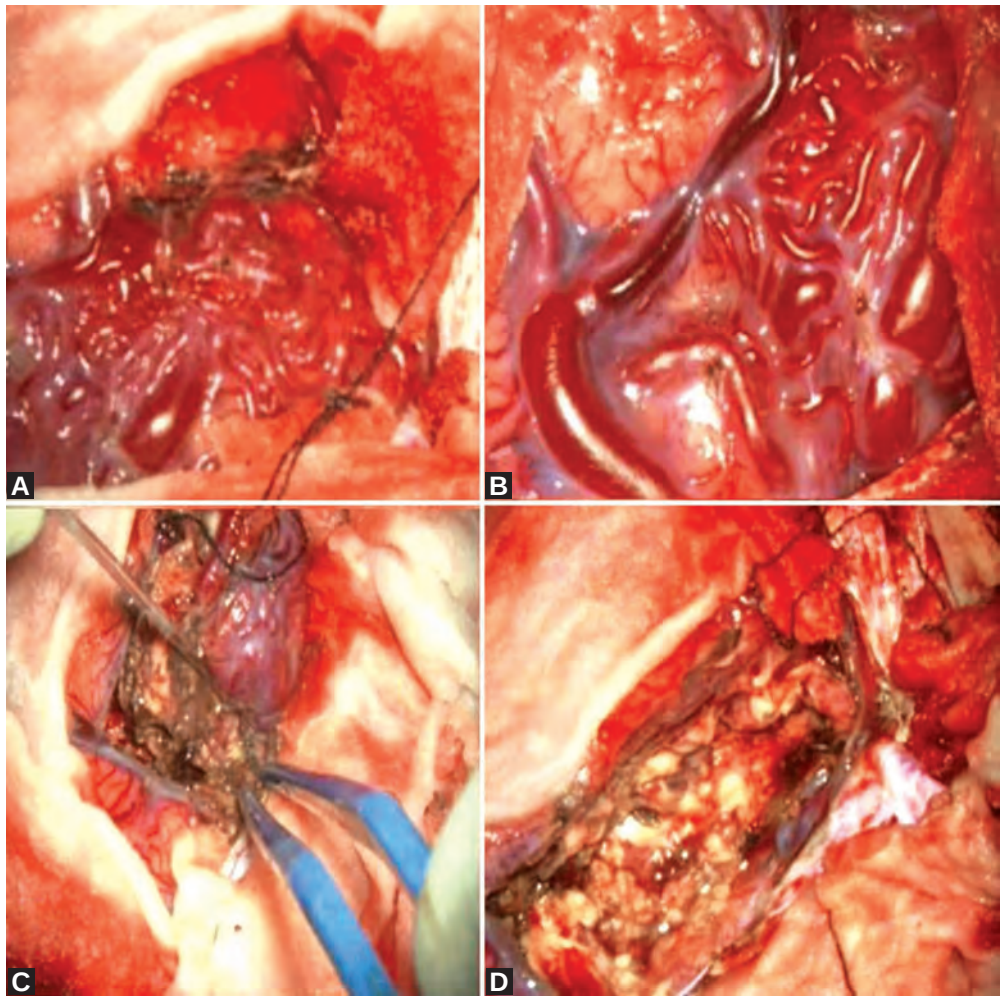
Principles of Surgical Treatment

Unlike in aneurysms, the risk of an immediate rebleed from an AVM is much less. Generally, the arterial feeders should be attacked first then followed by excision of the nidus and finally resection of the draining vein.[17,75] Care should be taken to preserve the veins (Figs 1A to D) until the very end of the operation. When an intracranial AVM is resected, the goal should be complete obliteration. The timing of angiography and elective excisional surgery is delayed 2–3 weeks for the brain to recover from the initial insult, unless a large and life-threatening haematoma warrants early evacuation. Early angiography often fails to delineate the exact morphology of a malformation in the presence of a sizeable haematoma. In the presence of a haematoma with attendant cerebral oedema and raised intracranial pressure, attempts at early surgical excision may often preclude the chances of total extirpation of the malformation. While awaiting angiographic evaluation and definitive surgery, patients are administered anticonvulsants and antioedema therapy if indicated.

Small AVMs located in the polar regions or on non-eloquent cortical surfaces, with or without a bleed, pose little difficulty for total excision. However, large high-flow AVMs or those with deep arterial feeders are often a challenge for one stage surgical excision. In such lesions, pre-operative embolisation, particularly of the deeper feeders, reduces shunt flow, minimises intra-operative bleeding and avoids post-operative autoregulation breakthrough syndrome.[54,66] Thus, it is an important adjunct to subsequent successful total excision.

For extensive malformations, certain surgeons employ planned staged surgical resection without pre-operative embolisation, depending upon sectorisation of the lesion.[50]

All patients are operated upon under general anaesthesia with the head positioned in such a way that the malformation is above the heart level to enable maximum venous drainage. Intra-arterial monitoring of blood pressure is mandatory. A generous craniotomy is made to have good access to the lesion. In patients with a dural component of the malformation, the dura should be excised and the dural defect repaired with



Figs 1A to D: Intra-operative image showing stages in excision of AVM. (A) AVM seen as a bunch of worms and surrounded by gliotic tissue. (B) Draining vein is seen entering into the superior sagittal sinus which should be preserved till the end of surgery. (C) Excision of AVM. (D) Post-operative stage

pericranium, fascia lata or lyodura. The dura is often adherent to a cortical malformation and should be separated with care using bipolar diathermy. The arachnoid over the surface of the malformation is usually thickened and often appears milky white.

Large arterialised draining veins are prominent landmarks of an AVM at surgery. However, the margins of most malformations buried in the parenchyma are usually not definable on the cortical surface. The dilated arterial feeders, when present on the surface, appear greyish-pink and are thin walled. On occasions it may be difficult to differentiate between an arterial feeder and an aterialised draining vein. In such a case, transient occlusion of the vessel helps in differentiation. The arterial feeders often lie buried in the sulci adjacent to the malformation and may be traced by dissecting the arachnoid over the sulci with the help of accurate anatomical localisation. The major arterial feeders are identified early in the dissection and are coagulated with bipolar cautery adjacent to the lesion. For reaching the arterial feeders buried in the sulci, it may be necessary to trace one or more superficial draining veins on to the nidus and the veins may often be used as a handle, as was described by Malis, for "marginal dissection" along the surrounding gliotic parenchyma.

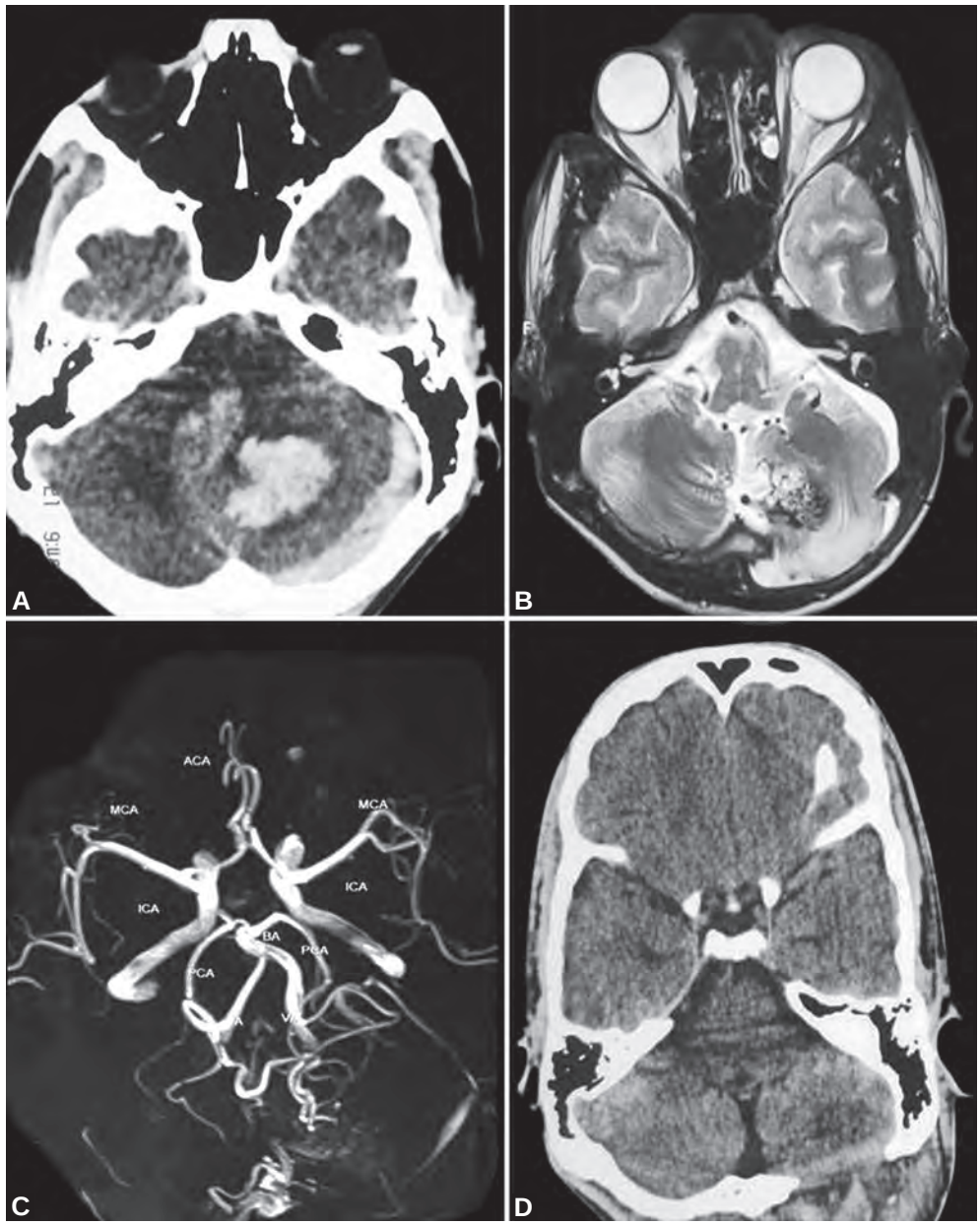
The presence of a haematoma, as seen in 42% in Rout's patients,[57] or small cystic cavities help in delineation of the margins of the malformation, facilitating its dissection. The adjacent gliotic parenchyma often appears as a "pseudocapsule"[16] and offers a plane of cleavage for the dissection of the lesion. The "pseudocapsule" is more often found in compact lesions as compared to the diffuse malformations. It is always essential to preserve any large draining vein till the end of surgical resection.[17,75] Although most arterial feeders can be coagulated with bipolar diathermy and divided, large arterial feeders are best clipped and coagulated. As the deep arterial feeders are most difficult to reach, identify and divide, it is often essential to shrink the size of the malformation using low voltage bipolar diathermy. Sometimes, it may be required to retract the malformation to reach the large feeders. Rarely one may encounter a normal artery coursing over the lesion with its branches supplying the malformation. In such situations it is essential to preserve the parent artery and selectively coagulate only the feeding branches. In the event of bleeding from a draining vein, the rent can be coagulated or may be temporarily packed with gelfoam and cottonoids and dissection continued in adjacent areas till the arterial feeders are taken care of.

While hypertension is avoided during dissection, temporary hypotension may occasionally be required to control troublesome bleeding. Under high magnification, one may dissect through the malformation and a coil of vessels lying outside the plane of dissection may arouse the suspicion of an incomplete resection. Following resection, persistent oozing from the bed of the malformation suggests either a torn and retracted vessel in the white matter or a residual AVM nidus which should be pursued till absolute haemostasis is achieved. It is mandatory to raise the blood pressure above the normal level or even perform Valsalva manoeuvre to confirm haemostasis prior to dural closure. In the event of brain oedema supervening during dissection, it is better to abandon the procedure and plan staged resection. Advances in pre-operative embolisation techniques have made planned staged resection of large high flow AVMs unpopular, except for some extensive lesions which may need different avenues of approach. Malformations in certain locations, like the medial temporal lobe, deep nuclei, internal capsule, corpus callosum, intraventricular, sulcal, along the tentorial incisura, and the posterior fossa require special operative approaches. Intraoperative embolisation prior to an attempt at surgical excision can be adopted, if there are angiographic monitoring facilities,[62] but this procedure has its own limitations.

Advances, like stereoscopic angiography, bipolar diathermy with automatic irrigation, improved neuroanaesthetic management, application of Nd-YAG laser photocoagulation, evoked potential monitoring for brainstem lesions, intra-operative DSA facilities, intra-operative cerebral blood flow studies and fluorescein angiography, as well as cortical mapping of the eloquent areas, have profoundly expanded the limits of successful total excision of AVMs that were previously considered inoperable, with an acceptable mortality and morbidity.[71]

Post-operatively, the patient's head is kept elevated by 30–40 degrees for optimal venous drainage. Anticonvulsants and decongestant therapy, including steroids, are continued. Hypertension is avoided; patients are kept relatively underhydrated for the first 48 hours to avoid hypervolaemia, to prevent the deleterious effect of hyperperfusion around the margins of resection and the surrounding brain. Some authors have even advocated elective ventilation and barbiturate coma for 48 hours following excision of large deep seated high flow AVMs. Steroids are tapered off 1 week after surgery. Post-operative check angiography is essential to evaluate the completeness of surgical excision of the malformation. Immediate post-operative angiogram may fail to reveal a small residual nidus because of cerebral oedema and blood clot. The ideal time for performing a check angiogram is 3–6 weeks after surgery. If a residual AVM is detected, it is operated upon at the earliest available opportunity (Figs 2A to D).

In most standard neurosurgical units excisional surgery carries a mortality of less than 2% and a morbidity of less than 10%. These results offer a better prognosis than the natural history of most of the cerebral arteriovenous malformations.[12,29] However, the risks of surgical excision still remain high for AVMs located within the brainstem and deep nuclei, as also for the very large lesions.



Figs 2A to D: Image showing left cerebellar AVM. (A) CT scan brain showing left cerebellar haematoma. (B) MRI scan brain showing left cerebellar AVM. (C) MRI angiogram showing AVM in the cerebellum. (D) Post-operative scan showing complete excision of the lesion

AVMs Associated with Aneurysms

Management of AVMs in association with aneurysms deserves special mention.[35] Aneurysms in such a setting may be either flow related, developing as a result of high flow through the AVM; or non-flow related, and located at the common sites for aneurysms in the circle of Willis. Flow unrelated aneurysms located outside the angioarchitecture of the AVM are unlikely to regress after surgery for the AVM and may in fact enlarge and rupture once the "sump" effect is eliminated following extirpation of the AVM. These aneurysms should be operated upon before treating the AVM. Regression has been noted[39] in the size of flow-related or dysplastic aneurysms, of distal aneurysms or aneurysmal dilatations located on the trunk of the main feeding arteries after restoration of normal flow following excision of AVM. The AVMs are associated with aneurysms in 3% of the cases.

Haemodynamic Changes after Removal of an AVM

The immediate change that occurs following removal of an AVM is the interruption of the nonperfusion flow and the conversion of shunt flow into perfusion flow pattern. There is an increase in the arterial end pressure, and the pressure at the venous end decreases which results in an increase in the cerebral perfusion pressure. This increase in the perfusion pressure could be due to elevated plasma renin and norepinephrine levels.[7]

Post-Operative Complications

Complications that may be encountered in the early post-operative period are:

- Brain swelling which can be caused by a venous infarct, retraction oedema, haemorrhage from residual AVM, perfusion pressure breakthrough syndrome or occlusive hyperaemia[45]
- In AVMs with large sized and long feeder vessels, when there is evidence of stagnation of blood in the post-operative angiogram retrograde thrombosis of the feeding artery may occur, especially in elderly patients
- Post-operative hyperthermia is another serious complication[3] which can be exacerbated by mild, intra-operative-induced hypothermia.[8] Hence, careful monitoring of the temperature in the intensive care unit is recommended.

Normal Perfusion Pressure Breakthrough Syndrome

Two hypotheses for the cause of brain oedema and haemorrhage during or after surgery in AVM have been proposed—normal perfusion pressure breakthrough syndrome (NPPB) and occlusive hyperaemia.

The NPPB syndrome was described by Spetzler et al.[63] in 1978 and is thought to be related to dysautoregulation in the brain parenchyma adjacent to an AVM. It is, however, a rare occurrence when there is a large high-flow AVM, the surrounding brain tissue is in a state of chronic ischaemia due to vascular steal by the same parent vessel which feeds the AVM. The vessels in this ischaemic, hypoperfused area will be in a state of chronic vasodilatation in response to the persistent ischaemia and they lose their inherent capacity for rapid autoregulation. The rapid interruption in the flow to the AVM and restoration of perfusion flow may result in an increased flow in these maximally dilated vessels which are unable to contract in response to the increased flow. This results in seepage of blood from these vessels into the adjacent brain parenchyma. This phenomenon is termed the perfusion pressure breakthrough syndrome. The key factor in prevention of this malignant post-operative haemorrhage and oedema is staged reduction of blood supply to the malformation. This can be accomplished by staged surgical ligation of the feeders[16,44,47,50,59,73]

The factors that help in predicting the risk of developing NPPB are:

- Clinical evidence of cerebral ischaemia, e.g. focal neurological deficits, headaches, seizures
- CT or MR evidence of cerebral atrophy resulting from hypoperfusion
- Angiographic evidence of large, high-flow AVM, numerous large calibre feeding arteries, steal from other vessels, border zone location, flow shift towards the AVM
- Pre-operative evidence of ischaemic rim around the nidus identified by cerebral blood flow studies, low feeding artery pressure before removal of AVM, immediate normalisation of arterial and venous pressures after removal of the AVM, increased regional cerebral blood flow after removal of the AVM.

Patients at risk for developing NPPB can be identified pre-operatively and such a complication can be prevented by converting the large high flow AVMs into smaller lesions by either pre-operative embolisation or staged resection.[2,64] However, partial embolisation of the nidus and staged resection are not without drawbacks. These procedures may fail to protect adequately against NPPB because it requires time to correct dysplastic regulation. There is always a risk of haemorrhage between the stages of resection. This risk may even increase, because of the alteration of haemodynamics in the AVM. Other points against staged resection are the risk of developing acute on chronic hypoperfusion, divergence of flow to deeper or non-accessible vessels and recruitment of new collaterals which may increase the surgical difficulty during attempts at complete obliteration of the AVM.

Occlusive Hyperaemia

This hypothesis postulates that the malignant post-operative haemorrhage and oedema can be caused by either arterial stagnation and obstruction or venous outflow obstructions, which are in turn related to resection of the AVM.

Post-Operative Seizures

The incidence of post-operative seizures after removal of an AVM ranges 6.5–50%. The incidence of *de novo* seizures has been reported as 11.6%.[75] However, it is to be noted that seizures occurring in the immediate post-operative period do not usually recur. The risk of delayed epilepsy is small, especially if the patient did not have pre-operative seizures.

Results of Surgery

Immediate mortality due to surgery can be expected in 1–6% of cases. Delayed mortality has been reported as 1–2%. Morbidity in the immediate post-operative period is seen in 20–44%, whereas over a period of time, the morbidity decreases to 2–6%. The dramatic improvement in the neurological deficits in the majority of patients is because of resolution of the pre-operative intra-cerebral haematoma and restitution of normal cerebral perfusion. However, patients developing fresh neurological deficit immediately after surgery also improve during the follow-up period. Development of immediate transient neurological deficits may be because of retraction oedema or due to the phenomenon of surrounding cortical suppression described by Yasargil[75] as "Temporary blocked syndrome". Patients in poor pre-operative clinical grade may be expected to have a poor outcome.

EMBOLISATION

Interventional neuroradiologists can embolise the AVM nidus or the feeders as definitive treatment, or as a part of the multimodality approach to the management of large high flow AVMs (Figs 3A and B). Embolisation (see chapter on Embolisation) is also useful in occluding inaccessible feeders.[54] Luessenhop and Spence reported, in 1960, the first successful embolisation of an AVM using methylmethacrylate.[39] Current indications for embolisation can be divided into: (1) Pre-surgical embolisation for large or giant cortical AVMs, and (2) Embolisation before radiosurgical intervention to reduce the nidus size.

Embolic materials can be divided into solid or liquid agents. Solid agents consist of fibres, microcoils and microballoons[5,19,21,31,48,60,67] and liquid agents include cyanoacrylate monomers such as I-butyl cyanoacrylate (IBCA) and N-butyl cyanoacrylate (NBCA), ethylene vinyl alcohol (EVAl) copolymer[4,6,40,41,49,70]) absolute ethanol, with or without the use of contrast agents for visualisation under digital subtraction fluoroscopy.[15,51,74] Usually the transfemoral route is employed. When the transfemoral route cannot be employed, Gomes[25] has suggested alternate approaches like direct injection of the embolic materials into the malformation or into the central vessels of the lesion under fluoroscopic guidance and selective catheterisation and embolisation of the abnormal veins draining the malformation.

Pre-Radiosurgical Embolisation

Endovascular therapy in radiosurgical interevention for AVMs has three potential goals:[13] (1) to decrease target size to less than 3 cm in diameter, because smaller volumes have a higher cure rate with less morbidity; (2) to eradicate angiographic predictors of haemorrhage, such as intranidal aneurysms or venous aneurysms and (3) to attempt to reduce symptoms related to venous hypertension. There is no ideal embolic material identified for pre-radiosurgical use.[13,14,23] Various authors have reported on the use of intra-operative embolisation, but it is not favoured by most neurosurgeons. Tissue reaction to embolotherapy with various embolic materials is variable.[53]

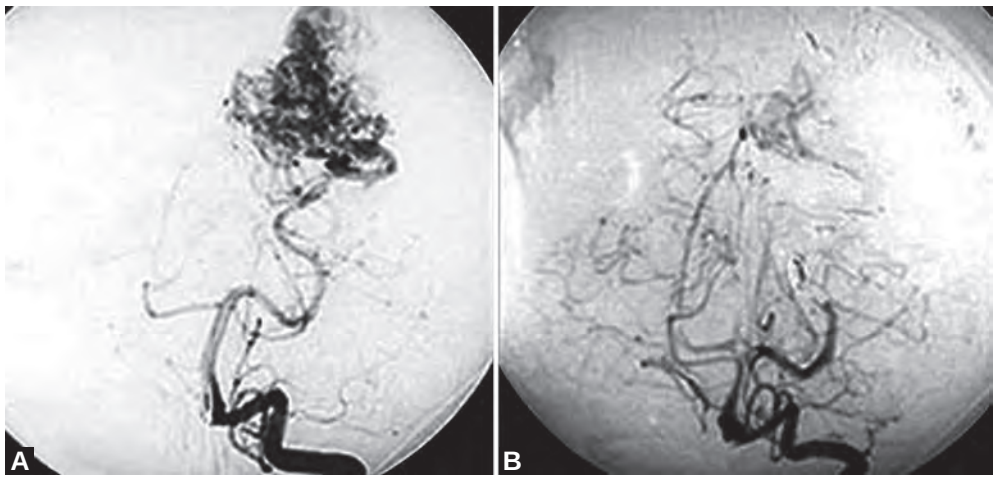
Palliative Embolisation

This may be recommended for patients who have large, inoperable cortical and subcortical AVMs and in those patients presenting with uncontrollable seizures or with progressive neurological deficit due to secondary venous hypertension and/or arterial steal phenomenon.[5,22,68]

Cyanoacrylates and polyvinyl alcohol (PVA) cause acute inflammation and angionecrosis in the early stage, followed by a late chronic inflammatory response and foreign body giant cell reaction. Avitene causes delayed endothelialisation. Hence, careful management of the coagulation profile is recommended to prevent thromboembolic complications during and after the procedures, although algorithms for anticoagulation remain controversial.[18,52,63]

Complications encountered with embolisation may be due to the haemodynamic alterations or due to the material used. Haemodynamic alterations may cause increased risk of haemorrhage because of pressure changes in the feeding artery and by recruitment of collaterals, in cases of partial embolisation of the nidus. Materials, like IBCA, may cause difficulty in dissection and retraction of the AVM during subsequent surgery, because of its hard consistency and failure of the vessels containing the IBCA cast to contract during coagulation. Rarely, the IBCA cast may dissolve, resulting in recanalisation of the AVM.

Other complications that may be encountered include neurological deficits due to occlusion of normal arteries, hyperaemia and swelling of the surrounding parenchyma, catastrophic haemorrhage due to rupture of arterial feeders or rarely, glueing of the catheter *in situ* due to rapid polymerisation of IBCA.[72] The role of partial embolisation of an AVM is limited due to the risks already enumerated; however, it may be indicated in special cases to reduce cerebral steal and hypoperfusion



Figs 3A and B: DSA image showing. (A) Left parietal AVM pre-embolisation. (B) Post-embolisation showing complete obliteration of the AVM

in patients presenting with chronic dementia or intractable headache.

RADIATION THERAPY

Conventional radiotherapy has no role in the treatment of AVMs.[36] However, stereotactic radiosurgery using charged particle beams (He, proton or neutron), Gamma knife (Co-60) or linear accelerator have all been found to be effective in the treatment of AVMs. Radiosurgery is indicated: (1) in small (<2–3 cm), deeply located, surgically inaccessible AVMs in eloquent areas of the brain with multiple small feeders; (2) in combination with surgery or embolisation for large AVMs, inaccessible or unresectable residual AVMs, and (3) in patients who are either not willing for surgery or poor surgical candidates because of concomitant medical illness. Ideal candidates for radiosurgery are the patients with small AVMs in eloquent areas, preferably with an isolated pedicle. Usually, the nidus of the AVM is irradiated in a single sitting; however, multiple sittings may be required in certain cases with large AVMs. Irradiation of the feeder vessel may also be tried in cases of large inoperable AVMs with discrete isolated pedicles of feeders. A successful obliteration rate of 62.5% at the end of 1 year, 83.2% at the end of 2 years and 94% at the completion of 3 years has been reported by Steiner[65] for Gamma knife therapy. Colombo et al.[10] reported a 100% obliteration rate after 3 years of treatment with linear accelerator radiosurgery. Fabrikant[20] reported an estimated complete obliteration rate of 90–95% at the end of 2 years using heavy charged particle (He) Bragg peak radiosurgery. Obliteration rate is determined by the volume of AVM treated, results being better for those of smaller volume. The radiobiological basis for the effectiveness of radiosurgery in the treatment of AVMs is still unknown. Changes seen in the early stage are swelling, degeneration and necrosis of the endothelial cells, followed by thrombosis, fissuring of the walls and punctuate haemorrhages which lead to progressive degeneration, fibrosis and perivascular infiltration of lymphocytes. Delayed changes over a few months or years are endothelial proliferation causing obliterative angitis leading to obliteration of the lumen, media proliferation and perivascular fibrosis.

The limiting factors in the successful outcome of radiosurgery are the size (3–3.5 cm for photons and 4 cm for charged particle) and the latency period. During the latency period of 2–3 years, till the AVM is completely obliterated, the risk of bleeding remains at 3–4% or may even be enhanced due to altered haemodynamics of the AVM. The other complication seen with radiosurgery is radiation induced damage by secondary occlusion of normal vessels causing focal neurological deficits in 3–4% of cases.[42] Major complications occur in about 2%, and rebleed is seen in about 4% of patients.[20] Transient asymptomatic white matter changes may occur in about 10% of cases, whereas, delayed radiation necrosis with permanent neurological sequelae is seen to affect about 1% of the patients. Patients' age, location and flow characteristics of the AVM, volume of the lesion, and dose and fraction schedule of radiation are some of the factors contributing to complications. Newer energy sources, such as Neon and Carbon, are being investigated to evaluate their potential as radiosurgical tools. Also, endovascular boron-neutron capture therapy,[43] as well as targeted radiotherapy using monoclonal antibodies against mesothelial cells of the AVM, is under investigation.

ELECTROTHROMBOSIS AND CRYOSURGERY

To overcome troublesome bleeding and facilitate total excision of deep seated and large AVMs, Handa et al.[26] employed electro-thrombosis using copper electrodes and direct current. If a check angiogram does not reveal disappearance of the nidus, the AVM is then excised easily. However, this procedure has not gained wide popularity and is of historical importance.

Walder[69] reported his experience of cryosurgical management in 27 cases of large, deep seated or eloquent area AVMs. The AVMs could be totally eliminated in 14 cases. It is of paramount importance that the cryoprobe should be immobile during freezing and is entirely above the freezing point when withdrawn to avoid a rupture. However Walder himself felt that this method of treatment has failed to provide a solution to the problem.

SPECIAL CONSIDERATIONS

Pregnant Patients

Most data regarding AVM haemorrhage risk during pregnancy are inconclusive. Robinson et al.[55] suggested that the risk of haemorrhage during pregnancy is similar to that at other times. The rebleeding rate during the same pregnancy may be higher than the early rebleeding rate in non-pregnant patients. Although haemorrhage during delivery is a major concern, vaginal delivery does not carry a higher risk for haemorrhage than delivery by cesarean section.[58]

Recommendations

(1) If a woman anticipates pregnancy and has a known AVM, treatment should be considered before the pregnancy.

(2) If the lesion is discovered during pregnancy, a decision should be made regarding the treatment risks versus the risk of haemorrhage during the remainder of the pregnancy. This also must include the potential risk to the foetus during intervention, whether it is by embolotherapy, surgical extirpation, or radiation and the associated diagnostic tests. In most cases, such risk-benefit analysis will not support elective treatment of AVMs during pregnancy.

Paediatric Lesions

The AVMs account for 30–50% of haemorrhagic strokes in children[9,24] and paediatric patients are more likely to present with haemorrhage than adults, with some authors like Humphreys et al.[32] and Kahl et al.[33] reporting 80–85% haemorrhage rate as their initial presentation.

Paediatric AVMs have been treated with surgical excision,[9,32,33] endovascular embolisation,[37] radiosurgery[1,34] and multimodality management.[30,46]
Humphreys et al.[32] reported a series of 160 paediatric AVMs in which the morbidity and mortality rates were 18% and 11%, respectively. Lasjaunias et al.[37] reported the largest endovascular series of 179 paediatric AVMs, in which the morbidity and mortality rates were 28% and 16% respectively. The largest radiosurgical series is, by Levy et al.,[38] of 40 paediatric AVMs, in which they found a 30% rate of permanent neurological deficits.

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93 Embolisation of Intracranial Vascular Malformation

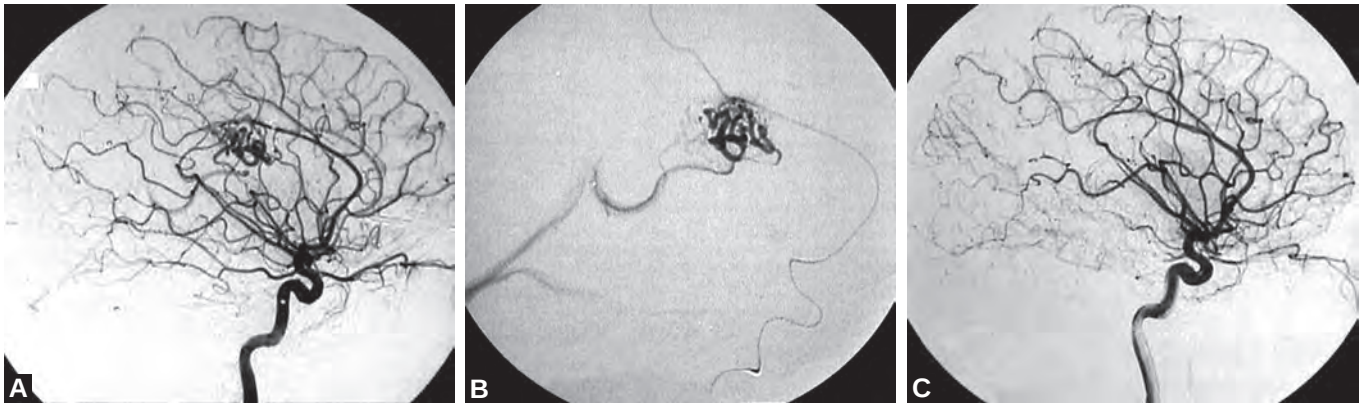
Anil Karapurkar, Nishant Aditya

Arteriovenous malformations (AVMs) are the second most common intracranial vascular malformations. They are believed to be congenital. Multiple AVMs are rare. *De novo* AVMs are rare but have been documented.[23] Familial AVMs are rare.[35] Ninety percent of intracranial AVMs are supratentorial. AVMs consist of a bunch of vessels, called nidus, which is made up of vessels of variable diameter and vessel wall thickness. Distinct vascular compartments within an AVM have been described.[109] Within the nidus there may be an arterial aneurysm[99] or an arteriovenous fistula (AVF). The nidus may be compact or diffuse. No two specialists would agree about the exact nidus of an AVM,[40] because it is usually obscured by large arterialised draining veins. The AVM may be fed by one or more branches from cortical and deep branches of all major arteries such as the ACA, MCA and PCA. If the AVM is of the high flow variety, feeding arteries are dysplastic and these dysplastic arteries may be associated with flow related aneurysms.[18,93,99] The draining veins have thick walls as they are arterialised. In high flow AVMs, with or without AVF, the draining veins may have large aneurysms or varices along their course. There may be stenosis of the draining veins. Anomalies of venous outflow are not infrequent and the deep venous system may be absent or there may be stenosis of the straight sinus or sigmoid sinuses. Haemorrhage may occur when there are venous anomalies or there are sudden changes in venous pressure.[63,64] The brain surrounding the AVM may show areas of gliosis due to ischaemia secondary to steal.[58] There may be calcification and cyst formation due to previous haemorrhage. Some parts of the AVM may be thrombosed.[55]

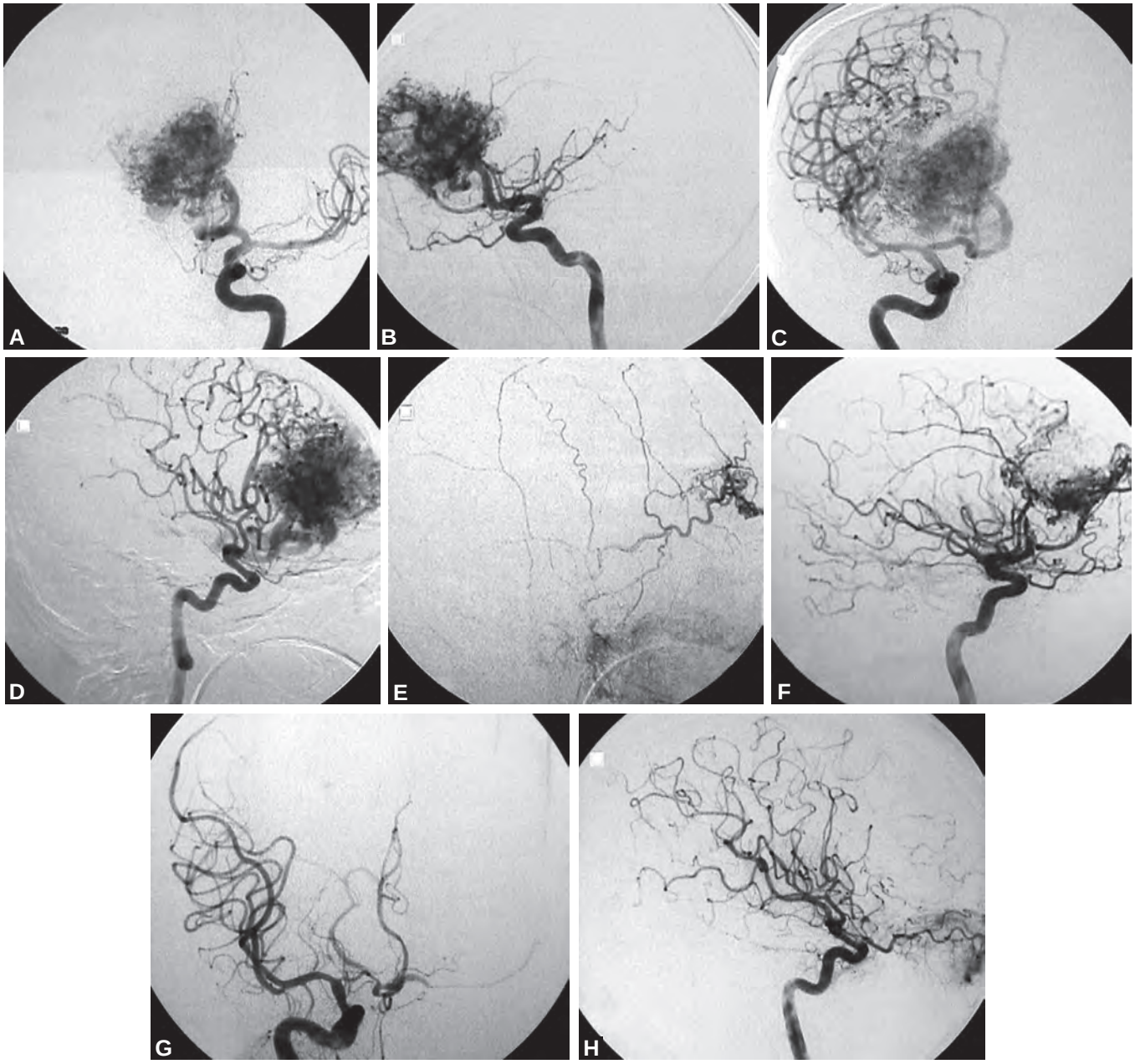
To standardise the management of AVMs, many classifications have been proposed. The one commonly accepted is that of Spetzler-Martin.[90] This takes into consideration three factors: (1) the size of the AVM; (2) the eloquence of the brain area involved and (3) the venous drainage. Grade I AVMs are the easiest to treat and Grade IV the most difficult. Grade V is inoperable and is best left alone. This is essentially a classification which is useful in identifying the surgical risks of AVM. However, most interventionists find this classification inadequate. The criteria which should be included in the classification are: (A) Weak spots—such as associated (1) juxta-nidal aneurysm, (2) intra-nidal arterial aneurysm, (3) aneurysm on the circle of Willis, (4) subependymal venous aneurysm, (5) stenosis along venous channels, especially when there is a (6) single draining vein, (7) congenital absence of the deep venous system which carries a higher risk of haemorrhage; (B) Associated intra-nidal A-V fistula with very high flow across the nidus which increases the risk of surgical extirpation and failure of stereotactic radiosurgery (SRS). In true intra-nidal A-V fistula, the microcatheter passes from the feeding artery to the draining vein without the intervening nidus. If there are "weak spots" even Grade IV or V AVMs according to Spetzler-Martin classification should undergo targeted embolisation to reduce the risk of haemorrhage.

The natural history of brain AVM is not precisely known despite several studies,[60] including those of captive populations.[24,36,106] The common presentations of brain AVM are: (1) haemorrhage;[63] (2) epilepsy; (3) progressive neurological deficit[55] and (4) migraine and intractable headache. Clinical signs depend on the location of the malformation[10,21,29,30,52,100,107] and the venous drainage.[49,50,63] Papilloedema due to raised intracranial pressure and venous hypertension has been reported.[21] Contralateral cerebral lesions due to raised venous pressure in the dural venous sinuses leading to impaired venous return have also been reported.[49]

Haemorrhage is the most devastating presentation in about 60% of patients [Figs 1(A to C) and 2(A to H)]. Haemorrhage is usually parenchymal, but it may be subarachnoid or intraventricular.[72] The average incidence is 2–4% per year of life. However, some studies have recorded less than 1% haemorrhage per year. The risk of re-bleeding is higher if there is a weak spot such as a false aneurysm, true arterial intra-nidal aneurysm, single draining vein with venous stenosis, or venous stenosis on a major venous outflow. Otherwise the risk is about 6–10% in the first year. Thereafter, it is the same as for other AVMs, i.e. 2–4% per year. The risk of bleeding is higher during pregnancy and parturition. If an AVM is diagnosed in the antenatal period elective caesarean section is mandatory. AVMs in some locations are prone to re-bleeding. These include those in the basal ganglia and corpus callosum.



Figs 1A to C: Callosal AVM with IVH. (A) ICA lat pre. (B) Superselective lat. (C) Follow-up after 1 year



Figs 2A to H: Large bifrontal AVM with haemorrhage. (A and B) Rt ICA. (C and D) Lt ICA. (E) Lt ECA angios showing AVM. (F and G) Post-embol Lt ICA angio. (H) Following surgical excision

INVESTIGATIONS

CT scan after double dose contrast and CT angiogram on spiral or multi slice CT scanning machines show the AVM nidus very well. However, feeders, draining veins, associated aneurysms and haemodynamics cannot be assessed. It is also impossible to often delineate the precise nidus because of the huge dilated early filling veins. It is difficult to distinguish arteries from arterialised draining veins. MRI sometimes is useful to show the true nidus.[11,45,88] However, it is difficult to get a true picture of the AVM on the MRI or MRA even with the latest machines. At best, static images can be obtained. No concept of the haemodynamics can be obtained.

Digital subtraction angiography (DSA) remains the gold standard in the diagnosis of AVM.[19,40,45,85] Magnification, rapid subtracted filming at 6 or 12 frames per second and multiple projections and rotational angiography provide all the desired information. For posterior fossa AVMs bilateral vertebral angiograms (VA) in addition to bilateral internal and external carotid (ICA and ECA) angiograms are mandatory. For supratentorial AVMs, bilateral ICA, ECA and at least one VA angiogram must be done. The angiogram must carefully be analysed to include: (1) the precise site and size of the AVM; (2) the arterial supply of the AVM; (3) the venous outflow, whether superficial or deep, or both; (4) associated arterial aneurysm; (5) associated venous anomaly such as stenosis, absence of deep venous system, aneurysm or varix; (6) competition between the venous outflow of the brain and that of the AVM; (7) functional antegrade flow in the superior sagittal sinus, as raised venous pressure can cause a rise in ICP [33,51] and papilloedema; (8) any evidence of mass effect due to associated clot as seen by stretching and separation of arteries and veins and (9) any supply from external carotid branches.[44,49,86]

An aneurysm may be remote from the AVM, e.g. in the circle of Willis. An aneurysm along the course of the feeding artery, remote from or close to the AVM is usually a flow-related aneurysm. Aneurysms on the feeding pedicle remote from the nidus usually need no treatment and regress after the AVM has been obliterated. Aneurysms close to the nidus need to be treated as they may rupture. There may be an aneurysm within the AVM nidus. The latter is especially common in deep AVMs of the basal ganglia, thalamus and brainstem. There may be multiple aneurysms on different branches. These may easily be missed because they are obscured by the nidus and may only be seen on super-selective angiograms. The author learned this much to his chagrin when he treated an aneurysm on the posterior cerebral artery and missed a small one on a lenticulostriate artery. The patient presented within 3 weeks with a fresh large haematoma from the second aneurysm, which had been missed. If there is an associated arterial aneurysm, whether in the circle of Willis or within the nidus it is almost certain to be the cause of the intracranial haemorrhage and must be dealt with first.[72]

INDICATIONS FOR TREATMENT

AVMs presenting with haemorrhage must be treated.[79] The mode of treatment—Surgery/Endovascular/Radiosurgery—would depend on the site, size and "weak spots" of the AVM. The management of incidental (those presenting with epilepsy) and Grade IV and V AVM remains controversial.[13,28,80,94,95] Small AVMs are thought to bleed more frequently than large AVMs.[24] They must be treated. AVMs, such as those in the basal ganglia and corpus callosum, which are prone to re-bleed should be treated. Spetzler-Martin Grade IV and V should be treated if there are weak spots, such as intra-nidal or large flow related aneurysms, subependymal venous aneurysms or significant flow limiting venous stenosis, which are likely to bleed. AVMs presenting with intractable epilepsy, severe headache which is usually due to extracranial dural arterial supply and incidental AVMs with "weakness" must be treated.

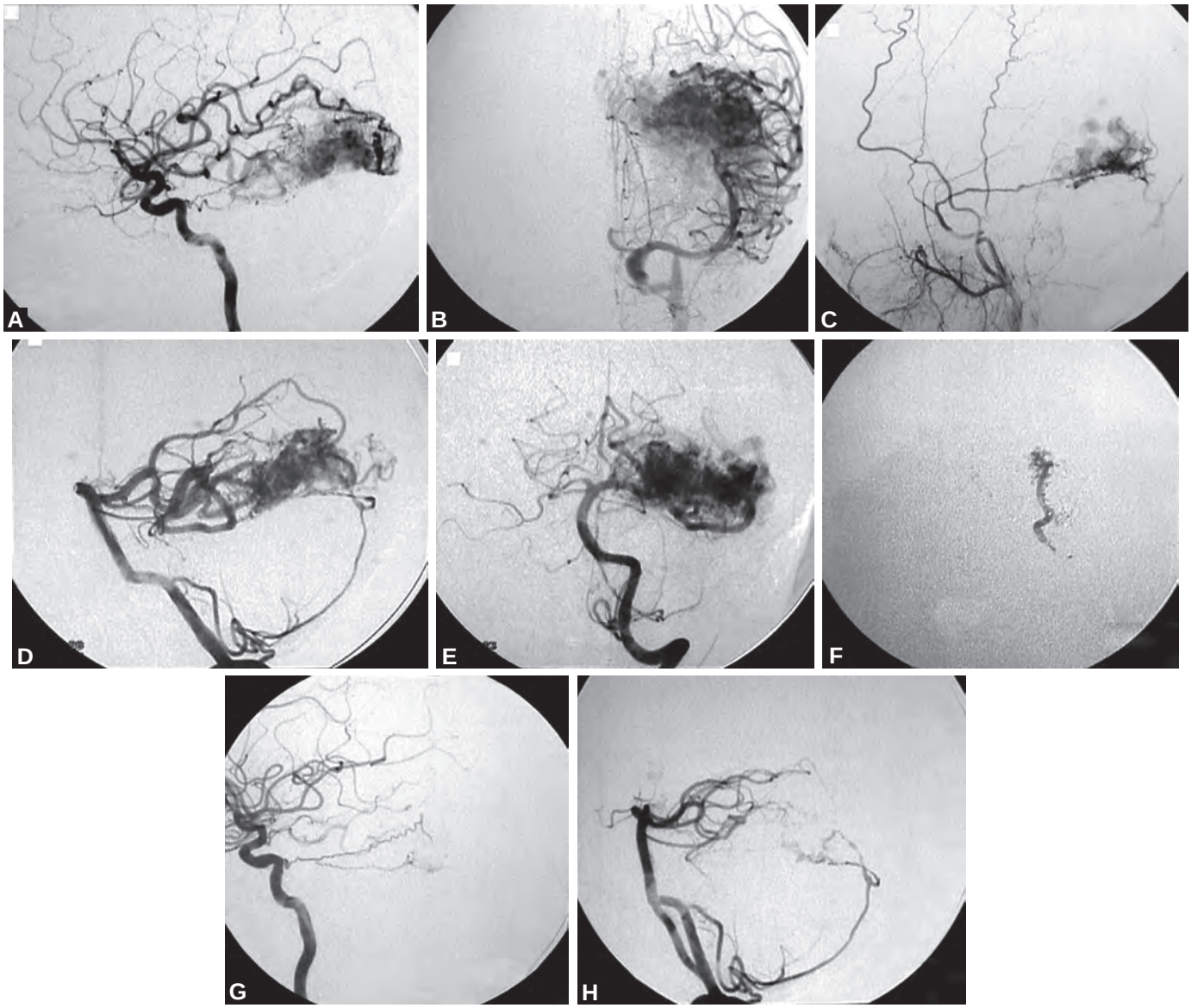
CONTRAINDICATIONS

- Spetzler Grade V
- Large diffuse AVM
- Incidental large eloquent area AVM
- Epilepsy as presenting feature in large AVM.

The results of treatment should be better than the natural history of the disease. Morbidity and mortality should be less than 4%. The actual results, whether surgical or endovascular, are far worse. In the best of hands, the complication rates are around 10–15%. Spetzler-Martin Grade I and II AVM presenting with haemorrhage must be treated. Grade VI AVMs are best left alone. Grade IV and V AVMs may also be left alone if the risk of treatment is higher than the natural history.[96,98] Only targeted treatment of weak spots such as intra-nidal or juxta-nidal aneurysm should be undertaken.[12,18,99] Targeted embolisation reduces the risk of haemorrhage.[61] It is believed that partial treatment of an AVM does not protect a patient from the risk of haemorrhage. There are reports of more devastating haemorrhage after partial treatment whether with radiosurgery (SRS) or embolisation.

Embolisation must be planned for a pati ent.[1,2,9,14,16,17,20,48,62,68,70,77,91] (Figs 3A to H) It can be: (1) definitive; (2) pre-SRS; (3) pre-surgery; (4) for remnant following microsurgery; (5) remnant following SRS; (6) targeted for intra-nidal aneurysm; (7) intra-operative embolisation followed by excision;[44] (8) targeted for other aneurysm (Guglielmi detachable coils)[18] and (9) targeted for headache.

Accessible small AVMs in non-eloquent brain with a single or multiple region of the cortical venous drainage, such as small right frontal or temporal AVMs, should surgically be excised unless there is a reasonable chance of cure with embolisation alone. A large AVM may be reduced in size by embolisation to make surgery easier.[37–39,57,93,101,103-105,110] Intra-operative angiography and magnetoencephalography are useful adjuncts.[45] Large AVMs, which are at higher risk, should be subjected



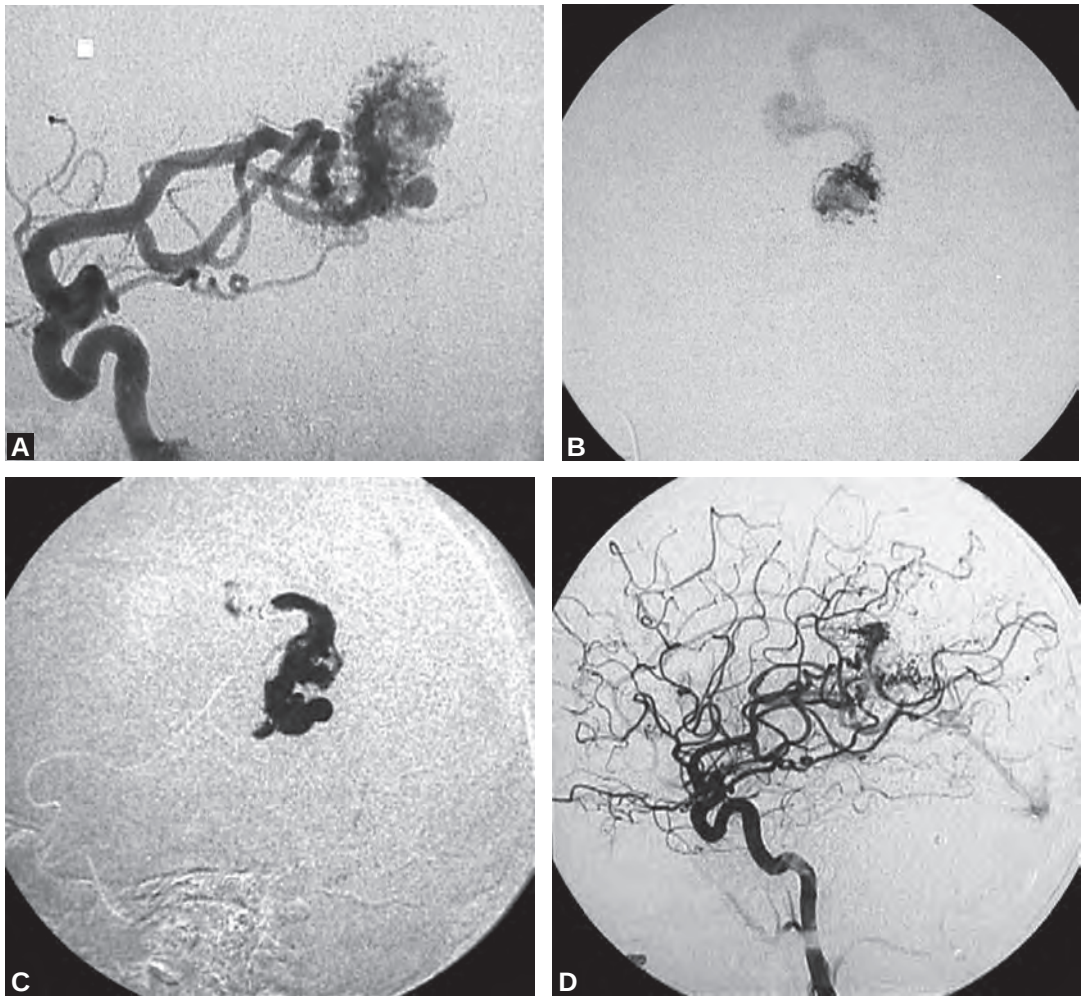
Figs 3A to H: (A and B) Lt ICA lat and AP pre. (C) Lt ECA lat Pre. (D and E) Lt VA lat and AP pre. (F) Superselective inj. (G) Lt ICA lat post. (H) Lt VA lat post

to targeted embolisation of "weak spots". A larger or deeper AVM, which is at a high risk of haemorrhage, may be treated by embolisation followed by SRS. The chance of cure with SRS is about 90% if the AVM is smaller than 3 cm in diameter. A large AVM may be reduced in size by embolisation so that it is amenable to treatment by SRS.[8,20,54,78,82,84]

EMBOLISATION

The ideal and curative treatment of AVM is to deposit liquid material like Histoacryl or Onyx inside the nidus.[22,25-27,46,67,73,102,105] If the glue is deposited in the feeding artery but not inside the nidus, it is useless, as collateral channels will recanalise the AVM immediately. Monitoring during embolisation (Figs 4A to D) is mandatory. EEG[71,83] and CSF pressure[47] have also been monitored during embolisation. Wada's test for eloquent brain is done by injecting amobarbital. Around 30 mg of amobarbital is injected through a microcatheter. If there is loss of function, embolisation is not done. Since there are false negative results, Wada's test has been abandoned. Glue is injected only if the microcatheter is within the nidus.[56,61,66,69]

For curative treatment, the entire AVM nidus including the proximal part of the draining veins must be filled with glue. Absolute alcohol has also been used for complete obliteration of the AVM.[108] Pre-operative embolisation can be with liquid embolic materials like Onyx or Histoacryl or with particulate materials such as polyvinyl alcohol (PVA), "cocktail" of PVA, absolute alcohol and Avitene, hydrogel particles,[27,75] or small pieces of surgical silk.[87] Balloons and liquid coils are useless as they only occlude the parent artery. Collateral vessels take up the supply immediately. Although the cast of glue is hard it can be easily cut with microscissors. Casts of Onyx have been found to be softer than



Figs 4A to D: AVM and intra-nidal aneurysm. (A) Lt ICA lat showing Lt parietal AVM with small posteroinferior aneurysm. (B) Superselective angio. (C) Inj of glue. (D) Post-embolisation lat view: aneurysm obliterated, small residual nidus treated by SRS

those of Histoacryl. If the AVM is large, embolisation is staged to forestall "break-through bleeding" described by Spetzler.[89] For pre-operative treatment the gap between the two procedures should be about 1 week. For definitive or pre-SRS treatment, sessions should be about 4–6 weeks apart. Pre-SRS embolisation must be with glue as particulate matter always gets absorbed and parts, which may appear to be obliterated, reappear after some weeks. Even in the best of hands, only about 35% of AVMs can be obliterated by embolisation alone. Large AVMs require multiple sessions several months apart. Angiogenesis has been reported after partial embolisation.[97] Animal models have been developed to perfect the technique of embolisation.[4,5,34,76]

The incidence of cure by radiosurgery is about 90% for small AVMs. It falls off to 70% for large AVMs.[8,20,78,82,84] Larger doses are associated with radiation necrosis. Multiple sessions of segmental SRS have recently been suggested. DSA must be done to document obliteration after SRS. Post-operative DSA is mandatory to confirm total excision, because the risk of haemorrhage persists even if there is a small remnant.

Technique

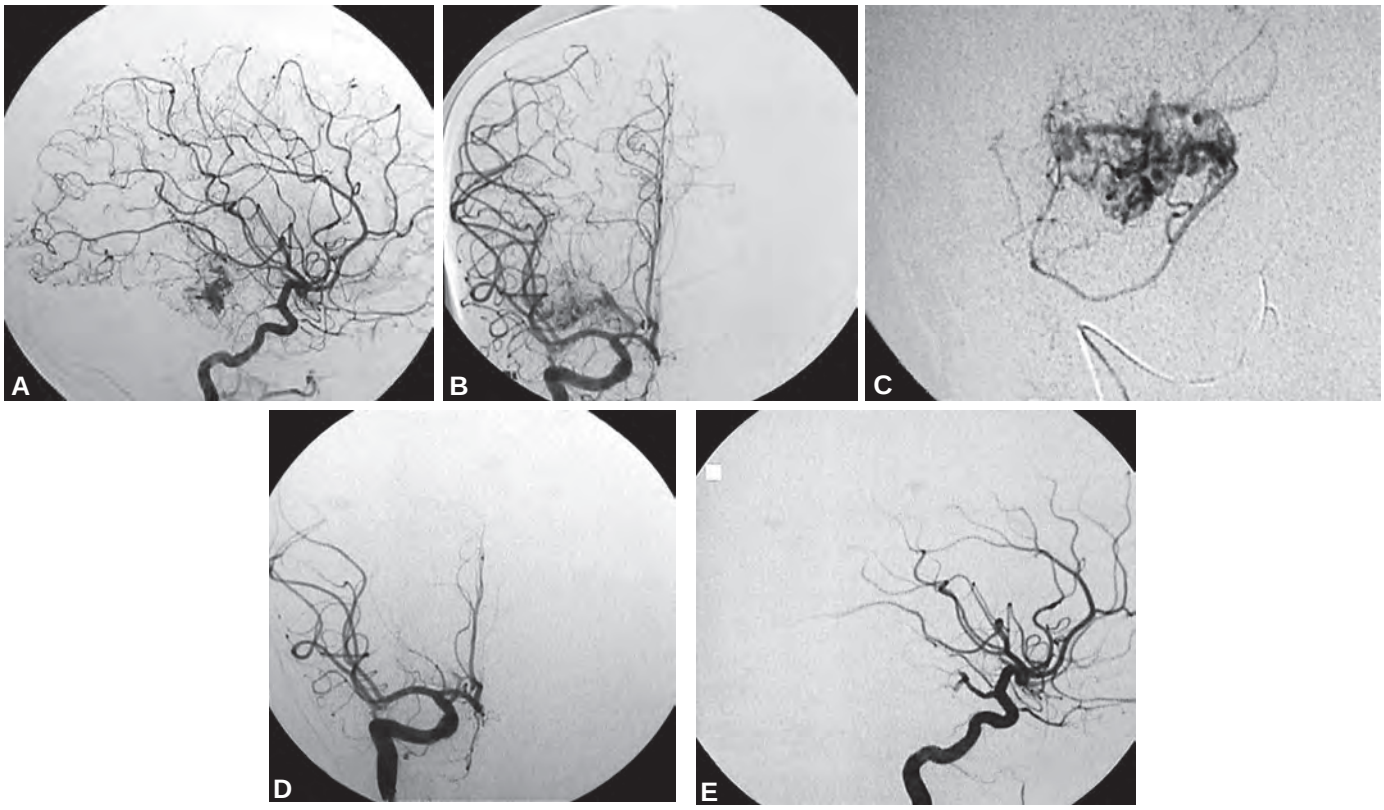
Every procedure must be planned meticulously. Simultaneous bi-plane road mapping is ideal because a true idea of the progression of glue can only be had by visualisation in two planes. Embolisation is done under general anaesthesia as the patient must be immobile for good road mapping. The transfemoral route is chosen. Rarely, especially for the left carotid artery, direct cervical puncture of the ICA may be necessary. For vertebral artery the brachial route is rarely chosen. A large lumen guiding catheter is placed in the appropriate artery.

Angiography is done at a rapid rate and in various projections. The two best projections for visualising the feeding artery and the nidus are chosen as the working positions. Under roadmapping, the microcatheter is navigated across the parent vessel into the nidus. Supple catheters of variable inner lumen and suppleness (3F, 2F, 1.8F, 1.5F or 1.2F), like the Magic (Balt SA) or UltraFlow (MIS, USA) are navigated by torque and taking advantage of flow dynamics. Catheters, such as Spinnaker (Boston Scientific), Renegade (Boston Scientific), Prowler

(Cordis), can be navigated only over guide wires. Even for supple catheters, after the first one or two segments have been embolised, the feeder becomes small and the catheter cannot be guided by flow alone. Fine, shapeable, platinum guide wires, such as Agility (Cordis), Transcend (Boston Scientific), Quicksilver (MIS), are used to navigate difficult, tight bends. Glue (Histoacryl, N-butyl-2 cyanoacrylate)[42,56,61,69,101] hardens as soon as it comes in contact with contrast, blood or saline. Adding Lipiodol, which also makes it visible, as the latter is radio-opaque, changes the polymerisation time (Figs 5A to E). If the flow is slow and there is a compact nidus, 20% glue (1 part glue : 4 parts lipiodol) is injected slowly over several minutes. If the flow is rapid, more concentrated glue, 33% or 50% is injected. If there is an associated AVF (which can be recognised when the microcatheter crosses from the artery to the draining vein), 90–100% glue is injected. It is made radio-opaque by adding tantalum powder. The glue is injected under road mapping.

The arterial supply to the nidus may be of two types: (a) End supply—The artery ends in the glomus of the AVM and (b) "En-passage". The artery goes on to supply the normal brain and gives off feeders at right angles to the long axis of the artery. End type of supply is ideal for embolisation. Glue can be injected safely. For en-passage type, if glue is injected, there is a high risk of occlusion of a normal artery. For such lesions liquid coils are injected into the arteries beyond the AVM. Once the arteries are occluded glue can be safely injected. Occluding arteries using coils proximally is safe because the pial network takes over immediately.

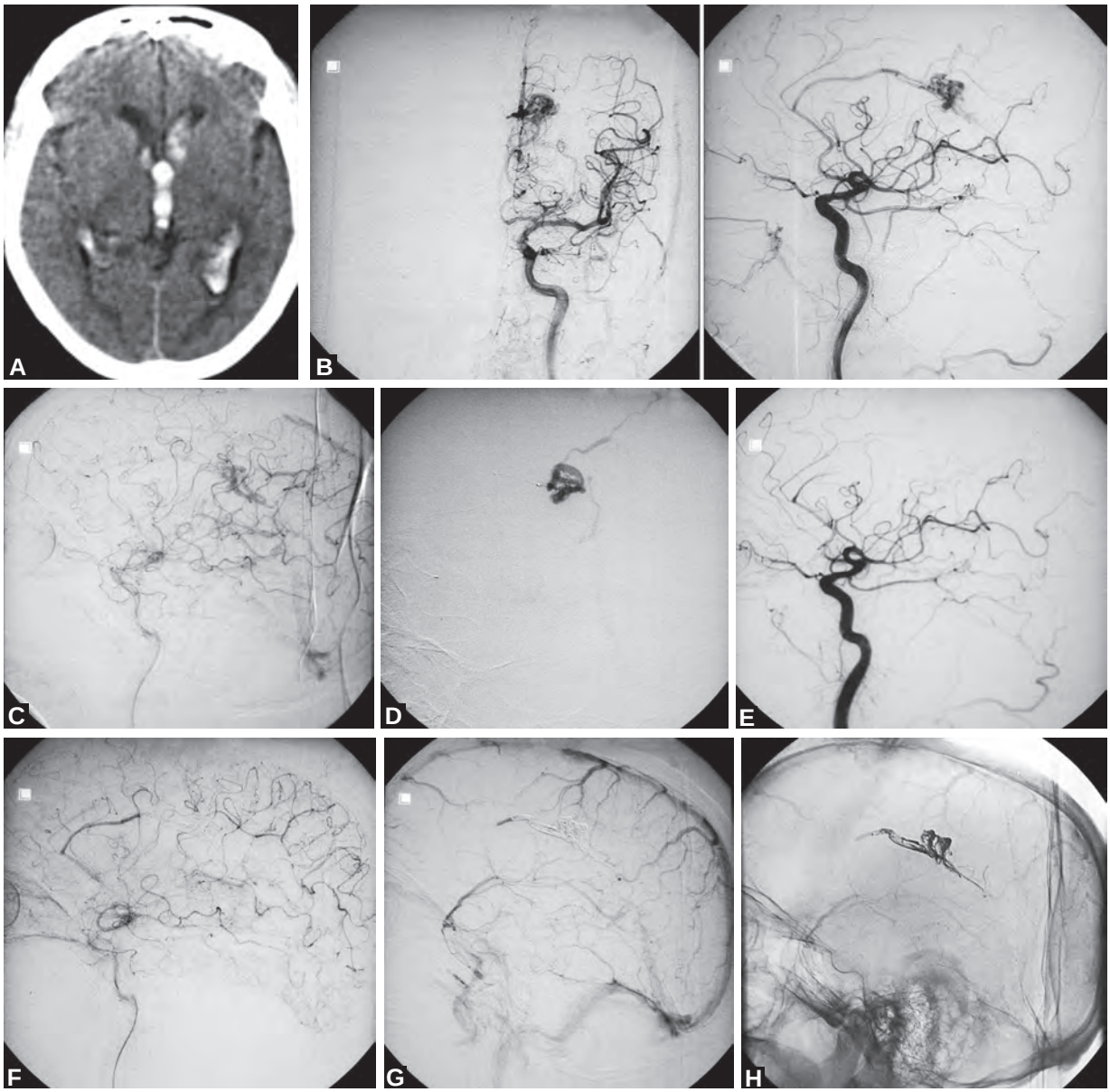
For good filling of the nidus, blood pressure may be lowered by injecting esmolol and venous pressure raised by performing the Valsalva manoeuvre during the injection. The aim is to enter the nidus and inject glue, filling the AVM from the draining vein backwards across the nidus to the feeding artery. If the vein gets occluded and the nidus escapes, there is a high risk of rupture. A large part of the AVM should be quickly embolised to prevent catastrophic haemorrhage. The microcatheter has to be pulled brutally at the conclusion of the injection lest it gets glued. Every interventionist has had catheters glued in different arteries, usually without any grievous consequences. For intra-nidal aneurysms, 50% glue is usually injected. In a single sitting 3–4 segments of the nidus may be embolised. The end points are change in the haemodynamics with slowing of passage of contrast across the nidus. If a high flow AVF has been obliterated, there may be considerable slowing with risk of venous thrombosis. If there is venous stasis, prophylactic anticoagulation with low molecular weight heparin is advisable. Whether to treat an associated aneurysm is a controversial subject. Aneurysm on the parent artery close to the AVM, or an aneurysm of the circle of Willis must be treated first whether by GDC technology or by surgery, as it may rupture after the AVM has been treated. Small, flow related aneurysms



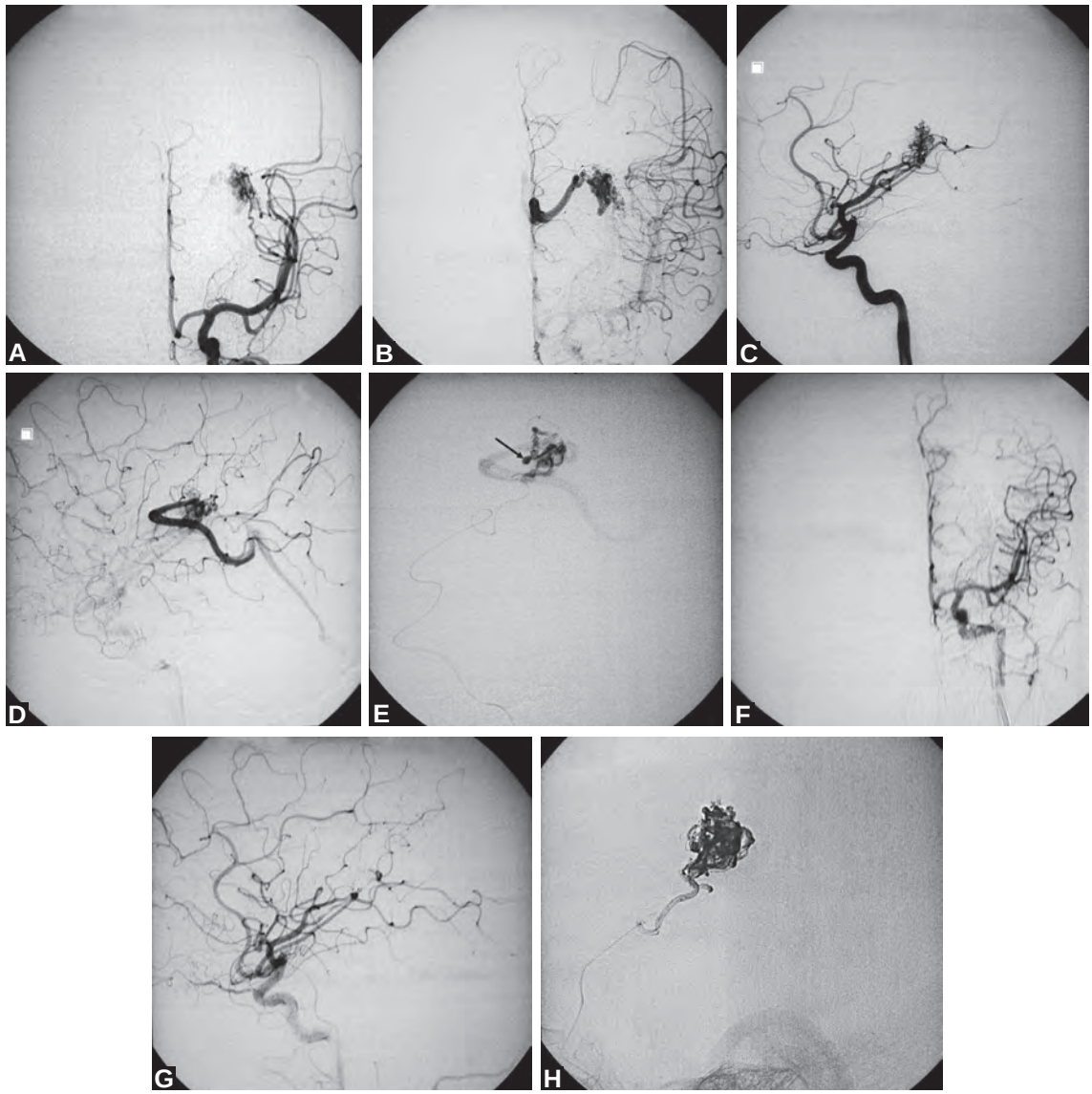
Figs 5A to E: Small deep temporal AVM. (A and B) Pre-embol ICA. (C) Superselective. (D and E) Post-glue lat and AP

on the feeding artery, remote from the AVM, might be kept under observation. These usually regress after the AVM has been obliterated.

Onyx is the other liquid embolic agent used in the treatment of brain AVM. Onyx is ethyl-vinyl-alcohol-copolymer which is dissolved in a solvent called dimethyl sulphoxide (DMSO). After the microcatheter, which must be DMSO-compatible, is in position in the AVM nidus, it is flushed with 10 ml of normal saline to wash out the contrast. Onyx 18 is injected into a compact nidus and Onyx 34, which is more viscous, into high flow AVMs and direct A-V fistulas. Onyx has to be mixed in the solvent by placing it in a special mixer for at least 15 minutes before it is injected. In large high flow AVMs, initially, Onyx 34 is injected. This is followed by Onyx 18. One vial of Onyx contains 1.4 ml and in a single sitting a maximum of 3–4 vials may be injected. The technique of injecting Onyx is different as can be understood from the illustrations [Figs 6(A to H) and 7(A to H)]. Injections often last up to 45 minutes to an hour. There is a high risk of haemorrhage if the catheter is pulled under some circumstances. If the injection lasts for more than an hour and if the feeding artery is small and tortuous, and reflux into the microcatheter is more than 1.5 cm, the microcatheter is not removed. It is cut in the groin and left behind. Sonic catheter from Balt has a detachable tip 2.5 cm from the tip. This catheter can be removed even if there is a reflux. CT scan is done immediately after the embolisation to rule out haemorrhage. If a large part of the AVM has been embolised and there is a significant change in the haemodynamics, the patient is paralysed and ventilated for 24–48 hours, with mean blood pressure lowered by 10 mmHg to prevent break-through bleeding. If there is large haematoma it may need to be surgically evacuated. SAH or a small haematoma is treated conservatively. The cure rate with



Figs 6A to H: (A) NECT brain shows extensive intraventricular haemorrhage. (B and C) Lt ICA lat and AP pre. (D) Superselective inj. (E to G) Lt ICA lat post. (H) ONYX cast



Figs 7A to H: (A and B) Lt ICA pre-AP. (C and D) Lt ICA pre-Lat. (E) Superselective inj shows intra-nidal aneurysm arrow. (F and G) Lt ICA post-AP and lat. (H) ONYX casts

Onyx has gone up to 50% for moderate and large sized AVMs and 100% for small AVMs. The risk of haemorrhage is also higher and is about 8–10%.

Curative Embolisation by Injecting Glue or Absolute Alcohol

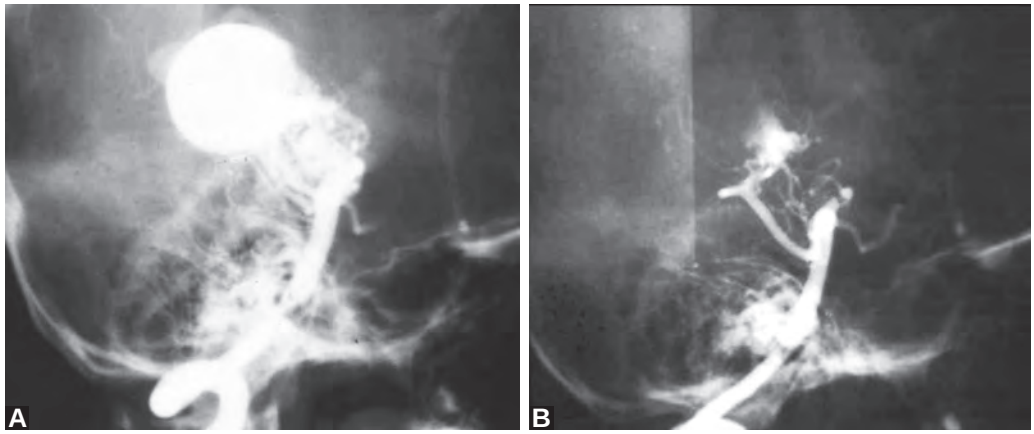
Not more than 30 ml alcohol should be injected in one sitting as there is a high risk of alcohol intoxication. Only about 35% of AVMs can be cured by embolisation alone. The rest need supportive treatment with SRS or surgery.

Following embolisation of large AVF, or large high flow AVM, the patient must carefully be monitored for "break-through bleeding" and haemorrhagic venous infarction due to venous stasis. After treatment of pial AVF in children and vein of Galen (VOG) malformation (Figs 8A and B), patients are electively ventilated for 48 hours and their blood pressure controlled with infusions of nitroglycerin (NTG), nitroprusside or esmolol to prevent bleeding.

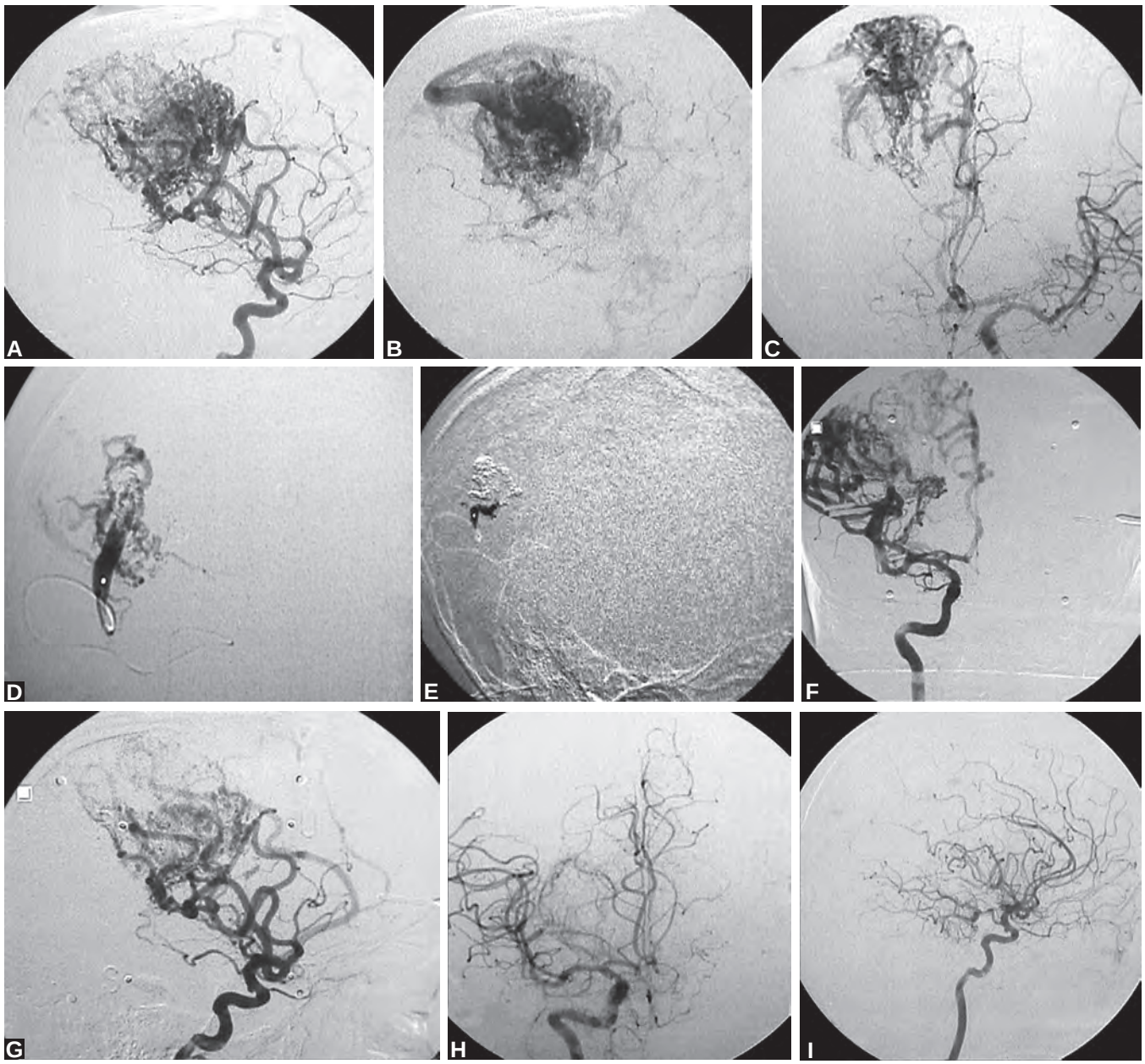
Selecting Sections Judiciously for Pre-SRS Embolisation

Ideally, concentric peripheral embolisation should be done so that the remnant central homogeneous segment can be treated adequately. Sector embolisation also is recommended so that planning for SRS is easy [Figs 9(A to I), 10(A to F) and 11(A to G)]. If central embolisation is done, small peripheral islands make planning difficult. Also radio-opaque glue interferes with proper target localisation.

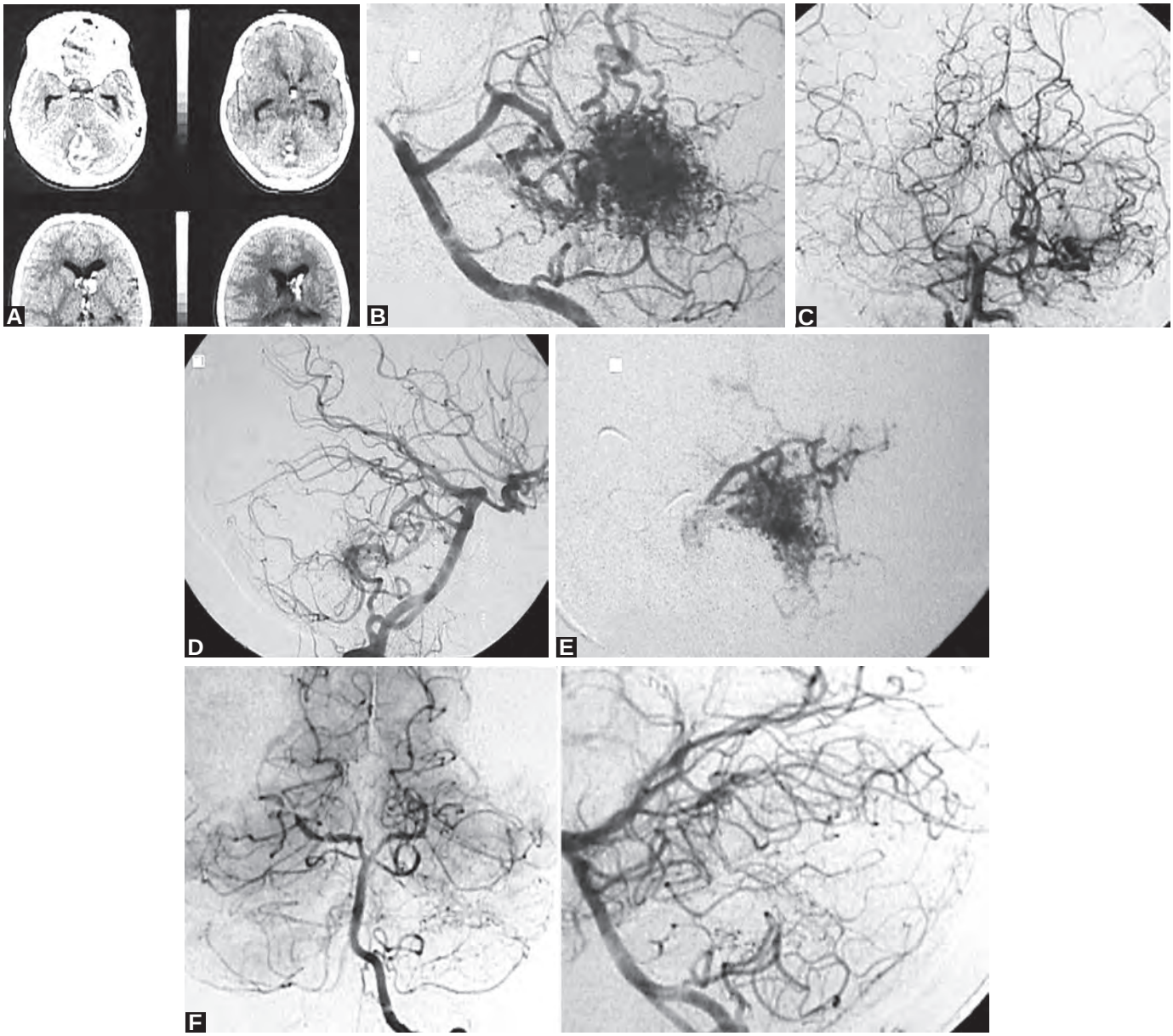
Pre-surgical embolisation can be done with glue, Onyx or particulate matter. Ideally, the less accessible deeper feeders from perforators should be targeted. However, these are difficult to catheterise because they are small and tortuous. Cocktail, surgical silk or PVA particles are injected slowly with intermittent contrast injections to monitor the progress.[59] The end point is when adequate slowing has been obtained or the AVM has been partially or largely obliterated. If the AVM is large, pre-operative



Figs 8A and B: Large vein of Galen malformation. (A) Before. (B) After embolisation using silk



Figs 9A to I: Large Rt parietal AVM: glue embolisation followed by SRS. (A to C) Rt lat and Lt towne to show MCA and ACA supply. (D and E) Superselective angio and glue. (F and G) After glue and before SRS. (H and I) 30 months after SRS; No trace of AVM



Figs 10A to F: SRS followed by glue embolisation. (A) CT showing cerebellar and IV haemorrhage. (B) Pre-SRS DSA. (C and D) 2 years post-SRS DSA. (E) Superselective DSA. (F) Post-embol. DSA showing obliteration of AVM

sessions may be spaced a week apart. Surgery should be carried out within 1 week of embolisation as there is a risk of recanalisation.

Targeted embolisation for intra-nidal aneurysm is by injecting glue into the aneurysm and the parent artery. Every effort is made to inject into the AVM downstream. If the nidus is at some distance from the aneurysm, only the latter is targeted.

Targeted embolisation for aneurysm on the circle of Willis or on the proximal feeding artery is done using GDC technology. The aneurysm is tightly packed with platinum coils.

Embolisation for headache is confined to the feeders from the external carotid artery (ECA). Particulate matter in the form of PVA is usually used.

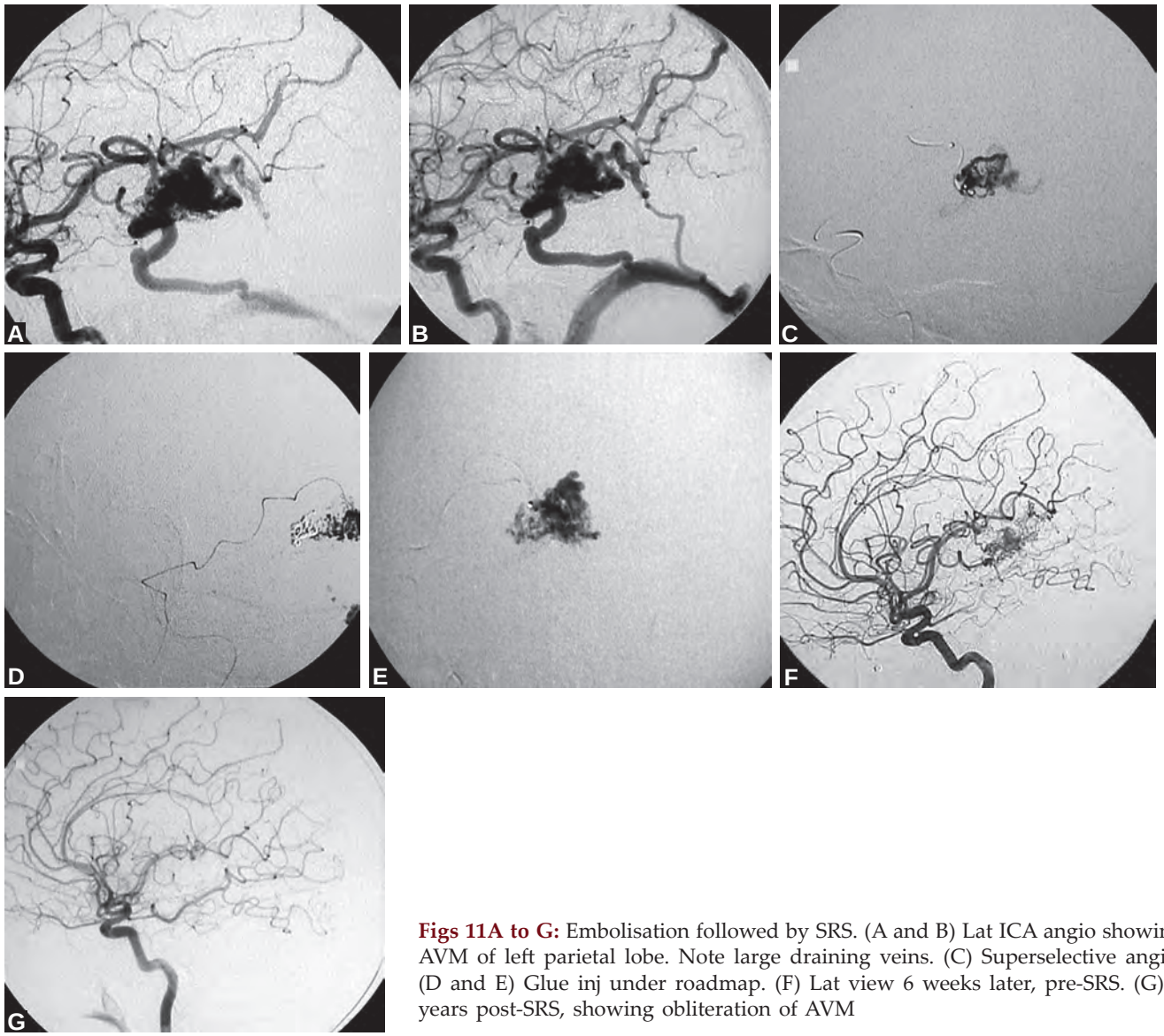
Following embolisation there may be a reduction in the incidence of epilepsy and headache. There are several reports that partial treatment offers protection against haemorrhage.[61] On the other hand, there are several reports of devastating haemorrhage after partial treatment.

COMPLICATIONS

Complications could be technical with or without any neurological sequelae. They can be neurological without any technical complication.[74]

Technical Complications

Technical complications are: (1) failure to reach nidus; (2) perforation of artery by catheter or guide wire; (3) spasm; (4) occlusion of normal branch by thrombus; (5) glue injection into normal artery; (6) passage of glue into a normal cortical or deep vein, a dural venous sinus



Figs 11A to G: Embolisation followed by SRS. (A and B) Lat ICA angio showing AVM of left parietal lobe. Note large draining veins. (C) Superselective angio. (D and E) Glue inj under roadmap. (F) Lat view 6 weeks later, pre-SRS. (G) 2 years post-SRS, showing obliteration of AVM

or the lung;[5,6,31,53] (7) catheter getting glued and breaking off; (8) catheter getting stuck in a small artery due to vasospasm; (9) perforation of microcatheter because of forceful injection; (10) rupture of missed small aneurysm; (11) occlusion of feeder without glue reaching the nidus and (12) occlusion of the draining vein without obliteration of the nidus.

Haemorrhage[3,32,41,61,65,92] and ischaemia are the two major complications. Glue should never be injected remote from the nidus. Glue should be injected only with the microcatheter inside the nidus. Rate of flow through the AVM should be estimated as accurately as possible. A careful analysis has to be made by making several injections into the microcatheter to evaluate flow to ensure adequate filling of the nidus. The concentration of glue can be varied according to the rate of flow. For low flow nidus, lower concentration of 20–25% is used, for high flow 50%, 66%, 90% or 100% glue is injected. Careful planning will prevent erratic embolisation and occlusion of normal arteries and veins. However, all estimates may be wrong as glue is more viscous than contrast and glue may pass to the venous side, occlude the feeder without passing to the nidus, or bypass the nidus and reflux to occlude a normal artery. Perforation of an artery can be a disaster, and should be quickly recognised.[15] Small perforations may be of no consequence and may be missed. These may be recognised only on post-operative CT scan. Injecting glue or depositing coils, after quickly neutralising the circulating heparin, closes larger holes. Breakage of catheter is usually of no consequence. Anybody who does interventions will have catheters broken from time to time. These catheters are left alone and need not be removed as they get endothelialised. In fact one may be able to go back into the same artery and embolise despite the presence of the catheter fragment in the lumen. Perforation of a catheter occurs at junctions of different segments, 3F–2F or 2F–1.8F because the supple catheter can get kinked. If force is used when there is resistance to injection of contrast, the catheter ruptures without any consequence. However, it is disastrous if it ruptures proximal to the tip during the injection of glue. Spasm occurs when

one is not gentle in manoeuvres and when catheters are reused. Spasm gets relieved if one just waits for 15 minutes. Sometimes, vasodilators, like papaverine, NTG or priscol, may relieve spasm.

Neurological Complications

Death may occur if a major artery or vein, such as the vein of Galen, is occluded. Rupture of a large artery or aneurysm may cause catastrophic haemorrhage and instantaneous death.[7] Neurological deficit may occur due to occlusion of a normal artery or vein. Sometimes, there may be oedema or inflammation around the glue.[81] The deficit would depend on the territory being treated and may vary from a minor deficit to major irreversible hemiplegia or aphasia. In the best of hands this is reported at 15%. If treatment is carefully planned, the risk of complications can be reduced.

CONCLUSION

Large Grade VI AVMs should be left alone except for targeted embolisation. Grade IV and V AVMs should be treated if they are at risk of haemorrhage. Targeted embolisation should be done for Grade IV and V. Grade I should be surgically excised. Grade II and III AVMs should be treated on merit, be it embolisation, embolisation combined with surgery or SRS. Grade IV and V can be treated by combining embolisation with SRS. Small remnants after surgery can be treated by embolisation or SRS. Small remnants after embolisation or SRS can be excised. Small remnants after SRS can be retreated by SRS, if safe, excised or embolised. Embolisation with Histoacryl and Onyx is permanent.[43] Particulate matter, like PVA, silk or cocktail, is not recommended, except as a pre-surgical procedure, as they get reabsorbed.

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94 Stereotactic Radiosurgery for Cerebral AVMS

Ganapathy K

And when the child was grown it fell on a day
That he went out to his father to the reapers
And he said to his father—my head, my head.
And he said to a lad, carry him to his mother
And when he had taken him, and brought him,
To his mother, he sat on her knees till noon,
And then died

—Old Testament II Kings

HISTORY

The earliest reference to a possible intracranial haemorrhage is in the Old Testament. Cerebral arteriovenous malformations (AVMs) as such were, however, first studied and classified in 1854 by Luschka and Virchow. Giordano surgically exposed an AVM in 1890 while an actual excision of an AVM was done in 1932 by Olivecrona. Radiation was considered as a treatment option in the management of cerebral AVMs by Cushing even 80 years ago. To use Cushing's own words "Nevertheless, when first exposed, the lesion was still highly active and the subjective improvement experienced by the patient from his *radiotherapeutic seances* was such that he persisted in having treatment given, in excess possibly of what we would have ventured to advocate. The result has been described, namely the disclosure at the second operation three years later of a particularly avascularised tumour".[13] Several decades later, radiotherapy was still a treatment option in the management of AVMs.[106,135]

In the 1950s, Leksell, and later Larson, conceived the idea of using stereotactically guided external radiation to produce a predictable irradiation effect at an accurately defined intracranial target.[72,73] After extensive experimentation, he developed the first generation cobalt gamma unit in 1968. He called the technique "Radiosurgery". One of the early reports on the use of stereotactic radiosurgery (SRS) for an AVM with the gamma knife was that of Steiner.[123] The earliest reports on the use of heavy charged particles as a method of radiosurgery for AVMs were in 1983.[18,66,67] Subsequently, there were a few more reports, but charged particle radiosurgery for AVMs is no longer routinely carried out.[112,120-122,127] Betti and Colombo pioneered the use of Linac based radiosurgery in the management of cerebral AVMs.[7,11]

The first publication on the use of SRS for cerebral AVMs from South Asia was from Ganapathy.[30] Several publications on SRS highlighting the Indian experience in the management of cerebral AVMs are now available.[31,33-35,114] To keep this treatment cost effective, without compromising standards of excellence, is a particularly challenging task, especially in a developing country. The fifteen-radiosurgical units presently available in India cater not only to more than a billion Indians but also to several hundred million from the adjacent countries. This results in different referral patterns, different standards in pre-treatment diagnostic imaging and work up, heterogeneous clinical presentations and problems in obtaining post-treatment imaging studies. Working in this milieu, the first SRS procedure in South Asia was carried out by the author on May 30, 1995. In a short span of 12 years, more than 1,500 cases of cerebral AVMs have been treated with SRS throughout India. Several reports are available on the successful use of Linac assisted radiosurgery, the gamma knife and the cyberknife[117] in the management of cerebral AVMs.[5,11,29,30,55,64,78,80,83,125,126] Several articles have compared the efficacy of SRS vis-à-vis microsurgery.[42,74,98,105]

INTRODUCTION TO STEREOTACTIC RADIOSURGERY

Stereotactic radiosurgery refers to the method of delivering a single high dose ultra precise radiation (8–15 times that of a single conventional dose), that is about 12–25 Gray (1,200–2,500 Rads), to a well-defined lesion, using fixed stereotactic reference points. Biological effects produced by radiosurgery range from blood vessel thrombosis to reproductive cell death and frank necrosis within the treatment volume. Recently, it has been shown[128] that the endothelium of AVMs has different molecular properties and that these inflammatory molecules may be biologically relevant in the response of vascular malformations to radiosurgery and embolisation. Initially, radiosurgery was advocated for patients not suitable for open surgery. With refinements in technique and long-term follow-up data, radiosurgery is on its way to becoming the treatment of choice rather than a choice of treatment. The source of radiation can be X-rays from a linear accelerator or cyberknife, gamma rays from a cobalt unit (gamma knife) or charged particles. The

source of radiation (cobalt or X-rays) does not appear to make a significant difference.[80,93] The revolution in medical imaging in the last two decades has provided sophisticated target definition. Stancanello[117] has used functional magnetic resonance imaging (fMRI) to identify specific regions which can be considered as "functional organs at risk" (fOARs), In five cases of cerebral AVMs, consideration of the fOARs allowed quality indices of treatment plans to improve in four cases compared to plans with no consideration of fOARs. Integration of functional information into AVM radiosurgery may help further to minimise undesirable side effects.

Phenomenal advances in computer applications and better understanding of radiobiology have also resulted in the increasing use of SRS. The practice of radiosurgery demands a good knowledge of neuroimaging. Understanding the radiobiologic effects of high dose irradiation is essential. Proficiency with stereotactic techniques and computer literacy are mandatory. Equally important is a thorough knowledge of alternative treatment modalities.

Advantages of Radiosurgery in the Management of Cerebral Arteriovenous Malformations

- Safe, post-treatment complications far less than in open surgery.
- Complications are usually transient, mild and reversible.
- No procedure related mortality.
- Minimal or no hospitalisation is required.
- No post-treatment convalescence.
- Pre-treatment activities can be resumed immediately.
- No procedure related risk of infection or bleeding.

Disadvantages of Radiosurgery in the Management of Cerebral Arteriovenous Malformations

- Not suitable for all cases.
- Total obliteration only in 60–80% of cases.
- Risk of haemorrhage till obliteration occurs.
- 15–36 months waiting period.
- Limitations and difficulty in post-treatment assessment.
- Not freely available.
- Considerable expertise and infrastructure required.
- Extremely rare cases of delayed complications like cyst formation,[43,52] haemorrhage even after angiographically demonstrated total obliteration[3,87] and radionecrosis have been documented.

DECISION-MAKING IN RADIOSURGERY

When a non-invasive, safe, high-tech procedure is available, there may be a tendency to be liberal in using the technique.[32] It is essential that injudicious applications do not detract from an otherwise elegant technology. Though the facility is available in India at a reduced cost (compared to international costs), it is still not inexpensive. The minor details of the procedure have to be discussed frankly with the patient, the relatives and the referring doctor, preferably with photographs. Too often, due to the hype in the media, there is an unrealistic expectation on the part of all concerned. It has to be clearly mentioned that the primary purpose of treatment of a cerebral AVM is to reduce the chances of a disastrous haemorrhage. Comprehensive, up-to-date knowledge of the long-term natural history of the AVM is imperative. Radiosurgery is a rapidly evolving subspeciality where indications keep changing.[101] Familiarity with current published literature in peer-reviewed journals is obligatory. This alone will ensure the use of rigid criteria for selecting patients. An inadvertent bias in the use of SRS should be avoided. Radiosurgery should be withheld if the natural history of the untreated lesion is likely to be more benign than possible delayed morbidity due to radiosurgery. SRS is not a procedure to be used with impunity. Although anecdotal, and not statistically significant, long-term follow-up has revealed insignificant and significant radiation induced changes at the site of the obliterated AVM. Considerable thought, therefore, has to go into every decision before advocating SRS for an AVM. This is particularly important because there is no procedure related mortality and morbidity, if it does occur, is delayed. SRS is not a fancy sophisticated tool to be used when nothing else can be done or as a desperate salvage measure. The argument "that there is no proof that it is not useful, so why not try it out" is unacceptable and must be resisted. In India, where medical insurance is still not freely available, the economic factor also has to be taken into account. In the author's experience, AVMs have constituted the single largest indication (about 60%) for radiosurgical procedures. It may take 18–24 months to achieve total obliteration of the nidus. Total obliteration has been reported as early as 12 months and as late as 60 months. Till such time as complete obliteration takes place, the patient continues to run the risk for haemorrhage, though some reports suggest that the risk is less even with partial obliteration.[28,62,102] It follows that when the risk of haemorrhage is more, e.g. a patient who has already bled twice or more open surgery is preferable if the attendant morbidity is acceptable.

Technical suitability for SRS should not be the only criteria for carrying out a radiosurgical procedure. Morbidity following SRS is related to the location and size of the nidus. A preliminary embolisation may be necessary to reduce the size of the nidus.[14] Since most AVMs occur in the younger age group, there is a significant risk of haemorrhage over a period of time. Hence, when suitable for SRS, there appears to be no justification now, for so-called "conservative management".[92] Since considerable data and long-term follow-up are available with the use of different modalities of treatment for different types of AVMs, decision-making can be based on scientific facts.[50] Mathematical models to predict patient survival rates in microsurgery and in radiosurgery have been designed and these are useful in logical decision-making.[42]

RADIOBIOLOGICAL EFFECTS OF STEREOTACTIC RADIOSURGERY ON ARTERIOVENOUS MALFORMATIONS

Though more than 16,000 SRS procedures have been performed worldwide to treat cerebral AVMs, the underlying histopathological process leading to obliteration of the nidus is still open for discussion.[110] Inflammatory proteins in the endothelium of AVMs may play a role in the pathophysiology of cerebral AVMs and their response to radiosurgery.[128]

The underlying goal of treatment of AVMs by using high dose focused radiation is to induce an inflammatory response in the vessel walls that will result in a permanent thickening of pathological vascular channels, leading to thrombosis. AVMs are hamartomatous lesions of the brain resulting from embryogenic maldevelopment. They are histologically composed of a parenchyma with abnormal vessels embedded in a connective tissue stroma. The ionising radiation delivered by radiosurgery probably induces proliferation of spindle shaped cells in both the sub-endothelial region of the vessel wall and connective tissue stroma. According to the immunohistochemical and ultrastructural characteristics, these proliferating spindle cells are probably myofibroblasts. The contractile capacity of myofibroblasts might explain the shrinkage of AVMs after irradiation.[130] Connective tissue stroma alterations may play an important role in the shrinking process. The most characteristic pathological feature of the necrotising radiation is the occlusion of most of the small vessels within the targeted zone, leading to a coagulative necrosis of all tissue elements. The vessels of the AVM are thickened and fibrosed and the majority are occluded by connective tissue over several months. Thickening of the walls of the abnormal vessels was shown by histological analysis.[91] Autopsy studies have revealed radiation-induced changes following SRS even in arteries unrelated to the nidus.[140] More information is now available on the radiobiological effects of SRS on AVMs[1,15,71,77,79] including the use of radiation sensitisers on brain and blood vessels using primate models.[125] Gamma linolenic acid has been used in clinical trials as a possible radiation sensitiser, but with disappointing results.[113]

CLINICAL PRESENTATION

Haemorrhage (more common in smaller AVMs,) is the commonest presentation of an AVM (Fig. 1). However, in the author's experience, more cases of AVM were referred for SRS before they had bled. This is in contradistinction to the Western literature.[12,69] Seizures are more common in larger AVMs. Other clinical presentations include headache, behavioural changes or progressive neurological deficit. The mortality could be as high as 10% in the first bleed, 13% in the second and 20% in the third episode. There is a 25% risk of rehaemorrhage in 4 years after the first bleed.[26] With increasing awareness and availability of CT and MRI, AVMs are increasingly being diagnosed before they rupture.

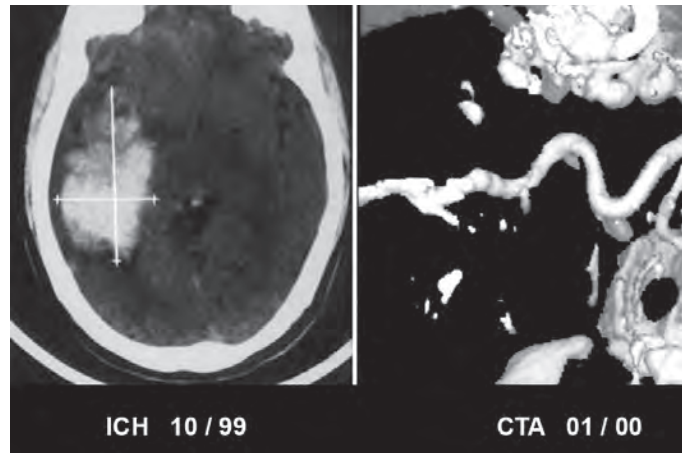


Fig. 1: CT scan showing intracerebral haematoma and CT angiogram demonstrating AVM

Investigations

Plain CT is insufficient. Double dose contrast with 2 mm slices in the region of interest is often diagnostic. Plain MRI with flow void signals and magnetic resonance angiography (MRA) are also suggestive of an AVM. CT angiography (CTA) is very informative, particularly in identifying associated arterial aneurysms. Invasive four vessel superselective angiography not only confirms the diagnosis of an AVM but also gives valuable information regarding the arterial supply, the venous drainage, presence of coexisting aneurysms, arterial and venous, and details of the nidus (Fig. 2). With increasing refinement and availability of 64 slice CT angiography even DSAs are being dispensed with for treatment planning of cerebral AVMs.[36] (Fig. 1) During the last 18 months, in 35 cases of cerebral AVM, the author has dispensed with DSA by using 64 slice CTA. Transcranial Doppler has also been used for screening and follow-up.[6]

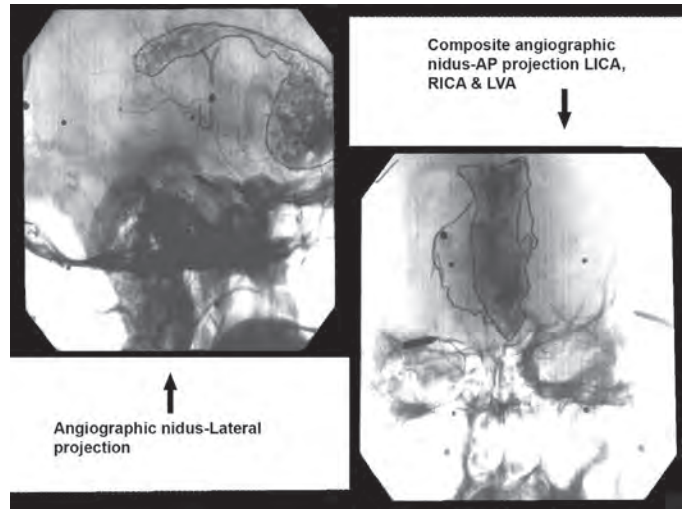


Fig. 2: Complex giant corpus callosum AVM

STEREOTACTIC RADIOSURGERY FOR CEREBRAL ARTERIOVENOUS MALFORMATIONS: THE PROCEDURE

SRS should be carried out only in a tertiary care referral centre. Well-equipped departments of imaging sciences and radiotherapy with medical physicists familiar with 3D treatment planning are a prerequisite (the latter if a Linac based system is used). The author reviews with the patient, before the procedure, the various steps showing photographs so that the patient knows exactly what to expect. An informed consent is obtained, wherein the absolute necessity for follow-up imaging studies is emphasised. The advantages and limitations of the procedure are clearly documented. Prophylactic steroids and anticonvulsants are at present no longer used as a routine. Baseline sedation with oral diazepam a few hours before the commencement of the procedure is sometimes resorted to. Occasionally, supplementary sedation may be necessary. Requirement for general anaesthesia is exceptional. In the case of patients who have already undergone open surgery, the neurosurgeon should palpate the craniotomy site and have a precise knowledge of the exact location of the burr holes or skull defect. Earrings, nose rings and even kumkum (a mark worn by Indian women on the forehead) are best not worn during the procedure. Even makeup, particularly eyeliners, sometimes produces artefacts on the MRI. The patient is instructed to keep the eyes closed all the time while undergoing CT or MRI scanning. Movement of the eyes can produce subtle changes in the position of the optic nerves. The patient gets admitted on the day of the procedure and is discharged the same day or the next day.

Step 1—Fixing the Frame

The stereotactic base ring is fixed with the patient in the sitting position. Shaving of the head is not required. Reusable screws (kept in Lysol or gas sterilised with ethylene oxide) can be used. The exact location of the screws and angulation of the base ring is crucial. The base ring has to be kept in position for periods varying from 4 to 6 hours. Hence, the screwing has to be done tightly into the inner table. The exact level at which the base ring is finally positioned would depend on the site of the lesion. The top of the ring should be at least 10 mm below the bottom of the lesion and at least 30 mm below the centre of the lesion. The artefacts produced by the screws should, therefore, be above or below the target volume (AVM). This requires considerable care. The screw is then inserted through the opening until a purchase is obtained on the inner table. When the angiographic localiser frame is used, the screws should be so positioned that as far as possible the nidus of the AVM is in the centre of the angiographic fiducials. In the future, frameless stereotaxy will be extended to radiosurgical procedures obviating this step.

Step 2—Computerised Tomography or Magnetic Resonance Imaging Data Acquisition

The CT or MRI localiser ring is placed over the base ring. 100 ml of meglumine diatrizoate (Angiografin) for CT or gadolinium for MRI is given rapidly as a bolus. One millimetre slices are taken from the vertex to the foramen magnum. MRI is desirable particularly when the optic chiasma/optic nerves/eighth nerve and other critical structures have to be identified with extreme precision. The images are transferred to the treatment-planning computer. The critical structures, like the brain stem, optic nerves and optic chiasm, are outlined besides the nidus.

Step 3—Angiographic Data Acquisition

The patient is positioned on the angiographic table so that the frame is in the centre of the table. The angiographic localiser ring is placed on the stereotactic base ring. A preliminary screening is done and fine adjustments made with the image intensifier and tube so that eight fiducial markers are seen on the PA projection and eight on the lateral projection. A four-vessel angiogram is done to ensure that different arterial systems contributing to the nidus are identified. The pictures are reviewed. The PA and the lateral picture, which displays the nidus best is chosen (Fig. 2). The nidus (the target volume) is outlined with a film marker in both the views. The images are transferred to the treatment-planning computer. Recently, with increasing availability of 64 slice CT and with the possibility of even a 256 slice CT, the use of DSA in treatment planning could progressively decline.

MRA has also been used for 3D treatment planning to identify the nidus.[17,129] Spatial distortion, if any, can be corrected[109] Stereotactic angiography alone may be an inadequate database for radiosurgery.[9,116] Blatt has pointed out that the angiographic nidus and the CT nidus may be different in as many as 75% of cases.[8] Image correlation of MRI and CT in treatment planning for radiosurgery of intracranial vascular malformations has also been done.[96] Sources of error in the angiographic nidus determination include overlapping vessels, bony structures, fine filamentous arterioles and irregular shapes. Accurate spatial representation of the nidus is essential to ensure its total coverage and to limit radiation to the surrounding brain. Treatment plans generated from the angiographic nidus interpretation need to be modified to conform to the CT nidus. Stereotaxic MRI and MRA has been used as an additional tool in defining the target.[39,40,69,108,129] Some authors believe that MRA permits semi-quantitative flow velocity assessment and may, therefore, be superior to stereotactic angiography.[95] Several attempts have been made to improve target volume definition in radiosurgery of arteriovenous malformations by stereotactic correlation of MRA, MRI, blood bolus tagging, and even functional MRI.[108] Estimation of the size of the nidus varies depending

on the imaging modality used.[90] Radiosurgery related imaging changes have been studied in detail.[21,23,141,144]

Step 4—Treatment Planning

The CT and MRI (if taken) images are studied. The anatomes (anatomical structures) normally contoured are the left and right eyes, the left and right optic nerves, the optic chiasma and the brain stem. Outlining these critical structures and the target volume (the volume to be irradiated) is the primary responsibility of the neurosurgeon. Before outlining the target volume, the entire imaging data available is studied including previous CT and MRI films. It is essential that a mental holistic 3D picture of the lesion be obtained. It is important that the clinician who outlines the lesion is familiar with vascular anatomy. Treatment planning differs depending on whether a gamma knife system is used or a Linac based system. It also depends on the specific equipment being used. In the earlier days, one or more collimators of appropriate size were chosen (Fig. 3). The author now uses the micromultileaf collimator system for ultra-conformal radiation. A set of radiation beams is devised so that all of them converge on the AVM. Their passage through critical structures (from entrance to exit) is avoided. The plans are studied and modified till the proper dose distribution within the target volume is obtained,—sparing critical structures and ensuring that the radiation dose outside the target volume is within 800 Cgy (Fig. 4).

The plan and the dose is finalised after a brain storming session. The neurosurgeon emphasises the pathology, the natural history of the lesion, the functional anatomy of the adjacent structures and the clinical status. The radiation oncologist takes into account the radiobiological effects and safety issues. This is particularly relevant if the patient has been irradiated earlier. The physicist is concerned with implementing the "prescription" and points out the technical issues in delivering the radiation. In several cases of AVMs, there may not be a perfect correlation between the angiographic nidus and the CT target volume. Considerable judgement and familiarity with the intricate details of different types of neuroimaging are required. Finally, each case will have to be judged individually and a decision taken. Optic radiation tractography based on diffusion tensor (DT) MRI has been integrated[85] into simulated treatment planning for gamma knife surgery. This appears to be a promising tool for preventing GKS-induced visual disturbances and headaches. Integration of time-resolved contrast-enhanced MRA into dosimetry planning has been reported by Taschner et al.[131]

Step 5—Treatment

The technical details of setting up a linear accelerator or the gamma knife unit are beyond the scope of this chapter. The actual treatment takes 30–60 minutes depending on the complexity of the AVM. After the radiation is completed, the frame is removed. The patient is kept under observation overnight and can resume normal activities the next day. Occasionally, the patient is discharged home after the procedure.

Procedure Related Complications

In the appropriately chosen patient and with meticulous attention to minute details, complications should be negligible. In the author's experience of 350 cases of AVMs treated with Linac based SRS, only one patient developed a procedure related major neurological deficit, which ultimately recovered. Fifteen patients,—all having grade III or IV Spetzler-Martin AVM,—developed mild neurological deficit, which responded to steroids and was totally reversible. Seizures occurred more often in the post-treatment period in AVMs than in other lesions. Hence, optimising anticonvulsant doses is essential, particularly in supratentorial AVMs. Alopecia, most often transient, occurred in a few cases in superficial lesions in the mid-nineties as part of the learning curve and

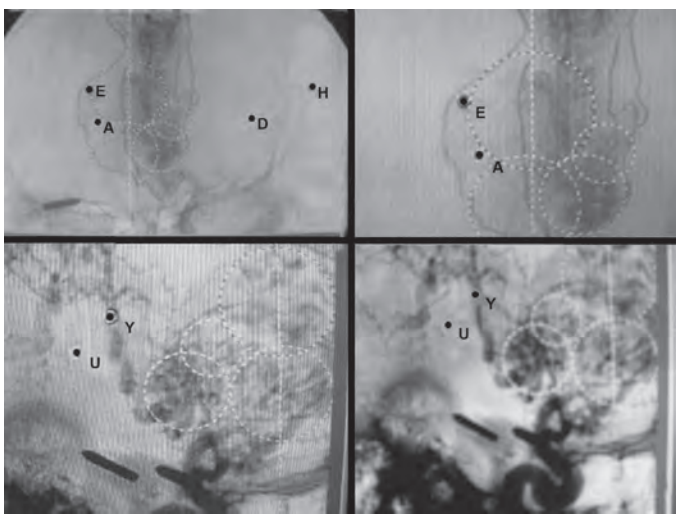


Fig. 3: Corpus callosum AVM—use of multiple collimators

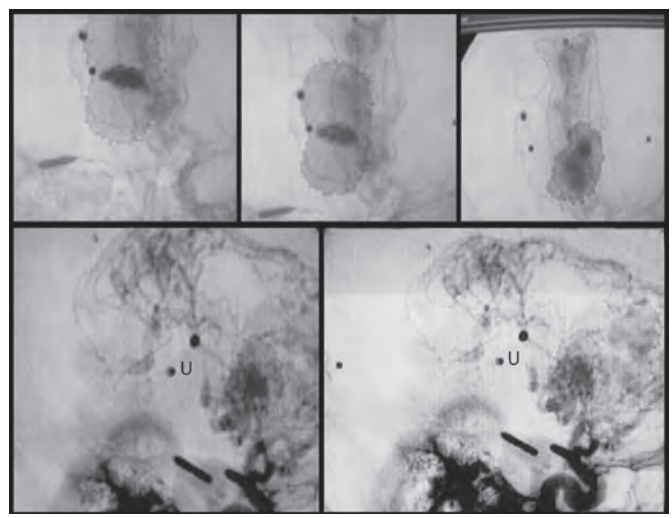
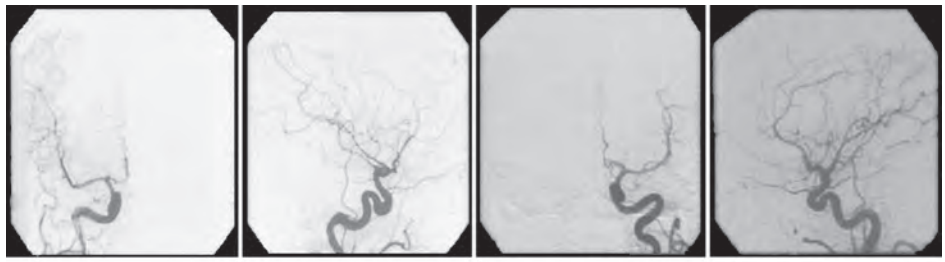


Fig. 4: Dose distribution of different portions of nidus

haemorrhage, while awaiting obliteration, occurred in 4% of cases (in the group where follow-up was available).

Follow-Up

In SRS for AVMs, unlike open surgery, results can be gauged only 12–24 and, sometimes, even 48 months later. The gold standard of successful treatment of an AVM is the angiographic demonstration of total obliteration of the AVM (Figs 5 to 9). A double dose contrast CT or MRI or CT angiogram is done initially after 12 months and then every 6–9 months. If the CT or MRI shows no nidus or is doubtful, an angiogram is done. If the CT or MRI itself shows a residual nidus, a repeat CT, CT angiogram or MRI is done later. The patient is advised angiography/64 slice CT angiography 3 years after SRS irrespective of the CT or MRI findings.



4 Vessel angiogram showing obliteration of AVM

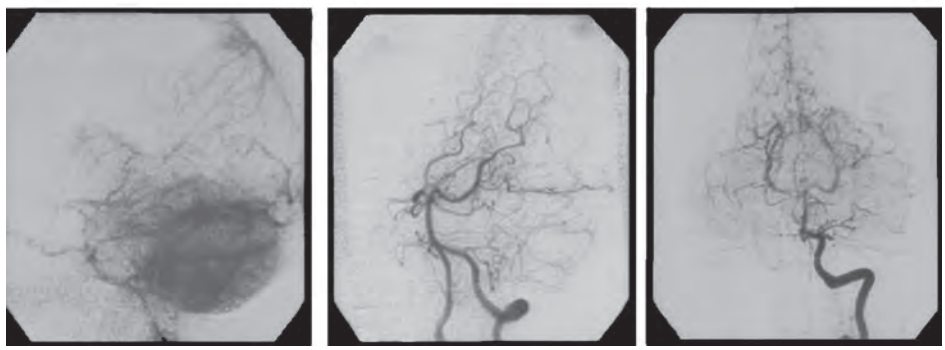


Fig. 5: Corpus callosum AVM—post-treatment angiogram showing total obliteration

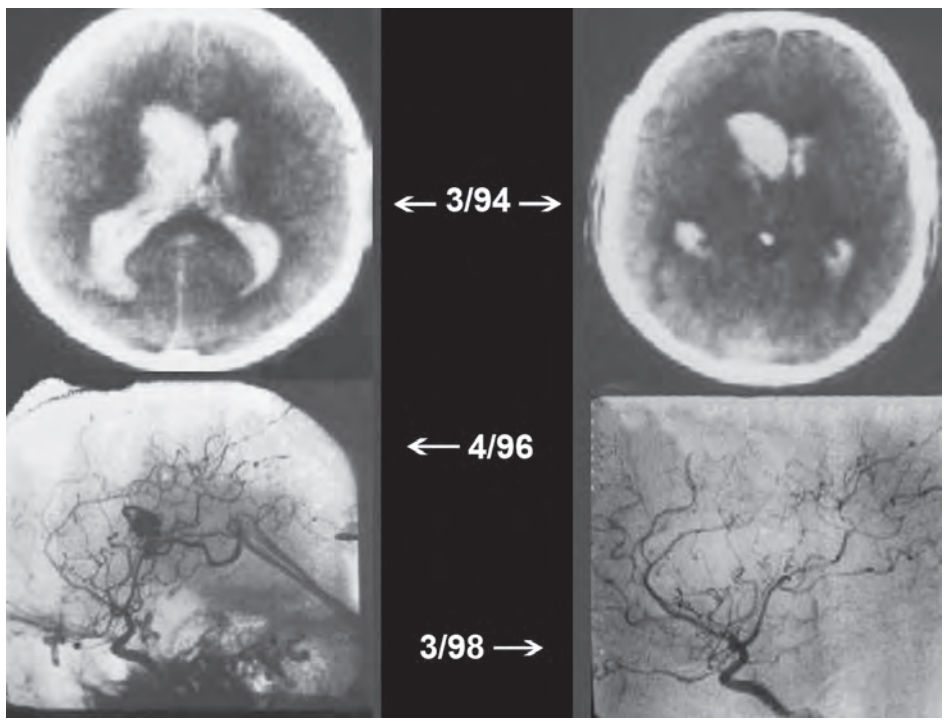


Fig. 6: Total obliteration following SRS (initial IVH)

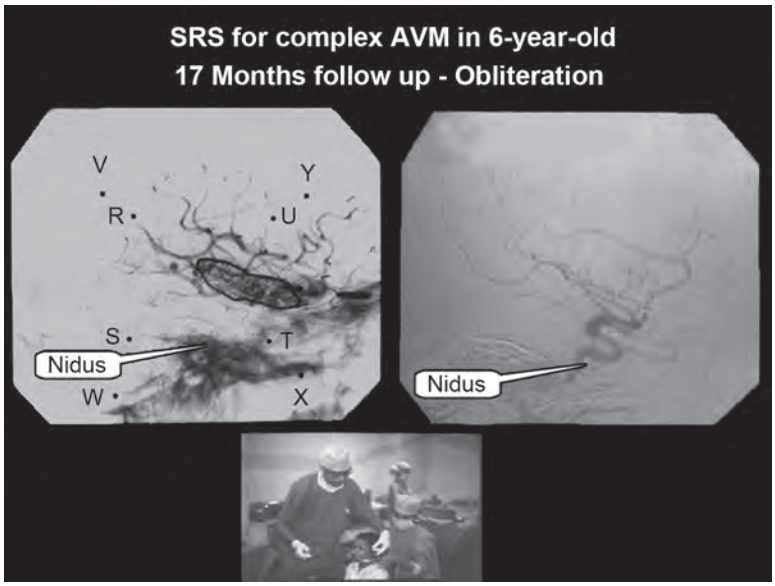


Fig. 7: Total obliteration following SRS in a 6-year-old patient

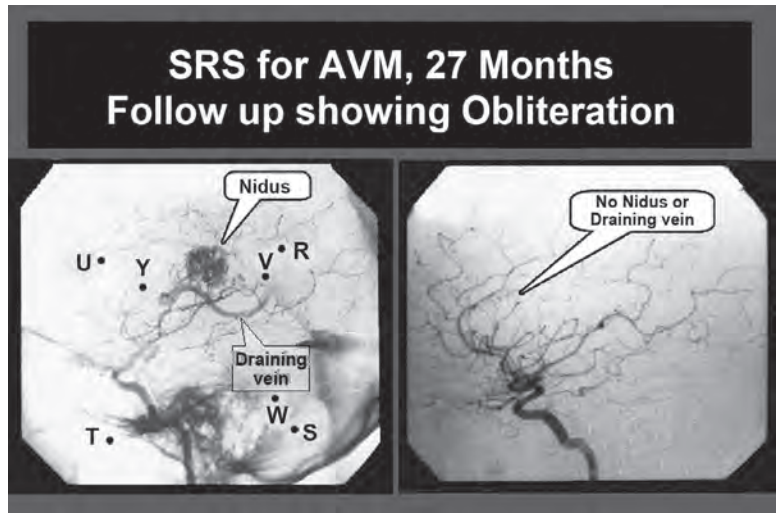


Fig. 8: Total obliteration following SRS

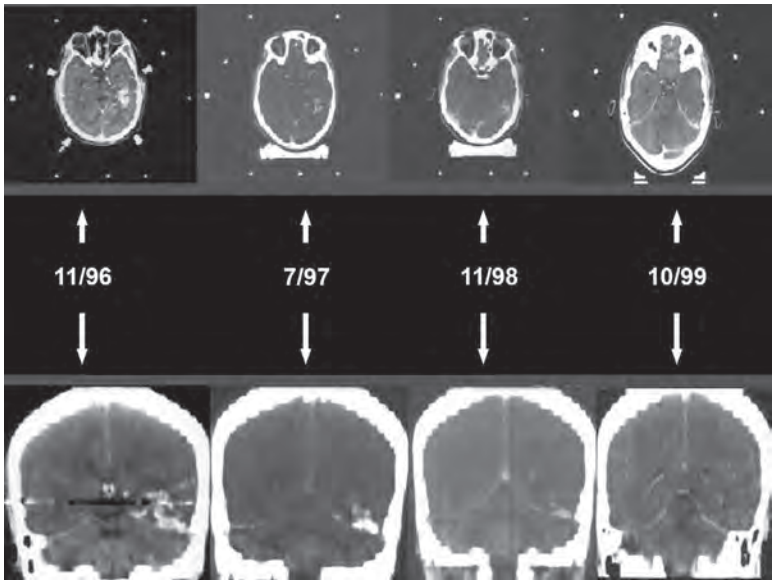


Fig. 9: Serial CT showing progressive reduction in nidus size

In the third world, where patients come from a very wide geographical distribution, including the neighbouring countries, post-treatment angiography in all cases will be difficult. Quisling et al. have used MRI to evaluate persistent nidus blood flow in cerebral AVMs following SRS.[107] In spite of the limitations, particularly in developing countries, post-treatment MRI evaluation will continue to offer some indirect evidence of "obliteration". The author, like Becker, has used transcranial Doppler in evaluating the size of cerebral AVMs. While it was useful in demonstrating lowered blood flow at the site of treatment, it was not possible to draw conclusions regarding the size and presence or absence of the nidus.[6] Heffez has stressed on the effect of incomplete patient follow-up on the reported results in the use of radiosurgery in the management of AVMs.[44] Long-term follow-up of 23 years following demonstration of complete angiographic obliteration is available.[65] Follow-up is advisable even after the treatment goal of obliteration has been achieved.

Embolisation Prior to Stereotactic Radiosurgery for Arteriovenous Malformations

Embolisation can be used as a preliminary procedure to reduce the size of the nidus and make it suitable for SRS.[2,14,41,97,99] Some authors question the value of pre-radiosurgical embolisation.[69] Embolisation is effective only if the arterial feeders contribute to the periphery of the nidus. Often, following embolisation, the blood supply is cut-off in different portions of the nidus making definition of the target volume difficult. If SRS is done immediately after embolisation, the target volume will not include portions of the nidus, which may form later following recanalisation. Presence of intranidal glue also makes outlining the target volume difficult in the CT and the MRI. The ideal time interval between embolisation and SRS is yet to be determined. Usually a 4–12 weeks' interval is preferred. Endovascular treatment of cerebral AVMs following radiosurgery has also been advocated.[84] The availability of Onyx has changed the concept of embolisation.[53,132,134]

Location

SRS is particularly suitable for AVMs located in eloquent areas. These include the post-geniculate visual pathway (to enhance the possibility of preserving visual function) and the brain stem.[10,70,86] In one series of 87 patients with brain stem AVMs, 95% improved or remained neurologically stable.[86] Re-bleeding occurred after SRS in three patients at 3, 6 and 16 months, respectively. The obliteration rate was 63% at 2 years and 73% at 3 years. A second SRS was performed in six patients with partial obliteration 3 years after the first procedure. The author has achieved total obliteration of giant AVMs following SRS in the brain stem and the corpus callosum. AVMs in the pineal region and the motor area are particularly suitable for SRS.[70,82] How the location influences the outcome is elegantly discussed by Kondziolka.[70]

Outcome

Two-year angiographic obliteration rates vary from 60% to 80%.[88] In some cases, the AVM is obliterated within a year. Several patients with a small remaining nidus, 2 years after treatment, were found to have complete obliteration at 3 years. Liscák[76] reported obliteration in 222 (74%) patients after the first round of radiosurgery and in 47 (69%) after the second. The risk of re-bleeding after radiosurgery was 2.1% annually until full obliteration and the overall mortality from re-bleeding was 1%. The risk of permanent morbidity after the first and the second radiosurgery treatments were 2.7% and 2.9%, respectively. Friedman has shown that the smaller the AVM the greater the chance of obliteration.[27] Some believe that even the smallest remnant of an AVM constitutes a risk of further bleeding.[38] Others are of the opinion that even partial obliteration offers some protection against the risk of haemorrhage.[60] There are no reports of haemorrhage occurring after angiographic demonstration of total obliteration.[75] Dose prescription and dose volume effects on the ultimate outcome have been studied.[24,81] SRS also appears to help control seizures.[19,37,49] The reduction of seizures was independent of angiographic results, suggesting that the ionising radiation by itself could lead to inhibition of epileptic activity around the AVM.[45] Headaches are a common symptom of cerebral AVMs, with a reported incidence varying from 3 to 79.2%. Headaches resolved or improved after SRS, the outcome correlating with the degree of obliteration.[47,133] Children, females and patients with deep-seated AVMs had a threefold increased risk of re-bleeding after an initial bleed. This increased risk was highest in the first year after the initial haemorrhage, and thereafter gradually decreased.[136]

Based on a prospective study of 72 patients with AVMs treated with microsurgery, Pikus concluded that microsurgery for grade I–III AVMs is superior to SRS.[98] It was also pointed out that results in microsurgery were very variable ranging from a mortality of 0.9 to 18.8% and morbidity ranging from 4.6 to 15.5%.[98] Sisti, a proponent of microsurgery, achieved total obliteration in 94% with a surgical morbidity of 1.5% and no operative mortality in a series of 67 intracranial AVMs less than 3 cm in diameter.[115] In a thought-provoking guest editorial, Steiner, a strong proponent of SRS,[124] comments on Sisti's arguments. Steiner concludes that AVMs should be managed by neurosurgeons familiar with microsurgery and radiosurgery and that both treatment options have a complementary role to play and are not exclusive of each other. The late results following surgical excision have been described by Heros.[46] Patient outcomes after SRS for operable arteriovenous malformations have also been studied.[104]

Causes of Treatment Failure

Heffez[44] has pointed out that quantifying the degree of treatment failure would itself depend on the extent of follow-up. If the analysis is limited to the patients who had follow-up angiography, the obliteration rate of AVM would be overestimated. The actual 2-year obliteration rate, if all data is considered, is in the range of 40% rather than the commonly reported 80%. Treated patients are exposed to the risk of intracerebral haemorrhage for a longer period than previously appreciated. The percentage of patients who actually undergo arteriographic confirmation of treatment efficacy 2 years after radiosurgery has ranged as low as 38%.[44] Angiography alone is not an ideal database for radiosurgery of AVMs because it can produce errors in the determination of the target centre and shape, when compared with modern CT imaging.[8,9,16,90] Other shortcomings include planar representation of 3D volume and simultaneous visualisation of feeding arteries and draining veins that overlap with the nidus and obscure its outline.[51] Stereotactically guided MRI may provide better spatial definition of the nidus and superior anatomical detail for the final design of the radiosurgical isodose distribution.

Recanalisation after embolisation, re-expansion after haematoma reabsorption and the presence of an intranidal fistula have been implicated as causes for treatment failure.[103,146] Inaccurate target definition could be due to substandard imaging equipment or operator error. Lower radiation doses used for AVMs in critical regions or when the AVM was unusually large may also contribute to treatment failure.

Statistically significant factors predictive of radiosurgical failure included higher Spetzler-Martin grade, increasing AVM volume, lower peripheral doses and a previous history of haemorrhage.[16] The maximum diameter, angiographic shape of the AVM nidus and number of draining veins are also significant. Smaller, compact AVMs with fewer draining veins respond well. Radiation dose, angioarchitectural and haemodynamic aspects, and flow pattern are also significant.[54,81] Effective radiosurgical treatment for AVMs requires accurate definition of the true tridimensional size and shape of the nidus. Over or underestimation may result in undue irradiation of normal brain tissue or suboptimal irradiation of the nidus leading to treatment failure.[116] Failure to precisely define the target volume leads to poor response. Stereotactic angiography alone, however, may not be the ideal database for radiosurgery because it can produce errors in the determination of the target centre, size and shape, when compared with modern CT imaging.[8,9] Early filling of the draining vein alone following SRS has been implicated as a risk for further bleeding.[38] Factors associated with successful AVM radiosurgery have been reviewed.[100] Gamma knife surgery for previously irradiated AVMs has been discussed by Karlson[59,63] (Table 1).

Table 1: Factors related to complete AVM occlusion

Unfavourable group	*Favourable group*
Large diameter nidus	Small diameter nidus
Multiple veins	Single vein
Higher Spetzler-Martin grade	Lower Spetzler-Martin grade
Complex shape of nidus	Compact shape of nidus
Low marginal dose	High marginal dose
High-flow pattern	Low-flow pattern
Prior embolisation	No previous embolisation
Critical location of nidus	Nidus located in non-eloquent area
Previous haemorrhage	Absence of prior haemorrhage
Presence of associated aneurysm	
Presence of associated AV shunting	
Presence of calcification	
Presence of intranidal fistula	

Complications

It is well known, although rare, that therapeutic radiation itself can produce iatrogenic radiation induced tumours.[89,111] Although occurring in very small numbers, complications following SRS for AVMs are being documented. Multivariate analysis and risk modelling studies regarding such complications have been carried out.[22] These complications may be asymptomatic, innocuous or clinically significant. Generally, the complication appears to be a result of large volumes treated, excessive dosage administered or due to use of less sophisticated treatment-planning systems. As in most neurosurgical procedures, the complications are also related to the learning curve. More complications are detected when it is looked for more aggressively. They include:

- Delayed cyst formation: This has been detected 5–23 years after SRS.[48,65,118] The clinical presentation has included hemi-Parkinson syndrome, hemiparesis and visual disturbances. Mechanisms underlying delayed cyst formation and spontaneous cyst shrinkage await clarification; breakdown of the blood-brain barrier appears to play an important role. Relatively high blood flow volumes and increased permeability of incompletely injured blood vessel walls in the treated nidus may prompt cyst formation within the area of radiosurgically induced degeneration. Coagulation necrosis leading to liquefaction necrosis may continue for several years after radiosurgery.[65]
- A new paranidal aneurysm, visualised 18 months after SRS for an AVM, in a 19-year-old woman has been described. Radiation changes in flow dynamics and vessel integrity has been implicated as a causative factor.[57]
- Asymptomatic middle cerebral artery stenosis: This has been detected 3 years post gamma knife radiosurgery. It has been postulated that the normal major artery, if located close to the target volume, may be

affected even by low dose irradiation (< 10 Gy).[138] Autopsy studies have demonstrated radiation-induced changes even in nidus-unrelated arteries.[140]

- Chronic encapsulated expanding haematoma: This has caused progressive deterioration 2 years after GKS;[48] a tough capsule containing multiple layers of organised haematoma resulting from previous bleeding was surgically confirmed. Histological examination revealed that the capsule consisted of a dense collagenous outer layer and a granulomatous newly vascularised inner layer with marked fibrosis. Haemosiderin deposits were frequently observed in the inner layer, which suggested recurrent minor bleeding from fragile vessels in this layer. An AVM was found in the haematoma, which had degenerated as the result of radiosurgery. A cross-section of the abnormal vessels showed various stages of obliteration due to intimal hypertrophy.
- Asymptomatic dural arteriovenous fistula (DAVF) in association with nidus obliteration after re-irradiation.[143]
- Haemorrhagic stroke, related to a previously irradiated, obliterated AVM.
- Radiation necrosis occurring at the site of radiosurgically treated AVMs.[48,118,126,140] These may present as a mass lesion with raised ICP or focal deficit several months after SRS. Imaging features may simulate a malignant neoplasm. Radiation necrosis appears to be a consequence of high doses employed.[48,68]
- Radiation-induced oedema detected on MRI following SRS is not uncommon.[137,142] The only major complication which the author encountered over a 7-year period while treating 170 cases of AVM with Linac based SRS was a case of "malignant" cerebral oedema resulting in post-treatment papilloedema and hemiparesis.
- Glioblastoma multiforme (GBM), histologically verified, associated with previous gamma knife radiosurgery has been described in a 20-year-old patient. Six and a half years earlier GKS had been done for an AVM. Maximum and margin radiation doses were 40 Gy and 20 Gy, respectively. In this case, complete obliteration of the AVM was confirmed by angiography. In addition to thickening of the walls of the abnormal vessels, GBM was also found in these abnormal vessels when the patient was operated upon for the tumour.[56]

Even the demonstration of complete AVM obliteration by angiography cannot be taken as a guarantee that patients will not develop delayed radiosurgery-related morbidity. Long-term neuroimaging is essential even after the "treatment goal" has been attained.[139] Additional experience with post-radiosurgical complications, potentially developing several years after irradiation, may elucidate the pathogenesis of these complications. Delayed radiation-induced complications, ranging from 3.2 to 12.5%, have been described by users of gamma knives, linear accelerator systems and particle beam systems.[145] Radiation induced oedema and haemorrhages are significantly higher in large AVMs than in small ones; however, the permanent neurological complication rate can be as low as 3.3%.[25] Gliosis and demyelination, which appeared to be dose dependent, were detected as signal changes in MRI even 23 years after complete obliteration.[65]

LARGE ARTERIOVENOUS MALFORMATION

Management of large AVMs (Spetzler-Martin grade V) has always been a daunting and challenging task. SRS has been used even for large AVMs to achieve partial obliteration, with a view to subsequent open surgery.[119] Combined embolisation and SRS for the treatment of large-volume, high-risk AVMs have also been advocated.[14,99] The advocates of open surgery concede that morbidity and mortality are higher for larger AVMs than for smaller AVMs.[98] As early as 1972, Steiner pointed out that large AVMs respond poorly to SRS.[123] Subsequently, several reports have confirmed the lower obliteration rate in larger AVMs.[24,25,51,94,137] Obliteration rate in AVMs with volumes between 10 cc and 15 cc was 77% compared to 25% for AVMs with a volume > 15 cc.[51] Staged radiosurgery, wherein portions of a large AVM are treated separately, has been considered a treatment option. The time interval between the staged radiosurgical treatments have varied from 1 to 8 months.[51,94] Although the time taken is more, complete obliteration has been achieved in many cases.[51,94,99] Karlsson[58] has suggested that a giant AVM can be treated with a low dose of radiation (≥ 10 Gy), and the treatment repeated if the AVM shrank but was not obliterated. In exceptionally large AVMs, where previous attempts at surgery and embolisation have failed following staged SRS, the nidus has sufficiently shrunk to permit subsequent surgical excision.[20] Due to the complexity of arterial feeders, embolisation alone or as an adjunct is often insufficient. A combination of SRS and stereotactic fractionated radiotherapy has also been proposed for the treatment of larger AVMs.[4] Recently, there have been reports that volumes of up to 30 cc have been treated effectively with radiosurgery with an acceptably low complication rate.[25] In patients with large AVMs, the treatment-related complication rate was 3.9% compared with 2.4% in patients with small AVMs. Larger AVMs need a longer time for obliteration. At 50 months follow-up, the complete obliteration rate of AVMs larger than 15 cm^3 (up to 26 cm^3) had increased to 58%. AVMs are radiosurgically classified as "late-responding targets embedded within late-responding normal tissue".[94] In large AVMs, the incidence of radiation induced oedema and haemorrhage is significantly higher than in small ones; however, the permanent neurological complication rate can be as low as 3.3%.[25]

Obliteration of an AVM following exposure to a single focused dose of irradiation depends essentially on total coverage of the total nidus with an adequate radiation dose. Large volumes and critical location often

necessitate suboptimal doses.[146] Lower treatment doses are also used to limit complications.[143] Since larger AVMs contain more normal brain within the AVMs towards the periphery, marginal doses also have been reduced.[61] Some have used margin doses of 18 Gy to 22 Gy in the 40–50% isodose (gamma knife) for volumes ranging from 11 cm^3 to 25 cm^3.[94] Others have kept the mean dose inside the nidus between 20 Gy and 24 Gy with a margin dose of 18 Gy (at the 55–60% isodose centres).[51]

The shape of the lesion also determines the degree to which a "tight fit" can be obtained,—that is the ability to place multiple collimators precisely over the nidus so as to generate a treatment plan, which would ensure maximal radiation to the nidus and a steep fall out resulting in minimal radiation outside the nidus. The use of a number of isocentres is particularly crucial in formulating an ultra-conformal treatment plan to cover the entire nidus. In large AVMs, different arterial systems contribute to different portions of the nidus. Accurate delineation of each portion of the nidus is to be followed by "making" a composite nidus truly representative of the giant AVM. Failure in achieving angiographic obliteration is often due to imprecise definition of the target volume due to incomplete angiography.[16] Imprecision is more when the target volume to be defined is large. Often, the entire nidus may not be included in the prescription dose.[143] For very large AVMs, staged volume radiosurgery may result in considerable size reduction making it suitable for subsequent microsurgical resection.[20] Surgical resection of large incompletely treated intracranial AVMs following SRS, is also a treatment option.[119] Large AVMs in non-eloquent areas, as over the corpus callosum,[31] can successfully be obliterated without complications with SRS, provided the angiographic nidus is accurately demarcated with pan angiography. Linear shape makes ultra-conformal treatment planning more accurate. Size and volume alone should not be the criteria for choosing or rejecting SRS as a treatment option. The shape and location should also be considered.

SRS is an elegant tool but, as Lars Leksell, the father of Radiosurgery, observed "A fool with a tool is still a fool". It is essential that the neurosurgeon planning to use SRS in the management of cerebral AVMs should be fully aware of its limitations and not only of its advantages. Considerable judgement needs to be exercised before choosing a treatment option for the management of cerebral AVMs. Today, we are in the era of evidence based medicine. Decision-making, however, has to take into account the socio-economic milieu, and the availability of the alternatives,—state of the art microsurgical and endovascular expertise,—in the management of cerebral AVMs. Ultimately, a paradigm has to be evolved for every specific clinical situation, which takes into account the several variables, which have been outlined. One should also remember that the different treatment options are not necessarily exclusive, but may even be complementary.

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95 Vein of Galen Malformations

Anil Nanada

Vein of Galen malformations are rare vascular malformations. They constitute approximately 1% of all intracranial vascular lesions and nearly one-third of them are in the paediatric age group.[6,9] With increased sensitivity and introduction of specific diagnostic tools, the frequency of this diagnosis has increased over the last two decades. These malformations are usually situated in the midline, producing dilation of the vein of Galen and are sometimes referred to as "aneurysms" of the vein of Galen. The high blood flow through this fistula or shunt is responsible for the majority of symptomatology associated with these malformations.

In 1895, Steinheil described this particular malformation for the first time and referred to it as a varix aneurysm.[19] In 1937, Jaeger and his colleagues provided the first thorough description of a case of vein of Galen malformation for which treatment was attempted.[4,16] Davidoff, in 1947, and Boldrey, in 1949, subsequently described the surgical approach.[1,11] Silverman and colleagues explained the pathophysiological features of the fistula in a vein of Galen aneurysmal malformation and its causative role in prompting high-output cardiac failure in neonates and infants.[18]

ANATOMICAL CONSIDERATIONS AND CLASSIFICATION

The vein of Galen is a centrally located short venous structure formed by the confluence of the internal cerebral veins and the basal vein of Rosenthal. It passes posteriorly, emptying into the straight sinus at its junction with the inferior sagittal sinus (Fig. 1). The anatomic landmark of a vein of Galen aneurysmal malformation (VGAM) is the presence of multiple arteriovenous shunts draining into a dilated median prosencephalic vein, an embryonic vessel normally absent at the adult stage.[2] The structures drained by the vein of Galen include the thalamus, the medial temporal lobes, the occipital lobes and the superior cerebellar vermis. The vein of Galen lies in the quadrigeminal cistern and receives veins from the ambient cistern, the pericallosal and occipital veins from the corpus callosum cistern, and the precentral cerebellar vein from the superior cerebellar cistern, as well as the internal cerebral veins from the velum interpositum cistern.

Yasargil classified vein of Galen malformations morphologically based on the arterial supply pattern of the malformation into four types.[23]

Type I: Direct anastomosis between the vein of Galen and the pericallosal arteries and the P3 segments of the posterior cerebral arteries.

Type II: Direct fistula between the thalamoperforating arteries (P1 segment) and the vein of Galen.

Type III: Combinations of Types I and II.

Type IV: It is simply a pial arteriovenous malformation that drains into the vein of Galen.

In 1992, Lasjaunias proposed an angiographic classification that differentiated "true" vein of Galen malformations (Yasargil Type I–III) from the secondary malformations or dilatations (Yasargil Type IV).[6]

CLINICAL FEATURES

Patients with vein of Galen malformations have clinical presentations that can vary with age of onset. The clinical classification for the malformation involves the

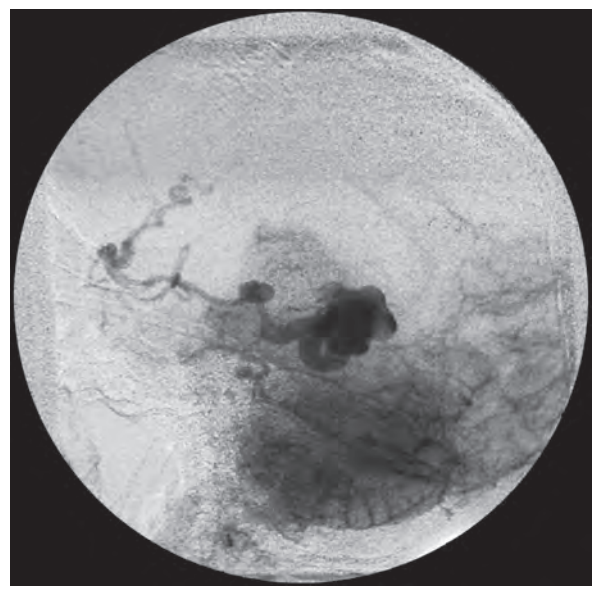

Fig. 1: A digital subtraction angiogram of the vertebral artery (lateral view) showing a dilated vein of Galen with malformation

correlation of three features: (1) age at presentation; (2) clinical syndrome and (3) pathophysiology. Three characteristic groups have been identified: (1) the neonate presenting with severe congestive heart failure; (2) the infant presenting with hydrocephalus and/or seizures and (3) the older child or adult presenting with headaches or subarachnoid haemorrhage. The basis for most clinical symptoms is not the mass effect, but rather the shunting of blood through the fistula that produces either cerebral or coronary artery "steal". There is evidence that an autosomal dominant factor caused by mutations in the *RASA 1* gene may be involved in the pathogenesis of vein of Galen malformations.[14]

Neonates

About 40% of patients with vein of Galen malformation are diagnosed during the neonatal period. The malformation typically produces congestive heart failure (hypoxia, low cardiac output, tachycardia and pulmonary oedema). Cyanosis is very common and is typically refractory to medical therapy. In addition, the cerebral artery "steal" can be associated with venous hypertension, cerebral ischaemia and infarction.

Infants

Infants have a smaller shunt as compared to newborns. Hydrocephalus and seizures are the most common presentations. Head enlargement in infants can be caused by ventricular dilatation in the presence of a distensible skull. The fontanelle is full but seldom tense. Overt signs of raised pressure (nausea, vomiting, lethargy, etc.) are rarely present. It is likely that the ventriculomegaly is a result of increased pressure in the sagittal sinus or venous system that affects CSF absorption. Typically, there is no periventricular fluid present on imaging studies.

Older Children and Adults

They typically have a low-flow fistula or may have a Yasargil Type IV malformation. They present with subarachnoid haemorrhage, intracranial bleeds, headaches or cognitive dysfunction. They, occasionally, may present with hydrocephalus, but congestive heart failure is very rare.

DIAGNOSTIC INVESTIGATIONS

Investigations of a patient with a suspected vein of Galen malformation fall into three categories: (1) imaging of the brain; (2) imaging of the cerebral vasculature and (3) various other investigations to assess the systemic effects associated with the malformation.

Brain Imaging

Computed tomography [(CT) Fig. 2] and magnetic resonance imaging (MRI) are the two definitive diagnostic modalities for this condition. On a CT scan, the characteristic features are calcification, low-density cystic spaces and post-contrast enhancement.[21] An MRI scan is more sensitive than a CT scan since it provides better information concerning the malformation and its effects on the surrounding brain. Additionally, it provides greater details about the ischaemic changes occurring in the affected brain and also depicts the patency and size of the large arteries, veins and venous sinuses.

Cerebral Angiography

The final diagnosis of the malformation is provided by cerebral angiography. This also provides information about the vascular anatomy that is essential for treatment planning. The vein of Galen forms an arc under the splenium of the corpus callosum, curving posterosuperiorly towards the tentorial apex. It is clearly seen on the lateral view, but is often obscured by the overlying superior sagittal sinus on AP projections (Fig. 3). The

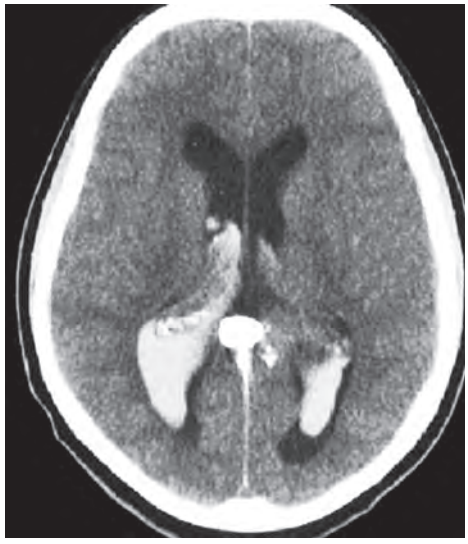

Fig. 2: A plain CT scan of the head showing a large vein of Galen malformation and accompanying haemorrhage into the lateral ventricles

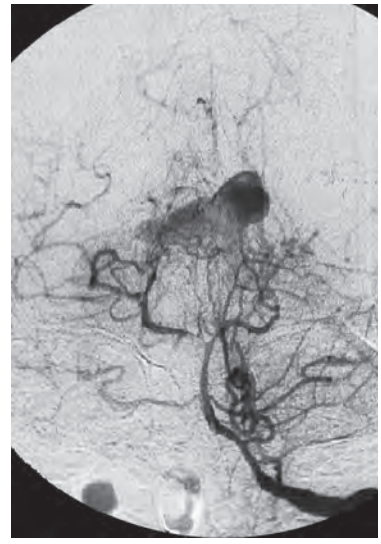

Fig. 3: AP view of a vertebral digital subtraction angiogram showing a vein of Galen malformation

two most widely referenced angiographic classifications are those of Lasjaunias and colleagues[6,15] and Yaşargil.[23]

Other Investigations

These are designed to assess systemic abnormalities associated with the condition such as hypertension, congestive heart failure and renal failure. These include studies of arterial blood gases, chest radiology, electrocardiography, echocardiography, serum electrolytes, serum creatinine and urinary electrolytes. Monitoring serial plasma BNP provides valuable information regarding the need for additional evaluation or treatment of newborns with CHF and is also helpful as a prognostic indicator.[20]

Prenatal ultrasonography shows the characteristic midline tubular anaechoic structure superior to the thalamus, which is contiguous with the dilated sagittal sinus (comet tail or keyhole sign)[17] and also reveals extracardiac left-to-right shunt, featuring as a high-output heart failure in a neonate and hypoxic-ischaemic brain lesions due to the 'steal' phenomenon. More precise anatomy and location of foetal pathology, and additional aetiologic information are the substantial advantages in doing fast MRI as an adjuvant to ultrasonography.

Doppler evaluation is important in differentiating this lesion from other cystic lesions of the brain because this is the only lesion that clearly displays blood flow within it.[13]

TREATMENT

Many series have been published that show patients with untreated vein of Galen malformation typically die from a combination of cerebral and cardiac events.[3,5] Most often, neonates succumb to their cardiac insufficiency, and older children and adults succumb to the cerebral injury. More important, despite modern treatment, the mortality rates for this condition still approaches 79% for neonates and 39% for the remaining population. Patient selection and timing remain the keys in the management of this condition. It is more important to restore normal growth conditions than a normal morphological appearance, with the primary therapeutic objective being normal development in a child without neurological deficit.[7]

Medical Treatment

In the newborn, initial treatment is usually aggressive medical stabilisation. Congestive heart failure should be aggressively treated to stabilise the accompanying pulmonary hypertension and cardiomegaly. Ideally, intervention should be delayed until the infant is 6 months old; however, if there are clinical signs of an acute deterioration, urgent definitive treatment may be indicated.

Interventional Strategies

The selection of treatment is influenced by the age of a patient at presentation and by the complexity of the malformation. These modalities may include embolisation, surgery, shunting for hydrocephalus or a combination therapy.

Treatment of Hydrocephalus

The results of most shunting procedures for ventriculomegaly in infants and neonates are disappointing because intraventricular pressure is invariably low. It is, therefore, best to avoid ventricular shunting and aim the therapy at correcting the basic pathology. This strategy has shown to normalise the head circumference.[6]

Endovascular Treatment

Sophisticated, high-resolution angiography and endovascular techniques have been applied to the management of vein of Galen malformations. This approach can be transarterial or transvenous through the torcula. The transarterial approach is considered to be most suitable for Yasargil Type I, II, or III malformations. Lasjaunias and associates recommend that the transvenous approach be limited to malformations where the arterial approach has failed.[8] Both approaches have been used with varying degrees of success for Yasargil Type IV malformations. Each technique can be used alone or in combination with surgery.[10,22]

Surgical Treatment

Surgery should be delayed until both the medical condition and the nutritional status of the patient are optimised. Many infants and children may require definitive management of the hydrocephalus before or after definitive surgery. In addition, pre-operative embolisation of the accessible feeders has been recommended to simplify the resection. The galenic region can surgically be approached by the subtemporal, transcallosal or transtentorial approaches. However, the posterior interhemispheric approach is most commonly used to adequately access a vein of Galen malformation and expose the feeding arteries.

Radiosurgery

Stereotactic radiosurgery using gamma knife has recently been tested as a treatment option for this formidable disease. Payne et al. published their series of 9 patients with vein of Galen malformations that were treated using radiosurgery.[12] They achieved a cure in four patients following a single treatment, while two others were cured after two and three sessions, respectively. In one case, the malformation failed to respond to treatment. These results, although small in number, definitely point to another potentially safe treatment modality in the future for vein of Galen malformations.

OUTCOME

Treatment for vein of Galen malformations is still evolving. Treatment modalities include surgery and endovascular

techniques. Newer modalities using focussed radiation have been suggested, but are yet to be universally accepted as definite alternatives. Although outcomes in comparison to natural history have improved remarkably, the mortality rate is still about 35% and significant morbidity is seen in another 30% of patients.

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CE Deopujari

Developmental malformations affecting the blood vessels supplying the brain most likely develop during the late somite stages of the 4th week of embryonic life.[15] The traditionally used classification, described by McCormick,[29] divides these lesions on the basis of histopathological features into four categories: (1) venous malformations; (2) arteriovenous malformations; (3) cavernous malformations and (4) telangiectases. However, the intermediate and combined forms of these vascular malformations that do not fit simply into one of the above categories have also been described.

Cavernous malformations constitute 5–10% of all cerebrovascular malformations[28,41] and are the second most common intracranial vascular malformations responsible for haemorrhage.[27] Cavernous malformations are variously known as cryptic angioma, cavernous angioma, cavernous haemangioma, cavernoma and "angiographically occult vascular malformation" (AOVM).[18] These vascular malformations are characterised by the presence of sinusoid like capillary vessels. These capillaries are adjacent to one another, with little or no intervening neural parenchyma, while feeding arteries and draining veins are most often normal in size. The association of cavernous malformations with venous angiomas is reported to be around 20–30% in the literature.[10,42] They are known to occur anywhere in the neuraxis including on cranial and spinal nerves but are most commonly found in subcortical white matter, external capsule and pons.[8,20] Locations of the 67 lesions operated upon in our unit are shown in Table 1.

Table 1: Location of cavernous malformations operated in our series

Location	*Number*	*Percent*
Supratentorial	47	70.1
Frontotemporal	22	
Frontal	11	
Occipital	4	
Parietal	5	
Intraventricular	2	
Thalamic	2	
Optic/Hypothalamic	1	
Infratentorial	18	26.8
Brainstem	15	
Cerebellum	3	
Spinal	2	3.1

INCIDENCE

The exact incidence and prevalence of cavernous malformations are unknown, as many of these lesions remain asymptomatic. Before the introduction of modern imaging technology, cavernous malformations were considered rare lesions. These lesions are more common than are generally suspected. Based on clinical series, the prevalence of cavernous malformation is estimated at 0.5%.[43] Autopsy series by McCormick[46] and by Otten[32] revealed a prevalence of 0.4% (16 of 4,069 autopsies) and 0.53% (131 of 24,535 autopsies), respectively. Similar results were reported by two groups reviewing more than 22,000 MRI examinations,[12,43] with incidence rates of 0.4–0.5%.

AETIOPATHOGENESIS

The exact aetiology of cavernous malformations is not known. Although cavernous malformations are known to be congenital in origin, cases of de novo formation with previously documented normal MRI have also been reported.[13,48] The lesions have also been known to appear following radiation therapy[9,25] and along the path of stereotactic biopsy.[31]

Cavernous malformations are known to occur in both sporadic and familial forms.[51] Almost 30% of the patients affected have the familial form of the disease and it seems to be more common amongst the Hispanic American population. Both the sporadic and familial forms of the disease appear clinically similar, except for the fact that there is greater incidence of multiplicity and relatively lesser incidence of bleeding in the familial group.[51] Moreover, de novo development of new lesions in the familial group necessitates serial imaging follow-up at regular intervals in these patients.

The genetic basis behind the development of cavernous malformations has been elucidated. The familial form of the disease is inherited as an autosomal dominant disorder with variable penetrance.[17] Kurth et al.[24] and Dubovsky et al.[14] linked the gene for familial cavernous malformations, designated *CCM1*, to chromosome

7q. Subsequent work by them and other investigators led to the discovery that mutations in the *KRIT1* gene are responsible for *CCM1*.[45]

PATHOLOGY

Cavernous malformations are well circumscribed, discrete and multilobulated lesions of various sizes. The average size of the lesion tends to be 1–2 cm. The gross appearance is likened to a mulberry owing to its dark red purple colour. Pathologically, they are composed of sinusoidal, dilated vascular channels (caverns-lakes) lined by a single layer of endothelium devoid of elastin or smooth muscle. These vascular lakes are separated by a collagenous stroma. On cut section, they appear like a honeycomb of thin walled vascular spaces. The lack of intervening brain parenchyma is a characteristic pathologic marker. Various degenerative changes, like hyalinisation, calcification, cyst formation and thrombosis with varying degree of organisation, are common. The surrounding parenchyma exhibits evidence of microhaemorrhages of varying ages with haemosiderin laden macrophages. A gliotic reaction of the surrounding parenchyma may form a pseudocapsule around the lesion.[29,37,44,49]

CLINICAL PRESENTATION

Cavernous malformations occur throughout life but are diagnosed more often in adults. The symptoms generally start in the 20s and 30s. The lesions tend to occur equally in men and women.[12,43]

Seizures

Seizures are the most common presenting symptom, seen in 40–70% of patients with cavernous malformations.[11] All types of seizures have been described in these patients including simple partial, complex partial, focal, generalised tonic clonic or in any combination.[52] The seizures do not arise from the lesion itself but rather from the irritated cortex adjacent to the lesion.[11] The exact mechanisms by which cavernous malformations produce seizures are unknown. The iron present in haemosiderin is a well-known epileptogenic material.[50] Local gliotic reaction, extensive haemosiderin deposition, recurrent microhaemorrhages, calcification and frontal and temporal location are frequently associated with the clinical presentation of epilepsy. There are no clear data indicating the long-term risk of developing seizures but seizure control becomes more difficult with time. The risk of developing seizures in these patients is estimated to be around 1.5–4.8% in various studies.[12,30] By the time of presentation, it is medically refractory in almost half (44.7%) of the patients.[7]

Haemorrhage

Though evidence of previous haemorrhage is present in almost every lesion regardless of clinical history, overt haemorrhage is less frequent. Overt haemorrhage has been defined as "symptomatic presence of extralesional blood outside the confines of the haemosiderin ring on MRI or at surgery".[22,43] Intralesional microhaemorrhages occurring within the confines of the haemosiderin ring are rarely associated with symptoms. The risk of overt haemorrhage is definitely less than classic AVM, and has been estimated to be around 0.25–13% per patient per year.[12] Since there is uncertainty about the definition of haemorrhage, Porter et al.[34] reported event rates where they defined an event as any subjective neurological worsening with or without radiologically verified haemorrhage. In their series, the overall event rate was 4.2% per patient year, which is nearly equal to that of classic AVM. Factors associated with increased risk of haemorrhage in these patients include prior symptomatic bleed,[3,43,51] size greater than 10 mm, age less than 35 years, female sex,[30,43] pregnancy[43] and deep location of the lesion.[3]

As the cavernous malformations are low flow and low pressure lesions, haemorrhage usually displaces and compresses adjacent neural tissue rather than destroying it.

Focal Neurological Deficit

This may occur in 20–40% of patients due to compression of the critical areas of brain function.[12,43,51] The deficit may be acute and maximal at the onset, especially in cases with lesions within the brainstem. In the brainstem, where crucial tracts and nuclei are compactly arranged, even small focal haemorrhage may be tolerated poorly. However, the symptoms tend to resolve completely as the haemorrhage is absorbed. Recurrent episodes of haemorrhage are associated with progressively more severe deficits and an increased risk of permanent neurological impairment.[3,12,43]

Focal deficits secondary to mass effect may be subacute and progressive if the lesion is located in the basal ganglia or thalamus.

Incidental

Between 15% and 20% of lesions are discovered incidentally during an evaluation for headache or other unrelated neurological problems.[16] In familial patients with multiple cavernous malformations, few lesions are symptomatic.

Other rare clinical presentations reported include cranial neuropathies (trigeminal neuralgia), hypothalamic symptoms and hydrocephalus.[16,41,49]

IMAGING

Computerised Tomography

CT scan is 70–100% sensitive but less than 50% specific in detecting cavernous malformations.[16,26,40] The lesion typically appears to be well circumscribed popcorn like and

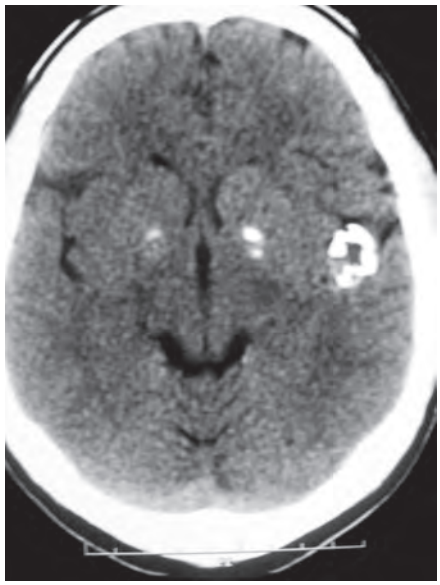


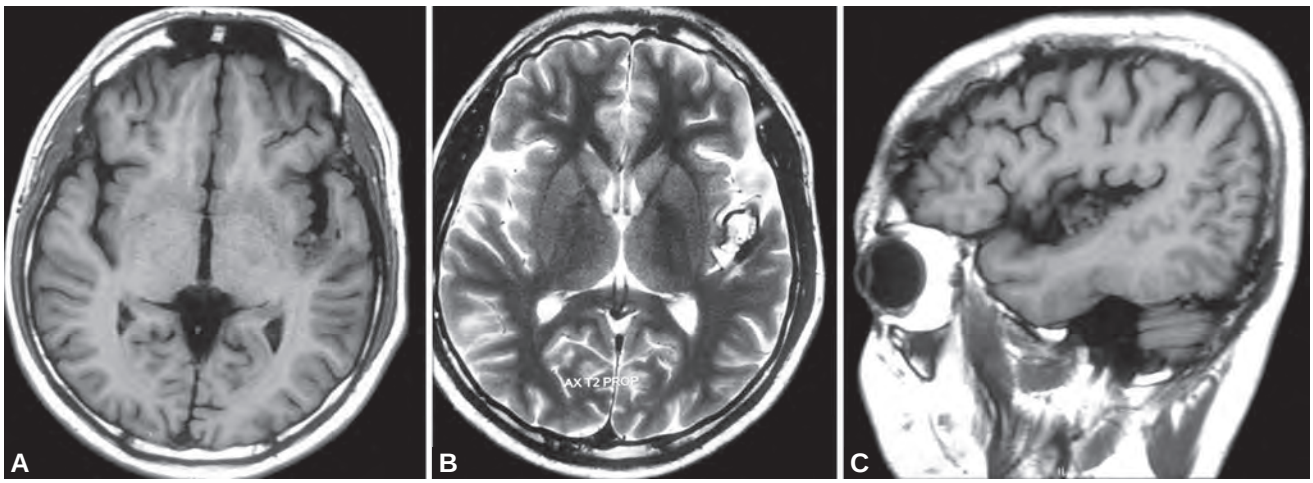
Fig. 1: CT scan of the brain plain study showing a hyperdense lesion (popcorn appearance) within the left Sylvian fissure in a patient who presented with seizures

slightly hyperdense with faint enhancement on contrast. Calcification and haemorrhage may also be seen (Fig. 1).

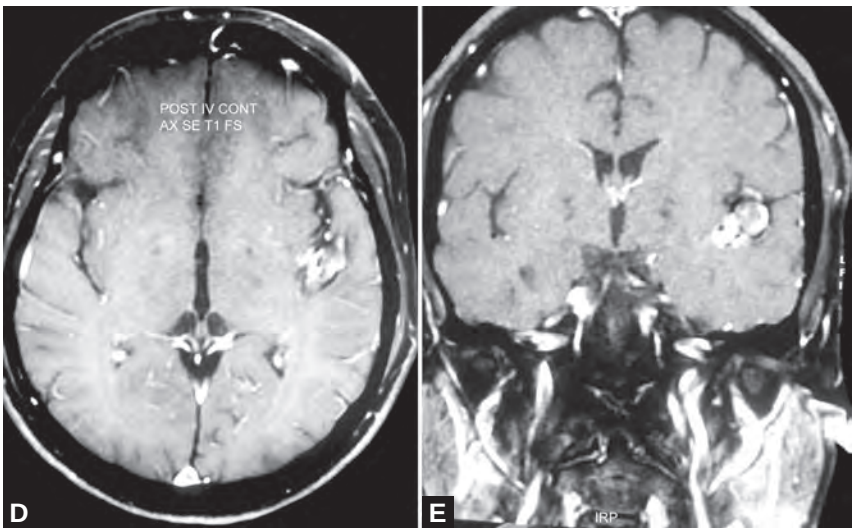
Magnetic Resonance Imaging

It is the most sensitive and specific imaging modality available for detection of cavernous malformations (Figs 2A to E). The lesion appears as a well-defined lobulated mass with a central core of mixed signal intensities surrounded by a rim of hypointensity.[5,33,38] The mixed signal reflects acute and subacute haemorrhage in different stages and the hypointense rim is due to perilesional haemosiderin deposition. The peripheral hypointensity blooms on T2 WI. Gradient-echo (GRE) images are much more sensitive than conventional sequences for detecting small cavernous malformations.

Based on the MRI appearance of cavernous malformations, Zabramski[51] classified these lesions into four types. Type I lesions are associated with subacute haemorrhage and have a hyperintense central region on T1 WI. Type II lesions contain loculated areas of thrombosis



Figs 2A to C: MRI scan of the brain in a patient having left Sylvian fissure cavernoma. (A) T1 axial. (B) T2 axial. (C) T1 coronal



Figs 2D and E: Contrast MRI scan of the brain in a patient having left Sylvian fissure cavernoma. (D)T1 axial and (E) T1 coronal

and haemorrhage of variable age. Type III lesions show the imaging correlate of chronic haemorrhage. Type IV lesions are difficult to detect on conventional imaging. Typically these lesions are small and hypointense on GRE sequences.

Angiography

Angiography is almost always normal and for this reason these lesions are also known as angiographically occult vascular malformations. Occasional abnormalities seen in association with cavernous malformation include avascular mass lesion, capillary blush or evidence of neovascularity. Other vascular malformations, like AVM or venous malformations, can be ruled out using angiography.

DIFFERENTIAL DIAGNOSIS

The MRI appearance of cavernous malformations is characteristic but not specific. Other lesions to be considered in the differential diagnosis include neoplasm with haemorrhage, especially haemorrhagic metastasis, calcified tumours like oligodendroglioma or pleomorphic xanthoastrocytoma.[26,33,40] Thrombosed AVMs which are angiographically occult may also be confused with cavernous malformations.

MANAGEMENT

Treatment options available for patients with cavernous malformations include surgical excision, observation or, occasionally, stereotactic radiosurgery. The choice of option depends on many factors like age, sex and general medical condition of the patient, number and location of the lesions and clinical presentation. The benefits and the risks associated with each treatment option need to be considered.

SURGERY

Well accepted indications for surgical excision of cavernous malformations are recurrent haemorrhage, progressive neurological deterioration, increase in the size of the lesion, intractable seizures and a large lesion surfacing near a pial or ependymal area.[12,43] Surgical resection of accessible lesions is associated with low rates of morbidity and mortality.[1,16,47,49] Surgical intervention in deep seated lesions, especially in the brainstem, should be considered only if they are approachable through an accessible surgical corridor (Fig. 3).

Intracranial cavernomas can be divided into two groups: (1) supratentorial and (2) infratentorial.

Supratentorial Cavernous Malformations

Supratentorial cavernous malformations constitute about 75% of all intracranial cavernous malformations.[12,28,43,49] They can be located superficially in either cortical or subcortical white matter or may be deep near the internal capsule or thalamus. Surgical strategies are modified based on the location of the lesion.

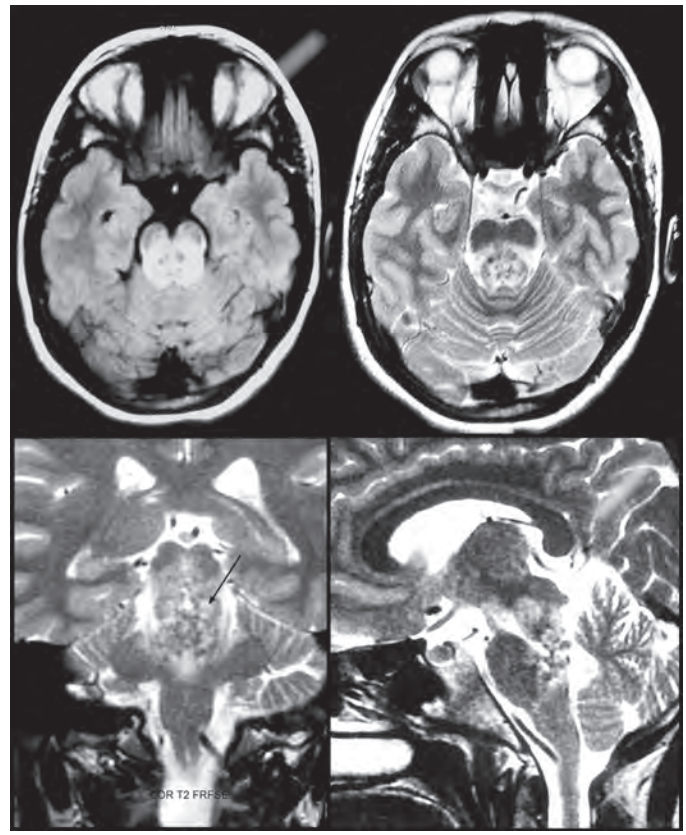


Fig. 3: MRI of the brain showing brainstem cavernoma with popcorn appearance

Pre-operative mapping of the critical brain areas using functional MRI allows better planning of the craniotomy. Frame based or frameless stereotactic devices are frequently used to minimise the size and invasiveness of the craniotomy. Surfacing lesions can be identified easily by their characteristic purple-blue mulberry-like appearance or by haemosiderin staining of the cortex. If the lesion is located deeply, intra-operative ultrasound or neuronavigation techniques can be used. Intra-operative mapping using electrocorticography or awake craniotomy should be considered while operating on lesions in eloquent areas.

The lesion can itself be entered into using a bipolar coagulator and is shrunk by emptying the larger blood filled caverns. The surrounding gliotic pseudocapsule aids the dissection. Working circumferentially around the lesion in the gliotic plane, the lesion is freed from all sides and is removed en mass. Care should be taken to inspect the resection bed under magnification for satellite like nodules.[19] Care should be taken to avoid the associated venous malformation as it may be the sole source of venous drainage for the surrounding normal brain. Damage to or resection of the venous malformation may cause haemorrhagic venous infarction.[35]

Surgical resection of capsular or thalamic cavernous malformation is associated with greater morbidity rates than for more superficial hemispheric lesions. Literature reports poor outcome for surgical treatment of thalamic lesions. Bertalanfy et al.[4] have reported around 50%

permanent neurologic complications after resection of deep seated lesions. Intervention should be reserved for lesions causing recurrent episodes of haemorrhage or progressive neurologic deficit and those that reach an ependymal or pial surface.

Surgical Strategies for Epilepsy

If the seizures can be controlled easily with medications, the indications for surgery in these patients are similar to those for patients with asymptomatic cavernous malformations. However, different surgical strategies need to be considered for patients presenting with intractable seizures. These patients should undergo a standard workup done for patients with intractable epilepsy including an ictal and/or interictal EEG, video EEG if required, neuropsychological testing, functional MRI to delineate speech and motor areas and WADA testing. Patients whose data are concordant with the lesion location by MRI may be good candidates for surgical intervention. Surgical options for these patients include lesionectomy alone, lesionectomy plus resection of adjacent gliotic tissue and lesionectomy plus resection of adjacent and even remote cortex that has been identified by electrophysiologic testing as foci of epileptogenicity. Removal of the lesion and the adjacent gliotic yellow stained tissue has shown to reduce the long-term frequency and severity of seizures.[12,39,43] Intra-operative aids, like image guidance or neuronavigation, intra-operative USG, electrocorticography or awake craniotomy for brain mapping, are helpful adjuncts. Surgery is, however, less successful if there have been more than five episodes of seizures or if the duration of symptoms is more than 2 years.

Infratentorial Cavernous Malformations

Infratentorial cavernous malformations include those involving the brainstem and cerebellum. The lesions in the brainstem are of distinct importance owing to the critical structures in the proximity.

To determine the best surgical approach for brainstem lesions, Spetzler[6] has described a "two point method" where one point is placed in the centre of the lesion and a second point is placed where the lesion most closely reaches the pial surface. Both the points are connected and the resultant straight line through the least eloquent tissue dictates the most appropriate surgical approach. Careful study of MRI scans is very helpful to plan the approach pre-operatively. The brainstem can be approached through various routes depending on the location of the lesion and pre-operative planning:[36]

- Midline suboccipital craniotomy with approach through the fourth ventricular foramen for lesions bulging into the floor of the fourth ventricle.
- Retrosigmoid suboccipital approach for lesions near the posterolateral surface of the pons, cerebellopontine angle or superior lateral medulla.
- Subtemporal approach for lesions in the anterolateral midbrain or pontomesencephalic region.
- Supracerebellar infratentorial approach for cavernous malformations of tectal plate.
- Far lateral or transcondylar approach to achieve an anterolateral trajectory to the brainstem.
- Orbitozygomatic approach to access the anterolateral midbrain and interpeduncular fossa.

Surfacing lesions are readily apparent by their characteristic mulberry appearance or by the haemosiderin staining of the overlying parenchyma. Use of the operating microscope and meticulous dissection are the key factors in determining success. Intra-operative monitoring of SSEP and BAER are useful adjuncts to help minimise complications during brainstem surgery.

Post-operatively patients are extubated only if they demonstrate good cough and gag reflex. Short-term tracheostomy and feeding tubes may be required in some patients.

OBSERVATION

For incidentally detected cavernous malformations, the rate of clinical or overt haemorrhage is very low and a first haemorrhage from a cavernous malformation rarely is life threatening. Therefore, before intervention is considered solely to prevent haemorrhage, other host-related factors need to be considered. Such patients can be managed expectantly, with follow-up imaging at regular intervals in order to detect lesion expansion or haemorrhage.

Conservative therapy is also indicated in patients who have had a single haemorrhagic episode from a lesion that does not reach the pial surface.

RADIOSURGERY

The role of stereotactic radiosurgery in the management of cavernous malformations is controversial. Kondziolka[23] has demonstrated a significant decrease in the haemorrhage rate over time; however, 26% of these patients developed neurological deterioration after the procedure. This correlated with hyperintense changes in T2 WI suggesting radiation injury. Similar results were shown by Amin-Hanjani and colleagues[1,2] and Karlsson[21] et al. As the complication rates are high and the reduced haemorrhage rate is not comparable to the zero rebleed rates after complete surgical excision, radiosurgical treatment should be reserved for lesions that are truly surgically inaccessible.

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97 Other Vascular Malformations of the Brain

Ravi Ramamurthi, Harinivas

VENOUS ANGIOMA

Pfannenstiel, in 1887, first recognised this entity as composed entirely of veins. A classical anatomical and pathological description was given in 1966 by McCormick. This lesion has also been termed as "Developmental Venous Anomaly" by Lasjaunias.[5] Saito and Kobayashi et al.[14] have postulated that venous angiomas result from an intrauterine accident, during the formation of medullary veins or their tributaries, either due to thrombus or some unknown mechanism resulting in the formation of collateral pathways to drain the brain so affected. These lesions are present at birth and remain largely static throughout life, though changes in these angiomas are reported with senescence.

Venous angiomas are generally silent lesions because of their dynamic features and are low-flow and low-pressure vascular structures draining normal brain tissue.[3] Venous angiomas form the alternative venous drainage of the surrounding nervous tissue because of the non-development of the normal venous system. They are made up of veins with abnormal structure with thick walls, dilated lumen and of irregular calibre that converge radially towards a wide draining vein (caput medusae).[14]

Pathology

The causes of developmental venous anomalies are incompletely understood. It is believed that they are formed in the late stages of foetal maturation.[14] The lesion is composed entirely of veins, which are commonly thickened and hyalinised, having minimal smooth muscle and elastic tissue. The interspersed neural parenchyma is entirely normal. Venous angiomas may be subclassified according to their pattern of venous drainage into superficial (cortical) and deep (subependymal) types. Two variants of the typical venous angioma have been described. These are:

1. Venous angioma with arterial feeders also termed as medullary venous malformations with an arterial component or venous angiomas with early filling vessels
2. Varix or phlebectasia

There is a radially arranged pattern of medullary veins converging centrally on a single draining vein which is known as star cluster.[9] Histological examination shows that the capsule consists of an outer collagenous layer and an inner granulated layer with deposits of haemosiderin.[15]

Natural History and Clinical Features

The natural history depends on the topography and location whether hemispheric, deep-seated, brainstem, cerebellar or intramedullary regions.[1] These are the commonest of the vascular malformations in large prospective autopsy studies, but the least common form encountered in surgical series. Their incidence may be still higher than is generally believed, since most of these remain largely asymptomatic. Patients may present with headache, nausea and vomiting, seizures, progressive neurological deficit and haemorrhage (0.2% per year).[11] Changes due to old age, in an angioma, may increase its propensity to cause symptoms. The presence of an associated arteriovenous malformation (AVM) or a cavernoma is not unusual in a patient with a venous angioma. Coexistence of a cavernoma with a venous angioma occurs in about 8% of cases,[10] and in such a case it is usually the cavernoma which becomes symptomatic and needs to be treated, rather than the venous angioma.

Investigations

First angiographic description of these lesions was described by Wolf and his colleagues.[17] The gold standard for diagnosing developmental venous anomalies is conventional cerebral angiography. Findings include normal circulation time, normal capillary and arterial phases of study with the venous anomaly seen during the late venous phase.[17]

Computerised tomography (CT) scan without contrast administration may show a hyperdense dot, caused by the pooling of venous blood. Contrast enhancement reveals a stellate tangle of veins coursing into a sharply defined linear interstitial vein draining towards the cortical or the central system. These are commonly seen in the frontal region near the angle of the ventricles or in the cerebellum.

The first angiographic description of these lesions was by Wolf et al.[17] Conventional or digital subtraction angiography may reveal a faint capillary blush passing into the venous phase or the classical "caput medusae" or "hydra" appearance which is pathognomonic of a

venous angioma. The angiomas, showing a persistent blush, are believed to have an increased tendency to bleed. Yasargil[18] has described the following criteria for diagnosis of venous angioma on angiography:

- Absence of arterial feeders
- Appearance of the lesion in the venous phase
- Presence of dilated medullary veins draining through a dilated transcerebral or subependymal vein

Magnetic resonance (MR) is superior to CT in the identification of a venous angioma. It delineates a curvilinear streak of signal void, best appreciated on T2W1 MR imaging (MRI) scan. Hypointense areas may be visible in the body of the angioma, representing the blood pool within. These enhance brightly with contrast and the draining vein is seen well on T2-weighted imaging.[16] There may be a paradoxical high-signal intensity as the flow in the draining vein is very slow. Some of these lesions may be diagnosed on "Time of Flight" MR angiography.

Management

It is to be noted that these lesions have a very benign natural history and only rarely do they cause haemorrhage. The propensity of these lesions to cause seizures or focal neurological deficit is difficult to ascertain. These veins are anatomically aberrant, but physiologically essential and, therefore, should not be interrupted. Surgery is only indicated in the presence of a large haemorrhage causing mass effect or a clearly documented seizure or focal neurological deficit attributable to the angioma. Radiosurgery has also been advocated for these lesions, but the results are variable.[7]

CAPILLARY TELANGIECTASIAS

Capillary telangiectasia (CTS) is a vascular malformation characterised by multiple thin-walled vascular channels interposed between normal brain parenchyma. It has been hypothesised that CTS is an acquired lesion caused by other underlying venous anomalies, but this theory is still debated.[19]

This type of vascular malformation is also called capillary malformation. It is usually asymptomatic and also remains angiographically occult, making it difficult to ascertain its incidence. However, rarely, intracerebral haemorrhage has been reported. These are commonly located in the infratentorial compartment, the pons being a favoured site. Familial as well as multiple lesions have been reported.

This malformation results from vascular dilatation rather than vascular proliferation and comprises of thin-walled capillaries which are devoid of smooth muscle tissue or elastic fibres and usually drain into an abnormally large central vein. The intervening neural parenchyma is normal.

Clinical Presentation

They are mostly asymptomatic. If symptomatic, haemorrhage, seizure, cranial nerve paresis, extrapyramidal disorders and focal hemispheric syndromes have been described.[4]

Investigations

Radiological diagnosis of these lesions is very difficult, unless associated with haemorrhage. The CT scan is not sensitive enough to detect these minute lesions and in most instances, these are not visible on angiography, although rarely an angiogram may reveal an abnormal vascular blush or an early draining vein. The MR may show an area of hypointense signal in T2W1 MRI scan.[12,13] Diffusion weighted imaging seems to be a useful adjunct for the diagnosis of capillary telangiectasias which can be differentiated from tumours, inflammatory and ischaemic lesions.[2] In some cases imaging diagnosis will be difficult with conventional, MRI because the lesion will not show characteristic signal loss on conventional gradient-echo images. In those cases susceptibility weighted imaging will be useful for diagnosis as it will demonstrate marked signal loss of the lesion.[19]

Management

Capillary telangiectasis may, at times, coexist with a cavernoma, and according to Russell's original hypothesis these two represent different stages in the development of the same disease entity. As a rule, when coexisting with a cavernoma, it is the cavernoma that becomes symptomatic, necessitating treatment. No therapeutic intervention is indicated in an asymptomatic telangiectasia. If presenting with haemorrhage, surgery may be indicated to evacuate the haematoma. It is usually on histopathological examination of the evacuated blood clot and its periphery that the diagnosis of telangiectasia becomes evident.

Hereditary Haemorrhagic Telangiectasia (Osler-Weber-Rendu Disease)

Hereditary haemorrhagic telangiectasia (HHT) is a form of capillary telangiectasia characterised by the presence of multiple AVMs that lack intervening capillaries and result in direct connections between arteries and veins. Although HHT is a developmental disorder and infants are occasionally severely affected, in most people the features are age-dependent with the diagnosis not suspected until adolescence or later. The most common clinical manifestation is spontaneous and recurrent epistaxis seen usually at a younger age. Approximately 25% of individuals with HHT have gastrointestinal (GI) bleeding, which most commonly begins after the age of 50 years.

Genetics

The HHT is caused by mutations in a number of genes involved in the TGF-β/BMP signalling cascade:

- ENG, the gene encoding the cell surface co-receptor endoglin

- ACVRL1 (ALK1), also a gene encoding a cell surface receptor
- SMAD4, a gene encoding an intracellular signalling molecule
- At least two other genes that have not been identified. Molecular genetic testing of ENG, ALK1 and SMAD4 detects mutations in approximately 80–85% of individuals who meet an unequivocal clinical diagnosis of HHT and is available on a clinical basis.[8]

Diagnosis

The diagnosis of HHT is based on the presence of epistaxis, cutaneous or mucosal telangiectases, visceral AVMs and family history.

Treatment

Epistaxis is treated with humidification, nasal lubricants, topical or systemic hormones or antifibrinolytic agents, laser ablation, septal dermoplasty and nasal closure. The GI bleeding is treated with iron replacement therapy and, if needed, endoscopic ablation, surgical resection of bleeding sites, and/or hormonal or antifibrinolytic therapy. Cerebral AVMs are treated, when indicated by location or symptoms, by surgery, embolotherapy and/or stereotactic radiosurgery.

Genetic Counselling

The HHT is inherited in an autosomal dominant manner with considerable intrafamilial variability. Most individuals have an affected parent. Prenatal testing is possible for pregnancies at increased risk if the disease-causing mutation in the family is known.[8]

CRYPTIC ARTERIOVENOUS MALFORMATIONS

The term "Cryptic" was proposed by Russell to denote a group of vascular "harmartomas", predominantly small AVMs, which often remained clinically silent during the patients' life time. Cryptic AVM can cause highly variable cerebral neurological defects.[6] These lesions may present with a catastrophic and often fatal haemorrhage. The terms "cryptic" and "angiographically occult vascular malformation" (AOVM) were adapted to clinical use to describe vascular malformations that are not demonstrable on angiography. The mechanisms for failure of angiographic detection of an AVM are manifold. It is to be noted that the terms "cryptic" and "AOVM" are not synonymous. While the cryptic AVMs are a histopathological entity, AOVMs may be diagnosed by CT or MRI.

Angiographically occult AOVMs can now be readily diagnosed and managed. The AOVMs constitute a heterogeneous group of entities. Robinson et al.[12] analyzing 34 AOVMs encountered over a 10-year period, found 21 cavernous malformations, 3 AVMs, 3 venous malformations, 2 capillary malformations and 5 mixed lesions. With increased understanding of the clinical significance of cavernomas and venous angiomas, a more rational approach to their management has become possible. Rapid advances in the field of radiosurgery have made it easier to tackle the small, deeply-located AVMs. Still, surgery remains the mainstay of treatment in most instances. Injection of 142Pr microspheres into arteries feeding an AVM in order to simulate radioembolism has been proposed as a novel treatment method.[6]

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98 Carotid Cavernous Fistula

Ravi Ramamurthi, Goutham Cugati

INTRODUCTION

The carotid artery in a part of its intracranial course traverses the cavernous sinus. Carotid-cavernous sinus fistula (CCSF) develops when there is an abnormal communication between the carotid artery (internal or external) or its branches, and the cavernous sinus. The cavernous sinus is not a dural sac carrying venous blood, as was thought earlier, but is a plexus of veins enclosed between two layers of the dura.

HISTORICAL

Carotid-cavernous sinus fistula was first reported by Travers[54] in 1809 and he ligated the carotid artery in the neck as part of the treatment. Later, Nunnely in 1865[40] and Rivington in 1875,[49] described the pathology, and attributed the signs and symptoms to a lesion in the cavernous sinus. Dandy and Tollis proposed that CCSF be divided into traumatic and spontaneous types.[13] Brooks in 1931 suggested using a muscle embolus introduced into the carotid artery to occlude the fistula.[42] Hamby[25] used carotid ligation intracranially, combined with a muscle embolus. Prolo et al.[46] described the use of a Fogarty balloon catheter to occlude the intracranial internal carotid and thus obviated the need for a craniotomy. Parkinson,[42] in 1965, opened the cavernous sinus and directly occluded the fistula. Serbinenko,[50] in 1974, was the first to develop and use a detachable balloon for vascular occlusion.

ANATOMY OF THE CAVERNOUS SINUS

The cavernous sinus is a plexus of veins encased in a double layer of dura and located on either side of the body of the sphenoid sinus (Fig. 1). The internal carotid artery (ICA), along with its surrounding sympathetic plexus and the VI nerve, courses through the sinus. The III, IV, V1 and V2 cranial nerves run forwards in the lateral wall of the sinus enclosed in the double layer of dura.[48]

Arteries

The carotid artery gives off three branches in the cavernous sinus:[26]

1. The meningohypophyseal trunk, a constant branch, is the most proximal and arises at the level of the dorsum sellae. This trunk gives off three branches:
   - A. The tentorial artery also called the artery of Bernasconi-Cassinari[9] which supplies the tentorium
   - B. The inferior hypophyseal artery which supplies the posterior pituitary
   - C. The dorsal meningeal artery which supplies the clival area and the VI nerve

   In about 6% the dorsal meningeal artery may arise directly from the intracavernous carotid artery.
2. The artery of the inferior cavernous sinus arises from the horizontal portion of the intracavernous

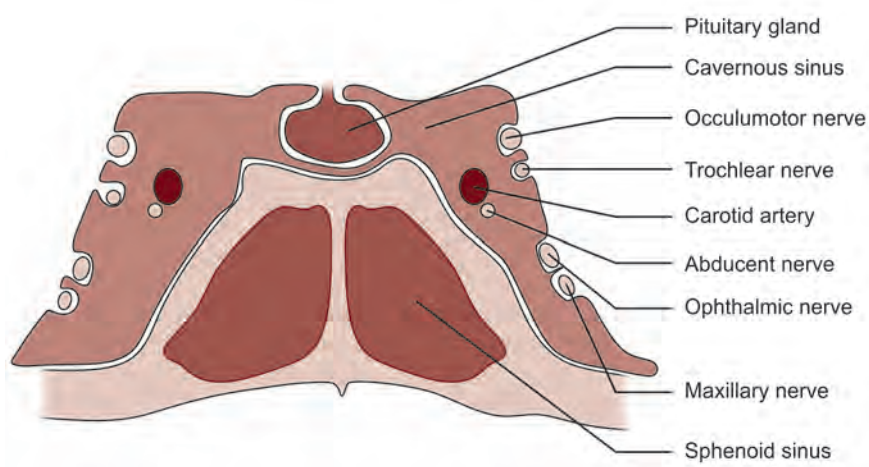


Fig. 1: Coronal section through cavernous sinus

carotid. Occasionally, it may arise from the meningohypophyseal trunk. It supplies the inferior wall of the cavernous sinus and the area of the foramen ovale and spinosum. This artery corresponds to the carotid remnant of the embryonic dorsal ophthalmic artery.

3. McConnell's capsular arteries are seen in about 30–50%. They arise on the medial side of the carotid artery about 0.5 cm beyond the artery of the inferior cavernous sinus.[33]

The ophthalmic artery may arise in about 8% from the intracavernous carotid artery. The branches of the ICA arising in the cavernous sinus anastomose with the various branches of the external carotid artery (ECA). The neuromeningeal trunk of the ascending pharyngeal artery, the recurrent and anterior meningeal branches of the internal maxillary artery and the cavernous branch of the middle meningeal artery are the arteries that commonly anastomose with the cavernous branches of the internal carotid. These arteries are important in Type C and D fistulas.

Veins

The tributaries of the cavernous sinus are many.

1. The superior and inferior ophthalmic veins and through them, the facial veins
2. The middle and inferior cerebral veins draining the cerebral substance
3. The central retinal vein, the middle meningeal veins, the superior and inferior petrosal sinuses and the emissary veins

The two cavernous sinuses on either side are connected by intercavernous communications.[1] These are:

- The anterior intercavernous sinus: This measures 0.57–5.43 mm. It may involve the whole of the anterior dura of the sella, may have a curvilinear shape or may run at the level of the pre-chiasmatic groove
- The posterior intercavernous sinus: This varies in diameter from 0.71–4.14 mm
- The inferior cavernous sinus is not always seen. It may be plexus like, a venous lake or of a mixed type and runs in the dura of the floor of the sella
- The basilar plexus is the largest intercavernous communication in the majority. It is located at the level of the dorsum sellae. There may be many irregular vascular channels or it may be heterogeneous

CLASSIFICATION

Carotid-cavernous sinus fistula has been classified in many ways which are as follows:

- Spontaneous or traumatic
- High or low-flow
- Direct or indirect (dural) fistulae according to their arterial supply determined angiographically

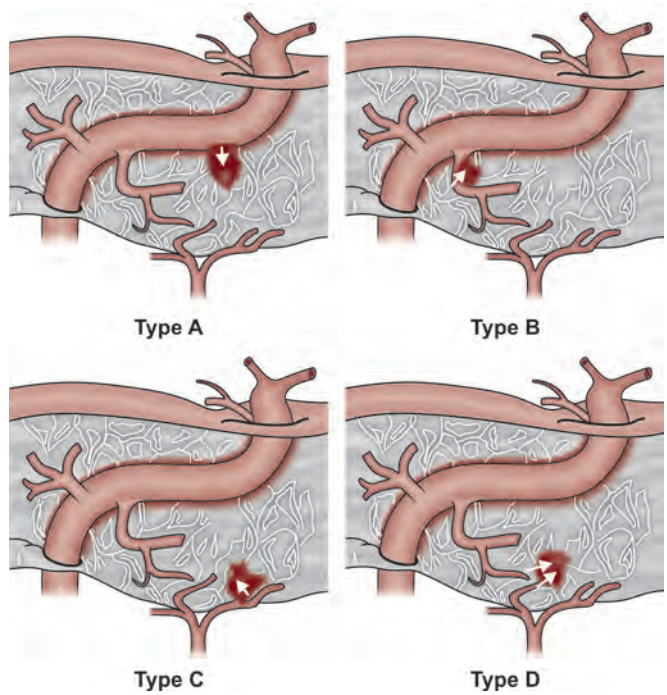
The first two do not take into consideration the factors that are required in the proper planning of the treatment of CCSF.

Barrow et al.[6] classified them angiographically into four types (Figs 2A to D). Type A are direct shunts from the ICA to the cavernous sinus. They are high-flow and are usually caused by trauma and base of skull fractures.[15] They may also be due to rupture of an intracavernous carotid aneurysm.[22,30,44] Young men are commonly affected and the majority require treatment as they do not close spontaneously. Types B, C and D are dural or indirect fistulas. They occur in middle-aged women, are low-flow and in 16–60% they resolve spontaneously.[6,17,46,56] In Type B there is a communication between the dural branches of the ICA and the cavernous sinus. These are extremely rare. Type C arises as a result of communication between the dural branches of the ECA and the sinus. Dural branches of the ICA and ECA take part in Type D fistulae which are the commonest indirect fistulae.[17]

In a study of consecutive patients having CCSF, Preechawat et al. were able to classify their 80 patients according to Barrow's classification after angiographic evaluation, as Type A (0%), Type B (14%), Type C (15%) and Type D (71%).[45]

SYMPTOMS AND SIGNS

The symptoms and signs depend upon the type of fistula, the direction of the venous outflow, either anterior or posterior, the anatomical location in the cavernous sinus and the size of the fistula. Rarely, there may be bilateral involvement.[19]



Figs 2A to D: Angiographically classification by Barrow et al. (A) Direct shunt from the internal carotid artery to the cavernous sinus. (B) Shunt from dural branches of the internal carotid artery to the cavernous sinus. (C) Shunt from dural branches of the external carotid artery to the cavernous sinus. (D) Shunt from dural branches of both internal and external carotid arteries to the cavernous sinus

Type A fistulae are direct, high-flow and mostly traumatic. They occur most frequently after a closed head injury, though they may occur as a result of direct penetrating injury or rupture of an intracavernous carotid aneurysm. A high index of suspicion is paramount in cases of polytrauma, where a CCSF can be easily missed. A relatively high incidence of traumatic CCSF occurs in patients with middle fossa fractures, especially those with transverse or oblique fractures.[32] Spontaneous non-traumatic direct CCSFs are extremely rare and an underlying predisposing factor like systemic connective tissue disorders such as Ehlers-Danlos syndrome may be seen.[58] It is probable that advancing age, menopause, hypertension and childbirth may affect some preexisting subclinical lesions in the arteriolar system like aneurysms, leading to the development of spontaneous CCSF.[14] Low-flow fistulae occurring after trauma are usually due to avulsion of a dural arterial branch.

Ocular signs and symptoms are produced when the major venous outflow is through the superior or inferior ophthalmic veins. The signs may be unilateral, bilateral or may occur only in the eye opposite to the side of the fistula due to predominant drainage through the intracavernous venous communications. The ocular manifestations are pulsating exophthalmos, chemosis, ocular nerve palsies causing diplopia, visual loss and exposure keratitis. Patients with CCSF may initially present to an ophthalmologist. There may be venous and arterial stasis resulting in decreased ocular and retinal perfusion. Retinal and choroidal changes may include venous dilatation, retinal haemorrhage, central retinal vein occlusion, central retinal artery occlusion, cotton wool patches and serous retinal detachment.[10] Facial pain may occur due to involvement of cranial nerves V1 and V2. A subjective and audible bruit will be present. Headache may occur due to dural distension, raised intracranial pressure (ICP) or subarachnoid haemorrhage (SAH). Flow through the cortical veins can produce raised ICP. Symptoms due to raised ICP, cerebral steal and SAH are uncommon. When the major outflow is posteriorly into the basilar plexus, there may only be a bruit. Rarely, lower cranial nerve dysfunction affecting the VIII, XI and XII nerves may occur.[8] In an occasional patient there may be only pulse-synchronous tinnitus.[2] Other rare presentations include brainstem compression and epistaxis.[19,28]

In the low-flow Types B, C and D fistulae the clinical manifestations are insidious in onset and include mild proptosis, chemosis, ocular pain and glaucoma. Sometimes they may lead to progressive visual loss. A bruit may be audible. The various theories and views regarding the pathogenesis of spontaneous low-flow CCSF have been described by Barrow.[7]

Differential diagnoses for CCSF include vascular lesions such as arteriovenous malformation and cavernous sinus thrombosis, cavernous sinus tumours, orbital tumours, skull base tumours and mucocoele. Thyroid eye disease, orbital pseudotumour, and orbital vasculitis resulting from Wegener's granulomatosis, polyarteritis nodosa, intracranial sarcoidosis and Tolosa-Hunt syndrome may present like CCSF.[10]

INVESTIGATIONS

Angiography is the best investigation for diagnosing and classifying CCSF. Selective external carotid catheterisation will help in Type C and D. The CT scan will be useful when there is evidence of steal or an intracerebral haematoma.

The imaging findings of carotid-cavernous fistula include dilatation of the superior ophthalmic vein, enlargement of the cavernous sinus, proptosis and thickening of the extraocular muscles. Dilation of the superior ophthalmic vein is a specific imaging sign of carotid-cavernous fistula. An engorged superior ophthalmic vein presents with a characteristic "hockey stick sign" on orbital B-ultrasound, CT and magnetic resonance imaging.[11,57] Colour Doppler imaging has been found to be useful and correlates well with the angiographic findings. Doppler also provides information about the direction and velocity of flow and is useful in post-treatment follow-up.[36,51] Transcranial Doppler is also useful in assessment,[37] as well as during balloon occlusion.[20,38] It is also useful in assessing tolerance to carotid occlusion during treatment.[5] Brain single photon emission computed tomography scanning has been used to assess the pre and post-embolisation blood flow to the brain, especially in patients with steal phenomenon.[24]

TREATMENT

Knowledge of the natural history of the disease is important in deciding whether treatment is necessary or not. Type A fistulae almost never close spontaneously, though this has been reported.[47] These require treatment. Type B, C and D are low-flow and have been reported to close spontaneously in 16–60% of cases. The indications for immediate treatment are progressive visual loss, a distressing bruit, diplopia and severe proptosis with corneal exposure. Others can be kept under observation for 6 months after investigations and angiography. Angiography itself has been reported to have promoted closure of the fistula,[39,56] though the exact mechanism is not known. Carotid compression therapy has also been successful in closure of 17% of direct and 30% of dural CCSFs.[10] Treatment is offered when the fistula does not close or there are progressive symptoms. The purpose of treatment is to occlude the fistula without occluding the carotid artery, as far as possible. The methods available include endovascular techniques, surgery and radiosurgery.

Endovascular Therapy

There have been tremendous technical advances in the field of interventional neuroradiology which have simplified the treatment and also given various endovascular treatment options while dealing with CCSF.

The majority of Type A fistulae can be treated by embolisation using balloons, coils or embolic agents. The balloons that are most favoured are silicone balloons filled with 2-hydroxyethylmethacrylate and radiopaque contrast material.[29,52]

Coils made of platinum[23,24,26] are used when balloon occlusion fails or cannot be used due to the fistula being very small, when bony spicules may puncture the balloon or when after balloon occlusion there is a small venous space into which a balloon cannot be introduced. Stent-assisted or balloon-assisted coil placement can be done. Liquid embolic agents like onyx are also used to complement balloons or coils, and rarely used as the sole strategy of management.[59]

The route of access to the cavernous sinus for embolisation can be intra-arterial through the carotid artery or intravenous through the superior ophthalmic vein or the superior or inferior petrosal sinus through surgical exposure.[16,25,53] The transvenous route through the inferior petrosal sinus is the best endovascular approach to achieve cure. Preliminary transarterial embolisation may be necessary if there are extensive ECA feeders.[27]

When endovascular techniques fail direct surgery is necessary to occlude the fistula.

Type B fistula is very rare. As it cannot be occluded with a balloon, a direct surgical approach should be considered.[5]

Type C fistula is also rare and can be treated by embolisation of the external carotid branches. The embolic materials that can be used are silastic beads, Ivalon, gelfoam and isobutyl-cyanoacrylate. Ivalon is preferred.

Type D fistula is treated initially with embolisation of the ECA feeders. This often leads to thrombosis of the fistula. In some instances the ICA feeder enlarges and if it is large enough, it can be occluded using a balloon; otherwise direct surgery has to be performed.

Covered stents have recently become available for various vascular conditions including carotid-cavernous fistulas. The CCSF can be treated while preserving the parent artery by reconstructing the arterial wall.[3,21,31,34] Li et al.[31] have reported a successful outcome in 11 out of 12 cases with traumatic CCSF. Though endoleak and spasm were among the common complications encountered, they could be dealt with easily.

Embolisation of CCSF may carry a risk of inherent complication either from the procedure or due to reopening of the fistula. Among the 80 patients treated by Preechawat et al.[45] intra-operative complications occured in three patients, which included ophthalmic artery occlusion and cerebral infarction. Eight patients experienced transient aggravation of symptoms, including increased proptosis, elevation of intraocular pressure, choroidal detachment that required suprachoroidal drainage and venous stasis retinopathy. Ophthalmic vein thrombosis resulting in central retinal vein occlusion developed in three patients and finally caused severe visual deficit. Other potential complications include uncontrolled bleeding, ophthalmoplegia and cavernous sinus thrombosis.[10]

Surgical Approaches

Surgery is indicated when embolisation fails or when it is contraindicated, or when previous procedures have occluded the ICA and the fistula is still patent. The first surgical procedure to be used was carotid ligation in the neck.[54] Various other procedures referred to under history have been tried. All these involved occlusion of the ICA. Parkinson[42] was the first to open the cavernous sinus and directly treat the CCSF. The cavernous sinus is opened between the III and IV nerves and this area is known as Parkinson's triangle.[43] Mullan, in 1979, exposed the cavernous sinus, opened it and introduced agents like gelfoam and surgicel to occlude the fistula and retain the patency of the ICA.[35] Dolenc,[18] in 1983, described exposure of the entire cavernous sinus and the petrous ICA. By removing the anterior clinoid process and de-roofing the optic canal, the entire intracavernous carotid artery can be visualised. Various methods have been used to occlude the fistula. These are direct clipping, packing with muscle or other material, or microsurgical reconstruction of the artery.

Radiosurgery

With the improved results of cerebral AVM treated successfully with stereotactic radiosurgery, CCSF is also being treated using the same principle. Stereotactic radiosurgery forms an integral part of the multidisciplinary and multimodality approach in treating carotid-cavernous fistulas. Though radiosurgery has been used in many instances for treating CCSF, its indications are still unclear. Elderly patients with medical comorbidities, failed repeated endovascular therapy and low-flow dural CCSF are among the few mentioned indications.[41]

Prognosis and Complications

The mortality associated with CCSF is 1–2%.[5] Any treatment option that is offered to the patient should not exceed this figure. CCSF being an uncommon condition, the complication and mortality rates depend on the experience of the interventional radiologist and the surgeon. Debrun achieved a 60% patency rate of the ICA in his first 54 cases[15] whereas it was 80% in the subsequent 41 cases.[17]

The complications that may occur are stroke due to ICA occlusion or balloon migration. The balloons that are used may rupture or shrink.[4,12,55] Venous rupture may occur when the transvenous route is used for emolisation.[25] False aneurysms can form due to balloon shrinkage. Cranial nerve deficits can occur due to pressure on the lateral wall of the cavernous sinus and these usually recover spontaneously.

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99 Dural Arteriovenous Malformations

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INTRODUCTION

Dural arteriovenous malformations (D-AVMs) were first reported by Sachs,[23] in 1931. These are defined as arteriovenous (AV) shunts from a dural arterial supply to a dural venous drainage channel and constitute 10–15% of intracranial arteriovenous malformations (AVMs).[23] These occur more frequently in women.

EMBRYOLOGY AND PATHOPHYSIOLOGY

Embryologically the circulation of the brain and its coverings including dura, skull and scalp is developed from a common origin. Therefore, it can be anticipated that a vascular malformation developing in one of these layers may have vascular participation from any or all of the adjacent layers. The dura mater has an extrinsic vascular supply. Branches of the external carotid artery (i.e. middle meningeal, accessory meningeal, posterior auricular, occipital and ascending pharyngeal arteries) supply the lateral aspects and convexity of the dura. Branches of the internal carotid artery supply the floor of the anterior cranial fossa (anterior and posterior ethmoidal branches of the ophthalmic artery) and the tentorium (dorsal meningeal branch and tentorial branch of the meningohypophyseal trunk). The dura of the posterior cranial fossa is supplied by branches from the vertebral system. Minute AV shunts exist between the meningeal arteries and the walls of the major dural sinuses, which may have an important role in the pathogenesis of D-AVMs.

The AVMs of the brain may receive blood supply from the dura mater in some cases, whereas the dura alone is the seat of malformation in 10–15%. The presence of the nidus within the leaflets of the dura mater or tentorium differentiates D-AVMs from the more commonly occurring parenchymal or pial AVMs. The nidus is usually in a well-defined region of the dural leaflet, often located near a dural sinus and is the point of convergence of all arterial feeders, which mainly arise from the dural arteries or from the pachymeningeal branches of the cerebral arteries. The venous drainage can be through either dural or pial channels, with 60–75% draining exclusively into the dural sinus.[1] It is probable that increased pressure within the dural venous drainage system results in retrograde leptomeningeal venous drainage and these channels may often be noted to become tortuous or variceal. Thrombosis of the transverse or sigmoid sinus has been reported in many cases of D-AVMs. The fact that the sigmoid sinus is often blocked was observed by Sundt and Piepgras,[26] who postulated that this obstruction may be a sequel to an inflammatory process. An inflammatory hypervascularity then develops into an arteriovenous fistula (AVF). Houser et al.[9] reported stenosis or occlusion of a dural sinus in 80% of their cases and documented two cases presenting initially with sinus occlusion and then going on to develop D-AVMs a few years later.

Most AVMs associated with the meningeal artery in the anterior cranial fossa are the pure dural type, where mixed pial-dural AVMs are rare. There are two types of mixed pial-dural AVM in the anterior cranial fossa based on the shunting point:

1. One with the nidus in the brain parenchyma of the frontal lobe
2. Other with the shunting point in the dura mater

Jimbo et al.[10] reported two patients with AVMs fed by the anterior ethmoidal arteries and the persistent primitive olfactory artery with the nidus located solely in the brain parenchyma of the inferior aspect of the frontal lobe and drained via abnormal cortical veins into the cavernous and superior sagittal sinuses. They recommended occluding the venous outflow to obliterate intracranial dural AVF (D-AVF) but observed removal of the nidus in the brain parenchyma was also required. They concluded that the presence of a pial feeder should be looked for before a diagnosis of D-AVF of the anterior cranial fossa is made and a pre-operative detailed evaluation of the pial supply and shunting point is mandatory.

AETIOLOGY

D-AVMs are acquired lesions and may result from traumatic[16] or non-traumatic causes. Traumatic D-AVMs are often asymptomatic and are on many occasions diagnosed as incidental findings on angiography. These are often located at sites remote from the region of trauma. Non-traumatic D-AVMs are postulated to occur secondary to venous obstruction, usually thrombosis of one of the dural sinuses. Venous obstruction may result in the formation of D-AVM, either by enlargement of the normally present micro AV shunts within the dura or by recruitment due to "sump" effect of arterial supply

from the scalp, the meninges and the cortex through AV shunting in the wall of the sinus. This leads to secondary venous hypertension and results in retrograde drainage in the leptomeningeal veins, predisposing to their tortuosity and dilatation.

NATURAL HISTORY

D-AVMs have a highly variable natural history. Patients may remain asymptomatic for many years. Symptoms usually become manifest in the sixth and seventh decades of life. Clinical symptoms may either remain benign throughout or may rarely follow an aggressive course. This is seen (in about 27%) more commonly with lesions located at the tentorial incisura and the anterior cranial fossa.

An aggressive course in relation to D-AVMs is defined as haemorrhage or progressive neurological deficit other than ophthalmoplegia.[1,2,11-13] The D-AVMs characterised by leptomeningeal venous drainage, variceal or aneurysmal venous dilatation and Galenic drainage are especially more prone to haemorrhage. Haemorrhage may be the initial presenting feature in 17–24% of patients. The risk of haemorrhage is more common with AVMs located at a distance from a sinus, than in the lesions adjacent to a dural sinus. The D-AVMs with haemorrhage as the initial presenting feature are associated with a mortality of 30% and the incidence of recurrent lethal intracranial haemorrhage (ICH) remains high.[1] Extensive D-AVMs may cause symptoms because of venous hypertension and the resulting malabsorption of cerebrospinal fluid.[22] Spontaneous thrombosis or regression of D-AVM is also known. This results from fibrosis of the thrombus causing occlusion of the fistulous connections.[1,21] Spontaneous occlusion is seen more commonly with lesions adjacent to the cavernous sinus. In patients with polycythemia and D-AVFs that have a relatively low risk of haemorrhage, polycythaemia should be treated first before any interventional treatment, because venesections may lead to spontaneous closure of the D-AVF.

CLASSIFICATION

The D-AVMs may be classified depending on the following:

- Involved sinus (sagittal, cavernous, straight, sphenoparietal, transverse or sigmoid)
- Region of the dura involved (anterior, middle or posterior cranial fossa, tentorium)[18]
- Venous drainage pattern (dural sinus, Galenic, pial, cortical)

The above mentioned systems may be combined and a reasonable working diagnosis can be arrived at by including the anatomic location and the venous drainage.

There are many classification schemes for D-AVFs. The most useful and recent ones are the revised Djindjian and Merland[7] classification proposed by Cognard et al.[4] and the classification proposed by Borden et al.[3] both of which are based on the initial classification. Cognard et al. defined five types of D-AVFs based exclusively upon the pattern of venous outflow:

- Type I, located in the main sinus, with antegrade flow
- Type II, in the main sinus, with reflux into the sinus (IIa), cortical veins (IIb), or both (IIa+b)
- Type III, with direct cortical venous drainage (CVR) without venous ectasia
- Type IV, with direct CVR with venous ectasia
- Type V, with spinal venous drainage. They all focus on the patterns of venous drainage.

CLINICAL FEATURES

The pathophysiological consequences and clinical manifestations are related to specific stages of the evolution of D-AVMs.[11] Obrador et al.[19] reviewed 115 cases and found that symptoms fell into one of the following six patterns:

1. Bruit (35%)
2. Headache, papilloedema and visual failure due to raised intracranial pressure (15%)
3. Subarachnoid haemorrhage (SAH) (17%)
4. Ischaemic neurological deficit (10%)
5. Hydrocephalus and bruit in infants (4%)
6. Combination of more than one of these (15%)

Clinical behaviour, inclusive of initial presentation and progression of symptoms, is dependent on multiple, inter-related factors including location, arterial feeders and venous drainage. A catastrophic neurological course is primarily determined by the venous drainage pattern.

In the first stage of evolution of D-AVMs, local increased venous pressure will result in venous congestion, which may cause seizures and non-haemorrhagic focal neurological deficits. Intracranial hypertension and papilloedema may result, due to a generalised increase in venous pressure. In the second stage of evolution, with recruitment of arterial feeders, symptoms related to increased flow in the individual neural structures are encountered. These are termed "neighbourhood symptoms" and include headache, pulsatile tinnitus, cavernous sinus syndrome, trigeminal neuralgia and hemifacial spasm. The final stage in the evolution is characterised by retrograde leptomeningeal venous drainage and variceal dilatations, which are responsible for ICH. Bleeding occurs from these engorged and brittle leptomeningeal venous connections and not from the nidus.[1,14,24] Non-traumatic D-AVF/D-AVM presenting with pure subdural haematoma (SDH) is rare. Ogawa et al.[20] reported one such case and recommend considering D-AVF/D-AVM and to perform angiography if necessary when a patient presents with non-traumatic SDH without ICH and/or SAH.

INVESTIGATIONS

Although computerised tomography and magnetic resonance (MR) may suggest a vascular abnormality, detailed

cerebral panangiography, especially using digital subtraction techniques, remains the mainstay in the diagnosis of D-AVMs. Selective studies of bilateral internal and external carotid systems, along with vertebral studies are essential. Arterial branches within the dura are normally not visualised on angiography, but in the presence of D-AVMs, the concerned vessels are dilated and clearly visible. Certain meningeal vessels, like the meningeal branch of the posterior cerebral artery also called the "artery of Davidoff and Schechter", is angiographically demonstrable only in the presence of a D-AVM. The nidus is usually limited to a well-defined focus within the dural leaflet and is best visualised on ultra early arterial views, or on injection of either contralateral or more distant feeding vessels. Late arterial views, venous views and superselective injection of major feeder vessels, demonstrate engorged vascular channels which may occupy diffuse areas of the dura. The shunt flow rate can also be estimated based on the evidence of steal from a more distant artery. The pathognomonic diagnostic feature of D-AVM on angiography is the premature appearance of venous structures within or adjacent to the dura mater during the arterial phase. The presence of dilated pachymeningeal arteries often lends supporting evidence to the other angiographic data.

Dural venous sinus thrombosis will be seen on the venous phase and may reflect:

- Thrombus preceding the genesis of the AVM
- Accompaniment of spontaneous or induced thrombosis of an adjacent D-AVM
- Angiographic artefact due to "steal" through other channels.

MR angiography is helpful in the non-invasive diagnosis of D-AVMs.

MANAGEMENT

Considering the wide variability of the natural history of D-AVMs it is mandatory to define the treatment strategy based on an individualised risk-benefit ratio. This depends on the clinical features, neurological status and the nature of D-AVM as regards its location, extent and angiographic patterns. A conservative approach and observation is advisable for lesions causing only benign symptomatology. Active intervention is indicated for D-AVMs associated with features predisposing to progressive neurological deficit or for lesions with benign but distressing symptoms. This definitive treatment may be in the form of arterial embolisation, transvenous occlusion, surgical excision and radiation therapy. One or more of these modalities may be combined in specific cases.

Arterial embolisation using balloons, particulate matter or polymerising chemical agents is a good adjunct in presurgical planning and is most useful for isolated AV communications. It has only a limited application in AVMs supplied by small, multiple feeders from the internal carotid artery, e.g. D-AVMs of the tentorial incisura. Transvenous occlusion using metal coils, gelfoam or balloons may be done but is associated with significant morbidity.

Trivelato et al.[27] reported their early experience in treating nine patients by transarterial embolisation of D-AVFs with direct CVR using Onyx®. They achieved complete occlusion of the fistula in all patients with only one procedure and injection in only one arterial pedicle. On follow-up, eight patients became symptom free, one improved and no patient deteriorated. Late angiography showed no evidence of recurrent D-AVF. They recommend that transarterial Onyx® embolisation of D-AVFs with direct CVR is to be considered as a treatment option, as they found it to be feasible, safe and effective.[27] Cognard et al.[5] found Onyx® injections, were easier to control than N-butyl cyanoacrylate injections and a much larger volume could be injected over a longer time period. Also injection in a single feeder allowed obtaining arterio-arterial reflux and avoided embolisation of other feeders. They suggested that Onyx can be used as a primary treatment option for most cases of D-AVFs with direct cortical venous reflux. Saraf et al.[25] from their analysis of 99 cases of D-AVFs recommended the use of Onyx as the embolic agent of choice in the treatment of D-AVFs.

Van Rooij et al.[29] published their experience in the management of D-AVFs with CVR. Surgery being the treatment of choice for anterior fossa D-AVFs, and for all other D-AVFs embolisation with glue was the first treatment option. Five patients with an anterior fossa D-AVF underwent successful surgery without complications. In 14 patients, the D-AVF was completely occluded with embolisation alone, and in seven patients, embolisation was followed by surgery. They were able to achieve complete occlusion, angiographically confirmed in 28 out of 29 D-AVFs. Embolisation was complicated by post-embolisation haemorrhage[17] in one patient (3%). Nelson et al. in their series of 21 D-AVFs, nine of which were type III-IV Cognard, were treated transarterially under flow-arrest conditions, and cures were demonstrated in all fistulae without complications.

Kennith described a novel approach for endovascular ultrasound-guided puncture of an arterialised extracranial venous pouch with transosseous microcatheter navigation through a mastoid emissary vein for the treatment of an aggressive type 4 D-AVF. This can be offered as a useful alternative to other endovascular approaches for treating D-AVFs.[15]

Surgical methods employed are:

- Ligation of feeder vessel(s) which at best gives only transient relief of symptoms
- Excision of the entire anomaly with or without preoperative embolisation

The object of surgery is to resect the dural leaflets containing the nidus and the adjacent sinus along with disconnection of leptomeningeal draining pathways—the harbingers of fatal ICH. Careful pre-operative

angiographic analysis, judicious use of adjuncts like pre-operative embolisation and meticulous haemostasis during surgery help to improve surgical outcome. Microscope-based intra-operative near-infrared indocyanine green (ICG) videoangiography is useful as an adjunct to intra-operative or post-operative digital subtraction angiography in aneurysm surgery. Hanggi et al.[8] found microscope-integrated repetitive ICG videoangiography during AVM and D-AVF surgery is fast, easy to perform, simple, safe and is a useful additional tool that can potentially lower the surgical risk in complex AVMs and help avoid missed residuals.

Anterior cranial fossa D-AVFs are typically supplied by the anterior ethmoidal artery, sometimes bilateral, and usually drain into the superior sagittal sinus via a unilateral cortical drainer, bilateral drainers being rare.[6] Kohama et al.[12] reported a rare case of anterior cranial fossa D-AVF with bilateral cortical drainers. They recommend drainer occlusion at two points is required for complete obliteration of the drainers as the fistulous connection may not be simple.[12,28]

Successful use of conventional radiotherapy for D-AVMs is only anecdotal. However, encouraging results with the use of stereotactic radiosurgery suggest that this may be the future therapy of choice for many D-AVMs.

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100 Embolisation of Spinal Vascular Malformation

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With the recent advances in imaging techniques, spinal vascular malformations are being diagnosed and treated frequently. Improved techniques of MRI, MRA, MR myelography[16,23] and improvement in techniques of spinal angiography have led to better understanding of the pathophysiology of the malformations and, therefore, better treatment.[39] Until the seminal papers by Kendall (1977), Merland (1980) and Symon (1984), the pathophysiology and treatment of spinal dural arteriovenous fistulae (AVF) was not understood. Dural AVF was confused with AVM of the spinal cord and extraspinal AVF with intradural venous drainage. Since, spinal AVM and AVF are complex malformations, these should be managed by specialised centres experienced in them.

CLASSIFICATION OF SPINAL VASCULAR MALFORMATIONS[5,53,63]

Spinal cord malformations are complex. Many classifications have been proposed over the years. None of them is satisfactory. The commonly accepted ones are given in Tables 1A to C.

Table 1A: Spinal vascular malformations

Type I	Spinal dural arteriovenous fistula
Type II	Spinal AVM—Intramedullary
Type III	Spinal AVM—Juvenile[51]
Type IV	Spinal AVM—Perimedullary AVF[45]

Table 1B: Casasco classification

A. Simple:
A1. Spinal canal vascular malformation:[44]
a. Intramedullary vascular lesions:
i. AVM
ii. AVF
iii. Cavernoma[25,41]
iv. Telangectasia
b. Perimedullary AV fistula:
i. Type 1-small AVF, ASA or PSA and vein
ii. Type 2-ASA/PSA and vein dilated
iii. Type 3-giant AVF, multiple feeders[43]
c. Spinal dural AVF with perimedullary venous drainage[17,30,31]
Contd...
Contd...
d. Intracranial dural AVF with perimedullary venous drainage
e. Epidural AVF and AVM:[21,22,50]
i. Single shunt
ii. Multiple shunts
A2. Perivertebral malformations:
a. Paraspinal
b. Costovertebral angle
c. Nerve root foramina
A3. Vertebral angiomas:
a. Non-progressive vertebral angiomas
b. Progressive vertebral angiomas
B. Complex:
a. AVM in spinal arteriovenous metameric syndrome (SAMS)[6] at each spinal level—involvement of all layers of integument, ectodermal and mesodermal, from skin, subcutaneous tissue, muscle, bone, dura, subdural tissue, spinal cord.[12]
b. Disseminated angiomatosis (Osler-Rendu-Weber disease).[15,20,59]

Table 1C: Classification (Spetzler)[52]

Neoplasm[47]
Aneurysm
Arteriovenous lesion:
A. AVF
a. Extradural
b. Intradural
1. Dorsal
2. Ventral
B. AVM
a. Extradural
b. Intradural
1. Intramedullary
2. Intramedullary-extramedullary
3. Conus medullaris

They are usually made up of single or multiple AVF.[4] Niduses similar to those in brain AVMs are uncommon. Since there is hypertrophy of the feeding artery, aneurysms along their course are not infrequent.[7,24,46] The dilated arterialised veins may also show aneurysms along their course.

VASCULAR SUPPLY OF THE SPINAL CORD[6,57]

Three longitudinal axes supply blood to the spinal cord; the single central anterior spinal axis (ASA) and the paired posterolateral posterior spinal axes (PSA). They arise from the vertebral arteries just proximal to their junction. The anterior and posterior axes receive tributaries at multiple levels as they descend down the spinal cord. These tributaries are known as radiculomedullary and radiculopial arteries. The radiculomedullary arteries supply the anterior spinal axis and the radiculopial arteries supply the posterior spinal axes. In the cervical region radiculomedullary arteries arise from both vertebral arteries, ascending and deep cervical arteries, and in the dorsal and lumbar region from the dorsospinal branches of the intercostal and lumbar arteries. The most important contribution to the ASA is from the artery of Adamkiewicz, which may arise anywhere from T8 to L1, more often on the left side. Another prominent radiculomedullary artery arises at the cervical level and is called the artery of the cervical widening. The anterior two-thirds of the spinal cord is supplied by the ASA and the posterior one-third by the paired PSA. The anterior spinal axis is a continuous channel extending from the cervicomedullary junction to the filum terminale. The axis lies in the anterior commissure of the spinal cord and gives rise to perforators throughout its length. These perforators are known as sulco-commissural perforators. These perforators are usually not visible on angiography unless they are hypertrophied in the presence of pathology like spinal cord AVM. For embolisation, these may have to be selectively cannulated to maintain the continuity of the anterior spinal axis. Sulco-commissural arteries supply the lateral surface of the spinal cord. Accidental embolisation of a posterior radicular artery may be of no consequence, but occlusion of the ASA is followed by devastating neurological deficit.

CLINICAL PRESENTATION

The clinical presentations[37,48] of spinal cord AVM[14,26] or AVF are different from that of dural AVF (Table 2).

The clinical signs are due to: (1) SAH; (2) haematomyelia; (3) steal into AVF/AVM; (4) venous hypertension; (5) thrombosis of draining vein, (6) pressure of aneurysm, venous or arterial, true or false; (7) arachnoiditis; (8) syringomyelia and (9) Foix-Alajouanine syndrome, a result of chronic venous ischaemia of the spinal cord.[42]

Table 2: Clinical Presentation

Dural AVF	*Intradural*	*AVM/AVF*
Gender	Predominantly Male	Male or Female
Mean age	40 years	25 years
Onset	Gradual	Sudden
First symptom	Paresis or pain	SAH
Exacerbation by activity	80%	25%
UL affected	Never	Sometimes

SAH is usually due to rupture of an aneurysm or AVM nidus. Thrombosis of the draining vein results in Foix-Alajouanine syndrome. Clinical cure with disappearance of the draining vein due to thrombosis is rare.

The clinical course is often characterised by exacerbations and remissions.[2] These are due to repeated haemorrhages from aneurysms or veins. Rise in venous pressure results in clinical deterioration, e.g. after constipation, coughing, sneezing, forward bending, pregnancy and menstrual period. Claudication pain is a common presentation in dural AVF. Claudication pain and neurological deficit may be worsened by a heavy meal. Spinal SAH may be confused with intracranial SAH. However, the pain starts at the site of the spinal AVM and spreads upwards. The neurological deficit usually starts in the lateral columns then spreads to the corticospinal tracts and posterior columns. Sphincter involvement is early, if the conus is involved. The story may go on for many years, punctuated by exacerbations and remissions. Diagnosis, especially of dural arteriovenous fistula, is difficult and delayed for several months before it is made (Table 3).

Table 3: Summary of Clinical Characteristics in AVMs (Spetzler 2002)

Characteristics	*Extradural-Intradural*	*Intramedullary*	*Conus Medullaris*
Pathophysiology	Compression, vascular steal, haemorrhage	Haemorrhage, compression, vascular steal	Venous hypertension, compression, haemorrhage
Presentation	Pain, progressive myelopathy	Acute myelopathy, pain, progressive myelopathy	Progressive myelopathy
Diagnostic modality	MR imaging, Angiography High-flow, multiple feeders	MR imaging, Angiography	MR imaging, Angiography
Previous nomenclature	Juvenile AVM, metameric AVM	Classic AVM, glomus type	None

INVESTIGATIONS

Plain X-rays may show scalloping of the posterior surface of the vertebral body, if there is a large venous varix. Usually plain X-rays are non-contributory.

Myelography

Myelography with non-ionic contrast in the prone and supine positions may show the coiled vessels on the dorsal surface of the spinal cord. Arachnoiditis may also be recognised.

Computerised Tomography Scan

Computerised tomography scan with intrathecal contrast may show the large serpiginous vessels. CTA on the newer machines, if done carefully, often provides good information. The feeding arteries, nidus (if any), draining veins and aneurysms along the feeders and draining veins may be seen.

Magnetic Resonance Imaging

Magnetic resonance imaging[29] usually shows the lesion within the cord very well. In dural AVF, fusiform oedema of the conus is pathognomonic. It may extend upwards into the dorsal cord for a variable distance. The vessels may be seen on MRI myelography or T2-weighted images. Associated lesions of the cord, cysts, arachnoiditis and syrinx are well seen. Old haemorrhage may be seen as haemosiderin deposits.

Magnetic Resonance Angiography

Magnetic resonance angiography (MRA), especially after contrast, shows the vessels very well. If pains are taken one may be able to identify the site of the AVF, the feeding artery and draining vein. The coiled vessels on the anterior and posterior surface of the cord are well-seen.[36]

Digital Subtraction Angiography

DSA is the gold standard.[40,49,58] For cervical lesions, bilateral vertebral (VA), bilateral subclavian, bilateral external carotid and at least eight upper dorsal intercostal arteries must be catheterised on both sides. For lumbar lesions, bilateral intercostals, all lumbar and internal iliac angiograms must be done. For slow flow dural AVF, delayed filming up to 20 seconds is mandatory. For better subtraction the respiration is stopped during filming and bowel movements are reduced by Buscopan injections. Subtracted and non-subtracted views are necessary for proper orientation of the vertebral level and to ascertain whether it is anterior or posterior to the cord. AP views are made of all vessels. Lateral and oblique views of the feeders to the spinal cord and the malformation are made to get a complete picture of the malformation. Since the long arteries and veins may extend over several segments, it may be necessary to acquire images over several segments and fuse sequential runs to get a true idea of the extent of the lesion. For example, the ASA may start at D8 and may feed a lesion at L3. Sometimes the artery turns around the sulco-commissural segment at the conus and reascends to supply a malformation. Similarly, draining veins may begin on the posterior surface, then ascend and descend on the anterior, posterior and lateral surface. The same feeder may be supplied by many intercostal or lumbar arteries, usually on the same side, but sometimes also from the opposite side. For sacral AVF or AVM, injection into the internal iliac artery may demonstrate low-flow small feeders from the lateral sacral arteries. Despite an exhaustive study AVM may not be demonstrated, and the AVM may be occult. Sometimes it may be necessary to repeat the angiogram.

The DSA must be analysed carefully. When analysing the DSA, one must find the feeders, draining veins and the nidus. As has already been stated there may be no nidus at all. There may be single or multiple AVF. Sometimes, the transition from artery to vein in Type 1 AVF is subtle and may be easily missed. There may be one or more aneurysms on the dysplastic enlarged feeder or feeders. There may be a concomitant venous aneurysm or varix. It is mandatory to demonstrate the normal supply of the cord and identify the ASA and the PSA. The same intercostal or lumbar artery may be supplying the cord as well as the AVM. One must identify the shortest and easiest route to the feeder.

TREATMENT

Indications for Treatment

Patients presenting with subarachnoid haemorrhage, spinal cord haemorrhage, progressive neurological deficit or severe root pains need to be treated. AVMs located in the cervical[54] and upper dorsal region are clinically more aggressive, present with recurrent bleeds which cause severe neurological deficits and need urgent treatment.[6] The aim of treatment is to find "weak spots" and obliterate them. Complete cure is rarely achieved as the morbidity is much higher due to erratic embolisation when attempting to obtain obliteration of the AVM. Ligation of proximal feeders, without tackling the nidus, should be condemned as collateral circulation from adjacent arteries immediately takes over the supply. The collateral feeders are usually small and tortuous rendering further surgical or endovascular treatment impossible.

Technique[8,13,18,56,64]

Embolisation is always done under general anaesthesia[3] (Table 4). Respiration is stopped during injection, if required. Buscopan is injected to reduce bowel movements for better visualisation of contrast and glue or Onyx.[11]

Table 4: Materials required

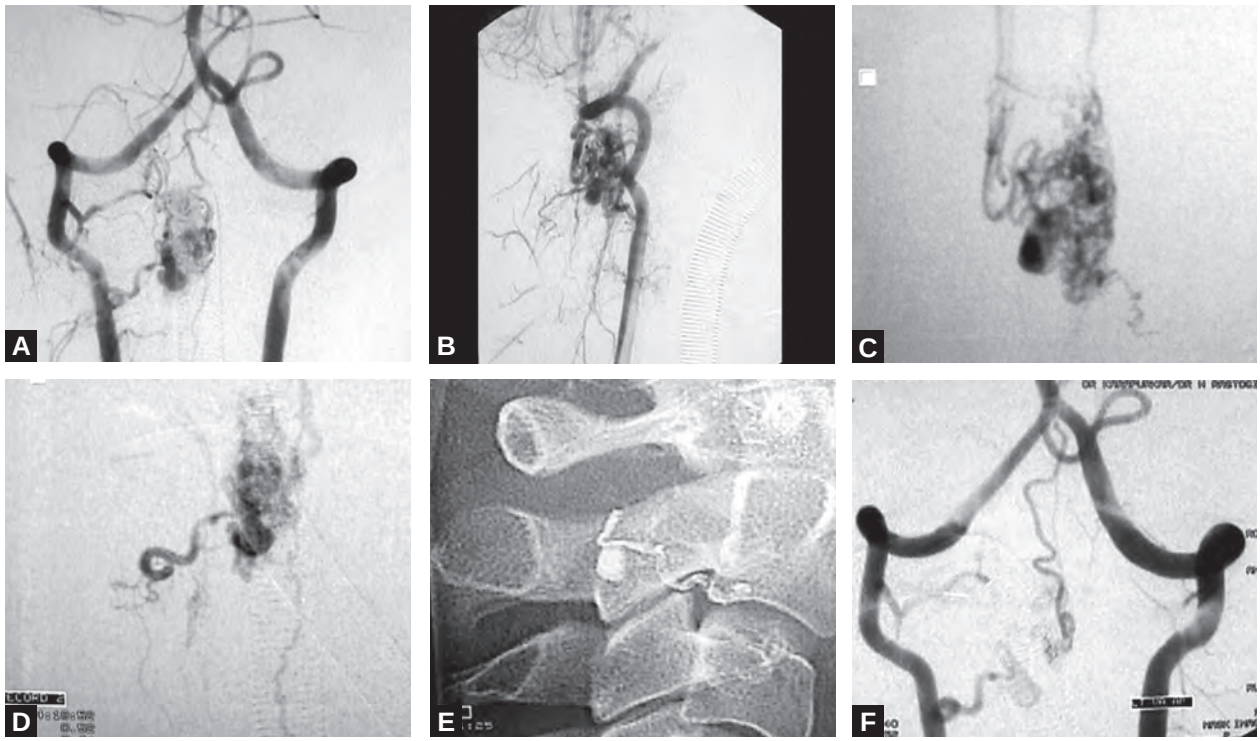
Access sheath
Spinal angio. Or Sim 1 cath
Non-ionic contrast
Microcatheter—Marathon, Magic 1.2 FM, Ultraflow
Microguide wire—Mirage 0.008"
Embolic material: Histoacryl with lipiodol, Onyx 18 or Onyx 34

Spinal Cord AVM[19,32,62]

Diagnostic angiogram and the therapeutic procedure should be carried out in two different sittings. Embolisation is done under general anaesthesia. Methyl prednisolone infusion may be started at the commencement of the procedure to protect the spinal cord. The 5F guiding catheter, usually Envoy (Cordis) or Cobra C1, is placed in the selected artery. Under road mapping the microcatheter, [Magic 1.2 FM (Balt SA), Ultraflow, or Marathon (EV3)] is advanced into the feeding artery over a microguide wire, usually the Mirage 0.008" (EV3). The catheter is navigated as close to the AVF or glomus (nidus) as possible. If there is an aneurysm, it is placed just short of it. Glue is prepared in bowls washed in dextrose. Histoacryl (glue) hardens as soon as it comes in contact with contrast, saline or blood. The polymerising time is changed by adding lipiodol which also makes it radio-opaque. For high-flow AVF 80–90% glue is injected. It is made radio-opaque by adding tantalum powder. After confirming satisfactory position, the microcatheter is washed by irrigating with 5% dextrose, so that there is no blood, contrast or saline in the catheter. Glue is injected under vision in the trace-fluoro mode. The glue is slowly injected over minutes for slow flow lesions and rapidly for high-flow lesions. For an aneurysm, the glue is deposited as close to the aneurysm as possible. An AVM or AVF downstream from the aneurysm is embolised at the same time (Figs 1A to F). For AVM or AVF the attempt is to fill the nidus with glue. Care is taken to push the glue across the nidus into the proximal few millimetres of the draining vein. The catheter is rapidly pulled out at the end of the injection, lest it gets glued. Control angiogram is performed immediately. For small lesions, if the glue does not penetrate to the vein recurrence is likely. For large lesions treatment is staged 4–6 weeks apart for fear of breakthrough bleeding.

PVA or hydrogel particles are rarely used today as recurrence is common. It is injected in saline mixed with contrast to visualise its passage. Small aliquots of 2 ml are injected gently under trace-fluoro mode or frequent runs are made to control the progress of embolisation. The endpoint is slowing of flow, stagnation in the feeder or complete obliteration. It is important not to occlude the ASA as it does not recanalise. The PSA may be occluded without any grave consequences. Particles get reabsorbed overtime.

Recently Onyx 18 (EV3) has been used to embolise the AVM nidus.[34] Onyx is a liquid embolic agent, Ethyl Vinyl Alcohol Co-Polymer, which is dissolved in dimethyl sulphoxide (DMSO) and mixed with tantalum powder to make it radio-opaque. Tantalum powder is made into a homogeneous suspension by pacing the vials in an agitator at least 15 minutes before the injection is made. Marathon, Ultraflow and Sonic (Balt SA) are DMSO compatible and can be used for injecting Onyx. Magic series of catheters cannot be used for injection of Onyx as they are not compatible. The technique of injection of Onyx is to allow reflux of Onyx onto the catheter and it may reflux for up to 2 cm, so one should have a margin of at least 2 cm between the tip of the catheter and an important branch or parent vessel. Hence, it can only be used in selective cases of spinal cord AVM. The



Figs 1A to F: Two episodes of haemorrhage. (A and B) VA angiogram, AP and lateral to show spinal cord AVM. (C) Superselective angiogram showing small intranidal aneurysm which is not seen on (A) and (B). (D) Cast of glue in nidus and aneurysm. (E and F) Control at 1 year showing small residual AVM

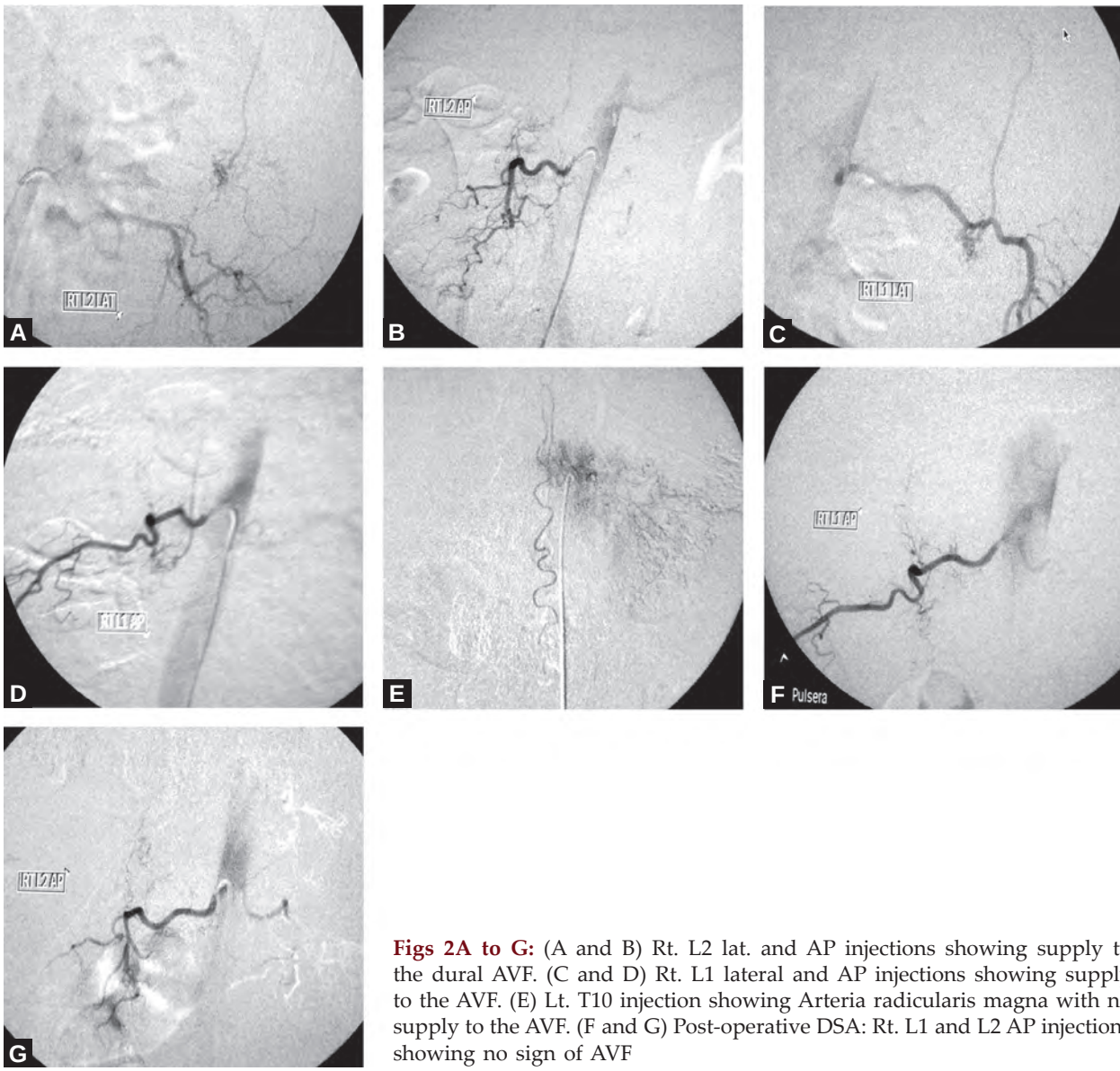
injection is made by trace-fluoro technique over several minutes, watching for reflux carefully. At the end of the injection, the microcatheter is pulled out with a jerk. As of today glue is preferred over Onyx in the treatment of spinal AVM.

Dural AVF

Dural AVF[9,33,38,55] can be treated by surgery[1] or by the endovascular route. The aim of treatment is to find and obliterate the single draining vein as it enters the spinal canal (Figs 2A to G). This is accomplished by depositing dilute histoacryl or onyx 18[60] in the draining vein and the dural malformation. Care should be taken not to let the glue or onyx reach the spinal cord veins. In dural AVF below L2 there may be a long safe length of vein available. PVA particles have no place in the treatment because it always recanalises. If there is even a small residue left, the AVF recurs. Retreatment is difficult or impossible as the adjacent lumbar or intercostals or small branches from the internal iliac supply the recurrent AVF through tiny tortuous collateral arteries. During surgery, a limited laminectomy is done on the appropriate side; the dura is exposed close to the intervertebral foramen where the bunch of vessles on the dura is recognisable. The dura is opened; the vein is identified as it enters the spinal canal. The vein is coagulated and divided. The dura containing the malformation may be coagulated and excised.

Spinal Cord AVF[10,61]

These must be treated because the long-term prognosis is poor. An attempt must be made to obliterate it completely. If cure is not possible, partial treatment is strongly recommended. Surgery is risky because the AVF may be on the anterior surface of the cord or buried within it. The angioarchitecture must be analysed. The ASA is a dangerous artery to embolise. Glue or Onyx is used only, if the microcatheter can be taken close to the AVF, so that the ASA patency is preserved. If it is not possible to catheterise the ASA, particulate matter,



Figs 2A to G: (A and B) Rt. L2 lat. and AP injections showing supply to the dural AVF. (C and D) Rt. L1 lateral and AP injections showing supply to the AVF. (E) Lt. T10 injection showing Arteria radicularis magna with no supply to the AVF. (F and G) Post-operative DSA: Rt. L1 and L2 AP injections showing no sign of AVF

PVA may be floated in very small aliquots to obliterate the AVF. The AVF may recanalise, but the ASA does not. For the PSA, onyx or glue can be used. Arterial true and false aneurysms must be obliterated with glue, onyx or by surgical clipping because they are prone to bleed again and again. For large high-flow AVF embolisation should be staged and should begin at the sulco-commissural arteries. As embolisation proceeds new segments may be identified (Figs 3 to 5). With PVA there may be recanalisation. However, with PVA, after some years the same arteries can be retreated safely. Histoacryl (glue) embolisation is permanent. Detachable balloons and coils have no place in the treatment of spinal AVM or AVF except for treatment of large high-flow direct AVF between the vertebral artery and the vertebral vein.

Giant metameric, paraspinal[28] AVF or AVM may be inoperable. The aim should be to treat the weak spots, such as false and true aneurysms, and to reduce the flow through the venous system to reduce backpressure and improve spinal cord function. Mounayer has described obliteration of a giant paraspinal AVF with perimedullary venous drainage.

Complications

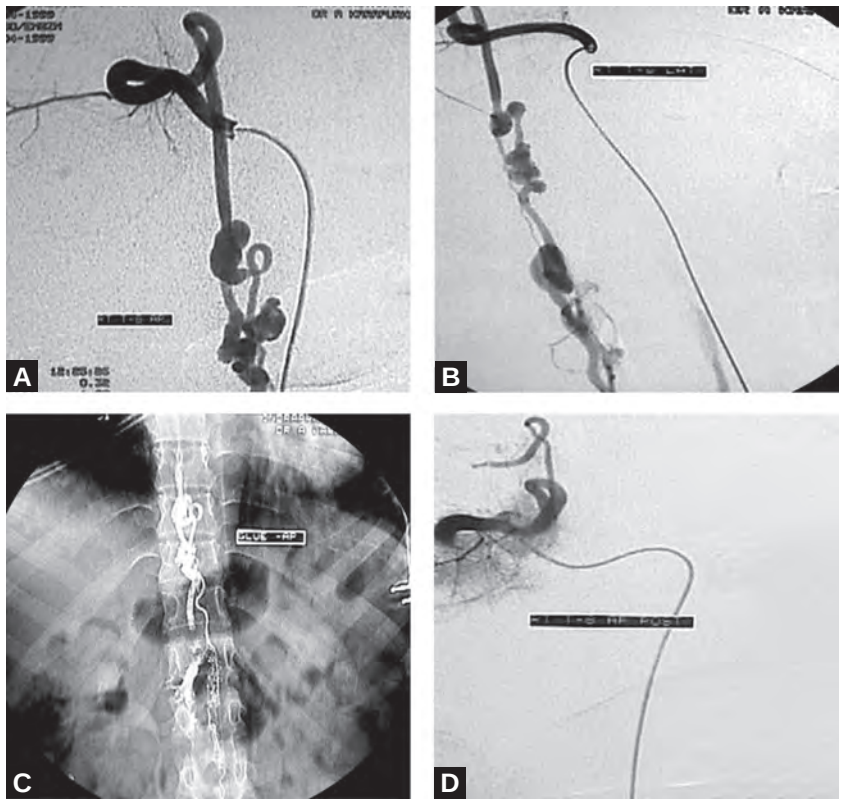
Rarely a patient may deteriorate after the diagnostic angiogram, especially, if ionic contrast is used. The cause for the deterioration is usually not found. Occlusion of the ASA is disastrous. Occlusion of the PSA may leave a small deficit. Occlusion of the draining vein without obliteration of the AVF or AVM may result in haemorrhage. Haemorrhage may occur due to rupture of an associated aneurysm. The neurological deficit is due to ischaemia of the cord or haematomyelia and may vary from complete motor and sensory paraplegia with sphincter involvement to minor problems like backache. The deficit usually recovers overtime with physiotherapy, but it may be permanent. Recovery of the sensory system, especially posterior columns, usually occurs rapidly. Motor recovery is slower. Recovery of sphincter function takes some months. Sometimes, the sphincters may not recover. Methylprednisolone, which is usually started at induction of anaesthesia, may need to be given for 5 days, if there is deterioration in function.[27] Rarely, patients may deteriorate after methylprednisolone. The author has seen three patients deteriorate after infusion of methylprednisolone before any invasive procedure was done.

Follow-Up

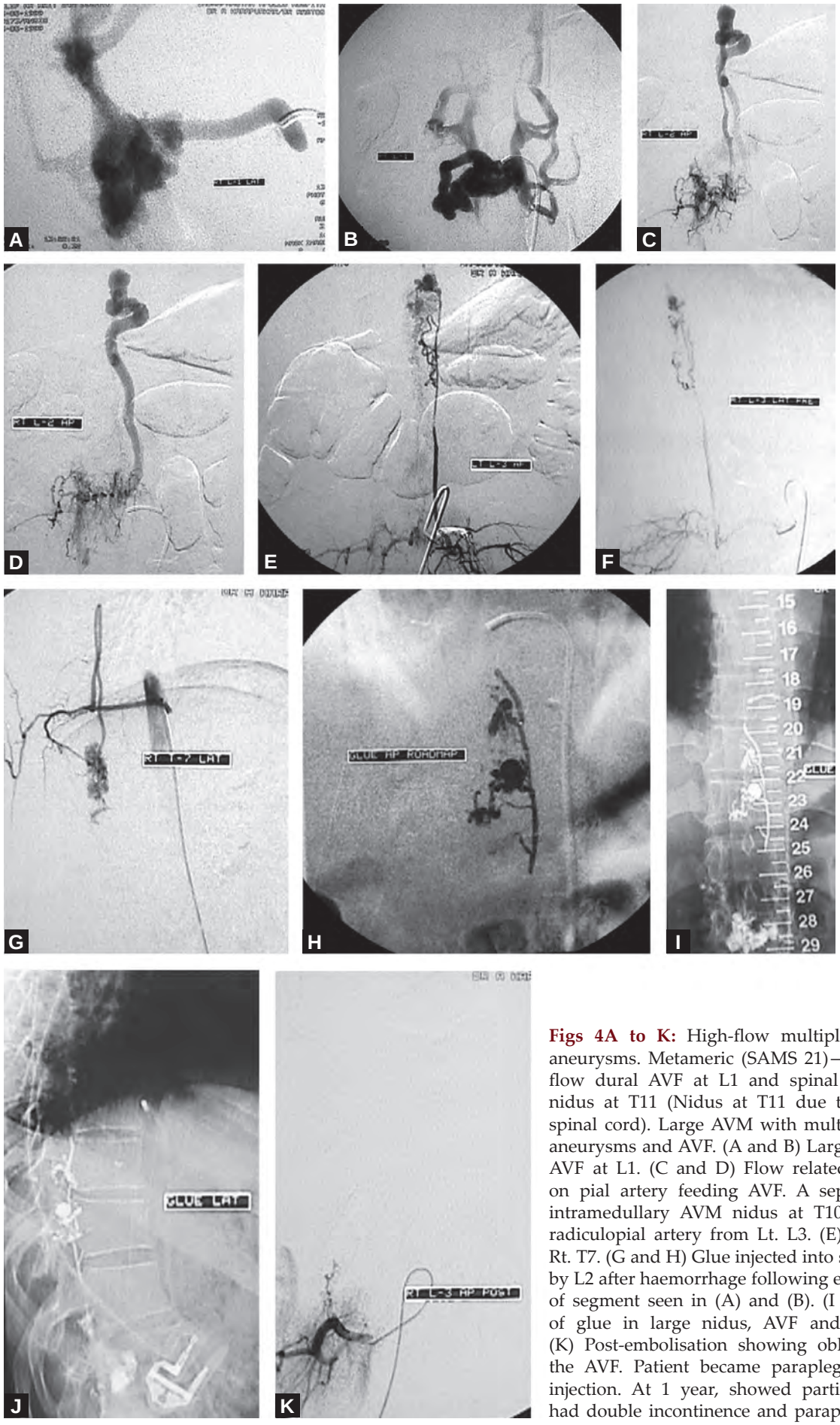
If partial treatment has been accomplished, annual DSA is mandatory. Retreatment may be necessary.

CONCLUSION

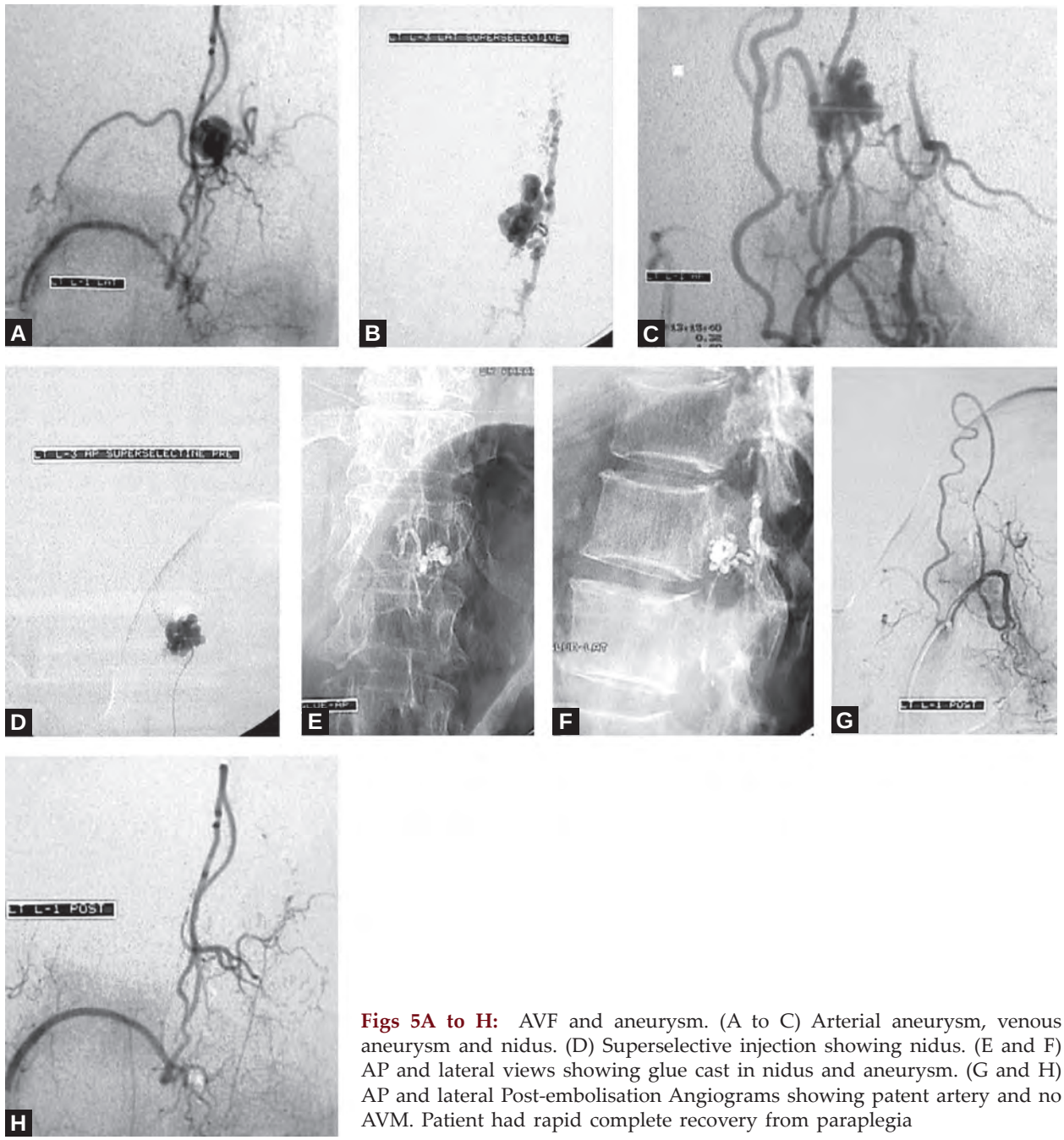
Spinal vascular malformation is a formidable disease.[35] It must be treated unless there is complete cord transsection with no recovery. The aim should be complete obliteration. However, safe complete obliteration may not



Figs 3A to D: Acute onset complete motor and sensory paraplegia with sphincter loss in 14-year-old girl. (A and B) AP and lateral high-flow AVF of spinal cord with multiple aneurysms. (C) Cast of glue in feeding artery and draining vein. (D) Post-embolisation DSA. Patient gradually recovered over 2 years, now continent and ambulant



Figs 4A to K: High-flow multiple AVF and aneurysms. Metameric (SAMS 21)—large high-flow dural AVF at L1 and spinal cord AVM nidus at T11 (Nidus at T11 due to ascent of spinal cord). Large AVM with multiple arterial aneurysms and AVF. (A and B) Large high-flow AVF at L1. (C and D) Flow related aneurysm on pial artery feeding AVF. A separate large intramedullary AVM nidus at T10–11 fed by radiculopial artery from Lt. L3. (E) Rt. L3. (F) Rt. T7. (G and H) Glue injected into segment fed by L2 after haemorrhage following embolisation of segment seen in (A) and (B). (I and J) Cast of glue in large nidus, AVF and aneurysm. (K) Post-embolisation showing obliteration of the AVF. Patient became paraplegic after 1st injection. At 1 year, showed partial recovery, had double incontinence and paraplegia



Figs 5A to H: AVF and aneurysm. (A to C) Arterial aneurysm, venous aneurysm and nidus. (D) Superselective injection showing nidus. (E and F) AP and lateral views showing glue cast in nidus and aneurysm. (G and H) AP and lateral Post-embolisation Angiograms showing patent artery and no AVM. Patient had rapid complete recovery from paraplegia

be possible. "Weak spots" must be treated. Associated aneurysms must be treated with liquid embolic material like histoacryl or surgically clipped. Large AVMs are treated in a staged manner. Follow-up DSA is essential to monitor the residual AVM and to look for any "recurrence".

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101 Spontaneous Intracerebral Haemorrhage

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INTRODUCTION

Intracranial haemorrhage (ICH) accounts for 10–30% of all stroke admissions to hospital, and leads to catastrophic disability, morbidity and a 6 month mortality of 30–50%.[30] Long-term outcomes are poor; only 20% of patients regain functional independence at 6 months.[30] ICH is classified as primary or secondary. Primary ICH is when the haemorrhage originates from spontaneous rupture of small arteries or arterioles damaged by chronic hypertension or amyloid angiopathy. Secondary ICH is when haemorrhage results from trauma, rupture of an aneurysm/vascular malformation, coagulopathy or other causes (Table 1).[28]

Table 1: Secondary causes of ICH[18]

Trauma
Arteriovenous malformation
Intracranial aneurysm
Coagulopathy
Haemorrhagic conversion of cerebral infarct
Dural sinus thrombosis
Intracranial neoplasm
Cavernous angioma
Dural arteriovenous fistula
Venous angioma
Cocaine or sympathomimetic drug exposure
CNS vasculitis
Anticoagulant therapy

RISK FACTORS

Chronic hypertension causes degeneration, fragmentation and fibrinoid necrosis of small penetrating arteries in the brain, which can eventually result in spontaneous rupture. Some people have discrete arteriolar microaneurysms (Charcot-Bouchard aneurysms) at the site of vessel rupture.[18] Hypertensive ICH typically occurs in the basal ganglia (putamen, thalamus or caudate nucleus), pons, cerebellum or deep hemispheric white matter.[28] Non-compliance with antihypertensive treatment increases the risk of ICH.[1]

The second most common cause of primary ICH is cerebral amyloid angiopathy, which accounts for about 15% of cases.[28] The disorder is characterised by the deposition of amyloid-β peptide in small to medium sized blood vessels of the brain and leptomeninges, which results in vascular fragility. However, spontaneous lobar haemorrhage in elderly patients with a history of cognitive decline by amyloid angiopathy is typically less severe. Recurrent haemorrhage occurs in 5–15% of patients with lobar ICH and probable amyloid angiopathy. After hypertensive ICH, repeat bleed occurs in as low as 2% of patients per year when blood pressure is well controlled.[1]

EMERGENCY DIAGNOSIS AND ASSESSMENT OF ICH AND ITS CAUSES

The classic clinical presentation includes the onset of a sudden focal neurological deficit while the patient is active, which progresses over minutes to hours.[4] The smooth symptomatic progression of a focal deficit over a few hours is uncommon in ischaemic stroke and rare in subarachnoid haemorrhage. Headache is more common with ICH than with ischaemic stroke, although less common than in subarachnoid haemorrhage.[12] Vomiting is more common with ICH than with either ischaemic stroke or subarachnoid haemorrhage. Increased blood pressure and impaired level of consciousness are common.[12] However, clinical presentation alone, although helpful, is insufficient to reliably differentiate ICH from other stroke subtypes.[4]

Diagnosis

ICH is confirmed by computed tomography (CT) scan. The volume of the haemorrhage can rapidly be estimated at the bedside from the CT with the ABC/2 method, which involves multiplying the diameter of the haematoma in three dimensions and dividing by two.[16] MRI is as sensitive as CT for the detection of ICH in the acute stage,[15] but is most commonly done as a follow-up study to detect vascular flow voids, which are indicative of an arteriovenous malformation, chronic lobar microbleeds on gradient echo imaging suggestive of amyloid angiopathy, or a contrast-enhancing neoplasm. Catheter angiography is the diagnostic test for vascular causes of secondary ICH, such as an aneurysm, arteriovenous malformation, dural arteriovenous fistula or cortical-vein thrombosis.[15]

Indications for catheter angiography include subarachnoid haemorrhage, abnormal calcifications, obvious vascular abnormalities and blood in unusual locations such as the Sylvian fissure.[4] In one study, no vascular malformations were found in people over the age of 45 years with a history of hypertension and haemorrhage in a classic hypertensive location (basal ganglia, cerebellum or pons).[43] However, angiography detected a vascular malformation in 65% of patients with primary intraventricular haemorrhage and in non-hypertensive patients with lobar haemorrhage. Angiography may also be indicated in patients with no obvious cause of bleeding, such as those subjects with isolated IVH. The yield of angiography declines in elderly patients with hypertension and a deep haematoma.[4]

PATHOPHYSIOLOGY

The two most important new concepts are that many haemorrhages continue to grow and expand over several hours after onset of symptoms—a process known as early haematoma growth—and that most of the brain injury and swelling that happens in the days after ICH is the result of inflammation caused by thrombin and other coagulation end-products.[18]

Early Haematoma Growth

Early haematoma growth is common and associated with neurological deterioration and poor clinical outcome. Even in the absence of known coagulopathy, about 38% of patients had an increase in haematoma volume of more than 33% shown by CT within 3 hours of onset.[5] Only up to 5% of patients have ICH growth when the baseline scan is done more than 6 hours after onset.[20]

Perihaematomal Brain Injury

Brain-tissue injury and swelling, which can result in increased intracranial pressure (ICP) or herniation related to compartmentalised mass effect, are the primary causes of neurological deterioration after the first day. The possible creation of an ischaemic penumbra in the brain tissue immediately adjacent to an ICH, resulting in secondary neuronal injury and cytotoxic oedema, was a major concern for many years. PET and MRI studies, done as early as 6 hours after onset of symptoms, have not shown tissue ischaemia in perihaematomal brain regions.[32] By contrast, an overwhelming haematoma-induced inflammatory response has been identified which causes less brain swelling and tissue injury.[6] Plasma, that is rich in thrombin and other coagulation end-products, released by the clotted haematoma seeps into the surrounding brain tissue, and is the primary trigger of the inflammatory process.[40]

PROGNOSIS

Mortality after ICH approaches 50% at 1 year.[38] Independent predictors for 30 days and 1 year mortality include large ICH volume, coma, older age, intraventricular haemorrhage and infratentorial location.[14,38] A useful clinical grading scale (the ICH score) that incorporates these five elements allows rapid estimation of 30 day mortality on admission (Table 2).

Table 2: The ICH score

Component	*Points*
Glasgow coma scale score	
3–4	2
5–12	1
13–15	0
ICH volume (mt)	
> 30	1
< 30	0
Intraventricular haemorrhage	
Yes	1
No	0
Age (years)	
> 80	1
< 80	0
Infratentorial origin	
Yes	1
No	0
30 day mortality at total points	
5+	100%
4	97%
3	72%
2	26%
1	13%
0	0%

MANAGEMENT

The patient's neurological status should be assessed frequently with the use of standard stroke scales such as the National Institutes of Health Stroke Scale (NIHSS) and coma scales such as the GCS. Blood pressure should be monitored adequately with an automatic cuff, whereas continuous monitoring of systemic arterial pressure should be considered in patients who require continuous intravenous administration of antihypertensive medications and in patients whose neurological status is deteriorating. Airway and oxygenation can be assessed per respiratory status and pulse oximetry. Cardiopulmonary instability in association with increased ICP is to be avoided to minimise deleterious effects in patients with limited autoregulatory capacity.[4] Monitoring and management of patients with an ICH should take place in

an intensive care unit setting because of the acuity of the condition, frequent elevations in ICP and blood pressure, frequent need for intubation and assisted ventilation and multiple complicating medical issues.[4] It has been reported that admission of ICH patients to a neurosciences intensive care unit may result in a reduced mortality rate.

Airway

Rapid neurological decline and depressed consciousness mandates immediate endotracheal intubation and mechanical ventilation. Imminent airway loss can result in aspiration, hypoxaemia or hypercapnia, which in turn can lead to cerebral vasodilatation and high ICP. Respiratory rate and tidal volume should be set to maintain a pCO_2 of about 35 mmHg and aggressive hyperventilation to pCO_2 below 28 mmHg should be avoided because of the possibility of excessive vasoconstriction and exacerbation of ischaemia.[18]

Blood Pressure

Blood pressure should be managed on the basis of individual patient factors such as prior history of hypertension on baseline blood pressure, presumed cause of haemorrhage, age and elevated intracranial pressure (ICP). The primary rationale for lowering the blood pressure is to avoid haemorrhagic expansion from potential sites of bleeding. This is particularly true for haemorrhage resulting from a ruptured aneurysm or arteriovenous malformation. However, in primary ICH, the risk of haemorrhagic expansion with mild blood pressure elevation may be lower and must be balanced with the theoretical risks of inducing cerebral ischaemia in the oedematous region that surrounds the haemorrhage.[4]
The American Stroke Association (ASA) has recommended the following guidelines for treating elevated blood pressure in spontaneous ICH:[4]

- If SBP is more than 200 mmHg or MAP is greater than 150 mmHg, then consider aggressive reduction of blood pressure with continuous intravenous infusion, with frequent blood pressure monitoring every 5 minutes.
- If SBP is greater than 180 mmHg or MAP more than 130 mmHg and there is evidence of or suspicion of elevated ICP, then consider monitoring ICP and reducing blood pressure using intermittent or continuous intravenous medications to keep cerebral perfusion pressure greater than 60–80 mmHg.
- If SBP is greater than 180 mmHg or MAP more than 130 mmHg and there is no evidence of or suspicion of elevated ICP, then consider a modest reduction of blood pressure (e.g. MAP of 110 mmHg or target blood pressure of 160/90 mmHg) using intermittent or continuous intravenous medications to control blood pressure, and clinically re-examine the patient every 15 minutes.

[SBP: systolic blood pressure; MAP: mean arterial pressure.]

Intravenous medications that may be considered for control of elevated blood pressure in patients with ICH include labetalol, nicardipine, esmolol, enalapril, hydralazine, nipride and nitroglycerin.

Management of ICP

An ICP monitor or external ventricular drain should generally be placed in all patients with ICH in coma (Glasgow Coma Scale score of 8 or less) with the goal of maintaining ICP below 20 mmHg and a minimum cerebral perfusion pressure greater than 60 mmHg. External ventricular drains have the disadvantage of a substantial risk of infection (about 10% during the first 10 days).

Emergency measures of ICP control are appropriate for stuporous or comatose patients, or those who present acutely with clinical signs of brainstem herniation. The head is elevated to 30 degrees, 1.0–1.5 g/kg of 20% mannitol is given by a rapid infusion, and the ventilation is controlled to maintain the pCO_2 at 30–35 mmHg. These measures are designed to lower ICP as quickly and effectively as possible to buy time before a definitive neurosurgical procedure (craniotomy, ventriculostomy, or replacement of an ICP monitor) can be done. Corticosteroids, such as dexamethasone, are not indicated in the management of ICH, based on the results of randomised trials that have failed to demonstrate their efficacy in ICH.[4]

Haemostatic Therapy

Eptacog alfa [recombinant activated factor VII (rFVIIa), Novoseven®, Novo Nordisk A/S] is a power initiator of haemostasis currently approved for treatment of bleeding in patients with haemophilia who are resistant to factor VIII replacement therapy. Although there is evidence suggesting that rFVIIa might improve haemostasis in patients with normal coagulation systems, results of recently published phase III Trial (FAST trial) comparing placebo with doses of 20 μg/kg and 80 μg/kg has shown that haemostatic therapy with rFVIIa reduced growth of the haematoma, but did not improve survival or functional outcome after intracerebral haemorrhage.[19]

Reversal of Anticoagulation

Warfarin anticoagulation increases the risk of ICH five to ten times.[42] Among patients with ICH, warfarin doubles the risk of mortality and increases the risk of progressive bleeding and clinical deterioration.[13] Failure to rapidly normalise the international normalised ratio (INR) to below 1.4 further increases these risks.[10] Patients with warfarin-associated ICH should be treated with intravenous vitamin K to reverse the effects of warfarin and with treatment to replace clotting factors.[4] Prothrombin complex concentrate, factor IX complex concentrate and rFVIIa normalise the laboratory elevation of the INR

very rapidly and with lower volumes of fluid than FFP, but with greater potential of thromboembolism. FFP is another potential choice, but is associated with greater volumes and much longer infusion times.[4]

rFVIIa in doses ranging 10–90 μg/kg has been used to reverse the effects of warfarin in acute ICH—primarily to expedite neurosurgical intervention—with good clinical results.[11] When this approach is used, rFVIIa should be used as an adjunct to coagulation-factor replacement and vitamin K because the effect will last only several hours. Unfractionated or low-molecular-weight heparin should be reversed with protamine sulphate,[41] and patients with thrombocytopaenia or platelet dysfunction can be treated with a single dose of desmopressin (DDAVP), platelet transfusions, or both.[18]

Fluids

Free-water given in the form of 0.45% saline or 5% dextrose in water can exacerbate cerebral oedema and increase ICP because it flows down its osmotic gradient into injured brain tissue. Solutions containing dextrose should generally be avoided unless hypoglycaemia is present, because hyperglycaemia can be detrimental to the injured brain. A state of euvolaemia should be maintained by monitoring the fluid balance, central venous pressure and body weight. Isotonic fluids, such as 0.9% saline (about 1 ml/kg/h), should be given as the standard intravenous replacement fluid.[18] Some centres increasingly use hypertonic saline in the form of 3% sodium chloride/acetate solutions as an alternative to normal saline in patients with significant perihaematomal oedema and mass effect. However, further studies are needed to clarify the risks and benefits of hypertonic saline for ICH.[18]

Anticonvulsant Therapy

Acute seizures should be treated with intravenous lorazepam (0.45–0.10 mg/kg) followed by an intravenous loading dose of phenytoin or fosphenytoin (15–20 mg/kg), valproic acid (15–45 mg/kg) or phenobarbital (15–20 mg/kg). The 30 day risk of clinically evident seizures after ICH is about 8%[27] and the risk of epilepsy is 5–20%.[27] ASA guidelines recommend antiepileptic treatment in selected patients for up to 1 month.[4] Continuous electroencephalography detects non-convulsive seizures or status epilepticus in 28% of stuporous or comatose patients with ICH.

Fever Control

The incidence of fever after basal ganglionic and lobar ICH is high, especially in patients with ventricular haemorrhage. In patients surviving the first 72 hours after hospital admission, the duration of fever is related to outcome and appears to be an independent prognostic factor in these patients. Paracetamol should be given and the body should be cooled externally in all patients with sustained fever in excess of 38.3°C (101.0°F).[33]

Management of Glucose

Evidence indicates that persistent hyperglycaemia (>140 mg/dl) during the first 24 hours after stroke is associated with poor outcomes. Insulin should be administered when the blood sugar level is >185 mg/dl and sometimes when it is >140 mg/dl.

Nutrition

Enteral feeding should be started within 48 hours to reduce the risk of malnutrition.

Deep Venous Thrombosis Prophylaxis

ICH patients are at high risk for deep vein thrombosis and pulmonary embolism. Dynamic compression stockings should be placed on admission. After documentation of cessation of bleeding, low-dose subcutaneous low-molecular-weight heparin or unfractionated heparin may be considered in patients with hemiplegia after 3–4 days from onset.

Anticoagulation after ICH

The issue of reinstitution of anticoagulation after warfarin-related ICH applies primarily to those who began taking warfarin for the prevention of cardiogenic embolism associated with either prosthetic heart valves or chronic atrial fibrillation.[4]

Recommendations for the Management of ICH Related to Coagulation and Fibrinolysis[4]

The decision to restart antithrombotic therapy after ICH depends on the risk of subsequent arterial or venous thromboembolism, the risk of recurrent ICH and the overall state of the patient. For patients with a comparatively lower risk of cerebral infarction (e.g. atrial fibrillation without prior ischaemic stroke) and a higher risk of amyloid angiopathy (e.g. elderly patients with lobar ICH) or with very poor overall neurological function, an antiplatelet agent may be an overall better choice for prevention of ischaemic stroke than warfarin. In patients with a very high risk of thromboembolism in whom restarting warfarin is concerned, warfarin therapy may be restarted at 7–10 days after onset of the original ICH.

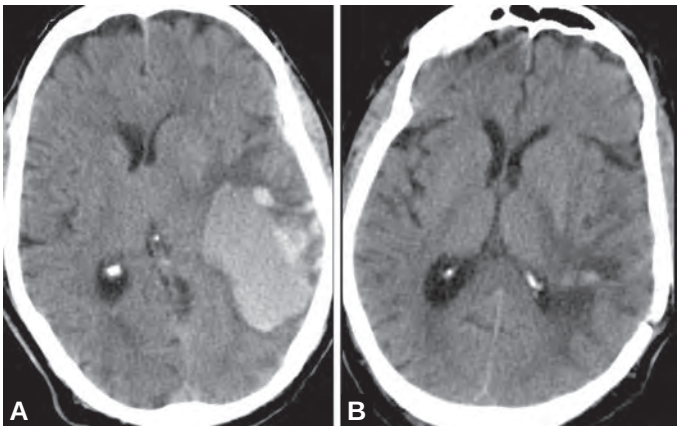
SURGICAL MANAGEMENT

To achieve the goals of surgical treatment,[23] the specific aims may include decompression to reduce or prevent elevated intracranial pressure and removal of the acute haematoma to reduce mass effect and toxicity to the surrounding brain. Several surgical options exist that vary in the degree of invasiveness and associated morbidity. These options include ventriculostomy, stereotactic aspiration of haematoma with or without rt-PA, endoscopic haematoma evacuation, craniotomy for evacuation of haematoma and hemicraniectomy for

decompression with or without evacuation of haematoma. The role of ventriculostomy is clear in patients with elevated intracranial pressure due to obstructive hydrocephalus, but no studies have directly evaluated the effect of ventriculostomy alone on the outcome of ICH patients. [Craniotomy is the most studied modality and is the most common surgical technique used. A complete evacuation under direct vision can be performed, which facilitates exploration for vascular lesions and control of bleeding sources[2]].

Of all the surgical therapies described for treating ICH, craniotomy has been the most extensively studied (Figs 1A and B) with 7 of the 9 randomised controlled surgical trials reporting results with craniotomy either primarily or exclusively.[2,4] The International Surgical Trial in Intracerebral Haemorrhage (STICH) randomised 1,033 patients from 107 centres over an 8-year period, beginning in 1995.[22] Patients were eligible if randomised within 72 hours and operated on within 96 hours of ictus for a clot >2 cm in diameter. Patients in very poor condition (GCS score <5) were excluded. Patients were randomised if the neurosurgeon was uncertain of the benefit of surgery, with 50% randomly assigned to a policy of either early surgery or initial medical management. Primary outcomes were the incidence of death and disability as measured by the extended Glasgow Outcome Scale (GOS) at 6 months, and secondary outcomes were death, the Barthel Index (BI) and the modified Rankin Scale (mRS) at 6 months.

Five hundred and six patients were randomised to surgery and 530 to medical therapy, with groups being well matched for all known variables. Twenty-six percent of the medical arm ultimately crossed over to surgery. This crossover was due to re-bleeding or deterioration in 85% of crossover subjects, and craniotomy was used in 85% in those subjects who crossed over to surgery. By contrast, only 75% of patients in the primary surgical arm underwent craniotomy, with the others being treated with less invasive surgical techniques.



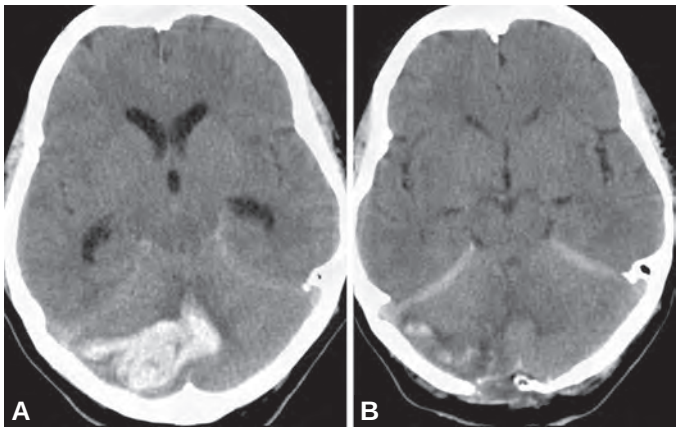
Figs 1A and B: (A) A 64-year-male patient, a hypertensive, presented with a large left temporal haematoma causing significant midline shift. (B) Surgical evacuation of the haematoma was done with complete regression of midline shift

Ninety-three per cent of patients were available for analysis at 6 months.

In an intervention-to-treat analysis, surgery within 96 hours of ictus was associated with a statistically insignificant absolute benefit of 2.3% (95% CI—3.2% to 7.7%) at 6-month follow-up. With GCS score of 9–12, those with lobar clots, and those with clots <1 cm from the surface who may have been helped by early surgery did not benefit statistically significantly. In contrast, those presenting in deep coma (GCS score 5–8) tended to do better with medical management. It must be remembered that the trial was based on the principle of clinical equipoise; patients whom the local investigator felt would most likely benefit from emergency surgery were not enrolled in the study. Thus, the STICH trial may not be applicable to certain subsets of patients who traditionally are thought to be good candidates for surgery, particularly young individuals with large lobar haemorrhages rapidly deteriorating due to mass effect. Moreover, the STICH results must be interpreted with caution because the high crossover from the medical group to surgery (140 out of 530 patients).[2]

Although the preponderance of evidence suggests that routine surgical evacuation of supratentorial haematomas is not superior to medical treatment alone, surgery may be beneficial in a subset of patients.[2] Surgery via craniotomy shows a trend towards benefit in patients with superficial clots located less than 1 cm from the surface and those with moderate initial impairment [Glasgow coma score (GCS), 9–12] and subsequent deterioration.[27] Both the American Heart Association (AHA)[4] and the European Stroke Initiative Writing Committee (EUSI)[35] guidelines recommend considering surgery in these limited situations. Otherwise, the AHA and EUSI guidelines agree on several points. Deep haemorrhages do not benefit from craniotomy, and there is limited evidence suggesting that minimally invasive treatment may be beneficial in patients with significant mass effect. Also, deeply comatose and very old patients have not been shown to benefit from surgery.

These randomised trials of surgery did not include patients with cerebellar haemorrhage. Despite a paucity of class I data regarding cerebellar haematomas, retrospective data suggest that surgical evacuation for patients with clots larger than 3 cm, hydrocephalus, or evidence of brainstem compression leads to improved outcomes (Figs 2A and B).[8,35,37] In these patients, medical management alone often results in bad outcomes. Smaller cerebellar haemorrhages without brainstem compression that are medically managed do reasonably well. For these reasons, neurosurgeons and neurologists have advocated that large cerebellar haemorrhages with compression of the brainstem or obstruction of the fourth ventricle should be surgically removed as soon as possible. Both the American Heart Association (AHA)[4] and the European Stroke Initiative writing committee (EUSI)[35] guidelines recommend considering surgery in large cerebellar haematomas.



Figs 2A and B: (A) A 47-year-old female patient presented with a large cerebellar bleed with effacement of fourth ventricle and mass effect on the brainstem. (B) CT scan done after surgical evacuation of haematoma revealed opening up of CSF spaces around the brainstem. The patient made an almost complete recovery

Minimally Invasive Surgery

The purported advantages of minimally invasive clot evacuation over conventional craniotomy include: (1) reduced operative time; (2) the possibility of performance under local anaesthesia and (3) reduced tissue trauma, especially for deep lesions. Together, these advantages may also facilitate earlier evacuation of ICH than is possible or practical with conventional craniotomy. On the other hand, the reduced surgical exposure, the inability to treat structural lesions (arteriovenous malformation or aneurysm), the potential for re-bleeding related to the use of fibrinolytics, and the possibility of an increased risk of infection related to prolonged indwelling catheters are limitations of this approach.

Endoscopic Aspiration

Endoscopic aspiration of supratentorial haemorrhage was studied in a small, single-centre randomised trial.[3] One hundred patients between 30 and 80 years of age, with haemorrhages at least 10 ml in volume, received treatment within 48 hours of onset via burr hole and continuous neuroendoscopic lavage of the haematoma cavity with artificial CSF at a pressure of 10–15 mmHg. The mixture of blood clots and blood stained CSF was removed by suction at regular intervals. More than 90% of the clot was evacuated in 15% of patients and between 70% and 90% in 30% of patients, with all patients having at least a 50% reduction in size. At 6 months, the mortality rate of the surgical group (42%) was significantly lower than that of the medical group (70%, P = 0.01). A good outcome with minimal or no deficit was also seen more frequently in the surgically treated group. In patients with large haematomas (50 ml), quality of life was not affected by surgery, but the mortality rate was significantly lower. By contrast, endoscopic evacuation of smaller haematomas led to a significantly better quality of life versus those treated medically, but survival was similar for the two groups. Moreover, the benefit was mainly limited to patients with lobar haematomas and patients less than 60 years of age.

The study by Cho DY et al. compared endoscopic surgery, stereotactic aspiration and craniotomy in non-comatose patients with spontaneous basal ganglia haemorrhage.[7] Ninety non-comatose patients with basal ganglia haemorrhages were randomised into three groups: group A (n = 30) underwent endoscopic surgery; group B (n = 30) underwent stereotactic aspiration and group C (n = 30) underwent craniotomy. There was significant delay in waiting time for stereotactic aspiration. Craniotomy had the longest operation time. Blood loss was most significant in the craniotomy group. The highest haematoma evacuation rate was seen in the endoscopic surgery group. The mortality rate was 0% in group A, 6.7% in group B, and 13.3% in group C (P = 0.21). The complication rate was 3.3% in group A, 10% in group B, and 16.6% in group C (P = 0.62). The most major complications were re-bleeding and infection. The FIM score was higher in the endoscopic surgery group than in the craniotomy group. The Barthel index score was also significantly better in endoscopic surgery than in craniotomy. However, the STICH trial suggests that subjects treated with any non-craniotomy approach in the trial had a worse outcome than those treated with conservative management (OR 1.3), but the confidence interval included 1 (95% CI—0.78 to 2.35). It is unclear whether the pathology chosen for these approaches was less ideal for intervention, because patients with deep haemorrhages and those in poor neurological condition (both of whom fared worse in the trial) were likely those most commonly chosen for minimally invasive techniques.

Thrombolytic Therapy and Aspiration of Clots

A multicentre randomised controlled trial (n = 71 patients) examined the utility of stereotactic urokinase infusion when administered within 72 hours for those patients presenting with GCS score >5 and clots of >10 ml.[36] Treated patients received 5,000 IU of urokinase every 6 hours for a maximum of 48 hours. Primary endpoints were death and degree of functional handicap (measured with the mRS) at 6 months. The median reduction in volume of ICH from baseline was 40% in the surgical group and 18% in the medical group. The re-bleeding rate was 35% in the urokinase group and 17% in the conservatively managed group. A significant reduction in death (40%) was found in the treated group, but no statistically significant difference in functional outcome scores was detected at different intervals of treatment.

Installation of tPA for clot evacuation in patients with severe IVH has been studied. Rohde et al. reported that IVH disappeared earlier (1–3 days) with tPA than with urokinase (5–8 days).[29] Compared with ventriculostomy alone, IVH treated with the addition of tPA decreased the mortality rate from a range of 60 to 90% to only 5%.

Other similar studies have indicated that the use of intraventricular tPA might improve the prognosis in patients with large IVHs.[9,21] The review of the current literature suggests that the use of intraventricular fibrinolytics carries a low incidence of complications, which usually consist of infections and haemorrhage.[9,21,26,34]

More recently, tPA has been used in the treatment of ICH. In pilot human trials, Lippitz et al.,[17] Schaller et al.,[31] and Vespa et al.[39] reported that daily administration of tPA into the haematoma cavity beginning 12–24 hours after stereotactic placement of a catheter resulted in an average 85% reduction in the haematoma volume by 2–4 days after onset.

Preliminary findings of the minimally invasive surgery plus rt-PA for intracerebral haemorrhage evacuation (MISTIE) clinical trial have been published.[24] Subjects randomised to surgery underwent stereotactic catheter placement and clot aspiration. Injections of rt-PA were then given through the haematoma catheter every 8 hours, up to 9 doses, or until a clot-reduction endpoint. After each injection the system was flushed with sterile saline and closed for 60 minutes before opening for spontaneous drainage. Average aspiration of clots for all patients randomised to surgery plus rt-PA was 20% of mean initial clot size. After the acute treatment phase (aspiration plus rt-PA), the clot reduced by an average of 46%. Recorded adverse events were within safety limits, including 30-day mortality, 8%; symptomatic re-bleeding, 8%; and bacterial ventriculitis, 0%. Patients randomised to medical management showed 4% clot resolution in a similar time window. Preliminary analysis indicated that clot resolution rates are greatly dependent on catheter placement. Location of ICH also affects efficacy of aggressive treatment of ICH.

The usefulness of minimally invasive clot evacuation utilising a variety of mechanical devices and/or endoscopy requires further testing in clinical trials; therefore, its current usefulness is unknown. Similarly, although stereotactic infusion of thrombolytic drugs into the clot cavity apparently reduces clot burden and risk of death, re-bleeding is more common and functional outcome is not improved; therefore, its usefulness is unknown.[4]

Decompressive Craniotomy

This technique has been reported to be beneficial in a number of conditions, including hemispheric ischaemia stroke and ICH associated with aneurysmal subarachnoid haemorrhage. To date, no prospective randomised controlled trials show a convincing beneficial effect on outcome for spontaneous ICH. In one series, 12 consecutive patients with hypertensive ICH were treated with decompressive hemicraniectomy.[25] Eleven patients (92%) survived, and 6 of them (54.5%) had a good functional outcome. This calls for further rigorous controlled trials, which may identify a subgroup of patients in whom this technique might prove to be worthwhile.[4]

Timing of Surgery[4]

No clear evidence at present indicates that ultra-early craniotomy improves functional outcome or mortality rate. Operative removal within 12 hours, particularly when performed by less-invasive methods, has the most supportive evidence, but the number of subjects treated within this window is very small. Very early craniotomy (within 4 hours) may be associated with an increased risk of recurrent bleeding.

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102 Surgery for Stroke

Vincent Thamburaj A

Stroke is the second commonest cause of death in India with a crude overall prevalence rate of 220 per 100,000.[105] With an increasing aging population at risk, the stroke burden can be expected to reach epidemic proportions. Irreversible disability is traditionally associated with cerebral vascular disease (CVA), and it is estimated that there are two million fatalities from vascular disease every year. Its incidence is rising with increasing life expectancy.[332]

Arterial thrombosis and atherosclerosis with occlusion of the cerebral arteries is considered as the single most common cause of stroke in more than 50% of patients. Around 30–50% of the cases have had previous transient ischaemic attacks (TIAs). TIAs may be caused by embolism arising from an atheromatous carotid lesion or from reduction in cerebral blood flow due to atheromatous occlusion. Coronary artery disease and rheumatic heart diseases are responsible for most of the cardioembolic strokes. Other rarer causes include trauma to the carotid/vertebral arteries, collagen diseases, moyamoya disease, fibromuscular dysplasia, vasospastic conditions [subarachnoid haemorrhage (SAH), migraine, etc.], and the conditions which alter the rheological properties of the blood such as, polycythaemia, leukaemia, etc. Epidemiological studies involving twins, siblings or families have found evidence of a genetic influence on stroke.[37,332] The most notable difference in India from the Western countries is the predominance of intracranial rather than extracranial location of large artery atherosclerosis.[61,170,252] Therefore, there is a need to find an alternative surgical intervention for the predominantly intracranial pathology found in the Indian population.

There are risk factors such as hypertension, hypercholesterolaemia, atherosclerosis, cardiac abnormalities, diabetes mellitus, obesity and lack of physical activity. Major risk factors identified in India are hypertension (>95 mmHg diastolic), hyperglycaemia, tobacco use (smoking/chewing) and low normal haemoglobin levels (less than 10 gm).[59]

CLINICAL FEATURES

Clinical presentations of cerebral ischaemia are commonly classified into:

1. TIA is traditionally defined as an episode of focal neurological dysfunction as a result of ischaemia and resolves completely within 24 hours. Most of them last for about 10 minutes. The proposed new definition of TIA is a "brief episode of neurological dysfunction caused by a focal disturbance of brain or retinal ischaemia, with clinical symptoms typically lasting less than 1 hour, and without evidence of infarction".[7] With the new definition, patients who have transient focal symptoms of brain ischaemia and who, on diagnostic evaluation, are found to have an acute infarction, would no longer be classified as having a TIA, regardless of the duration of clinical symptoms. With this new definition, the difference between a TIA and a stroke becomes similar to the distinction between an episode of angina pectoris and a myocardial infarction. TIAs are an important determinant of stroke, with 90-day risks of stroke reported as high as 10.5% and the greatest stroke risk apparent in the first week.[151,271]
2. 'Crescendo' TIAs describe a cluster of attacks occurring at increasing frequency or duration over a few hours or days. The patients are at risk of imminent brain infarction.[283]
3. Prolonged reversible ischaemic defect is one where the signs and symptoms last longer than 24 hours, followed by complete recovery within 3 weeks. They have a stuttering or gradual onset unlike a TIA, which has an abrupt onset; they are most likely to be due to cardiogenic embolism. It is prudent to treat these patients as threatening stroke patients.
4. Progressing stroke/stroke in evolution is one where the deficit continues to progress in a stepwise fashion despite adequate medical therapy. It appears to be more common in the vertebrobasilar territory and 50% of the patients will die if untreated.
5. Completed stroke is a stable, focal ischaemic neurological deficit. There may be sudden unheralded progressive neurological deficit (embolic stroke) or the deficit, more commonly, becomes complete in a few hours (thrombotic stroke). It is usually associated with altered sensorium in a few hours (thrombotic stroke).

The earliest sign of the CVA is TIA. Monocular blindness, dysphasia, localised sensory loss and hemiparesis are some of the symptoms that strongly suggest a focal ischaemic episode, and the location of the symptoms defines the vascular distribution of the ischaemia.

Other symptoms, such as diplopia alone, syncope, etc. are far less specific symptoms.[240]

Carotid Territory

The classic history for TIA in the carotid system is one of abrupt onset of contralateral weakness or numbness of the arm or leg. Dysphasia occurs if the dominant hemisphere is involved. Impaired vision of the eye on the side of diminished carotid flow takes place.[240] There are five clinical findings which would make one suspect involvement of the carotid arteries: (1) Blindness in one eye during the TIA attack; (2) Emboli in the retinal vessels; (3) Bruit over the carotid artery; (4) Significant lowering of the retinal arterial pressure on the affected side; (5) Any sign of retinal artery ischaemia. Associated carotidynia (pain over the carotids) suggests a carotid pathology.

The more common shade or curtain altitudinal symptoms suggest reduced circulation to the posterior ciliary arteries or circle of Zinn, which is more likely to be susceptible to the effects of reduced blood flow.[256] The uncommon wedge shaped visual defects, typical of central retinal artery branch occlusion is due to an embolus.

Vertebro-Basilar Territory

Damage to this system is also characterised by a very swift onset of symptoms with neurological phenomena such as ataxia, monoparesis, hemiparesis, quadriplegia, numbness (frequently shifting from one side to the other), vertigo, defects in either visual field, diplopia, dysarthria, aphasia and, occasionally, clouding of consciousness. Vertigo is perhaps the most common symptom of TIA in this distribution.[240]

Vertebro-basilar TIAs are mainly flow related. The incidence of vertebral, subclavian, and brachiocephalic artery stenosis may be as high as 17% in patients with cerebral ischaemia, especially with posterior circulation symptoms.

Attention should be given to the tempo and localisation of the clinical syndrome, as multiple and hemispheric TIAs are associated with the greatest incidence of early stroke. Evaluation of TIAs depends on the clinical symptoms, physical examination and investigations. Attention should also be given to clinical evidence of generalised atherosclerotic disease, as death due to the complications of ischaemic heart disease is the commonest outcome in patients with TIA. Early attention should focus on risk factor modification, with emphasis on the treatment of hypertension and smoking cessation.

Investigations

TIAs should be regarded as an emergency. The risk of stroke is greatest in the weeks following TIA and patients should be referred for further investigations as the earliest.[121] The initial evaluation of a patient in whom a TIA is suspected should include laboratory tests, electrocardiography and imaging studies. Imaging of the head may reveal a non-ischaemic cause, such as a tumour or subdural haematoma, and may provide information about the cause of ischaemia.[98] It is recommended that CT or MRI of the head be part of the evaluation of all patients. Doppler ultrasonography[24] or other noninvasive investigations of the carotid arteries should be performed rapidly, ideally within 24 hours. CT will demarcate the area of ischaemia and exclude haemorrhage and also show previous infarcts, if any. Small lacunar infarcts suggest an arteriolar pathology (of the penetrating branches of major cerebral arteries). Wedge shaped infarcts suggest thromboembolism. Ill-defined border zone infarcts suggest haemodynamic ischaemia.

Fig. 1: CT angio-ICA occlusion

CT angiography[30] of cervical vessels reveals enough vascular details to be useful as a diagnostic screening method in patients with presumed atherosclerosis of the carotid bifurcation and accurately excludes and detects aneurysms and AVMs (Fig. 1).[57] MRI is more sensitive, in particular for previous vascular episodes. MR Angiography, a noninvasive test, can yield information regarding collateral blood flow and is nearly as effective as conventional angiography in estimating disease at the carotid bifurcation. It is suitable for replacing the invasive conventional angiography method in most (Fig. 2).[45,62,266]

Further technical developments with regard to spatial resolution are still required for improved visualisation

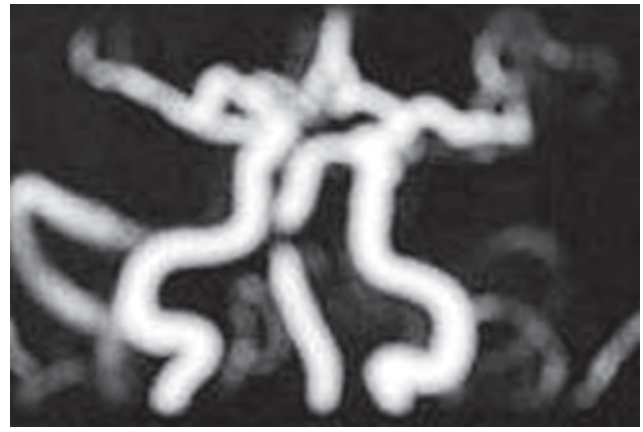


Fig. 2: MR angio-basilar occlusion

of small vessels and terminal branches of intracranial vessels.

Ultrasonography, being cost effective, should be used as a screening tool to exclude patients with no carotid artery disease from further testing. Ultrasound evaluation of carotid artery morphology and flow has been widely accepted as a noninvasive measure and has replaced ophthalmodynamometry and oculoplethysmography that offer an indirect indication of ipsilateral carotid occlusion (Fig. 3).[103,250]

B-mode ultrasound imaging provides images of various levels, or planes, enabling the creation of a 3D image of the carotid artery wall and surrounding structures.[325] This technique provides information on the type and extent of arterial damage, but blood clots sometimes do not appear and the method cannot distinguish a severely narrowed from a completely occluded artery.

Doppler testing measures the speed of arterial blood flow. Duplex ultrasound (DUS) combines B-mode imaging and Doppler to provide more detail on the condition of the arteries than either test alone can provide (Fig. 4).[310,311] DUS may be more sensitive than angiography in determining the presence of ulceration.[284] However, its reliability is highly dependent on the technician. The recent availability of ultrasound contrast agents helps to distinguish between pseudo and true occlusions, improves ultrasound images and should help to reduce operator variability.[41]

Transcranial Doppler (TCD) assesses intracranial arterial flow in the distal internal carotid artery (ICA), the middle, anterior and posterior cerebral artery stems, and the ophthalmic artery. The haemodynamic significance of extracranial and intracranial ICA occlusion and the availability of collateral circulation may be studied satisfactorily.[12,241] Transorbital (ophthalmic artery), submandibular (distal ICA), transtemporal (anterior cerebral, middle cerebral and posterior cerebral) and foramen magnum (posterior circulation) approaches are employed for a comprehensive assessment. Serial TCD examination may reveal dynamic changes in cerebral circulation that may be missed on a single MRA study.[5]

Pre-operative TCD can be used to identify patients who do not require a shunt during carotid endarterectomy.[341] In acute ischaemic stroke, TCD can be used to elucidate stroke mechanisms, plan and monitor treatment, and determine prognosis. In an era, when stroke is increasingly being recognised as an emergency requiring immediate treatment, TCD may be capable of providing rapid information about the haemodynamic status of the cerebral circulation.[265]

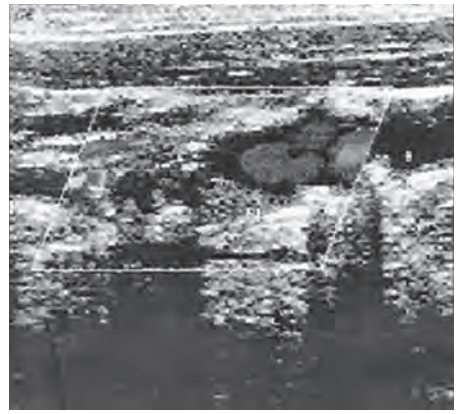


Fig. 4: Colour Doppler—grossly reduced colour flow in the left ICA

Conventional four vessel arteriography should include cerebral, carotid and aortic arch studies and with cross carotid compression. One may also find post-stenotic lesions of the bifurcation, patency of the anterior cerebral vessels, absence of the vertebral artery, occlusion of the vertebral artery and partial occlusion of the internal carotid vessels (Fig. 5). Internal carotid patency along with cross filling of the anterior, middle cerebral and the posterior communicating vessels may be evaluated. However, conventional arteriography fails to demonstrate some vascular mural changes that may be responsible for the development of clinical manifestations, such as intraplaque haemorrhage and thrombus attached to the arterial wall. These mural changes may be identified with duplex ultrasound and CT angiography.[57,80] With increasing experience with noninvasive imaging, angiography may be required less often.

Doppler C02/Acetazolamide (diamox) test: Cerebral blood flow (CBF), measured early after acetazolamide administration, could be useful to confirm the clinical

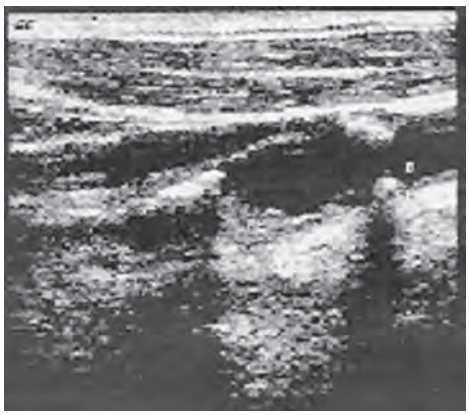


Fig. 3: Real time B mode—plaques at the bulb and left internal carotid artery ICA

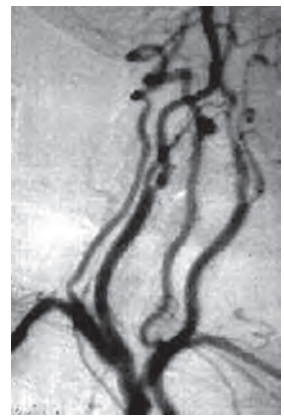


Fig. 5: ICA occlusion-DSA

diagnosis of TIA. No increase in CBF during hypercapnia or following acetazolamide suggests that the cerebral arterioles are maximally dilated and the procedures to improve the blood flow, such as EC-IC bypass will not help.[286,299]

Single-photon emission computed tomography (SPECT) studies combine nuclear medicine with computed tomography. Used in the early hours after infarction, cerebral SPECT is able to reveal a deficit in local blood flow before changes appear on CT or MRI. However, SPECT does not reliably distinguish between haemorrhage and infarction. In patients who are marginal candidates for endarterectomy, the haemodynamic effect of stenosis on cerebral perfusion may be assessed with SPECT and is useful in predicting neurological outcome in ischaemic stroke patients.[57]

Positron emission tomography (PET) can be used to measure CBF, cerebral blood volume (CBV) and metabolism (CMR). Patients with low CBF and high oxygen extraction (OEF) have compromised cerebral circulation and are expected to benefit from revascularisation. These studies are helpful in an established stroke, and to differentiate between flow-related TIAs, and thromboembolic TIAs.[250] SPECT and PET are not sufficiently widely used in clinical practice.

SURGERY FOR STROKE PREVENTION

Carotid occlusive disease is the primary pathophysiological source of 10–20% of all strokes.[287] The risk of a first or recurrent stroke has been found to increase with the degree of severity of the carotid stenosis, although a linear relationship between degree of stenosis and risk of stroke has not been demonstrated.[356]

Carotid occlusive disease may be caused by a variety of disorders; but the great majority of strokes of carotid origin are related to atheromatous narrowing of these arteries.[88,198] Atherosclerotic lesions are almost invariably present at multiple sites.[88] These include the origins of the carotid and vertebral arteries, the carotid bifurcation, the cavernous ICA, the basilar artery and the middle cerebral arteries. Significant atheromatous disease in these sites is associated with the presence of similar lesions in the coronary circulation.[314] Fibromuscular dysplasia is a non-inflammatory vasculopathy and is the second most common cause of extracranial carotid stenosis[202] usually at the level of C2–C3, with sparing of the proximal ICA at the bifurcation.[54]

Dissections of the cervical carotid artery have been categorised as traumatic or spontaneous. Spontaneous dissections can be associated with atherosclerosis or fibromuscular dysplasia. Traumatic dissections typically involve the distal extracranial ICA and are thought to originate from impingement of the artery against the C2 transverse process during rotation with extension of the neck.[227]

Radiation induced stenosis is an occasional cause. Murros and Toole summarised the existing literature regarding radiation injury to large arteries and concluded that, although radiation occasionally accelerates atherosclerotic lesions, doses in excess of 5,000 Rads are required to produce significant changes.[235]

Direct Revascularisation Procedures

Carotid Territory

Carotid endarterectomy (CEA): The use of carotid endarterectomy (CEA) in the prevention of ischaemic stroke was first described in 1954[73] and has been the most widely accepted surgical procedure for prophylaxis of stroke since. By symptomatic presentation or pathological criteria, the majority of cerebral ischaemic events correspond to embolic phenomena.[85,91,96,101,247] Removal of the stenotic, atheromatous lesion eliminates potential sites of thrombi, thereby eliminating a potential source of emboli and improve cerebral blood flow.

Indications[40,63]: Carotid occlusive disease can be clinically divided into two types: (i) Symptomatic and (ii) asymptomatic. Symptomatic carotid stenosis usually refers to ischaemia in the distribution of the ipsilateral stenotic ICA resulting in TIAs, amaurosis fugax or completed stroke.[256] A diagnosis of asymptomatic disease is made in patients with any of the following:

1. Incidentally found carotid bruit.
2. Cerebrovascular symptoms referable to one carotid artery territory, and demonstration of an asymptomatic contralateral carotid artery stenosis or ulceration.
3. Patients, scheduled to undergo general or cardiac surgery with auscultatory or radiographical evidence of carotid artery disease.

Prospective co-operative studies confirm that surgery has a role in the treatment of this disease. A review of these trials is imperative if these data are to be applied to an individual patient.

In 1991, the North American Symptomatic Carotid-Endarterectomy Trial (NASCET)[238] and the European Carotid Surgery Trial (ECST)[81] concluded that carotid endarterectomy is highly beneficial to patients with high-grade stenosis greater than 70% of the ICA. A reanalysis of the final results of the ECST and NASCET suggested that CEA is highly beneficial for 70–99% stenosis and moderately beneficial for 50–69% stenosis. Patients with a stenosis less than 30% need not be operated.[282] Benefit in patients with near total carotid occlusion is marginal in the short-term and uncertain in the long term.[281] Patients with transient monocular blindness only, especially those with few risk factors, and women with few risk factors may be harmed by endarterectomy. The benefit is muted in those presenting with lacunar stroke as well.[20]

Early endarterectomy for severe carotid artery stenosis after a non-disabling ischaemic stroke can be performed with rates of morbidity and mortality comparable to those who receive delayed endarterectomy.[76,100]

The estimated prevalence of intracranial atherosclerotic disease in patients with stenosis of the extracranial ICA varies between 20% and 50%. The benefits of carotid endarterectomy in patients with both intracranial atherosclerotic disease and symptomatic extracranial ICA stenosis are uncertain.[160]

Indications for asymtomatic carotid stenosis are still unclear. In 1995, the Asymptomatic Carotid Atherosclerosis Study (ACAS)[82] looked at the benefits of surgery in patients with narrowing in the carotid artery in the range of 60–99% stenosis. The study showed that over 5 years, the risk of stroke or stroke and death caused by narrowing in the affected artery were reduced from 11% to 5.1%. There was no evidence of any more or less benefit as the narrowing approached 99%. The Asymptomatic Carotid Stenosis Trial (ACST)[113] study essentially confirms and extends the findings of the ACAS trial. ACST confirms there is overall benefit from carotid surgery in patients with asymptomatic carotid narrowing of 60–99% in patients under the age of 75 years. In patients over the age of 75 years, potential benefits are uncertain. Probably, most importantly, the ACST study clearly showed a reduction in the risk of fatal or disabling stroke following carotid surgery. The two studies together provide very strong evidence of a benefit for carotid surgery in highly selected patients with asymptomatic carotid disease.

The most recent extensive analysis[267] recommends the following for stroke prevention:

a. Patients with recent TIA or ischaemic stroke within 6 months and ipsilateral severe (70–99%) carotid artery stenosis should receive CEA by a surgeon with a morbidity and mortality of less than 6%.
b. Patients with recent TIA or stroke with moderate carotid stenosis (50–69%) may have CEA depending on comorbid factors, whereas CEA is not recommended for those with less than 50% stenosis.
c. When CEA is recommended, surgery should be performed within 2 weeks.
d. In those with symptomatic severe stenosis greater than 70% in whom the stenosis is difficult to assess, carotid angioplasty is not inferior to CEA, and may be considered.
e. Among patients with symptomatic carotid occlusion, extracranial-intracranial bypass is not routinely recommended.
f. Endovascular treatment[196] of patients with symptomatic extracranial vertebral stenosis may be considered when patients are having symptoms despite medical treatment.
e. For those with haemodynamically significant intracranial stenosis who have symptoms despite medical therapy, the usefulness of endovascular therapy is uncertain.

In clinical practice, surgeons must manage patients whose risk of stroke varies greatly. In our practice, the ideal patient for carotid endarterectomy is one who presents with a history of TIA, hemispheric[309,353] or retinal and has no neurological deficit on physical examination and who has a stenotic lesion at the origin of the ICA. Individual selection is applied in traumatic occlusion of the carotid and spontaneous dissection of the carotid, and progressive stroke despite all medical measures.

Surgical Risk Factors

To maximise the benefits of surgery, careful pre-operative risk assessment and the maintenance of low rates of major peri-operative complications are mandatory.
The risk of stroke and death from carotid endarterectomy is related to clinical and angiographic characteristics.[222] Reina Gutierrez et al.[269] suggest that the patient's risk profile has a greater influence on the results than the technique used. Several baseline patient characteristics predict surgical risk.

The patients may be classified into the following four groups to assess the risk factor:[302]

Group 1: Neurologically stable without medical or angiographic risk.
Group 2: Neurologically stable without medical, but with angiographic risk.
Group 3: Neurologically stable with medical and with or without angiographic risk.
Group 4: Neurologically unstable with or without medical/angiographic risks.

Events at presentation, recent history of stroke, stroke in progression, frequent TIAs, female sex, systolic hypertension and peripheral vascular disease are independent risk factors.[32,222] Patients with hypertension and chronic hemispheric hypoperfusion with impaired autoregulation are at risk.[259] 'Silent' cerebral infarction is found in 20–30% of patients with significant ICA disease and they seem to be at increased risk of peri-operative stroke.[119]

Evidence of ICA thrombus and ICA stenosis near the carotid siphon suggest a peri-operative risk.[216] Extensive ICA pathology and high common carotid bifurcation present a technical difficulty. Collaterals are associated with a lower risk of hemispheric stroke and TIA, both long term and peri-operatively.[120] Diastolic flow velocities within severe ICA stenosis are dependent on the level of the collateral perfusion pressure distal to the stenosis (i.e. high values indicate a low ICA stump pressure), which seems to be a risk factor for early post-operative strokes.[354] Contralateral stenosis and low stump pressures can be used in combination to identify high-risk patients likely to develop neurological complications during or following endarterectomy.[39]

As in any form of major surgery, patients with hypertension, chronic obstructive airway disease, obesity and congestive cardiac failure are at risk. Carotid endarterectomy performed in preparation for coronary artery bypass surgery with a history of angina carries a risk.[222]

There is a widespread belief, unsupported by reports, that carotid artery stenting (CAS) is advisable in high-risk patients. Lower rates of cranial nerve injury[263] and restenosis[261] have been reported with CAS. Over

all, results of carotid endarterectomy are superior to similar data regarding CAS. As of now, use of stenting in those with high risk for endarterectomy should be deferred.[165,234]

Surgical Technique

Pre-operative counselling is important as preparation of the patient mentally helps a great deal in overcoming the fear and anxiety. If the patient is on antiplatelets already, ASA may be continued through the procedure, but Clopidogrel is stopped two days pre-operatively in our practice.

In the operating room the patient is sedated with 1 mg midazolam intravenously after securing venous access and arterial pressure monitoring catheter. Arterial pressure is monitored continuously as fluctuations during the procedure can affect the cerebral circulation.

Positioning of the patient is extremely important as hyperextension of the neck may kink the vertebrals, which will be the likely source of blood supply during cross clamping of the ICA.

Intra-operative Monitoring

1. Electroencephalography is widely available and correlates well with diminished hemispheric cerebral blood flow and is a valuable tool for determining the need for shunting during carotid endarterectomy.[293] A statistically significant increase in intra-operative stroke rate is associated with the development of an abnormal EEG (1.1%), contralateral ICA occlusion (1.8%) and the combination of both (3.3%).[83]
2. Somatosensory evoked potentials (SSEP), if available, is an ideal monitoring modality under general anaesthesia, and indicates critical cerebral hypoperfusion during cross clamping, with high sensitivity and specificity. Progressive reduction of up to 50% of N20, P25 amplitude suggests cerebral ischaemia. SSEP not only helps to identify patients with insufficient collateral blood flow who benefit from specific cerebral protection, such as shunt, but also to avoid improper and hazardous application of these measures in patients with sufficient cerebral perfusion. In addition, correct shunt function is immediately indicated by recovering potentials.[68]
3. Measurement of ICA stump backpressure helps in deciding on the need for a shunt. Reports suggest that surgery without a shunt when the ICA backpressure is low (< 50 mm Hg), produces a significant deficit.[118,322]
4. Transcranial Doppler (TCD) detects high blood flow velocities. The peri-operative stroke rate can be reduced by taking appropriate measures based on findings of TCD monitoring.[242,303] The clinical significance of bilateral flow velocity increases soon after surgery is uncertain, but very high blood flow velocities might be a signal for cerebrovascular hyperfusion.[355] In those patients, increased post-operative surveillance is recommended.

The usefulness of monitoring cerebral function during the procedure is closely related to the experience of the surgical team. No one method of monitoring in selective shunting has been shown to produce better outcomes. No prospective randomised or quasi-randomised trials have been performed and the conclusions therefore remain unchanged.[22,32,33,328] Recommendations, whether to practice cerebral monitoring or not, and what method should be used for this purpose, cannot be given presently.

Procedure

We prefer regional anaesthesia as it obviates the need for extensive intra-operative monitoring for cerebral ischaemia. Assessment of cerebral perfusion can be made by direct interaction with the patient. This is by far the best mode of assessment of cerebral perfusion when compared to other modalities such as TCD and SSEP. A randomised controlled trial comparing general anaesthesia and cervical block found no significant differences in mortality or morbidity.[192] Propofol has no significant effect against neurological complications in CEA patients.[237]

Regional anaesthesia is obtained by both superficial and deep cervical block. Deep cervical block involves infiltration of local anaesthetic agents around C2, C3 and C4 at the exit foramina. Superficial block involves infiltration around the cervical plexus at the lateral border of the sternocleidomastoid muscle at the level of the external jugular vein. We use approximately 40cc of 0.375% bupivacaine as the resultant anaesthesia lasts as long as 6–8 hours. Just before making the skin incision the patient is given Fentanyl 25 mg intravenously for additional sedation.

A long high incision is made along the anterior border of the sternomastoid muscle, almost to the mastoid tip (Fig. 6). It often necessitates the division of a branch of the great auricular nerve as it crosses the anterior margin of the sternomastoid muscle, resulting in, usually, temporary ear and/or lower jaw skin numbness.

The plane beneath the investing fascia of the neck is followed under the sternomastoid muscle, and after the

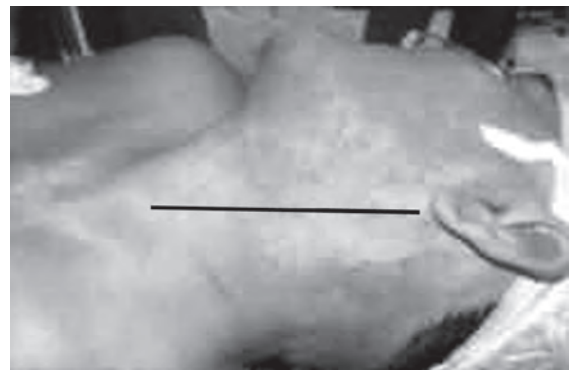


Fig. 6: Skin incision

sternomastoid muscle is mobilised, blunt self-retaining retractors are used to expose the underlying areolar tissue, beneath which lies the internal jugular vein and carotid sheath.

Sharp dissection is continued, first skeletonising the internal jugular vein and the common facial vein. The common facial vein and any nearby vein emptying directly into the internal jugular vein are divided so that the jugular vein can be retracted posteriorly, exposing the carotid arteries beneath (Fig. 7).

The carotid sheath is opened to expose the common carotid artery above the upper margin of the overlying omohyoid muscle, and dissection proceeds distally to the bifurcation and to the external and internal carotid arteries.

It is necessary at all times, but particularly at this stage to handle the tissues gently and disturb the arteries from their bed as little as possible, especially when manipulating the ICA near the plaque. It is not wise to palpate the plaque within the ICA, which is usually located at the site where the artery is most adherent to adjacent tissues, because of the risk of dislodging an intraluminal thrombus into the cerebral circulation. The sinus nerve at the bifurcation of the carotids is blocked with 1% lignocaine during carotid dissection.

During distal exposure of the ICA, care is taken not to injure or excessively manipulate the hypoglossal, vagus and accessory nerves, although the latter is high and posterior in the carotid sheath and infrequently exposed. The hypoglossal nerve, which is routinely exposed, descends deep to and beneath the digastric muscle and curves forward superficial to the external carotid artery; it often can readily be traced to this location by following a branch, the descendens hypoglossi, proximally from its course within the carotid sheath. Vessel loops are then passed around the common, external and internal carotid and superior thyroidal arteries, and heparin (75 IU/kg) is administered. Mean arterial pressure has to be maintained around 100 mm Hg before the carotids are clamped. After 3 minutes, the carotids should be cross clamped sequentially. Internal carotid first followed by common carotid and external carotid. Care should be taken to palpate the artery at the precise point where one intends to put the clamp and one should be certain that it is below a hard, calcified plaque, which could easily fracture. The superior thyroid artery, which arises from the external carotid close to the bifurcation, has to be occluded separately.

At this stage, careful neuro-monitoring is done by the anaesthetist by assessing the level of consciousness and motor activity. Any deterioration in the assessment at any stage will be an indication for shunt insertion to protect the cerebral circulation. The only method currently accepted by all surgeons to achieve cerebral protection is the use of shunt during carotid endarterectomy.[148]

However, the use of a shunt during carotid endarterectomy is controversial with various authors advocating uniform shunting,[149] no shunting,[306] and selective shunting based on monitoring.[315] The potential disadvantages of shunts are dislodgement of embolic material during placement, need for additional distal exposure, and limited visualisation at the critical distal margin of the plaque. It has been suggested that an external shunt, placed between the common carotid artery and the ICA, is safe and efficacious in cases that do not permit the placement of an internal shunt.[337]

A new type of temporary extraluminal shunt, connecting the femoral to the ICA with the interposition of roller pumps to regulate the blood flow has been reported. This method allows one to perform carotid endarterectomy without interrupting the blood flow to the brain.

An arteriotomy is extended proximally from the common carotid artery with care being taken to keep it in the middle of the lateral exposure of the ICA and away from the apex of the carotid bifurcation (Fig. 8). The internal carotid clamp is opened to assess the back bleeding, which is another indicator of cross circulation.

The atheroma is separated, particularly at the distal end of the internal carotid endarterectomy, followed by complete removal of all small, loosely adherent circumferential plaque remnants from the endarterectomy site (Fig. 9). Constant heparinised saline irrigation is recommended. The greatest care should be taken with the upper end of the endarterectomy, and if the plaque has not come out smoothly, the surgeon should be prepared

Fig. 7: Exposure of carotids

Fig. 8: Arteriotomy

Fig. 9: Removal of atheromatous plaque

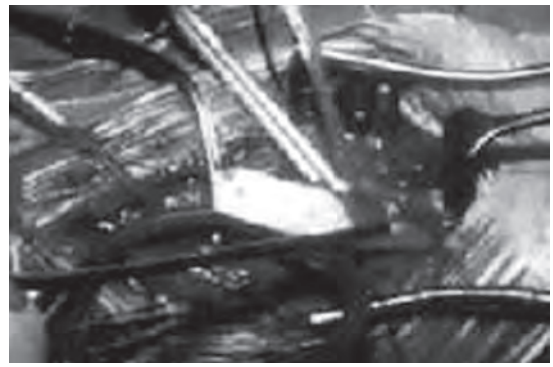


Fig. 11: Arteriotomy closure with a patch

and able to open the ICA another 5 mm in order to improve the distal repair. Any significant distal intimal step-off or shelf not firmly adherent to the arterial wall should be tacked down with 7-0 monofilament sutures. A partial or circumferential plaque should never be pulled down and away from above the level of the arteriotomy within the internal carotid, because a loose distal intimal attachment, vulnerable to subintimal dissection and carotid occlusion, can neither be fully appreciated nor properly repaired in this location. The atheroma extending up the external carotid artery is mobilised circumferentially, and the plaque is everted from the arterial lumen. Microsurgical methods increase the precision and safety of every aspect of carotid endarterectomy, including complete plaque removal, prevention of intimal flaps and non-stenosing arteriotomy closure (Fig. 10).[285]

After irrigating of the area, the arteriotomy is closed with 6.0 prolene. Before the final arteriotomy suture, the ICA temporary clip and the common carotid artery clamp are removed momentarily in turn, allowing air to be expelled from the nearly repaired arteriotomy. If the ICA is small, which is the case in small built females, a Gortex patch can be used as angioplasty (Figs 11 to 13).

Patients with complicated recurrent atherosclerosis can be treated with endarterectomy and patch grafting, but interposition vein grafts should be considered in cases in which the vessels are extensively damaged by the recurrent plaque or with an unexplained thrombus at the site of previous endarterectomy.[260]

Clamps are sequentially released after arteriotomy closure. The external carotid circulation is established first as any small debris from the operative site may be released into the extracerebral circulation. The internal carotid clamp is released last. If haemostasis is satisfactory reversal of the heparin may not be required. The wound is closed after placing a suction drain.

Post-operatively, close neurological observation is necessary by a dedicated nurse. Post-operatively the patient can be started on oral fluids after 2 hours as well as all the medications as before including antiplatelets. There is no indication for routine anticoagulant therapy. Post-operatively, our patients are put on 75 mg of aspirin. There is a suggestion that antiplatelets may increase the odds of haemorrhage, but there are currently too few data to quantify this effect.[79] Low-dose aspirin (75 mg) is effective in preventing recurrent stroke after CEA.[285] None of the newer antiplatelet agents has been specifically studied in patients requiring CEA. Further trials comparing the effects of the combination of dipyridamole with aspirin and with aspirin alone are justified.

Complications

Peri-operative complications of carotid endarterectomy are uncommon but potentially devastating. Appropriate patient selection, including careful assessment of techniques aimed at prevention and monitoring of intraoperative complications and post-operative care are mandatory.

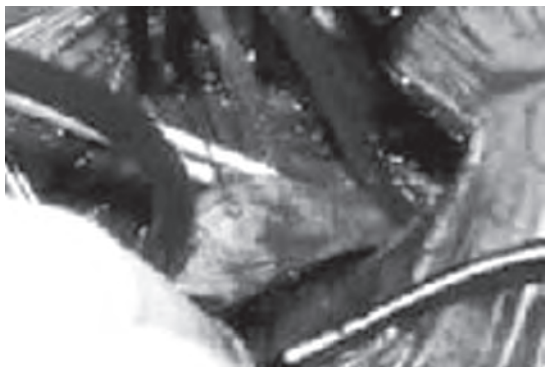


Fig. 10: Endarterectomy completed—Javid shunt being inserted

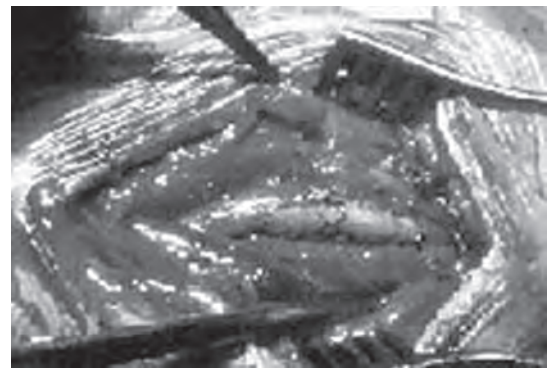


Fig. 12: Completed closure with a patch

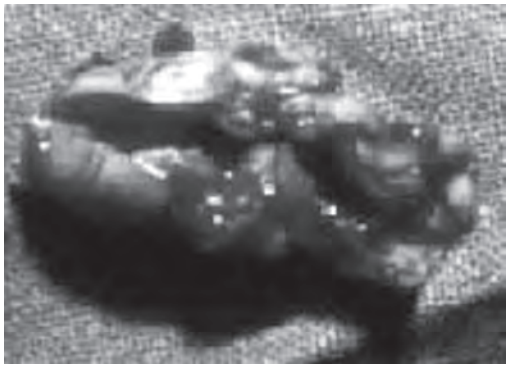


Fig. 13: Atheroma

The operative mortality and morbidity is 1–5% in various studies.[74] Reported incidence of peri-operative ischaemia after endarterectomy is about 2.5% for reversible deficits, about 1.3% for minor stroke and about 2.9% for major stroke.[209,238,314,333] Embolism is the principal cause; hyperperfusion and hypoperfusion are also important causes.[127]

Abu Rahma[3] reviewed the data on 478 consecutive patients who underwent 544 CEAs since 1976. Follow-up was complete in 83% of patients (mean 44 months). There were seven early deaths (1.3%), only one stroke related (0.2%). Peri-operative stroke rates (overall 2.9%) varied according to operative indications: asymptomatic-1.4%; TIA/amaurosis fugax (AF)-1.3%; non-hemispheric symptoms (NH)-4.9% and prior stroke (CVA)-7.1%. Five- and 10-year stroke-free rates were 96% and 92% in the asymptomatic group, 93% and 87% in the TIA/AF group, 92% and 92% in the NH group and 80% and 73% in the CVA group. Late ipsilateral strokes occurred infrequently (8 patients, 1.7%). Late deaths were primarily cardiac related (51.3%). Stroke-free rates were significantly greater. Restenosis greater than 50% according to duplex scanning developed in 13%, most (67%) within 2 years after CEA. Most of these (77%) were asymptomatic, and only 0.3% (1 patient) presented with a permanent neurological deficit. Patients with contralateral occlusion had a higher incidence of contralateral TIAs and strokes than patients without contralateral occlusion; however, the peri-operative and all late stroke rates and survival rates of CEA were comparable in patients with or without contralateral occlusion.

Intracerebral haemorrhage is an unusual complication. The incidence of intracerebral haemorrhage is increased in patients with critical carotid stenosis; this is probably related to chronic impairment of cerebral autoregulation.[27]

Restenosis occurs in about 20%. The incidence of symptomatic restenosis is in the range of 1–2%.[260] Use of dacron or vein patch during arteriotomy closure when the internal diameter of the ICA is less than 5 mm is recommended. Reoperation for carotid stenosis is a technically difficult procedure and is associated with significantly higher risks than primary CEA. Sundt et al.[312] have documented a risk of complications of 10.5%, which is four times higher than their customary rate.

Aside from technical inadequacies, the continuation of cigarette smoking post-CEA proved to be a significant risk factor; however, hypertension, diabetes mellitus, family history, lipid studies, aspirin use and coronary disease were not found to be significant risk factors.[51]

Injuries to the cervical cranial nerves are a common consequence of carotid endarterectomy. The reported incidence of cranial neuropathy after endarterectomy is 12–20%.[51,124,197] Hypoglossal, vagus, mandibular branch of the facial, and greater auricular nerves are at risk. Precise bipolar coagulation, use of magnified vision, and gentle handling of the nerves help to avoid this occurrence. Wound haematoma and infection are other possible complications.

We have operated on 67 patients between December, 2000 and September, 2006. There was no mortality. Out of 9 patients with acute stroke, one recovered his neurological deficit. One patient developed transient vagus nerve palsy, and another a marginal mandibular nerve weakness. The largest Indian series (300 patients) is from Sir Ganga Ram Hospital[298] and includes 12 patients for whom the endarterectomy was combined with simultaneous coronary bypass grafting. Sethi et al.[298] reported 3 deaths, 3% peri-operative stroke, and re-exploration due to haematoma formation was done in 6. (Figs 14 and 15).

Extracranial to Intracranial (EC-IC) Bypass

Superficial temporal to middle cerebral artery bypass (STA-MCA) is the most widely used. The first STA-MCA bypass was performed by Yasargil in 1969.[70] It involves anastomosis of the superficial temporal artery to one of the cortical branches of the middle cerebral artery.

Technique

The skin in incised over the proximal STA, just above the zygoma. The STA has at least two major branches

Fig. 14: ICA stenosis—pre-operative

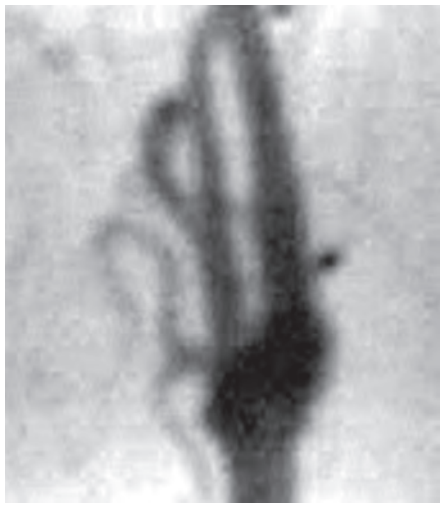


Fig. 15: ICA stenosis—post-operative

(frontal and parietal) and they should both be followed distally. The STA is dissected with a small cuff of tissue to prevent vessel injury. The larger branch is freed.

A small craniotomy centred over the Sylvian fissure is made. The dural opening is fashioned in such a way as to preserve the main branches of the middle meningeal artery, as these vessels often provide critical collateral circulation to the cerebrum. Once the dura is opened, the cortical surface is examined and generally the largest diameter vessel is selected. The ideal recipient is a surface cortical vessel without significant branching. The STA is ligated and divided and the proximal STA is occluded with a temporary clip.

The recipient artery is transiently occluded between two atraumatic temporary clips and an 'end to side' anastomosis is performed with 10-0 monofilament suture. The sutures are placed under little or no tension and then tightened after ensuring the suture does not capture the back wall of the vessel. Interrupted sutures have also proven effective and remain a reasonable alternative to a running suture. Vessel flow can then be restored, with the distal MCA clip being removed first followed by the proximal MCA clip. The temporary clip on the STA is removed last.

The donor STA and recipient MCA are irrigated with diluted papaverine, to prevent vasospasm. Warm saline is used for the remainder of the operation as an additional means to reduce arterial spasm. The dura is closed leaving a large durotomy for the graft that can be covered with muscle. The bone flap is fashioned so as to prevent compression or kinking of the graft. The temporalis muscle is then reapproximated, and the scalp is closed over a subgaleal drain.

Post-operatively, aspirin (325 mg/day) is administered and normal blood pressure is maintained. This provides initial flows of 25–50 ml/min. With time, the bypass may mature, allowing enlargement of the STA leading to a higher flow. Occipital artery to the intracranial circulation anastomosis has also been tried. When the STA is not satisfactory, Spetzler et al. suggested that the occipital artery[304] can be used, and interposition vein graft is recommended by some.[142,313] Complications include aneurysmal dilatation and rupture of the graft, and emboli from the graft site.

Anecdotal reports and uncontrolled patient series suggest that STA-MCA bypass may be beneficial. Small vessel disease (about 20% of all ischaemic patients), middle cerebral artery occlusion where endovascular thrombectomy has failed or is not feasible, and total ICA occlusion may benefit from an EC-IC bypass procedure. However, National Institute of Health (NIH) study in 1985[75] concluded that these procedures do not help in preventing a stroke, despite an overall graft patency rate of 96% and low surgical morbidity. They may have a place when everything else fails in the highly selected patients where the metabolic reserve studies suggest a compromised CBF. Chronic biochemical abnormalities due to brain ischaemia may improve after cerebral revascularisation.[220] In the treatment of inoperable ICA giant aneurysms, where the risk of ischaemic complications due to ICA ligation is high, EC-IC bypass may be used as a prelude to ICA ligation.[46]

Vertebro-basilar Territory

Cerebellar infarctions carry a poor prognosis with an acute mortality rate of 20–30%. They are mostly due to diffuse atherosclerosis of the vessels with poor flow due to stenosis and poor collaterals. Medical therapy is the first line of management. Several procedures have been tried in those with persisting symptoms.[186,253] There have been no randomised studies.

The simplest procedure, perhaps, is carotid endarterectomy if a significant stenosis is found while investigating a vertebrobasilar TIA and the stenosed carotid may be asymptomatic.[280,310] It is most readily accepted if the angiogram shows filling of the posterior cerebral artery via the stenotic ICA, or filling of the posterior circulation from the ICA because of vertebral occlusion or a persistent hypoglossal or trigeminal artery.

Anson and Spetzler[10] reported good outcome with vertebral endarterectomy which is similar to carotid endarterectomy. Ausman and colleagues[15–17] have described anastomosis of occipital artery to the PICA for occlusion proximal to the PICA and a superior cerebellar artery or P1 segment of the posterior cerebral artery anastomosis for lesions at the mid or distal basilar and also recommend vertebral endarterectomy in symptomatic patients with a functioning collateral or bypass. A vein graft interposition facilitates the bypass. Hopkins and Budny[133] reviewed a major series of posterior circulation bypass. Complications occurred in 55% of patients and 20% of them were serious.

Extracranially, the left subclavian artery, next to the carotids and the vertebrals, is the most commonly involved in atherosclerosis. Subclavian steal syndrome is the most commonly treated by carotid-subclavian bypass. The cervical vertebral artery may occasionally be compressed

by cervical osteophytes. Spetzler and colleagues[305] have reported relief with anterior decompression.

Indirect Revascularisation Procedures

Intracranial occlusive diseases form a heterogeneous group with diverse pathogenesis. Moyamoya, the commonest, is a progressive occlusive cerebrovascular disorder characterised by bilateral stenosis and occlusions of the intracranial arteries with extensive neovascularisation at the base of the brain[318]. It was first described in Japan and is now reported from all over the world. The term moyamoya (Japanese for "puff of smoke") was coined by Suzuki and Takaku[317] in 1969 in reference to the angiographic appearance of these fine basal collaterals, and has since become the accepted term to define the disease throughout the world. The incidence of persistent primitive arteries is significantly higher in patients with moyamoya disease, suggesting that congenital factors may be important in the pathogenesis of this disease.[183] In paediatric-onset moyamoya disease, asymmetrical involvement of bilateral ICAs and PCAs is common, and the ipsilateral ICA and PCA tend to be predominantly involved.[233] There is some suggestion that the pathogenesis may vary between races.[106]

The term quasi-moyamoya disease or moyamoya syndrome is typically used to refer to patients who display intracerebral steno-occlusive lesions and associated collaterals in other areas of the brain (Fig. 16). Treatment of all the patients with intracranial small vessel occlusive diseases is similar to that of moyamoya patients.

Patients present with stroke or intracranial haemorrhage due to bleeding from the friable vessels with major morbidity and mortality. Children usually present with cerebral ischaemia, while intracranial haemorrhage is common in adults.

CT, MR imaging and MR angiography help in diagnosis. CT may show multiple low density areas, and general atrophy, and contrast enhancing curvilinear vessels in the basal ganglia and cortical surface.[320,342]

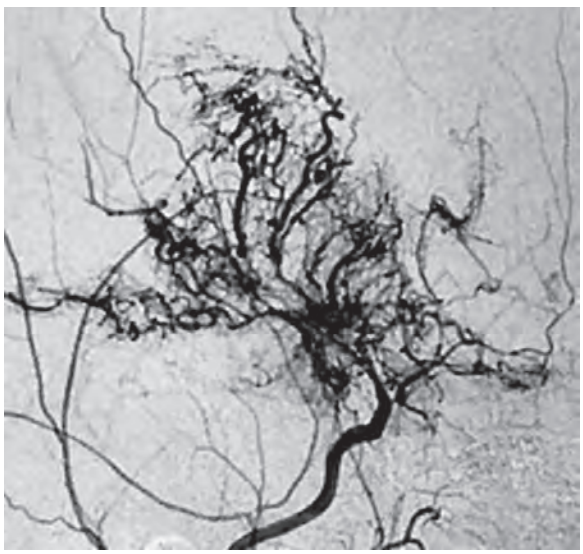


Fig. 16: Moyamoya-DSA

Conventional four vessel angiography is rarely required. 3D CT angiography is becoming an alternative. Without treatment, there is progressive deterioration of neurological function and recurrent haemorrhages.

Medical therapy with vasodilators, steroids and antibiotics is only minimally effective. Until 1975, most of the 700 reported cases of ischaemic moyamoya disease were treated conservatively. Medical therapy with steroids, vasodilating agents and low-molecular-weight dextran had been tried without success.[162]

STA-MCA bypass with or without a graft is re-emerging as a popular procedure in adults. Direct superficial temporal artery to middle cerebral artery bypass is considered the treatment of choice, although its efficacy, particularly for haemorrhagic disease, remains uncertain.[307]

Technical difficulties, especially in children, such as small STA, prompted the surgeons look for alternatives. Various surgical procedures have been tried with mixed results. All share the common goal of providing a mechanism to promote collateral blood vessels to reduce haemodynamic stress across fragile moyamoya collaterals, and ischaemia. They provide no immediate revascularisation. They rely on the subsequent formation of collateral vessels to enhance blood delivery.

Tsubokawa et al.,[334] in 1964, reported a surgery in which a dural graft containing branches of the meningeal artery was laid onto the surface of the brain of a patient with ischaemia. Suzuki and colleagues[317] suggested cervical carotid sympathectomy and superior cervical perivascular ganglionectomy with good results in improving clinical symptoms; but in most cases the procedure could not prevent the progression of the disease and the deterioration of the angiographic pattern.

Encephalo-duro-arterio-synangiosis (EDAS): In 1979, Matsushima and colleagues[207] developed EDAS with the assumption that the operation would cause the formation of spontaneous anastomoses between the arteries of the cerebral cortex, dura mater and scalp to treat moyamoya disease. The STA is mobilised and placed directly on the cortex. The free artery with a cuff of surrounding soft tissue is simply sutured to the dura.

Encephlomyosynangiosis (EMS): It involves direct placement of the temporalis muscle on the cerebral cortex. The clinical and experimental basis for using EMS in moyamoya was based on the reports of Henschen,[122] and Tsubokawa et al.[334] This may, however, induce seizures.[117, 162]

Encephalo-omental-synangiosis (EOS) may provide an alternative.[1,2] The omentum is mobilised from the abdomen in a subcutaneous tunnel and placed over the cerebral cortex as a pedicle graft or, as a free graft with microsurgical anastomosis of the gastroepiploic artery and vein to the STA and the superficial temporal vein. Karasawa and colleagues reported clinical improvement.[161] Omentum contains biologically active substances taking part in neural transmission and has angiogenic and neurotrophic action.[140]

The EMS, EDAS and STA-MCA anastomosis treatments induce vascularisation of the cerebral surface, especially in the territory of the MCA, but the vascularisation is poor in the territories of the anterior and posterior cerebral arteries.[321] Placement of multiple burr holes to improve the vascular supply has been suggested with good outcome.[78] The placement of burr holes was described as a treatment after it was noticed that neovascularisation was occurring at the site of previous ventriculostomies.[140]

Combined procedures, direct and indirect procedures or a combination of indirect procedures give the best results.[11,136,177,178,206,319] Studies such as xenon-enhanced computed tomography, single photon emission tomography and positron emission tomography can be utilised to measure regional cerebral blood flow and metabolic distribution and to the appropriate surgery, and also in post-surgery follow-ups. Follow-up evaluation with magnetic resonance angiography has advantages over conventional angiography because it is noninvasive, and the post-operative improvement of cerebral perfusion reserve show better correlation with disappearance of ischaemic attacks than does the angiographically demonstrated collateral formation.[139]

Indirect procedures are not limited by the distribution of a single major arterial division, unlike in STA-MCA anastomosis. This can be useful when both anterior and middle cerebral artery territories are affected or when there is holohemispheric involvement. Moreover, indirect procedures are technically easier to perform, as compared to STA-MCA anastomosis, and multiple indirect procedures on the same hemisphere can be performed over time, if required. Spontaneously developed leptomeningeal anastomosis might be the key factor for the efficacy of indirect bypass in elderly patients with moyamoya/stenotic cerebrovascular disease.[143] Reduction of haemorrhagic stroke is not clearly documented. There is no controlled study available. Several reports suggest that the indirect revascularisation techniques consistently lead to the development of significant collaterals in paediatric patients[135,136,274] and not in adults.[11,135,171]

SURGERY IN ACUTE STROKE

Stroke is a generic term for a clinical syndrome that includes infarction, haemorrhage and SAH (discussed elsewhere). Acute strokes may be classified into two general types: ischaemic and haemorrhagic. Approximately 80% of strokes are ischaemic.[226] Bland infarction is characterised by bland widespread leukocyte infiltration and macrophage invasion, with only scattered red cells being found. Twenty percent of strokes are haemorrhagic stroke which is due to "spontaneous" intraparenchymal haematoma in 10% of cases; in 10% it is haemorrhagic transformation of an ischaemic infarct.[6,155]

Pathophysiology

Some degree of mass effect due to brain swelling is associated in acute stroke. It ranges from very insignificant, as in lacunar infarcts, to a massive swelling due to multilobular infarcts with increase in intracranial pressure[109,295] (ICP), brain shift and uncal or cingulate herniation.

In early ischaemia, there is intracellular swelling due to derangement of Na^+/K^+ pump in the glial membrane and cell metabolism resulting in Na^+ and H_2O accumulation resulting in cytotoxic oedema. Cytotoxic oedema precedes the onset of vasogenic oedema.[93] The blood-brain barrier (BBB) is not disturbed initially. The cerebrospinal fluid (CSF) formation is not increased. Both the white and the grey matter are involved. Within a few hours, the BBB is disrupted, and there is increased cell permeability. The extracellular space is enlarged; there is abnormal diffusion of nutrients with consequent acidosis, hypoxia, and inflammatory changes. Polymorphs intensively accumulate in the region of cerebral infarction; this accumulation correlates with the severity of brain tissue damage and poor neurological outcome.[3] Endogenous substances, such as histamine, bradykinin, excitatory aminoacids, arachidonic acid, superoxide, hydrogen and hydroxyl radicals, are released and vasogenic oedema is superimposed.[20,326] Superoxide dismutase is one of the major free-radical scavenging systems that might play a role in both degenerative and acute diseases of the central nervous system; its activity in serum is reduced in acute stroke.[208] Lactic acidosis due to lactic acid accumulation, and increased pCO_2 can denature the proteins and alter the activities of pH dependent enzymes. Lactate enhances brain oedema. This oedema aggravates the mass effect which in turn aggravates the ischaemia. Cytotoxic and vasogenic oedema is maximal by 24–72 hours after the ischaemic event.[279] The '3rd day oedema' is a well known entity.[322] The critical time lasts until the 5th day in the majority, unless there is another ischaemic event.

Pressure gradients have been demonstrated in experimental models, the pressure being higher on the side of the infarct than on the opposite side or the posterior fossa.[248] Increase in ICP and subsequent reduced cerebral perfusion pressure (CPP) aggravate ischaemia. In addition, CSF flow is disturbed due to brain shifts, compounding brain ischaemia. Several studies[138,191,338] have suggested that brain swelling and herniation is an important cause of death in acute stroke.

Management[71]

Principles in the treatment of acute stroke aim to minimise secondary tissue damage caused by impaired microcirculation. One way to achieve this is to treat the brain swelling and control the rise in ICP, which improves leptomeningeal reperfusion of the medial territory.

Cerebral Infarct

Medical Therapy

Recent studies have shown a very high mortality rate despite aggressive medical treatment strategies to lower ICP, which have included osmotherapy, hyperventilation, barbiturate administration, hypothermia and anticoagulation therapy guided by ICP monitoring.[110] None of these medical treatment options have improved outcome in randomised clinical trials.[112,130,200]

The long-term effects of osmotherapy with mannitol or hypertonic solutions have not been ascertained yet. There is not enough evidence supporting a prophylactic standard therapy with hypertonic solutions.[297]

Vigorous prolonged hyperventilation has been discouraged because it may reduce the brain's ability to tolerate ischaemia and may, therefore, be more harmful than beneficial. Forced hyper-ventilation as a therapy for intracranial hypertension is obsolete. Patients with increased ICP and pre-existing ischaemia are at risk from hyperventilation, because hypocapnic vasoconstriction worsens ischaemic lesions.[346]

Barbiturate therapy has failed to be of any benefit in the treatment of oedema after severe brain ischaemia. Barbiturate coma leads to a reduction in ICP under certain circumstances.[275] The use of high doses of barbiturates, however, is associated with several side effects. The side effects include a reduction in cerebral perfusion pressure, suppressed brainstem reflexes and EEG abnormalities,[179] in addition to respiratory complications, myocardial depression with reduction in heart volume per minute, increased infection rate, disturbances in electrolyte balance, impairment of liver function and leukocyte depression.[290] The mortality rate in patients treated with high doses of barbiturate medications for raised ICP is extremely high.[107,258]

It has been reported that hypothermia induction within 14 hours of ischaemic injury and maintained for 72 hours significantly reduced ICP and mortality.[308] But side effects of this therapy are irregular pharmacokinetics, disturbances in the monitoring of vital parameters, impairment of coagulation and immunosuppression.[38,218] There are many unanswered questions concerning this therapy, such as the optimum safe brain temperature for maximum neuroprotection, and the duration of this therapy. Obviously, the centre should have the infrastructure for such therapy.

Fatal space-occupying brain oedema is rare, and occurs in 1–5% of patients with a supratentorial infarct.[129] Mortality rates are highest when lesions involve the trunk of one or more of the main cerebral vessels. In fact, occlusion of either the distal ICA or proximal MCA trunk has been characterised as a "malignant" stroke.[111] It is characterised by rapid clinical deterioration due to brain swelling and downward transtentorial herniation, and is associated with a mortality of 80%. None of the available medical therapies provide substantial relief from the oedema and raised ICP, or at best, they are temporising in most cases, and surgery has a definite role. There are a number of recent advances in the management of stroke, but here we are primarily concerned with the management of cerebral oedema which complicates ischaemic infarct and adversely affect the outcome.

Surgical Therapy

Craniectomy and decompression: Decompression of the brain by turning the closed cavity of the skull into an open one is an old neurosurgical technique and it has been applied to treat conditions of uncontrollably elevated ICP. In 1905, Cushing reported the use of this procedure to relieve the pressure caused by the growth of an intracranial tumour.[58,351] Since then, surgical decompression has been reported as a treatment option for various neurological problems. Indications included rare clinical situations such as Reye's syndrome[18] or hepatic failure,[316] as well as epidemiologically more important conditions such as head injury[330] and cerebellar infarction.[144] In the 1950s and 1960s, an increasing number of reports were published in which the authors[4,300,338] have described cases of massive cerebral ischaemia accompanied by acute and severe brain swelling. In 1968, Greenwood[108] described cases of massive cerebral ischaemia accompanied by acute and severe brain swelling and used surgical intervention in the treatment of such cases, which decreased the mortality rate to below 50%. In 1981, Rengachary and co-workers[270] reported the first case in which straightforward craniectomy was undertaken. Since then there have been regular reports of decompressive craniectomy for this condition.

A decompressive procedure in selected stroke patients is the most practiced surgical intervention in acute strokes. Any surgery should be effective, rational and safe. An ipsilateral decompressive surgery fulfils all three criteria. The procedure is, certainly, simple and safe.

Various studies support the rationale for decompressive surgery.[60,115,272] The intracranial mass effect can be compensated without an increase in ICP by resorption of CSF and by shifting CSF into the spinal canal. When the reserve spaces become completely exhausted, mass effect leads to an exponential increase in ICP. The equation is expressed by the pressure-volume curve. The studies[53,60,115,273] provide evidence that decompression leads to a shift to the right of the pressure-volume curve and, therefore, to a massive increase in compliance and a reduction of ICP.

The available results support the effectiveness of decompressive surgery as a salvage procedure. Gower et al.[107] were able to reduce ICP by 34% in seven patients by performing a subtemporal decompressive craniectomy. Jaeger et al.[146] reported that the mean ICP decreased from 59 to 10 mmHg in a two-step fashion, relating to bone flap removal and dural opening. Simultaneously, PO_2 increased rapidly from 0.8 kPa (6 mmHg) to 3.07

kPa (23 mmHg). PO_2 and ICP remained at noncritical ranges post-operatively. It is being used extensively in head trauma patients, with varying results, with a significant decrease in mortality and morbidity in comatose patients. In trauma the role of decompressive surgery is still under debate, although its use has been repeatedly reported in rather large numbers of patients.[330] It is, perhaps, more appropriate in acute stroke where the mass effect is restricted to one side only, unlike in head injury. The idea is to give room for the swollen brain, reduce the pressure gradient between the intracranial compartments, and tide over the crisis. Recent studies also demonstrate a reduction of mortality rate to less than half that reported for medical therapy alone, even using aggressive medical protocols.[110,111,272,339,352]

The technique is simple. Associated illnesses and the attitude of the family members to accept a severe neurological deficit, especially in developing countries where there are no adequate rehabilitation centres, must also be considered. As in any surgery, patient selection and meticulous post-operative management play a major role in the outcome. Associated illnesses must be attended to. Judicious timing is the key for success.

Historically, hemicraniectomy has been used as a last resort to prevent impending death after all medical therapies have been attempted. Signs of 'coning' were used to indicate the need for decompressive surgery.[270,272,296] After initial effectiveness, additional medical therapeutic efforts often fail to control or prevent herniation, and the physicians may wait too long to intervene surgically. Studies[69,94,185,296] report that craniectomy should be performed early, before severe impairment of brain perfusion occurs. A follow-up study by Doerfler and colleagues[69] compared decompression at 4, 12, 24 and 36 hours, and reported improved neurological outcome, and a significant reduction in the length of time of critical care therapy. Once the pupils are fixed and a deep coma has indicated an irreversible decline of cerebral function, surgery should not be performed.[270]

'When is early?' is still a dilemma. ICP monitoring has been recommended as a guide to surgical timing.[43,272] Increased ICP measurements are preceded by worsening clinical signs and symptoms and the usefulness of ICP monitoring in these cases has been questioned.[296]

Nausea and vomiting within 24 hours after stroke onset, a systolic blood pressure of 180 mmHg or more at 12 hours after onset, a history of hypertension or heart failure, elevated white blood cell count, an activity deficit covering the complete MCA territory on SPECT imaging, a hypodensity of more than 50% on the initial CT scan, attenuated corticomedullary contrast on CT, involvement of additional vascular territories on CT and volume of MRI diffusion-weighted imaging abnormalities of more than 145 ml have been suggested as independent early predictors of fatal space-occupying oedema formation by various small studies[29,114,166,189,251] It is generally recommended that surgical intervention should be carried out before the midline shift shows on CT. The ongoing HAMLET trial,[129] hopefully, will help us avoid unnecessary decompressive craniectomies.

There are several different types of decompressive craniectomy: (1) the lateral temporal or frontotemporal approach; (2) the bifrontal approach[182] and (3) the suboccipital approach. Traditionally, craniectomy is planned according to the area of infarct. A wide craniectomy with a duraplasty is, routinely, recommended. Bifrontal craniectomy is more commonly employed in traumatic brain injury, especially in children.

The need for a radical approach, in terms of extension of bone removal has been recommended[175] in the event of severe post-traumatic cerebral oedema, to avoid prolapse of the oedematous brain through the edges of the craniectomy defect, with possible exacerbation of brain damage. In the case of cerebral infarction, however, this phenomenon does not result in significant increase in cerebral damage or venous stasis, as in traumatic brain injury, because most likely the protruding tissue is already necrotic.[270] There are no systematic reports about quantitative analysis of the size of craniectomy required to be effective.

The author recommends a fronto-temporal craniectomy extending to the base of the middle cranial fossa, and excision of the sphenoidal ridge. Achieving decompression down to the floor of the middle fossa (subtemporal decompression) seems to be important in this surgical technique, because this procedure relieves pressure from the basal temporal lobe. Good results with this technique were reported,[8] even though there is a risk of temporal lobe herniation and necrosis.

Since the cranial vault has essentially been expanded during surgery, there is an immediate decrease of ICP. Jourdan et al.[152] have found that initial ICP values of 25–60 mm Hg decreased by 15% once the bone flap was removed and by 70% once the dura was opened, resulting in the normalisation of the ICP after surgery. A decrease in ICP allows for an increase in cerebral perfusion pressure, aiding blood flow to the ischaemic penumbra and optimising circulation to the damaged area through collateral vessels.[272]

As the dura is opened, pale infarcted brain herniates out. The herniation may subside with hyperventilation and osmotherapy. Some groups[144,156] have recommended resection of infarcted and even non-infarcted brain tissue. Some others recommend resection of the infarcted cerebral tissue and a temporal lobectomy.[205] A group of Japanese surgeons recommend additional excision of the hippocampal gyrus also to relieve peduncle compression, and blockage of CSF circulation.[335] Although resection of infarcted tissue or "strokectomy" has been associated with post-operative improvement in some cases, it is impossible to differentiate at surgery between ischaemic tissue (potentially salvageable) and necrotic tissue (irreversibly compromised). Functional MRI combined with periodic clinical follow-up suggests that the patients may experience functional recovery as a result of activation in both the infarcted and contralateral

hemispheres. Hence, excision of infarcted areas, once recommended, is avoided.[49]

Duraplasty is performed with either silastic lyodura or pericranial grafts. The graft is secured with sutures in a way that allows the initial incision to spread not more than 2–3 cm. This achieves smooth bulging rather than fungus like herniation of the brain into the craniectomy, avoiding shearing injuries, impairment of venous drainage, and enhancement of cerebral oedema, as described by Cooper et al.[53] It is also recommended that in bifrontal craniectomy, the sphenoidal ridges and the anterior walls of the middle cranial fossa be preserved to prevent temporal lobe forward migration. Csokay et al.[55,56] suggested placing vascular tunnels at the margins of a durotomy when performing decompression. This new surgical technique consists of a stellate type durotomy and the creation of a vascular tunnel by supporting pilasters made of haemostatic sponge around the main cortical veins and arteries of herniated brain with the aim that the vessels do not become compressed by the dural or bone edge to reduce vascular congestion and the subsequent ischaemia in brain tissue which herniates through the durotomy. This is reported to lead to better clinical outcomes.

The temporal muscle and skin flap are reapproximated and sutured in place. The bone flap may be preserved frozen[64, 270] or preserved in a subcutaneous pocket in the abdominal wall.[43] Cranioplasty is then performed at a later date, when functional recovery has stabilised. Artificial flaps have also been used to close the bone defect.[152,272]

The influence of hypothermia-related neuroprotection during decompressive craniectomy has been suggested.[69] Further studies are necessary to confirm its efficacy.

The author recommends subdural positive pressure drainage at the end of the procedure to help facilitate CSF drainage, if required post-operatively, and the same may be incorporated with an ICP monitor. Post-operatively, intensive medical therapy is continued.

Complications: The complication rate after decompressive craniectomy is low and has no influence on the patient's prognosis. Few complications have been reported in the literature; subdural haemorrhage as well as hygroma has occurred. Puncture was found to be sufficient for the treatment of the hygroma. Next frequent is, hydrocephalus; some may require ventriculo or lumbo-peritoneal shunt. There is no report of death or permanent deficits related to the surgical decompression itself.[67]

Outcome: Decompressive craniectomy appears most promising as a method of avoiding death from brain compression. In patients with surgical decompression, there is less risk of shifting from a fatal outcome to a vegetative state. Several studies[67,159,308,345] have reported better outcome with decompressive surgery, compared to medical therapy alone. Rieke and co-workers[272] have reported the results of a prospective, non-randomised, single institution controlled study. In this study, the mortality rate was 76.2% in the control group and 34.4% in the surgically treated group. Functional outcome, as reflected by the Barthel Index scores obtained 4–36 months after surgery, was consistent: excellent level of activity in one patient, minimal assistance required by 15 patients, and a severe disability in 5 patients. In the control group, 4 of the only 5 survivors had global aphasia.

Most reported cases are in the non-dominant hemisphere with a chance for a reasonable neurological recovery. Most recent series[167,296] suggest good outcome following craniectomy for both dominant and non-dominant infarcts. Therefore, surgery can be considered in highly selective patients with dominant hemisphere infarction, especially if some residual language function is present at admission.

A slowly developing deterioration seems to carry a better prognosis than a rapid one. The prognosis is better in patients whose midbrain symptoms developed over days instead of hours.

Recent studies have reported good outcome in patients in whom the procedure was done early and whose pre-operative Glasgow coma scale (GCS) score was 8 and above. It offered no benefit in patients whose pre-operative GCS was below 5.[95,116,268]

In theory and in practice, it would seem that younger patients with ischaemic stroke would benefit from early decompressive surgery. Individuals aged 50 years and younger have been identified as benefiting more from bilateral decompressive craniectomy in cases of subarachnoid haemorrhage because of their unatrophied brains, as compared with those over 50 years of age.[89] The young brain is less atrophied, and the ventricular system in younger persons is smaller than in older persons, allowing less room for oedematous expansion within the cranial vault.[185]

In patients younger than 50 years, recovery to a state of near-independence is possible. More than half of the surviving younger patients have a good outcome and live independently. Attention deficits are prominent in all patients; visuospatial and constructive deficits are less pronounced in patients with higher formal education.[43,194]

Craniectomy in elderly patients with space occupying MCA infarction improves survival rates compared with medical treatment alone. However, functional outcome and level of independence are poor.[132]

The author recommends that the decompressive procedure is performed prior to frank clinical deterioration despite aggressive medical therapy; the patient should be young with a GCS of greater than 5, and no serious systemic illness, and must have a supporting family. There may be occasions when patient selection needs to be individualised. The procedure is mainly to give the maximum chance to preserve life. There is a group of reluctant surgeons who feel a decompressive procedure does not alter the final outcome. Discouraging outcomes in patients do not invalidate the method; good results

confirm its usefulness. The increase in brain oedema after decompressive craniectomy led to a discussion in the neurosurgical literature and to questioning the usefulness of the procedure when treating severely brain-injured patients. Brain oedema only increases if the brain is already irreversibly severely damaged. Such patients have a poor prognosis, which is no argument against decompressive craniectomy. At present decompressive surgery might be the most promising therapeutic option to save life. Since decompressive craniectomy can be a life-saving procedure in patients who will most likely be left with a significant neurological deficit, the operation has important ethical and psychological implications. It is most essential that the family understands and be supportive.

Cerebellar Infarcts

Several treatment strategies for cerebellar infarcts (Fig. 17) have been proposed. Decompressive suboccipital craniectomy is readily accepted by neurosurgeons and physicians, unlike in cerebral infarct. Associated obstructive hydrocephalus is an added problem. Khan et al.[176] reported good results in 10 of 11 patients treated either conservatively or with ventriculostomy only. Horwitz and Ludo[134] proposed ventriculostomy in patients who do not improve with medical management and suboccipital craniectomy if there is no improvement despite ventriculostomy. Heros and Chen[47,123] recommend combined ventriculostomy and suboccipital decompression in one sitting.

Our practice is to perform a simple suboccipital craniectomy in the prone position with resection of infarcted tissue. The posterior arch of the atlas is removed for wider decompression. Ventricular drainage is established for concomitant hydrocephalus and converted to a shunt if necessary at a later stage. It must be understood that patients with brainstem infarction have poor outcome; but, brainstem compression is potentially reversible.

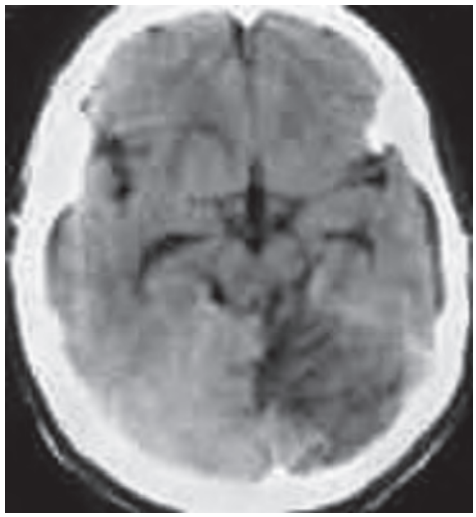


Fig. 17: Cerebellar infarct-CT

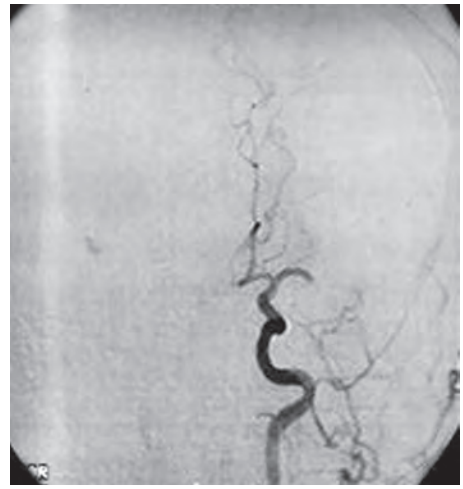


Fig. 18: MCA occlusion-DSA

Revascularisation Procedures

The role of revascularisation procedures (Fig. 18) in acute stroke is still in the experimental stage. Emergency carotid endarterectomy[188,210,347] is a controversial indication, becoming less and less controversial of late. Patients must have an angiographically demonstrated lesion and no infarction on a CT. There is no randomised trial. Tissue plasminogen and interventional endovascular procedures are more often preferred. Recent reports[102,201] suggest moderate success of emergency carotid endarterectomy in patients: (a) with cresendo TIAs[125]; (b) with severe stenosis in angiography and (c) with disappearance of a previously auscultated bruit, presumably indicating acute occlusion. The presence of good collateral flow is a favourable prognostic sign.

The technique is the same as in elective endarterectomy. Clinical results are best in patients with mild-to-moderate deficit and a rapid course from onset of deficit to surgery. Although higher than elective surgery, morbidity and mortality are acceptable with urgent carotid endarterectomy, given the severity of illness in this patient population.

Despite excellent post-operative angiographic results, the outcomes in patients after STA-MCA anastomoses are not better than the results from medically treated patients.[267]

Other procedures such as posterior circulation bypass, vertebral endarterctomy, arterial anastomses and correction of subclavian steal have not been tested sufficiently. A number of experimental studies on embolectomy of intracranial vessels have also been done.[223,228] At present they remain as a few interesting attempted procedures.

Haemorrhagic Stroke

As mentioned earlier, about 20% of strokes are haemorrhagic, which is due to "spontaneous" intraparenchymal haematoma (SICH) in 10% of cases, and haemorrhagic transformation (HT) of ischaemic stroke in 10% of cases. HT may vary from patchy petechial bleeding to

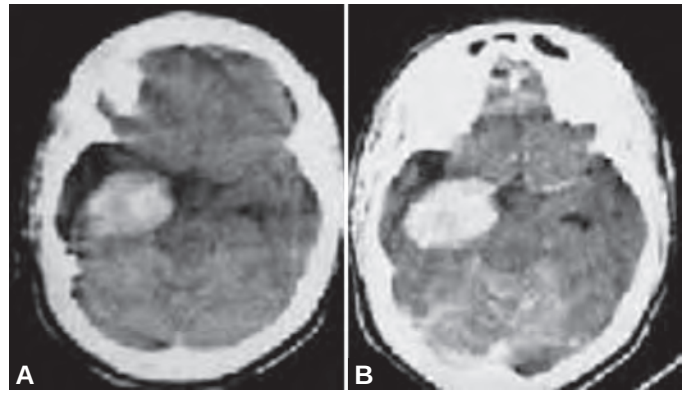
more confluent haemorrhages, representing multifocal extravasation of blood from capillaries or venules. Approximately 20% of patients with cardioembolic stroke have haemorrhagic transformation in the infarcted zone, usually occurring within 48 hours.[192,193,249] The pathogenesis of HT appears to relate to reperfusion and bleeding from recanalised but ischaemically injured vessels by the natural, dynamic dissolution of thrombi. Reperfusion into the ischaemically injured vessels can therefore result in varying degrees of blood extravasation through the damaged blood-brain barrier. It is suggested that hyperglycaemia, hypertension and restoration of blood flow to ischaemic territories were strong risk factors for a haemorrhagic infarct to develop.[248] On CT, HT appears as a discontinuous heterogeneous mixture of high and low densities occurring within the vascular territory of the infarct in contrast to SICH which appears as a discrete, homogeneous collection of blood that often exerts mass effect and may extend beyond the original infarct boundaries or even into the ventricles. The available reports suggest that haemorrhagic transformation of an ischaemic infarct is managed the same way as an ischaemic infarct is. Its prognostic value is controversial.[331]

Traditionally, non-traumatic intracerebral haemorrhage is defined as 'spontaneous' intra-cerebral haemorrhage (SICH); it may, further be classified as primary or secondary depending on the underlying cause.[219] Primary ICH accounts for approximately 70–80% of cases and is due to spontaneous rupture of small vessels damaged by hypertension or amyloid angiopathy. Secondary ICH is associated with a number of congenital and acquired conditions such as vascular anomalies, coagulopathies, tumours and various drug therapies. The common sites in order of occurrence are the basal ganglia, thalamus, subcortical white matter of the cerebral lobes, cerebellum and brainstem. Men are more likely to suffer an SICH than women and the likelihood increases with age.[35]

Cerebrovascular damage to small arteries and arterioles due to chronic hypertension is recognised as the most significant cause of primary SICH.[90] Cerebral amyloid angiopathy (CAA) is the other major cause of primary SICH and an important cause of lobar SICH in elderly populations.[340] In CAA, amyloid protein is deposited in the media and adventitia of cortical and leptomeningeal blood vessels. Histological examination of brain tissue obtained during surgery or at autopsy is necessary for the definitive diagnosis of CAA.

Vascular anomalies are the second most common cause of SICH overall. Venous malformations are the most frequently occurring vascular lesion demonstrated in autopsy and radiological series. Their clinical significance remains controversial, with some authors reporting a negligible haemorrhage risk[99] and others suggesting a higher risk.[204]

Haemorrhage is not an uncommon presentation in cases of previously unsuspected brain tumour;



Figs 19A and B: (A) Intratumoural bleed-CT plain. (B) Intratumoural bleed-CT contrast

melanoma, choriocarcinoma, renal cell carcinoma and bronchogenic carcinoma are the most frequent tumours responsible for producing ICH (Figs 19A and B). An indentation of the haematoma's surface revealed on pre-contrast CT scanning should prompt suspicion of a tumoural haemorrhage.[145] In young patients without hypertension, follow-up imaging is warranted if initial studies are unequivocal regarding cause. Hypertension continues to be the single greatest modifiable risk factor for SICH.[35] Diabetes mellitus is more commonly associated with SICH than with SAH.[154,329] Other risk factors include anticoagulants, especially in elderly patients[92] and hepatitis C virus infection as a result of subclinical clotting disorder or vessel wall friability.[163]

Pregnancy and puerperium can be associated with SICH due to dural venous sinus thrombosis and eclampsia. SICH occurs in 1–5 per 10,000 pregnancies.[215]

The clinical presentation is of a sudden onset of focal neurological deficit progressing over hours with accompanying headache, nausea, vomiting, altered consciousness and elevated blood pressure. Supratentorial haemorrhage is commonly accompanied by vomiting and altered consciousness, which is rare in ischaemic stroke.[41] Elevation in blood pressure occurs in as many as 90% of patients with SICH. Seizures occur in

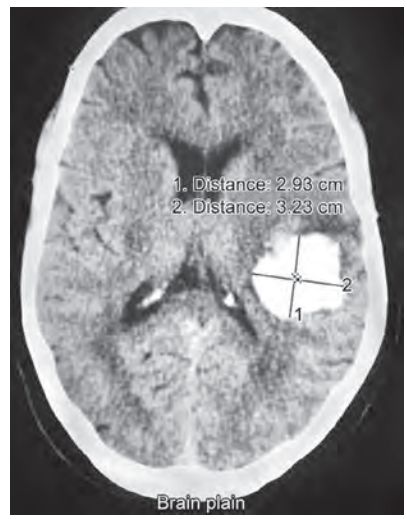


Fig. 20: Lobar haemorrhage-CT

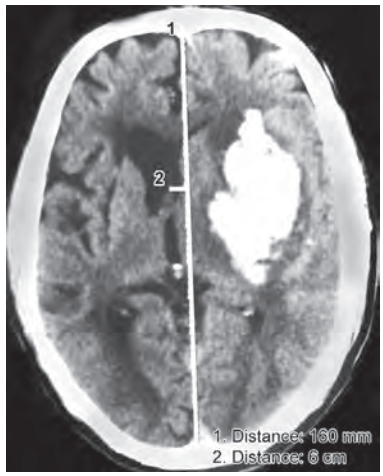


Fig. 21: Ganglio-capsular haemorrhage-CT

approximately 10% of patients.[31] The type of focal neurological deficit, of course, depends on haematoma location.

Blood may rupture into the ventricles and cause hydrocephalus. Rarely, blood finds its way into the subarachnoid space. Depending on clot location, this can result in brain herniation, compression of the brainstem and death.

Investigations

Haematomas, even just a few millimetres in diameter, are rapidly and accurately identified on CT scans (Figs 20 to 22). In addition to the size and location of the SICH, CT can also suggest potential causes, such as tumour, vascular malformation or aneurysm, and SICH related complications, such as hydrocephalus, oedema, herniation and intraventricular extension, are easily identified.[52]

Haematoma expansion and oedema formation are believed to be the major factors involved in secondary deterioration in level of consciousness, which occurs within the first 24 hours after onset.[212] Haematoma expansion, reportedly occurs in 14–38% within the first 24 hours of admission.[97,173] Fujii et al.[97] reported that repeat CT scanning within 24 hours of admission

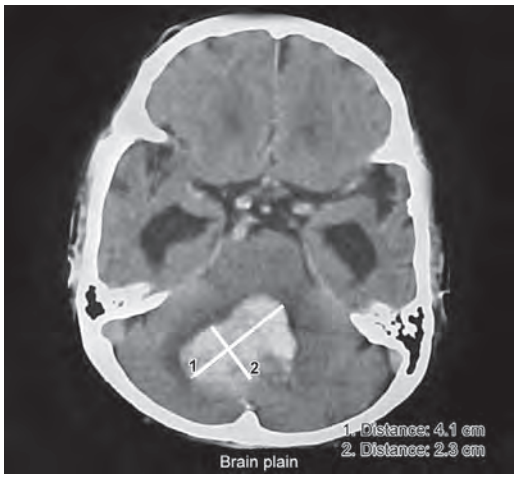


Fig. 22: Cerebellar haemorrhage-CT

demonstrated enlargement of the haematoma in 14% of patients. Five factors were found to be associated with enlargement: (1) admission shortly after onset of symptoms; (2) heavy alcohol consumption; (3) irregular shaped haematoma; (4) reduced level of consciousness and (5) low level of fibrinogen. Kazui et al. have reported that although expansion of ICH on CT is common in the hyperacute stage, 17% of haematoma expansion occurs even after 6 hours of onset. Haematoma enlargement after 24 hours is rare.[173]

Haematoma volume calculation by CT helps in deciding on surgery. Calculation of haematoma volume is directly possible with special software. If direct volume measurements are not possible, a rapid, simplified method of determining haematoma volume has been described and validated. The formula used (A x B x C)/2 is an approximation for the volume of an ellipsoid where A is the greatest haemorrhage diameter on axial CT scans, B is the largest diameter 90° to A and C is the number of CT slices with haemorrhage multiplied by the slice thickness.[187] In clinical practice, these measurements are usually performed informally.

MRI is more sensitive in detecting cavernous malformations than CT scanning or angiography. The MR imaging appearance of SICH is complex and depends on haemoglobin breakdown products over time.[41,84] Recent reports have shown that multi-sequence MR imaging is as reliable as CT scanning in the assessment of hyperacute SICH.[254,291]

Four-vessel angiography may be needed for a definitive diagnosis of the aetiology. Based on their results, Zhu et al.[358] recommend that the use of angiography should be considered in all patients with SICH in thalamic, putaminal or posterior fossa haemorrhage except in those older than 45 years of age with pre-existing hypertension. CT scanning features in patients with SICH that warrant angiography include the presence of SAH, abnormal intracranial calcification, prominent vascular structures and perisylvian location of haemorrhage. In their study, angiography was positive in 32 (84%) of 38 patients in whom there was one or more of these CT findings. Follow-up angiography may be considered in these high-risk patients if initial studies are negative.

Histological examination of sampling of adjacent haematoma wall or preservation of tissue fragments identified at the time of surgery can be of important diagnostic value, with about a 25% rate of positive findings.[128]

Pathophysiology

Primary tissue damage and distortion occur at the time of haematoma formation when the blood spreads between planes of white matter cleavage. Haemorrhage most commonly results from rupture of the small penetrating arteries damaged by the degenerative effects of chronic hypertension. In 1868, Charcot and Bouchard described the rupture of "microaneurysms" as the cause

of SICH. Recent investigators have questioned the existence of such microaneurysms, suggesting that many of these structures are complex vascular coils, subadventitial haemorrhages, or extravascular clots resulting from endothelial damage by the haematoma.[44,90]

The vasculopathy of chronic hypertension affects the perforating arteries resulting in lipohyalinosis or focal necrosis. This helps explain the distribution of hypertensive haemorrhages in territories supplied by the lenticulostriate arteries (basal ganglia), the thalamoperforating arteries (thalamus), the perforating branches of the basilar artery (pons), and the superior and anterior inferior cerebellar arteries (cerebellum).[90] Lobar haemorrhages in the elderly are often considered to be a result of amyloid angiopathy, which preferentially involves the cortical and leptomeningeal blood vessels.[340]

Both necrotic and apoptotic neuronal death appear to play a role.[126,264] Blood and plasma products, and thrombin formation mediate many secondary processes initiated after SICH.[349] Inflammatory mediators from the blood can induce an inflammatory reaction in and around the haematoma. Neutrophils, macrophages, leukocytes and activated microglia can be found. The release of cytotoxic enzymes, free oxygen radicals, nitric oxide and products of the phospholipid cascade is thought to contribute to secondary neural injury and cell death.[350]

A delayed phase of oedema formation and injury in the 2nd or 3rd weeks after SICH in humans may be due to haemoglobin and its degradation products.[348]

Breakdown of the haematoma consists of invasion by macrophages, progression of surrounding oedema, development of microvessels at the clot margin and, eventually, gliosis.[181] The end result is a haemosiderin-stained scar or a cavity containing old blood surrounded by fibrous tissue.

An unusual form of chronic intracerebral haematoma has been defined by Roda and colleagues.[276] Their term "encapsulated intracerebral haematoma" refers to a chronically encapsulated intraparenchymal haematoma found in normotensive patients, usually caused by vascular malformations. These lesions exhibit progressive mass effect, oedema, and ring enhancement. The self-perpetuating nature of these lesions has been compared with chronic subdural haematomas.

Secondary brain injury and oedema represent potential therapeutic targets. Astrup et al.[13] proposed the term "ischaemic penumbra" to describe brain with CBF values above a lower limit of membrane dysfunction and cell death, but below an upper limit corresponding to electrophysiological dysfunction. In more recent clinical studies, evidence does not clearly support the concept of perilesional hypoperfusion without perilesional ischaemia in SICH as a result of reduced metabolic demand or diaschisis.[292,336,357] Perilesional blood flow is found to be lowest during the first 24 hours postictus, but it normalises as oedema formed over the next 2–3 days.[211] Siddique and colleagues[301] demonstrated that some of the ischaemic perilesional brain recovered its perfusion in the long term.

Management

The management of intraparenchymal haemorrhage is essentially the same and as controversial as in ischaemic infarcts; the clot is the additional problem. In general, there has been a pessimistic attitude among many medical professionals, including neurosurgeons, regarding treatment of SICH. Some surgeons prefer a non-surgical approach.[72,150,239] Their claim is the damage occurs at the time of bleeding as the blood rips through the brain and that attempts to remove the clot will only add to the trauma. Some others advocate early surgery in spite of the additional risk of damaging the intact brain tissue.[14,158,257] They claim that the neurological deterioration does not always respond to medical therapy alone, and, therefore, removal of haematoma should be accomplished as soon as possible to decompress the clot and decrease ICP to prevent secondary deterioration, and to improve perifocal vasogenic oedema and local cerebral blood flow by preventing compartmental pressure changes and consecutive reduction of the blood flow perfusion pressure or by removing the changes caused by toxic breakdown of blood byproducts.

Patients with relatively normal consciousness (GCS Scores 13–15) rarely require surgery, whereas deeply comatose patients (GCS Scores 3–5) rarely benefit from surgery. There is good theoretical rationale for early surgery. Haematoma evacuation may decrease the toxic effects of blood and plasma products, diminish surrounding oedema and ischaemia, and prevent haematoma expansion. A reduction in haematoma volume in experimental studies decreases mass effect, lessens ICP and limits the potential stimulus for oedema formation and cell death.[9,25,344] Raised ICP is also treated, when appropriate, by aggressive medical measures. Although size or volume may influence surgery related decisions,[26,232] the actual surgical accessibility of the clot is more important. Lobar haematomas and those located near the cortical surface are much more likely to be surgically treated than those located deeper in the thalamus and putamen.[86]

The ideal goal of surgical treatment of ICH is to remove as much blood clot as possible, as quickly as possible, with the least amount of brain trauma from the surgery itself. If possible, surgery should also remove the underlying cause of ICH, such as an arteriovenous malformation, and prevent complications of ICH such as hydrocephalus and mass effect of the blood clot.

Neurosurgeons and neurologists invariably advocate that large cerebellar haemorrhages with compression of the brainstem or obstruction of the fourth ventricle should surgically be removed as soon as possible. Associated hydrocephalus may require a drainage procedure. Surgical removal of large lobar haemorrhages in young patients who are clinically deteriorating has also been recommended based on anecdotal experience.[36,164]

The optimal surgical technique for haematoma evacuation is not agreed upon. Craniotomy and evacuation

of the clot has been the standard approach for removal of intraparenchymal haemorrhage and remains the most common.[89] In addition, a decompressive craniectomy with a duraplasty is performed by most, including the author. Its major advantage is adequate exposure to remove the clot. It is not difficult or time-consuming. The major disadvantage of a more extensive surgical approach is that it may lead to further brain damage, particularly in patients with deep-seated haemorrhages. In addition, the effectiveness of clot removal by craniotomy is far from ideal.[36,231]

Newer Techniques

The grim results of conventional craniotomy have stimulated a search for more tolerable, less traumatic and safer methods of clot removal. Technical advances in removal of ICH include improved localisation of the haemorrhage by stereotactic devices or intra-operative ultrasound and better surgical techniques.[14,19,36,131,157,195,244]

Stereotactically controlled endoscopic evacuation is gaining popularity. It permits localisation of the lesion, and removal of the clot is performed under optic control, which may be important in cases of cryptic arteriovenous malformations. This hightech method may be simple, fast, safe and effective. Auer and colleagues[15] conducted a randomised trial of endoscopic aspiration of haemorrhage compared with best medical treatment. More than 90% of the clot was evacuated in 15% of patients, between 70 and 90% in 29% of patients, and between 50 and 70% in 56% of patients. At 6 months, the mortality rate of the surgical group (42%) was significantly lower than that of the medical group (70%). A good outcome with minimal or no deficit was also seen more frequently in the surgically treated group. In patients with large haematomas (>50 cm^3), quality of life was not affected by surgery, whereas the mortality rate was significantly lower. By contrast, endoscopic evacuation of smaller haematomas led to significantly better quality of life compared with those treated medically, but survival was similar for the two groups. Surgical benefit was mainly limited to patients with lobar haematomas and patients less than 60 years old.

Innovations in devices to break up and remove the blood clot include, modifications of an Archimedes screw inside a cannula,[28] a specially designed ultrasonic aspirator,[243] a modified nucleotome,[168] a double track aspiration,[245] and intra-operative CT monitoring.[141]

Clot evacuation may be combined with pharmacological therapy targeting the inflammatory response, shown to develop around the haematoma and leading to delayed cellular death as observed in experimental animal models.[126]

Fibrinolysis aids rapid dissolution of the remaining blood. The aim is to achieve a mass reduction as well as to reduce the extension of perifocal oedema and minimise the amount of tissue damage. Stereotactic evacuation and thrombolysis of cerebral and cerebellar haemorrhage[194,224,225] has been reported with good results. Instillation of thrombolytics has also been used successfully for haemorrhage within the ventricular system as well.[87,214] These innovative stereotactic aspiration techniques have been used on haemorrhages in all brain locations. The most commonly used thrombolytic protocol has been administration of 6,000 U of urokinase once or twice daily via a catheter into the bed of the haematoma with subsequent drainage and aspiration. A urokinase wash out can be performed for up to 7 days after the bleeding.[169] This procedure is often repeated over several days until the majority of the haematoma has been aspirated.

Haematoma puncture and catheter placement for fibrinolytic therapy could be achieved with high accuracy and safety using frameless stereotaxy. This method, reportedly, allows unrestricted trajectory selection with catheter positioning along the main haematoma axis.[277] Some investigators have reported that aspiration with thrombolytic agents is less successful in removing clotted blood in the first hours after haemorrhage onset compared with removal of haemorrhage that has been present for several days.[168] Further studies are needed to assess optimal thrombolytic dosage, and must include controlled comparisons of mortality, disability outcome, time until convalescence and cost of care in treated and untreated patients.

Kanaya and Kuroda[157] reported that rebleeding after surgery was seen in 10% of patients who underwent craniotomy, 5% who underwent CT guided aspiration, and 6% who had ultrasound guided aspiration. On average, CT-guided aspiration removed 71% of the original haematoma, whereas ultrasound-guided aspiration removed 81%. The percentage of haematoma removed did not significantly vary with the timing of the operation. Other investigators using various CT guided aspiration techniques, including thrombolytic instillation, have reported aspiration rates ranging on average from 30 to 90% over the first several days.[131,243,245] Early evacuation might also be combined with haemostatic therapy such as recombinant activated factor VII to help prevent the risk of rebleeding.[213,229]

Outcome

The natural course of spontaneous ICH leads to a 30-day mortality rate of 45%.[35] Spontaneous ICH is associated with a higher mortality rate than either ischaemic stroke or SAH.[65,137] The patient's initial level of consciousness, haematoma size, and intraventricular extension of blood has proven to be accurate predictors of outcome. Less commonly, age, sex, hypertension and mass effect may indicate harmful effects on outcome in patients with ICH.[262]

No prospective randomised controlled study, in which surgical and medical management of SICH has been compared, has claimed a significant superiority of either medical or surgical management.[23,48,153,229,230,327,359]

However, there are non-randomised series reporting the benefits of surgery.[35,158,257] Recently, three randomised control trails evaluating new strategies for the treatment of the ICH have been completed.

The International STICH trial[219] (early surgery versus initial conservative treatment in patients with spontaneous supratentorial ICH) concluded that there is no evidence of an overall benefit of early surgery when compared to initial conservative treatment. One finding in a predefined subgroup, that patients with superficial haematomas might benefit from surgery (craniotomy), needs further exploration.

Stereotactic aspiration combined with instillation of fibryinolytic agent[327] (the SICHPA trial): The trial was prematurely stopped due to low recruitment. A cautious conclusion could be made that stereotactic aspiration of supratentorial haematoma after instillation of a plasminogen activator can be performed safely. It may reduce the haematoma volume significantly.

Ultra-early haemostatic therapy by using the recombinant activated factor VIIa[213] (the Novo-7 trial): Treatment with activated factor VII within 4 hours reduced haematoma expansion, decreased mortality, and improved clinical outcome significantly, despite slight increase in the risk of thromboembolic events.

The author recommends that patients with smaller haematomas who are alert, stable or improving should be treated medically and the patients with larger haematomas who show progressive neurological deficit, prolonged functional impairment and intracranial hypertension should be treated surgically. Patients with a GCS score less than 5 should also be treated medically because they uniformly die or have extremely poor functional outcome that cannot be improved by surgery. Easily accessible supratentorial haematomas with mass effect, especially in the young and in those with a GCS score greater than 5, must be evacuated. Patients with cerebellar haemorrhages greater than 3 cm or in whom brainstem compression and hydrocephalus are present, should undergo evacuation of the clot.

Further study of the dynamics of haemorrhage and additional results are needed prior to making a decision on how to divide patient management into the two categories of surgical and non-surgical treatment. The proposed STICH II Trial, hopefully, will solve many unanswered questions.

Pontine and Midbrain Haematomas

Pontine haemorrhages are devastating events. This haemorrhage is most commonly at the junction of the tegmentum and the basis pontis. The classical findings are those of quadriplegia, pin point pupils, paresis of horizontal eye movements and rapid progression to coma. Initially, the weakness may be asymmetrical but in the later stages, as the neurological deficits advance, quadriplegia predominates. The pupils are classically pin-point because of interruption of bilateral sympathetic fibres. Hyperpyrexia can occur but its abscense does not preclude the diagnosis.

These are unique brainstem lesions. The presentation is acute in about two thirds of the cases, and subacute and chronic cases do occur. Presentation is with neuro-ophthalmological abnormalities, loss of consciousness and headache. This may be accompanied by hemiparesis, hemisensory loss or ataxia. Vascular malformations are suspected in about a third of cases and in a similar number no underlying cause is found. Most patients improve with supportive care, although in rare instances surgery may be required if there is an underlying vascular malformation like cavernous angioma.

Cerebral Venous Thrombosis

Cerebral venous and dural sinus thrombosis (CVT) is an infrequent stroke type often described as having an unpredictable outcome.[34] A series of publications from India suggest that venous strokes, especially in women, during pregnancy and puerperium are not uncommon. Puerperal CVT may account for 15–20% of stroke victims in the younger age group. Bansal et al. reported an incidence of 4.5 per 1,000 obstetric admissions. Comprehensive reports have been provided by Chopra and Banerjee, and Srinivasan. Nagpal reported surgical treatment of primary cortical vein thrombosis in 32 selected cases.[21,50,236,308] Neurosurgeons are often involved in the care of patients with cerebral venous sinus thrombosis. Under rare circumstances, open surgical interventions may be considered, including open thrombectomy and decompressive craniectomy. Neurosurgeons should also be prepared to treat late complications of cerebral venous sinus thrombosis, including pseudotumour cerebri and dural arteriovenous fistulas[27,174]

Paediatric Stroke

The first population-based study of stroke in children from the 1970s found an incidence rate of 2.52 per 100,000 children for all stroke types.[294] The reported incidence and prevalence of stroke in children has increased over time due to improvement in imaging techniques. Neonatal/Perinatal stroke (CVAs that occur between 28 weeks of gestation and 28 days of post-natal age) is under recognised clinically. The reported causes of neonatal stroke have included cardiac disorders, infection, blood abnormalities, and/or perinatal events, yet in a large number of cases the cause remains undetermined.[77]

Cardiac disease is a common cause of childhood stroke (CVAs that occur between 30 days and 18 years of age), accounting for up to 50% of strokes, and coagulation abnormalities account for 38%.[66] Other risk factors for stroke in children include infection, moyamoya disease, arterial dissection and other rare genetic disorders.[172,180]

Haemorrhagic stroke is less common than ischaemic stroke in children as in adults. Excluding neonatal

intraventricular haemorrhage, structural vascular lesions are the most common cause of SICH in children.[199] Arteriovenous malformations (AVM) are the most common cause of haemorrhagic stroke in children. Approximately 10–20% of all AVMs will become symptomatic during childhood.[221] The most common cause of cerebellar haemorrhage in an otherwise healthy child is the rupture of a vascular malformation.[278] An underlying structural lesion should be sought in all paediatric patients presenting with SICH. We recommend that MR imaging and angiography be undertaken in all paediatric patients suffering unexplained SICH as well as follow-up imaging if no cause is found. Treatment recommendations are based on small, non-randomised trials or adult stroke studies.[42]

SURGERY IN STROKE REHABILITATION

There are no pharmacological measures available to enhance central nervous system restorative processes after acute stroke, and implantation of stem cells provides one promising approach, not only for cell replacement but also for the provision of therapeutic molecules.[104]

Stem cell therapy is still at the beginning of the road.[190] Cell transplantation is an experimental approach to restore brain function in neurodegenerative disorders such as Parkinson's and Huntington's disease.[343] Various cell types are under investigation in experimental stroke studies. Human neuronal cells can be produced in culture, delivered frozen to a hospital, thawed and processed, and implanted stereotactically into the brains of patients with stroke. Douglas Kondziolka et al.[184] reported the safety and feasibility of neuronal transplantation for patients with motor stroke and noted improvement in patients with stroke. Following transplantation, progenitor cells proliferated and differentiated into all the different brain cell types, including neurons, and they repopulated the ischaemic infarct.[288] The survival, integration and efficacy of neural transplants in stroke patients will depend on the type, severity, chronicity, adequacy of circulation and location of the stroke lesion.[289]

The first clinical trial[246] of neural transplantation in stroke patients is a milestone in stroke therapy.

While the consensus is to create a functional neuronal circuitry in the damaged host brain, there is growing evidence that trophic action of the grafts and host, as well as exogenous application of trophic factors may facilitate functional recovery in stroke. Experimental work at AIIMS, New Delhi, India, suggested a partial recovery of the vocalisation response following amygdala tissue transplantation.[147]

Stem cell research presents many ethical and scientific questions as well as future challenges. Validation of neural transplantation and any other treatment for stroke should critically be assessed in laboratory experiments and limited clinical trials. A multricentric trial, supported by the Department of Biotechnology, Government of India, on stem cell therapy is ongoing in India. Lessons learnt from earlier experimental studies on foetal neural transplant at the All India Institute of Medical Sciences need to be given heed to in this regard; and more recently highlighted by Magnus et al.[203,323,324]

CONCLUSION

Stroke is an age old problem. Sushrutha called it 'pakshavada', while Hippocrates called it 'apoplexy'. There have been many terms since. Now, the term is 'Brain Attack'. The idea is to create awareness among the public and the family physicians of not only the severity of the problem, but also the urgency, similar, in almost every way, to that of a heart attack.

Risk factor management and primary prevention continue to be key measures. Unfortunately, despite recent advances in stroke treatment and research, the general approach to caring for the acute stroke patient has been one of benign neglect and stroke continues to be the second leading cause of death and the most common cause of disability in the world. A hospital-based prospective study in North-West India,[255] evaluating the knowledge of stroke among stroke patients has shown that even after self-recognition of stroke symptoms, patients have responded late as they interpreted their symptoms as 'not serious'. For prompt treatment and prevention of stroke effective educational campaigns are necessary. While designing these programs, it should be recognised that patients often fail to identify and misinterpret stroke symptoms and this is independent of their educational status.

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SECTION

9

Tumours of the Spine and Spinal Cord

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103 Clinical Features and Diagnosis

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The most important surgical problem with reference to the spinal cord and the cauda equina is compression by lesions arising from structures outside the spinal canal, in the vertebrae and intervertebral discs or by lesions arising inside the spinal canal. The compression may be the result of congenital malformations, trauma, infection or neoplasms and the clinical syndromes are often similar.

HISTORICAL BACKGROUND

Morgagni,[31] the founder of modern pathological anatomy, referred in 1769 to the occurrence of spinal cord paralysis due to compression by a tumour. According to Elsberg,[12] the first convincing description of a primary spinal cord tumour was by Phillips[37] who described, in 1792, a tumour of the dorsal and lumbar cord.

Velpeau,[53] in 1825, published a paper in the Archieves de Medicine in which he gave a good description of an apparent cauda equina tumour and also referred to another case published by Chaussier. In 1837, Olivier[35] published his remarkable work "Traite de la Moelle Spiniera et de ses Maladies" which contains in its second volume, the complete clinical histories of four cases of extramedullary spinal tumours. In 1842, Curveilhier[8] in his pathological atlas of tumours gave an illustration of a spinal cord tumour causing 'paraplegic douleureuse'. Thus, it is seen that the entity of spinal cord tumour was recognised since the 18th century, though it was only in the latter part of the 19th century that surgical relief became possible. Victor Horsley, in 1887, was the first to successfully remove a spinal cord tumour diagnosed by William Gowers.[18] In 1883, MacEwen of Glasgow removed an epidural neoplasm in a boy aged nine, the first such operation in a child. Elsberg,[10] starting from 1911, published a number of monographs, the last one in 1940.[12]

CLASSIFICATION

Neoplasms causing cord compression may originate from structures inside the spinal canal or the vertebral column, or may spread into the spinal canal from outside.

TUMOURS OF THE SPINAL CORD

According to their anatomical location, spinal tumours are conveniently classified as extradural and intradural, although some tumours could be both inside and outside the dura. Intradural tumours could be intramedullary or extramedullary. Benign and malignant neoplasms may arise from intraspinal structures like the meninges, spinal cord, nerve roots, blood vessels and other tissues. These are ten times less frequent than intracranial tumours, with the majority of them being benign.

Primary Extradural Tumours

These tumours are relatively uncommon, accounting for 19% in the series of Elsberg.[11] Neurinomas, meningiomas and lipomas occur in that order of frequency. Rarely, a secondary malignant tumour is encountered in the extradural space without involvement of the bone. Extradural cysts, congenital or acquired, may cause cord compression as also a traumatic or spontaneous spinal extradural haematoma. The other causes of extradural compression are non-specific granulomas, tuberculomas and hydatid cysts. Cases of spinal compression due to extramedullary haematopoiesis in the epidural space have been reported.[3,7,21,28] Cord compression may also be produced by expanding aortic aneurysms.[33,42,43]

Intradural Extramedullary

These tumours are the most common intraspinal tumours (67% in the series of Elsberg),[12] neurinomas and meningiomas being the most frequent. Due to the presence of the filum terminale, intradural extramedullary ependymomas can occur in the cauda equina region. Huge tumours growing in the region of the cauda equina have been termed giant tumours of the cauda equina and include neurinomas, meningiomas and ependymomas.[5,38]

Intramedullary Tumours

Most of the intramedullary tumours (14% in the series of Elsberg)[12] are malignant and belong to the glioma group. Both astrocytomas and ependymomas are more benign

in the spinal cord than in the brain. Intramedullary tumours may become partly extramedullary when they break through the confines of the cord. Most of the developmental tumours, epidermoids, dermoids and lipomas are intramedullary lesions. Angiomas, AV malformations and haemangioblastomas also belong to the same group, though the bulk of these lesions may be truly extramedullary.

TUMOURS OF THE VERTEBRAL COLUMN

Benign tumours of the vertebral column are rare, and include haemangioma, chondroma, giant cell tumour, osteoma and fibroma. As these arise from the body of the vertebra, the spinal cord is compressed from the front. Aneurysmal bone cyst usually affects the posterior neural arch, i.e. the spinous process, the lamina and the transverse process, producing a cystic enlargement of these structures.[39] Other benign lesions are chondromas, chondromyxoid fibroma[41,46] and giant cell tumour secondary to primary hyperparathyroidism. Non-neoplastic benign lesions of the vertebral column that cause cord compression are multiple hereditary exostoses, Paget's disease,[44,49,52] fibrous dysplasia, achondroplasia, severe kyphoscoliosis and fluorosis. The diagnosis is easily confirmed on X-ray examination because of the characteristic radiological appearance.

Primary malignant tumours of the vertebrae are uncommon, and include chordoma and solitary plasmacytoma. Sarcoma is an uncommon tumour, seen most frequently in children and young adults. As the neural arches are usually involved, a swelling may be palpable in the paraspinal region.

Secondary malignant deposits are the commonest tumours of the vertebral column, being in some series more frequent than even the intraspinal neurogenic tumours. Breast, lung, thyroid and prostate are the common sites of the primary lesion. Reticuloendothelial tumours, like lymphomas and multiple myelomas, may cause multiple deposits in the bone.

Intraspinal Extension of Paravertebral Tumours

Malignant lesions, like neuroblastomas, Ewing's tumour, reticulum cell sarcoma, lymphosarcoma and Hodgkin's disease, frequently invade the extradural space through the intervertebral foramen or by destroying the bone. Benign paravertebral lesions may also cause cord compression or cord ischaemia. Tumours in the neck, mediastinum or the abdomen may rarely extend into the canal through the intervertebral foramina, for example, neurofibromas, ganglioglioma, sympathicoblastoma, dermoids and benign cysts.

PATHOPHYSIOLOGY OF CORD COMPRESSION

Like the brain, the spinal cord is also confined in a space which has no capacity for expanding. Space-occupying lesions in the spinal canal cause compression of the structures with resultant neurological deficits. Rapidly growing lesions cause severe loss of function as there is no time for the spinal cord to adjust itself. On the contrary, a slow growing tumour may attain a large size and the cord may still be viable although displaced and thinned out. The lesion may compress and occlude vascular structures on the surface of the cord or in the intervertebral foramina. As the lesion grows, the veins are compressed resulting in congestion and oedema. Arterial compression occurs at a later stage and may sometimes lead to distant effects as happens when the vertebral artery is compressed by a foramen magnum lesion. Pressure at the level of the 4th and 5th dorsal segments may cause a greater deficit because of the watershed area in the vascular supply of the cord at this level. Extradural metastatic tumours often cause symptoms by interfering with the vascular supply of the cord. Vascular tumours may produce a steal syndrome by taking away the blood from the affected region of the spinal cord.

In addition to the vascular effects, direct pressure on the cord and nerve roots leads to interference with conduction, the long tracts being affected early. Hard tumours are likely to cause early and greater disturbance than soft tumours which can exist for a long time and grow to a bigger size. This is similar to the varying effects of hard and soft acoustic neurofibroma on the brainstem.[45]

The presence of a tumour interferes with the normal movements of the cord which occur during movements of the spinal column. Such impairment contributes to cord damage. Lumbar puncture and myelography can sometimes cause a shift in the position of the tumour leading to a sudden increase in the neurological deficit. The degree and rate of recovery after removal of the compression depends on various factors like the duration, severity and location of the compression and the changes in the vascular supply of the spinal cord already produced by the lesion. In long-standing tumours, there may be gliosis in the spinal cord due to ischaemia and the recovery may be incomplete, despite complete removal of the tumour. This is more commonly seen in a meningioma where the recovery is often slow.

SYMPTOMS AND SIGNS OF SPINAL COMPRESSION

While the diagnosis of cord compression may be obvious in a few cases, it is often delayed because of variations in the presenting symptoms which may simulate other diseases and the variability of the progress of the symptoms. However, once the suspicion of the diagnosis is aroused, the symptomatology falls into place with precision because of the well-defined specific functions of the spinal cord at various levels.

The symptoms and signs include those produced by the involvement of the nerve roots (posterior and anterior), the cord segments and the long tracts, viz. the

motor, sensory, autonomic and other tracts. Some signs pertaining to the spinal column may also become apparent.

Involvement of the Posterior Root

Root pain, a symptom of posterior nerve root involvement, is the result of pressure or, more commonly, of stretching of the nerve root by the tumour. It occurs as an early symptom of an extramedullary tumour, and is usually unilateral in benign tumours and bilateral in malignant tumours. The pain radiates from the proximal to the distal region, although, occasionally, a root irritation may manifest itself as a spread of pain from the periphery to the centre. The pain is often of a burning, hyperaesthetic type in the early stages. When the thoracic roots are involved, the constricting pain is referred to as girdle pain, especially when bilateral. Root pain is increased by coughing, sneezing and movements of the spine, or by any manoeuvre which increases intraspinal pressure like compression of the jugular veins. It can persist for months before the occurrence of symptoms of cord compression, at the onset of which it may disappear. Though root pain is most commonly seen in extramedullary tumours, it may appear in about 20% of intramedullary tumours also. Elsberg[12] in his series reported root pain in 2/3rds of intradural, 1/3rd of extradural and is less than 1/6th of intramedullary growths.

In clinical practice, the proper understanding and appreciation of root pain becomes important; otherwise it may result in a wrong diagnosis. This is not uncommon in patients in whom the root pain is the sole complaint without any other clinical sign. Thus, D4 root pain on the left side may simulate heart disease. D8-D10 root pain may simulate diseases of abdominal organs, like the gallbladder, appendix and kidney, while cauda equina pain may simulate disease of the pelvic viscera. The radiation of pain, the accompanying hyperaesthesia and the worsening of pain with certain postures or with coughing or sneezing help to arouse suspicion of nerve root involvement. Irritation of the posterior root may result in pruritis in the dermatomal distribution and a rash.[25] With posterior root involvement, objective sensory loss occurs when at least two adjacent roots are involved.

Involvement of the Anterior Nerve Root and Anterior Horns

As the symptoms and signs of involvement of the anterior nerve root and the anterior horn are the same, it is clinically impossible to differentiate one from the other. While the anterior nerve roots are involved only in extramedullary tumours, the anterior horns can be involved in both intramedullary and extramedullary tumours.

Involvement of either the anterior nerve root or the anterior horn is indicated by progressive lower motor neuron paralysis, wasting and fasciculations of the involved muscles with loss of reflexes. The symptoms are more conspicuous when the cervical or the lumbosacral segments of the spinal cord or the nerve roots are compressed. In case the dorsal segments are involved, the wasting and weakness of the paravertebral muscles results in scoliosis. As the muscles have multisegmental innervation, involvement of a single anterior nerve root or anterior horn cells of one spinal cord segment may not produce recognisable weakness or wasting of the muscles. Lower motor weakness with wasting or loss of a tendon or a cutaneous reflex has an early localising value. For example, weakness of extension of the elbow with normal power in the flexors, or a loss of the triceps jerk with an intact biceps jerk indicates a lesion of C7 cord segment. Fasciculations of the muscles are more common when the anterior horn cells are involved and, thus, are more frequently seen in intramedullary tumours. With a careful and detailed search, it is possible to detect fasciculations in the wasted muscle more frequently.

Chronic irritation of the anterior horn cells by tumour or their isolation from other neuronal influences may occasionally lead to a very high rate of firing by these neurons, resulting in continuous activity or spasm of the muscles of the concerned segment[26,47] or in a localised myoclonus.[15,19] Pseudomyotonia of the hands and fingers, similar to that seen in Thomsen's disease, may occur in cervical cord compression.[13,14,48] In some rare instances, one may see the fasciculations in regions of the body far removed from the involved spinal segment due to interference with pyramidal tract function, a phenomenon termed parabiosis by Okhrimenko and Brodovskaya in 1961.[34]

Segmental Involvement

Although segmental involvement of the cord may occur in extramedullary lesions, it is common in trauma, haematomyelia and intramedullary lesions. The clinically significant areas affected are the anterior horns and the crossing of the spinothalamic tracts, in addition to the long tracts affected at that level. The symptoms of anterior horn cell involvement have been discussed. Anterior horn cells will be involved early when the tumour is situated either anterior or anterolateral to the spinal cord, and late if the tumour is situated posterior to the spinal cord.

Involvement of the Long Sensory Tracts

Subjective disturbances resulting from the involvement of the long sensory tracts are widespread unlike those caused by posterior root involvement. Subjective numbness, tingling, burning, sensation of cold and 'pins and needles' are produced by irritation of the sensory pathways in the spinal cord. Initially prominent on the side opposite to that of the tumour, the symptoms become bilateral with gradual increase in pressure.

Subjective sensory disturbances are more common in intramedullary lesions. In cervical lesions, irritation of the posterior column leads to Lhermitte's sign.[1] The patient feels a sudden electrical shock-like sensation all over the body when the neck is flexed. In 1918, this symptom was originally described by Babinski and Dubois.[4] Lhermitte, in 1924, only pointed out the value of this sign in multiple sclerosis, but somehow his name got attached to the sign. The Lhermitte's sign is seen in 38% of patients with multiple sclerosis (MS). It was first described in neck flexion. It is not specific to MS. An increase in pyramidal tract deficit caused by neck flexion and a corresponding improvement of the symptom with neck extension is suggestive of a compressive pathology in the cervical cord. This is called Bristow's symptom.[29] Lhermitte's sign in flexion is an electric shock like sensation in the trunk and limbs on neck flexion. This is seen in MS plaques at DREZ, subacute combined degeneration of the cord, cervical extramedullary tumour and radiation myelopathy. Reversed Lhermitte's sign is the same symptom seen in neck extension and is due to the buckling of the ligamentum flavum into the already compressed cervical cord as seen in cervical spondylosis.[20]

Sensory Disturbances

The objective disturbances vary according to the site of origin of the lesion and direction of its spread and, thus, many varieties of involvement may be seen. A few definite patterns are identifiable with regard to the levels of sensory loss, their direction of spread and the modalities involved. From these it is possible to differentiate between extramedullary and intramedullary lesions.

There is a lamination or grouping of fibres in the lateral spinothalamic tract, the fibres originating from the most distal parts of the body being situated peripherally and those from the proximal parts of the body situated centrally. This arrangement accounts for the differences in sensory disturbances in extramedullary and intramedullary tumours.

In extramedullary tumours the sensory disturbance is maximal in the distal parts of the body, being minimal near the level of the lesion. In other words, the sensory disturbance is of the ascending type, the sensory loss starting in the distal parts of the body and slowly progressing proximally. Depending upon the stage at which the patient is seen, it is possible to find an area of normal sensation between the band of root hyperaesthesia or anaesthesia and the main area of loss of sensation.[22] In such cases, if the more proximal root disturbance is missed, the neurological localisation of the tumour may be made erroneously at a level many segments lower.

On the contrary, in intramedullary growths the maximum sensory disturbance is at and below the segmental level of the lesion. The degree of sensory loss diminishes in a descending direction and hence 'anal sparing' or sparing of sacral dermatomes is a characteristic feature of an intramedullary growth. Ghosh et al.[17] pointed out that sacral sparing is neither a consistent feature of intramedullary tumours nor restricted to them.

In intramedullary growths, there may be dissociation between the degrees of sensory loss for the various types of sensory modalities. As the crossing of the spinothalamic fibres is affected early, pain and temperature loss may be the only sign for some time before the bulk of the lesion increases and compresses the posterior columns leading to loss of touch sensation. This dissociation of anaesthesia is not as commonly seen in intramedullary tumours as in syringomyelia. It must also be remembered that in both extramedullary and intramedullary tumours, the intensity of loss of tactile sensation is less than that of pain and temperature because of the presence of dual pathways for touch.

In advanced cases these finer differences are lost. There is neither anal sparing nor dissociation of anaesthesia in intramedullary tumours; nor is an area of normal sensation between the root lesion and the main area of sensory loss found in extramedullary lesions. Under such circumstances the clinical picture of the two lesions may be identical.

In spinal compression due to tumours there are always some differences between the sensory changes on the two sides of the body, these being more pronounced on the side opposite to that of the tumour.

MRC Classification of Sensory Nerve Dysfunction[23]

Grades:

S0—No sensation.

S1—Deep pain sensation.

S2—Skin touch, pain and thermal sensation, i.e. protective sensations present.

S3—S2 along with accurate localisation but deficient stereognosis. Cold sensitivity and hypersensitivity are often present.

S3^{+}—Object and texture recognition but not normal sensation. Good but not normal two point discrimination.

S4—Normal sensation.

Motor Disturbance

Involvement of the pyramidal tract results in loss of voluntary power, spasticity, exaggerated tendon reflexes and positive Babinski's sign on the same side. The ipsilateral limbs are affected first, followed by the opposite limbs, unless the tumour is in the midline, when both sides are affected simultaneously. Asymmetry in weakness, in spasticity and in reflex disturbances between the two sides is characteristic of a tumour, in contrast to degenerative disorders like primary lateral sclerosis or amyotrophic lateral sclerosis. By the time the compression is far advanced, the asymmetry gives place to a symmetric total paralysis on both sides resembling the picture of transverse myelitis. An extramedullary tumour in the cervical region affects the ipsilateral upper limb first, followed by the ipsilateral lower limb, the opposite lower

limb and finally the opposite upper limb. Occasionally, the motor disturbance may start in the contralateral limb first due to pressure on the opposite pyramidal tract by the bony margin of the neural arch as the spinal cord is being displaced by the tumour.

Pressure on the spinocerebellar tracts produces ataxia and tremor in the limbs of the same side. Hypotonia may occur early and may be so prominent as to suppress exaggeration of reflexes even when Babinski's sign has become positive. Unstable gait or difficulty in jumping or standing on one foot may be obvious in the early stages, before weakness sets in. But, in practice, this is seen only rarely, as by the time the patient presents, the pressure has involved not only the spinocerebellar tracts but the pyramidal tracts as well. Nystagmus has been observed as a distant sign of spinal cord tumours. Sercl and Kovarik[51] observed this in 21.3% of cervical tumours.

Though a tumour may arise from one side and cause predominant involvement of one half of the spinal cord, the Brown-Sequard syndrome is not a common finding in spinal cord tumours. Partial types of the syndrome may be seen, especially in the cervical region and are more commonly due to extramedullary than intramedullary lesions.

Sphincter Disturbances

Disturbances of micturition appear when there is a loss of function in both the pyramidal tracts, in the sacral spinal cord centres or in the corresponding nerve roots in the cauda equina. Depending upon the location of the lesion, the bladder disturbances would vary. Intramedullary tumours affect bladder function early, as the upper motor neuron fibres to the bladder lie deeper in the lateral column and occupy an area nearer the centre of the spinal cord.[32] The autonomic fibres subserving micturition travel on the dorsal aspect of the lateral columns.[24] If the tumour is situated above the level of the sacral centres of micturition and the compression is partial, uninhibited neurogenic bladder results, manifesting as urgency and precipitancy. Advanced compression results in a reflex or an automatic bladder. Pressure on or destruction of the sacral centres or the corresponding roots of the cauda equina causes an autonomous bladder.

Bowel Function

Tumours above the level of the sacral centres impair voluntary control of the sphincter and the sensation of rectal urgency is lost, resulting in constipation. Involvement of the sacral centres or the corresponding roots of the cauda equina leads to paralysis of the sphincter and faecal incontinence.

Disturbances of Autonomic Functions

Interference with the sympathetic pathways in the spinal cord leads to a characteristic dryness of the skin below the lesion. By running one's hand across the body the level of the tumour could be localised by noting the level at which the dryness of the skin starts. The skin of the involved areas is not only dry but often warm (occasionally cold) and flushed also. Segmental hyperhidrosis is an uncommon finding which is usually associated with irritation or infiltration of preganglionic sympathetic fibres or the sympathetic chain. Segmental hyperhidrosis should trigger a search for structural disease in the spinal and paraspinal region.[50] Trophic disturbances of the skin may also be seen. Interference with the parasympathetic centres in the sacral region leading to disturbances of bladder function has already been mentioned. Autonomic, sensory and motor deficits also interfere with the complex sexual function. Rarely, priapism may be seen in thoracic cord lesions, with retention of the ejaculatory mechanisms. At lower levels sexual function is lost.

Skeletal Symptoms and Signs

Gibbus and, sometimes, a paraspinal swelling may be present in malignant tumours of the vertebral column. Dumb-bell neurofibromas in the cervical region may be palpable in the anterior or posterior aspect of the neck. Obliteration of cervical or lumbar lordosis with limitation of movements may be seen in extramedullary tumours of the spinal canal and is the result of muscle spasm due to root irritation. Intramedullary tumours, when slow growing, may cause scoliosis due to weakness of the muscles supplied by the involved segments.

In primary and secondary malignant tumours of the vertebral column, the spinous process of the affected vertebra often becomes tender. On the contrary, in extramedullary tumours, the tenderness of the spinous process is felt not at the vertebra overlying the tumour, but a lower level, viz. at the vertebra supplied by the affected posterior nerve root. Thus, a tumour situated at the level of the D4 vertebra will cause tenderness of the D6 spine, as the concerned spinal cord segment is D6. In tumours of the cauda equina several spines of the lumbar vertebra may be tender, as several roots are stretched. Head compression can elicit radicular symptoms. This is known as Spurling's neck compression test.[6]

There are three methods of eliciting spinal tenderness, each with its own significance. The first is direct tenderness which is elicited by pressure over the spinous process. A pathology involving the process or an advanced stage of the pathology of the vertebral body will cause tenderness. The second is twist tenderness elicited by attempting to twist the spinous process between the thumb and the hand. Early vertebral pathology and posterior element pathology produce tenderness. The third method is deep thrust tenderness which is elicited by a guarded thrust with the proximal part of the ulnar side of the fist. This must be done very carefully.[36]

CLINICAL FEATURES OF TUMOURS AT DIFFERENT LEVELS

Because of the precise anatomical structuring of the spinal cord based on its function, careful examination of the various functions of the cord should give one an

accurate idea of the level of the lesion. In practice this is not often true and though one can predict the presence of a compressing lesion, exact localisation may not be possible in a number of cases. Ghosh et al.[17] analysing 60 cases of spinal compression, found that in 40% clinical examination failed to establish the level of the lesion. They also found that total myelographic block of the spinal subarachnoid space was compatible with intact sensations.

Errors may also occur sometimes in the diagnosis of the side of the tumour. The tumour, as it grows, displaces the spinal cord which gets compressed against the bony margins of the neural arch. In case the signs and symptoms of such compression predominate over those due to direct pressure by the tumour on the cord, then the side of the tumour is incorrectly localised to the opposite side. Thus an anterior tumour is diagnosed as a posterior one and a right sided tumour may be mistaken for one arising from the left side.

Despite these observations, a careful neurological examination helps not only to diagnose and localise the tumour but also to predict the prognosis and to evaluate improvement after therapy.

Pyramidal tract dysfunction and disturbances of the long sensory tracts are less useful in indicating the level of lesion, than root pain, root hyperaesthesia, lower motor neuron muscle paralysis or loss of reflexes, when present. At some levels, clinical localisation is more difficult than at others, for example, at the level of the foramen magnum and the conus medullaris.

Tumours at the level of the foramen magnum or cervicomedullary junction are notoriously difficult to diagnose and are often missed in the early stage. They may grow to a large size before symptoms appear, because of the relatively large subarachnoid space in the cervicomedullary region.[9,27,40] They may cause spinal cord symptoms, intracranial symptoms or both, depending on the direction of spread.

Intracranial symptoms may appear early or later and include papilloedema and hypoglossal weakness or paralysis. Sleep apnoea can be a presenting symptom.[2,54] Suboccipital headache is an early and constant feature of lesions in this region, present long before the signs of cord pressure become evident. This headache is due to spasm of the suboccipital muscles as well as to irritation of the C2 sensory nerve root. Pain in the C2 dermatome becomes clinically significant if numbness and paraesthesia develop in the same dermatome. Torticollis may occur due to unilateral muscle spasm.

Signs and symptoms, referable to a clinical level far below the tumour, may occur and confuse the clinical picture, e.g. wasting of the small muscles of the hand and of the muscles of the neck may be seen in foramen magnum tumours and is due to compression of one or both vertebral arteries or the anterior spinal artery, whose branches supply the cord down to the D4 segment. Compression of the vertebral arteries may occur on turning the neck resulting in vertigo, dizziness, unsteadiness or syncope. In 1993, an excellent review of their experience of 230 tumours at the level of the foramen magnum, collected from 21 French departments, has been presented by George et al.[16]

Lesions above C4 are said to be in the blind zone of the cervical cord. They can be elicited by the Shimizu reflex. This was first described by Shimizu in 1993. The patient is seated with the elbow flexed to 90 degrees and the forearm supinated. The examiner taps the tip of the spine of the scapula in a caudal direction with the reflex hammer. The reflex involves movement of the scapula from an abrupt stretching of the upper part of the trapezius. The reflex is said to be positive if there is scapular elevation with or without abduction of the humerus and is suggestive of cord compression between C2 and C4.[6]

Upper cervical cord lesions assume serious significance, because of interference with respiratory and vasomotor functions. Bilateral phrenic nerve paralysis may occur in the later stages or may follow surgery requiring assisted respiration. Owing to poor respiratory excursions, the patient may not be able to speak or raise his voice above a whisper. Occasionally, the respiratory paralysis may set in only during sleep, thus requiring a constant watch. The vasomotor paralysis may be extensive so as to cause sudden hypotension with change of posture.

Pain in the neck and in the occipital region made worse by movements of the neck is a characteristic feature of high cervical lesions. The pain may also radiate to the interscapular region. All the limb reflexes are exaggerated with positive Hoffman's reflex. Examination of the functions of the cervical and sternomastoid muscles and detection of sensory loss in the area supplied by the cervical cutaneous plexus helps in localisation of the level. It is to be remembered that C3-4 roots supply the region over and just below the clavicle in front of the chest up to the level of the sternal angle.

Tumours arising opposite the lower cervical segments can be localised by examination of the muscles and reflexes in the upper limb. Lesions at the 5th cervical segment cause wasting and weakness of the deltoid. When the biceps is intact but the triceps is involved, the lesion must be as high as the C6 nerve root. Inversion of the radial reflex with loss of the biceps jerk, and an exaggerated triceps reflex point to a lesion at the C5 level. The triceps is spared in C7 lesions. Examination of the hand muscles will differentiate between C7, C8 and T1 lesions. In addition, the distribution of the root pain or the presence of hyperaesthesia or subjective numbness also helps to localise the cervical root levels. While C5 sensory involvement causes hyperaesthesia or pain over the shoulder and the lateral aspect of the arm, in C6 root involvement there is pain or diminished sensation along the outer aspect of the forearm, the thumb and the index finger. Pain radiating to the middle finger indicates C7 involvement, whereas irritation of C8 and T1 causes pain along the ring and little fingers and the medial aspect of

the upper limb. Horner's syndrome may be elicited in T1 level lesions due to involvement of the sympathetic system.

Clinical assessment of the diaphragm is important in all cases of cervical spine lesions. Sniffing is an important sign which is impaired in diaphragmatic lesions. Shoulder paresthesia or tenderness is of clinical significance. Hoover's sign wherein there is epigastric angle widening with intercostal contraction; this is counterbalanced by the diaphragm and is absent in paresis of the diaphragm. Tidal percussion done in the lower border of the 5th rib in the midclavicular line gives an idea of diaphragmatic excursion. The normal diaphragm moves up to the 6th intercostal space during inspiration.

Dorsal Lesions

The level of the lesion in the dorsal region can be assessed accurately from the root pain or sensory loss. In the upper part of the trunk, the C3-C4 roots supply the infraclavicular region and the D3 root the area just below on the trunk; the D4 level is at the nipple, D6 over the epigastrium, D10 at the umbilicus and D12 over the hypogastrium. When the lesion is at D10 level, the upper abdominal muscles are normal while the lower muscles are paralysed. This results in upward movement of the umbilicus when the patient attempts to sit up from a supine position (Beevor's sign). Extensive involvement of the dorsal cord may result in wasting of the paraspinal muscles leading to kyphosis or scoliosis and is more common in intramedullary lesions.

Upper Lumbar Segments

Following compression of the first and second lumbar segments the abdominal reflexes are preserved, the cremasteric reflex is lost and the knee jerks are exaggerated. If the tumour involves the second, third and fourth lumbar segments, the cremasteric reflexes are intact, the knee jerks are diminished or lost and the ankle jerks are exaggerated. There is wasting of the quadriceps with weakness or loss of extension of the knee.

Epiconus Syndrome

This results from involvement of the L4-L5-S1 and S2 spinal cord segments. It is characterised by weakness of abduction, external rotation and extension of the thigh, and impaired flexion of the knee, and dorsi and plantar flexion of the ankle. Sensory disturbances occur in the L4 to S2 dermatomes. The knee jerk is preserved and the ankle jerk is lost. The bladder and rectum empty reflexly.

Conus Syndrome

The lower three sacral and the coccygeal segments comprise the conus medullaris. The clinical picture due to involvement of the conus is characterised by: (1) retention of urine with overflow; (2) faecal incontinence; (3) impotence and (4) perianogenital or saddle anaesthesia. Sensory disturbances occur in the S3, S4 and S5 dermatomes. There are no motor disturbances in the lower limb. The plantar reflex is flexor and the knee and ankle jerks are normal.

At the level of the conus medullaris a large number of nerve roots take origin and thus a differentiation between a conus lesion and a cauda equina lesion is sometimes difficult.

Cauda Equina Syndrome

The cauda equina consists of the five lumbar, five sacral and two coccygeal nerve roots in the spinal canal (a total of about 48 nerve roots) and extends over several vertebral levels; thus the clinical picture in tumours of the cauda equina varies according to the level and the number of nerve roots affected. If the tumour is small, only a few nerve roots will be affected with corresponding lower motor neuron signs, whereas a large tumour will implicate all the nerve roots at that level. Pain is a common symptom and occurs in 95% of cases.

At the L2 vertebral level all the nerve roots can be implicated excepting L1 which exits between the L1 and the L2 vertebrae. All the muscles of the lower limb manifest lower motor neuron weakness. Anaesthesia is present anteriorly below the level of the groin including the genitalia and, posteriorly below the upper part of the buttocks. There is retention with overflow of urine and incontinence of faeces. All the reflexes in the lower limbs are lost. At the L4 vertebral level, the L1, L2 and L3 nerve roots escape. Hence, sensations are normal over the front of the thigh, and the function of the quadriceps and the knee jerks are normal. Except for this, the picture is the same as seen at the level of L2 vertebra.

When the lesion is below S2 level, there is no paralysis of the muscles of the lower limb. A characteristic saddle shaped area of anaesthesia is seen over the buttocks, perineum, scrotum and penis, and over a small strip running from the perineum down the posteromedial aspect of the thigh. The anal reflex is lost and the reflexes of the lower limbs are normal. Retention of urine with overflow and rectal incontinence will be present. This is similar to or even identical with the conus syndrome and, therefore, neurologically it is not possible to differentiate between them.

A pure conus medullaris lesion is not seen in practice. An extramedullary tumour at the level of the conus compresses both the cauda equina and the conus. Hence, the clinical picture is mixed in the early stages, whereas, in the later stages, a pure cauda equina type of picture is seen. An intramedullary tumour of the conus will initially produce a conus syndrome, but in advanced cases the enlarged spinal cord compresses the roots of the cauda equina and produces either a mixed or a cauda equina type of clinical syndrome.

Differentiation between Extramedullary (Intradural) and Intramedullary Tumours

The clinical differences between an extramedullary and an intramedullary tumour are discussed in Table 1. No single symptom or sign is pathognomonic. The total clinical picture should be critically assessed without giving undue importance to any one symptom or sign.

ALIGNMENT OF CORD SEGMENTS AND VERTEBRAE

The spinal cord is much shorter than the vertebral column and hence the spinal cord segments are not situated opposite the corresponding vertebrae. In the adult, the spinal cord ends at the lower border of the L1 vertebral body. There is a progressive increase in the difference between the cord segments and the vertebral bodies, from above downwards. The eight cervical cord segments extend from the foramen magnum to the upper half of the C7 vertebral body. The twelve dorsal cord segments lie opposite the lower half of the C7 vertebral body up to the lower border of the D9 vertebral body. The D12, D8 and D4 cord segments are opposite the D9, D6 and D3 vertebral bodies, respectively. The lumbar cord segments are opposite the D10, D11 and D12 vertebral bodies. The sacral and coccygeal cord segments, therefore, lie opposite the L1 body.

This knowledge is essential for determining the relationship of the tumour to the level of the spinal column, thus helping in the clinical and radiological examination of the vertebral column, in focusing the site for careful examination during imaging and in helping the correct placement of the incision during surgery. In spite of all recent advances in imaging, even today, it is vital to ascertain first clinically the site of the lesion before ordering an investigation. It is not infrequent, if this dictum has been bypassed by the clinician, to see patients with missed or wrong diagnosis, and investigations ordered for the wrong level.

Table 1: Clinical differences between an extramedullary and an intramedullary tumour

S. No		*Extramedullary*	*Intramedullary*
1.	Root pain	Common and early	Late and uncommon
2.	Sensory loss at the level of the tumour	Nil or slight	Wide
3.	Dysaesthesiae and paraesthesiae (due to irritation of long sensory tracts)	Seldom, if at all	Common at all stages
4.	Subjective sensation of intense cold	Characteristic of high cervical tumour	Not seen
5.	Distant sensory loss (due to involvement of long sensory tracts)	Ascending sensory disturbance and no dissociation	Descending sensory disturbance with dissociation
6.	Muscle spasms (due to irritation of anterior nerve roots)	Fairly common	Infrequent
7.	Lower motor neuron paralysis with muscle atrophy	Absent except when nerve roots with extensive motor supply, like C8 and T1, are involved	Wide
8.	Upper motor neuron paralysis	Late	Early
9.	Sphincter disturbances	Late unless it is in the region of sacral cord	Early
10.	Brown-Sequard type of clinical picture	Late unless it is in the region of sacral cord	Early
11.	Trophic disturbances of skin	Absent	Fairly uncommon
12.	CSF protein	Marked increase	Moderate increase
13.	X-ray spine	Bone changes common	Bone changes only in a few cases
14.	Tenderness of spine	Common	Uncommon

DIFFERENTIAL DIAGNOSIS

In its early stages, a spinal cord tumour may mimic diverse diseases, the root pains in different areas of the body being mistaken for local involvement. In patients with obvious spinal cord involvement, the insidious onset, the progressive course, the initial asymmetrical involvement, the pattern and evolution of the neurological signs and an identifiable clear-cut level of involvement, usually indicate the correct diagnosis. Amyotrophic lateral sclerosis and multiple sclerosis may sometimes simulate a spinal cord tumour in their symptomatology.[30] Vascular malformations of the spinal cord may also result in progressive involvement of the cord with a well-defined level of neurological signs. Syphilitic lesions of the cord, arachnoiditis, disc lesions and syringomyelia are to be considered in differential diagnosis. Radiation myelitis may simulate a spinal cord tumour syndrome. In rare cases, a spinal cord tumour may present with papilloedema. Although this is not uncommon in foramen magnum and high cervical cord lesions, papilloedema may occur in cord tumours lower down, mimicking an intracranial lesion. Such papilloedema is due to increased CSF proteins, diminution of CSF absorption space or basal meningitis.

FUNCTIONAL SCORES IN SPINAL CORD DISEASE

In recent years great importance has been given to scoring systems which provide data about the patient's function in daily life. There are several scoring systems. The systems which are commonly used are given below.

McCormick Classification

McCormick classification[30] of clinical function in patients with intramedullary spinal cord tumours:

Class I: Neurologically normal. Mild focal neurological deficit not significantly affecting the function of the involved limb. Mild spasticity or reflex abnormality. Normal gait present.

Class II: Presence of sensorimotor deficit in the involved limb, mild to moderate gait difficulty, severe pain or dysaesthesia significantly impairing the quality of life, although the patient can still function and walk independently.

Class III: More severe focal neurological deficit with the patient requiring a cane or a brace to walk or with significant bilateral UL involvement, the patient may or may not be able to function independently.

Class IV: Severe deficit with the patient requiring a wheelchair/cane/brace with bilateral UL impairment. Patient not walking.

Nurick's Grading for Cervical Myelopathy

G0: Signs and symptoms of root involvement present, no signs of cord involvement.
G1: Signs of spinal cord involvement, normal gait present.
G2: Slight difficulty in walking, full time employment is not prevented.
G3: Difficulty in walking present which prevents full time employment. The patient is ambulant without support.
G4: The patient is not usefully employed and is able to walk only with help/support.
G5: The patient is chair bound/bed ridden.

Frankel's Grading

A- Absent motor and sensory function.
B- Sensations present, motor function absent.
C- Sensations present, motor present but not useful (corresponds to MRC grade 2 to 3).
D- Sensations present, near normal motor function.
E- Normal motor and sensory function.

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104 Vertebral Tumours

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BENIGN TUMOURS OF THE SPINE

Eight per cent of primary benign bony tumours occur in the spine.[6] Amongst primary tumours of the spine, benign tumours account for 25–35%. Benign tumours tend to occur much earlier than their malignant counterparts with the peak age of incidence being in the second and third decades of life. Benign tumours are sometimes classified according to the part of the vertebra that they affect. Osteoid osteoma, osteoblastoma and aneurysmal bone cyst tend to involve the posterior elements, whereas the anterior elements are affected by giant cell tumour, haemangioma and eosinophilic granuloma. Similarly, different tumours tend to occur at different segments of the spine with giant cell tumours usually seen in the sacrum. Haemangiomas are more commonly seen in the thoracic and lumbar spine. Osteoid osteomas are more commonly seen in the lumbar region, whereas osteoblastomas equally occur in the thoracic and lumbar spine.

Clinical Presentation

Pain is the most common presenting complaint.[13] The pain is initially focal. With progressive increase in size of the tumour, neural elements may get compressed resulting in unilateral or even bilateral radicular pain. In adults, this may be confused with the clinical manifestations of a herniated disc. In children, pain is less often a presenting complaint. Osteoid osteoma and osteoblastoma are characterised by night pain which is relieved by non-steroidal anti-inflammatory drugs (NSAIDs).[24]

The symptoms of myelopathy occur with progressive increase in the size of the tumour resulting in epidural compression. This occurs more commonly with thoracic tumours due to the narrow canal diameter at that level. Tumours at the cranial or the caudal end of the spinal axis may occasionally, present as large mass lesions due to the more capacious spinal canal at these locations, that results in a relatively delayed neurological involvement. Lesions of the lower end of the spinal canal may present with sphincteric disturbances.

Sometimes, the patient may present with spinal deformity in the form of scoliosis. If this is accompanied with back pain then it suggests a bony tumour. Along with this, the mobility of the patient is hampered with restriction of body movements in all directions. This entity needs to be differentiated from the scoliosis of idiopathic origin.

Investigations

Plain radiographs show varying features according to the type of the tumour. Sclerotic changes are evident in osteoblastoma and osteoid osteoma. Expansile-lytic lesions are seen in giant cell tumours and aneurysmal bone cysts.[25] Vertebra plana is characteristically seen in eosinophilic granulomas whereas haemangiomas are identified by their vertical trabeculae. Scoliosis can be seen on the antero-posterior films.

MRI is the investigation of choice and reveals the extent of soft tissue involvement along with the bony component.[8] It is much more helpful in demonstrating cord compression as compared to the CT image, but the bony details are best delineated by the CT scan. In osteoid osteoma and osteoblastoma, the surrounding inflammatory response may be picked up by the MRI giving an impression of a highly aggressive tumour.

A bone scan, although non-specific, is frequently used as a screening tool. In patients with sclerotic tumours, a high tracer uptake is seen. A CT guided biopsy may be performed when there is a dilemma regarding the nature of the lesion. This, however, is invasive and carries the risk of neurological deterioration.

Treatment

Surgical intervention is based upon the presentation and the type of the tumour. Enneking's Type 1 (latent) tumours refer to incidentally discovered tumours which require no treatment.[14] This category includes incidentally discovered haemangiomas and osteochondromas that are not endangering the thecal sac. Type 2 (active) lesions refer to symptomatic tumours. These need local resection with curettage and include osteoid osteoma, haemangioma, aneurysmal bone cyst and eosinophilic granuloma. Type 3 (aggressive) tumours include giant cell tumour and osteoblastoma which require wide excision. Adjuvant therapy is determined according to the surgical decompression performed.

Radiation therapy is used in cases of neurological deterioration where surgery is contraindicated or in cases of highly radiosensitive tumours. Tumours responding

well to radiotherapy include haemangiomas and aneurysmal bone cyst. Radiation therapy carries risk to the underlying neural tissue which needs to be addressed.

Osteoid Osteoma

Jackson's series revealed a 10% occurrence of osteoid osteoma in the spine.[20] Male patients are affected more than the female ones (2:1). There is no familial or racial predilection with the peak incidence being in the second decade. Usually, they tend to present within one year of symptoms. Pain is usually the presenting symptom with persistent night pain seen in more than 50% of patients. Radicular involvement is seen in less than 25% of the cases. Scoliosis is seen in up to 70% of the cases.

The lumbar spine is the most commonly affected area. Radiographic changes are seen in the lamina or the pedicle and tend to involve a single vertebral level. The tumour is seen as an isolated radiolucent area surrounded by a zone of reactive sclerosis. Soft tissue or epidural extension is unusual. Sclerotic changes are seen on the radiographs and are due to reactive bone formation. Hence, bone scan is positive in all the cases. CT is the investigation of choice to delineate this bony lesion and characteristically shows a well-defined oval area of lucency surrounded by hyperdense reactive bone. The area of lucency, also known as the "nidus", may show contrast enhancement due to the high vascularity of the lesion.

The treatment is complete surgical excision with curettage. The osteoid osteoma appears as a soft, dark red or yellowish white nodule surrounded by dense reactive bone. Remission of pain is the indicator of complete excision. In order to prevent scoliosis, excision should be undertaken as early as possible before the supporting spinal pillars are compromised by the tumour. Radiotherapy has no role in the treatment of this lesion. At microscopy, irregular and haphazardly arranged woven bone trabeculae are embedded in a fibrovascular stroma. The amount of woven and unwoven (osteoid) bone varies among lesions.

Osteoblastoma

Although the overall incidence of these lesions is less than many other bony tumours, they have a predilection for the spine with nearly 40% of them involving the latter.[21] Male patients are affected more than the female ones. These lesions share a common presentation of painful scoliosis with osteoid osteoma, yet are larger as compared to the latter with a more aggressive potential.

Patients usually present within 6–12 months of symptoms with pain that persists during the night and is relieved by NSAIDs. Radicular symptoms may occur in 50% of the cases with some cases showing signs of myelopathy. The thoracic and the lumbar segments are commonly affected. Multiple vertebral levels are more frequently affected than occurs in patients with osteoid osteoma. Another interesting feature is the higher incidence of epidural extension as compared to paraspinal soft tissue involvement.

Radiographs may miss small lesions. When seen, they usually appear to be expansile-lytic lesions. Sclerotic changes are evident in 10–15% of the cases. The lesion appears as a "hot spot" on the bone scan and, therefore, this investigative modality can be used for follow-up of patients. CT scan is the investigation of choice and is very effective in deciding the surgical plan of the patient. It shows an expansile-lytic lesion with internal bone formation within the areas of lucency and surrounding sclerosis.

At the time of surgery, the tumour gives a variable picture of a homogeneous, red to purple hypervascular friable granular mass. Histologically, rich fibrovascular stroma with abundant osteoblasts is seen. Cartilage is absent. The latter feature differentiates it from an osteosarcoma. Epithelioid osteoblastoma is an aggressive malignant variant with atypical osteoblasts.[18]

The treatment is complete surgical resection with radical curettage of surrounding normal vertebra. Patients with symptoms of cord compression need to be decompressed on an emergent basis with the expectation of a good neurological recovery. Partial excision results in persistence of pain. Radiotherapy has a role in debilitated patients who cannot undergo surgical resection. Malignant transformation following radiotherapy has been noted in some cases.

Osteochondroma

The incidence of spinal osteochondromas is not very high despite it being the most common benign skeletal tumour. Some patients have a familial background in the form of hereditary multiple exostoses[23] that usually occur in patients less than 20 years of age and have a male preponderance. All parts of the vertebra are equally affected. A solitary lesion is a cartilage-capped broad based growth on a broad base or stalk related to the epiphyseal growth plate.

Although most of these patients are asymptomatic, they usually present with mass effect in the form of myelopathy. Another characteristic feature is that these tumours tend to stop growing at skeletal maturity. In cases of persistent growth, malignant transformation to chondrosarcoma should be considered. Both CT and MRI are highly effective as diagnostic modalities with MRI being preferred since, the soft tissue margin surrounding the tumour can be better identified.

Surgery is indicated only for symptomatic lesions or for lesions which show persistent growth. Complete excision is mandatory for symptomatic relief which is possible in 70–90% of the patients. Histology shows a hyaline cartilage cap covered by a fibrous membrane, the perichondrium and an underlying pedunculated bony stalk connected to the underlying bone without any intervening cortex between the two.

Giant Cell Tumour

These tumours have certain unusual characteristics. They are rarely seen before 20 years of age since they occur after skeletal maturation. They tend to occur more commonly in females. The ends of the spinal column are the favoured sites with the sacrum being most commonly affected. In fact, they are the most common benign tumours of the sacrum.[31] Sometimes they are seen in patients with Paget's disease.

Pain at the tumour site is the chief presenting complaint. Due to their predilection for the ends of the spinal column, the duration from the initiation of symptoms to their detection is much longer, sometimes as long as 8 months. Thirty to seventy-five per cent of patients present with neurological deficits in the form of paraparesis with bladder and bowel involvement. On plain radiology, they appear as expansile, septated, lytic lesions with cortical breach and a small soft tissue component. The vertebral body is more commonly involved. They require complete en bloc resection with wide margins. Recurrence rates are high, especially following intralesional resection. Grossly, the tumour appears light brown to bloody with focal necrotic areas with a rubbery feel. The main histological features of giant cell tumours are sheets of mononuclear round cells, scattered multinucleated osteoclast type giant cells, with identical nuclei found in mononuclear and multinuclear cells.

Due to the vascular nature of the tumours that may result in large amounts of intra-operative blood loss, pre-operative embolisation is recommended. Incomplete resection mandates adjuvant therapy due to high recurrence rates. However, 5–10% of patients undergoing radiotherapy have reportedly shown sarcomatous degeneration.

Eosinophilic Granuloma

The tumour is characterised by spontaneous regression often with an excellent prognosis. This entity is the most benign form of histiocytosis X and demonstrates a solitary benign lesion. This is usually seen in patients less than 20 years of age, with the thoracic spine being the most commonly affected.[30]

The clinical presentation is like that of any other bony tumour. Sometimes, systemic symptoms of fever with weight loss may be seen. On plain radiology, these characteristically show vertebra plana with disc sparing. This needs to be differentiated from the relatively uncommon presentation of spinal tuberculosis primarily affecting the body of the vertebra. Sometimes posterior involvement may be seen. On bone scan, they reveal cold spots. MRI may give the false impression of these tumours being aggressive due to a 'Flare up' response that may often occur. Focal lytic areas with sclerosis may also be seen. At histology, histiocytic cells with characteristic cytoplasmic granules (seen by electron microscopy), known as Birbeck granules, may be seen.

Since these tumours tend to spontaneously regress with reconstitution of the vertebral body, surgical intervention is not required. Hence, the role of percutaneous biopsy is important, which can provide tissue diagnosis thereby obviating the need for surgery. Surgery is indicated in patients with spinal instability and neurological deficit. There is no role for radiotherapy. Recurrence is rarely seen.

Aneurysmal Bone Cyst

These tumours tend to affect patients less than 20 years of age. There is no predilection for either sex. Characteristically, these lesions tend to involve the posterior elements much more as compared to the vertebral body. In fact, multiple levels of involvement are commonly seen.

Pain is the most common presenting complaint along with spinal deformity in the form of scoliosis and spinal rigidity. MRI with contrast is the investigation of choice. Multiple septations may be seen within the lesion. The lesions are lytic and expansile with a thin reactive bony rim. They consist of large blood filled spaces and a network of fibrous tissue containing immature bone, giant cells and macrophages.

Surgical resection with curettage is the treatment of choice. These tumours are vascular and tend to bleed a lot. Hence, pre-operative embolisation, if possible, is recommended. Sometimes, embolisation alone is found to be sufficient for controlling these tumours.[12] Radiation therapy has no role as adjuvant therapy since even partial resections are sufficient for tumour control. Sometimes, low dose radiation is pre-operatively utilised to decrease the vascularity of the tumour which may even be curative.

Haemangioma

Haemangiomas are true benign neoplasms of the bone and may occasionally be hamartomatous in nature. They tend to occur in the third decade of life with a slight predilection for the female sex. Sometimes, they are seen in patients with systemic conditions such as Klippel-Trenaunay-Weber syndrome. When associated with multiple skeletal and extraskeletal haemangiomas, they may cause consumptive coagulopathy.[5] These tumours characteristically enlarge during the third trimester of pregnancy, resolve following the delivery, but recur during subsequent pregnancies.

They usually present with pain. Neurological compromise is also seen. Pathological fracture is uncommon. Radiographs demonstrate a characteristic vertical striated appearance of the vertebral bodies due to ossification around areas of haemangioma. This is termed as 'honeycomb' or 'coudroy cloth' appearance. On CT, these lesions give the appearance of polka dots. The vertebral body is more commonly involved than the posterior elements. Many studies have reported contiguous

multiple level involvement. The thoracic spine is more commonly affected [Figs 1(A and B) and Fig. 2].

Grossly, the lesion arises from the periosteum or the marrow spaces producing a honeycomb bloody mass. Microscopically, numerous capillary channels with large feeding vessels are seen. These tumours are usually supplied by the intercostal arteries. Cavernous vascular channels may also be seen. Angiographically, these lesions demonstrate extensive tumour blush.

Embolisation of the vessels supplying the tumour should be performed, if surgery is being contemplated. Risk of ischaemia to the cord is probable, if more than three vascular pedicles are embolised. Recent reports favour embolisation followed by radical excision in patients presenting with neurological compromise or with spinal instability. Radiotherapy has also been found to be useful. The recommended dose is 30–40 cGy in a single course over 6–8 weeks. It is often used when complete surgical resection has not been performed. If detected during pregnancy, treatment should be undertaken after delivery even though the symptoms may subside, since the tumour may recur in subsequent pregnancies. Spinal instability may require instrumentation.

PRIMARY MALIGNANT TUMOURS OF THE SPINE

Chordomas

These are rare, slow growing tumours with a peak incidence in the 5th–7th decade of life. These are considered to be the remnants of the embryonic notochord.[19] Muller was the first person to have enunciated this theory. Male patients are affected more than females. Though chordomas may occur at any level in the spine, the sacrococcygeal region is the most commonly affected region followed by the clivus.

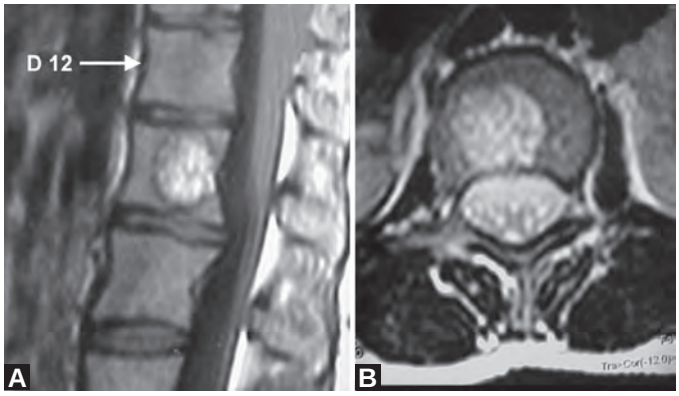
Pain is the most common presenting symptom. It is initially local becoming radicular later on with nerve root compression. In the lumbar region, the tumour may give rise to neurogenic claudication. Due to the capaciousness of the spinal canal in the sacrococcygeal region, these tumours may grow to a large size before they are detected. Bladder and bowel involvement occur late in the course of the disease. Clival tumours present with headache, multiple cranial nerve palsies and visual disturbances. Myelopathy is seen with cervicothoracic lesions that are compressing the thecal sac.

On MRI and intrathecal contrast sagittal reconstructed CT scans, they present as destructive lesions usually spanning more than one level, with disc sparing. Tumour calcification may also be seen. CT helps to define the bony destruction, whereas the soft tissue extent is shown best by the MRI (Figs 3A to E). Grossly, the tumours appear lobulated, grey, cystic or solid, firm to soft in consistency. They tend to be well-circumscribed. Microscopically, physaliphorous (soap bubble) cells are seen with a vacuolated cytoplasm. These tumours are locally aggressive with late metastasis.

Complete surgical resection is the treatment of choice, although it is often technically difficult. In such cases, the patients are advised post-operative radiotherapy. Since this tumour usually affects the sacrum, sparing of S2 root is essential for bladder and bowel control. Recurrence rates are high for incompletely resected tumours. Adjuvant therapy is essential in such cases. Sometimes, radical resections result in spinal instability which requires bone grafting with instrumentation.

Osteosarcoma

This is the most common primary malignancy of the skeletal system other than a myeloma. The spine is relatively less affected as compared to the rest of the skeletal system. Usually these tumours show a peak in the second decade of life with spinal tumours appearing later as compared to osteosarcomas of long bones. There is no sex predilection. These tumours can occur in the spine as primaries, may be metastatic or may result due



Figs 1A and B: MRI of a patient showing vertebral haemangioma without vertebral compression

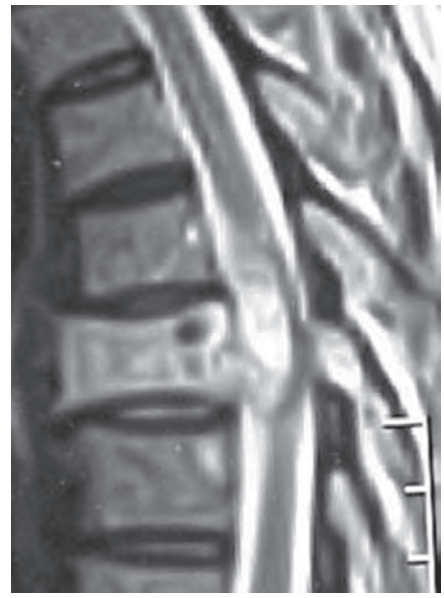
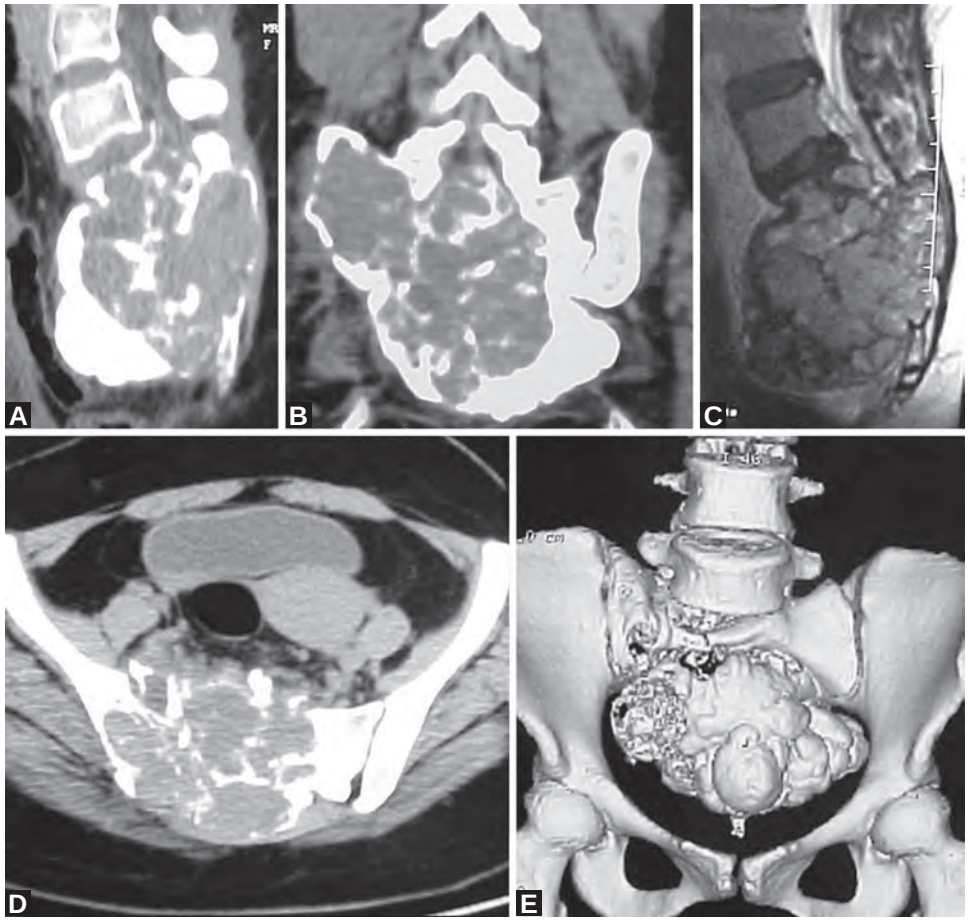


Fig. 2: MRI of a patient showing vertebral haemangioma causing cord compression



Figs 3A to E: Images of a patient with chordoma. CT scan with reconstruction (A, B, D and E) showing bony destruction. MRI (C) showing soft tissue component of chordoma

to malignant transformation in diseases such as Paget's disease, and following radiotherapy.[10]

Pain is the most common presenting complaint which is initially localised. Neurological deficits are commonly seen indicating epidural extension of the lesion.

The classical findings in patients with limb osteosarcoma are periosteal elevation and presence of Codman's triangle. These, however, are not seen in the spine. In the spine, a mixed picture of osteolytic and osteoblastic lesions is seen. Lesions usually involve the body, and posterior element involvement is much less frequent. Pathological fractures may also be seen. CT scan helps to show the bony anatomy, whereas the MRI is helpful in assessing cord compression along with the whole extent of the tumour. Bone scans are helpful in identifying multiple lesions, which may be in the form of 'skip' lesions. Biopsy of the lesion should be undertaken before surgical resection is performed.

Osteosarcomas are large vascular tumours with areas of grittiness. Grey-white tissue, suggesting fibrogenic areas, may also be seen. Microscopically, it is characterised by the presence of woven bone formed by osteoblasts, which may or may not be mineralised. There are disorganised spicules or masses, or woven bone enmeshed in a vascular bed. The bony spicules are surrounded by anaplastic spindle or polygonal cells with mitosis and atypia. Areas of haemorrhage and necrosis are common.

The standard treatment protocol is neoadjuvant chemotherapy followed by complete resection. The aim of surgery is to achieve tumour-free margins failing which the patient is subjected to post-operative radiotherapy. Treatment is started with two or three cycles of chemotherapy. Surgery is planned after 10–16 weeks, allowing the tumour to regress, following which radical excision of the tumour is done. This is usually followed by adjuvant chemotherapy. Radiation is given if negative margins are not achieved. Despite all these measures, the prognosis remains dismal.

Chondrosarcoma

It is a malignant tumour forming hyaline cartilage (without bone) composed of malignant chondrocytes. It is more common in males with a peak age of incidence in the fifth decade of life. Although it usually arises primarily in the spine, it may occasionally occur following malignant transformation of enchondromas or osteochondromas. A hereditary association is seen in some cases with Ollier's disease and familial osteochondromatosis.

Patients usually present with pain in the involved segment with an occasional radicular component depending upon the extent of the tumour. The pain is exacerbated in the supine position. Imaging characteristics depend upon the grade of the tumour. Low grade tumours result in scalloping of the bone with cortical expansion. With higher grade lesions, the lytic component increases. Calcification may also be seen, which decreases with higher grade of tumours. There are often foci of spotty calcification. There may be calcified shadows with radiating spicules arranged at right angles to the cortex. CT and MRI are done for further delineation of the tumour and its characteristics. CT of the lung should also be done due to the tendency of this tumour to metastasise to the lung. Biopsy should be performed keeping in mind the surgical plan. Needle biopsies yield little tissue, hence incisional biopsy is preferable.

Chondrosarcomas have been graded according to their histological appearance. Grade 1 tumours have mild cellular atypia with abundant hyaline matrix; Grade 2 have significant atypia with abundant cartilaginous matrix; whereas, Grade 3 have marked atypia with little cartilage matrix, mitotic figures, necrotic foci and multiple giant tumour cells.

Complete surgical excision is the treatment of choice. Instrumentation may be required for resultant spinal instability. However, it is often technically not possible to completely remove these tumours. In these cases, radiotherapy should be given to prevent the high rates of recurrence that follow incomplete resection. Cryosurgery has also been used when tumour-free margins are not achieved during surgery.[4] Long-term survival is dependent upon the histological grade of the tumour.

Ewing's Sarcoma

The overall incidence of Ewing's tumour of the bone is around 6%. Spinal involvement by this tumour has not been studied in great detail. This is a highly malignant tumour with male predominance and peak incidence in the second decade.[7] The sacrum is commonly involved with the lumbar region being the next in frequency.

The presenting symptom is pain with a variable severity of neurological deficits in the form of sensorimotor and bladder/bowel involvement. The patients may also present with cauda equina syndrome. Radiographs show lytic lesions with a thin rim of sclerotic bone around the margins. Due to the tendency of these tumours to metastasise, particularly to the lungs, CT chest should also be done. Grossly, the tumour is grey-white to blue with semi-solid to gelatinous consistency, and is extremely friable and highly vascular. Microscopically, small round cells larger than lymphocytes with scant cytoplasm are seen. Sometimes, a pseudorosette pattern may also be seen. Tumours are disposed in sheets with a uniform population of tumour cells displaying round nuclei, fine granular chromatin and a thin rim of cytoplasm.

Due to the difficulty in achieving complete excision of the tumour, which is the aim of treatment, a multimodality approach is taken combining chemotherapy, radiotherapy and surgical excision. Incomplete resection results in higher recurrence rates. Hence, post-operative radiotherapy is given in all such cases, the total dose being 4,000–6,000 cGy. The 5-year survival rate is approximately 20% after using multimodality treatment.

Plasmacytoma

These tumours are composed of malignant plasma cells and form a subgroup of plasma cell dyscrasias. These present as single bone lesions or occur at extramedullary sites. In the skeletal system, the spine is most commonly affected with the thoracic spine being the favoured site. Males are more commonly affected with the peak incidence occurring in patients older than 50 years of age. Fifty per cent of these tumours may convert into multiple myeloma, if allowed to persist for a sufficient time without treatment.

Pain is the most common presenting complaint. Radicular involvement is uncommon. However, bone destruction with collapse can result in cord compression leading to myelopathy and even paraplegia in some cases. On plain radiology, in the long bones, a characteristic "soap bubble" appearance has been described. This, however, is unusual in the spine where usually a large destructive lesion is seen. The bone scan shows minimal or no uptake. Further tumour details are obtained with the help of CT and MRI. These patients may produce paraproteins. These may be secretory or non-secretory with occasional light chain urinary excretion. Histologically, the entire spectra of plasma cell maturation may be seen with basophilic cytoplasm and an eccentric nucleus. Lesions can vary from being poorly differentiated to well-differentiated.

These tumours are highly radiosensitive. Hence, radiation therapy is the first line of treatment with the radiation dose being up to 3,500 cGy.[29] Surgical intervention is required for spinal instability and in cases of cord compression. Patients generally require stabilisation procedures. In cases of partially resected tumours, post-operative radiotherapy is given.

Patients with single lesions have better survival rates than with multiple lesions. Poor prognosis is indicated by the extent of soft tissue extension, old age and persistent paraprotein production following treatment.

Multiple Myeloma

This is the most common primary malignancy of the bone. It is a systemic plasma cell disorder where the bone marrow is first affected resulting in its replacement by plasma cells followed by involvement of the cortical surface with local extension. Destruction of the bone marrow may result in normochromic anaemia, thrombocytopaenia and neutropaenia.[26] Male and female patients are equally involved with 62 years being the peak age of

incidence. The whole skeletal system is equally vulnerable. Pain is usually the presenting feature with radicular and myelopathic features depending upon the growth of the tumour. Patients often present with pathological fractures. Patients may also develop constituent symptoms, like fever and fatigue, due to chronic anaemia. On plain radiographs, multiple destructive lesions are seen, which may result in vertebral pathological fractures with cord compression. Urinary examination is carried out for Bence Jones protein. Serum electrophoresis is also carried out to investigate for other paraproteins. Bone marrow smears reveal increased number of plasma cells which show atypical features. The beta-2 microglobulin level is measured and followed as a prognostic factor. Hypercalcaemia is reported with normal or slightly increased alkaline phosphatase. Renal function tests are also required, since this disease may result in acute tubular damage causing renal failure. Definitive diagnosis requires CT guided bone biopsy which shows fibrocollagenous tissue infiltrated by a monotonous population of mature and immature plasma cells displaying predominantly eccentrically placed nuclei with coarse chromatin, and moderate amount of cytoplasm.

Combined radiotherapy and chemotherapy form the first line of treatment. Surgical therapy is indicated only in cases of spinal fractures resulting in spinal instability or cord compression. In such cases, decompression followed by instrumentation is required. Since complete resection is not usually possible, radiotherapy should be instituted following surgery. A large number of chemotherapeutic agents are available with cyclophosphamide and melphalan being equally effective. Radiation therapy in conjunction with chemotherapy is especially helpful in relieving pain and may also result in relief of neural compression.

Lymphoma

The spine is usually affected in cases of Non-Hodgkin's lymphoma.[11] Usually multiple level involvement occurs although, occasionally, solitary lesions are seen. The peak age of incidence is after 40 years. Lymphoma tends to involve the anterior column and the posterior columns tend to be relatively spared. Lymphomas are highly radiosensitive and chemosensitive. Surgical therapy is reserved for cases with neurological deficits. In such cases, instrumentation may be required to restore spinal stability.

Metastatic Tumours of the Spine

Technical advances leading to earlier detection, and prolonged survival due to continuously improving treatment modalities have led to higher detection rates of metastatic disease in the spine. The emphasis is on 'early detection', since the prognosis is determined by the neurological status at the time of presentation. Despite recent advances in the management of various localised tumours, metastatic tumours have proven to be a surgical challenge. The present consensus is on a multidisciplinary approach involving surgery, radiotherapy and chemotherapy.

It has been widely accepted that lung and liver are the most common sites for the seeding of metastatic foci.[3] The skeletal system is the third most common site for metastatic disease with the spine harbouring the majority of these lesions. The thoracolumbar and the lumbar spine are the commonest sites of spinal metastasis perhaps due to increasing amounts of bone marrow from the cervical to the lumbar region. However, the propensity for the disease to present with neurological dysfunction is highest in the thoracic spine as the canal diameter is the narrowest in this region. Dommisse had suggested that the thoracic spine has the most critical vascular area of the spine, particularly at the levels from T4 to T9.[9] However, this fact has been refuted and the thoracic region too has a well-developed segmental blood supply.

The four common primary lesions that result in spinal metastasis are breast, lung, prostate and kidney cancers. In the paediatric population, neuroblastoma is the most common tumour responsible for neurological dysfunction.

PATHOGENESIS

The pathogenesis of the spread of the primary tumour to the spine has been studied in great detail. Four pathways of spread have been determined. The most common pathway for the metastatic spread is the venous system. Batson had demonstrated the presence of valveless veins in the spinal canal.[1] The blood from the vertebral body is drained by the basivertebral veins which connect to the epidural venous plexus. The whole pathway is devoid of valves resulting in retrograde flow of blood to the vertebral body whenever, there is a rise in the intra-abdominal pressure. This provides a pathway for the tumour cells to travel from the primary site to the spine. The vertebral venous plexus is in communication with the upper and lower extremity, the head, the neck and the trunk allowing the spread of a variety of tumours.

Arterial spread of the tumour occurs by means of the nutrient arteries. Tumours of the lung and the prostate have been known to utilise this pathway for their spread. Some tumours have shown to have perineural and lymphatic spread. Tumours that have a perineural spread tend to enter through the intervertebral foramen resulting in epidural compression.

Local extension of the tumour cells to the spine is also well-known with lung carcinoma, tumours of the retroperitoneum and the mediastinum.

In order for the tumour cells to establish themselves at the target site, two conditions need to be met. Firstly, the tumour cells should be in adequate number, which in the spine is facilitated by the valveless system of veins. The second is the availability of an environment

which allows the tumour cells to proliferate. Paget proposed his "seed and soil" hypothesis but could not provide conclusive evidence in its favour. It is now, believed that multiple factors are responsible for the spinal seedling. The cancellous bone within the vertebral body has been shown to be the favoured site for tumour deposits. Following tumour cell deposition, the metastatic foci proliferate with the aid of production of many substances that promote bone resorption. Both osteoplastic and osteoclastic activities ensue following tumour cell deposition. Indirect mechanisms responsible for tumour destruction have been the production of parathyroid hormone, PG E2, ACTH and calcitonin. Overall, osteoclastic activity predominates in the majority of the cases resulting in vertebral body destruction. In fact, the quality of reactive bone formation is the same for both lytic and blastic activities. It is merely the quantity of bone formed which differs.

The intervertebral disc tends to be involved late in metastatic disease with the cartilaginous endplates providing the barrier to the spread. Tumour spread tends to occur beneath the anterior or posterior longitudinal ligament or through the anterior and posterior body rims which are frequently uncovered by cartilage.

The neurological dysfunction resulting from spinal metastasis usually occurs in a stepwise manner. Direct compression of the spinal canal occurs due to the extension of the metastasis from the vertebral body. This results in compression of the vertebral venous plexus initially, which results in the development of vasogenic oedema due to plasma exudation and production of mediators such as prostaglandins. Indomethacin which inhibits prostaglandin formation has been shown to decrease cord oedema.[16]

Persistent cord compression results in aggravation of the vascular insult, finally resulting in arterial compromise leading to spinal cord infarction. It is the rate of development of the vascular compromise that results in slow or rapid neurological deterioration.

CLINICAL PRESENTATION

Although the clinical syndrome varies depending upon the site of involvement in the spine, pain is the presenting feature in up to 90% of these patients.[2] The pain initially is localised, being mild at the onset with progressively increasing severity. The duration of pain varies from 2 weeks to a year. The character of the pain changes to a boring or burning nature with progression of the disease. The pain tends to persist at night. Localised pain occurs due to periosteal or dural involvement. In the earlier stages, the pain is non-specific, resulting in a delay in the diagnosis of spinal metastasis. The pain may later demonstrate a radicular nature due to the involvement of the nerve roots. The radicular pain may be unilateral or bilateral and is aggravated by movements of the trunk. Recurrence of pain in patients who have previously been treated signifies tumour recurrence.

Motor deterioration tends to precede sensory or urological involvement. The pattern of motor involvement results from the site of the involvement. Anterior horn cell involvement leads to lower motor neuron weakness at that level with spastic weakness below. Similarly, asymmetrical compression of the cord by the tumour results in asymmetrical weakness with the ipsilateral side being affected earlier in comparison to the contralateral side. Lesions of the conus present with lower motor neuron weakness of the lower limbs with absent plantars and hypotonia. Sensory loss occurs much later and again the pattern depends upon the site. Saddle anaesthesia, for instance, is commonly seen in lesions of the conus. The sensory level is usually localised to one or two dermatomal levels below the vertebral levels.

Posterior column involvement may be manifested in the form of paresthesias or numbness below the level of involvement. Lhermitte's sign may occasionally be positive in patients with cervical spine involvement, especially occurring on flexion of the neck. The posterior columns may be involved early in dorsally located tumours.

Bladder and bowel disturbances often occur late in the course of the disease. Early involvement occurs in intramedullary metastasis. In lesions above the level of the conus, patients present with spastic bladder and constipation. However, patients with conus lesions have a neurogenic lower motor neuron type of bladder involvement with faecal incontinence. Conus involvement may also result in impotence in males, whereas priapism is seen with lesions above the conus.

Based on the neurological grades, various staging systems have been devised. Frenkel's system is often used for assessing the neurological involvement.

Frenkel's Classification

Grade A: Complete motor and sensory loss
Grade B: Complete motor and incomplete sensory loss
Grade C: Some motor function, incomplete sensory loss
Grade D: Useful motor function, incomplete sensory loss
Grade E: Normal motor and sensory function

RADIOLOGICAL EVALUATION

Plain radiographs are often the first investigation performed, especially since the initial presentation is that of non-specific back pain. For radiological changes to be seen, 40–65% lytic activity should have occurred. The pedicles usually show the first evidence of metastatic disease.[22] "Winking Owl sign" refers to the absence of the pedicle on AP views. Other findings are changes in the vertebral body morphology leading to vertebral collapse, osteolytic lesions or focal/diffuse osteopaenia. Sclerotic changes are suggestive of osteoblastic metastasis seen with prostate and breast secondaries. Sometimes, gastric cancers, cervical or bladder cancers may give rise to a similar picture.

Bone scans form an integral part of the work up of metastatic disease.[17] This is usually performed with technetium-99m polyphosphate isotopes. The diseased segments tend to light up following isotope administration and demonstrate the extent of metastasis in the whole skeletal system. Tracer uptake is due to reactive bone formation. In areas of highly malignant lesions, where reactive bone formation is minimal, the test may be false negative. Positive results are seen in a variety of benign lesions including inflammatory lesions making this test non-specific. However, this is useful in determining the extent of bony involvement and to identify the 'hot' spots where the biopsy is most likely to yield positive results in cases with multiple levels of involvement. In patients with recurrent lesions who have undergone spinal implants that show artefacts on radiological imaging, bone scan may be useful in defining new lesions.

MRI with contrast has been accepted as the investigation of choice and is considered superior to CT myelography. MRI is extremely accurate in identifying the soft tissue extension, paraspinal lesions and cord compression (Fig. 4). In cases of multiple levels of involvement, CT myelography tends to be ineffective in demonstrating the whole length of the block. This is overcome by the MRI. Metastatic lesions tend to enhance with gadolinium and the extent of enhancement following treatment may be utilised to evaluate the response. In the thoracic spine, however, due to motion artefacts produced by heart and lung movements, MRI becomes less accurate. Similarly, MRI cannot be undertaken in patients with steel implants, aneurysmal clips and pace makers. CT myelography is useful in recurrent cases with steel implants *in situ*. The invasive nature of this investigation and the chances of neurological deterioration are its major drawbacks. CT delineates the bony margins better than the MRI, yet the soft tissue delineation is not of the desired order.

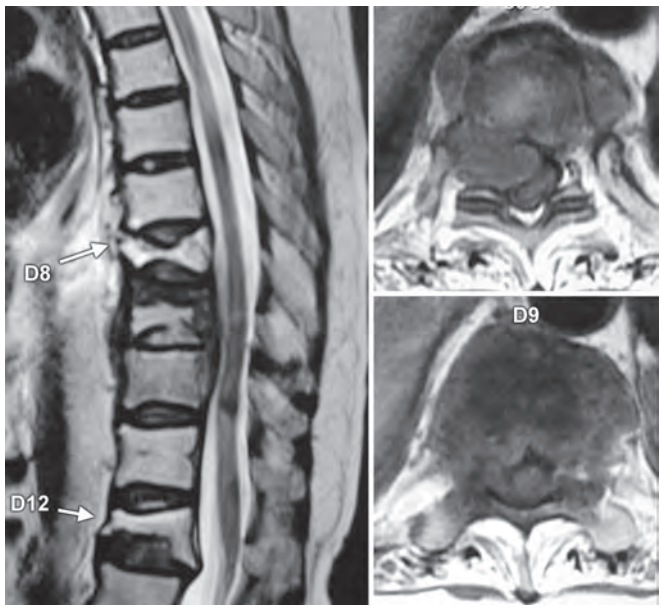


Fig. 4: MRI of the dorsolumbar spine of a patient treated for breast carcinoma showing multiple vertebral lesions with soft tissue component causing compression of the spinal cord suggestive of metastatic deposit

Tumour markers are increasingly being measured to evaluate for metastatic disease. Prostate specific antigen and carcinoembryonic antigen are routinely done and their levels are believed to correlate with treatment efficacy. Among other blood investigations serum electrophoresis, albumin to globulin ratio and gammaglobulin levels are performed for detection of myeloma. Alkaline phosphatase is usually raised in metastatic disease except in patients with multiple myeloma.

Percutaneous biopsy is useful in confirming the histological diagnosis of metastatic disease. However, the accuracy of the procedure has been found to be variable since, appropriate sampling is necessary for making the right diagnosis. This depends on accurately localising the lesion, taking the needle of the appropriate size for extracting sufficient quantity of sample and successfully evaluating the representative tissue. In cases where open biopsy is performed, the subsequent surgical plan should be kept in mind.

MANAGEMENT

The treatment of spinal metastasis has undergone modifications over the years with advancements in both the surgical and the conservative aspects. The indications for surgical intervention are being more clearly defined. With technological advancements radiotherapy can be given more effectively with lesser side effects. The other options are steroid therapy, hormonal manipulation and chemotherapy. Chemotherapy has a limited role since, it has not been found to reverse the neurological deterioration caused by compression. However, hypercalcaemia is a known complication of metastatic disease which is targeted by diphosphonates. Chemosensitive tumours such as osteosarcoma and germinoma form a subgroup where chemotherapy plays an important role in the management. Hormonal manipulation has been found useful in metastases originating from prostate tumours.

Steroids have been shown to partially reverse the neurological deficit caused by metastatic disease. Steroids are believed to prevent oedema and also have oncolytic activity. Some studies have shown that an initial high loading dose with gradual tapering is more effective in reducing oedema rather than administering low maintenance doses. However, steroids have significant side effects since, the duration of therapy tends to be prolonged. Similarly, when a patient is on steroids for a long duration and surgical intervention is being contemplated, wound complications and poor immunological responses need to be considered. Due to its high potency and salt retaining properties, dexamethasone is the drug of choice.[15]

Radiotherapy has been shown to have a definitive role in the treatment of compressive metastatic disease.

However, it is not helpful in arresting the clinical symptomatology in a patient with rapidly deteriorating neurological status. Matsubayashi et al. have shown normal bone formation in place of the tumour tissue following radiotherapy administration. Twenty to forty per cent of patients who previously were bedridden have been found to be able to walk following treatment, and this improvement was maintained up to one year.[28] There is significant relief of pain in up to 80% of the patients. The optimal dosage of radiation therapy is still not universally accepted. Approximately, 3,000–5,000 cGy given in daily fractions of 200 cGy over a 5-week period is recommended. In cases with multiple-level metastasis, the whole spine needs to be irradiated. For this, hemibody radiation is given first on one side followed by the other. With availability of proton therapy and IMRT, higher and more target specific radiation therapy can be given.

Radiation therapy has significant side effects both in the acute and long-term period. Early complications include severe neutropaenia, which is more common with upper body radiation. Radiation-induced myelopathy with poor prognosis is seen as a long-term sequel. Similarly, radiation induced malignancy is well-documented in the literature. To prevent these complications, it is important to keep the daily fraction of radiation within tolerable limits. The length of the spine to be irradiated should be defined and the interval of dosage should be reduced. The thoracic spine is more susceptible as compared to the cervical or lumbar region.

Surgical Management

Historically, posterior decompression in the form of laminectomy used to be performed for spinal tumours. Later on, it was realised that it is not more effective than radiotherapy and steroids given together. Also, this approach was helpful only for posteriorly located tumours. However, most of the tumours are anterior to the cord and cause anterior epidural compression. Gradually posterolateral, anterior and anterolateral approaches have gained wide acceptance. It has also been realised that mere decompression is not sufficient in cases where spinal instability results and spinal stabilisation is necessary.

The well-accepted indications for surgical intervention are:[27] (1) acute neurological deterioration; (2) progressive neurological deterioration while on conservative management; (3) persistent unbearable pain despite all measures; (4) extensive destructive lesions causing spinal instabiltity and (5) radioresistant tumour.

The aim of surgical intervention should not only be debulking the tumour, but also to realign the spinal elements with restoration of spinal stability. Pre-operative evaluation of the patient should be detailed and in cases having significant medical complications, which make the patient a poor candidate for withstanding the surgical procedure, conservative measures should be opted for.

For surgical decompression, laminectomy has been found to be ineffective. The posterolateral approach is often favoured as it allows tumour resection around the circumference of the dural sac and nerve roots bilaterally. This can be performed along the whole length of the spine and can be extended intra-operatively. Anterior approaches are particularly helpful for the cervical spine. In the thoracic and abdominal regions, the anterior approaches give good exposure, but anterolateral access is available on one side only.

Anterior Approaches

C1-C2 : Transoral/transmandibular
C3-C7 : Transcervical
C7-D1 : Trans-sternal/transthoracic
T3-T10 : Transthoracic/posterolateral thoracotomy
T11-L1 : Transthoracic, extrapleural, thoracoabdominal
L2-L4 : Retroperitoneal
L5-S1 : Transabdominal

Spinal stability needs to be maintained after the decompression. For this, bone grafting with instrumentation is the procedure of choice. Grafts can be autologous from the iliac crest, fibula or ribs. They can be artificial grafts made of hydroxyapatite, methylmethacrylate or ceramics. Instumentation procedures have undergone rapid development and rods, pedicle screws and cages are widely used. Spinal instrumentation, however, only provides temporary stability; bony fusion is necessary for long-term stability.

The most important factor affecting the prognosis is the ability to walk at the time of initiation of therapy, irrespective of the treatment modality. In other words, it is the pre-operative neurological status which determines the outcome. Loss of sphincter control indicates a poorer outcome.

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105 Spinal Schwannomas and Meningiomas

Trimurti D Nadkarni

INTRODUCTION

Spinal cord tumours account for about 15% of central nervous system (CNS) tumours. Primary spinal cord tumours may be benign or malignant. Five to ten percent of primary spinal cord tumours originate from cells within the spinal cord parenchyma. The other 90–95% of primary spinal cord tumours arise from cells adjacent to the spinal cord, such as those of the spinal nerve roots or meningeal coverings. Meningiomas and neurofibromas are the most common benign intradural extramedullary spinal cord tumours.

HISTORICAL CONSIDERATION

The first successful surgical removal of an intradural spinal tumour is credited to Victor Horsley in 1887.[3] The tumour was a fibromyxoma and removed via laminectomy. More than 100 years later, despite vast improvements in imaging, anaesthetic care, and surgical instruments, the technique remains basically the same. At a meeting of Roswell Park Medical Club in 1908, Dr William C Krauss presented a paper, by invitation, on spinal cord tumours. The paper illustrated how nerves, motor and sensory were affected by spinal cord tumours.

The technique of intramedullary spinal cord tumour surgery as well as diagnosis and treatment of all spinal cord tumours was elaborated in detail by Elsberg in 1925.[1] After the landmark work of Elsberg in 1925, little progress was achieved in the field of spinal tumour surgery until the operating microscope was introduced. As a result of continual technical advancements since 1975 the safety and effectiveness of tumour resection has vastly improved resulting in better outcomes in patients undergoing spinal procedures.

CLASSIFICATION AND TERMINOLOGY

Spinal tumours are broadly classified as extradural or intradural based on their relation to the dura. Intradural spinal cord tumours can further be classified as intramedullary and extramedullary according to their relationship to spinal cord. A small number of spinal neoplasms can have both intramedullary and extramedullary components communicating through the nerve root entry zone. Similarly, some intradural tumours may extend into the extradural compartment through the nerve root sleeve.

Nerve sheath tumours are the most common type of intradural extramedullary (IDEM) spinal cord tumours accounting for 25–30% of all primary spinal cord tumours. Meningiomas account for 20–25% of spinal cord tumours.[15,18]

Epidemiology

Incidence

Nerve sheath tumours: Nerve sheath tumours are uncommon tumours in the general population with an annual incidence of 0.3–0.4 per 100,000 persons.[14,15] Nerve sheath tumours account for 40% of all intradural spinal cord tumours in adults.[5] In the spine, there is a male preponderance and the male to female ratio is 1.25 to 1.5:1, in contrast to intracranial and peripheral sites where there is a female predominance (1.5:1). The peak incidence of these tumours is in the fourth to sixth decade. Most are solitary schwannomas and occur proportionally throughout the spine.

With nerve sheath tumours, two tumour populations need to be distinguished which are schwannoma and neurofibroma. Schwannomas are more common and are the largest category of nerve sheath tumours. Whereas schwannomas are encountered in patients with neurofibromatosis (NF)-2 and in patients without NF, neurofibromas are found in patients with NF-1.[16] Most nerve sheath tumours arise from a dorsal nerve root. Neurofibromas represent a higher proportion of ventral root tumours and often exhibit a dumb-bell configuration.[15]

Meningiomas: Spinal meningiomas account for 25% of all primary spinal cord tumours and 12% of all meningiomas of the CNS.[11,17,18] They occur predominantly in the fourth to seventh decade; with a female to male ratio of 3.5 to 4:1. Females usually between the fourth and fifth decades account for approximately 80% of spinal meningiomas.[9,11,12,17] Spinal meningiomas occur predominantly in the thoracic region (82%), followed by cervical (15%) and rarely lumbar areas (2%).

Spinal meningiomas are mostly intradural and extramedullary in location. Extradural meningiomas account for 5% of spinal meningiomas and are more common in the younger age group. Multiple meningiomas are quite rare, but may occur in patients with NF.

Histopathology

Nerve sheath tumours: Nerve sheath tumours usually arise from the dorsal roots at various segmental levels of the spinal cord. They are avascular and globoid, and without calcification.

Neurofibromas and schwannomas merit separate consideration because of their distinct histological characteristics. Although electron microscopy and immunohistochemistry supports a common cell origin, the morphological heterogeneity of neurofibroma suggests participation of additional cell types like perineural cells and fibroblasts.

The gross appearance of a neurofibroma is of a fusiform enlargement of the involved nerve, without any identifiable nerve. Microscopically neurofibromas consist of an abundance of fibrous tissue and the nerve fibres are within the tumour substance.

Schwannomas appear as grossly smooth, globoid, eccentric masses with identifiable attachment to the nerve root from which they are arising. Microscopically, schwannomas consist of elongated bipolar cells with fusiform, darkly staining nuclei arranged in compact interlacing fascicles with a tendency towards palisade formation (Antoni-A). A loosely arranged pattern of stellate shaped cells (Antoni-B) is less common.[14,18]

Meningioma: Meningiomas usually arise from arachnoid cap cells located at exit zones of nerve roots or the entry zones of arteries into the spinal canal, accounting for their predominant lateral location.

Macroscopically they vary from smooth lobulated to a fibrous sheath like en plaque variety. Consistency can vary from soft friable, fleshy rubbery to stony calcified. The dural attachment is broader than expected. Unlike intracranial meningiomas spinal meningiomas never penetrate the pia. This simplifies surgical resection. Microscopically, meningothelial, fibroblastic and psammomatous are common histological variants found in spinal meningiomas. Atypical or malignant meningiomas are exceedingly rare in the spine.[13]

GENETIC ASPECTS

The genetic aspects of these benign spinal intradural tumours have extensively been studied during the past decade. A detailed genetic analysis of these tumours is beyond the scope of this chapter, but few points are mentioned that most researchers agree upon. Genetic alterations in the long arm of chromosome 22 play an essential role in the development of a meningioma. The chromosomal region involved has been localised to the centre of the long arm of chromosome 22 in the bands 22q12.3-qter. This is the same area that harbours the neurofibromatosis Type 2 (NF2) tumour suppressor gene. Other chromosomal abnormalities noted in meningiomas with clinical progression to malignancy include loss of heterozygosity (LOH) for foci on chromosome arm 1p, 9q, 10q and 14q.[4,8]

As with meningiomas, monosomy 22 is the most frequent cytogenetic abnormality in schwannomas. NF2 is defined by bilateral vestibular schwannomas. The NF2 gene codes for a protein called merlin (i.e. meosin-ezrin-radxin-like protein). Loss of expression of this protein was demonstrated in the pathogenesis of schwannomas and meningiomas.[4]

CLINICAL SYMPTOMS AND SIGNS

Spinal schwannomas and meningiomas are slow growing benign extramedullary tumours of the spine and typically present with slowly progressive signs of spinal cord compression. Pain is a common initial symptom in extramedullary lesions and usually is present for months before a diagnosis is established. Pain can have localising value in case of schwannomas as it arises from the dorsal sensory root producing radicular pain. Pain can also be an ill defined non-localising discomfort with multi-segmental involvement.

Most spinal cord tumours produce symptoms and signs due to a combination of local segmental and distant features. Segmental involvement of the dorsal root entry zone or anterior horn cell and roots result in specific sensory or lower motor deficit. Distant clinical features result from long tract involvement like corticospinal, spinothalamic and posterior columns. In general these tumours tend to arise eccentrically, lying on one side of the spinal cord either dorsally or ventrally. This eccentric tumour position results in asymmetric cord compression with higher incidence of Brown Sequard syndrome, i.e. ipsilateral involvement of corticospinal and dorsal columns with contralateral involvement of the spinothalmic tract. However, the clinical picture can be variable and inconsistent. Other factors, such as age, vascularity, relative size of the spinal column and tethering of structures, can modify the clinical picture.[14,18]

Specific clinical features related to the rostrocaudal location of tumours can be identified (for more details refer to chapter on Clinical Features and Diagnosis of Tumours of the Spinal Cord). Lesions of the upper cervical spine present with a unique syndrome which produces disproportional loss of dorsal column sensation in the upper limbs compared to the lower limbs, atrophy of intrinsic muscles of the hand, apart from variable involvement of long tracts below the level of lesion. Rarely, foramen magnum tumours can cause nystagmus due to pressure on sulcomarginal fibres. Increased intracranial pressure and hydrocephalus rarely occur with extramedullary tumours at any level, but are more common with upper cervical tumours. Involvement of the mid and lower cervical segments can lead to Horner's syndrome apart from long tract involvement. Involvement of the upper thoracic segments can cause girdle type pain, which is sometimes mistaken for pain of cardiac origin. Thoracic lesions produce sensory loss well below the actual level of the tumour.

Tumours of the lumbosacral and conus medullaris region of the spinal cord can affect parasympathetic innervations of the bladder, bowel and sexual organs. These symptoms can precede for months or even years the overt neurological deficits. Tumours of the cauda equina may selectively involve a single dorsal root causing persistent discrete dermatomal pain for many months and may be mistaken for disc prolapse. Worsening pain on recumbency is an important clinical feature of extramedullary tumours and is most commonly associated with large cauda equina tumours.

DIAGNOSTIC IMAGING

Magnetic resonance imaging (MRI) is the best imaging modality for diagnosis and evaluation of tumours involving the spinal cord. Intradural extramedullary masses, like meningiomas and schwannomas, compress and displace the spinal cord and cause widening of the adjacent cerebrospinal fluid (CSF) spaces. Gadolinium enhanced imaging increases the sensitivity of MRI in detecting small tumours.[18] Almost all spinal cord tumours exhibit some degree of contrast enhancement.

Spinal nerve sheath tumours, like schwannomas and neurofibromas, are difficult to distinguish on neuroimaging.[10] Both are isointense on T1-weighted images, have high signal on T2-weighted images and enhance with gadolinium (Figs 1 to 3A and B). Similarly, they can enhance faintly with iodinated contrast on computed tomography. Schwannomas can have cystic regions or fatty degeneration, whereas neurofibromas usually are homogeneous (Figs 4A, B and 5A, B). Nerve root tumours may have extradural extension through neural foramina giving them a dumb-bell shape (Fig. 6). Since these tumours are slow growing, bone remodelling can occur around them. MRI is the best imaging modality to characterise these lesions when the lesion is within the spinal canal. For lesions that extend into the plexus, MR neurography can localise and show the exact extent of nerve involvement.[7]

Imaging characteristics of spinal meningiomas are similar to their cranial counterparts with iso- to hypointense signal on T1-weighted images, hyper-intense on T2-weighted imaging and contrast enhancement (Figs 7 to 9). Meningiomas typically demonstrate intense uniform enhancement. Enhancement of adjacent dura strongly supports the diagnosis of meningioma. Peritumoral hypointensity is commonly seen around a meningioma which is due to CSF spaces.

Myelography and CT myelography are rarely used presently with advancement in MR imaging.

Treatment

Surgical excision is the treatment of choice for benign intradural extramedullary tumours of the spinal cord. The goal of surgery is complete and safe removal, thereby

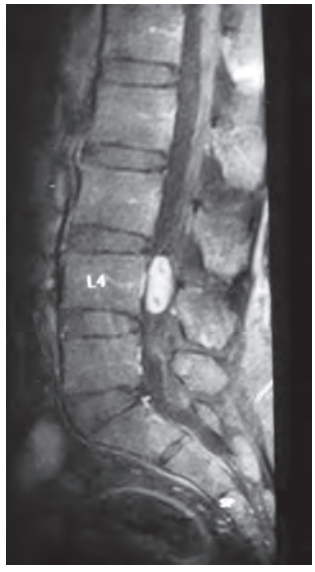
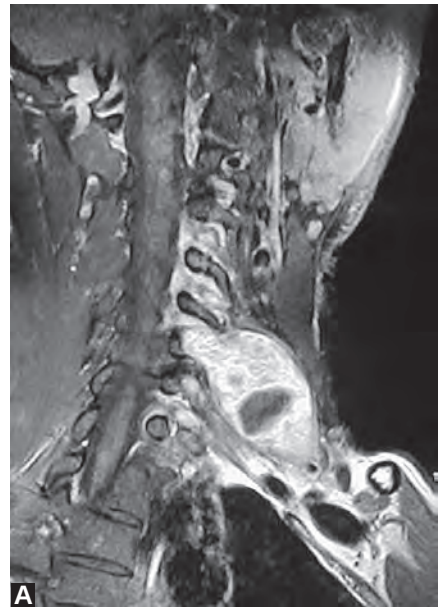
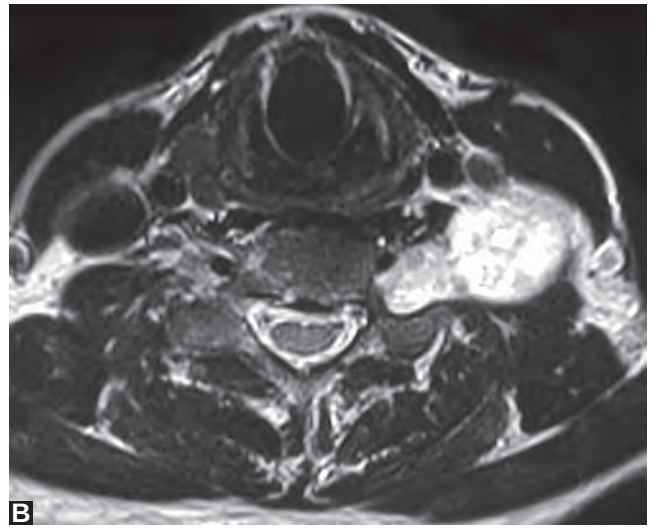
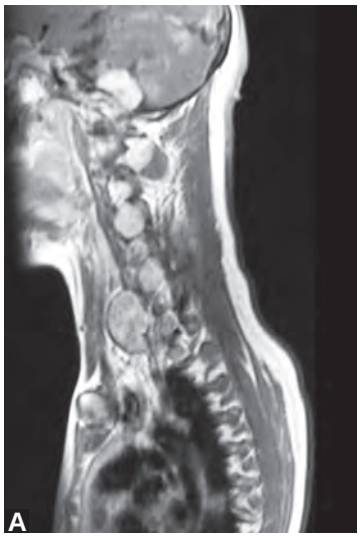


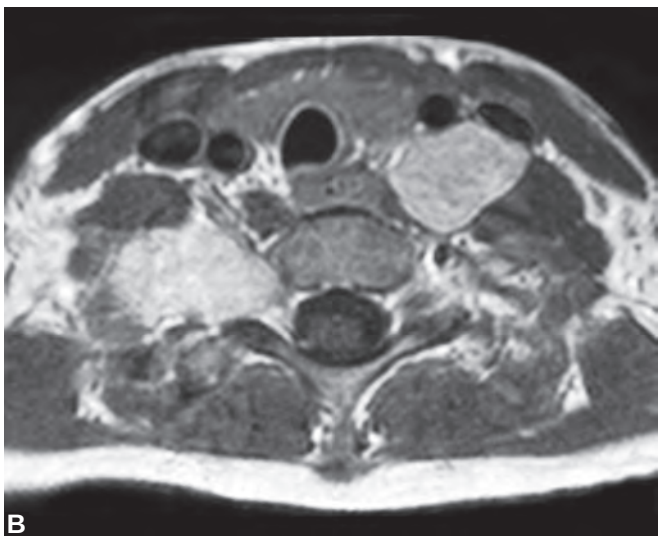
Fig. 1: Post-contrast T1-weighted sagittal MR image shows a lumbar (L4) schwannoma



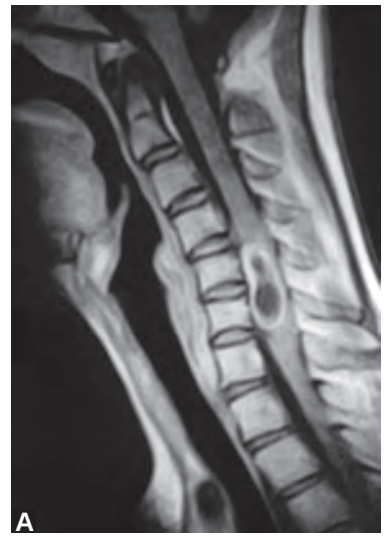


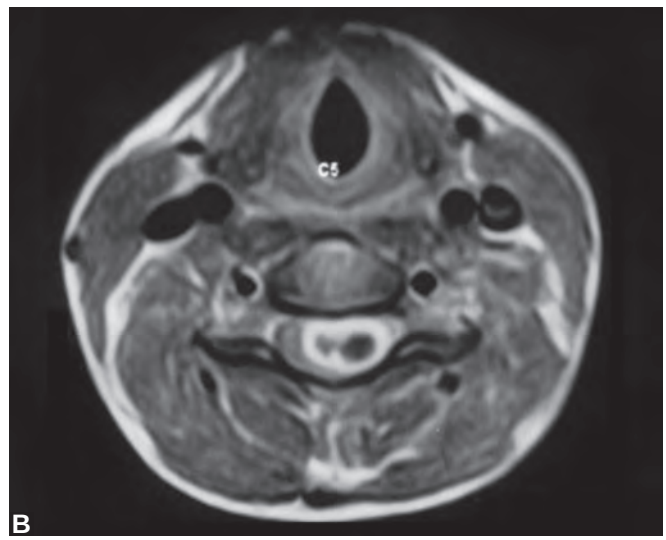
Figs 2A and B: Post-contrast T1-weighted MR images. (A) Coronal. (B) Axial show a cervical schwannoma with a predominant extension along the nerve root outside the spinal canal





Figs 3A and B: Post-contrast MR. (A) Sagittal image shows multiple neurofibromas within the cranium, nerve root canals and soft tissue of the neck in a case of neurofibromatosis (NF1). (B) Axial image shows a neurofibroma within the nerve root canal on the right and another in the soft tissue of the neck on the left





Figs 4A and B: Post-contrast T1-weighted MR images. (A) Sagittal. (B) Axial show a cervical (C5) cystic schwannoma which lies entirely within the dura

decompressing the spinal cord and obtaining tissue for pathological analysis. Surgical principles employed elsewhere for removal of benign tumours also hold true for these benign extramedullary intradural spinal tumours like nerve sheath tumours and meningiomas. This includes patient positioning, optimum exposure, microscopic assistance, tumour debulking, preservation of normal neural elements and meticulous haemostasis.

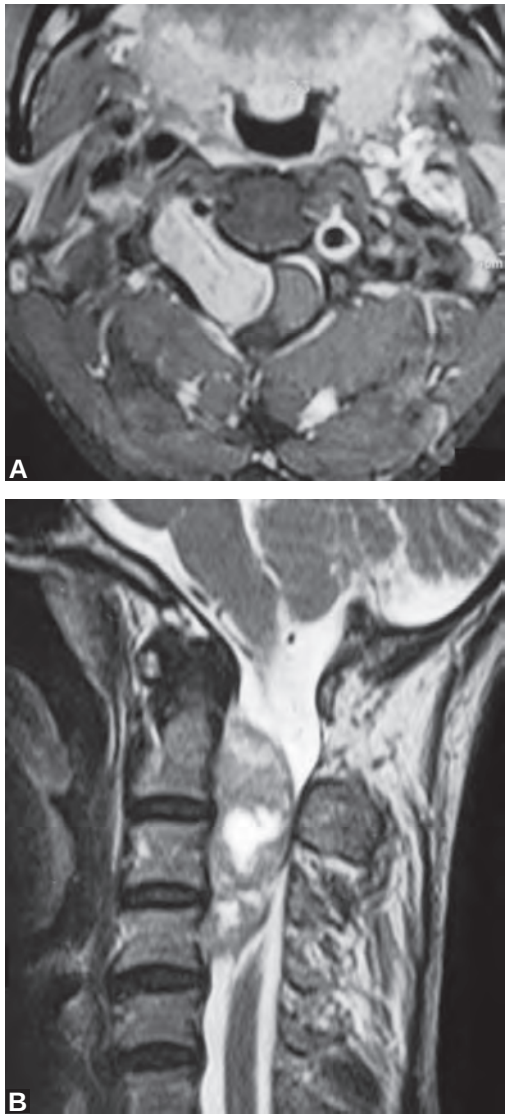
Pre-operative Preparation

Intra-operative electrophysiological monitoring of both motor and sensory tracts should be made available for the surgeon planning to resect an intradural extramedullary tumour. A Foley catheter and sequential compression device are routinely used. Pre-operative antibiotic to cover gram-positive bacteria and, steroids are routinely given.

Operative Procedure

A typical intradural extramedullary tumour is approached posteriorly through a posterior midline incision and multilevel laminectomy. This facilitates rostrocaudal extension as needed for resection of the tumour. The patient is positioned prone supported on chest bolsters. For tumours above the D2 level, the sitting position may be used as per the surgeon's preference. All pressure points should be padded adequately. There should be no compression of the genitals or abdomen in the prone position.

A standard laminectomy extending approximately one level rostral and one level caudal to the lesion usually provides sufficient exposure. Occasionally, a facetectomy or partial pedicle resection may be necessary to



Figs 5A and B: (A) Post-contrast T1-weighted axial MR image shows a cervical schwannoma extending from the spinal canal through the root canal. The tumour is entirely extradural in location. (B) T2-weighted sagittal image shows a large cervical cystic schwannoma

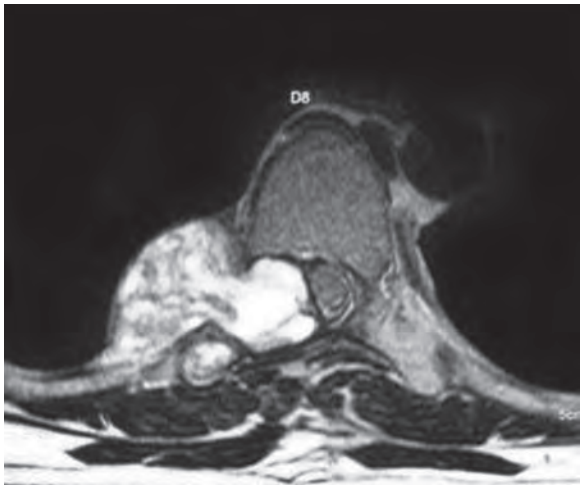


Fig. 6: Post-contrast T1-weighted axial MR image shows a dumb-bell shaped dorsal (D8) schwannoma that extends into both the spinal canal and the thoracic cavity

establish a ventrolateral corridor. Meticulous haemostasis must be achieved before durotomy. Collagen sponges (gel foam), oxidised cellulose strips (surgical) and collagen/thrombin suspension are all used to ensure a dry field prior to opening the dura.

A midline, linear dural opening is made carefully with double dura tooth forceps after making a small opening in the dura. Silk sutures are used to retract the dural sleeves by suturing them to the paraspinal muscles.

After the dura is opened, a careful inspection of the spinal cord and tumour is made. The arachnoid membrane is carefully opened over the entire extent of tumour. In a ventral or ventrolateral tumour, division of the dentate ligament would be necessary. After identification of the rostral and caudal poles of the tumour a cottonoid strip is placed to demarcate the tumour from normal spinal cord. Microdissection techniques are used to develop a plane, if possible, between the tumour and the spinal cord. Small tumours, particularly schwannomas, which tend to be associated with the dorsal roots can be removed after division of the entering and exiting roots. It must be kept in mind that temptation of having a trophy of en bloc total removal of even a medium sized tumour, specially those situated anteriorly, could result in regrettable neurological deficit. Large tumours require internal debulking and piecemeal resection. Internal debulking is done with graduated suction or sharp instruments depending upon the consistency of the tumour. The capsule is kept intact for counter traction and to keep a margin of safety from the spinal cord parenchyma. A portion of the capsule may be resected as internal volume is reduced for better visualisation of the tumour and its interface with the spinal cord. After the tumour has completely been resected the cavity is inspected to confirm complete haemostasis.

Nerve sheath tumours: Most nerve sheath tumours are dorsal or dorsolateral to the spinal cord and are well visualised once the dura is opened. Lumbar tumours may be covered by the cauda equina or conus medullaris. The nerve roots must be separated to provide adequate visualisation. Tumour removal requires identification of the proximal and distal end of the nerve root to which the tumour is attached. In large tumours, the site of origin may not immediately be apparent. The nerve root of origin usually must be sacrificed to remove the tumour. The corresponding intradural nerve root, however, can usually be preserved because the fenestrated arachnoid sheaths allow anatomic separation of the dorsal and ventral nerve roots to a point just distal to the nerve root ganglion.

Dumb-bell extension through the nerve root sleeve usually necessitates resection of the entire spinal nerve.[14] This resection rarely causes significant deficit as the function of this nerve root is already compensated by adjoining nerve roots. Significant extension into paraspinal tissues through an enlarged foramen may require an extended procedure. Although a two stage operation

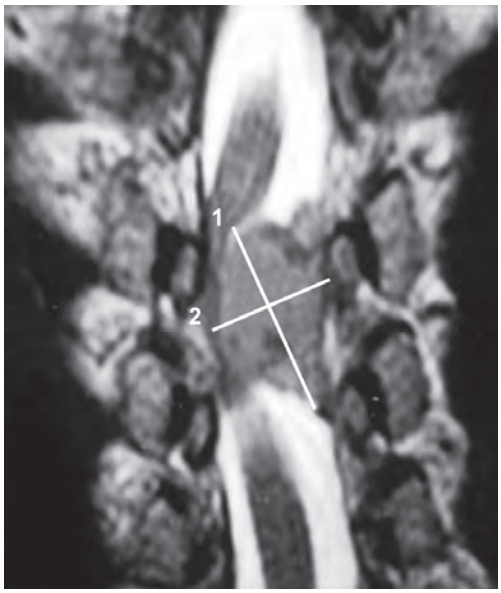
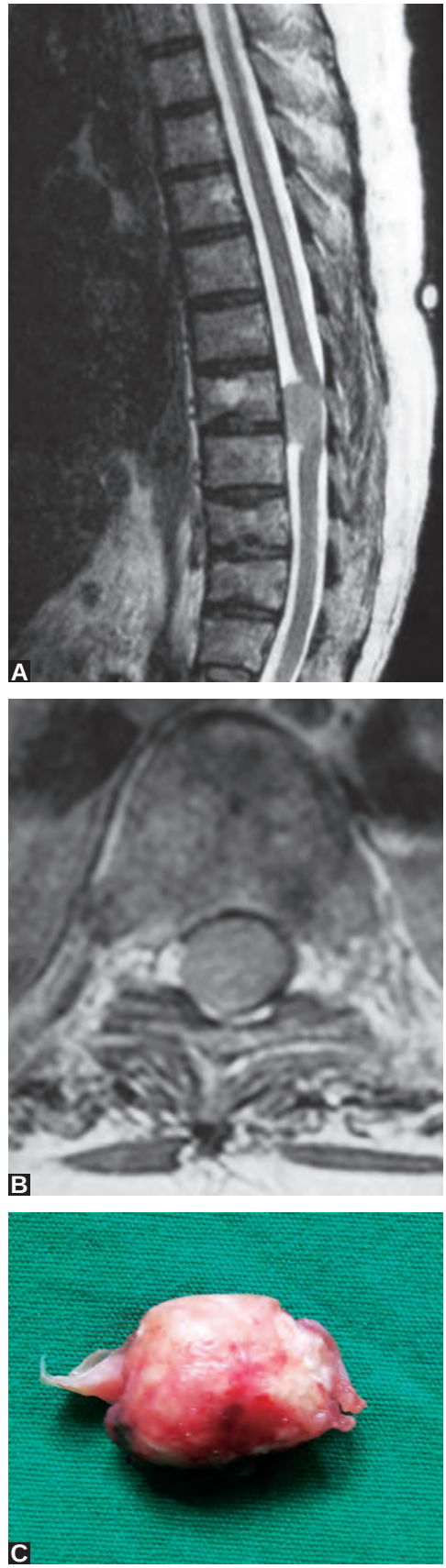


Fig. 7: T2-weighted coronal MR image shows a dural based meningioma displacing and compressing the spinal cord to the right. Note the widened adjacent cerebrospinal fluid spaces

may be performed to manage separately the intraspinal and paraspinal tumour components, a single stage procedure is preferable. The cervical paraspinal region is difficult to access anteriorly due to the narrow confines of the neck and numerous neurovascular structures. Fortunately, most cervical tumours can be removed completely and safely by an extended posterior exposure. Complete unilateral facetectomy allows paraspinal access up to 3 cm. Paraspinal extension from thoracic tumour can be a small or a large mass in the thoracic cavity. A standard posterior approach provides inadequate exposure to the anterior paraspinal muscles. An anterior transpleural or extrapleural thoracotomy provides excellent visualisation of the paraspinal region. The lateral extracavitary approach is useful as a single stage operation in cases that require concomitant exposure of intraspinal and paraspinal compartments.[14] This exposure is achieved through a hockey stick incision and allows the surgeon to work on either side of the paraspinal muscles. Lumbar dumb-bell tumours can also be exposed well through a lateral extracavitary approach. Dumb-bell sacral tumours usually require both anterior and posterior exposures, which can be staged or performed simultaneously with the patient in the lateral position.

Meningiomas: A complete surgical excision is the treatment of choice for spinal meningiomas and can be achieved in more than 90% of cases. Despite favourable features, the recurrence rate of spinal meningiomas after gross total or near total excision is 10–15%.[11,17]

Posterior laminectomy provides adequate exposure in most cases. A unilateral laminectomy or facetectomy can be used for eccentrically located or ventral tumours. Most of the meningiomas displace the cord laterally and can be satisfactorily removed by the posterior route. The



Figs 8A to C: (A) T2-weighted sagittal MR image shows D8 meningioma. (B) Axial T1-weighted MR image shows the tumour to have nearly filled the entire dural sac. The cord cannot be distinguished separately from the tumour. (C) Postoperative specimen of the dorsal meningioma. A dural tail is noted on the right side

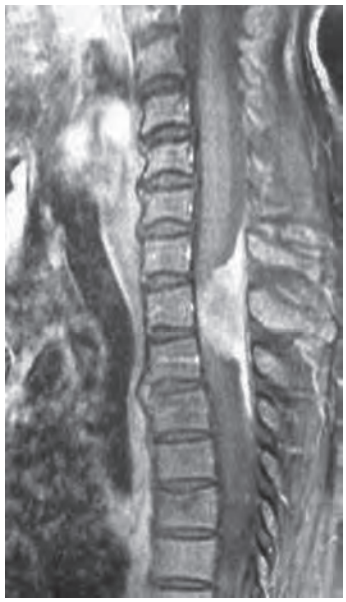


Fig. 9: Post-contrast T1-weighted axial MR image demonstrates a dorsal meningioma that has dural extensions (tail) extending on either side of the tumour

arachnoidal plane between the tumour and spinal cord can be easily identified and developed by gentle traction on the tumour away from the spinal cord. En plaque meningiomas tend to be associated with a significant amount of scarring rendering surgery more difficult.

The tumour removal involves correct identification and localisation. The rostral and caudal poles of the tumour should be identified. For lateral and ventral tumours, the arachnoid over the exposed tumour is incised and reflected so that dissection can proceed directly on the tumour surface. Large tumours are internally debulked and the tumour component adjacent to the spinal cord is delivered into the resection cavity using gentle traction and surface retraction. The remaining tumour is amputated from the dural attachment and the dural attachment is then excised wherever possible. If not possible, the involved dura is coagulated. Dural grafting may be necessary.

Management of the dural base is the most controversial aspect of treating spinal meningiomas. The options include excision of the involved dura and reconstruction with graft, or extensive *in situ* coagulation. However, in the recent literature, a significant difference in recurrence rates between the two procedures could not be established and the long-term recurrence rates range between 3% and 29.5%.[2,6,17] We prefer flush amputation of the tumour followed by coagulation of the dural origin.

Outcome and Prognosis

Spinal intradural and extramedullary tumours have a favourable immediate outcome and long-term prognosis. These tumours are benign, and if removed carefully and completely, the patient should be cured with an excellent long-term prognosis. Even patients with severe neurological deficit and cord compression can have marked improvement and long-term cure. It may take six months to two years to maximise the resolution of these deficits.

Nerve sheath tumours: The outcome of schwannoma correlates to the pre-operative neurological condition of the patient. The symptoms and signs of our patients improved in 95%. Total removal of neurofibromas and schwannomas that are not associated with neurofibromatosis is generally curative. However, tumours with extensive paraspinal involvement that are subtotally resected have a definite propensity to recur. Deficits resulting from sacrifice of the involved nerve roots are usually minor and well tolerated.[7,15,16,18]

Meningioma: The recurrence of spinal meningiomas after total extirpation is rare, and in most series the rate ranged from 1.3 to 6.4%.[9,11,12,17] The slow growth of spinal meningiomas and their presentation in patients at a late age contributed to the low recurrence rates. Significantly higher recurrence rates were found in cases of en plaque or infiltrating meningiomas, tumours with arachnoid scarring and in partially resected lesions. Klekamp and Samii have stated that patients in whom complete resection was performed, 29.5% experienced a recurrence within 5 years of surgery, whereas in all patients with partially removed tumours the lesion had recurred by that time.[6] In general, the course of a spinal meningioma appeared to be more benign than its intracranial counterpart. Mirimanoff et al. reported a recurrence rate of 13% at 10 years, which was far lower than those reported for convexity meningiomas (3% and 25% after 5 and 10 years, respectively) and parasagittal meningiomas (18% and 24% after 5 and 10 years).[11] Unlike intracranial meningiomas, there was no correlation between recurrence and resection of the dural attachment.

Although the optimal treatment for primary spinal meningioma was total microsurgical resection, some authors advocated adjunctive radiotherapy in cases of recurrent tumours. Its role as adjuvant therapy after subtotal resection is controversial due to the tumour's typically indolent nature. It has been indicated that radiotherapy should be considered after subtotal primary excision in cases of recurrent meningiomas, or as an alternative to surgery when the operative risk is too high due to co-morbidities or tumour location. Surgery is the preferred treatment in cases of spinal meningiomas because of its associated excellent functional improvement and low recurrence rates. Radiosurgery should be considered for the exceptional case of recurrent and symptomatic spinal meningioma.[6]

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106 Intramedullary Tumours

Bhawani S Sharma, Manish S Sharma

INTRODUCTION

Intramedullary spinal cord tumours account for 15–20% of all intradural tumours and only 2–4% of all intrinsic tumours of the central nervous system.[34] The most common initial symptom is generalised back pain, which is very difficult to distinguish clinically from back pain due to musculoskeletal conditions. Patients are often diagnosed only after the development of neurological signs and symptoms that may occur later in the course of the disease. Early diagnosis is important, however, because surgical removal for most tumours is curative, and surgical results are best when tumours are smaller. Moreover, neurological deficits resulting from intramedullary spinal cord tumours are rarely reversible and surgical results strongly correlate with the patient's pre-operative functional status.

HISTORY

The first successful removal of a spinal cord tumour dates back to 1887. Gowers and Horsley are to be credited for this as diagnosis and localisation at that time was entirely clinical.[28,36] In 1925, Charles Elsberg in his seminal analysis of 119 laminectomies for spinal cord tumours recognised the role of cerebrospinal fluid (CSF) manometry and roentgenography in aiding clinical diagnosis. He reported 21% mortality in a cohort of 14 intramedullary tumours of whom only three could be removed completely.[12] This laid the foundation for the subsequently adopted conservative approach consisting of biopsy and adjuvant radiotherapy which lasted for more than a quarter of a century. The foundation for the current practice of aggressive surgical resection was laid by Fred Epstein who published good results after aggressive resection of intramedullary tumours in both paediatric and adult patients.[7,13] These results have further been validated by several other authors who gained enormously by the technological advances in neuroimaging, microsurgery and intra-operative neurophysiological monitoring. Aggressive resection of these lesions with acceptable peri-operative morbidity has become a more realistic treatment goal.[3,9,11,14,19,23,27,32]

AETIOPATHOLOGY

Intramedullary spinal cord tumours mostly have a glial origin as they are histologically and immunohistochemically similar to normal ependymal cells and astrocytes. The exact aetiology remains unclear but is perhaps linked to genetic mutations. This is especially so in patients with neurofibromatosis; patients with the NF1 gene may develop spinal astrocytomas, whereas patients with the NF2 gene are predisposed to spinal ependymomas. Patients who develop sporadic spinal ependymomas have also been shown to harbour somatic mutations in the NF2 gene.[32] Spinal haemangioblastomas too may occur as a consequence of mutations in the VHL gene in patients with von Hippel-Lindau disease and also in those patients without the syndrome.

HISTOLOGICAL SUBTYPES

Astrocytomas and ependymomas are the most common histological types of intramedullary tumours. In modern series', these occur in almost equal frequency in adults.[3,14,27]

Astrocytomas

Astrocytomas comprise 90% of paediatric (<10 years) and 60% of adolescent intramedullary tumours. These have a predilection for the cervical and cervicodorsal cord (60%) and are rare in the filum terminale.

This category covers all subtypes of tumours from Grades 1 through 4. These include but are not limited to low grade fibrillary and pilocytic astrocytomas, malignant astrocytomas, glioblastoma multiforme, gangliogliomas and rarely oligodendrogliomas. Most of these are Grades 1 and 2 fibrillary astrocytomas though 25% of adult astrocytomas may be malignant.[7,32]

Patients with neurofibromatosis 1 have been known to develop intramedullary astrocytomas.[21] Most astrocytomas are infiltrative. This makes tumour excision very difficult and highly morbid. Yet, some tumours may have a good plane of cleavage. This has led us not to favour the plan of a simple biopsy in all cases. A radical removal should always be the primary goal because a simple biopsy does not guarantee a fair neurological outcome. Failure to adequately sample the tumour, in the latter case, may lead to misdiagnosis.

Ependymomas

Some authors believe that ependymomas are the most common intramedullary tumours in adults.[23,18] It appears

that, as age increases, the incidence of ependymomas increases, whereas that of astrocytomas decreases. Histological subtypes include epithelial, tanycytic (fibrillar), subependymoma and myxopapillary variants.[32] Unlike astrocytomas, these tumours are associated with neurofibromatosis 2 and are usually well circumscribed.[21]

Haemangioblastomas

These benign tumours of vascular origin are commonly located in a dorsal or dorsolateral position under the pia mater. They account for about 3–8% of all intramedullary tumours and may be associated with von Hippel-Lindau syndrome in 15–25% of all cases.[32]

Lipomas

Lipomas in an intramedullary location comprise about 1% of all intramedullary tumours. These are commonly located subpially and become symptomatic in adulthood.[32]

Metastases

These account for fewer than 5% of all intramedullary tumours and are relatively rare as both the spinal cord blood supply and the volume of the cord are low. Commonest primaries are malignancies arising in the lung and breast.[10]

Miscellaneous Lesions

Melanocytomas, melanomas, fibrosarcomas, primitive neuroectodermal tumours and cavernous malformations all can occur in an intramedullary location within the spinal cord although this is exceedingly rare. Intramedullary location of dermoid, epidermoid and neurenteric cysts have also been described. Another important differential diagnosis of a mass lesion within the cord substance, especially in our country, is intramedullary tuberculoma and cysticercus cyst.[33]

Epidermoids, dermoids and neurenteric cyst can also occur. (See chapter on Congenital Tumours of the Spine)

CLINICAL FEATURES—SYMPTOMS

As elsewhere within the central nervous system, the signs and symptoms of intramedullary tumours are related to the site, level, pathology and biological progression of the disease. The initial complaints are likely to be non-specific which may explain the lag time to diagnosis of 3–4 years. The following comprise some of the more common presentations.

Pain

Pain and motor weakness are the most common presentations in adults and children. Intramedullary tumours produce an ill defined pain which is seldom radicular (except in cauda-conus lesions) but localises at the level of the lesion. It is said to be more prominent at night in the supine position. In a very young child, localisation of the pain may be difficult. A sudden onset of pain indicates either an osseous collapse or an intratumoural haemorrhage. In fact, the absence of pain in a patient with radiographic and clinical features of an intramedullary pathology may indicate a diagnosis of myelitis.

Motor Function

Intramedullary lesions classically produce a long segment lower motor neuron type of weakness at the level of the lesion with atrophy, hypotonia, areflexia and fasciculations, along with features of upper motor neuron weakness below the lesion. Weakness is maximal at the level of the lesion.

Sensory Abnormalities

Patients often complain of numbness which begins distally and then extends proximally. This often takes the form of "glove and stocking", "cape distribution" or "dissociated anaesthesia". Anaesthesia may predispose to trophic ulcerations, especially in the upper limbs in cervical lesions.

Autonomic Dysfunction

Urinary incontinence, especially in a toilet-trained child, is a significant symptom which merits a detailed clinical and radiographic examination. Myelopathic patients who develop a Horner's syndrome or early onset orofaecal incontinence should be suspected to harbour an intramedullary pathology.

Spinal Deformity

Scoliosis may be the earliest sign of an intramedullary tumour in a young child. Local lumps, spinal point tenderness and the presence of stigmata of spinal dysraphism are all indicators of underlying pathology.

CLINICAL EXAMINATION

A detailed clinical examination should narrow down the cause, possible aetiology and the level of the cause of myelopathy. Care should be taken to evaluate the fundus and cranial nerves too as intramedullary tumours may seed down from an intracranial pathology. High cervical lesions may also affect the lower cranial nerves and the spinal nucleus and tract of the trigeminal nerve. Rarely hydrocephalus may occur even in the absence of an intracranial pathology due to an elevated protein concentration in the CSF, arachnoidal fibrosis and subarachnoid metastases. This is more common in malignant spinal cord tumours.

INVESTIGATIONS

Imaging

Contrast enhanced MRI remains the investigation of choice for the patients with a suspected spinal tumour. It

is not possible using current MRI techniques to reliably differentiate between the above mentioned histological subtypes of the tumour. A few points that may help are described.

Most intramedullary tumours expand the spinal cord, are hypointense on T1- and hyperintense on T2-weighted sequences and enhance with contrast. Ependymomas are more symmetrical, enhance with contrast uniformly and are more frequently associated with polar cysts. Up to 65% of ependymomas may be associated with a syrinx.[29]

Astrocytomas tend to be poorly marginated, enhance heterogeneously with contrast and may be associated with intratumoural cysts and necrosis. Up to 20% of astrocytomas may be associated with a syrinx.[29]

Haemangioblastomas are intensely enhancing lesions located dorsally or dorsolaterally within the spinal parenchyma and may be associated with flow voids and large cysts or a syrinx out of proportion to the size of the tumour. The entire neuraxis should be screened, if this pathology is suspected.

Metastases and lymphomas may be associated with leptomeningeal enhancement. This sign also indicates tubercular, bacterial or fungal myelitis.

Lipomas are unmistakable because of their MRI signal characteristics and do not enhance with contrast.

Non-tumourous conditions to be differentiated against include syringomyelia, acute multiple sclerosis and tuberculomas.[1] A pure syrinx does not enhance with contrast and is often associated with a Chiari malformation. Acute multiple sclerosis usually does not produce cord expansion. Tuberculomas may appear hypointense on T2-weighted sequences.

Angiography

This investigation is seldom used in the investigation of intramedullary spinal cord tumours except to rule out an arteriovenous malformation. This may also be used to embolise haemangioblastomas pre-operatively.

MANAGEMENT

Rationale of Treatment

A surgeon's primary objective should be total tumour excision but this has to be tempered by the need to maintain motor, sensory and sphincter functions, especially when most patients will develop significant, possibly transient, neurological deficits after intramedullary tumour resection. Up to 20% of operated patients will develop permanent deficits.[23]

Patients have to be counselled extensively before embarking on a surgical exploration. Those with a poor functional status prior to surgery are unlikely to improve significantly. In addition, the risk of neurological dysfunction is highest in this category. Some surgeons do not consider surgery in patients with complete sensorimotor loss below the level of the lesion.

The ideal surgical candidate is a patient with a progressive neurological deficit who is still ambulant. Though the risk of inducing a significant neurological deficit in the immediate post-operative period is high (34.6–43.6%), more than half of all patients (14–31%) will recover significantly from this.[19,23,24,25,30] If left unoperated, the progress of neurological dysfunction is unceasing after motor deficits set in. This inevitably leads to total paralysis. Taking the natural history of the disease into account, the risks of surgery seem acceptable.

Surgical Management

The goals of surgery are total tumour removal with preservation of neurological function. These objectives cannot always be achieved because some tumours infiltrate adjacent neural structures and make total removal impossible without incurring an unacceptable loss of function. Even when a tumour is delineated clearly from normal spinal cord, removal may result in a permanent increase in neurological deficit.

Patients need realistic guidance, especially those who are functionally intact, continent and have minimal neurological deficits. These patients are likely to refuse surgery. They should be closely monitored for the development of new neurological deficits, the appearance of which will probably lead to consent for surgery.

Radical surgery for malignant spinal cord astrocytomas (WHO Grades 3 and 4) does not appear to be beneficial.[32] This diagnosis can only be established by histological examination of tissue obtained at surgery. It is important not to perform a limited biopsy in such a case as a sampling error, especially from the tumour-cord interface, may cause the lesion to be under graded or worse, misdiagnosed. Thus a generous decompression should be performed as it will eliminate this source of error, decrease the tumour load, diminish pain and enhance the effect of post-operative chemoradiotherapy.[26]

A realistic neurosurgeon should recognise that preservation rather than restoration of neurological function is a reasonable goal after intramedullary surgery.[32]

Pre-operative Management

Patients are usually administered intravenous steroids (dexamethasone 4 mg IV Q 6H) for 48 hours prior to surgery. Patients with high cervical lesions are instructed in incentive spirometry. The period to surgery must be used by the operating surgeon to prepare the patient psychologically for a likely post-operative neurological deficit that may potentially devastate his/her morale. We prefer to use intravenous methylprednisolone succinate in loading doses of 30 mg/kg at the time of induction followed by a maintenance dose of 5.3 mg/kg for the next 24–48 hours depending on the patient's post-operative neurological recovery.

SPECIAL INSTRUMENTS/TECHNOLOGY

Evoked Potential Recordings

At the very outset, it must be mentioned that there is no statistical evidence to support the use of evoked

potential monitoring in improving outcome after operation for intramedullary spinal cord lesions.[23] Some surgeons routinely monitor somatosensory evoked potentials (SSEP) during surgery by stimulating the median/ulnar nerves in the upper, and the posterior tibial or peroneal nerves in the lower limb with low-voltage electrical current and the evoked responses in the sensory cortex are recorded through scalp electrodes. Multiple responses recorded via scalp electrodes in the sensory cortex are averaged on a computer to generate a standard reproducible waveform. This waveform may be affected by the stimulus frequency, amplitude, patient temperature and the concentration and type of anaesthetic agent. SSEP recordings, while theoretically attractive, have several disadvantages. Patients with profound pre-operative sensory deficits may have absent or very low amplitude baseline SSEP traces to begin with. Of graver consequence is the fact that SSEP traces are generally affected 10–60 seconds after the dorsal columns are damaged. This lag period may result in irreversible surgical damage as SSEP changes are seldom irreversible unlike during scoliosis surgery when changes are frequently reversible by releasing the instrumentation. Another drawback of SSEP monitoring is that it does not correlate with corticospinal tract damage which is far more critical to the patient's post-operative functional status. Thus, injury may occur to the motor pathways without any change in SSEP. Motor Evoked Potentials (MEPs) recorded via EMG electrodes in the musculature of the upper and lower limbs after motor cortex stimulation by scalp electrodes aims to obviate this problem. Direct epidural recording of spinal cord motor and sensory pathways may be used for a more comprehensive assessment of intra-operative spinal cord function.[8] For these reasons, SSEPs are not routinely used during intramedullary surgery in our centre.

Ultrasonic Aspirator

One of the absolute indications for the use of the ultrasonic aspirator is intramedullary surgery. The advantages of this equipment are several. High-frequency ultrasonic waves are used to fragment the tumour, which is subsequently aspirated. The fragmenting intensity of the ultrasound and the suction power of the device can both be varied independently. This obviates the need to dissect the tumour sharply off the cord interface and lessens traction on normal tissue. This minimises cord manipulation and has helped to vastly improve outcome after surgery. However, great care must be exercised while using this instrument under direct microscopic vision as normal cord can easily be aspirated as well if the tumour capsule is breached. Newer models now include a pen type attachment that will only fragment tissue without aspiration. At low intensity, this device can be used as a dissecting tool, as it were, to gently peel off the tumour from its interface with the cord. Unfortunately, hard calcific tumours cannot be decompressed with this device.

Laser

The CO_2 laser has been used with varying degrees of success in the excision of intramedullary tumours. The advantage of laser is that it is haemostatic for capillaries and can help resect hard tumours impervious to ultrasonic aspiration. Its disadvantages lie in that it can indiscriminately vapourise normal tissue and often slices through larger venules and arterioles producing haemorrhage. It is also expensive and frequently cumbersome to use.

Tissue Vapouriser

This implement assists cold cautery and is used in our centre with a needle attachment to incise the pia over the dorsal midline of the cord substance. The advantage of this tool is that the incision is precise and the cut is made without charring.

Intra-operative Ultrasound (iUSG)

Ultrasound is a valuable tool which can be used intra-operatively prior to durotomy to determine whether the laminectomy/laminoplasty is adequate or else needs to be expanded. This saves time and ensures that the intradural part of the surgery is not interrupted by the need to increase the bony exposure. Likewise, after durotomy, iUSG can confirm the position, length and adequacy of the myelotomy.

SURGICAL STEPS

Positioning

The patient is positioned prone on a Wilson's frame such that he lies closer to the side of the operating surgeon. Some surgeons prefer to immobilise the head in a rigid pin fixation device to prevent pressure sores developing on the forehead and malar eminences. This system also ensures that there is no pressure on the globes of the eye. Pneumatic compression devices may also be used to prevent intra-operative deep vein thrombosis.

Bone Removal

Great care is taken to ensure that the marking of the spinous processes is correct. We rely on intra-operative C-arm to accurately map out the area of interest after the patient is positioned supine. Pre-operative marker X-rays may prove inaccurate in the prone position and the resulting inadequate laminectomy can unnecessarily prolong the operative procedure and demoralise the surgeon. Most surgeons prefer to perform an extensive laminectomy to ensure that the origins of the dorsal nerve rootlets are clearly visible on both sides and also that the lateral margins of the tumour can be adequately decompressed. Smaller tumours may be approached by a trap door laminoplasty, but the authors' personal experience with this approach has not particularly been favourable. A pneumatic drill is used in our centre to drill away the laminae till the ligamentum flavum and

epidural fat is clearly visualised. As the cord itself is bulky and the dura is compressed against bone, great care must be taken to ensure that a deficit does not result from careless bone removal itself. We use 2 mm size Kerrison upcuts to remove thin slivers of bone left behind after the use of the pneumatic drill. The laminectomy should encompass the rostral and caudal ends of the enhancing parts of the tumour as visualised on the mid-sagittal MR images. Polar non-enhancing cysts do not need to be excised but need to be encompassed by the laminectomy so that a clear plane of cleavage can be established at the outset itself. After bone removal, iUSG is used to confirm the adequacy of bone exposure.

Durotomy

We prefer to incise the dura under microscopic vision beginning from cranial and proceeding caudally using a pair of fine toothed forceps for greater control. As far as possible, the arachnoid mater is kept intact till the dura is hitched up with 4-0 silk sutures to the drapes. This prevents rapid dural decompression and the consequent epidural haemorrhage from obliterating the operative field.

Myelotomy

We perform the myelotomy using a tissue vapouriser as close to the dorsal midline as possible. This prevents inadvertent damage to the dorsal columns and the resulting severe incoordination because of the loss of proprioceptive function. We identify the midline not by the presence of the midline septum or a vein but by a line equidistant from the origins of the dorsal nerve rootlets on either side (Figs 1 and 2). This is so because the tumour might have rotated the cord and the true midline in any position is the landmark described above. This is another reason why an extensive laminectomy is preferred as we should be able to see both sets of nerve rootlets arising from an expanded spinal cord. This myelotomy is then deepened till the tumour is reached. The tumour is entered and biopsied using fine grasping or curette type forceps (Fig. 3). A part of the biopsy is sent for frozen section examination while the remainder is preserved in formalin for histopathology. The report of the frozen section is an additional guide for the surgeon regarding the aggressiveness of the contemplated surgical resection. If a large vein is present over the midline, it should be sacrificed without hesitation using either the tissue vapouriser on low coagulation mode or else with bipolar electrocautery as a paramedian incision on the cord can produce a significant neurological deficit. Unlike other experts, we do not routinely endorse the practise of holding the pia-arachnoid on either side of the myelotomy apart using 7–0 atraumatic nylon sutures as we believe this produces additional traction on an already compromised spinal cord.

Specific techniques of tumour removal are guided by the provisional radiological and histopathological diagnosis, but more importantly by the intra-operative plane of separation between the tumour and the normal cord.

Ependymomas

Ependymomas push the normal spinal parenchyma aside, are distinct from the surrounding spinal cord, usually with a well defined plane of cleavage and may be dissected from it. They are firm and reddish-grey or

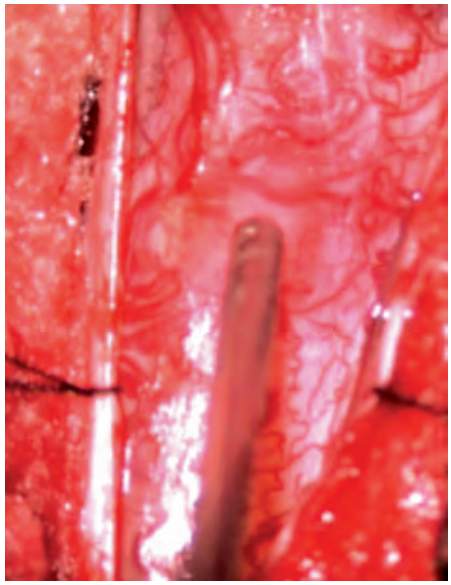
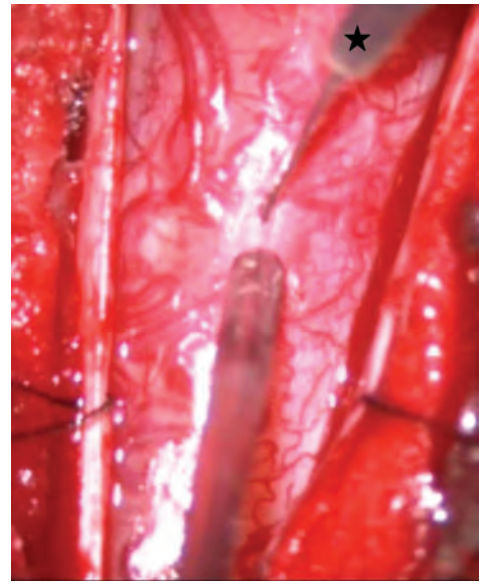


Fig. 1: Intra-operative photograph. Resection of a dorsal intramedullary ependymoma. The origins of the dorsal sensory rootlets indicate that the tumour has rotated the cord as they are not in the same plane. The suction catheter indicates the midline. The solid arrow designates the line of myelotomy over the expanded reddish spinal cord



Figs 2: The tissue vapouriser (star) is being positioned to fashion the dorsal myelotomy along the midline indicated by the suction catheter. Intra-operative photograph taken at maximum zoom. The myelotomy has been commenced parallel to a large paramedian arterialised vein

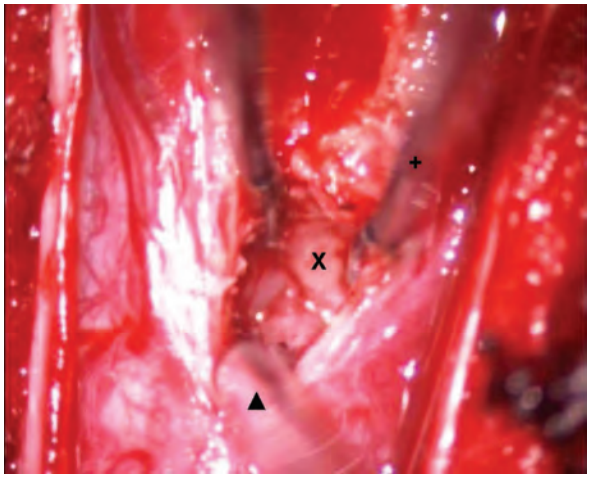


Fig. 3: A biopsy forceps (+) is being introduced through the dorsal myelotomy to grasp the ependymoma (X). The suction catheter (arrowhead) is being used to keep the myelotomy patent

yellow. Cysts may frequently be found at either end of the tumour. Smaller lesions often can be removed in one piece, but larger tumours should be debulked so that the blood supply which is located ventrally may be cauterised and cut before the tumour is finally removed (Figs 4 and 5). The ventrally located tumour should be dissected out with utmost caution using high magnification as the slightest breach of normal cord integrity will damage the ventrally located corticospinal tracts producing a catastrophic neurological deficit. If the cord-tumour interface is not clear, it would be prudent to terminate the procedure.

Astrocytomas

Spinal cord astrocytomas do not have a clear interface with the normal cord as they are infiltrating lesions. Subtotal excision is the accepted norm though some authors have found no difference in resectability vis-à-vis ependymomas. Unfortunately, recurrence after incomplete removal is common, and transformation to histologically malignant tumours has been noted to occur. Benign tumours with subarachnoid spread have also been reported.[8]

Malignant tumours (WHO Grades 3 and 4) are not amenable to complete resection. Extent of resection has not been associated with improved survival. Rapid recurrence and disabling subarachnoid spread is the norm with universal fatality before the first post-operative year.[4,5,20]

Haemangioblastomas

Haemangioblastomas may occur sporadically or in association with the VHL gene. These highly vascular lesions appear yellow-orange to bright red and are generally located subpially on the dorsal surface of the spinal cord as isolated lesions or in association with the VHL gene. These lesions have a clear demarcation from the rest of the cord and are amenable to total resection.

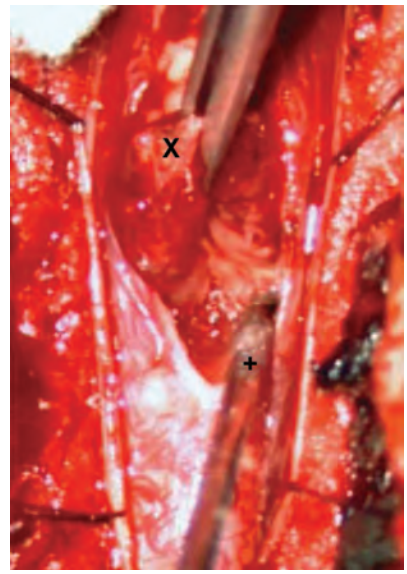


Fig. 4: The cranial apex of the tumour (X) has been grasped with the biopsy forceps and is being gently separated from the normal ventral corticospinal tracts by the suction catheter (+)

Microsurgical resection is performed along the same lines as that for AVM surgery. The lesion is not to be entered into at any cost. The arterial supply, which is usually evident, must first be interrupted before the tumour is shrunk using bipolar diathermy with copious saline irrigation. Patients have to undergo lifelong radiological surveillance to rule out recurrences locally as well as *de novo* in other parts of the cord.

Lipomas

Intramedullary lipomas are most commonly seen in the conus medullaris in association with a dysraphic spine. Isolated lipomas are very rare and are located on the dorsal surface of the thoracic or cervical spinal cord.

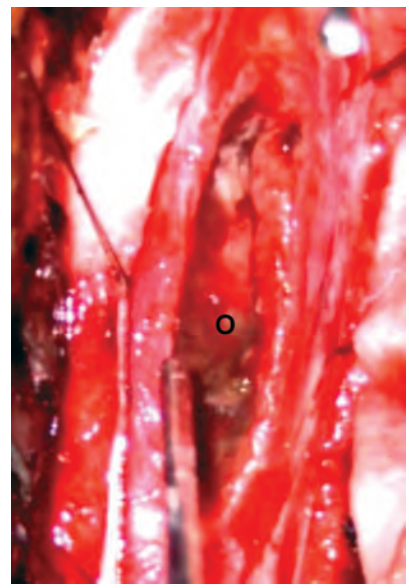


Fig. 5: The cavity formerly occupied by the tumour (O) is visualised through the myelotomy. Oxidised cellulose strips are used to ensure haemostasis

These tumours are indistinct from lipomas seen elsewhere within the human body and are clearly demarcated but densely adherent to the adjacent neural tissue. The acceptable surgical technique is a subtotal removal as these lesions are slow growing and are unlikely to recur after a generous debulking has been performed. Authors have reported using laser with great effectiveness as the performance of the ultrasonic aspirator is affected adversely by fibrous bands within the lesion.

Intramedullary Metastases

These represent less than 8% of all intramedullary spinal cord tumours.[5] The most common primaries are lung and breast carcinomas. In one third of all cases, the intramedullary metastasis may be the only sign of the primary. Progression is rapid and more than 80% of the patients die within 3 months of first seeking medical attention.[8] Operative management is similar to that for haemangioblastomas described above.

Closure

The pial hitch sutures, if used, are released. We do not close the pial incision or the myelotomy in our centre. Other authors believe this should be done to prevent cord tethering to the dura at the operative site.

A watertight dural closure is performed using a continuous interlocking 4–0 polydioxanone suture. If only debulking has been performed, a fascial patch duraplasty is essential to prevent spinal cord venous infarction. In malignant tumours, we sometimes leave the dura open to provide for an external decompression. In all cases, the wound is closed in several layers encompassing muscle, fascia and subcutaneous tissue. Vertical mattress nylon sutures are essential to close the skin incision.

POST-OPERATIVE MANAGEMENT

Methylprednisolone succinate is continued into the post-operative period for 48 hours at the rate of 5.3 mg/kg/hour. Proton pump inhibitors, antibiotics and precautions against deep vein thrombosis and pulmonary atelectasis are instituted in every patient. Patients with cervical intramedullary tumours are electively ventilated for 24 hours at the very least. Extensive physiotherapy (active and passive range of motion) is instituted from the first post-operative day. Air mattresses, two hourly change of posture, graduated compression elastic stockings, laxatives and care of indwelling Foley's catheter are routine aspects of post-operative care.

POST-OPERATIVE COMPLICATIONS

Neurological Deficit

Around 50–70% of patients undergoing intramedullary tumour surgery are likely to worsen neurologically. At least 20% of patients are expected to remain severely disabled. Patients with better neurological function fare better than those with poor function at presentation.[29]

The commonest neurological deficit that a patient is expected to experience is loss of joint and position sense as a consequence of the injury to the dorsal columns from the myelotomy.[23] The spinothalamic tracts may be injured during lateral dissection while the corticospinal tracts are vulnerable during the ventral separation of the tumour from normal cord. Though the benefits of SSEP appear intuitive, controversies abound as has been dealt with previously.

Neurological deterioration several days after surgery may be associated with tapering or withdrawal of corticosteroids. For reasons that remain unclear, a subsequent increase in corticosteroid dosage may not result in an improvement in neurological function.[8]

Wound Dehiscence

This dreaded complication occurs more frequently in patients who have either been previously operated upon or irradiated. An associated CSF leak may result in meningitis and a possible fatality. Management includes CSF diversion, debridement and primary resuturing or plastic reconstruction using rotational flaps of the trapezius or latissimus dorsi muscles.

Spinal Deformities

This delayed complication is seen more often in children and may result in thoracic or lumbar spine kyphoscoliosis or swan-neck deformity of the cervical spine. Its appearance in adults is unusual if it was not present pre-operatively. Causes include denervation of paraspinal muscles by the tumour or during surgery with a resulting unopposed flexion, especially in the cervical spine. Following a laminectomy, the paraspinal muscles also no longer have an osseous attachment. Severe flexion deformity may result in spinal cord kinking and dysfunction resulting in a delayed progressive neurological deficit which can mimic tumour recurrence. Re-exploration, instrumentation and fusion are indicated in this clinical situation.

ADJUNCTIVE TREATMENT

No study has demonstrated a beneficial effect of radiation therapy on neurological function or survival in patients with glial spinal cord tumours.[8,17] The efficacy of radiation therapy is difficult to determine because the natural history of the disease is unpredictable and long-term survival without radiation may occur. Moreover, most studies which have revealed a therapeutic benefit were not controlled.[16,35,37,38]

Most experts irradiate all adult patients with spinal cord astrocytomas, regardless of the completeness of removal or the histological grade of the tumour using 4,500 Gy given in divided doses.[8] Garcia noted improved outcomes in patients treated with 4,000 Gy compared with those treated with smaller doses.[15]

Most authorities do not irradiate paediatric patients after a gross total tumour resection. Radiation is reserved for paediatric patients with recurrent low-grade tumours or for those who have had rapid neurological progression of deficits.[8]

Patients with ependymomas should not be irradiated after documented complete excision. Recurrences should be dealt with by redo surgery and radiation if a residual tumour burden exists. When a residual tumour exists after surgery, radiation is an option if redo surgery is deemed risky.

The effectiveness of chemotherapeutic regimens using Carmustine and BCNU similar to intracranial astrocytoma management is not clear.

Regardless of tumour histology or grade of resection, all patients require lifelong surveillance with a contrast MRI of the craniospinal axis.

PROGNOSIS

Malignant intramedullary astrocytomas are considered universally fatal within one year. Median survival has been variously estimated at 6 months.[8] Patients with low-grade astrocytomas fare better but succumb to complications, such as respiratory paralysis, quadriplegia, pulmonary emboli, sepsis and pneumonia. Sandler et al. reported an actuarial survival of 68% at 5 years in 21 patients with spinal cord astrocytomas, of whom two were anaplastic.[31]

Patients with ependymomas do better than those with astrocytomas. Haemangioblastomas are benign tumours that are potentially curable if they are removed totally.

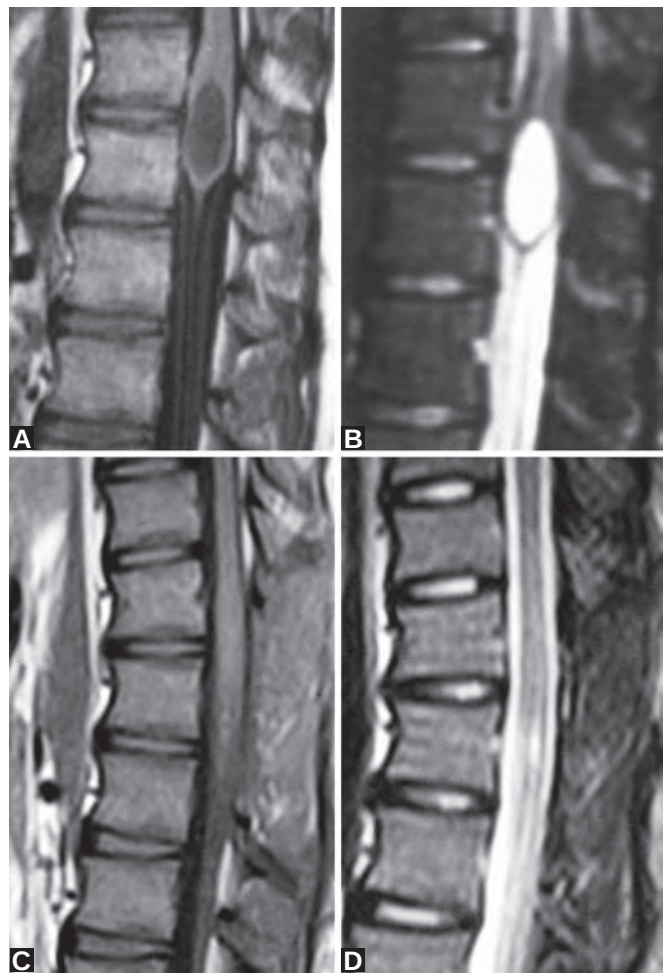
THE AIIMS EXPERIENCE

In a 4 years retrospective analysis of 75 patients operated upon for intramedullary tumours at our institute (2000–2003), 83% had motor, 77% had sensory and 41% of all cases had bowel and bladder dysfunction. Thirty-one patients had a pre-operative McCormick grade of 2. The commonest locations were cervical and thoracodorsal. All haemangioblastomas, 38% of astrocytomas and 36% of ependymomas were associated with a syrinx. Fourty-four patients (58.7%) underwent a total excision while 26 patients (34.7%) underwent a near/subtotal excision. The commonest tumours were ependymomas (33.3%), astrocytomas (28%) and epidermoids (8%). In children, the commonest tumours were astrocytomas while ependymomas occurred in the adults. There was no operative mortality. Seventeen patients (22.7%) experienced a neurological deterioration of at least one McCormick grade in the immediate post-operative period. At the time of last clinical evaluation, 33% had improved while 9.3% had deteriorated. Outcome correlated statistically only with the pre-operative neurological status. Sex, age, tumour location, histopathology, extent of tumour resection and the presence of a syrinx did not correlate with outcome. This is in agreement with other series.[8,29] Cristante et al. reported clinical improvement in 20% of the operated patients, while 50% deteriorated after surgery.[11] Constantini, in his series of intramedullary tumours in children under the age of 3 years, found that only 16% improved while 25% deteriorated.[6] Brotchi et al. on the other hand reported improvement in 53% of all cases while 10% worsened.[2] Similarly, Maira et al. in a series of cervical intramedullary tumours found that 63% of surgically treated patients got better while only 6% worsened.[22]

Illustrative radiology (Figs 6A to D) depicts total excision.

CONCLUSION

Although advances in imaging and microsurgery have revolutionised intramedullary spinal cord oncological surgery, these tumours pose a formidable challenge to most experienced neurosurgeons. Intramedullary ependymomas and haemangioblastomas are potentially curable through surgery. However, most spinal cord astrocytomas are locally infiltrative and not totally resectable. Malignant spinal cord astrocytomas are universally fatal and recur frequently. The role of adjunctive therapy still remains poorly defined.



Figs 6A to D: Pre-operative T1-weighted. (A) and T2-weighted. (B) sagittal MR images revealing an intramedullary conus pilocytic astrocytoma which was excised totally via a laminectomy. Post-operative T1-weighted (C) and T2-weighted (D) sagittal MR images confirm total excision

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107 Congenital Tumours of the Spine

CE Deopujari, AB Kakani

Congenital tumours of the spine usually cause progressive impairment of lower extremity and bladder or bowel function in an insidious manner through compression or by cord tethering. These tumours are a result of defective embryogenesis and may or may not be evident at birth. Surgical intervention for excision of these tumours to relieve the compression or to release the tethering of the cord is helpful in preventing or reversing neurological deficit. Tethered cord syndrome has been covered in other chapters and further discussion will, therefore, be restricted to lesions mainly presenting with compression.

Tumours or tumour-like conditions that may affect the spinal cord congenitally are dermoid and epidermoid cysts, teratomatous tumour, lipoma, neurenteric cyst, arachnoid cyst, hamartomas, cavernomas and angiolipomas. Occasionally, astrocytomas may occur congenitally.

EPIDERMOID AND DERMOID CYSTS

Epidermoid and dermoid cysts account for less than 2% of all central nervous system (CNS) lesions, the cranial to spinal ratio being 6:1.[38] However, these lesions make up to 17% of all spinal cord tumours in children. The pathogenesis of spinal epidermoid and dermoid cysts, as mentioned by Dias and Walker, is mainly congenital, the origin being epithelial tissue displaced during closure of the neural tube between the 3rd and 5th week of gestation.[19] Repeated lumbar puncture, especially multiple lumbar punctures done in the same patient, such as in the treatment of tubercular meningitis or lumbar puncture done without a stylet in the needle, is an acquired cause for occurrence of similar tumours which are then called implantation dermoids.[31,68] Such cysts are also reported to develop after surgery or trauma.

Unlike true neoplasms, which grow by progressive cell division, epidermoid and dermoid cysts enlarge by desquamation of normal cells and secretions of dermal elements into the cystic cavity. The cysts contain keratinous material arranged in a lamellar fashion. The outermost layer which is homogeneous gives this tumour its beautiful pearly sheen. Diagnosis of epidermoid and dermoid cysts is usually based on the characteristic nature of their contents revealed by histological examination.[38] Both the cysts are lined by stratified squamous epithelium supported by an outer layer of collagenous tissue. The differentiation between the two is made by the fact that the lining of the dermoid cyst also contains dermal appendages such as hair follicles, hair, sebaceous glands and occasional sweat glands. It is for this reason that dermoid cysts may contain hair. The connective tissue capsules that are located within the spinal cord are surrounded by a zone of reactive gliosis.

The location of spinal epidermoid and dermoid cysts is variable, more common sites being the lumbosacral (involving the conus medullaris and cauda equina) and thoracic area.[30] Only a few reports of cervical epidermoid and dermoid cysts have been reported.[58] These may be either extradural, intradural extramedullary or intramedullary in location within the spinal cord. These tumours are soft with a pliable capsule and grow very slowly. As the cyst increases in volume, it conforms in shape to any available cerebrospinal fluid (CSF) space and thus it attains a large size without producing any symptoms from compression of neural elements. These tumours thus become apparent usually in the second decade of life.

Around 50% of spinal epidermoid and dermoid cysts are associated with other congenital anomalies of the spinal cord, vertebrae, overlying soft tissue or skin.[48] This may be in the form of posterior spina bifida occulta, hypertrichosis and similar other dermal abnormalities, especially posterior dermal sinuses. The latter anomaly may predispose to recurrent pyogenic meningitis, and should actively be sought while operating upon a patient with an epidermoid or dermoid cyst. The presence of these cutaneous markers aids in early diagnosis of these tumours. The occurrence of these anomalies in association with these tumours further strengthens the theory of these lesions being of developmental origin.

The clinical presentation may not be different from other space occupying lesions of the cord and includes backache, progressive weakness in the lower limbs, bladder or bowel symptoms and sensory dysfunction. Leakage of the cyst contents in the CSF space is associated with recurrent episodes of aseptic meningitis.[6] Constant irritation caused by this keratinous material is also responsible for spinal arachnoiditis. This allows the capsule of the cyst to intimately adhere to the surrounding tissue and any attempt at complete removal under such circumstances carries a high-risk of neurological injury.

With the advent of MRI, the pre-operative diagnosis of these lesions has become much easier.[60,75] MRI has become the investigation of choice for early detection of these tumours. These cysts are typically isointense to slightly hyperintense compared to CSF on all sequences. Occasionally, the capsule may show enhancement on administration of contrast. The disparity in signal intensity most likely reflects variable lipid and protein composition in these lesions (Fig. 1). Other radiological characteristics of these tumours include absence of oedema in the surrounding spinal cord. Kukreja et al.[42] have evaluated the role of diffusion weighted MRI in differentiating spinal epidermoid-dermoid cysts from arachnoid cysts and have suggested that this technique may be useful in the evaluation of these lesions.

Ideal treatment of these lesions consists of complete surgical excision including excision of the capsule. Many epidermoid and dermoid cysts have a clear plane of cleavage between their lining membrane and the arachnoid membrane, enabling the surgeon to excise them totally. However, in some cases, due to the granulomatous reaction, the cyst lining becomes nodular and becomes densely adherent to the surrounding structures. Any attempt at complete excision in such cases increases the risk of neurological impairment.[11] In such circumstances, it is wiser to excise the easily separable portions of the capsule, leaving behind the densely adherent portion. Lunardi et al.[47] in his series of 16 patients, left the capsule partially *in situ* in 9 patients and in the follow-up study up to 30 years, only one of his patients showed recurrence. Maiuri et al.[49] have also demonstrated that even partial resections of spinal epidermoid and dermoid cysts to avoid neural damage results in a good clinical outcome and a very low risk of recurrence. Use of the operating microscope, good knowledge of surgical anatomy, gentle handling of the tissues, intraoperative monitoring of evoked potentials, use of CUSA and LASER allows many tumours to be excised totally. Spilling of the contents into the subarachnoid space should be avoided as the cholesterin and desquamated keratin act as irritants and cause aseptic chemical meningitis and arachnoiditis. Peri-operative use of steroids and intra-operative use of steroid containing irrigation fluid is believed to help in alleviating the chemical irritation.[6]

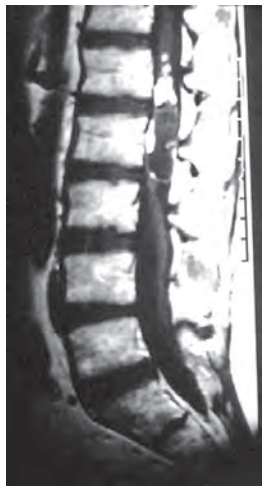


Fig. 1: Lumbar intradural epidermoid cyst (lipomatous lesion just above the cyst)

SACROCOCCYGEAL TERATOMA

Sacrococcygeal teratoma, the most common congenital tumour,[33,79] is a very rare tumour occurring congenitally with an incidence of approximately one in 40,000 births. Almost 75–85% of these tumours occur in females.[8,65,76] The exact aetiology for the occurrence of sacrococcygeal teratoma is not clear but it is thought that this tumour arises from totipotent cells of the primitive knot.[20,34] Another theory suggests that the teratoma is an abortive attempt at twinning. Well-defined body parts attached to these tumours suggest an incomplete conjoined twin.[20,34]

Sacrococcygeal teratomas are now increasingly being recognised antenatally with the use of foetal sonography which may reveal foetal hydrops, placentomegaly or polyhydramnios.[44] The foetal hydrops, as postulated by Langer et al.[44] results from high output cardiac failure caused by arteriovenous shunting within the tumour. They even demonstrated reversal of foetal hydrops by foetal surgical excision of the mass at 24 weeks' gestation. Danzer et al.[16] have demonstrated that ultrafast foetal MRI characterises the intra-abdomial and intrapelvic extensions of the tumour more accurately as compared to foetal sonography and provides more information on the compression of the surrounding structures. This additional information helps in better pre-operative planning in these cases.

Other reported presentations during the perinatal period include renal failure and respiratory distress,[55] trauma during delivery resulting in rupture or severe haemorrhage,[8,53,66] spontaneous rupture resulting in severe foetal anaemia,[79] consumption coagulopathy and steal syndrome.[53]

Clinically sacrococcygeal teratomas may entirely be asymptomatic or may present at birth as huge masses extending out from the sacrum and coccyx. However, a few cases may entirely be intrapelvic or presacral and can only be identified on rectal examination. Altman et al.[1] have classified sacrococcygeal teratomas into four types. Type I—primarily external with a minimal presacral component (47%). Type II—presenting externally, but with a significant presacral component (35%). Type III—tumour apparent externally, but the predominant mass being pelvic with abdominal extension (9%). Type IV—presacral without an external component (10%).

The presacral component may sometimes be large enough to cause compression of the urinary or gastrointestinal tract resulting in obstructive uropathy and chronic constipation.

Altman et al.[1] reported an 18% incidence of associated anomalies. The Currarino triad of anorectal anomalies, anterior meningocoele and presacral teratoma has also been described.[35,40] Delayed detection of teratoma in adult life has also been reported.

Pathologically a teratoma contains elements from all three primitive germ cell layers. The sacrococcygeal region is the most common site of occurrence of these tumours, the second most common being the gonads. They may be solid or cystic, but mostly are made up of both components. Actual organ formation has rarely been described, but tissues from any organ in the body can be detected in these tumours. Dehner,[17] who has described the histopathology of teratomas extensively, describes them as having "one or more somatic tissues in haphazard arrangement with little evidence of organisation".

These tumours present in three distinct forms: (1) entirely mature adult type tissue, which is clearly benign; (2) a mixture of mature and embryonic tissue, the latter often having malignant potential and (3) tumours containing frankly malignant tissue. Most series report an overall malignancy rate of 25–30%.[65,76] The longer the tumour remains after infancy, the higher are the chances of developing malignancy so that by one year of age well over 50% are frankly malignant.

Clinical diagnosis of sacrococcygeal teratoma may not be difficult; however the externally presenting tumour must be distinguished from lipoma and a low myelomeningocoele. Sacrococcygeal teratoma in the presacral region is unfortunately seldom discovered during early infancy and it needs to be differentiated from anterior meningocoele, rectal duplication or other tumours like neuroblastoma.

The only curative treatment for sacrococcygeal teratomas is complete surgical excision. The role of chemotherapy and radiotherapy in these cases is not well defined. Donnellan and Swenson have stressed the importance of complete coccygectomy in these patients.[20] None of the 51 patients with benign teratomas showed any recurrence after complete coccygectomy in their series. However, there are instances where the tumours with all mature elements have recurred despite complete excision with coccygectomy.[17] Some tumours with predominant presacral or intrapelvic components may require an additional abdominal approach for complete excision.[25] Cowles et al.[14] have described the use of pre-operative angio-graphy with embolisation and radiofrequency ablation as useful adjuncts to surgical excision of giant hypervascular sacrococcygeal teratomas. Kaneyama et al.[36] have demonstrated the use of Ligasure vessel sealing system for controlling intra-operative haemorrhage. With careful technique and a team approach including the urosurgeon, colorectal surgeon and oncosurgeon, it is usually possible to remove most of these tumours without rupture or excessive blood loss, but the obviously invasive malignant tumours cannot be removed so easily.[28]

LIPOMA

Spinal lipomas are usually associated with dysraphism, in which the intraspinal component communicates with a subcutaneous lipoma through a defect in the posterior elements of the spine.[7] Nondysraphic true intradural spinal lipomas must be differentiated from cauda equina lipomas or lipomas associated with dysraphism. The clinical, radiological and surgical problems raised by these tumours are totally different. These tumours, also known as subpial lipomas, are unique in that they may occur anywhere in the spinal canal, unlike lipomas associated with spinal dysraphism which occur predominantly in the lumbosacral region.[26] The dural layer is intact in true intradural lipomas and there is no tethering of the cord. The origin of these tumours is poorly understood but is thought to have an embryological basis. As mentioned by Finn and Walker,[26] one of the earliest theories put forwards by Virchow was based on the observation that adipocytes were present in the normal meninges and that spinal lipomas resulted from the hyperplastic overgrowth of these cells. It is postulated that lipomas develop when there is premature dysjunction of the cutaneous ectoderm from the forming neural tube.[7] The surrounding mesenchyme migrates into the developing neural tube and differentiates into fat.

True intradural lipomas are rare, accounting for less than 1% of all spinal tumours.[45] In literature, these tumours are represented as scattered case reports of 1 or 2 cases. Lee et al.[45] have reported a series of six cases where most of the patients were young adults, and the tumours were mostly located in the cervical region. Bhatoe et al.[7] have reported 14 patients with nondysraphic spinal lipoma with almost similar statistics.

Patients with lipomyelomeningocoele can generally be identified at birth because of the subcutaneous fatty masses or one or more cutaneous markers of spinal dysraphism.[9] However, in patients with nondysraphic spinal lipoma, the cutaneous anomalies are generally absent and the clinical presentation is usually with symptoms secondary to mass effect owing to the size of these lesions and not due to tethering of the cord. These tumours present with symptoms of progressive myelopathy including gait difficulties, motor weakness, dysaesthetic sensory symptoms and sphincter incontinence.[45,61] Acute neurological deterioration has also been reported. Infants and children on the other hand often develop tetraplegia or are diagnosed as floppy infant syndrome.[52] Clinical presentation simulating muscular dystrophy[21] and development of scoliosis[39] is also reported. Fujiwara et al.[27] have reported gradual deterioration in symptoms during pregnancy and after delivery.

MRI is the investigation of choice to diagnose these lesions pre-operatively.[7,27,45] Hyperintensity seen on T1-weighted images is very characteristic of fat, and further confirmation can be obtained by fat suppression studies. The lesions are usually located in the dorsal aspect of the cord in the cervical or thoracic region (Fig. 2).

The treatment of these lesions, like any other intramedullary lesion, is challenging. These tumours are not truly intramedullary but only subpial. Complete

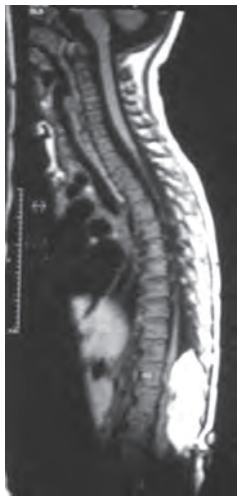


Fig. 2: Lipoma presenting with mass effect in lower dorsal spine

surgical excision carries the risk of neurological impairment and hence partial decompressive resection is recommended.[7,27,45,50,61] Improvement in neurological status of the patient following surgery is exceptional; however, the pain disappears due to relief of pressure on the dorsal columns. Intra-operative ultrasonography may be useful to delineate the extent of the lesion as lipomas are anechoic.[7] LASER vaporises the fatty tissue without physical manipulation of the neural tissue and is an important adjunct in the surgery.[7] Long-term results of surgical treatment are satisfactory and no recurrences have been reported so far following surgery.

NEURENTERIC CYST

Neurenteric cyst,[5,15,32,41] reported in the literature by variable names as an enterogenous cyst, enteric cyst, gastrocytoma, dorsal enteric fistula, split notochord syndrome and teratoid cyst, is an infrequently reported congenital anomaly believed to be derived from an abnormal connection between the primitive endoderm and the neuroectoderm during the third week of gestation. These cysts may be found within the brain, in the cerebellopontine angle, mediastinum, abdomen and pelvis or even in a subcutaneous location, but are more frequently located in the spinal canal.[24,51] Intraspinal neurenteric cysts account for less than 0.5% of all spinal tumours.[51]

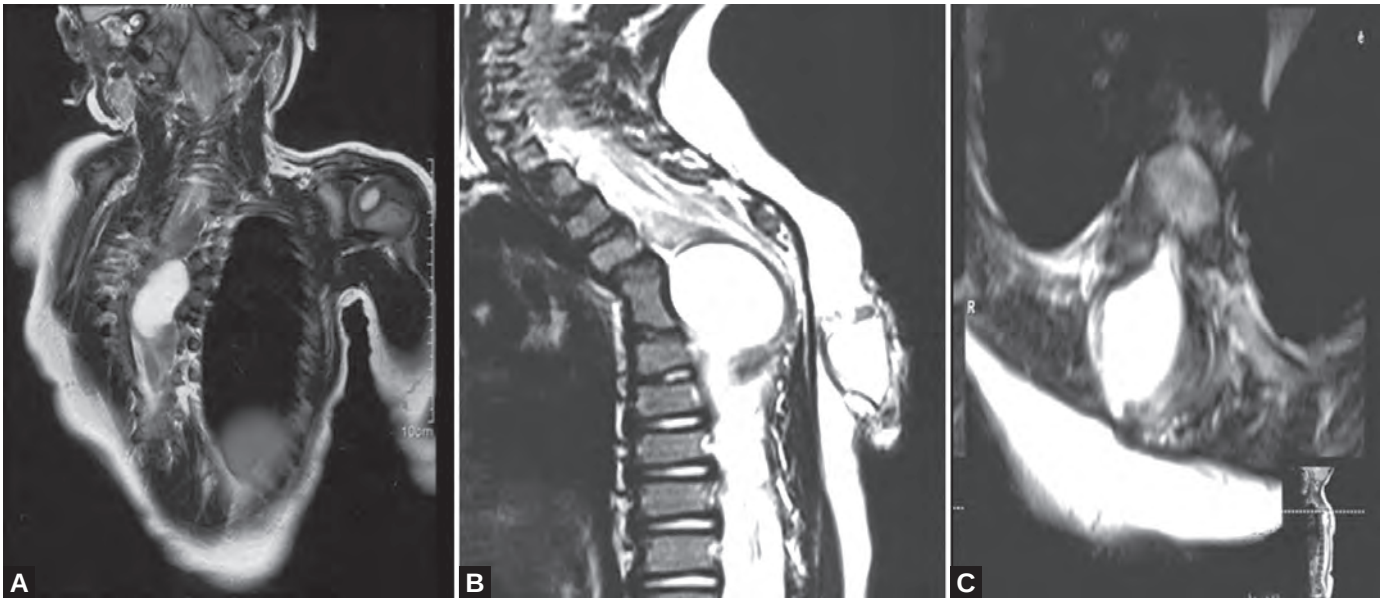
A number of theories have been proposed to explain the occurrence of endodermal tissue in the CNS. In the trilaminar germ disc formed during the third week of development, the outer layer, the ectoderm, faces the amniotic cavity and the inner layer, the endoderm, faces the yolk sac in the opposite direction. Between these two layers lies the mesoderm which gives rise to the notochord. The neurenteric canal is a temporary direct connection between the yolk sac and the amniotic cavity through the primitive pit, thus connecting the anlagen of the spine and gastrointestinal tract. Therefore, malformation at this stage of development results in combined anomalies of the vertebrae, spinal cord and the gut. The embryological basis of development of neurenteric cysts has been detailed by Rauzzino et al.[62] Patients with neurenteric cysts usually present in the first two decades of life,[43] although infrequent presentation well into adulthood is also reported.[70] The common location of these cysts is the cervical or thoracic region however, these cysts may occur at any location in the spinal canal from the craniovertebral junction[23] to the lumbosacral region.[80] Most of the cysts are located anterior or anterolateral to the cord, the dorsal location being less frequent. These may appear as intradural extramedullary masses or rarely as intramedullary lesions[70] (Figs 3A to C).

Pathologically these cysts vary in complexity and composition. Wilkins and Odum[78] have classified these lesions on the basis of the histological features of the cyst wall and its contents. The walls of Type A cysts mimic gastrointestinal or respiratory epithelium with a basement membrane supporting single or pseudostratified cuboidal or columnar cells, which may be ciliated. Type B cysts also contain glandular organisation, usually producing mucin or serous fluid. Type C cysts are the most complex containing ependymal or glial tissue within the cyst. The World Health Organization has classified these cysts under the heading of "other malformative tumours and tumour-like lesions" and has described them as cysts "lined by mucin secreting epithelium resembling that of the gastrointestinal tract".[81]

Neurenteric cysts are associated with multiple anomalies at single or multiple levels including scoliosis, fused vertebrae, hemivertebrae, Klippel Feil anomaly or spina bifida.[62] Cutaneous stigmata, as with other forms of occult spinal dysraphism, also occur in association with these cysts.[69] Other reported associations include intradural lipoma, a meningomyelocele[57] and syringomyelia.[12]

ARACHNOID CYST

Intradural spinal arachnoid cysts are amongst the rarest causes of spinal cord compression. They have been described by various names including arachnoid diverticula, subdural arachnoid cysts, leptomeningeal cysts, meningeal hydrops and arachnitis cystica. These are congenital collections of CSF contained within the arachnoidal membrane and subarachnoid space. The origin of arachnoid cysts is still a matter of debate, but most of the cysts are thought to arise as developmental anomalies. Very few are associated with other causes like neoplasm, arachnoiditis,[29] trauma[13] and surgery. Tumialan et al.[73] have reported a case of T1-T2 arachnoid cyst developing after subarachnoid haemorrhage. There are many theories in the literature to explain the development and expansion of these cysts. Basaldella et al.[4] have summarised these theories: (1) a ball valve mechanism, i.e. a possible anatomical communication between the cyst and the subarachnoid space that can act as a one way valve mechanism responsible for cyst enlargement; (2) an osmotic gradient between the intracystic and the extracystic medium responsible for a gradient driven



Figs 3A to C: Thoracic neurenteric cyst with split cord

fluid transport (this theory lacks support because of the compositional similarity between the CSF and contents of the cyst); (3) a primary malformation of the arachnoid membrane and (4) hypersecretive fluid production by cells lining the luminal cyst's wall. Ultrastructural examination of the cyst wall has revealed that it is formed from splitting of the arachnoid membrane, with an inner and outer leaflet surrounding the cavity.[63] Despite their apparent developmental origin, these cysts are not associated with spinal dysraphism or other congenital anomalies.

As the cyst expands it causes progressive compression of the spinal cord. The symptoms and signs typically progress over several years. The usual age of presentation is adolescence and young adulthood, males being more frequently affected than females. Wilkins and Odom, in their review of 66 cases, have found a nearly equal sex distribution and a peak age of occurrence in the fifth decade of life.[78] The location of the cyst within the spinal canal and the severity of cord and root compression determine the clinical presentation. These cysts occur most commonly in the middle to lower thoracic spine but are also known to occur in the lumbosacral and, rarely, cervical regions.[3] These lesions usually arise posterior to the spinal cord and can also protrude into the neural foramen. Caruso et al.[66] have also described an intradural arachnoid cyst occurring anterior to the cord in the thoracic spine.[10] Sharma et al.[67] have reported a case of an intramedullary arachnoid cyst in a 4-year-old child presenting with acute quadriparesis. A single cyst usually extends over a long segment; however, cases with multiple cysts occurring at different levels in the cord have also been reported.[71]

The most common clinical presentation is with motor weakness in the form of spastic quadri or paraparesis. Other symptoms include back pain, radiculopathy, sensory impairment and sphincter disturbances. Symptoms can be intermittent or fluctuating and may be exaggerated by Valsalva manoeuvres or positional gravitational forces. Osenbach et al.[59] and Wilkins and Rossitch[77] have reviewed the subject of spinal arachnoid cysts in greater detail.

MRI is the most effective modality for the diagnosis of arachnoid cysts. The imaging characteristics of the arachnoid cysts are similar to CSF in all sequences (Figs 4 and 5). The anatomical relationship to the surrounding structures can be well defined. Scalloping of the vertebral body and expansion of the spinal canal from osseous remodelling suggests long standing mass effect from the lesion.[46] To demonstrate a communication between the cyst and the subarachnoid space, water soluble CT myelography has been the investigation of choice which demonstrates filling of the cyst through the communicating pedicle. Nakagawa et al.[72] have reported the usefulness of constructive interference in steady state (CISS) imaging in demonstration of the communication.[54]

Treatment is usually conservative for patients with asymptomatic cysts, with clinical and radiological follow-up. The mainstay of treatment in patients with symptomatic neurological deterioration is laminectomy with complete excision of the cyst.[46] If a portion of the cyst wall appears to be fused with the pia mater, attempts at complete excision are not recommended. The patient usually shows clinical improvement even after partial excision of the cyst wall. Delayed deterioration of neurological function after initial improvement may occur, and is attributed to either spinal cord ischaemia or spinal instability. Cystoperitoneal shunt is recommended if the cyst extends over multiple spinal segments or recurs after surgical excision. Kikuta et al.[37] have described an expansive duraplasty for treatment of spinal arachnoid

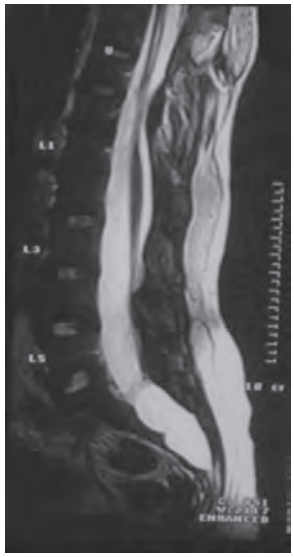


Fig. 4

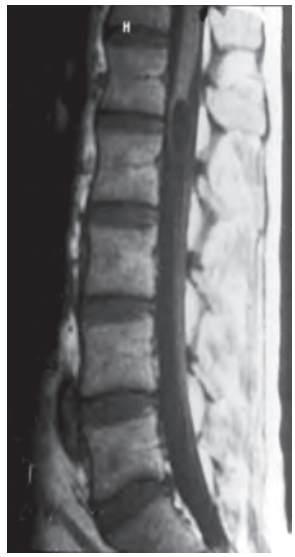


Fig. 5

Figs 4 and 5: Sacral and dorsal arachnoid cysts

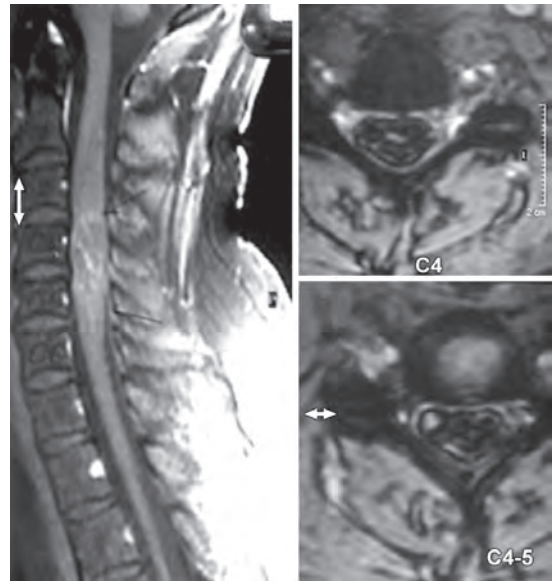


Fig. 6: Intramedullary cavernoma of cervical cord

cyst and recommend it as an alternative option where complete resection is not possible. Histological examination of the cyst wall should always be performed to establish the diagnosis because it is difficult to distinguish an arachnoid cyst from a neuroepithelial cyst on gross inspection.

MISCELLANEOUS LESIONS

Cavernous Malformation

Cavernous malformations are a subset of vascular malformations and are variably referred to in the literature as cavernomas, cavernous angiomas or haemangiomas. These malformations are typically discrete, well circumscribed reddish lobulated masses creating an overall appearance that has been likened to "a cluster of mulberries". Microscopic examination of these lesions reveals blood containing sinusoidal chambers lined by simple endothelium and lacking mature vessel wall components. There is no intervening neural parenchyma and they are surrounded by a gliotic margin. The exact cause of cavernous malformations remains obscure but these lesions do have a familial predisposition.[2] MRI is the only confirmatory imaging technique showing salt and pepper appearance due to haemosiderin deposition caused by multiple haemorrhages (Fig. 6). Clinically these patients may present with either an acute onset of neurological compromise or a slowly progressive neurological decline.[18] The surgical principles used in the resection of cavernous malformations are the same as for other intrinsic cord lesions. Once found, the presence of a gliotic plane surrounding the lesion often facilitates resection.

Angiolipoma

These are very rare congenital lesions affecting the spinal cord, and consist of abnormally differentiated vascular and mature adipose tissue, usually located in the epidural space.[64] The diagnosis of this lesion is usually suggested by the presence of a richly vascularised component and its lipomatous contents.

Astrocytoma

Spinal astrocytomas are common tumours accounting for 25–30% of all intramedullary spinal tumours in adults.[22] In children these tumours occur with a greater frequency accounting for up to 90% of all intramedullary tumours. Spinal astrocytomas occurring congenitally are very rare. Ng et al.[56] have described a case of low grade astrocytoma in an infant and stressed on the adverse neurodevelopmental outcome despite adequate surgical resection. Infants with these tumours may also show rapid neurological deterioration. Umemoto et al.[74] have also described a congenital astrocytoma in the cervical spinal cord.

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Venkatramana NK

HISTORICAL OVERVIEW

Sir William Macewen[79] of Glasgow, in 1883, removed an epidural 'fibrous neoplasm' 1/8 inch in thickness from a nine-year-old boy with relief from paraplegia. This was the first operation for a spinal tumour in a child. Gowers and Sir Victor Horsley pioneered the management of spinal tumours in 1887.[49] Harvey Cushing's refinements of Halstead's surgical technique lead him to achieve good results in surgery of spinal neoplasms.[21] The first successful removal of an intramedullary tumour was by Anton von Eiselsberg[33] in Vienna in 1907, and the first report on intramedullary tumour was by Elsberg in 1911.[34] Elsberg also described a two-stage surgical excision and pioneered the surgery of spinal tumours, and many others have contributed to this difficult field; Greenwood,[50] Cooper,[24] Guidetti,[51] McCormic, Malis, Stein,[110] Epstein[36–41] and Brotchi[12,13] among others. One of the earlier classical papers on intraspinal tumours was by Rasmusseu, Kernohan and Adson in 1940.

EPIDEMIOLOGY

Spinal tumours are rare in children with an approximate annual incidence of one per million. Spinal cord tumours account for 4–10% of central nervous system tumours in children[4,9,18,26,30,55,102,111,114,116] of which 25–35% occur within the parenchyma of the cord.[16,114] Longitudinal "holocord" tumours are very rare and comprise 1% of these lesions.[16,114] Common adult intradural extramedullary lesions, such as meningiomas, neurofibromas and schwannomas, are rarely found in children.[95] Epidural deposits are the commonest non-traumatic cause of paraparesis in children.

In children, 40% of spinal tumours are intramedullary, 20% are intradural extramedullary and 40% are extradural. The cervical spine is the region most frequently affected, followed by the thoracic and thoracolumbar spine.[112,118] Spinal tumours are evenly distributed between males and females,[22] but a slight male preponderance is noted if congenital tumours are included. Thirty to thirty-five per cent of histologically verified tumours are malignant.[22,35] Tumours of the posterior fossa in children may metastasise to the spinal subarachnoid space and may rarely present with a spinal syndrome.[63] Ingraham and Matson[56] reported that spinal cord tumours are 1/5th as common as brain tumours in childhood. Balaparameswara Rao and Dinakar[8] found the ratio to be 1:8.5. In a 25-year experience at the Institute of Neurology, Madras, there were only three neurinomas and one meningioma in children below the age of ten.[95]

PATHOLOGY

The most common paediatric spinal tumours are astrocytoma (16%), sarcoma (10%), neuroblastoma (9%), ependymoma (8%), dermoids (7%) and teratomas (7%). Medulloblastoma, neurofibroma, metastatic carcinoma and lipoma account for another 5%. Spinal haemangioblastomas are very rare in children. Ninety percent of intramedullary tumours in children are astrocytomas, whereas 60% of adult intramedullary lesions are ependymomas.[110]

The most common intradural metastatic lesion is medulloblastoma and seeding may occur in 9.4–44% of cranial lesions. Neuroblastomas are the most common cause of extradural cord compression in children.[7]

CLASSIFICATION

1. Congenital tumours: Teratomas, teratoid tumours, epidermoid, dermoid cysts and lipomas.[69,121]
2. Intramedullary gliomas: Astrocytomas,[85] ependymomas,[6] medulloblastomas, glioblastomas[15] and gangliogliomas.
3. Tumours of the meninges and nerve roots—meningiomas[75] and neurofibromas.[100]
4. Extradural extension of paraspinal tumours—neuroblastomas,[26] reticulum cell sarcoma and lymphosarcoma.
5. Vascular lesions such as cavernomas[29,72] and haemangiomas.[101]
6. CSF leptomeningeal secondaries—medulloblastomas, ependymomas, glial secondaries and germ cell tumours.[2]
7. Rare entities, PNET,[117] ependymal cyst.[68]

Most classification systems of childhood spinal tumours are based on the anatomic location of the tumour. They may be intramedullary, intradural extramedullary or extradural.[18] The most common intradural extramedullary masses are dermoid, neurofibroma, schwannoma, epidermoid, PNET and meningioma. Of these,

neurofibroma, schwannoma and meningioma are usually associated with NF type 1. Meningiomas are rare in childhood and may behave aggressively.[75,86] Extradural masses include sarcoma, neuroblastoma, teratoma, ganglioneuroma and lymphoma.[103] Extradural lesions account for about 25% of childhood spinal tumours. Primary metastatic lesions are usually sarcoma and neuroblastoma. Extramedullary tumours are quite evenly distributed throughout the spine. Sacral involvement is less common, except in developmental tumours.[18]

Of these four categories, intrinsic gliomas of the spinal cord and congenital tumours are more common in children than tumours of the meninges and nerve root. Congenital astrocytomas have been reported, the pathology being similar to astrocytomas in older children.[62] Gangliogliomas compromise 30% of tumours in children under 3 years of age. Intramedullary cavernomas are rare and there is a male preponderance (2:1) and they occur commonly in the cervical region.

CLINICAL PRESENTATION

It is difficult to get a proper history from children. It is equally difficult to get an adequate history from the parents, as they do not carefully observe the progress of the disease. In addition, there are few reliable physical signs due to the difficulty in examining the child. The diagnosis is usually long delayed and it is not unusual even to miss the diagnosis.[109] A period of close observation after hospitalisation is necessary to bring to light signs and symptoms which were not recognised earlier. Weakness of one of the extremities, usually a lower limb, and axial pain in the spine are the most frequent symptoms in children. This axial pain, which is the commonest symptom, increases during the night due to venous congestion and dural tube distension during recumbency. Radicular pain is rare and is caused by nerve root pressure, distension of the root or infiltration of dorsal root entry zone, and in extra medullary tumours. The pain can be atypical, simulating abdominal disease or disease elsewhere in the body.[99] An early and common symptom is diffuse rigidity of the spine, often out of proportion to the objective neurological signs.[53,100] In the developing countries, this sign would most commonly suggest tuberculosis of the spine. Many spinal tumours in children used to be mistaken for anterior poliomyelitis.[96] An intramedullary cervical cord tumour may be diagnosed as brachial plexus palsy. A few cases masquerade under the diagnostic label of general prostration, malnutrition, behaviour problem and polyneuritis. Hydrocephalus can be a manifestation of a spinal tumour. It is reported in 15% of cases and may be due to metastatic arachnoiditis, but 8% of benign tumours are also associated with hydrocephalus due to reactionary leptomeningeal thickening or due to increased levels of CSF proteins.[98,104]

Gait disturbance, torticollis and kyphoscoliosis have been reported. Scoliosis occurs in 25% of children with spinal tumours. Prior history of surgery, especially for spinal dysraphism, should be asked for as an intramedullary dermoid or lipoma (second tumour) may manifest after many years.[78,89] In case of lipoma, there may be a tell tale subcutaneous lipomatous mass. There may be either lower limb deformity, weakness or atrophic skin ulcerations.[69,121] Neurological deterioration years after closure of a meningocoele may be due to an intramedullary dermoid.[78,89]

Signs and symptoms depend on the location of the tumour, plane, extent of spinal cord compression and bony involvement.[18] The median duration of symptoms is 9.2 months (range 1.6–27 months).[22] Malignant tumours have a shorter prodrome (median 4.5 months). In most situations, the progression is indolent and may be associated with exacerbations and remissions. Rarely, there could be rapid progression, leading to acute paraplegia. Tenderness and paraspinal muscle spasm may be present on examination. The other symptoms include motor disturbances, sensory disturbances like paraesthesias, dysaesthesias, torticollis and sphincter dysfunction.[112,118] Detecting spinal cord compression, in an infant or a toddler, is very difficult. The only signs or symptoms may be inadequate motor milestones, irritability and frequent urinary tract infections. Children with slow growing extradural tumours may suffer from frequent urinary infections and, also loss of bladder control in toilet-trained children should raise the suspicion of a spinal lesion.

Motor deficits vary depending on the level of the lesion and the severity of the compression. Mild spasticity, increased reflexes and extensor plantar response with or without clonus occur relatively early in upper motor neuron compression. Sensory changes are infrequent and quite often difficult to assess accurately.

Dermoids, epidermoids and lipomas may be associated with a dermal sinus and present with bouts of recurrent bacterial meningitis or rarely chemical meningitis which may be confirmed by microscopic observation of keratin in CSF.

LABORATORY INVESTIGATIONS

Serum and urine levels of catecholamines: VMA and homovanillic acid levels are elevated in patients with neuroblastomas. Ewing's sarcoma may manifest with leucocytosis, increased ESR and elevated levels of LDH.

Imaging

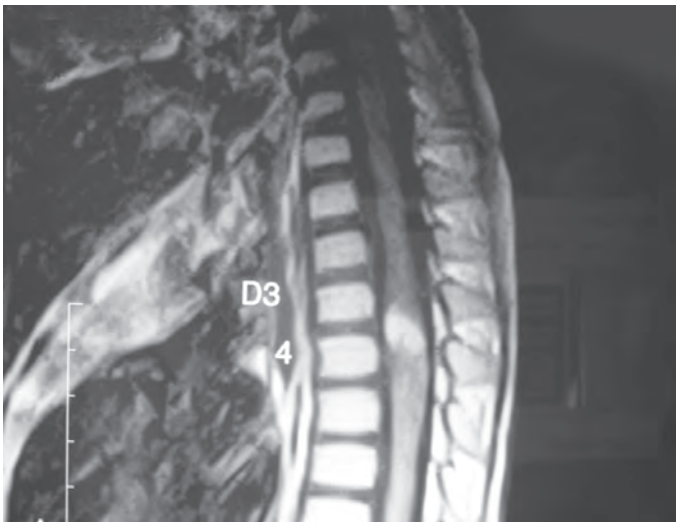
Plain X-rays of the spine are abnormal in 70–80% of cases of spinal tumours in children, as the immature spine of children is more vulnerable to increased intraspinal pressure.[28,70,96,108] The high incidence of congenital tumours in children is also one of the reasons for the higher incidence of vertebral changes. A tomogram may disclose a diffusely widened spinal canal with relatively localised erosion or flattening of pedicles. Scalloping and scoliosis may also be present in long standing lesions.

Oblique X-rays may show an enlarged foramen as many childhood spine tumours arise as a transforaminal extension of a paraspinal lesion and loss of a pedicle through bony destruction is characteristically seen as "winking owl sign" on AP views. Plain X-rays are also very important for planning instrumentation for deformity correction and stabilisation.

CT and myelography, though performed frequently in the past, had posed problems in interpretation especially in holocord tumours, association of syrinx and in complete spinal block. CT delineates the bony anatomy and reveals osseous destruction and calcification.

MRI with or without contrast is the imaging modality of choice.[18,73,92,113] It provides excellent images of extramedullary and intramedullary neoplasms. The T1-weighted image reveals the presence of rostral, caudal and intramedullary cysts, as well as the solid component of the tumour (Figs 1 and 2). T2-weighted images give a myelographic appearance to CSF and cysts (Fig. 3). Gadolinium enhancement is mandatory in spinal tumours, which usually enhances the solid component and helps delineate the tumour from surrounding oedema.[92,106,113] In most circumstances, malignant tumours appear hypodense on T1 and hyperdense on T2 with a non-uniform enhancement.[18,107,111,113]

Ependymomas enhance brightly and homogeneously. They have polar cysts with haemosiderin caps at their poles. On axial view, they are usually located in the centre of the cord[6] (Figs 4 A to D, 5A and B). Astrocytomas[85] and gangliogliomas do not enhance as brightly and their enhancement is not homogeneous and these are commonly eccentric causing asymmetric enlargement of the spinal cord. Cavernomas appear with a target sign, with an outside rim of haemosiderin which is hypodense on T1 and T2.[29,72] Haemangioblastomas will show the brilliantly enhancing tumour nodule and adjoining cysts.[25] Neuroblastomas are usually isointense



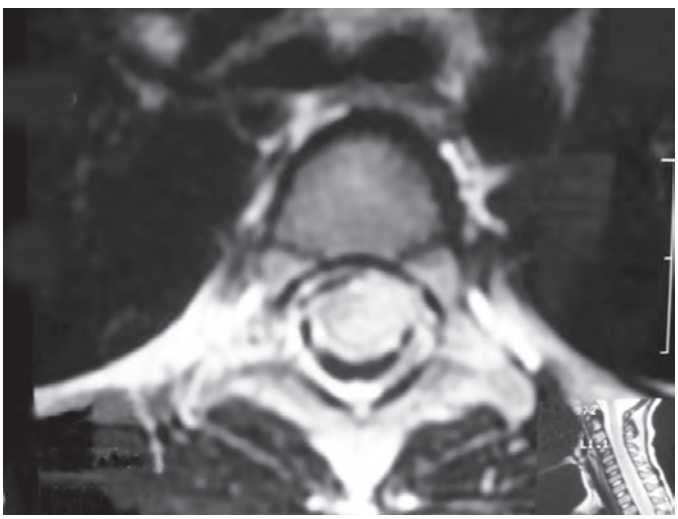


Fig. 1: MRI of the upper dorsal spine showing intramedullary tumour

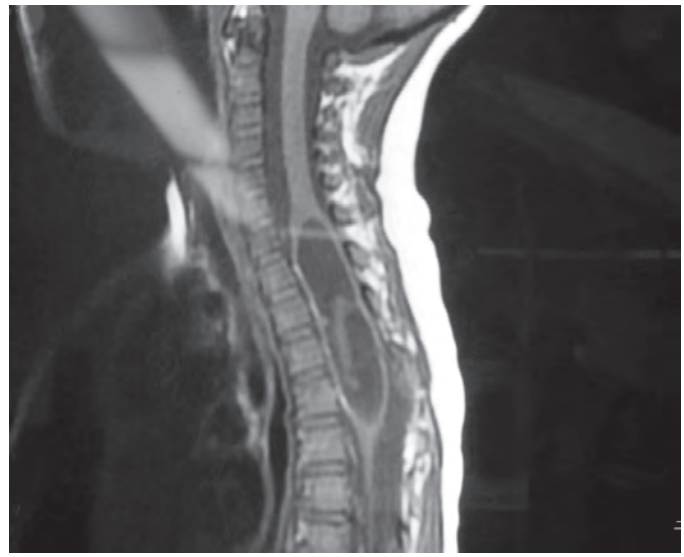
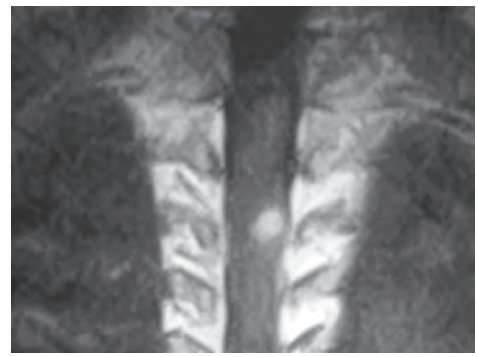


Fig. 2: MRI of the upper dorsal spine showing an intramedullary astrocytoma



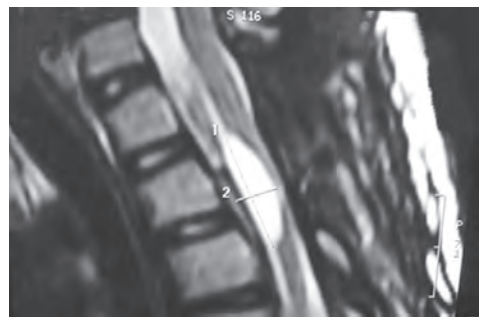
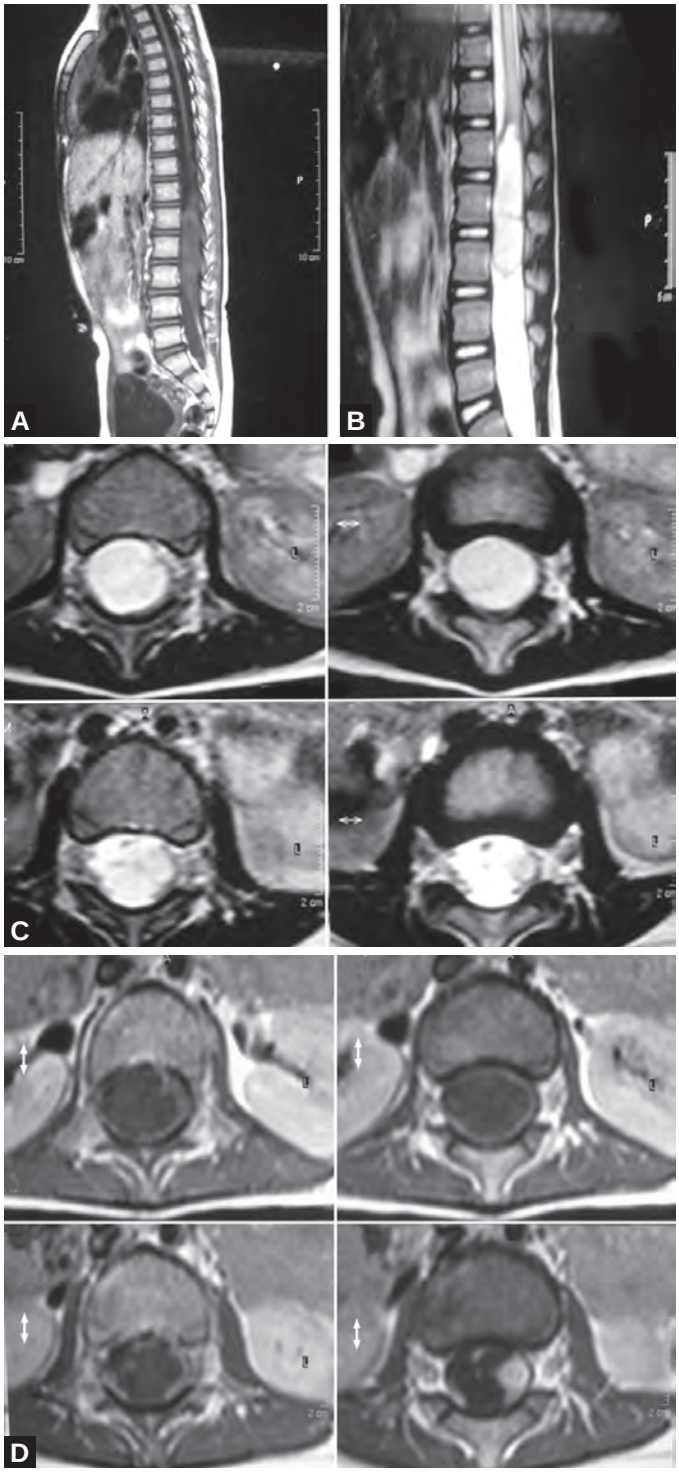


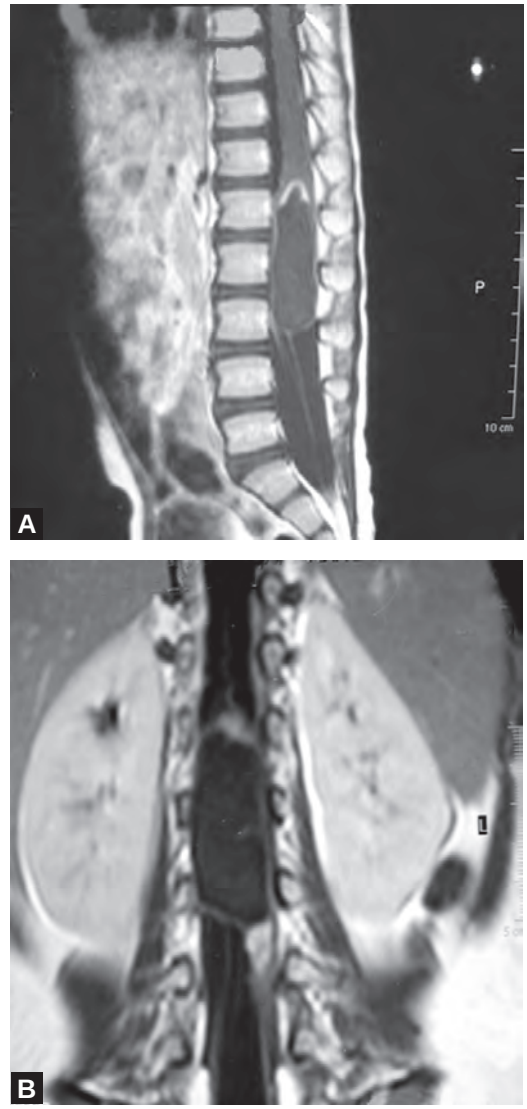
Fig. 3: MRI of the upper dorsal spine showing a ventral intradural cystic tumour



Figs 4A to D: MRI of the lumbar spine showing spinal ependymoma. (A) T1-weighted image–sagittal. (B) T2-weighted image–sagittal. (C) T2-weighted image–axial. (D) T1-weighted image–axial

or hypointense with areas of necrosis. Tumours, like dermoids, epidermoids and lipomas which contain fat or cholesterol, have characteristic high signal intensity on plain MRI.[87]

Positron emission tomography may help to categorise the lesions by abnormal uptake of 18F and 11C-methionine.[119]



Figs 5A and B: MRI of the lumbar spine showing spinal ependymoma. (A) T1 contrast sagittal. (B) T1 contrast coronal

THERAPEUTIC CONSIDERATIONS

The principles of management involve ascertaining the histological diagnosis, preservation of neurological function, tumour debulking or gross total resection, pain relief and spinal stabilisation. Often, it requires a multidisciplinary approach. The majority of paediatric spinal neoplasms are benign, low-grade astrocytomas[85] or gangliogliomas with a slow indolent course and, whenever feasible, gross total resection should be done without a neurological compromise.[83,112,118] Conservative expectant management may be an option in multiple small lesions seen in a child with neurofibromatosis and von Hippel-Lindau disease. Spinal CSF leptomeningeal seeding and disseminated disease do not warrant aggressive surgery. Modern surgical instrumentation has paved the way for successful removal of the tumours. The operating microscope, ultrasonic surgical aspirator, laser and micro-instruments are extremely useful tools to achieve this objective.[22,23,40–42,47,71]

Surgery

It is always advisable to perform a laminotomy in this age group to prevent future spinal deformity. Complications of laminectomy in children are extensive. Laminectomy in children may be followed by a deformity of the spine,[1,20,27,81,91,108,123,124] which is usually not observed in adults. In the lumbar region, an increase in lordosis, in the dorsal region, a kyphoscoliosis and in the cervical region, an exaggerated lordosis may ensue. Therefore, as a preventive measure, an ambulatory plaster jacket or a brace should be employed for at least 6–12 months when the laminectomy has been extensive in a young child, with emphasis on regular spinal exercise. The technique of osteoplastic laminotomy[1] helps to preserve the posterior elements, especially when a large area of the cord has to be exposed. Following such a procedure, complete to partial bridging of the laminar roof and reossification of the replaced bone segment occurs.

Limited laminectomy encompassing the solid component of the neoplasm is necessary. C-Arm imaging and intra-operative ultrasound help in the exposure.[23,39] Laminotomy is performed with a high speed drill. The dura is opened. The expanded spinal cord is commonly rotated and distorted. In extramedullary tumours, the arachnoid is gently opened, the tumour is debulked, the capsule is mobilised and gently removed from its attachment and care is taken to avoid injury to the neurovascular structures. In intramedullary lesions, CO_2 laser is helpful in doing the myelotomy.[47]

Conus and cauda equina lesions expand the filum terminale, which appears as a sausage shaped mass that displaces the nerve elements circumferentially around it. In such situations, it may be possible to remove the tumour en bloc taking care of the neural structures and adequately dissecting the arachnoid around.

Extradural Tumours

Primary Bone Tumours

Extradural tumours in children may be benign and include osteoid osteoma, osteochondroma, osteogenic sarcoma, osteoblastoma, aneurysmal bone cyst and eosinophilic granuloma. These are usually amenable to resection and even partial tumour removal provides excellent results.

Osteoid Osteoma and Osteoblastoma

These involve the lamina and pedicles of the cervical and lumbar spine and result from a benign osteoplastic process comprising of numerous osteoblasts which produce osteoid and woven bone. Osteoid osteoma when small may be kept under observation and spontaneous remission may occur. If symptomatic, total excision should be achieved.

Osteochondroma and Osteogenic Sarcoma

These originate from hyaline cartilage during adolescence, usually in the posterior elements of the dorsal and lumbar vertebrae. Surgical excision should be radical and gives good results. Rarely, malignant transformation to osteogenic sarcoma can occur.

Aneurysmal Bone Cysts

Aneurysmal bone cysts are benign and highly vascular lesions and can be cured with surgery and bone curettage.[5,22]

These lesions usually present in the second decade of life with local pain, swelling and rarely, spinal cord compression. They are expansile with blood-filled spaces in trabecular osteoid tissue with multiple haemosiderin containing macrophages, multinucleated giant cells and fibrous tissue. The aetiology of these lesions is yet unknown. Treatment includes pre-operative angiography with preparation for embolisation followed by complete excision. If inadequately excised, these lesions recur.

Eosinophilic Granuloma

These are benign lytic lesions that affect the anterior portions of the cervical vertebral bodies. They may be isolated or part of syndromes, histiocytosis x, Hand-Schuller-Christian disease and Letterer-Siwe disease. Many small lesions may undergo spontaneous regression. Low dose radiation or decompressive surgery with reconstruction is recommended for expansile lesions causing neurological deficits.

Malignant Tumours

The role of surgery is palliative with most malignant extradural tumours.[94] Metastatic epidural spinal cord compression occurs in 3% of all children with malignant solid tumours.[18,63] Neuroblastomas and ganglioneuroblastomas are operated upon for establishing the diagnosis or in case of a rapidly deteriorating clinical condition. These tumours are sensitive to radiation and chemotherapy. Sarcomas may require surgery in order to decompress the neural elements. Surgical decompression of neural elements significantly facilitates the neuronal recovery and outcome, especially in children. A combination of steroids, radiotherapy and chemotherapy may be suitably adopted to improve the outcome.

Neuroblastomas

In children, the most common tumour to metastatise to the extradural spine are neuroblastoma and the less aggressive ganglioneuroblastoma. This is the most common malignant paediatric spinal tumour and is derived from embryonic sympathetic neuroblasts and primordial neural crest cells. The tumours originate from the sympathetic chain and enter the spinal canal via the neural foramina taking a dumbbell shape. Surgical resection with multi agent chemotherapy and radiation is advocated.

Ewing's Sarcoma

These highly mitotic tumours arise from postganglionic parasympathetic neural crest cells. These occur

mostly in the sacrum followed by the dorsal and lumbar spine. These tumours are managed by initial biopsy. If the lesion is low grade, radical excision is followed by radiotherapy and chemotherapy. If high grade then initial radiotherapy and chemotherapy are followed by surgery. Lymphomas, chordomas and rhabdomyosarcoma also fall into the malignant group.

Weinstein described a system of surgical staging of spinal column tumours and this is currently called Weinstein, Boriani, Biagini Surgical Staging system. Boriani et al. have emphasised the importance of applying the Enneking system of musculoskeletal tumours to these spine tumours. This divides benign tumours into three stages: S1–S3, and malignant tumours into four stages: Ia, Ib, IIa and IIb. Two additional stages include metastatic high-grade intra- and extra-compartmental tumours IIIa and IIIb. Surgery can be tailored to be vertebrectomy, sagittal resection or posterior arch resection with stabilisation as necessary.[97,116]

Intradural Extramedullary Tumours

The management of these tumours is less controversial than that of intramedullary tumours. The majority of them are benign and gross total removal is the cure. Care should be taken to avoid cord manipulation. Radiation therapy is reserved only for malignant lesions.

Intermedullary Tumours

They constitute 35–40% of all intraspinal tumours in children.[57,77,90] To begin with, surgeons were more aggressive and a radical approach was adopted leading to several complications like infection, paralysis and even death. Subsequently, a conservative approach of biopsy and radiation became popular.[118] With the advent of modern neurosurgical appliances and imaging advances, i.e. operating microscope and intraoperative monitoring, laser and ultrasonic aspirator,[71] radical surgery once again has become the order of the day. The majority of intramedullary tumours are histologically benign and so a radical approach has to be adopted.[1,29,35–38,50,51,84,90]

The child is positioned prone with head fixation, if required. All the pressure points must be protected with adequate padding. Laminotomy is performed and the dura is opened over the entire length of the tumour. The opening should be just sufficient to expose the solid component of the tumour. Rostral and caudal cysts need not be exposed fully.[12,47] The spinal cord is usually expanded and often rotated. The asymmetric expansion and rotation of the spinal cord makes the identification of the midline difficult. Intra-operative ultrasound gives a two dimensional image and echogenic patterns are often helpful in identifying the cyst and the solid components.[23,39] Brotchi et al.[12,13] advocate a midline myelotomy between the posterior columns for glial tumours and for vascular lesions, like cavernomas[29,72] and haemangioblastomas,[25] which are subpial, they advocate approaching them where they are seen surfacing. The myelotomy is performed in the midline or through the dorsal root entry zone. Astrocytomas or gangliogliomas have a greyish yellow appearance with occasional calcification but without a plane between the tumour and the spinal cord. Hence, no effort should be made to develop an interface. Ependymomas are typically red grey in colour and well demarcated from the surrounding spinal cord. A good plane of cleavage can be developed in such tumours.[6,37,47,54,57] Lipomas are characterised by exceedingly poor demarcation between the normal cord and the tumour.[69] Internal debulking with ultrasonic aspirator and then gradual removal of the tumour is practiced. It is better to start at the mid-portion and then go towards the rostral and caudal poles. The surgeon should constantly be aware of the various displacements of tracts that can occur due to the expansion of the tumour.[26] Haemangioblastomas, cavernous malformations and intramedullary lipomas are uncommon intramedullary lesions.[25,29,69,101] Haemangioblastomas are associated with significant oedema and syrinx.[25] Removal of the solid tumour takes care of the associated syrinx.

The dura is closed watertight. The laminotomy is replaced and secured in position. One must close the layers without tension.[125] A transient post-operative neurological deterioration may be observed in the majority, but the deficit will improve in a few weeks.[13,48,65,67] The incidence of post-operative deterioration is related to pre-operative motor status. Total resection has a better long-term outcome than partial resection, but great care has to be taken so that the patient doesn't have an unacceptable disability even if the tumour excision remains partial.[60,90,105,115,120,122]

EVOKED POTENTIAL MONITORING

The information provided by SSEP is sufficient to assess functional integrity. However, during intramedullary tumour surgery, motor tracts may be damaged independent of the sensory system and, in addition, sensory potentials are often lost soon after myelotomy. Therefore, motor evoked potentials (MEPs), which allow direct monitoring of corticospinal tracts is preferable.[11,14,26,45,46,65,67,88] A single electrical impulse results in the direct activation of fast conducting axons leading to a potential D-Wave.[93] This can be recorded by an epidural electrode placed just distal to the intramedullary tumour. D-Wave amplitude signifies the measure of the number of functioning fast conducting corticospinal fibres. These motor potentials follow an on-off pattern and their presence indicates intact motor control. Improved electrical conductivity after tumour removal is invariably associated with a benign post-operative course. Impaired activity in comparison with the preoperative baseline is not necessarily associated with neurological morbidity. However, the majority with deterioration in activity have a greater chance of neurological dysfunction.[22]

COMPLICATIONS

Surgical morbidity is usually related to the location of the tumour, associated malignancy and the degree of pre-operative disability. In general, extensive tumours and non-cystic tumours carry a higher risk of post-operative deterioration.[45,46,83,122] Though intramedullary tumours have a relatively higher risk of surgical deterioration, it appears that the length of the tumour has no real bearing.[16] The risk of post-operative deterioration is higher in removing smaller nodules and in patients undergoing partial resection.[54] Children are more easily prone to shock when there is blood loss.

Radiotherapy to the spinal cord at this young age carries greater risks of radionecrosis[32,80] and chemotherapy carries its own complications and disabilities.[3,10]

The incidence of hydrocephalus is higher in patients with malignant tumours and up to 15% may develop hydrocephalus.[59,98]

Post-operative Spinal Deformity

The treatment of an intraspinal tumour, as in adults, is surgical excision through laminectomy. The technique does not vary from that in adults, except that, in children, because of the preponderance of congenital and malignant tumours, a comparatively greater exposure is necessary. When more than three laminae are to be removed, it is desirable to do an osteoplastic laminotomy to prevent a post-operative spinal deformity.[1,20,27,55,81,91,108,123,124] Scoliosis and kyphosis commonly evolve after surgery. Sometimes, they may be progressive and lead to myelopathy. Scoliosis usually does not cause spinal compression though it can potentiate the existing neurological disability. Several authors[1] have described that osteoplastic laminotomy is superior to simple laminectomy although it does not totally prevent post-surgical evolution of spinal deformity, especially if the tumour recurs. The causes of instability may be vertebral involvement by tumours, paraspinal muscle denervation or fibrosis, asymmetric radiation of the spine and post-surgical destabilisation.[18,81] It is reported that 24–100% of patients experience instability after laminectomy for resection of tumour.[91] Therefore, the surgeon must limit the laminectomy to as few segments as possible and care must be taken to preserve the integrity of the facet complex. The need for spinal fusion is commonest in the thoracic and thoracolumbar region. The need to remove a greater number of laminae and pre-operative kyphotic deformity are linked to spinal sagittal malalignment in children. Age less than 3 years, pre-operative scoliotic deformity (Cobb angle >10 degree), thoracolumbar region and tumours associated with a syrinx increase the odds of post-operative progression of deformity requiring fusion.[27,123,124] Osteoplastic laminectomy or bilateral laminotomy is preferred.[19]

ADJUVANT THERAPY

There is enough evidence to show that radiation is deleterious to the nervous and osseous systems.[20,32,80] The alterations in motor and sensory evoked potentials in patients who received radiotherapy have been documented.[88] Some authors do recommend radiotherapy routinely for intramedullary gliomas.[74,85,105,106,120] In a review of literature, several papers advocate RT for low-grade astrocytomas with a 5-year-survival rate of 50–91%.[19,44,58,64,74,106] Epstein, in his series, reported a five year survival of 88% with surgery alone.[45] Overall, there seems to be no evidence that radiation improves the outcome in low-grade astrocytomas or ependymomas.[38,40,46,58,106] Hence, radiation should be reserved only for malignant tumours. Survival rates of 55% at 5 years, 39% at 10 years and 79% overall 5-year-survival rate have been reported with conservative surgery and radiotherapy.[60]

Chemotherapy has rarely been used in intramedullary tumours and there are no large studies documenting its efficacy.[3,10,31,32,43,52,76,83] Temozolamide has been used but larger studies are awaited.[17]

Neurologic outcome is decided by the extent of safe microsurgical resection possible and location of the tumour. Cystic tumours are associated with a much better outcome. Early surgery before deterioration is absolutely necessary and prophylactic surgery has a role in spinal lipoma.[61,87] Patients should be operated upon early and those patients in McCormick grades 1 and 2 do much better than grades 3 and 4.[82]

There has been no difference in the long-term progression free survival period in patients who have undergone more than 80% tumour removal when compared with those who underwent 98–100% resection.[66] Hence, it may not be necessary or mandatory to achieve a total removal for an optimal outcome. Five and ten year survival has been reported as 88 and 82%. High-grade neoplasms had a 5-year survival of 18%. Minimally invasive neurosurgical microscopic techniques using lasers and CUSA,[115] improved spinal instrumentation in the form of lateral mass plates, anterior self locking plate systems, occipitocervical systems and vertebral body prosthesis allow for greater extent of excision with excellent results.[112,118]

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SECTION

10

Disc Disease and Other Spinal Pathologies

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109 Pathophysiology of Disc Degeneration

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INTRODUCTION

Intervertebral discs contribute to the stability and flexibility of the spinal column. The discs normally carry out an admirable job of balancing these two opposite functions. Ageing of the population and shift to a sedentary life style, punctuated by unusual occupational or recreational strains have contributed to the increasing incidence of degenerative disc disease (DDD). In this chapter, the physiological basis for DDD and its effects are explored.

ANATOMY OF INTERVERTEBRAL DISC

The 6 cervical, 12 thoracic and 5 lumbar discs (23 in all) are basically similar in structure but they differ in size and shape according to the vertebrae in between which they are interposed. In each disc, the centrally located nucleus pulposus (NP) is contained by the outer fibrous shell of the annulus fibrosus (AF). (Note: 'anulus fibrosus' is an accepted variant spelling.) The end plates (EP) form the interface between the disc and the vertebral body (VB) above and below it. The NP accounts for 50% of the volume of the healthy adult lumbar disc but only for 33% of the volume of the thoracic disc.[26]

Nucleus Pulposus

The nucleus pulposus is a hydrated gel made up of proteoglycans interspersed by a random and loose network of fine fibrils of type II collagen and elastin. The major proteoglycan is aggrecan. This substance is composed of anionic glycosaminoglycan (chondroitin sulphate and keratan sulphate) and it contributes to the osmotic pressure in the disc needed to resist compressive loads. In infants the water content of the disc is 90% and this comes down to about 70–80% in young adults.[26] As age advances, there is progressive desiccation of the NP. The water content of the NP is reflected by the T2 signal intensity on magnetic resonance imaging. The NP is derived from the notochordal cells, which stop proliferating after infancy. The extracellular proteoglycans are secreted by the notochordal cells in foetal life and early infancy. Later in life, these cells are gradually replaced by chondrocyte-like cells with a low cell density.

Annulus Fibrosus

The annulus fibrosus is organised into about 12–25 lamellae. Each lamella is composed of spirally running collagen fibrils with randomly dispersed elastic fibres. There are also other types of collagen (notably, type IX collagen forming cross links and maintaining the network integrity) and other proteoglycans such as lumican, biglycan, decorin and fibromodulin. The direction of collagen fibrils in each lamella is tilted to the spinal vertical axis by about 60° and alternates between one lamella and the next by 120°, thus producing a woven basket appearance.[26] The lamellar arrangement is better developed in the anterior part of the disc. Elastin fibres lie between the lamellae, passing radially from one lamella to the next. The lamellae in the outer zone of the annulus attach directly to the VB above and below (Sharpey's fibres). These outer lamellae contain type I collagen, which has high tensile strength and they serve to stabilise the spine during torsional or bending movements. The lamellae of the inner zone attach to the EPs and are composed of the smoother and weaker type II collagen. The inner annulus acts as a container for the NP and absorbs the force exerted by the nucleus on compression loading. The synthesis of collagen is genetically determined but non-genetic factors, such as sex hormones or physical loads, may regulate the gene expression. The water content of the AF (about 70% of its weight) does not decrease much with age, unlike the NP. However, the annular fibromodulin undergoes age related changes. The cells in the annulus are elongated fibroblasts. The AF develops from the dark zone of the densely packed mesenchymal cells in each sclerotome.

End Plates

The vertebral EPs are entirely composed of cartilage in infancy. A rim of ossification appears in the periphery of the cartilaginous EP and this annular epiphysis fuses with the VB. By 20 years of age only a small central disc of cartilage remains. The EPs merge with the lamellae of the inner AF, completing the encasement of the NP. Unlike articular cartilage, there are no strong fibrous moorings for the EP to the cancellous bone of the VB. The vertebral EPs are derived from the light zone of the densely packed mesenchymal cells in each sclerotome.

Blood vessels penetrate the EPs during foetal life but as the disc cells involute, so do the blood vessels. The empty channels left behind by the involuting vessels are possible origins for Schmorl nodes.[26]

Blood Supply

There are no blood vessels inside the NP at any age and in most of the annulus during adult life. The intervertebral disc is the largest avascular structure in the body. The disc derives its nutrition from the capillary bed in the VB adjacent to the EP. The arterial supply to this vascular bed is derived from: (a) the centrum branches in the VB supplying the central region of the EP; (b) from the ascending and descending branches of arteries on the anterolateral surface of the VB and (c) from the anterior intraspinal arcade on the posterior surface of the body. Blood flow in the paradiscal capillaries is under humoral control, effected by acetylcholine through muscarinic receptors. This is the one mechanism by which nicotine might adversely affect the disc nutrition.

Nerve Supply

There is no nerve supply to the NP or inner annulus.[53] Unmyelinated nerve fibres, unencapsulated and capsulated nerve endings are found in the outer annulus. The nerve endings in the lateral and anterior annulus serve a proprioceptive function while those in the posterior annulus are also nociceptive. In the lumbar region, the nerve endings on the posterior annulus are derived from the sinuvertebral nerve (recurrent nerve of Luschka). The sinuvertebral nerve arises from the dorsal division of the spinal nerve root, re-entering the intervertebral foramen, dividing into a superior and inferior branch to supply the disc above and below, as well as the posterior longitudinal ligament, ventral dura, facet capsule and VB. Pain originating from the structures supplied by the sinuvertebral nerve in the lumbar region is referred to the buttock but not to the thigh or further distally (unlike spinal nerve root pain) and is known as dorsal ramus syndrome. The nerve endings on the lateral and anterior annulus are derived from the grey rami communicans. In the cervical region the fibres from the grey rami communicans join the sinuvertebral nerve. The C1 and C2 sinuvertebral nerves also supply the atlantoaxial joints and the dura of the posterior fossa.[26]

Ligaments

The anterior longitudinal ligament (ALL) with a stronger attachment to the VB and the posterior longitudinal ligament (PLL) with a stronger attachment to the posterior annulus strengthen the disc, though they are not integral parts of the disc. The ALL and PLL act as multisegmental tension bands resisting extension and flexion forces, respectively. Each disc forms a motion segment unit with the zygoapophyseal (facet) joints at that level. The facet capsules, ligamentum flavum, interspinous, supraspinous and intertransverse ligaments are important in maintaining the stability of the motion segment, while at the same time allowing motion to occur.

PHYSIOLOGY OF INTERVERTEBRAL DISC

Nutrition and Metabolism

The smaller molecules diffuse in and out of the disc through the EP. The larger molecules are transported by bulk fluid flow. Oxygen tension is low in the central region leading to anaerobic metabolism and build up of lactate. End plate permeability and, therefore, disc metabolite transport normally decrease during growth and ageing, but increase in the presence of disc degeneration and following endplate damage. The relative lack of blood supply causes limited cellular replication and this accounts for the poor repair capacity in the injured adult disc. In spite of the low blood supply, the matrix and disc cells are metabolically active. There are matrix metalloproteinases (MMP), a disintegrin and metalloprotease (ADAM) and aggrecanases that break down the matrix proteins, which are rebuilt by the disc cells. A healthy balance between breakdown and accumulation, which is regulated by genetic and non-genetic factors, is essential for maintaining the disc integrity.[41,70]

Biomechanics

The water content of the nucleus is vital for its biomechanical properties. On applying a compression force, water is expelled from the disc and it is reabsorbed into the disc once the force is removed. At low loads, the disc does not resist deformation but, beyond a certain load, the stiffness increases abruptly. This property allows the disc to remain flexible on minimal loading while it contributes to the stability as the loading increases. When the load limits are exceeded, the EPs fail first before the AF. This happens with compression loads of about 14000N in lumbar disc and 3000N in the cervical disc.[26] Water loss in the disc associated with ageing, reduces the viscoelastic adaptability of the disc making it prone to fail. The dehydrated disc behaves as a fibrous solid rather than a watery gel in its biomechanical properties. Apart from compression loads the other loads that the disc withstands are tension, shear and torsion loads. During day-to-day activities, the loads acting on the disc are a combination of these pure loads.

The pressure in the disc is studied *in vivo* by placing a miniaturised strain gauge mounted on a needle passed percutaneously into the disc, as done by Nachemson in the 1960s. A recent telemetric discometry study shows that the original studies had overestimated the intradiscal pressure on sitting. The pressure increased from 0.1 megapascal (MPa) on lying flat, to 0.46 on sitting, 0.5 on walking, 0.92 on performing Valsalva manoeuvre, 1.1 while standing up from a chair, 1.9 while holding a 20 kg weight well in front of the chest and to 2.3 on bending forwards to lift a 20 kg weight (note that 1 MPa = 10 bar = 10^6 newton/sq.m).[76]

Ageing Changes

The loss of water content in the NP with ageing has already been mentioned. The dehydration is caused by the decrease in the proteoglycan content of the matrix in the NP. There is decrease in the collagen content with replacement of type II collagen by type I collagen in the inner annulus.[65] The type I collagen fibres become coarser and become more cross-linked, thus increasing their stiffness. The collagen becomes non-enzymatically glycated, which further increases cross-linking. These biochemical changes are accompanied by histological changes such as the appearance of microstructural clefts that are seen as early as at 15 years of age. There is fissuring and clumping of parts of the NP. The EP undergoes thinning, altered cell density, formation of fissures, and there is sclerosis of the subchondral bone.[62] The histological changes of ageing are believed to be the result of reduced vascularity and they affect the EP first, then the NP, and, finally, the AF.[7] N-(carboxylmethyl) lysine (CML), a biomarker for oxidative stress has been found to accumulate in areas of maximal age changes.[45] The loss of vertebral body bone mass in osteoporosis leads to bulging of the EPs into the body and reduces the intradiscal pressure.

The changing microstructure and biochemistry alter the biomechanical characters of the ageing disc. As the NP becomes desiccated, the AF has to bear more of the compression load. The AF becomes stiffer but structurally weakened. The ageing changes are somewhat (but not exactly) similar to those due to DDD but are less intense, more or less similar at all levels and occur over longer periods. This situation is comparable to the twin conditions of senile dementia and Alzheimer's dementia, where the difference is quantitative and temporal rather than qualitative. The age-related DDD does become symptomatic. In a radiological study, degenerative disc and facet pathology in those over 65 years of age was ubiquitous, regardless of the presence or absence of pain, with greater than 90% demonstrating some level of degeneration. Higher radiographic severity scores were associated with the presence of backache but did not correlate with pain severity.[19]

DEGENERATIVE DISC DISEASE

Structural Changes

The changes of degeneration occur simultaneously in all parts of the spinal motion segment and progress over time as described by Kirkaldy-Willis.[79] The rate of progression of degenerative changes is variable. Mechanical loading in an acute or repeated chronic manner has been held as the primary factor in producing structural failure of the disc.[79] Current evidence indicates that mechanical load is only one of several factors.

The structural failure manifests as three types of tears in the AF. *Circumferential tears* occur between the laminae and are postulated to be due to interlaminar shear stresses.[15] The circumferential defects are equally distributed in the anterior and the posterior AF. *Radial fissures* progress outwards from the nucleus, usually posteriorly or posterolaterally. Biomechanical studies on cadaveric discs show that cyclic loading in bending and compression causes radial fissures. Radial fissures are associated with degeneration of NP but it is not clear which comes first. *Peripheral rim tears* are more often found in the anterior AF. Mechanical and histological considerations suggest that they are related to trauma.[51] Rim lesions are also a function of age, being commoner in older discs. Less than 15% of these tears show any tendency to heal. Only the smallest tears can seal in experimental situations and the larger tears induce progressive degeneration.[22] Blood vessels and nerves grow into the peripheral annular tear and contribute to making it painful.[72]

The NP tends to herniate along annular defects resulting in a disc prolapse. The result may be a focal protrusion, extrusion or sequestration. The biomechanical load that produces a posterior protrusion is a combination of flexion and compression. With flexion, the compressed anterior NP exerts a force on the posterior AF, which has been put under tension stress by the same flexion force. Addition of a compression force causes the NP to herniate out. Such purely mechanical disc herniations occur in the 30–40 years age group, as the discs at this age have enough hydration in the NP and are beginning to accumulate AF tears.[26] Older desiccated discs cannot extrude in this manner. In experimental settings, it requires much higher forces (than one normally encounters) to cause a NP herniation in a non-degenerated disc.[23] In fact, such loads cause injury to the VB rather than produce herniation of NP. Hence, even in mechanically induced disc hernia, there is likely to be a preceding structural degenerative change.

The EPs fail in compression and accumulate trabecular micro-damage with age. Since the EPs enclose the NP, the pressure inside the NP can no longer be maintained.[1] The load bearing shifts to the AF, causing the inner layers of AF to buckle in towards the low-pressure area of NP. This stage is spoken of as 'internal disc disruption'. The NP can then be driven up towards the VB, forming a Schmorl node. The structurally weakened outer AF bulges out radially, seen in MRI as a diffuse disc bulge. The combination of these changes in the EP, NP and AF causes loss of disc height and the disc becomes akin to a flat tyre.[8] The loss of height in the disc shifts the load bearing to the posterior elements and the stage is ripe for osteoarthritis of the facet joints and dynamic instability. Disc height loss also causes the ligaments to buckle into the canal adding to the soft tissue component of canal stenosis. Excessive annular loading also causes osteophyte formation or bony enlargement and the end result of these changes is degenerative canal stenosis. It is now possible to study the abnormal segmental motion with kinematic MRI. The lumbar functional unit with more disc degeneration, facet joint disease and flaval hypertrophy has abnormal sagittal plane translation and angulation.[31]

Biochemical Changes

Loss of proteoglycan is the fundamental abnormality in DDD. Aggrecan gets broken down to smaller molecules, thus reducing its water retaining capacity. There is elevation of decorin and biglycan, and the disappearance of 4-sulphated core region in aggrecan.[24] Undersulphation of chondroitin occurs more in the posterior part of the inner AF and this might explain the occurrence of radial fissures in this region.[41] Loss of aggrecan allows penetration of molecules, such as interleukin-1 into the disc, which accelerate the progression of degeneration.[21] The increased neural ingrowth seen in the degenerated outer AF (discussed above) is also associated with loss of aggrecan, which normally inhibits neural growth.[43] The changes in the matrix proteins are in turn caused by increased MMP activity. A recent study shows the upregulation of the MMP-3 mRNA in degenerated disc.[2] Cathepsin and prostaglandin E2 may also play a part.[28]

SA-beta-gal (senescence associated beta-galactosidase) is a marker for cellular ageing. A higher proportion of senescent cells in herniated discs has been demonstrated by this technique.[61] The herniated-free disc fragments show increased apoptosis and this might explain spontaneous resorption of herniated discs.[54] Results from human samples, mouse models and AF cell culture experiments demonstrate that the mechanical overload-induced disc degeneration is mediated through the mitochondrial apoptotic pathway in the disc cells.[60] Nitric oxide, released by the disc cells subjected to mechanical loads in an autocrine fashion, induces apoptosis.[30] Insulin-like growth factor (IGF-1), platelet derived growth factor (PDGF) and basic fibroblast growth factor (bFGF) are potent mitogens that stimulate the proliferation of disc cells.[57] These growth factors also exert anti-apoptotic effects.[16] The fact that these growth factors are overexpressed in degenerated discs indicate that there is an attempt at repair and regeneration along with the process of degeneration. In ochronosis (alkaptonuria), homogentisic acid accumulation in the elastic tissue of the disc causes early degeneration and calcification in the disc.

Vascular Changes

A fall in nutrient supply will ultimately lead to degeneration of the disc. The vascular supply can be reduced by calcific atherosclerosis of the aorta and lumbar artery stenosis and these are associated with DDD as shown by a recent systematic review.[29] Lumbar arterial stenosis has been documented by magnetic resonance angiography.[32] Even if the blood supply remains normal, nutrients may not reach the disc cells if the EPs calcify, as is known to occur in scoliosis. An elegant intraoperative study demonstrated that the concentration of diffused anaesthetic nitrous oxide into the disc was lowest in the disc at the apex of the curve in scoliosis (the most calcified and degenerated disc), indicating decreased solute transport.[71] Using contrast enhancement patterns on MRI, a group from Coimbatore, India, has demonstrated that greater abnormalities of diffusion in the end plate correlate with higher grades of DDD.[59] The adverse effects of smoking on DDD are also likely to be ischaemic, as proved by studies on animals.[25]

Inflammatory Changes

The lack of blood supply suggests that inflammation is not an important issue in the causation of DDD. However, inflammatory cells, mainly macrophages, have been found in surgical disc specimens. Both the acute and chronic herniations show activated T and B lymphocytes.[18] This may be a foreign body reaction and it can possibly result in pain, as those with inflammatory change have a better pain outcome after surgery.[77] Surgical disc specimen analysis shows inflammatory cytokines, such as interleukin-1 alpha, which in turn increases prostaglandin E2 (PGE-2) production.[67] Positive straight leg raising test has been correlated with higher PGE-2 content in the disc.[49] Antiglycosphingolipid antibodies have been detected in about 2/3rds of patients with herniated lumbar disc raising the question of an autoimmune mechanism, at least in the causation of pain, if not in the aetiology of DDD.[9] An endoscopic exploration of discs in conscious patients has shown inflammatory pathology, neoangiogenesis and neurogenesis in the AF to correlate with pain.[78]

Cause of Pain

It is simplistic to assume that pain in DDD is solely due to compression on the nerve roots. There are patients who present with back and/or leg pain without any demonstrable dural tube or root compression. Mere touching of the posterior annulus in patients undergoing surgery under progressive local anaesthesia was found to cause severe pain.[33] Substance-P nerve endings have been demonstrated deep in the AF of painful discs but only superficially in non-painful discs. This study also showed simultaneously a marker for axonogenesis in DDD, suggesting new nerve growth.[13] Experimentally acute exposure of a nerve root to NP material results in axonopathy and nerve mechanosensitisation. Chronic exposure results in mechanical desensitisation.[10] A recent MR based study shows that even the discs that reach the end stage of degeneration ('burnt out') do not become painless.[6]

Experimental Models

The animals used in laboratory experiments, such as rats, rabbits, pigs or sheep, have more cellular and vascular discs with good regenerative capacity as compared to the human disc. These animals are quadripedal and their discs do not bear the same loads, as does the human disc. Hence, inferences from laboratory studies must be made with caution. The response to standardised trauma such as needle pricks or annulus cuts have been studied in these animals. Compression loading of tail discs

in rats is another experimental model. Cadaver human vertebrae and discs dissected en bloc have been studied extensively for biomechanical properties but these lack the action of muscles or blood flow and, hence, are only a rough approximation of the *in vivo* situation.

AETIOLOGY OF DEGENERATIVE DISC DISEASE

Degenerative disc disease is multifactorial in aetiology. Ageing and mechanical stress have been implicated for long but only recently the genetic factors have gained ground as an important cause for DDD.

Mechanical Load Injury

Throughout the last century, mechanical load injury was proposed as the most important cause of disc prolapse. The higher incidence of DDD in persons doing manual work supports such a hypothesis.[39] It is now realised that the straining activity that precipitates acute disc herniation might merely be the last straw that broke the camel's back! When mechanical pressure is experimentally applied, degenerated discs herniate at lower loads.[23] Trauma seems to act by creating microscopic damage to EPs, which allows the NP pressure to get deflated, setting in motion the chain of events of DDD.[1] Nitric oxide may be the pathway mediating the suppression of proteoglycan synthesis in response to abnormal loads.[35] In sportsmen, who subject their backs to inordinate loads, MR abnormalities were found even at young age and these worsened considerably on follow-up after 15 years.[3] Weight lifters had greater DDD in the lumbar spine than other sportsmen.[73] As opposed to unusual loads, regular exercise seems to strengthen the disc by increasing the proteoglycan content.[70]

Another good example of mechanical overload is the occurrence of accelerated DDD in levels adjacent to congenital or surgical fusion. The rate of symptomatic degeneration at an adjacent segment after surgical lumbar fusion was found to be 16% at five years and 36% at ten years.[14] Of course it is difficult in such cases to separate the effects of excess loading on the one hand and a susceptibility to DDD or ageing effects on the other. The L4-5 disc is more prone to degenerate in persons with L5 sacralisation, obviously due to abnormal load distribution.[40] Yet another example of mechanical causation is DDD in relation to obesity. There is evidence from population based studies that body mass index (BMI) > 25 kg/m increases the risk of lumbar disc degeneration.[2] Being overweight at young age seems to be particularly detrimental.[36]

Genetic Factors

The first evidence for a genetic factor in causing DDD was the finding of a high familial incidence of lumbar DDD. Blood relatives of persons operated for lumbar disc disease had a significantly greater incidence of MRI abnormalities of DDD than matched controls.[42] The other clinical evidence comes from twin studies. When monozygotic twins with very different patterns of driving motor vehicles (which causes chronic vibratory stress) were compared, the degree of degeneration assessed by lumbar MRI did not significantly differ, implying that familial factors may be more important than mechanical stresses.[4] Another study calculated the heritability of cervical DDD to be 73%, as assessed by MRI in a twin study.[63] The Twin Spine Study, began in 1991 in Canada, Finland and the United States and reported in 2009, has shown only moderate influence of environmental factors such as smoking, occupation and leisure activities on the rates of DDD, but the genetic contribution was far greater.[5]

There is mounting molecular evidence for genetic factors in determining DDD. Degenerated human discs show higher expression levels of asporin gene, that codes for a small proteoglycan and this gene is known to be a susceptibile gene for osteoarthritis.[17] An association has been made with allelic variants of 25 structural, degradative and inflammatory candidate genes with lumbar DDD in humans.[74] These genes code for collagen, interleukin and MMP. Presence of at least 1 tryptophan (Trp 3) allele in the collagen IX gene (COL9A2) increased the risk of lumbar DDD about threefold, in a study from Finland.[52] Persons with little pain but severe DDD on imaging are routinely seen in clinical practice. The propensity to develop pain and response to analgesic drugs may also genetically be influenced, as shown in a recent study.[68] Peroxynitrite is a tissue-damaging molecule generated at sites of inflammation or degeneration and indicates oxidative or nitrosative stress. Peroxynitrite stimulated cytokine synthesis by increasing gene expression in an *in vitro* study of disc cells.[56] Thus, disc degeneration appears to be the end result of a complex interplay of many genetic and environmental factors.

DISC REGENERATION

It is a cherished hope of many a patient that one day medical science would be able to halt the disc degenerative process and indeed, actually effect regeneration. Two possible approaches are preventing breakdown of disc matrix and augmenting growth.

Pharmacotherapy

Anti-catabolic therapy (e.g. inhibitors of MMP), mitogens (e.g. growth factors), morphogens (e.g. bone morphogenic protein) and intracellular regulators (e.g. Sox 9) are possible classes of molecular drug therapies for the future.[80] It has recently been reported that resveratrol, a phytoestrogen found in grapes and red wine, exerts several actions to prevent disc matrix breakdown and augment disc regeneration in a bovine disc cell culture study.[34] One wonders if this compound is also responsible for the fact that moderate alcohol consumption is associated with a lower incidence of DDD, apart from the lowered rate of atherosclerosis.[81]

Cell Based Therapy

Some substances required for molecular therapy are large proteins and it is ideal to have them locally synthesised by means of cell transplants or gene therapy, rather than administered exogenously. Freeze dried whole disc allografts have been shown to maintain function and stability in the laboratory and in patients.[38] Animal experiments show that transplanted disc cells survive and produce matrix, and effect restoration of disc height. Patients who received autologous disc cell transplantation had greater pain reduction at 2 years compared with patients who did not receive cells following their discectomy surgery. Autologous disc-derived cells and adipose tissue derived cells were used in this study.[20] Bone marrow derived stem cells can migrate, survive and produce matrix in the rabbit disc.[66] Murine stem cell derived chondroprogenitors form new notochordal cells in experimentally injured rabbit discs and do not elicit an immune response.[64]

Gene Therapy

This involves the transfer of genes so that the recipient cells express these genes and synthesise the RNA and the protein they encode. The lasting effect of gene therapy is attractive as compared to exogenous replacement of the protein for chronic conditions such as DDD. Viral vector mediated transfer of genes was originally used.[69] Non-virus-mediated gene therapy is also now feasible. RNA interference technique helps down-regulate a specific gene expression (say, MMP) in the disc making it a novel avenue for therapy.[48]

Other Methods

Another possible approach is to improve the diffusion into the disc. The diffusion enhancing effect of oral nimodipine has been shown in an Indian clinical study and is yet to be exploited therapeutically.[59] Engineering and biology meet to provide hyaluronic acid nanofibrous scaffolding over which stem cells rebuild the destroyed disc.[46] It remains to be seen what the clinical efficacy and cost of these novel therapies would be.

CLINICAL CORRELATIONS

Understanding the pathophysiology of DDD helps us appreciate the wide clinical spectrum of disc disease. The young woman who develops an acute cauda equina syndrome due to a lumbar disc extrusion that occurs during labour, has *almost* a pure mechanical causation – mainly because there ought to be an element of structural weakening caused by the hormones associated with pregnancy, apart from the physical strain of labour. What about the executive who had to be operated for a far lateral lumbar disc herniation, when all he had done to precipitate it was to stoop forwards to plug in his office printer? The precipitating event served only to unmask the ongoing DDD in him, and who has not seen a patient with hardly any symptoms but with a ghastly DDD on radiography or MRI? Or a puny little thoracic disc prolapse producing paraplegia? One factor that demystifies the situation is the canal size. It is intuitive to understand that those who are blessed with a congenitally wide canal can tolerate DDD without developing neural compression. A recent report based on cervical spine kinematic MRI suggests that those with congenitally narrow canals actually have a greater propensity for DDD and not merely a greater tendency to become symptomatic.[44]

Deductions made from basic sciences have to be backed by relevant clinical data. One example is DDD occurring adjacent to a level of surgical fusion. Biomechanically, fusion is expected to wreak havoc on the adjacent disc. This fact became a strong weapon in the hands of the anti-fusion and the pro-disc replacement camps. As a radiological phenomenon, adjacent level disease (ALD) was indeed more in fused patients in a prospective randomised study. However, ALD seems to contribute little to symptoms. Simultaneous laminectomy along with the fusion seems to correlate even more strongly with ALD.[12]

IMAGING CORRELATIONS

MRI is uniquely sensitive to the changes in the biochemistry of the degenerating disc. The loss of T2 signal from the NP on desiccation has been mentioned. There is now evidence that the T1-rho relaxation time has a strong correlation to the glycosaminoglycan content and the intradiscal pressure, thus providing a means for imaging a biomechanical property.[47] By using dGEMRIC (delayed gadolinium-enhanced magnetic resonance imaging contrast), the percentage of decrease in T1 was found to correlate with the grade of DDD. Scanning at 3 Tesla with sodium based imaging helps quantify the proteoglycan content. Magic-echo pulse sequences show areas of inhomogeneity within the NP and are able to clearly distinguish the pathology in the EP from that in the NP; making these distinctions is not possible with the standard spin-echo sequences.[75]

Annular changes are also well imaged by MRI. High intensity zones (HIZ) in the posterior annulus indicate painful peripheral rim tear.[55] T2 and apparent diffusion coefficient (ADC) mapping has shown characteristic diurnal differences in the NP, inner AF and outer AF from morning to evening, again reflecting a physiological event.[37] The paradiscal vertebral marrow changes described by Modic have extensively been investigated. Type I change (T1 hypointense and T2 hyperintense) is associated with fissured EPs and oedematous, vascularised fibrous tissue in the marrow. It is significantly associated with segmental instability and low back pain. Type II change (T1 hyperintense and T2 isointense or slightly hyperintense) is due to replacement by yellow marrow. It is less clearly correlated with back pain. The

type III change (T1 and T2 hypointense) is thought to be due to bony sclerosis.[58]

CT discography is another technique that reflects the pathology in the NP and AF even before the disc herniates out. Picking up internal disc disruption with discography has helped in selecting back pain patients with near-normal MRI for fusion (in the past) or disc replacement (currently). However, there are false positives, and we should err on the side of caution.[11] Provocative discography relies on reproducing the patient's symptoms by injection. Disc block with bupivacaine is held to be better than provocative discography alone.[50] The MRI finding of disc protrusion-with-HIZ correlates better with positive provocative discography than the finding of normal/bulging disc-with-HIZ.[27] Thus, in the near future, we may be able to get the data on the altered physiology with MRI refinements alone and dispense with invasive tests such as discography.

CONCLUSION

Knowledge of the normal and altered physiology of the intervertebral disc helps the neurosurgeon to understand the patient's symptoms, interpret the imaging and plan the correct treatment. It also cautions the surgeon to think twice before performing a discectomy,—a tissue that is irreplaceable. This background knowledge is invaluable in keeping abreast with the rapid advances in the fields of disc prosthesis and molecular therapy.

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110 Cervical Disc Disease and Spondylosis—Clinical Features and Diagnosis

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INTRODUCTION

The term "cervical spondylosis" is used broadly to describe the morphologic manifestations of progressive degeneration of the spine. It is considered the most common progressive disorder in the ageing cervical spine and results from the process of degeneration of the intervertebral discs and facet joints of the cervical spine.

Several predisposing factors, such as occupations requiring repetitive motion of the cervical spine, previous injury with fracture or disc prolapse and segmentation defects like hemivertebrae or fused vertebrae, may cause acceleration of these changes.

Most people with degenerative changes of the cervical spine remain asymptomatic. Symptomatic patients are usually older than 40 years of age.[14] There are three main presentations related to cervical spondylosis: (1) neck pain and brachialgia; (2) radiculopathy and (3) myelopathy.[3]

Neck pain is the most common presentation and is frequently encountered without a precipitating incident. It may be acute or chronic and occurs more often from degenerative disc than from degenerative facet changes.

Cervical radiculopathy refers to symptoms and signs of nerve root compression and can be acute, subacute or chronic. Patients younger than 55 years are more likely to present with radiculopathy caused by herniated nucleus pulposus, whereas patients older than 55 years are more likely to have canal or foraminal stenosis caused by osteophyte formation.[11] Radiculopathy due to soft herniated disc commonly produces weakness and atrophy while a hard herniated disc produces sensory symptoms consisting of paraesthesias, hyperaesthesias or hyperalgesias. Motor and reflex changes occur less frequently and are often associated with a chronic condition.[15]

The most common roots affected are C5 and C6. This can be explained by Sunderland's[12] observation that C4, C5 and C6 roots have a strong attachment to the vertebral column while the others are relatively free. Primary compression of the nerve root without impingement of the spinal cord can result in a radicular pain pattern, loss of strength and/or sensation, or diminished to absent reflexes. Distribution of signs and symptoms in nerve root lesions are summarised in Table 1. Lesions affecting the C3 root cause sensory disturbances on the lower occiput, the angle of the jaw and the upper neck. A C3-4 disc resulting in C4 root compression does not produce motor deficit or reflex changes but will produce pain and sensory changes in the neck, scapular region and anterior chest wall. A C4-5 disc produces C5 radiculopathy with pain in the shoulder and anterior arm, weakness of the deltoid and biceps and loss of the biceps jerk. A C6 radiculopathy affects the thumb and the index finger with loss of biceps jerk. A C7 radiculopathy causes pain and sensory changes in the medial aspect of the forearm, weakness of the middle and index fingers and loss of triceps jerk, whereas C8 root affection will affect the ring and little fingers and weakness of the small muscles of the hand without reflex changes. The abduction relief sign and Spurling's sign are two examination manoeuvres that implicate compression of a nerve root at the level of the foramen.

Table 1: Distribution of signs and symptoms in nerve root lesions

Root involved	*Distribution of pain*	*Distribution of paraesthesia*	*Weak muscles*	*Reflex change*
C5	Neck, shoulder, and lateral arm	Lateral arm	Deltoid, supraspinatus, infraspinatus	Diminished biceps, brachioradialis
C6	Lateral arm and forearm, thumb	Lateral arm and forearm, thumb and index finger	Biceps, brachioradialis, wrist extensors	Biceps, brachioradialis
C7	Dorsal arm and forearm, interscapular area	Middle and index finger	Triceps and wrist extensors	Diminished triceps
C8	Medial forearm and hand, fifth digit	Medial forearm and hand, fifth digit	Intrinsic muscles of hand	Finger flexor

Myelopathy may be precipitated by a large central disc herniation, but is more commonly the result of spondylotic changes superimposed on a congenitally narrow canal. The definite time of onset of symptoms is usually not known to most patients and a change in the gait or dexterity of hand function is the most common presentation. The clinical pattern of myelopathy is characterised by the presence of long tract signs which includes hyporeflexia of the deep tendon reflexes at the level of affection and hyperreflexia at the levels below the affection in the upper limbs as well as lower extremities, increased muscle tone or clonus, and the presence of pathological reflexes, including Babinski's sign or Hoffman's sign. Inability to grip and rapidly release the fingers is an additional sign of a myelopathic hand.[9] Spillane et al.[10] noted that the early phase of cervical spondylotic myelopathy is also characterised by clumsiness and unsteadiness of gait. Severe muscle atrophy caudal to the level of stenosis is uncommon with a spondylotic myelopathy, except in the later stages.

Frequently, a combination of radicular and cord symptoms is found (radiculomyelopathy). Acute exacerbation of radiculomyelopathy can occur in spondylotic patients after minor trauma and occasionally after unrelated surgery.[5] Cervical radiculopathy may occur in a subset of myelopathic patients. In this process, the spinal canal is stenotic along with concurrent focal compression of one or more nerve roots. The majority of the patients who present with myelopathic features have concurrent axial neck pain. The most frequent clinical finding or myelopathic sign found in these patients is spasticity, followed by weakness.[4]

Various autonomic symptoms can be produced by cervical disc disease, e.g. vertigo, flushing, tinnitus and visual blurring. These may be mediated by the sympathetic contribution to the sinuvertebral nerves from the stellate ganglion. Spondylotic changes at the uncovertebral joints may cause direct kinking of the vertebral artery and produce similar changes, especially if the wall of the vessel is atheromatous.[6] Vertebrobasilar insufficiency induced by spondylotic compression of the vertebral artery is uncommon, although popularly diagnosed.[2] Autonomic pathways may also be responsible for the cervical angina syndrome. Anterior chest wall pain is described with C6-7 disc prolapse.[16] Occasionally, anterior osteophytes may cause swallowing difficulty.[8,13]

The differential diagnoses of cervical radiculopathy (Table 2A) are brachial neuralgia, carpal tunnel syndrome, vascular compression syndrome, vasospastic disorders and shoulder pathology. The pain and weakness of C5 radiculopathy is very similar to brachial plexitis which presents with early deltoid weakness. The pain and paraesthesiae of C6 radiculopathy may mimic carpal tunnel syndrome. Carpal tunnel syndrome is characterised by nocturnal dysaesthesia, weakness and occasionally thenar atrophy. The pain of lower cervical radiculopathy can mimic thoracic inlet syndrome. Conditions that can mimic spondylotic myelopathy (Table 2B) are amyotrophic lateral sclerosis, myelitis, multiple sclerosis and demyelinating conditions.

Table 2: Differential diagnosis

A. Cervical radiculopathy	*B. Cervical myelopathy*
Brachial neuralgia/neuropathy	Amyotrophic lateral sclerosis
Carpal tunnel syndrome	Primary lateral sclerosis
Vascular compression syndromes	Multiple sclerosis
Vasospastic disorders	Demyelinating conditions
Shoulder pathology	Syringomyelia
Autonomic disorder	Extramedullary tumours
Cardiac diseases	Myelitis
Gallbladder	Spinal AVM and Dural AVF

IMAGING EVALUATION

The diagnostic workup includes static and dynamic cervical spine X-rays and magnetic resonance imaging (MRI). Cervical X-rays (Fig. 1) may demonstrate loss of disc space height, spondylotic bars, foraminal osteophyte, kyphosis, subluxations, posterior compression from facet arthropathy or late autofusion of adjacent cervical segments. Flexion-extension lateral films may be useful to assess significant instability. Oblique views (Fig. 2) can also demonstrate foraminal osteophytes.

MRI is the preferred diagnostic modality for cervical spondylosis. MRI is useful for evaluating the spinal canal diameter, spinal cord and various components responsible for stenosis and compression, viz. intervertebral discs (Figs 3 and 4), ligamentum flavum hypertrophy (Fig. 5) and vertebral ligaments. Signal intensity changes on T2-weighted MRI scans (Fig. 4) at the level of spinal compression are often increased in patients with cervical spondylotic myelopathy. This represents oedema, inflammation, ischaemia,

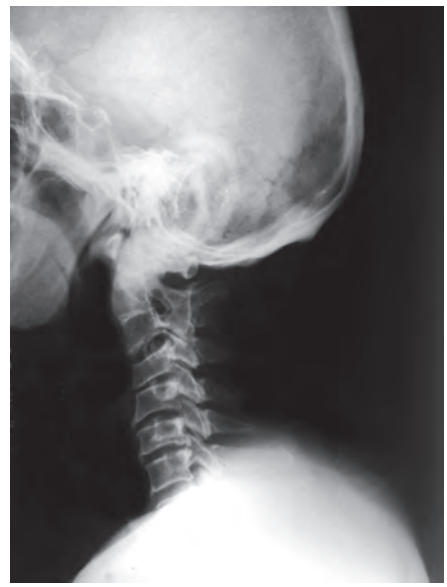

Fig. 1: X-ray cervical spine showing loss of lordosis, decreased disc space and osteophyte formation

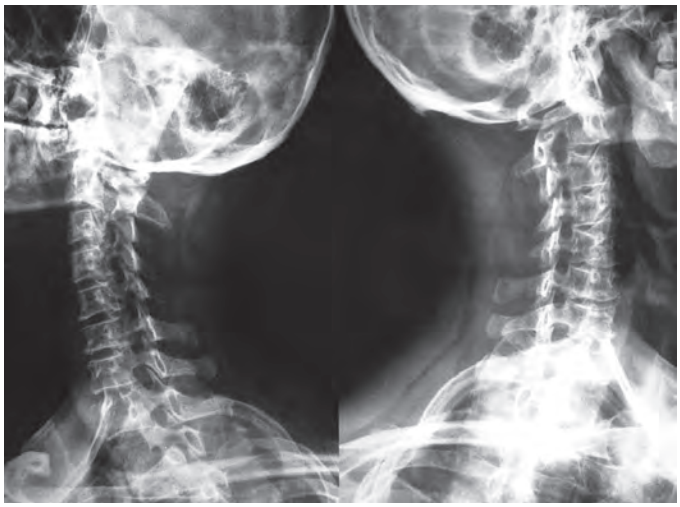

Fig. 2: Oblique cervical spine X-rays showing foraminal stenosis by osteophytes mainly at left C3/4

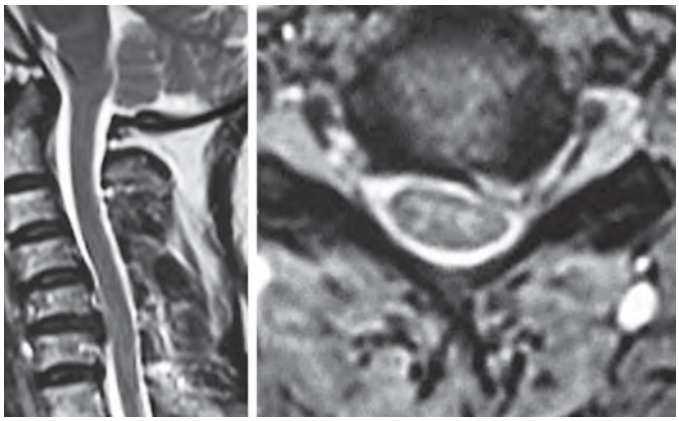

Fig. 3: MRI showing loss of lordosis with anterior compression at C5/6 disc level, axial plane confirming the left lateral (foraminal) disc prolapse

myelomalacia or gliosis.[7] However, bone quality assessment on MRI scans is not as good as with CT.

Occasionally, CT may be required for better delineation of bone anatomy such as in OPLL (Figs 6 and 7). CT is also useful for evaluating the transverse foramina, size and shape of the spinal canal, facet and uncovertebral

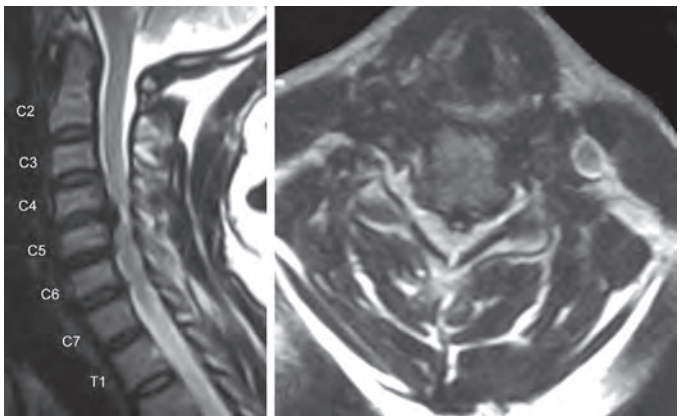

Fig. 4: MRI cervical spine showing C4-5 central disc prolapse with increased signal intensity in T2 images

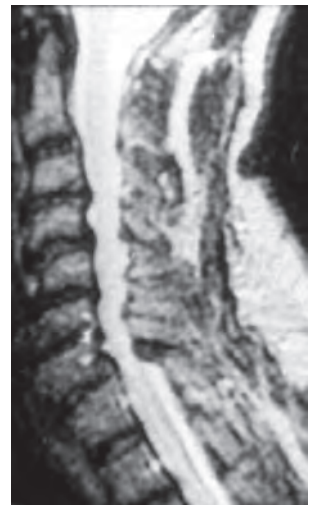

Fig. 5: MRI showing cervical canal stenosis with posterior compression due to ligamentum flavum hypertrophy

joints. Dynamic CT scans are most useful for evaluation of instability (Fig. 8). CT myelography provides excellent visualisation of radicular or cord compression in patients in whom MRI cannot be performed for some reasons.

Neurophysiologic Studies

Electromyography (EMG), nerve conduction velocity (NCV) and somatosensory evoked potentials (SSEP) may be used to evaluate patients with radiculopathy or myelopathy. Brachial plexitis, carpal tunnel syndrome and thoracic inlet syndromes can accurately be diagnosed with the help of neurophysiological studies. In nerve conduction studies amplitude, distal latency and conduction velocity are measured. While amplitude corresponds to the number of intact axons, distal latency and conduction velocity reflect the degree of myelination. EMG

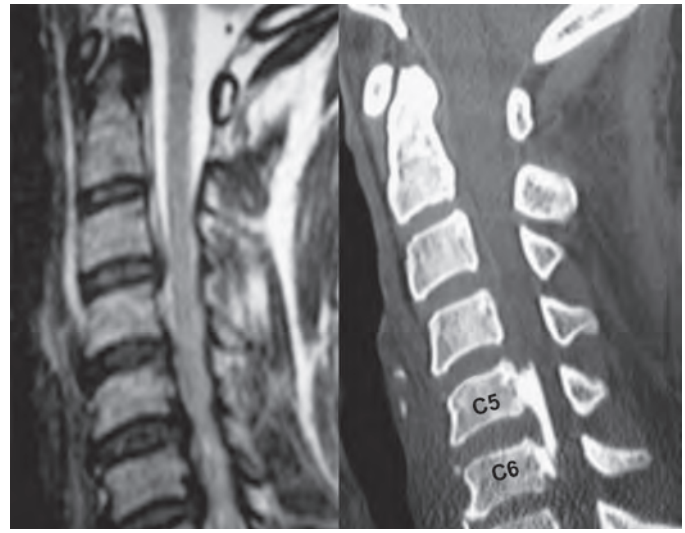

Fig. 6: MRI and CT scan showing cervical canal stenosis due to anterior compression by opacified posterior longitudinal ligament

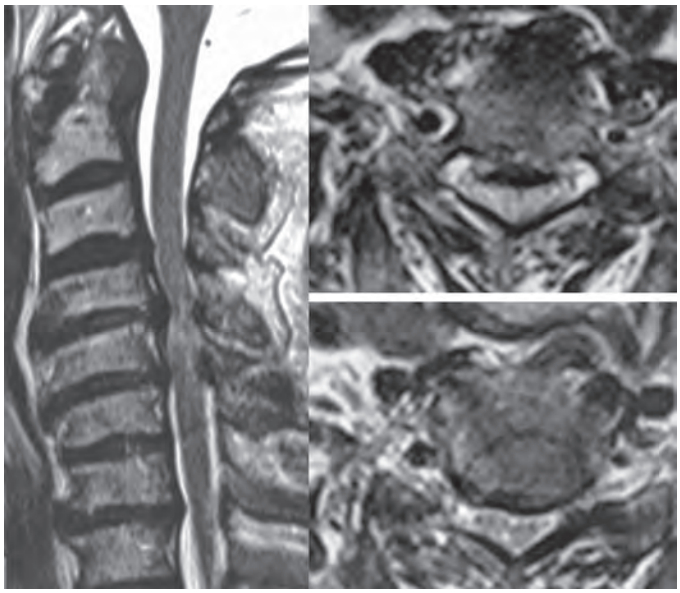

Fig. 7: MRI cervical spine showing global cervical canal stenosis, anteriorly due to opacified posterior longitudinal ligament and osteophytes, and posteriorly due to ligamentum flavum hypertrophy along with signal changes in the cord in the compressed segment

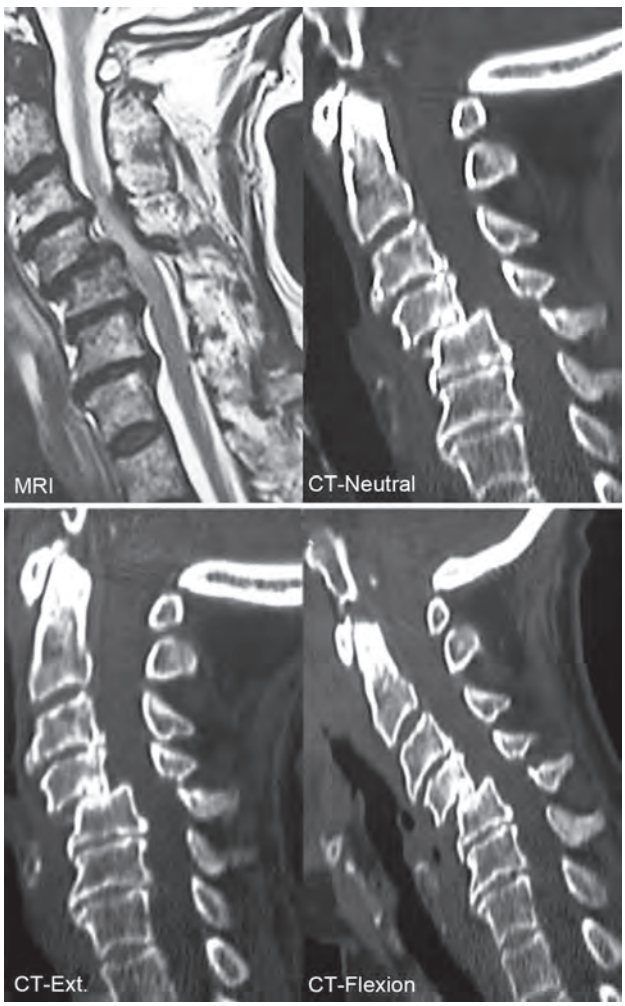

Fig. 8: MRI and CT (flexion, extension) showing degenerative C4-5 anterolisthesis with cord compression and cord signal changes. Instability is evaluated by dynamic CT

helps to establish the degree of muscular impairment and the number and the level of roots involved, and the duration of the syndrome. Motor neuron disease can accurately be diagnosed with proper EMG examination. Segmental dysfunction of the cervical cord can also be confirmed by an abnormality of the spinal N 13 potential on SSEP. Al-Mefty and co-workers,[1] in the experimental model of chronic compressive cervical myelopathy found that changes in SSEP occurred almost immediately before or at the time of neurological presentation. A combination of electromyography and somatosensory evoked potential evaluation can be very useful for confirmation in some patients presenting early with only subtle signs of upper and/or lower motor neuron dysfunction.

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111 Cervical Disc Disease and Spondylosis Management

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Cervical disc disease and spondylosis is a common pathological entity and is characterised by increasing degeneration of the intervertebral disc with subsequent changes in the bones and soft tissues. From skeletal maturity to the age of 30 years, few morphological changes occur in the cervical spine. Thereafter, the process of normal ageing in the cervical spine contributes and is difficult to differentiate from pathophysiological changes. From the fourth to the fifth decades, it is clear that the intervertebral disc undergoes progressive desiccation, becomes more compressible and less elastic, and secondary changes ensue. Although the majority of individuals over 50 years of age demonstrate significant radiological evidence of degenerative disease of the cervical spine, only a small percentage develops symptoms and neurological consequences.

In 1892, Horsley successfully operated upon a young man who developed quadriparesis after a fall, due to "a transverse ridge of bone projecting backwards from the body of the sixth cervical vertebra and pressing upon the cord".[30] In the early 1900s, the usual surgical approach to the cervical spine was through a posterior approach. In the 1940s, Spurling and Scoville[58] and Frykholm[22] described posterior foraminal decompression. In the 1950s, anterior cervical discectomy with fusion using the Smith-Robinson[55] and Cloward[13] techniques became popular and the mainstay of surgical treatment with some variations. Anterior discectomy without fusion was described in 1960 by Hirsch.[29] Since then numerous modifications have been made in the treatment of cervical spondylosis through an anterior approach. Similar advancement has been made in the treatment of cervical spondylosis through the posterior approach. Cervical laminoplasty was developed by Japanese surgeons after encountering a high incidence of post-laminectomy kyphosis.

The treatment options available for the management of cervical spondylosis are medical therapy and surgery.

MEDICAL MANAGEMENT OF CERVICAL SPONDYLOSIS

Medical management of cervical spondylosis includes pharmacological and rehabilitation components and mainly targets at pain relief. The use of these components is largely empirical as controlled studies are lacking. A systematic review of 24 randomised controlled trials of pharmacological and non-pharmacological treatment of mechanical neck pain concluded that, "in general, conservative interventions have not been studied in enough detail to assess efficacy or effectiveness adequately".[1]

Medical therapy in patients with radiculopathy and unremitting severe pain despite a full trial of non-steroidal anti-inflammatory drugs may be managed with a short course of steroids and paraesthesiae may respond to antineuralgic drugs, viz. gabapentin, pregabaline, etc. Acute neck pain can also be managed with either non-steroidal anti-inflammatory drugs or acetaminophen, supplemented with muscle relaxants in the first 2 weeks of symptoms. Development of radicular deficit and/or progressive myelopathy should be considered for termination of conservative management and surgical intervention is recommended.

Physical therapy has an important role in the management of cervical disc disease. The main objectives are to decrease the duration of disability, to reduce the use of drugs and to prevent chronicity and recurrence. The preference is to use active rather than passive modalities. Passive modalities should be used only temporarily as an adjunct. Active modalities are isometric exercises of the neck, postural re-education and strengthening exercises for the neck, shoulder and back muscles. Passive modalities are heat and cold application, ultrasound, cervical collar, traction, massage, trigger point treatment and low power cold laser.

A majority of patients with non-myelopathic cervical radiculopathy respond to non-operative care consisting of analgesic, anti-inflammatory therapy and physiotherapy. In patients with mild or subtle myelopathy, non-operative treatment can be used with regular monitoring of neurological deterioration. Traction or manipulation should be avoided.

SURGICAL MANAGEMENT OF CERVICAL DISC DISEASE AND SPONDYLOSIS

Surgical intervention is indicated for patients with spondylosis who have disabling pain refractory to conservative measures, acute cord compression, signs of progressive cord dysfunction and progressive muscular weakness or sensory impairment. Precise correlation between clinical and imaging studies is necessary before

surgical intervention. The goal of the surgical management of patients with radiculopathy or myelopathy is decompression of the nerve root and spinal cord, elimination of the anteroposterior flattening and distortion of the cervical cord. Secondary surgical considerations include realignment of the cervical spine, correction of cervical spinal instability and rectification of cervical spinal deformity. Two surgical approaches are available: the anterior approach and the posterior approach with various degrees of laminectomy and laminoplasty.

ANTERIOR APPROACH

Patients with spondylosis with osteophytes, herniated disc or in those with evidence of spinal cord compression or mechanically produced neck pain can be approached via the anterior route. The anterior approach to the cervical spine is easy and safe from levels C3 through C7. The anterior intervertebral route exposes the vertebral bodies, the discs and the osteophytes that form in the ventral aspects of the root foramina and spinal canal which can directly be removed. The anterior approach has two distinct advantages: (1) osteophytes can be removed safely and (2) fusion of the affected disc space provides permanent immobility of that joint. The disadvantage is that it affords no access to posterior elements that may be compressing the neural structures. For cervical spondylotic myelopathy, the anterior cervical approach is preferred if the compressive pathology is primarily ventral, localised to the interspace or is associated with cervical instability, spondylolisthesis or kyphotic deformity.

Anterior Cervical Discectomy

Anterior cervical discectomy for cervical disc protrusions started with the techniques described by Smith and Robinson in 1955, and Cloward in 1958. In 1960, Hirsch showed that good stability and fusion could be achieved without grafting. In 1965, Robertson used the operating microscope for removing cervical disc protrusions. He removed the disc material including the cartilaginous end plates and the posterior annulus to varying degrees. Hankinson and Wilson (1975) removed only the central portion of the disc using a high-speed drill, leaving columns of disc intact laterally. On approaching the posterior end of the disc space, the drilling was stopped and curettes and pituitary rongeurs were used for further dissection. Osteophytes were removed and the posterior longitudinal ligament usually opened. Maurice-Williams described an extended decompression with removal of posterior osteophytes, but leaving the cartilaginous end plates intact.[38] The term 'extended' refers to the removal of bone posteriorly and was described by Dunsker in 1977.[17] This involves removal of the posterior-inferior margin of the upper vertebra and for foraminotomy, the removal of the posterior-superior margin of the lower vertebra. Watters did not remove posterior osteophytes and the posterior longitudinal ligament.[38] However, he reported similar results in the anterior cervical discectomy (ACD) and the anterior cervical fixation (ACF) groups, although he stated that the satisfaction for the surgical outcome was better in the ACF group in comparison with ACD group.[38]

The rationale for removing the posterior longitudinal ligament is that following discectomy narrowing of the space could cause the ligament to buckle and produce anterior spinal cord compression. Removal of the posterior longitudinal ligament when it is involved in the spondylotic compression appears necessary and essential. However, routine removal of the stronger ligament in young patients when it is not a component of the compression seems unnecessary. Most surgeons feel that removal of the foraminal osteophytes is an essential part of the procedure, whether carrying out ACD or ACDF. However, Klaiber reported that persistence of foraminal osteophytes post-operatively did not correlate with clinical outcome.[34]

Technique of Anterior Cervical Discectomy

Exposure of the cervical spine by the anterior approach involves careful placement of the patient on the operating table with a head rest. Moderate extension is obtained by placing a small pillow or towel roll under the interscapular shoulder region. The upper cervical spine is best approached from the right side for a right handed surgeon. Although the lower cervical spine (below C6) can also be exposed well through a right sided incision, a left sided approach may be preferred for easy manoeuvrability, as well as avoiding injury to the recurrent laryngeal nerve. Crutchfield tongs are used for traction for traumatic and other cases requiring corpectomy and fusion. The head is slightly rotated to the side opposite to the skin incision. A neck skin crease incision (approximately 6 cm and medially reaching up to the midline) is adequate for single- or two-level surgeries. An incision at the level of Adam's apple is suitable for exposure of C5 and the incision can be placed above or below this level depending on the level to be exposed. However, for more extensive surgery, viz. corpectomy or plate fixation, a vertical incision is preferred running along the anterior border of the sternomastoid. The platysma is also incised in the same line and the middle layer of the fascial plane between the sternomastoid and the strap muscles is split open with blunt and, occasionally, sharp dissection. For exposure of C7 and lower down, the inferior thyroid artery and the omohyoid may need to be divided, and for exposure of C2-3, the common facial vein and the digastric tendon will need division, and retraction of the mandible may be necessary. The carotid sheath should remain on the lateral side of the dissection, avoiding injury to the sympathetic trunk.

The deep cervical fascia overlying the longus colli muscles and the anterior longitudinal ligament of the cervical spine are then visible. Once the prevertebral fascia is reached, a needle is inserted in the probable diseased disc space and the level is confirmed using a

C-arm. The needle is rostrally directed against the body above to avoid inadvertent dural penetration. The prevertebral fascia is then incised in the midline and the anterior spinal ligament and anterolaterally the longus colli muscles are exposed. The muscles are then dissected on both sides with sharp dissection well above and below the required area, to ensure that the blades of the self-retaining retractors can be placed underneath to maintain proper exposure during the entire procedure. Either Cloward or Caspar self-retaining retractors are then applied vertically.

The operating microscope is brought in at this stage. The annulus is then incised and the nucleus is entered. Anterior osteophytic ridges, especially of the upper body, may obscure the view in the presence of gross spondylotic changes and can be removed by small nibblers or Kerrison punch or burred away with a high speed drill, facilitating entry into the disc space. The nucleus is then removed with curettes and rongeurs. A vertebral spreader is then inserted in the disc space. Further disc removal is then performed and a complete disc excision can then be done in most cases of soft disc protrusion till the posterior longitudinal ligament is completely exposed. The posterior longitudinal ligament is then inspected for any tear, as the disc can sequestrate through the ligament into the spinal canal. Both the foramina can be probed with a blunt micro hook for disc fragments. In the presence of a hard disc protrusion with gross posterior osteophytic ridges, it is necessary to curette them or preferably remove them with high speed burrs after thorough removal of the hyaline cartilage attached to the vertebral body end-plates. This is important for proper decompression and frequently soft disc protrusion under these osteophytic ridges are observed. It is also necessary to create parallelism for the graft to fit precisely. Uncovertebral joint spurs projecting into the neural foramina should be curetted or burred away to enlarge the foramen till a blunt micro hook can be passed along the nerve root, ensuring adequate decompression. This is more important, and should be done generously, if a bone graft is not being used. In Figure 1, MRI of a patient has been shown who presented with radiculopathy due to C4-5 disc prolapse, and who underwent anterior cervical discectomy.

Results of Anterior Cervical Discectomy

In 1960, anterior cervical discectomy without fusion was first described by Hirsch, and is usually adequate for soft disc protrusions at one or two levels in the absence of severe spondylotic changes or significant canal stenosis.[6,40,53] Anterior cervical discectomy without fusion is followed by narrowing of the disc space and a degree of *anterior angulation (kyphosis).* Martin[37] and Dunsker[17] reported post-operative kyphosis in their study. However, they stated that it did not correlate with clinical outcome. The consensus appears to be that major kyphosis is significant, but very rare and the majority have no more than minor angulations which resolve by 1 year. Discectomy by itself leads to collapse of the disc space and subsequent *foraminal narrowing*. Strachan and West quantified this, and found that reduction in area was 12% and not statistically significant.[59] They suggested that the foraminal narrowing is not clinically significant as reported outcomes were similar after both ACD and ACF.

Complications of Anterior Cervical Discectomy

Anterior cervical surgery may have complications, viz. hoarseness, tongue paralysis, swallowing difficulty, Horner's syndrome, oesophageal perforation and fistula, spinal cord/root injury and vertebral artery injury. A post-operative infection or haemorrhage may also result.

Anterior Cervical Discectomy with Fusion

The clinical benefits of combining anterior cervical discectomy with bone grafting (ACDF) versus performing anterior cervical discectomy alone for cervical spondylosis remains controversial. Many surgical series reported over the last 30 years give consistently excellent results with ACDF.[12–15,24,29,36,45,46,48,55] However, Hirsch reported his experience with simple cervical discectomy alone

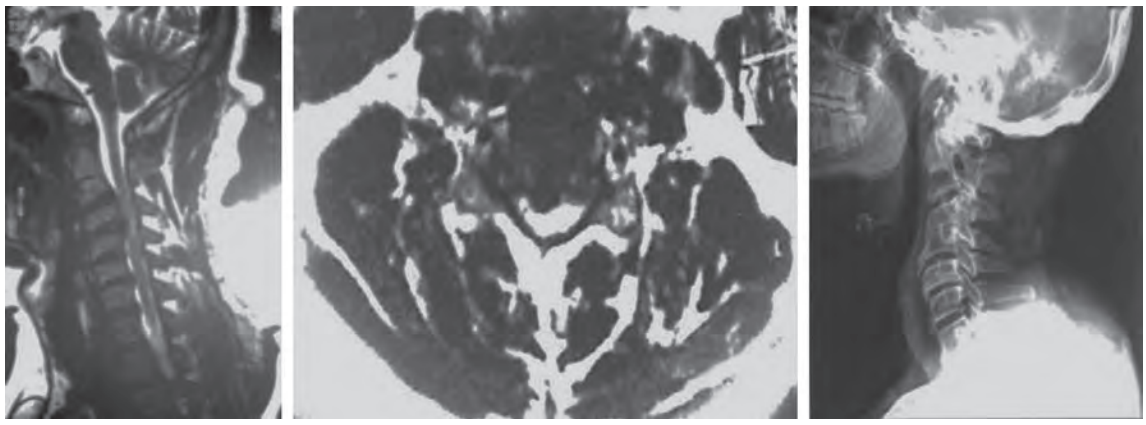

Fig. 1: Sagittal and axial view MRI showing C4-5 disc prolapse. Patient underwent anterior cervical discectomy C4-5. X-ray after 1 year showing fusion

(ACD) for the treatment of cervical spondylosis.[29] His results and those of others suggest that ACD can result in surprisingly good results challenging the need for routine arthrodesis after cervical discectomy.[5,23,24,37,44,46,57,66] Both techniques have theoretical advantages. Discectomy alone requires less surgical time is associated with fewer complications and lower cost. Discectomy with fusion results in a more rapid resolution of neck and arm pain while preventing post-operative deformity of the spine by stabilising the abnormal motion segment, arresting spur formation and preventing buckling of the ligamentum flavum and the posterior longitudinal ligament. The range of motion at the operated segment increases after anterior cervical discectomy as compared to anterior cervical discectomy and fusion. Later on, when fusion occurs in patients with anterior cervical discectomy, the biomechanics approach those of fusion. Thus, it has advantages of both, initially providing some motion at the operated segment and in later stages when fusion occurs, providing advantages similar to grafted fusion. In a prospective randomised study, Savolainen et al.[49] have shown that after anterior cervical discectomy alone, complete bony union occurs invariably.

Fusion of the Cervical Spine

The term fusion has become synonymous with insertion of the bone graft. Bony fusion, if it occurs, does so after at least a few months, and in a proportion of patients, never occurs. Some reports indicate that there is resolution of neck and arm pain quite early after fusion procedures when true fusion is unlikely to have taken place.[61] Early resolution of neck pain in this circumstance must be related to the maintenance or restoration of alignment and biomechanics. In other words, the graft is acting as a 'spacer' in the first instance and fusion has nothing to do with it.[47] There are a number of reports of anterior cervical discectomy and fusion in which a few patients who had a non-union, did not necessarily experience a poor result.[32,63] Eventually it was obvious that a good prognosis for operative intervention was not related to obtaining a bony fusion, but rather to operating on patients with classical radicular symptoms.[17] A prospective randomised study of anterior single level cervical disc by Savolainen[49] using three different methods (discectomy without fusion, fusion with autologous bone graft and fusion with autologous bone graft plus plating) had shown that ultimately all patients had complete bony union. In this study the fusion rate was slightly better with fusion and plating after 6 months, but, after an average of 4 years of follow-up, this difference vanished.

The majority of early authors assumed that fusion was necessary. They were troubled by the possibility of developing an unstable cervical spine with resultant threat to the underlying spinal cord, or of developing angulations that might lead to the chronic signs and equivalents of spondylotic myelopathy that one is trying to prevent or treat.[17] In Figures 2A and B, MRI cervical spine of a 50-year-old lady has been shown with C4-5 disc prolapse, who underwent ACDF.

The goals of the spinal internal fixation procedures are to achieve anatomical alignment, protect the neural elements and mechanically stabilise the spine while attempting to preserve the motion of normal spinal segments. These goals can only be attained by a satisfactory arthrodesis. The success of a fusion ultimately depends on satisfactory bone healing as instrumentation provides immediate but only temporary spinal fixation and is susceptible to failure due to fatigue, loosening or

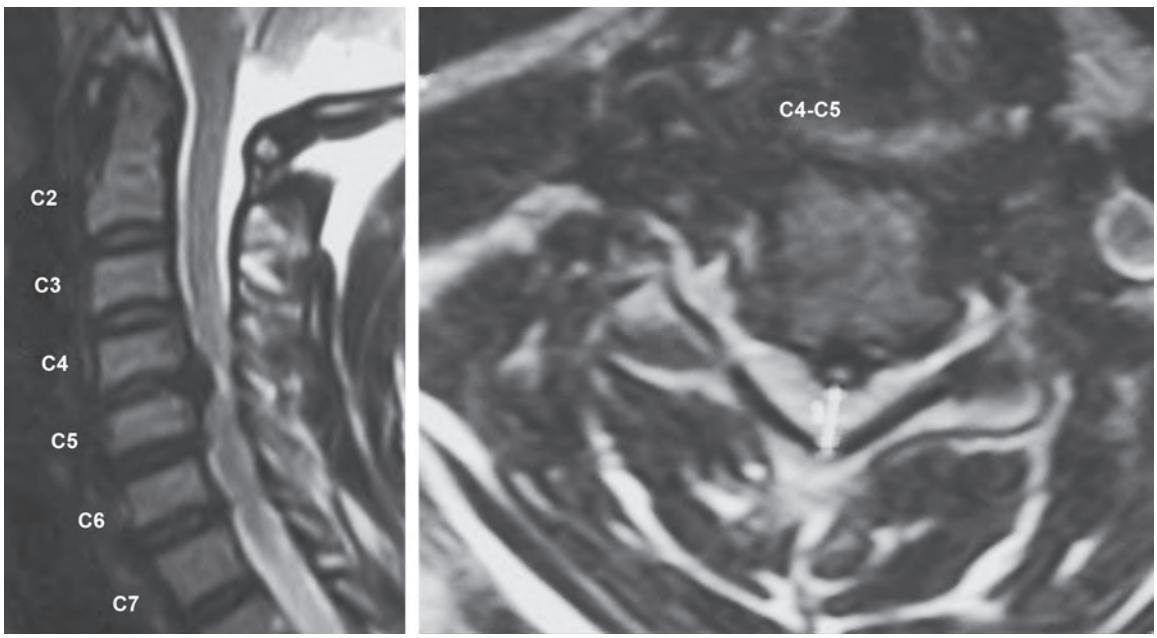

Fig. 2A: MRI cervical spine of 50-year-old lady showing C4-5 disc prolapse, underwent ACDF

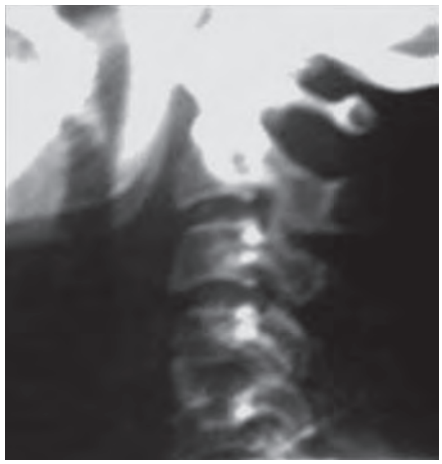

Fig. 2B: X-ray on 1st post-operative day of patient (Fig. 2A) who had underwent ACDF

breakage. Surgery for fusion depends, therefore, largely on meticulous preparation of the fusion bed, and the ability of graft material to induce bone healing apart from the local fixation method and systemic factors.

When a fusion is undertaken, graft-related complications may be added to the already mentioned complications associated with discectomy such as infection, collapse, extrusion, donor site complications like pain and infection followed by failure of fusion.[25] In addition, fusion is said to predispose to accelerated adjacent level degeneration.[31]

Techniques of Anterior Spinal Fusion

The *Smith-Robinson technique* involves a thorough discectomy followed by the insertion of a tricorticate iliac crest bone graft (Fig. 3). The cartilaginous plate is meticulously removed. Bony spurs along the posterior edges are removed taking care not to remove the anterior cortical edges. The disc space is usually 1.6–2 cm deep and usually a 1.5 cm long graft is necessary. A tricorticate graft is obtained from the anterior part of the iliac crest so that its cancellous surfaces will lie against the subchondral bone above and below the space, while its cortical part forms the support between the vertebrae. Vertebral spreader is used for increased distraction before inserting the graft. The graft is inserted carefully and tapped into place. The graft is countersunk just posterior to the anterior margins of the vertebral bodies. The distractor or traction is then removed so that the graft fixes firmly. The empty space around the graft may be filled with cancellous bone chips.

The *Cloward technique* accomplishes fusion with the use of a bone dowel (Fig. 3). An autologous iliac crest graft is removed as a dowel or the allogenic bone graft may be obtained from the bone bank. All disc material is removed and the depth of the interspace is precisely measured. The drill guide is adjusted to this depth and is centered over the disc space. After completion of drilling, the remaining osteophytes can be curetted or drilled away. The bone graft is obtained from the anterior superior iliac spine by applying the dowel-cutter transversely on the ilium and a full thickness graft is obtained, leaving the crest intact. The dowel is then firmly tapped into place with a length slightly less than that measured for the interspace. The step is facilitated by first applying the vertebral spreader and removing it after placement of the graft for proper impaction.

The *Bailey-Badgley technique*[3] involves cutting a trough with a drill in the anterior aspect of the vertebral bodies, which should approximately be 1.2 cm wide and

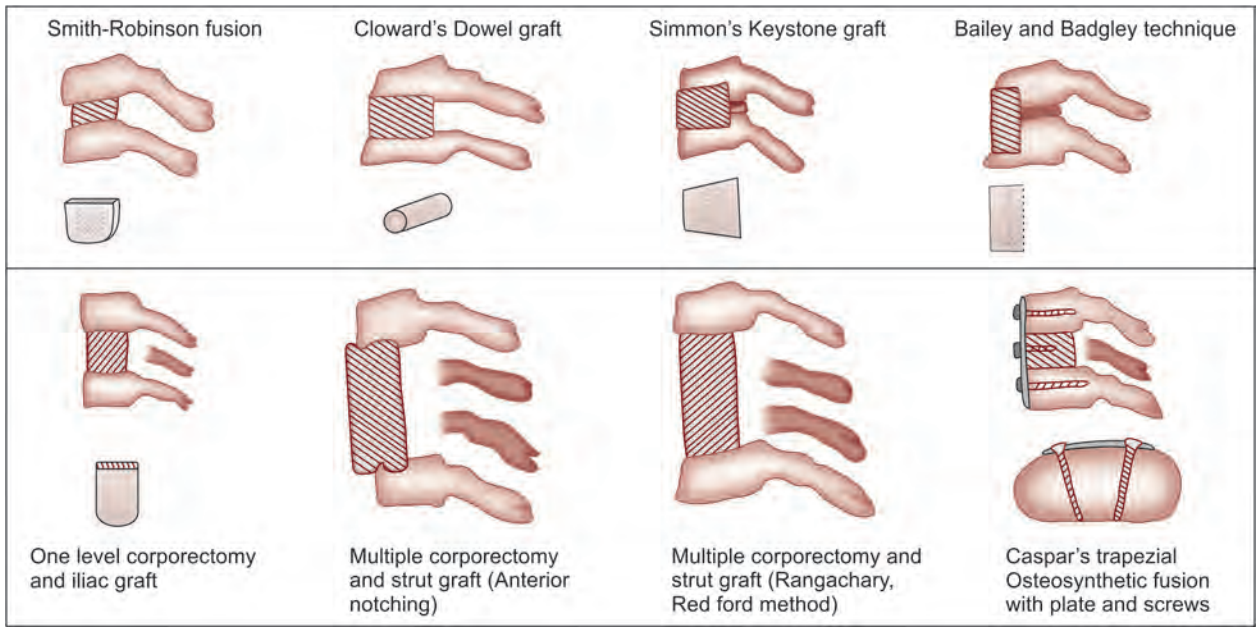

Fig. 3: Techniques of anterior cervical fusion

4.7 cm deep near the top of the upper vertebra (Fig. 3). Disc is then removed along with the cartilaginous plates of the vertebrae to be fused. Cancellous chips from the iliac bone are packed into the disc space and then an appropriate sized graft is inserted into the trough after applying traction. The graft must not project anteriorly beyond the vertebral bodies and is wedged properly after removal of traction. Suturing the fascia over the graft is important in this type of fusion, which is especially useful for multi-segmental disease.

Bloom and Raney[7] recommend reversing the orientation of the graft so that the round cortical edge of the iliac crest is placed posteriorly and the cancellous edge anteriorly so that the protruding portion of the graft can be trimmed without sacrificing the cortex and decreasing the strength of the graft. However, this may result in collapse of the graft anteriorly with some kyphosis in elderly patients.

White and Hirsch[62] have found the Smith-Robinson configuration of graft to be the strongest in compressive loading. The strong configuration of *Smith-Robinson* arthrodesis is the result of leaving the cortical shell of the vertebral body intact as 40–75% of the strength of the vertebra comes from the cortical bone, and the emphasis given to preservation of the end plate.

Simmons et al.[52] use a key stone graft for fusion (Fig. 3). A keystone square or rectangle of tissue is removed, bevelling it upwards into the vertebra above and downwards into the vertebra below using an osteotome and chisel or high-speed burr. After this, a thorough discectomy is performed. A rectangular graft is obtained from the iliac crest and shaped to fit the trough by bevelling the ends upwards and downwards to approximately 14–18 degrees. After distraction, the graft is placed into the defect and it gets locked firmly on removal of the distraction.

Bone Grafts and Other Materials Used for Fusion

Autogenous bone grafts are mostly obtained from the *iliac crest.* The advantages of autografts are that they are live, sterile and non-reactive being genetically identical to the host. *Autogenous cancellous bone* is currently the best material for its osteogenic, osteoconductive as well as osteoinductive properties. *Cortical bone* adds to the mechanical strength of the graft, but it is slowly vascularised and is minimally osteoconductive. A bicorticate or tricorticate iliac bone graft as used in most cervical fusion procedures has the advantages of both. *Autogenous vascularised bone grafts* can be obtained from the fibula, rib or iliac crest for spinal fusion as they have superior healing capabilities. These grafts hypertrophy when subjected to mechanical stress while non-vascularised grafts resorb early and weaken. Vascularised bone grafts are particularly helpful when the recipient bed is devascularised, irradiated or scarred. *Allografts* are transplanted from genetically known identical members of a species and heal in a similar fashion when used for spinal fusion as the autografts, although the vascular ingrowths are slower, lesser and new bone formation is, therefore, delayed. Allografts elicit an immunological reaction and may, occasionally, be rejected.

Cages (Fig. 4) are now available into which a bone graft can be incorporated. Cages are hollow implants that restore physiological disc height, prevent disc space collapse and stimulate bony fusion by allowing new bone growth within and around them. Cages have fusion rates similar to those associated with bone grafts.[2] Complications related to the implantation of the cages are subsidence into the adjacent vertebral bodies, cage dislocation, non-union and painful pseudoarthrosis.[65] *Methyl methacrylate* usually acts as a *spacer*, which

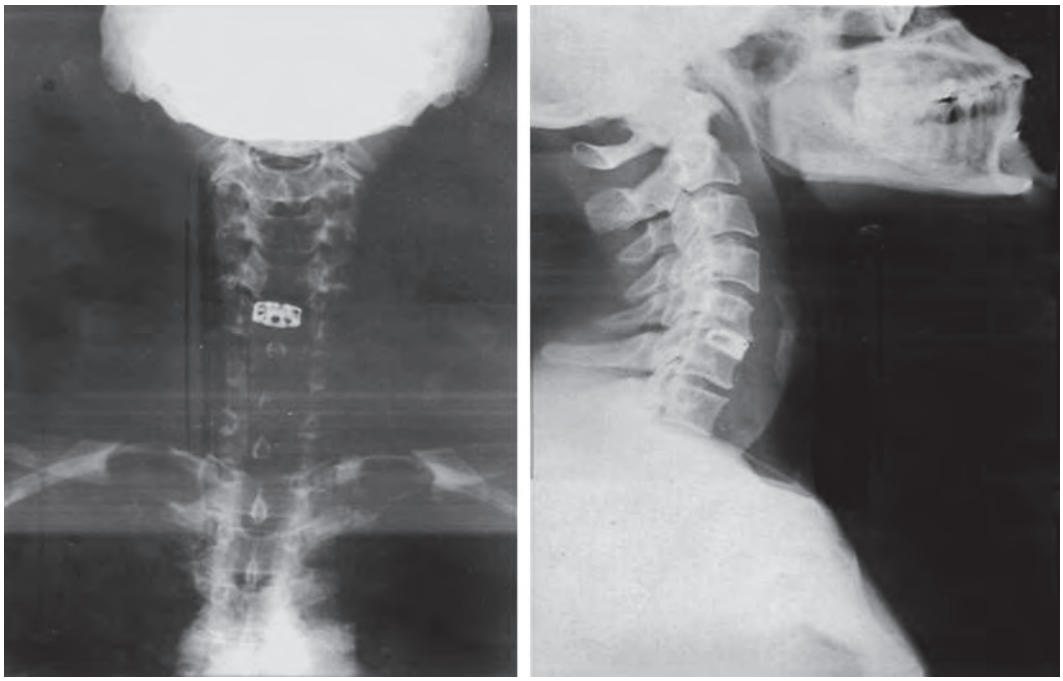

Fig. 4: Cage insertion after anterior cervical discectomy

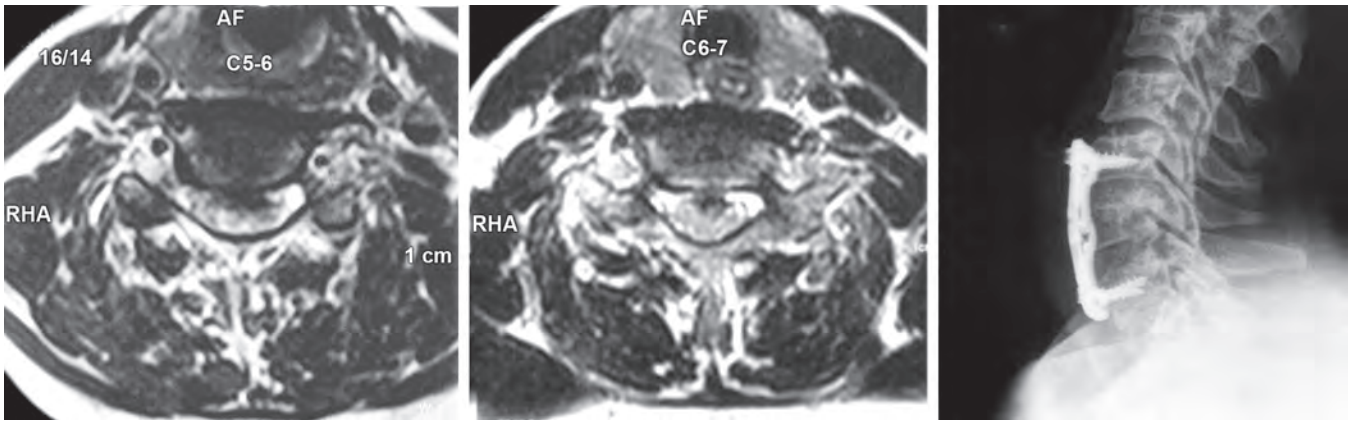

Fig. 5: MRI cervical spine axial view showing C5-6 and C6-7 disc prolapse of patient who presented with cervical myelopathy. She underwent ACDFI. X-ray cervical spine showing fusion after 5 months

resists compression and around which cancellous bone may be inserted to promote bony fusion. This is usually reserved for patients with malignant tumours or when good bone stock is not available, as it does not promote bone healing. A prospective randomised study of *polymethyl methacrylate* versus titanium cage after anterior cervical discectomy by Schroder et al.[50] had shown that the radiological result of the titanium cage is superior to that of *polymethyl methacrylate* with respect to the fusion rate. Although the titanium cage achieves a better fusion rate, there is no difference between titanium cages and *polymethyl methacrylate* with respect to the clinical outcome.[50] *Ceramics* are being increasingly used by some workers[42] as they not only act as a spacer but also have osteoconductive properties and osteoblasts form bone directly on their surface and, therefore, may be a better substitute.

Instrumented Fusion

Hardware in cervical spine surgery has been utilised for practical reasons like prevention of graft displacement, greater fusion rate, prevention or correction of scoliotic deformity and avoidance or simplification of external orthotics.[8] However, there is 10–12% short-term morbidity related to instrumentation.[60]

Casper's trapezial osteosynthetic plate technique[9] was originally described for the treatment of cervical spine injuries but has successfully been employed for treatment of spondylotic myelopathy, post-laminectomy kyphosis, infections and tumours. Deopujari et al. have found it to be a technically safe and satisfactory procedure in over 60 cases with a fusion rate of almost 100%.[8] It permits neural decompression and immediate stability, is useful for reducing spinal deformity, prevents bone graft migration and improves fusion rates. The posterior cortex should be engaged to provide immediate stability and avoid pull out observed in the Casper and the AO plate systems.

The second generation systems (e.g. CSLP from *Synthes,*[39] Orion from Sofamer-Danek, Codman plate) allow screws to lock up with the plate and engaging the posterior cortex may not be necessary. Titanium plates (Fig. 5), like in the Orion system,[49] are much lighter, easy to use and avoid difficulties in post-operative imaging. The latest, third generation systems are the dynamic semi-constrained plates to prevent stress shielding and allow subsidence.

Dynamic Fusion

Dynamic fusion or cervical total disc replacement has emerged as an alternative for the management of cervical disc herniation.[18] The goals of cervical total disc replacement are to remove the offending disc while maintaining disc height and segment motion. Although never proved, motion preservation with total disc replacement is intended to reduce adjacent-level disease.[18] Preservation of motion at the affected disc level restores normal biomechanics and offers several advantages such as avoidance of adjacent segment degeneration, donor site morbidity and early post-operative mobilisation. Inclusion criteria for cervical disc replacement includes symptomatic disc disease at a single level, and young patients (less than 60 years), while exclusion criteria includes prior fusion at an adjacent level, instability, and severe facet arthrosis at the affected level.

Total disc replacement involves anterior decompression of the disc space, similar to ACDF. The cervical disc prosthesis is then inserted into the evacuated disc space in place of bone graft. The cervical total disc replacement implants with the most extensive clinical experience are the ProDisc-C (Synthes, Oberdorf, Switzerland), the Bryan cervical disc (Medtronic Sofamor Danek, Memphis, Tennessee) and the Bristol disc (Medtronic Sofamor Danek, Memphis, Tennessee).[4] Although there are no long-term data available, these three cervical prostheses appear promising for the non-fusion treatment of cervical degenerative disc disease.[4]

Partial Median Corpectomy and Grafting

Anterior discectomy, osteophytectomy and interbody fusion by these various methods have yielded results superior to decompressive laminectomy, if the disease

process is confined to one or two levels. Surgery for more than three levels is not commonly performed because of morbidity, prolonged operating time and concern regarding kyphotic or swan neck deformity. The results are also less satisfactory, as decompression is confined to the intervertebral disc spaces, and canal stenosis is not adequately tackled. Partial median corpectomy and grafting has been recommended for such cases. The anterior longitudinal ligament and the annulus are excised from the lowest and then higher disc spaces till the posterior longitudinal ligament is visualised and the end-plates are also curetted or burred away. The intervening cancellous bone is then removed with rongeurs, curettes and high speed burrs. The central two-thirds of the body is resected to ensure decompression of the spinal canal, but not far enough laterally to disrupt the pedicles. An iliac crest, tibial or fibular bone strut is then inserted into the slots in the vertebral end plates at the rostral and caudal extremes of the resection sites.[26] The graft is locked in the slotted place with two-thirds of the graft coming to lie posterior to the anterior aspect of the vertebral column.[64] Rengachary and Redford have modified this approach where a trough is created in the superior and inferior end plates and the whole graft fitted in the slots beneath the anterior cortex, to allow good contact and compression of the graft.

POSTERIOR APPROACH

Dorsal compression is best treated by a posterior approach. Posterior approach affords easy access to the posterior elements of the vertebrae, dorsal and dorsolateral aspects of the spinal canal and its contents from C1 to D1. Cervical canal stenosis, either congenital or degenerative with hard disc protrusions or hypertrophied ligamentum flavum compressing the cord is readily removed by laminectomy. Also, decompression of the cervical roots posteriorly is easily accomplished with foraminotomy. Laminectomy was developed early in the nineteenth century and received little support initially because of a high mortality rate. The first successful laminectomy was performed in 1828, by Alban G. Smith in Danville, Kentucky.[54] The patient's paraplegia improved after three-level laminectomy. Till the 1950s, posterior approaches dominated over anterior cervical operations.

A variety of posterior surgical procedures exist, including laminectomy, laminoplasty, foraminotomy and posterior spinal instrumentation with or without laminectomy. Posterior surgical approaches have several advantages. They generally require less surgical time and they frequently do not require stabilisation, fusion or instrumentation. The nerve roots are decompressed under direct visualisation, and there is little risk to major vessels and structures. Disadvantages include post-operative neck pain, spinal instability stimulating further bone spur formation and an inability to access ventral canal osteophytes.

Cervical Laminectomy

A good decompression can be achieved by a wide and extensive laminectomy from C3-7 in cases of cervical canal stenosis, either congenital or degenerative. Northfield reported that one-third to half of the patients showed good improvement after decompressive laminectomy.[41] Snow and Weiner[56] reported improvement in 77% and Chakravorty[11] found good improvement in 64%. Chakravorty[10] felt that occasionally compression may be due to fibrous tissue only and this should be removed as far outwards as possible to decompress the neurovascular structures and relieve cord ischaemia. It may also help by release of the anchoring effect of the spinal root sleeves, permitting dorsal migration of the cord.[19,51]

Posterior decompression of the spinal cord, nerve root or both may be done with the patient in the prone or sitting position, although the prone position is preferred because of lesser anaesthetic risks. A midline incision is made to expose the spinous processes. The paraspinal muscles are stripped away subperiosteally to expose the laminae and the facets completely. The spinous processes, laminae and ligamentum flavum are then removed with either rongeurs or a high speed drill. It is better to start at the lower level, proceeding rostrally in a segmental fashion and care must be taken not to compress the already compromised dural sac.[33] Absence of epidural fat indicates lack of space within the spinal canal. The laminectomy must be wide enough to demonstrate the posterior and posterolateral aspects of the dural sac.[21] If the clinical features and pre-operative investigations indicate radiculopathy without myelopathy, segmental hemilaminectomy and foraminotomy provide excellent decompression.[33] Here, the paraspinal muscles are stripped away on one side of the spinous process only and the spinous process remains intact. The complications of extensive laminectomy are late development of spinal deformity and peridural fibrosis. These can possibly be avoided by expansive laminoplasty. Hirabayashi first described the procedure in 1977.[28] The expansive open door laminoplasty is performed by completely incising the laminae on one side and partially on the opposite side (Fig. 6). Elevation with tilting of the

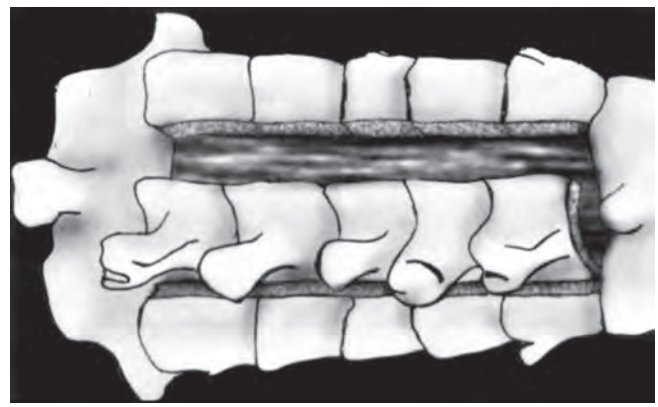

Fig. 6: Left open-door cervical laminoplasty

laminae upwards on the incised side allows enlargement of the canal. This has been used by others with success[20,27] and several modifications have been suggested with interposition of implants.[35]

Foraminotomy

Root compression in the absence of cord compression is best managed by simple foraminal enlargement at the involved level.[33] Foraminotomy is also important for radiculopathy caused by osteophytes or by an extreme lateral soft disc herniation.[16] Posterior laminoforaminotomy is also an effective option in patients with persistent radicular symptoms following an anterior procedure. Raynor has shown the limits of nerve root exposure obtained by anterior and posterior approaches.[43] He found that 30–70% facetectomy can give good root decompression by the posterior approach and a greater amount of facet removal can result in instability. The region anterior to an adequately decompressed nerve root can then safely be explored and decompressed.

The successful management of cervical disc disease and spondylosis requires proper understanding of the aetiopathogenesis and a careful analysis of the clinicoradiological features. Patient selection and adequate surgical decompression remains the key to achieve desirable clinical results. No single gold standard procedure exists for the treatment of patients with cervical spondylosis. The treatment strategies need to be tailored to match the specific changes present in a given patient.

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112 Cervical Ossification of Posterior Longitudinal Ligament

Anil Pande, M Vikram, Ravi Ramamurthi

INTRODUCTION

Ossification of the posterior longitudinal ligament (OPLL) was first reported in England by CA Key in 1838[50] and, in 1960, Tsukimoto[103] reported an autopsy of a patient with myelopathy due to OPLL. Terayama et al.[100] gave the disease its name. It was reported extensively thereafter from Japan and came to be known as the '*Japanese disease*'. Hakuda S et al.,[35] on the basis of a paleopathologic study of ancient human skeletons in Japan, found that cervical OPLL was the only ossification that increased significantly in prevalence in people of the near-modern period when compared to the Neolithic gathering-hunting people. They hypothesised that socioeconomic changes from a subsidence gathering-hunting economy to the near-modern livelihood depending on rice-eating and a diet high in vegetable protein was responsible for the increased incidence of OPLL.

As the awareness of this condition grew it was seen to occur in all parts of the world.[21,22,29,52,64] In India too this condition has been known to cause compressive myelopathy quite frequently and many centres have substantial experience with its management.[2,6,8,26,42,44,59,87,95] OPLL is a distinct disease entity and should not be confused with ankylosing spinal hyperosteosis, ankylosing spondylitis and diffuse idiopathic skeletal hyperostosis (DISH)[62,92] although nearly 50% of patients with DISH can have concomitant OPLL on cervical radiology. Sharma et al.[92] found OPLL in 12.2% of their patients with DISH (9 out of 74 patients).

INCIDENCE AND PREVALENCE

A high incidence of OPLL has been reported in the Japanese and other Asian populations.[1,51,72,101] In Japan, 4.3% of asymptomatic 60-year-old men and 2.4% of 60-year-old women had radiographic evidence of OPLL in the cervical spine.[81] The prevalence of cervical OPLL in Koreans was 0.6%, and in non-Japanese Asians, Lee et al. reported an incidence of 0.8%.[64] OPLL tends to manifest in the 5th to 6th decade of life with the cervical region[75] being the most common region followed by thoracic[98,102] and lumbar[66,92] with an incidence of less than 10% of cases.

Among patients older than 60 years of age, the prevalence of OPLL was greater than 20%. Nakanashi et al.[81] found an incidence of 11% in the sixth decade of life and the most common region was at C4 and 67% of these patients were asymptomatic. Lee et al.[64] reported it to be four times more common in men and its incidence increases with age.[104] At autopsy, OPLL was found in 20% of patients who had no earlier history of OPLL. OPLL has also been reported from North America and in Non-Asian countries.[7,21,22,29,64,88] Most patients with OPLL are asymptomatic.[39,101]

AETIOPATHOGENESIS

The aetiology is multifactorial,[39,73,90] in which complex genetic[99,101,106,110] and environmental factors interact.[39]

Genetics

The genetic background in the development of this disease has been demonstrated by pedigree survey, twin survey and HLA haplotype studies.[90] Siblings of patients who share an increased number of human leukocyte antigen haplotypes are at increased risk of developing OPLL.[39,73,98] Specific polymorphisms that may be associated with OPLL occur in several collagen genes, which encode for extracellular matrix proteins. Polymorphisms in the nucleotide pyrophosphate gene, which is involved in regulation of calcification in chondrocytes, may also be associated with OPLL.[39]

The results of gene linkage study show that patients with OPLL have a significantly higher incidence of genetic abnormalities found in the XI collagen (alpha) 2 gene (COL11A2) region of chromosome 6. From the gene mapping of this abnormality, the abnormal N-propeptide of the COL11A2 gene was found to be responsible. Wang H et al. reported that the BMP-2 gene is not only associated with occurrence with OPLL but also is a factor related to more extensive OPLL.[107] Other genetic factors, like HLA-BW40 and HLA-SA5, were found more frequently in Japanese patients.[98,99,104]

Growth Factors and Cytokines

Many growth factors and cytokines, including Bone morphogenic protein (BMP) and Transforming growth factor-beta, are involved in the pathogenesis and several transcription factors controlling cellular differentiation may also have a role.[39]

Among the cytokines that are involved in ectopic bone formation in OPLL, CTGF/Hcs24 plays a major role in endochondral ossification. TGF beta and CTGF/Hcs24 enhance the expression of ALP mRNA in OPLL cells and these are responsible for initiating osteogenesis in spinal ligament cells.[110] Epidemiological studies found that diabetes mellitus is a distinct risk factor for OPLL.[39,63] Lee et al. reported that high glucose promotes collagen synthesis in the OPLL via endogenous TGF-Beta1 resulting in hypertrophy of ligaments. The incidence of diabetes and impaired glucose tolerance test are greater in patients with OPLL and in those with DISH. They found that 18% of their patients with OPLL had diabetes mellitus.

The analysis of blood group, serum group, erythrocyte isoenzyme groups, C reactive protein, erythrocyte sedimentation rate, rheumatoid factor and HLA-B27 were inconclusive.[104] There has also been association of high growth hormone and hypoparathyroidism in cases of OPLL.[37,62,67,82]

PATHOLOGY

OPLL occurs by the process of enchondral bone formation, beginning with the most superficial layer, progressing to deeper layers and this frequently involves the dura.[89] There are many cascading events like genetic factors of polygenic character, anatomical stress, age and sex in the formation of OPLL.[89] There is heterotopic bone formation[28] Fibroblast hyperplasia and cartilaginous proliferation with increased collagen deposition occurs and this is followed by mineralisation of the thickened ligament with lamellar bone and Haversian canal formation.[83,84,105,114] The annulus fibrosus remains separate and uninvolved with ossification at certain levels. The ossified ligament is not always continuous with the vertebral body. Hypertrophy, calcification and ossification of the ligament occur segmentally. OPLL then extends beyond its posterior margin causing progressive occlusion of the spinal canal.

OPLL involves the cervical spine predominantly followed by the thoracic[98,102] and lumbar spine.[66,92] Multiple level involvement is also commonly noticed with a mean of 2.25 vertebral bodies.[29] OPLL grows with a reported annual increase in size of 0.47 mm longitudinally and 0.67 mm anteroposteriorly.[91] The enlarging mass may have a round, cuboidal, triangular or polypoid shape with its base of attachment varying from flat to broad and narrow to pedunculated.[44] Yasui et al.[114] found a difference in the collagen composition of the OPLL, OPLL containing Type I, II, III whereas normal tissue has Type I and III. Choi et al.,[11] on analysing surgical results by multiple logistic regression analysis, found that diabetes mellitus was the only statistically significant factor producing poor prognosis for patients who underwent surgery.

The encroachment of the spinal canal causes spinal cord deformation into a thin, crescent-shaped structure. Neurological symptoms and signs can be expected to develop when the lesion occupies more than 65% of the neural canal.[84,91,96]

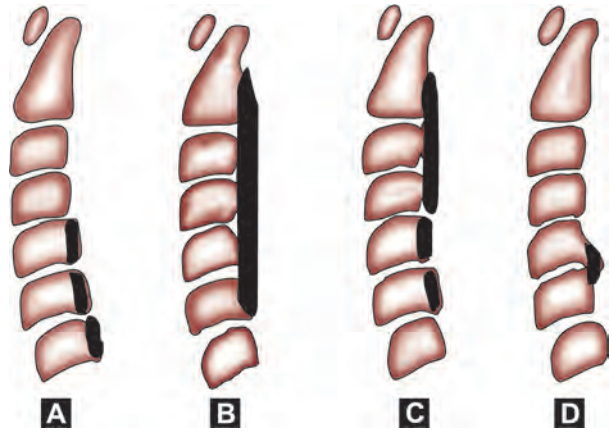
Two major mechanisms are involved in neural injury, one being mechanical compression which is both static and dynamic and the other is due to vascular compromise. Pathological changes in the spinal cord have been observed in the advanced stages. The extent of gray matter changes and the degree of spinal cord compression is proportional to the anterior horn deformity. Venous stasis, oedema, ischaemic neuronal necrosis and infarction are seen leading to cavitations and gliosis in the gray matter and spongiform atrophy, demyelination and axonal loss in the white matter. The central gray matter and the adjacent dorsal and lateral column are severely damaged. Progressive myelopathy has been explained by arteriolar degeneration of the central perforating branches of the anterior spinal artery. Demyelination, axon loss and atrophy have also been noticed in the nerve roots that have been stretched or compressed.[28,83,84]

CLASSIFICATION OF OSSIFICATION OF THE POSTERIOR LONGITUDINAL LIGAMENT

OPLL is classified as early OPLL and classic OPLL.[1] OPLL in evolution is an early variant and shows focal hypertrophy and punctuate calcification at the interspaces.

- On the basis of lateral radiographs, classic OPLL is further classified into four types: (1) segmental; (2) continuous; (3) mixed and (4) localised[13,101](Figs 1A to D).

  Segmental OPLL is located behind the vertebral bodies and not at the disc spaces. Continuous type extends from body to body, mixed has both segmental and continuous components and the localised variety is confined to the disc spaces alone. According to Tsuyama[104] 39% were segmental, 27% continuous, 29% mixed and 7.5% were localised.
- Hirabayashi et al.[31,32] suggested a CT based classification and suggested square, mushroom and hill types of OPLL to reflect its lateral extension (Fig. 2).



Figs 1A to D: Classification of OPLL. (A) Segmental. (B) Continuous. (C) Mixed. (D) Localised

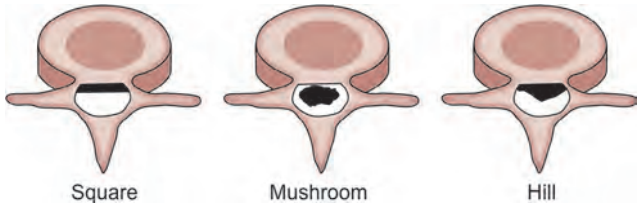


Fig. 2: Diagrammatic representation of Hirabayashi's CT based classification showing square type, mushroom type and hill type

- Hida et al.[30] described single and double layered OPLL on the basis of the ossification of the superficial and deep layer separated by the hypertrophied non-ossified layer.
- Mizuno et al. classified dural ossification in OPLL into three types: (1) isolated; (2) double layer and (3) en block type.[76]

MICROSURGICAL ANATOMY OF POSTERIOR LONGITUDINAL LIGAMENT

The posterior longitudinal ligament (PLL) is composed of collagen fibres with elastin, densely concentrated at its centre and extends from the base of the clivus to the sacrum. It is attached to the annulus of each inter vertebral disc and the posterior cortical surface of the vertebral bodies. Its thickness varies from 1 mm to 2 mm. It consists of two layers, a deep ventral layer and a superficial layer.[57] The superficial layer joins the dura at its lateral portion. It is wider at the disc level and is narrow at mid-body level. The longitudinally oriented collagen and elastin fibres are most dense centrally and thinnest at the site of the most lateral attachment to the annulus adding substantial strength and stability to the vertebral column during flexion and, mainly, extension movements. The normal ligament has both type I and type II collagen. Ossification involves replacement of the type I collagen matrix with lamellar bone structure with Haversian canals and a few bone marrow canals.[114] The posterior margin of the vertebral body where the PLL is attached is the common site of occurrence of OPLL and this extends both rostrally and caudally.[57] The internal vertebral venous plexus is located in the lateral posterior longitudinal ligament space.

CLINICAL PRESENTATION AND NATURAL HISTORY

OPLL occurs in association with degenerative disc disease or spondylosis causing radiculopathy, myelopathy and myelo-radiculopathy.[52,83,84] Asymptomatic OPLL has also been reported.[81] Patients with *early OPLL*, often in their mid-forties, present with radiculopathy or mild/moderate myelopathy.[88] Imaging shows hypertrophy of the posterior longitudinal ligament with punctate ossification opposite multiple disc spaces.

Patients with *classic OPLL* frequently become symptomatic in their mid-fifties. Symptoms include neck pain, radicular pain, dysaesthesia, arm weakness, leg weakness and urinary incontinence.[5,75] In a study of 47 Indians with OPLL, Jayakumar et al.[43] reported that 57.4% of symptomatic patients had myelopathy, 25.5% had myeloradiculopathy and 12.7% had radiculopathy alone.

Hypalgesia below segmental levels on the torso, and radicular sensory loss is also seen. Subacute development of symptoms over one to two years is common. Acute onset of symptoms or signs and exacerbation of existing neurological impairment were precipitated after trivial trauma in about 10–21% of patients.[22,27,29,56,64,70,89,117] The pathomechanism of myelopathy[56] in OPLL involves both static and dynamic factors.[67] The static factors include: spinal canal stenosis and PLL hypertrophy, and the dynamic factors include: Instability and association with a protruded disc.[118]

The pathological compression by the ossified ligament above a certain critical point may be the most significant factor in inducing myelopathy, whereas below that point dynamic factors may be more significant. Some patients with large OPLL have not exhibited myelopathy for long periods of time. Predicting the course of future neurological deterioration in asymptomatic patients with OPLL is difficult.[69,72] The mobility of the cervical spine and the type of OPLL are important factors contributing to the development and aggravation of myelopathy in patients with OPLL induced spinal canal stenosis.[69,79]

The axial ossified pattern is classified into two types: (1) a central type and (2) a lateral deviated type.[69] The incidence of myelopathy in patients with less than 60% spinal canal stenosis was significantly higher in the lateral deviated-type group than in the central-type group.[69] All patients in whom there was 60% or greater stenosis of the spinal canal developed myelopathy, regardless of a history of trauma.

The proportion of patients showing motor deficits of the lower extremities significantly increased when the sagittal canal diameter was narrowed to less than 8 mm.[56] Myelopathy has been quantified by many authors. The Nurick scale and the Japanese Orthopaedic Association (JOA) scale are frequently used (Table 1).

JOA categorises the myelopathy based on severity using a 17 point scale and the reliability of the system has been confirmed by Yonenobu et al.[115,116]

Table 1: Nurick scale of myelopathy

Grade 0	Intact, mild radiculopathy without myelopathy
Grade I	Mild myelopathy
Grade II	Mild to moderate myelopathy
Grade III	Moderate myelopathy
Grade IV	Moderate to severe myelopathy
Grade V	Severe myelopathy, quadriplegic

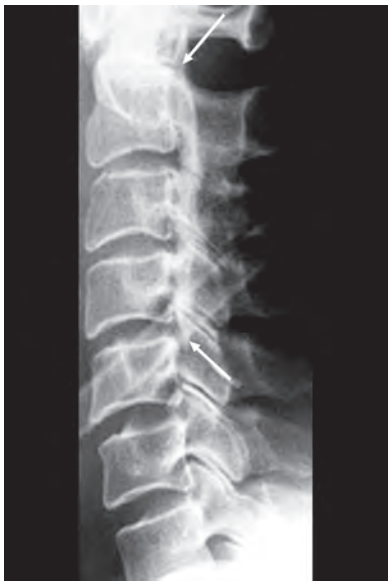


Fig. 3: X-ray of the cervical spine showing OPLL extending from second cervical vertebra to the upper border of fifth cervical vertebra

MANAGEMENT

Radiodiagnosis

Patients with OPLL frequently show associated ossification of the ALL, thoracolumbar PLL and yellow ligament. It has been recommended that a radiological survey of the entire spine is done in every patient with cervical OPLL.[5,23,30]

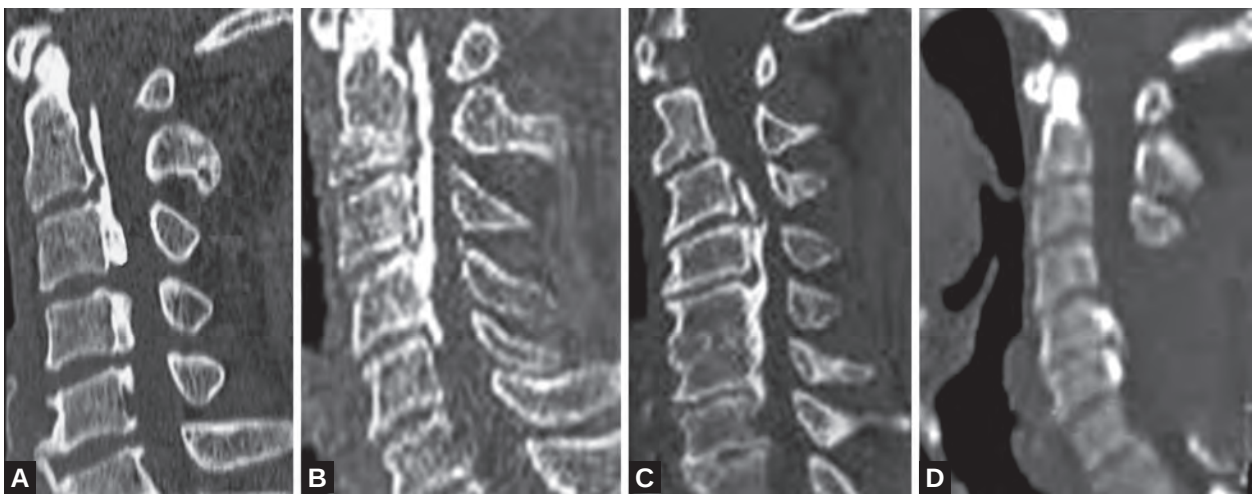
Plain X-rays

Nakanishi et al.[81] found OPLL in 11% of people in the 6th decade of life on plain X-rays. Plain X-rays are very useful in diagnosing and classifying OPLL and dynamic X-rays are useful to check for abnormal mobility. OPLL is visible as retrovertebral calcification on plain films in approximately one third of cases (Fig. 3). The normal spinal canal diameter is 17 mm from C3 to C7 on plain X-rays taken at a distance of six feet.[116] Absolute stenosis is when the diameter is 10 mm or less and relative stenosis is when it is 10–13 mm.[115,116] Occupancy ratio (OR) is obtained by dividing the thickness of the OPLL by the AP canal diameter. If the OR is greater than 40%, there is an increased risk of myelopathy. Yoo et al.[117] proposed that it may be beneficial to take a check lateral radiograph of the cervical spine as a screening tool for early detection of cervical spinal stenosis, especially in Asian people older than 40 years.

COMPUTED TOMOGRAPHY (CT) SCAN AND CT MYELOGRAPHY

The computed tomographic features of OPLL are distinctive. A 2–5 mm thick linear ossified strip along the posterior vertebral margin is usually seen at the mid cervical (C3 to C5) level. CT more readily identifies the foci of frank ossification (Figs 4A to D). Patients with OPLL frequently show concomitant ossification of the anterior longitudinal ligament and posterior longitudinal ligament in the thoracolumbar region and the yellow ligament. OPLL was most frequently observed at C5 and the number of vertebral bodies on average was 3.1.[5,23,30] Jayakumar et al.[43] in a study of 47 symptomatic Caucasoid Indians found the most frequent location to be at C3 and C4. The thickness of the OPLL ranged from 2.5 mm to 11.5 mm. Canal stenosis was most severe in patients with 'total' type of OPLL. Ossification of other spinal ligaments was seen in 50% of the patients. Chiba et al.[10] proposed a new computerised assisted measurement of OPLL where X-ray films are transformed via scanner into digital images and the length and thickness of the OPLL is measured using a computer assisted measurement system.

Bone window studies may show two signs of dural ossification: (1) the double layer or (2) the single layer sign. On pre-operative computed tomographic studies, Hida et al.[30] have described the single-layer sign characterised by a solid mass of hyperdense OPLL and the



Figs 4A to D: CT showing various types of OPLL

double-layer sign defined by two (anterior and posterior) ossified rims surrounding a central non-ossified but hypertrophied posterior longitudinal ligament. When the single layer sign is associated with a lateral C-shaped configuration of ossification, dural involvement is seen more frequently.[17,74]

The *double-layer computed tomographic sign* is more pathognomonic for dural penetration than the single-layer sign. The smooth-layer sign, indicating a clean dural plane, is more typical in North American patients. The size of the spinal canal is a factor that contributes to the neurological deficits associated with OPLL.[54] The spinal canal was narrowed by OPLL to 2.9–10.0 mm. The CT scan imaging of OPLL can miss an associated disc prolapse as highlighted by Yoshino et al.[118]

Min et al.[74] reported several differences between thoracic and cervical OPLL in regard to dural ossification signs. The incidence of these signs with thoracic OPLL was higher than that with cervical OPLL and these signs can develop in a segmental OPLL as frequently as in a non-segmental OPLL. Dural defects were present in 60% of the patients with a double-layer sign and in 50% of the patients with a single-layer sign. Therefore, surgeons should be alert for the high possibility of a dural defect when these signs are present in thoracic OPLL, although a dural defect can develop even in the absence of these signs.[74] Non-segmental OPLL is likely to be accompanied by dural ossification. Mizuno et al.[76] on retrospective analysis of neuroimaging findings found three patterns of dural ossification: (1) double layer; (2) isolated and (3) en bloc type. 2D and 3D non-contrast CT reconstructed images provide a sagittal overview of the extent of cord compression without incurring the risks associated with myelo-CT studies.[115,116]

CT myelography is recommended, especially when previous surgery has been performed or in cases of anterior spinal instrumentation with metallic implants restricting the MRI sequences. The interpedicular distance can be measured and varies from 14 to 20 mm and helps in deciding upon the width of the corpectomy. Post-operative myelo-CT studies are used to confirm the adequacy of decompression.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) should be the initial diagnostic imaging procedure in any patient with non-traumatic myeloradiculopathy. Due to the lack of MR signal from cortical bones, MRI is inadequate for diagnosing ossified lesions in the spinal canal. However, MRI provides information on spinal cord structure and associated soft-tissue abnormalities and is especially useful in the cervicothoracic junction.[55] The length of the lesion, cervical axial canal area, anteroposterior (AP) diameter of the cervical canal, spinal sagittal angles, cervical curvature index (CCI) and signal changes in the cord can be made out. MRI is valuable in studying associated cord damage and associated disc lesions prior to surgery. The T1-weighted images clearly demonstrate the spinal cord deformity caused by OPLL.

Associated disc protrusion is found to be present at the maximum compression level in 60% of the patients. A calcified central sequestrated disc is the only condition that may be mistaken for the segmental and retrodiscal forms of OPLL. The highest incidence of disc protrusion (81%) was found in patients with segmental OPLL. OPLL appears as a low signal intensity band between bone marrow of the vertebral body and the dural sac on T1- and T2-weighted images. The continuous type is easier to diagnose than the segmental type. Formation of bone marrow is shown by increased signal or intermediate signal in 56% and 11% of the segmental type. Intramedullary hyperintensity on T2-weighted imaging was noted in 43% of patients. On T1-weighted and T2-weighted images, ligamentous calcification or ossification appears as a region of low-signal intensity.[13,111,118] A sagittal image details the longitudinal extent and anatomical type of OPLL (Figs 5A to D). Axial images can demonstrate the extent of neural canal stenosis, including developmental and acquired anterior and posterior components.[96,97,109]

However, MRIs tend to exaggerate the severity of stenosis and the extent of obliteration of the subarachnoid space. Early OPLL mimicking disc disease appears opposite multiple disc spaces associated with significant retrovertebral extension, helping to differentiate it from spondylosis. MRI is often ineffective in recognising dural ossification.[76] In cases of borderline stenosis, magnetic resonance imaging during spinal flexion or extension may demonstrate compression and show where it is most severe. MRI shows signal intensity changes which may be due to cystic necrosis of the cord, which is irreversible, but sometimes the signal intensity may be due to venous infarction and this progression can be halted by early surgery.

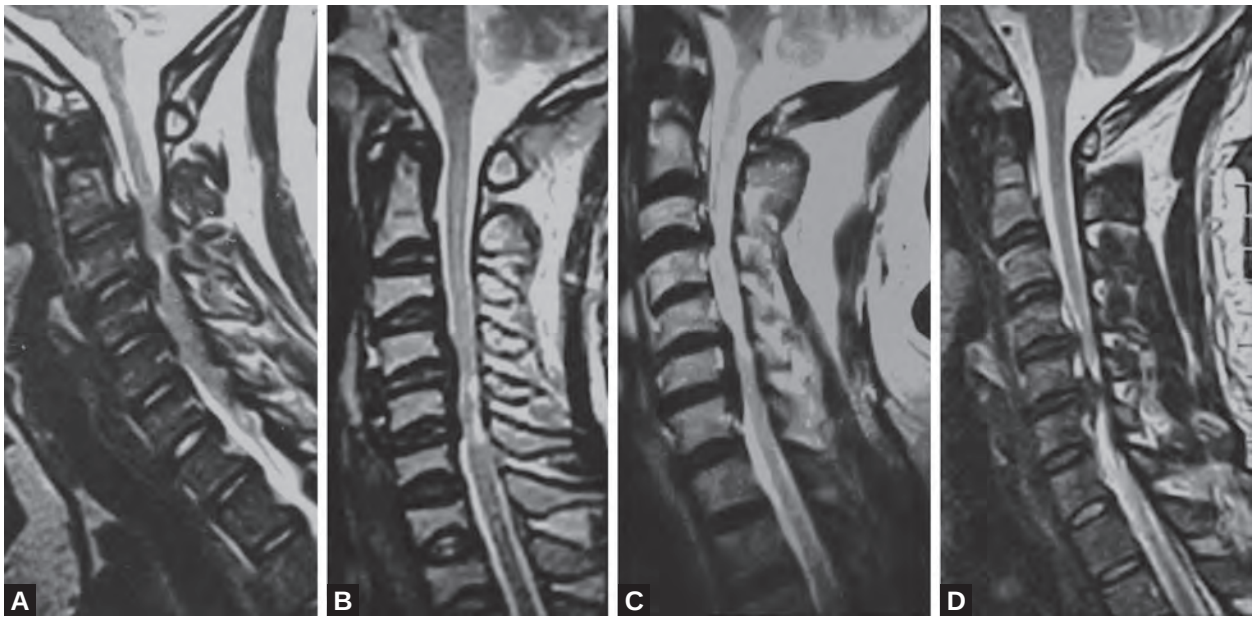
TREATMENT

Conservative

Acute episodes of pain and the onset or increase of neurological deficits are treated with rest, external spinal immobilisation with a collar or brace and administration of analgesics, including anti-inflammatory or antispasmodic medication. Treating asymptomatic patients surgically or advising prophylactic total excision of all OPLL is not advisable as the natural history is variable.[68,72]

Operative

Surgery is aimed at enlarging the spinal canal by decompressing the bony ring and is indicated for patients with acute or chronic progression of neurological deficit. MRI showing signal intensity changes in the cord suggestive of cord oedema in T2-weighted sequence indicates sub-clinical dorsal cord compromise and warrants surgical intervention. Similarly, SSEP responses indicating



Figs 5A to D: MRI showing various types of OPLL. (A) Segmental. (B) Continuous. (C) Mixed. (D) Localised

sub-clinical dorsal cord compromise may also indicate surgical intervention.[5,23,30] Compression by a large bone mass directly on the anterior surface of a chronically constricted spinal cord causes anterior spinal artery compromise that leads to vascular myelopathy and neurological deficit, which could be irreversible. Preventive surgery may be offered to patients wishing to avoid such risks. Even indirect minor trauma to the neck can cause irreversible changes in the spinal cord if there is marked stenosis of the cervical spinal canal.[27,117] Preventive surgery prior to onset of myelopathy is generally unnecessary in most patients with OPLL.[78,79]

Selection of Surgical Procedure

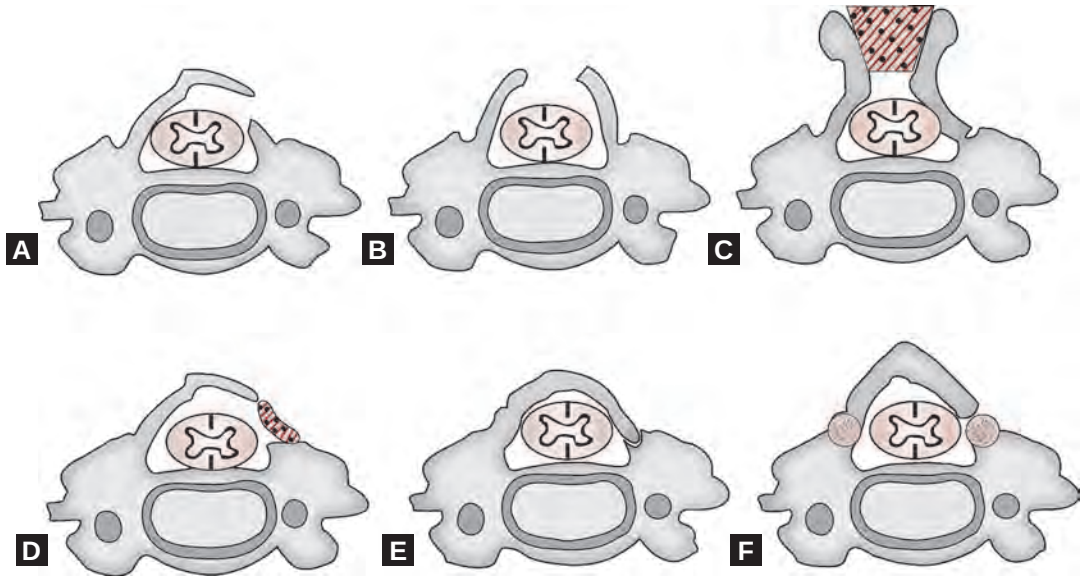
The choice of surgery depends on the age of the patient, location of the lesion and the extent of OPLL causing spinal cord and nerve root compression.[15,19,60,115,116] Developmental size of the spinal canal and the canal diameter compromise due to OPLL causing spinal cord compression are important factors influencing clinical management and the neurological state.[56] Being an anterior pathology, anterior procedures offer direct access and removal of the pathology. Posterior procedures give indirect decompression for multilevel involvement, leaving behind the progressing anterior pathology untouched. The rate of post-operative progression at two years was 56.5% and progression occurred more frequently in the younger-age group than in the older-age group.[10] Kyphotic alignment of the cervical spine and a large OPLL are major factors causing poor surgical outcome after laminoplasty for cervical OPLL.[33,40,41,47] Yang et al.[113] stated that cervical OPLL with disc protrusion is more common at C5-6 levels followed by C3-4, 4-5, 6-7. OPLL with disc protrusion causes greater spinal cord compression at the disc level.

The K-line is a simple and practical tool for making decisions regarding the surgical approach for cervical OPLL patients. The K-line[25] was defined as a line that connects the midpoints of the spinal canal at C2 and C7. The group of patients in whom the OPLL did not exceed the K-line are the *K-line (+) group*. Those in whom the OPLL did exceed it are the *K-line (-) group.* A sufficient posterior shift of the spinal cord and neurological improvement was not obtained after posterior decompression surgery in the K-line (-) group.

Matsunga et al.[72] found in a 10-year cohort study comprising of 450 patients that a significant difference in final functional outcome was not observed between non-surgical and surgical cases in which pre-operative Nurick grades were 1 or 2. In patients with Nurick grades 3 or 4 myelopathy, only 12% of those who underwent surgery eventually became wheelchair bound or bedridden as compared with 89% of those who were managed conservatively. Surgery proved ineffective in the management of patients with grade 5 disease.[72] He also found that more than 60% OPLL induced stenotic canal compromise of the cervical canal and increased range of motion of the cervical spine as the risk factors for evolution of myelopathy in OPLL.

Surgical Technique

Anaesthetic considerations: Fibreoptic pre-operative intubation is electively performed by specifically trained anaesthesiologists when deemed appropriate. Intubation is maintained during the 1st post-operative night. Patients exhibiting three or more major risk factors (repeated anterior surgery, operations lasting more than 10 hours, involving four or more levels (including C-2), obesity, asthma, and blood transfusions of more than four units (1000–1200 ml) are considered candidates for delayed extubation and, rarely, tracheostomy.[23]



Figs 6A to F: Schematic representation of various laminoplasty methods. (A) Open door. (B) Bilateral French door. (C) Splitting the spinous process and lamina with a spacer. (D) Modified open door method with a spacer. (E) Z-shaped laminoplasty. (F) Laminotomy and fusion with ceramics[30]

Posterior procedures: Posterior procedures are preferred when the OPLL is continuous, involves a long segment, in elderly high-risk patients, when the upper limit of OPLL includes C2 and in cases with a normal spinal sagittal balance. These include laminectomy alone, laminectomy with fusion,[3] laminoplasty and various newer techniques of laminoplasty, e.g. Modified Hirabayashi-type Unilateral Open-Door Laminoplasty[31] (Figs 6A to F). They offer adequate decompression in the presence of adequate cervical lordosis and the removal of multiple laminae and hypertrophied yellow ligament allows dorsal migration of the cord. The presence of kyphosis may leave the cord tethered to the anterior pathology and cause neurological deterioration.

A mean dorsal cord shift of greater than 3 mm was co-related with good clinical outcome.[94] Neurological outcome after posterior procedures was equal to multilevel anterior procedures in certain series.[34] After laminectomy, post-operative progression of kyphotic deformity was observed in 47% of patients but these changes did not cause neurological deterioration.[48] However, it is inappropriate for either older or younger patients with predominantly anterior disease, as that will fail to achieve a similar degree of neurological recovery and may promote a more rapid progression of OPLL growth with concomitant neurological deterioration.[14] Laminoplasty has about 96% of bone fusion rate, 83% of preserved range of movements and 42% increase in the canal diameter.[80] Development of the buckling-type alignment was found in 33% of patients following laminectomy and only 6% after laminoplasty.[71] These results favour laminoplasty over laminectomy from the aspect of biomechanics. Cervical range of movement (ROM) reduces after cervical laminoplasty. Post-laminoplasty cervical ROM had a positive correlation with extended motion; however, gradually it became reduced.

Surgical outcome was significantly poorer in patients with occupying ratio greater than 60%. The most significant predictor of poor outcome after laminoplasty was hill-shaped ossification, followed by lower pre-operative JOA score, post-operative change in cervical alignment and older age at surgery. Laminoplasty is effective and safe for most patients with occupying ratio of OPLL less than 60% and plateau-shaped ossification.

Agarwal et al.[2] reported that cord decompression with expansive laminoplasty using titanium miniplate fixation may improve the neurological outcome even in patients presenting late and improvement by even one grade may have major 'quality of life' benefits for these patients. Anderson et al.[3] advocated that laminectomy with fusion is an effective strategy to improve functional outcome in cervical spondylotic myelopathy and OPLL.

OPLL is a progressive disease, and an increase in the area of ossification following laminoplasty affects the surgical results. Around 21.8% had progression in the OPLL thickness. Young patients with continuous or mixed-type OPLL and C3 involvement had a risk for progression in OPLL thickness following surgery. [100,113]

Tension band laminoplasty described by Tsuzuki[105] helps to minimise the severe post-operative contractures seen in laminoplasty. In this technique, the lamina are reflected unilaterally in an open door fashion keeping the interspinous and ligamentum flavum intact and these behave as a tension band. *Double door laminoplasty* was developed by Kurokawa,[61] and in this the spinous process and laminae are split centrally and retracted symmetrically in a double door manner. Increase in segmental motion may lead to deterioration after posterior approaches which may be aggravated by the progressive atrophy of nuchal muscles. In patients with either CSM or OPLL with instability, cervical laminectomy with fusion (arthrodesis) improved the functional outcome.

Anterior procedures: The overall improvement of the neurological status of the patients were better in the anterior procedures than the posterior procedures.[1,20-22,42] Anterior discectomy, corpectomy and fusion are now considered the optimal operative treatment.[6,53] Segmental plate fixation is biomechanically better than end construct plate fixation.[93] Iwasaki et al.[40,41] opined that anterior decompression and fusion yielded a better neurological outcome than laminoplasty and is preferable in patients with occupying ratio of greater than 60%.[41]

In focal segmental lesions that do not extend above or below the disc, a simple interbody discectomy,[113] excision of OPLL and fusion may be adequate. Complete resection of the lesion requires microsurgical removal of the involved posterior longitudinal ligament and the adjacent osteophytes.

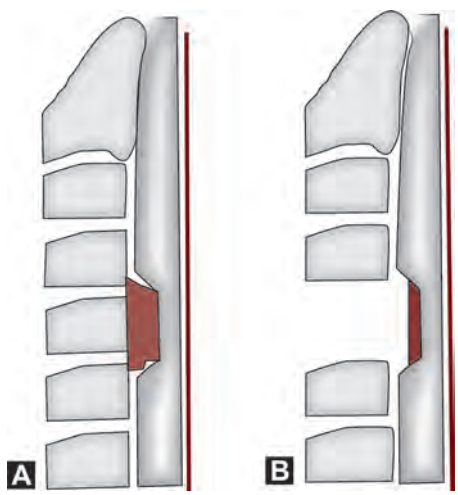
The technique of resection of OPLL with floating of dural ossification provides satisfactory decompression and avoids dural defect or neural injury in OPLL associated with dural ossification.[77] Kamikozzuru[46] and Yamaura[112] developed the original *floating method* and this technique requires more extensive corpectomy to free the ossified dura leading to a ventral migration of the OPLL mass but this procedure does not remove the OPLL and there is an increased risk to the vertebral artery and root injury while doing this extreme lateral resection technique. Hida, et al.[30] advocated the *microfloating technique* that makes the OPLL paper thin by using a high speed drill under a microscope and resecting it (Figs 7A and B).

Anterior procedures after a failed laminectomy carry a greater risk of post-operative instability due to a defective posterior vertebral column, as the ligamentous structures having already been removed.[88] Modifications of corpectomy in the form of open-window corpectomy, oblique corpectomy and floating methods have been advocated for avoiding instability and instrumentation.[26,46,85]

The high anterior cervical approach[86] to the upper cervical spine is a favourable method that provides direct and wide exposure for fusion and anterior decompression of the upper cervical spine. This is a useful surgical technique for an upper cervical lesion without severe morbidity, which allows direct anterior access to C2 and C3 while allowing extension to the lower cervical spine.

In cases where there is extensive and massive ossification, the ossification is continuous from the posterior surface of the vertebral body to the dura. Identification of the plane of the posterior surface of the vertebral body and the posterior longitudinal ligament at the level of the disc space is important, before progressing with the corpectomy and it is advisable to do a complete discectomy with osteophyte removal before corpectomy, as the placement of a vertebral spreader helps in the removal of osteophytes.

The diamond head drill should be used on reaching the posterior cortex of the vertebral body and to proceed with the decompression in a uniform manner over the entire width. This step needs to be followed as, very often, OPLL is eccentric and invaginates deep into the cord on one side and asymmetric decompression allows the cord to get hitched at the edge against the ossification leading to neurological deterioration. If there is dural involvement, careful dissection is warranted and on occasion a small thinned-out fragment of dural ossification can be left behind when the cord is completely decompressed.[77] Inadequate decompression is avoidable if the surgeon orients his corpectomy trench, depending on the MRI/CT findings of the anatomy of the OPLL. Reorienting the microscope frequently to the midline and keeping the width of the corpectomy in between the longus colli muscles facilitates adequate decompression. Continuous intra-operative somatosensory evoked potential (SSEP) monitoring also appears to limit operative morbidity.[5,22] Yonenobu et al.[115,116] suggested that anterior corpectomy results are better (Fig. 8).



Figs 7A and B: Schematic representation of microfloating methods. Before corpectomy: after corpectomy and thinning of the dura[30]

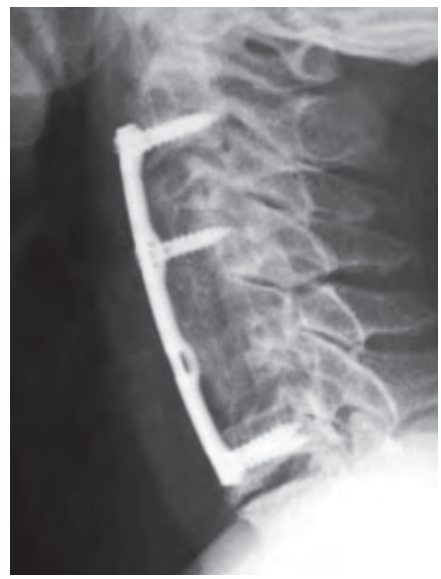


Fig. 8: Post-operative X-ray of a patient who underwent C3,4,5,6 corpectomy and fixation

Open window corpectomy: Ozer et al.[85] described this operation which involves minimal bone removal with high speed drilling, dorsal surface removal after appropriate microdiscectomy leaving the anterior and lateral parts of the vertebral bodies intact. This provides a more stable construct with three point fixation and offers better load sharing.

The oblique corpectomy:[8,26] It preserves the ventral half of the vertebral body and does not require stabilisation. Chacko et al.[8] emphasised that this is a surgical option in patients with asymptomatic OALL in the setting of progressive myelopathy due to OPLL with intrinsic stability as a result of their OALL. It avoids a multilevel central corpectomy that is associated with significant instability often requiring reconstructive procedures. Goel et al.[25] have elaborated on partial oblique strategic corpectomy involving extended midline and lateral undercutting of the vertebral body.

The skip corpectomy technique: Dalbayrak et al.[12] have demonstrated the effectiveness and safety of this technique. This is characterised by C-4 and C-6 corpectomy, C-5 osteophytectomy and C-5 vertebral body preservation; the preservation of the C-5 vertebral body provided an additional screw purchase and strengthened the construct. OPLL often coexists with cervical disc herniation and the disc may be the more important compressing factor. The area of greatest spinal cord compression is at the disc levels because of herniated cervical discs. Staged or combined anterior and posterior decompression may be necessary in a small segment of patients with mixed or continuous long segment OPLL.[32]

Anterior, anterolateral decompression and fusion for ossification of posterior longitudinal ligament in the thoracic spine by transthoracic trans-sternal approach is possible with good neurological outcome compared to posterior decompression and fusion with laminectomy or laminoplasty.[36,102] Complex cases of thoracic ligamentous ossification involving both the ligamentum flavum and the posterior longitudinal ligament may require combined procedures.[102]

Complications

Complications of anterior cervical surgery include a risk of quadriplegia of about 2–10%, root injury of about 17%, typically the C5 root, which has been attributed to rapid cord migration and the so-called "untethering effect".

Temporary paraparesis and new cervical radiculopathy may be caused due to residual foramen stenosis. CSF fistulas, bone graft displacement, pin site infection, graft site complication (iliac bone fracture, meralgia paraesthetica) implant failure, restenosis, tethering, wound infection, epidural haematoma, deformity, respiratory insufficiency, oesophageal perforation, bladder disturbances, Horner's syndrome and retropharyngeal abscess have been reported.[4,5,16,24,38,75,95,115]

Temporary recurrent laryngeal nerve and superior laryngeal nerve palsy due to retraction injury may cause hoarseness of voice and swallowing difficulty. Phrenic nerve dysfunction[24] may be due to bilateral C4 nerve root stretching, iatrogenic injury of the gray matter in the ventral horn, alteration of blood circulation related to spinal oedema or re-impingement on the spinal cord at the cranial part of the decompression site. Phrenic nerve dysfunction should be considered as a possibility when it is difficult to wean a patient from the ventilator after surgery. Kulkarni et al.[58] reported accelerated spondylotic changes in the adjacent segment in 75% of patients after cervical corpectomy and this adjacent segment disease can also develop after expansile laminoplasty.

Post-operative cerebrospinal fluid leak and pseudomeningocoeles: Patients with OPLL are especially prone to dural leaks and these are managed with dural repairs and rarely lumboperitoneal shunting procedure.[18] Post-operative pseudomeningocoele after an anterior approach to the cervical spine is an uncommon complication and may be difficult to treat.

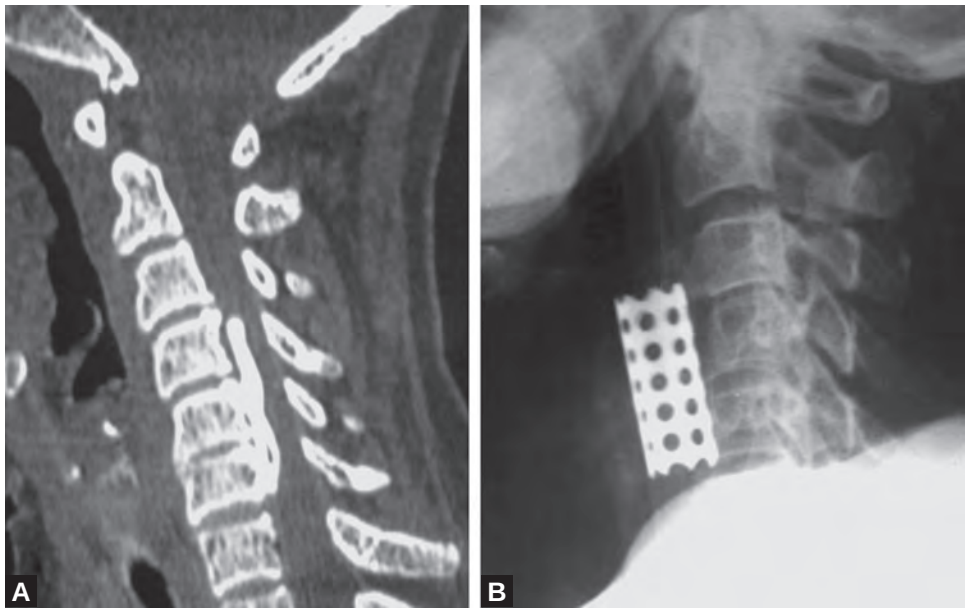
The surgeon is required to recognise dural ossification.[9] and be cautious during drilling of the OPLL. Hida et al.[30] described the (CT) findings that indicated the association with dural ossification and suggested that the 'double-layer sign' appeared more specific. The double-layer sign, as a specific indicator was sensitive in patients with mild OPLL but less frequent in those with severe OPLL. The arachnoid membrane in these cases can be preserved with the aid of the operating microscope to avoid a large area of membrane defect. The rate of dural tear is higher in patients with OPLL compared to other causes of cervical spinal stenosis. Intra-operative CSF leak[44] was encountered in 6.3% of patients in one series. The dural defect can be repaired with an onlay graft of crushed muscle/fascia and a layer of gelatin sponge. Bed rest and a lumbar subarachnoid drain are used for 5 days after surgery.

Graft Extrusion

Normally, the corpectomy defect is reconstituted using an iliac crest graft, titanium cages and very rarely fibular graft. Kumar and Rajshekhar[59] reported that when the surgical series was divided into three eras, the graft extrusion rate in the first era was significantly higher than in the other eras (6%, 1%, 1%, 0%; p = 0.01) implying a significant learning curve (Figs 9A and B). The extrusion rates for one-level, two-level and three-level CC were not significantly different (3%, 1.6%, 0% respectively; p=0.3). Wang et al.[108] emphasised that greater the number of corpectomies and longer graft fusion ending at C7 body has high rates of graft migration.

OUTCOME

Outcome analysis can be done using tools such as the Odom's criteria. Kawano et al.[49] found that the overall mean improvement on the neurosurgical cervical spine scale score (NCSS) was 78% for those who underwent anterior decompression and 46.1% for those who had a



Figs 9A and B: (A) Pre-operative CT of cervical spine showing OPLL. (B) X-ray lateral view of the cervical spine shows anterior extrusion of the cage from the corpectomy defect

posterior decompression. Yagi et al.[109] found that long-term clinical outcome was significantly worse in patients with intramedullary signal intensity changes on MRI. The other risk factors were instability of the cervical spine and severe anterior spinal compression. The long-term clinical outcome was also significantly worse in patients with post-operative expansion of the high signal intensity area.[65] The fact that cervical instability is a risk factor for post-operative expansion of the high signal intensity indicates that this high signal intensity area occurs not only from necrosis secondary to ischaemia of the anterior spinal artery but also from repeated minor trauma inflicted on the spinal cord from segmental instability. The post-operative progression at 2 years was 56.0% with progression occurring more frequently in younger patients than in older ones.[10]. In both these groups of patients at 1–2 years post-operatively it was found that mixed and continuous type OPLL grew more frequently than segmental.[10] Mizuno et al.[78] used the anterior approach in 11 patients and expansive laminoplasty in 10 patients with excellent outcome in 88% and favourable in 12%.

OPLL thickness, effective canal diameter, anteroposterior cord compression ratio, the traverse area of the spinal cord, the spinal cord-evoked potentials (SCEPs), the increase of the range of motion in the cervical spine (ROM), diabetes, history of trauma, the onset of ossification of the ligament flavum (OLF) in the thoracic spine, snake-eye appearance (SEA) and incomplete decompression may be other factors influencing outcome.[63] Age at surgery seems to be closely related to the outcome of the posterior surgical procedure.

Long-term functional outcome even in poor-grade patients (Nurick grades 4 and 5) with cervical spondylotic myelopathy (CSM) or OPLL after central corpectomy has been reported to be good by Rajshekhar and Kumar.[87] Improvement was uniformly correlated with myelopathic symptoms of 12 months' duration or shorter. The other favourable prognostic indicators for improvement after decompression were a diagnosis of CSM and pre-operative Nurick grade 5; however, patients with a pre-operative Nurick grade of 4 were more likely to experience a cure.

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113 Thoracic Disc Prolapse

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INTRODUCTION

Protrusion of the intervertebral disc in the thoracic region is rare. In 1911, Middleton and Teacher[36] described a patient who, while he was lifting a heavy steel plate, sustained an injury to the spinal cord due to rupture of a thoracic intervertebral disc. The incidence of thoracic disc prolapse is about 0.04 of all cases of disc prolapse (1.14). With the increasing use of magnetic resonance imaging (MRI) more cases with subtle lesions are picked up, and Russell et al.[44] found a much higher incidence of 4.5%. A few cases have been reported from India.[4,25,28,46,52]

PATHOLOGY

It may occur at any age, being most frequent during middle age. Due to the resilient bony thoracic cage which permits only limited movements and the relatively small size of the thoracic disc, actual protrusion of the intervertebral disc into the thoracic canal is uncommon, although degenerative changes in the form of Schmorl's nodes and anterior and posterior osteophytes are seen frequently. Such changes are more common in people carrying loads on the back. The cause of nucleus pulposus herniations in the thoracic spine is similar to those occurring in the lumbar and cervical regions. The lower incidence of herniations is ascribed primarily to the reduced allowable flexion at the thoracic level compared with the lumbar and cervical levels and, to a lesser extent, the contribution of the ribs to weight bearing. Repeated trauma predisposes to disc degeneration and, at times, provokes an acute prolapse.[39] Svien and Karavitis[50] and Love and Schorn[35] found T-11 as the most common level affected. Multiple protrusions are rare.[47] The protrusion is commonly central, but may be centrolateral or lateral. Intradural disc herniation in the thoracic region occurs in less than 5%, but is a well-recognised entity in the lumbar region, where over 90% of all intradural herniations are seen. Almond et al. described a case where acute neurological deficit was caused by an intradural thoracic disc herniation at the T11-T12 level, the intradural nature of which was not diagnosed on pre-operative MRI.[1]

CLINICAL FEATURES

The diagnosis of thoracic intervertebral disk herniation is often missed due to its complex and variable presentation. The signs and symptoms are often of a relatively long duration, usually vague and frequently misleading. Pain localised to the back, girdle pains, pain in the abdomen, testicular pain or limb pain may be present. The symptoms may range from mild paraesthesiae to paraplegia.[46] Bladder, bowel and sexual disturbances are late features. Position sense is frequently intact.[12] Mild scoliotic or kyphotic deformities may at times be present and act as a natural protection in accommodating the prolapsed disc segment. The delay in diagnosis is often a consequence of failure to consider protrusion of a thoracic intervertebral disc as a diagnostic possibility. Bilateral drop foot due to thoracic disc herniation has been reported.[41]

Linscott et al. reviewed 78 patient charts with thoracic disc herniations, which is the largest single study in the World's literature. Injury was associated with disc herniation in approximately half of the patients, much higher than reported in previous studies. Back pain was the most common presenting symptom (73% of cases) and weakness was the most common physical finding (42% of cases). Eighty-five per cent of patients had findings consistent with neuropathy and 26% had multiple thoracic disc herniations.[32]

DIFFERENTIAL DIAGNOSIS

Ossification of the ligamentum flavum (OLF) and ossification of the posterior longitudinal ligament (OPLL), occurring in the thoracic region, may simulate cord compression by thoracic discs.[20,43] OLF is common in males and occurs at a lower thoracic level, while OPLL may occur at any level. Plain radiology, myelography, CT myelography and MR are useful for correct localisation. The approach to treatment for OLF is different from that of thoracic discs and OPLL.

INVESTIGATIONS

Calcification may be seen at the site of disc degeneration on plain X-rays. The affected disc space is narrowed. Bony spurs may be seen along its anterior and posterior surface. MR is the investigation of choice and shows the prolapse clearly, even when this is minimal. The extent of the prolapse, and the exact relationship of the bulge to the cord and roots are clearly seen.[9,19] Extradural tumours can easily be differentiated from disc prolapse.

CT and myelography are less sensitive, when compared to MR.

TREATMENT

Surgical Management

Evidence of cord compression is an indication for surgery. Various surgical approaches for the excision of a prolapsed thoracic disc have been described.[45] When indicated, discectomy may be performed via an anterior, posterior or anterolateral approach depending on the location of the disc herniation.

Posterior routes include the transpedicular,[42] lateral extracavitary approach, and the more recently described minimally invasive extracavitary approach.[31] Chi et al. have described a minimally invasive technique via a transpedicular route with the use of tubular retractors and microscope visualisation. This technique provides a safe method to identify the thoracic disc space and perform a decompression with minimal paraspinal soft tissue disruption.[13] They compared the results of this approach with clinical results after open transpedicular discectomy. Hospital stay, blood loss, modified Prolo score and Frankel score were used as outcome variables. Patients who underwent mini-open transpedicular discectomy had less blood loss and showed greater improvement in modified Prolo scores ($p = 0.024$ and $p = 0.05$, respectively) than those who underwent open transpedicular discectomy at the time of early follow-up within 1 year of surgery. However, at an average of 18 months of follow-up, the Prolo score difference between the two surgical groups was not statistically significant. Black described a technique of thoracic discectomy that has evolved from the posterolateral transfacet and the transpedicular approaches. The pedicle and most of the facet joint are spared. He found the technique safe and effective, and no specialised instruments are required.[8] The transpedicular approach also appears to be most suitable for discectomy for dorsolumbar junction disc prolapse. The approach is minimally invasive considering the size of the incision, minimal bone removal and avoidance of vital structures. Post-operative pain is minimal and ambulation can be begun within 24 hours of surgery.[6]

Decompressive laminectomy without dealing with the prolapsed disc has been described.[17,22,34,37,38] The results of such an operation are unsatisfactory and may even be deleterious, as the compressive element persists. Approaching the prolapsed segment through a laminectomy is dangerous as the thoracic disc prolapse is central or centrolateral and the dorsal cord tolerates retraction poorly.

The thoracic disc is best approached by the anterolateral route[15] through the lateral costotransversectomy approach,[54] transpedicular approach[42] or by an anterior route through a thoracotomy (transpleural or retropleural approach).[1]

Intra-operative fluoroscopy or plain radiographs are traditionally used to localise thoracic spine levels during thoracic spine operations. Unfortunately, such localisation can occasionally be difficult in the midthoracic levels due to lack of landmarks, scapular shadows and the body habitus of the morbidly obese. For efficient and accurate intra-operative localisation of thoracic spinal levels during anterior thoracic spine procedures, Hsu et al. have described a method that uses pre-operative percutaneous placement of polymethyl methacrylate (PMMA) into the vertebral body using the standard vertebroplasty technique.[24]

Video-assisted thoracoscopic microdiscectomy is gaining acceptance as a minimally invasive, safe and efficient technique suited for herniated thoracic discs from T4-T5 up to T11-T12. However, here also correct localisation is difficult and wrong level exploration is an ever-present threat. Cornips et al. present a reliable and time-efficient localising technique, which they used in 86 consecutive cases. One day pre-operatively intrathecal contrast is administered and a computed tomography (CT) scan was performed in the prone position. Using local anaesthesia, a hollow needle was advanced above the corresponding rib and through the pleura. The inner wire and corresponding pathological level were easily identified endoscopically. Myelo-CT provides detailed anatomical information, which is often helpful in determining the side of operative approach and the extent of bone removal needed. Needle localisation obviates fluoroscopy, saves OR time and allows the surgeon to focus on the technically demanding procedure. Furthermore, it is relatively a simple and safe technique.[14] During surgery the curetting of the disc must be done very carefully as the disc material might have protruded through the dura and lie embedded in the cord substance.[18,33] Singaunas et al.[49] found best results with costotransversectomy and microsurgical techniques.

Kim et al. used computer-assisted image guided costotransversectomies for thoracic disk herniation from T5-6 to T8-9 level, and found it to be invaluable in planning the corpectomy and aiding visualisation in situations in which the dura or disc were obscured, allowing successful surgical excisions in the most challenging circumstances.[29] As experience accumulates in the use of multiple approaches for the treatment of thoracic disc herniations, the role of each is becoming more clearly defined. The transpedicular approach is most applicable for lateral or centrolateral calcified or soft discs. The more anterior (transthoracic or thoracoscopic) and lateral (costotransversectomy or lateral extracavitary) approaches may be more useful for excision of central calcified discs.[7]

Another approach that has been described is the transmanubrial osteomuscular sparing approach for the treatment of T1-T2 thoracic disc herniation, and is likely to be the only one described in the literature for this disease so far.[51] Newer, minimally invasive techniques with a nearly absent learning curve are evolving. One of these techniques is the mini-TTA. Bartels et al. compared the mini-thoracotomy (mini-TTA) and

thoracoscopy for the treatment of calcified thoracic herniated disc. They found the mini-TTA has some theoretical advantages over thoracoscopy. It is also a minimally invasive approach. Thoracoscopy has a steep learning curve, whereas the mini-TTA is simple to apply. Classic microsurgical bimanual techniques can be used.[5] Sheikh et al. have described a novel minimally invasive procedure for the surgical treatment of thoracic disc herniations referred to as a minimally invasive thoracic microdiscectomy. It uses a series of muscle dilators, a tubular retractor and microscopic visualisation by way of a posterolateral approach in an effort to minimise many of the complications that are associated with the more traditional approaches.[48]

To reduce the invasiveness and risk of thoracic disc surgery, endoscopic approaches have been developed. Thoracic microendoscopic discectomy is a safe and effective treatment for surgical removal of herniated thoracic intervertebral discs.[27] This approach allows access through a minimally invasive muscle-splitting posterolateral approach that does not place the contents of the thoracic cavity at risk. In the lumbar spine, this approach has been proven effective, with a shorter length of hospital stay, less post-operative pain, decreased blood loss and shorter recovery time. These same advantages can be expected in the thoracic spine with appropriate patient selection and proper surgical technique.[11,16]

Jho has described the transpedicular endoscopic approach. The surgical technique of posterior transpedicular thoracic discectomy was modified to endoscopic transpedicular surgery. A 1.5 cm trocar was placed in the interlaminar space via a 2 cm transverse paramedian skin incision. At the ventral aspect of the spinal cord discectomy was performed under direct visualisation by using a 70 degrees lens endoscope. He found this approach to be minimally invasive and effective surgical treatment.[26]

Giant herniated thoracic discs (HTDs) can be defined as occupying more than 40% of the spinal canal. Hott et al. found that patients with giant HTDs who underwent thoracoscopic surgery had worse short-term and long-term functional outcomes than those in whom open thoracotomy was performed. They concluded that patients with giant HTDs presented more frequently with myelopathy and experienced worse functional outcomes than those with smaller HTDs and recommend open thoracotomy rather than thoracoscopy for the treatment of midline giant HTDs.[23]

Utility of interbody fusion after transthoracic discectomy is still debatable. Krauss et al., from their results, indicate that interbody fusion may not be necessary for selected patients undergoing transthoracic discectomy.[30] Ohnishi et al. recommend anterior decompression and fusion for multiple thoracic disc herniations through a transthoracic approach.[40] Further long-term follow-up is needed to evaluate the development of late spinal instability and resultant deformity after this procedure.

Complications

The procedure-related complications include death, neurological deterioration, post-operative vertebral column instability, incomplete disc resection, discectomy at the wrong level, cerebrospinal fluid leak and fistula, infection, pulmonary embolism, pneumothorax, pneumonia and intercostal neuralgia.

Unusual complications include chylorrhea. The thoracic duct along with the cisterna chyli is a major lymphatic pathway near the anterior thoracolumbar spine. Despite the fragile nature of the lymphatic system and its proximity to the spinal column, chylorrhea is rarely encountered by spine surgeons. Amini et al. reported a unique case of chylorrhea associated with a left thoracoscopic, transdiaphragmatic discectomy and fusion for a T12-L1 herniated disc.[2]

Outcome of Surgery

The differences in the surgical outcome based on disc characteristics using pre-operative CT scanning and MRI have been analysed by Yi et al. The direction of the disc was classified as either central or lateral, and disc consistency classified as either soft or hard. Clinical outcome was assessed according to the Japanese Orthopaedic Association (JOA) Score for thoracic myelopathy, by analysing motor, sensory and bladder function. Recovery rate was assessed, comparing pre-operative and post-operative status based on disc characteristics, and the correlation between outcome, symptom duration and recovery rate. Clinical outcome, according to the JOA Score, showed significant post-operative improvement, increasing from 7.0 +/- 3.1 points to 8.2 +/- 2.7 points post-operatively ($p < 0.01$). The mean recovery rate was 12.4 +/- 56.9%, and 16 patients (55.2%) showed improvement. In the soft disc group, there was improvement in all categories, but the hard disc group showed no improvement. The central disc group showed improvement in sensory function, but the lateral disc group showed little improvement. Regression analysis revealed a statistically significant correlation between the pre-operative and the post-operative score, symptom duration and recovery rate. Clinical outcome after surgery of a herniated thoracic disc proved successful, especially when the disc was considered to have a soft consistency. They concluded that in order to decide the optimal surgical strategy and prospective surgical outcome, disc characteristics, including consistency and direction of prolapse should be considered pre-operatively.[53]

Conservative Management

Conservative treatment rarely helps, as the relatively narrow dorsal canal cannot accommodate intrusions and as the thoracic cord is very sensitive to mechanical compression and vascular compromise.

Haro et al. have treated two cases conservatively. The herniated discs exhibited marked decrease in size,

corresponding to a favourable clinical outcome within a few months after the initiation of conservative treatment with prostaglandin E[3] and/or steroids in conjunction with physical therapy. The authors conclude that thoracic herniated discs are capable of undergoing natural resorption and that conservative treatment could be indicated, even in the presence of moderate myelopathy, when the myelopathy is not accompanied by bladder dysfunction or progressive muscular weakness.[21]

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114 Lumbar Disc Disease

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INTRODUCTION

The term "lumbar degenerative disc disease" includes a spectrum of disorders like disc bulge, disc protrusion (central, paracentral, intraforaminal or far lateral), disc extrusion (with or without mitigated fragment) and internal disc disruption. Patients suffering from this condition present with low-back pain or radiculopathy of long duration or, acutely, as cauda equina syndrome. This chapter focuses mainly on the various management strategies of this commonly encountered condition in the outpatient department, their outcomes and the unresolved controversies.

HISTORICAL PERSPECTIVES

Thousands of years ago, Susruta (800 BC), the Father of Surgery in India and Charaka, a great physician of ancient India, identified the condition "sciatica" and named it *gridhrasi*. They attributed the pathogenesis of this condition to *vata dosha* wherein the local factors of blood, muscles, bones, ligaments and tendons are involved in a vicious manner. The symptoms of sciatica were also mentioned in the ancient Greek and Roman textbooks, but were often grouped with pain originating from the hip joint. The other notable events in the history of lumbar disc disease are summarised in Table 1.

ANATOMY AND BIOMECHANICS OF THE LUMBAR INTERVERTEBRAL DISC

The intervertebral disc (IVD) is composed of three elements which include the nucleus pulposus, annulus fibrosus and cartilaginous end-plate. The nucleus pulposus is the central portion of the disc which is composed of cells from the primitive notochord. It is composed of type II collagen and a very hydrophilic polymer called glycosaminoglycan, which is capable of absorbing a large amount of water and forming a gel-like matrix. The amount of water absorbed by the nucleus depends not only on the composition of the polymer matrix but also on the external pressure exerted on the disc. At a young age and when the disc is healthy, 80% of the nucleus is constituted by water, even under normal loading conditions, which keeps the annulus well inflated. It becomes more solid and fibrous with age (Fig. 1).

The annulus is a fibrous structure composed largely of type I collagen that restrains lateral forces produced by the compressed nucleus which is located within it slightly dorsal to the midline. It is a multilayered structure, much like an automobile tyre, composed of 10–12 concentric layers of well organised collagen fibres running in opposite directions in adjacent layers at approximately 30 degree to the horizontal plane. This arrangement provides the annulus with a high tensile modulus and strength, as well as equal torsional modulus in either direction. The annular bands are subdivided into inner fibres, which are connected to the

Table 1: Notable events in the history of lumbar disc disease[2]

1555—Vesalius described the intervertebral disc
1764—Contugno associated the symptoms of sciatica to irritation of the sciatic nerve by "acrid humors" derived from blood
1858—Luschka observed degenerative processes of the disc in autopsy specimens
1909—Oppenheim and Krause performed the first surgery, documented in literature, for disc herniation
1929—Myelography was described, Dandy attributed cauda equina syndrome to material derived from the intervertebral disc
1934—William J Mixter, a neurosurgeon at Harvard Medical College, and his orthopaedic colleague Joseph Barr elucidated the pathophysiology of lumbago and sciatica and described an intradural approach for removal of the offending ruptured disc
1948—Discography was described by Lindblom which provided an insight into the pathology of degenerative disc disease
1956—Concept of artificial disc was set forth by Van Steenbrugghe
1964—The concept of chemonucleolysis was demonstrated in a rabbit model by Smith which was later applied in humans
Early 1970s—The introduction of magnetic resonance imaging revolutionised the management of lumbar disc disease
1975—Hijikata described the first percutaneous discectomy
1977—The technique of microsurgical discectomy was described by Yasargil in Switzerland, Caspar in Germany and Williams in the United States
1984—Aschner and Heppner introduced the concept of percutaneous laser assisted discectomy with NdYAG and carbon dioxide lasers
1990s—Tubular microdiscectomy was popularised wherein a smaller incision was made with muscle splitting (MED, MEDRx systems) rather than subperiosteal dissection
2000—Saal and Saal described the concept of intradiscal electrothermal therapy

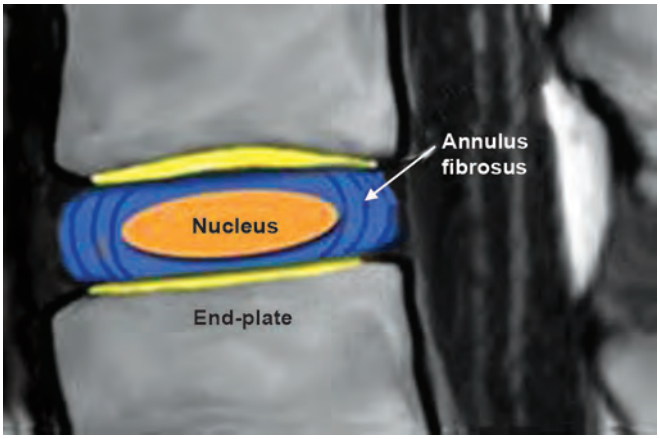

Fig. 1: Normal disc on magnetic resonance sagittal

cartilaginous end-plate, and outer Sharpey fibres, which are attached to the vertebral body.

The mechanical properties of a disc are a function of the structure and integrity of both the annulus and nucleus in combination. A change in either one of these parameters can affect the overall properties of the disc. The anterior longitudinal ligaments (ALLs) and posterior longitudinal ligaments (PLLs) further strengthen the disc space. The ALL attaches more strongly to the vertebral body edges than to the annulus and acts like a tension band to resist forces applied in extension. The PLL, which is not as strong as the ALL, strongly attaches to the annulus fibrosus and acts like a tension band to resist flexion forces. It is frequently torn in cases of free fragment disc herniation. The cartilaginous end-plate is made of thin hyaline cartilage which binds the IVD to the vertebral body above and below it. The function of the end-plate is more biological than biomechanical in that it plays an important role in allowing nutrients to pass into the disc.

The disc has a low metabolic rate and receives most of its nutrition by diffusion. The majority of the disc nutrition is supplied via the capillary beds of the cartilaginous vertebral body end-plate. The capillaries receive blood from the lumbar arteries which arise from the aorta and supply the vertebra in a segmental fashion. Vascular and lymphatic tissue is present in the annulus of young patients but the nucleus pulposus does not have blood vessels or lymphatics at any age.

A meningeal branch of the spinal nerve, known as the recurrent sinuvertebral nerve of Luschka, which arises from the posterior ramus of each nerve root, innervates the dura, PLL and the fibres of the annulus fibrosus. The outer annular regions are innervated but the inner regions and the nucleus pulposus are not innervated. Degenerated human lumbar discs have been found to contain more nerve tissue and more vessels than normal discs.

PATHOPHYSIOLOGY OF DEGENERATIVE DISC DISEASE[7,13]

The IVD performs two important but somewhat conflicting duties, i.e. it maintains spinal column stability while providing the column with necessary flexibility. By keeping the vertebral bodies separated from each other, the IVD holds the foraminal space open and prevents compression on the exiting nerve roots.

Lumbar disc degeneration and herniation are multifactorial processes to which both mechanical and biochemical derangements contribute. Disc degeneration often occurs in patients at a much younger age than knee or hip degeneration. Although the degenerative processes progress with age, the incidence of disc herniation does not; it peaks in the fourth decade. Degenerated discs show abnormal vascularity, abnormal distribution of collagen and collagen cross links and, abnormal and non-uniform elastic modulus that distributes stress to critical portions of the disc. Repetitive or continuous axial overloading is the key determinant in the pathogenesis of lumbar degenerative disease. Obese individuals, manual labourers, truck drivers and those involved in athletic activities like weight lifting and gymnastics are at risk for repetitive axial overloading of the spine. Defects in DNA for collagen have been identified in family clusters predisposed to degenerative disc disease. Multilevel disc herniation occurs at a younger age in such family clusters.

The process of disc degeneration occurs in both the annulus fibrosus and the nucleus pulposus. With advancing age, the mechanical strength of the annulus decreases and the nucleus also loses its water binding capacity. As a result, the stress in the vertebral column, which in normal individuals is transmitted to the centre of the end-plate, is transmitted to the peripheral portion of the vertebral body and the weakened annulus, resulting in disc herniation and compression on the adjacent nerve root. This, in turn, accelerates the degeneration of the facet joints (Figs 2 and 3).

Radicular pain associated with disc herniation has been attributed, in part, to the inflammatory response at the site of disc herniation, resulting in an increase in the number of macrophages and IL 1β with subsequent release of PGE_2. However, the severity of inflammatory

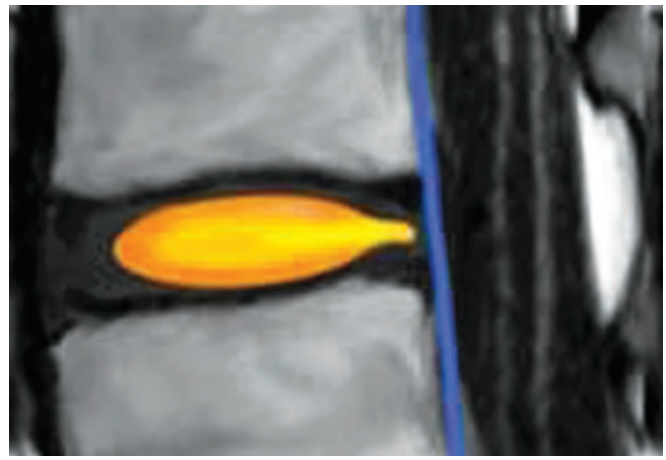

Fig. 2: Disc herniation is displacement of disc material beyond the limits of the disc

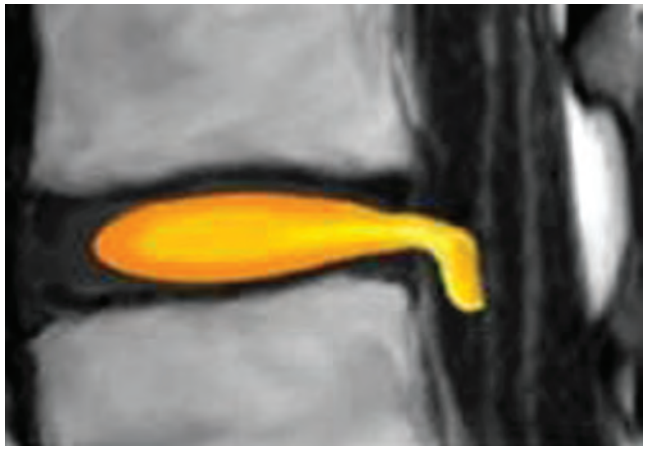

Fig. 3: Migration indicates displacement of disc material away from the site of extrusion

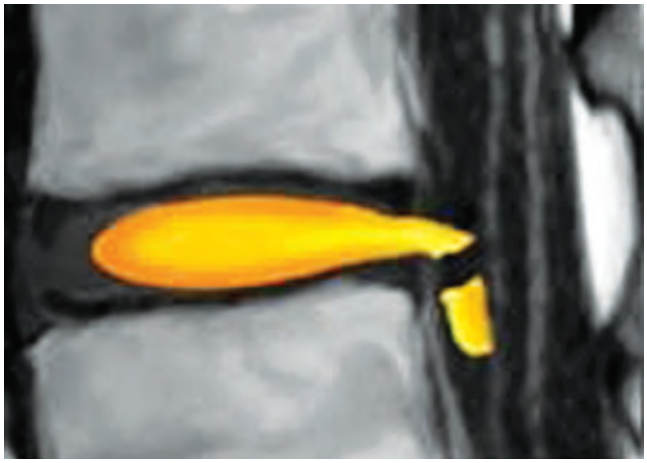

Fig. 4: Sequestration is used to indicate that the displaced disc material has lost completely any continuity

response does not correlate with the severity of symptoms. Interestingly, the presence of inflammation in patients does correlate with a better post-operative outcome when compared with those with herniated discs showing no inflammation.

An autoimmune component to lumbar disc disease has been suggested based on the findings of increase in anti-glycosphingolipid antibodies in two-thirds of patients with lumbar disc disease and radicular symptoms. However, this autoimmune theory is challenged by some researchers. The role of apoptosis in lumbar disc degeneration is not fully understood. Inappropriate disc matrix produced in degenerated lumbar discs stimulates apoptosis. It may be the possible mechanism of spontaneous resorption and remodelling of the extruded material in free disc herniations.

The majority of disc herniations occur in a posterolateral direction, i.e. corresponding to the region of the spinal canal between the midline and the neural foramen, because the nucleus pulposus is situated somewhat posteriorly within the annulus and the PLL reinforces the annulus fibrosus in the midline posteriorly. The degree of disease in the lumbar spine is characterised by the location of the abnormal portion of the disc. A disc bulge is a symmetrical extension of the disc beyond the endplates, whereas a disc protrusion is a focal area of extension still attached to the disc. An extruded or free fragment disc herniation refers to the part of the herniated disc that is no longer connected to the disc, and herniated disc material that is contained within the PLL is termed a sequestrated or subligamentous disc herniation (Figs 4 to 8).

CLINICAL FEATURES

Symptoms

A patient with a herniated lumbar disc may present with radiculopathy, neurogenic claudication or cauda equina

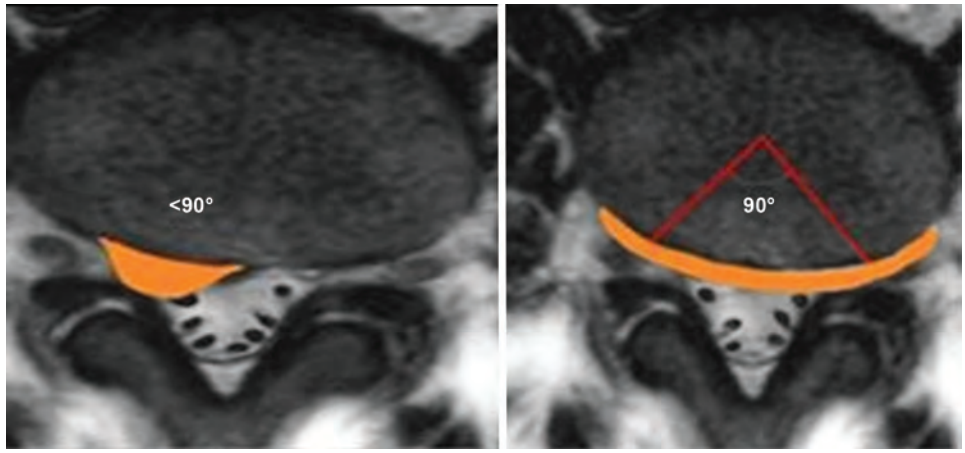

Fig. 5: Focal herniation is a herniated disc less than 90° of the disc circumference. Broad-based herniation is a herniated disc in between 90° and 180° of the disc circumference. Bulging disc is the presence of disc tissue "circumferentially" (180°–360°) beyond the edges of the ring apophysis and is not considered as a form of herniation

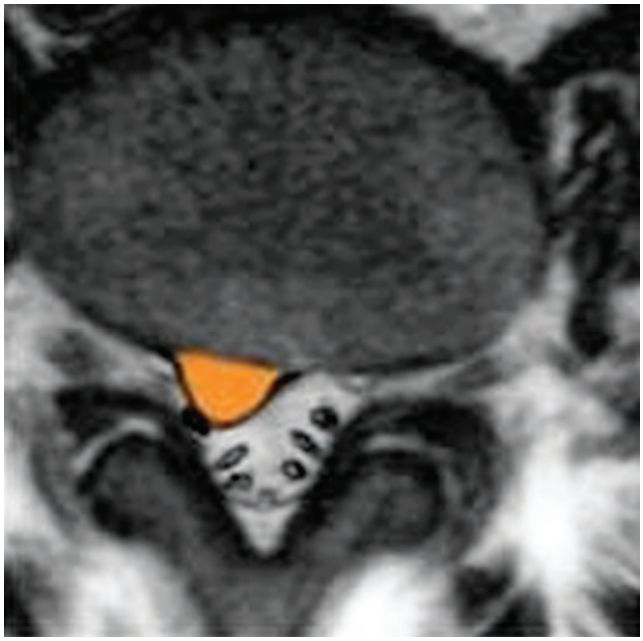

Fig. 6: Disc protrusion indicates that the distance between the edges of the disc herniation is less than the distance between the edges of the base

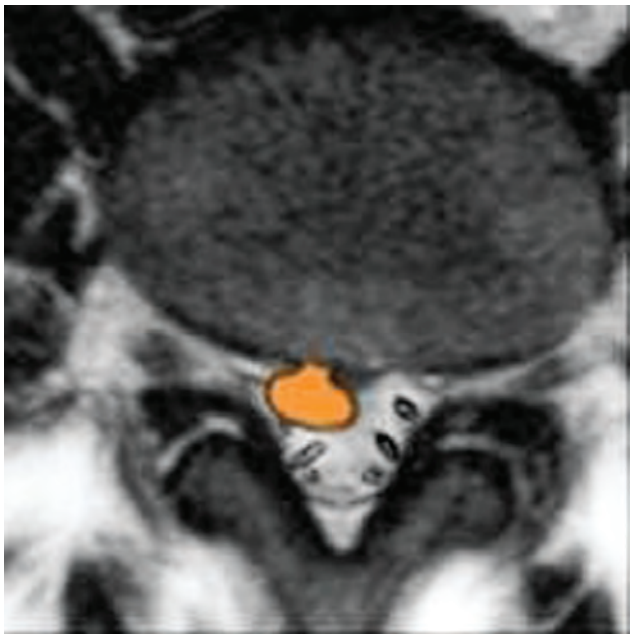

Fig. 7: Disc extrusion is present when the distance between the edges of the disc material is greater than the distance at the base

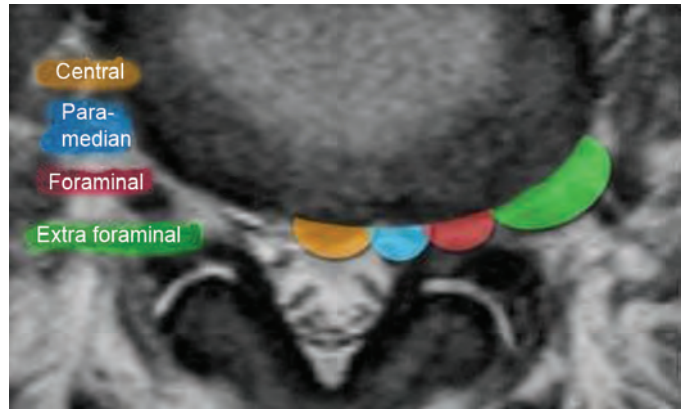

Fig. 8: Axial localisation of herniated lumbar disc

syndrome. The initial symptom in a patient with a disc herniation is pain, which may be in the back, buttock, thigh, leg or foot which is present either in all areas or a few of these areas. Radicular pain is aggravated by bending, coughing, sneezing and lifting a grounded object. The pain is usually relieved by lying down in a hip-knee flexed posture. The back pain often resolves to be replaced later in the course of the disease by weakness and numbness in the lower extremity.

The radiation of pain helps the clinician localise the nerve root that is involved and, in many but not all cases, the level of the herniated disc (Table 2). A posterolateral disc herniation compresses the ipsilateral nerve root at its exit from the dural sac (under the pedicle of the lower vertebral body) rather than in the neural foramen. For instance, a patient with posterolateral left L4-L5 disc herniation would present with left L5 radiculopathy. On the other hand, a far lateral disc herniation often affects the ipsilateral nerve root exiting through the adjacent neural foramen (under the pedicle of the upper vertebral body), i.e. a patient with left far lateral L4-L5 disc herniation would present with left L4 radiculopathy. Paraesthesias in the form of tingling, pins and needles sensation or numbness is of great value in localising the level of root compression. The more distal its location, the more reliable it is in helping with root localisation.

Patients who have large central disc herniation and resultant spinal canal stenosis present with neurogenic claudication which is asymptomatic at rest. They experience bilateral lower extremity pain after a variable duration of exertion, associated with numbness which

Table 2: Common neurologic changes in herniated lumbar disc

	Motor weakness	*Sensory loss*	*Reflex depression*	*Muscle wasting*
L2	Hip flexion and abduction	Lateral thigh	Nil	Thigh
L3	Knee extension	Patellar region	Knee	Thigh
L4	Knee extension, ankle dorsiflexion	Medial shin below knee	Knee	Thigh
L5	Extensor hallucis longus	Dorsum of foot, lateral calf	Tibialis posterior, lateral hamstrings	Calf, minimal thigh
S1	Plantar flexion at ankle	Lateral border of foot, posterior calf	Ankle	Calf

is relieved with a brief period of rest. A central lumbar disc herniation may result in cauda equina syndrome with perineal numbness, loss of bowel and bladder control and some degree of motor weakness in legs.

Signs

The clinical examination of a patient presenting with back pain is described in the chapter "Clinical Features and Diagnosis of Spinal Cord Tumours". Examination of the sensory system is the most subjective part of the neurologic examination, while assessment of muscle strength is less subjective and eliciting the reflexes is the least subjective. It is important to look for paraspinal muscle spasm, range of movements of the spine and perform a rectal examination when cauda equina syndrome is suspected. It is important to interpret straight leg raising test of Lasegue—a positive test implies reproduction of radicular pain and not back pain.

DIFFERENTIAL DIAGNOSIS

Although back pain is the most common symptom of a herniated lumbar disc, it is also the least useful symptom in making the diagnosis. The following conditions also present with symptoms similar to a herniated lumbar disc:

- Tumours involving the nerves (neurofibroma, Schwannoma, ependymoma) or metastatic deposits in the pedicle
- Peripheral neuropathy in diabetes mellitus and entrapment neuropathies involving the sciatic nerve in the pelvis
- Osteoarthritis of the hip
- Fractures involving the vertebra caused by trauma, osteoporosis or metastatic deposits
- Arachnoid cyst and Tarlov's cysts of the spinal region
- Vascular claudication

INVESTIGATIONS

Radiographs of the Lumbar Spine

Manifestations of degenerative disc disease that may be identified on plain X-ray films include IVD space narrowing, accumulation of gas within the disc (vacuum disc phenomenon), calcification of the disc, sclerosis of the adjacent vertebral body end-plates (collectively termed intervertebral osteochondrosis) and end-plate osteophytes secondary to anterolateral disc protrusion with traction by Sharpey's fibres at the site of the osseous attachment of the disc (spondylosis deformans). However, plain films are insensitive to early changes of disc degeneration and are incapable of demonstrating herniated nuclei pulposi and many cases of spinal stenosis.

Standard anteroposterior and lateral radiographs rule out other causes of back pain. Dynamic flexion and extension views are needed to rule out associated spondylolisthesis.

Myelography

It is possible to delineate the thecal sac, spinal cord and exiting nerve roots on myelography. The myelographic signs of disc herniation include:

- Compression of the nerve root and thecal sac with an angular indentation on the anterolateral aspect of the thecal sac
- Compression of the nerve root with fusiform widening of the more distal end of the involved root
- Central compression of the thecal sac by a centrally located herniated nucleus pulposus

Myelographic findings of disc herniation correlate well with operative findings at the L4–L5 level but are less accurate at L5–S1, owing to the wider epidural space and greater amount of epidural fat at this level, which minimises deformity or displacement of the sac by a disc herniation. Myelography is insensitive to the detection of lateral disc herniations and foraminal stenosis. The sensitivity and specificity of myelography have improved considerably since the introduction of water-soluble contrast agents and the use of myelography followed by computed tomography. However, in many cases, either computed tomography or magnetic resonance (MR) imaging can provide adequate information concerning degenerative disease of the spine.

Computerised Tomography

Computerised tomography revolutionised the evaluation of patients with degenerative disc disease. With myelography and plain films, only the secondary effects of the degenerative process on osseous structures, the thecal sac and exiting nerve roots are identified. Computed tomography demonstrates both the primary abnormality and the secondary effects. It is more accurate than myelography in the detection of lumbar disc herniations, owing to its ability to show lateral disc herniations and to evaluate the L5–S1 level reliably. The accuracy of computed tomography is greater than 90% in the detection of lumbar disc herniations. Computed tomography accurately demonstrates the central canal, lateral recesses, neural foraminal stenosis, facet joint disease, ligamentous hypertrophy and reactive bone changes associated with disc degeneration, including end-plate sclerosis, osteophyte formation, and facet joint narrowing or hypertrophy.

Magnetic Resonance Imaging

The development of high-resolution surface coil MR imaging, with its multiplanar capability and high contrast sensitivity, has made this the single best method for the evaluation of degenerative disease of the spine. The MR imaging is the preferred initial study for the evaluation of degenerative diseases of the lumbar spine including disc herniations and central canal, lateral recess and neural foraminal stenosis. Prospective comparisons of surface coil MR imaging, computed tomography and myelography have demonstrated that MR imaging is

as accurate as computed tomography and slightly more accurate than myelography in detecting disc herniations and stenosis. Moreover, MR imaging is more sensitive than myelography in detecting lateral disc herniations at all levels as well as disc herniations at the L5–S1 level. At this level and, occasionally at more superior levels, the epidural fat acts as an endogenous contrast agent on both computed tomography and MR imaging, allowing for the detection of small herniations. However, this fat reduces the sensitivity of myelography, since it is interposed between the opacified thecal sac or nerve roots and the adjacent herniated nucleus pulposus.

The MR imaging findings[11] of a degenerated disc are:

- Decrease in signal intensity on T2-weighted scans of the nucleus pulposus, compared with a normal disc, because of desiccation of the degenerated disc and resultant diminished water content
- Irregularity of the outline of the nucleus pulposus
- Decrease in disc height
- An intense dot like high intensity signal in the posterior annulus signifying an annular tear
- Modic changes in the cortical end-plate and the adjacent marrow.[11]

A disc herniation is best detected on axial images (either computed tomography or MR imaging) because in this plane the focal, usually eccentric posterior extension of the disc material is readily visualised. The protruding disc obliterates the epidural fat, displaces the nerve root sleeve, or both. Sagittal T1-weighted and T2-weighted MR images often demonstrate posterior bulging of the IVD. This *per se* is not conclusive evidence of a disc herniation, since this finding may be seen in degenerative disc disease in the absence of rupture of the annulus fibrosus. Sagittal T1-weighted and moderately and heavily T2-weighted images provide information regarding the level of herniation, presence of extruded or sequestrated fragments, if any. T2-weighted scans are, however, degraded by pulsation artifacts; and the axial T1-weighted scans, while providing an excellent image of the spinal cord, may be relatively insensitive to the presence of spinal stenosis and lateral spinal canal lesions, including osteophytes and herniated nuclei pulposi. Gradient-echo imaging provides excellent views of the spinal cord free from pulsation artifacts, with the high-intensity cerebrospinal fluid (CSF) and low-intensity spinal cord. On axial gradient-echo images, high intensity in the lateral recesses allows for identification of degenerative stenosis and lateral disc herniations.

Discography[14,17]

It is the technique of injecting the IVD with radiopaque contrast which provides physicians with several useful pieces of information. First, this modality provides radiographic evaluation of the integrity of the nucleus pulposus and annular rings to determine tears or other lesions that could be responsible for low-back pain. Second, and more important, is its measure of disc nociception and that targeted therapy directed at that disc is warranted. A normal disc should not cause pain when injected; however, a disc that is physiologically compromised can elicit the pain previously experienced by the patient. No more than three discs should be injected during any single study.

Significant controversy exists as to whether discography contributes any more than diagnostic information that is ascertained using the non-invasive and certainly less painful MR imaging. Discography has been viewed upon as a potential solution to the diagnostic dilemma concerning which patients to treat surgically and at what segmental level. Discography is exquisitely sensitive, but not very specific, when used to diagnose discogenic low-back pain.

The primary indication for lumbar discography is chronic low-back pain with or without radicular pain in the absence of MR imaging–documented neural compression, i.e. it can be used for identifying disc lesions and pain generators when MR images are equivocal. Discography is also indicated in the following scenarios:

- When clinical findings point to one level or one side and myelography or MR imaging indicates a different level
- When the disc protrusion is asymmetrical to the contralateral side of the patient's symptom

In some cases, far-lateral disc herniations may be confused with nerve sheath tumors or haematomas. Again, discography is indicated to resolve these diagnostic dilemmas. It is also helpful in the investigation of adjacent-level disease and the elimination of patients with psychogenic complaints from surgical therapy. In patients with a positive discography finding and equivocal MR imaging or plain radiographic findings, a thorough psychological evaluation is recommended. Such patients should not be considered for any type of surgical intervention.

Electromyogram/Nerve Conduction

This study may sometimes be required to rule out peripheral neuropathy.

MANAGEMENT

Progress made in the management of disc ailments can be divided into four distinct stages:

1. Stage I involved the correct diagnosis of the problem and the selection of surgical treatment.
2. In Stage II, advances were made in diagnostic methods and in the understanding of the physiological and biomechanical aspects of the disc.
3. Stage III consists of a period during which both progress made in stage I and II continued with new trends of disc replacement by prosthetic devices.
4. In Stage IV, more aggressive research into the field of disc degeneration and possible regeneration with stem cells is being carried on.

Table 3: Management options for a patient with degenerative disc disease

Non-operative management	*Operative management*
• Bed rest • Physiotherapy - In the acute phase: Use of hotpacks, short wave diathermy, microwave therapy. After the acute phase: graduated regime of back exercises is instituted • Use of lumbar corset whenever the patient is active • NSAIDs • Muscle relaxants • Epidural corticosteroid injections	• Open techniques • Endoscopic techniques • Microdiscectomy • Minimally invasive techniques – Chemonucleolysis – Automated percutaneous lumbar discectomy – Laser assisted percutaneous discectomy – Arthroscopic microdiscectomy – Intradiscal electrothermal therapy – Percutaneous nucleoplasty

Summary of the treatment options available in the management of patients with degenerative disc disease is given in Table 3.

Conservative Management

An important decision for the clinician is whether to advise bed rest for patients with low back pain. One rationale for bed rest is that many patients experience relief of symptoms while in a horizontal position. Another rationale is that the supine position minimises intradiscal pressure. However, the Cochrane review of nine trials with 1435 patients, comparing bed rest with other treatments or different lengths of bed rest concluded that bed rest compared with advice to stay active at best has no effect, and at worst may have slightly harmful effects on low-back pain.[4] There is no important difference in the effects of bed rest compared with exercises in the treatment of acute low-back pain, or 7 days compared with 2–3 days of bed rest in patients with low-back pain of different durations with and without radiating pain.

Microdiscectomy

Microsurgical approach for lumbar discectomy is currently the gold standard in the management of herniated lumbar disc disease (Table 3). Success rates in microdiscectomy range from 88 to 98.5% while the complication rate is around 1.5%. The biggest advantage is the shorter incision and hence reduced post-operative pain which reduces the hospital stay.

Surgical Outcomes

Between 10% and 30% of patients undergoing primary discectomy for radiculopathy continue to experience unsatisfactory results. A meta-analysis of outcomes after limited disc removal and aggressive disc removal has reported a 2.5-fold increased incidence of long-term recurrent back and leg pain after aggressive discectomy while limited discectomy resulted in 2-fold increase in incidence of recurrent disc herniation.[8,10] However, the short-term outcomes did not differ between the two techniques. The O'Connell technique of aggressive discectomy has been criticised for causing nucleus and end-plate injury, accelerating degenerative changes at the operated disc level, leading to disc space collapse with loss of foramen height, and potentially leading to an increased incidence of post-operative back and leg pain. The more conservative Williams and Spengler technique of limited discectomy emphasises removal of the disc fragment alone with little invasion of the disc space, hence is associated with a higher incidence of disc reherniation. The extent of disc removal must be based on a case by case decision regarding the intra-operative appearance of the herniated lumbar disc after discussing the pros and cons of each procedure with the patient.

Potential predictors of poor outcome include misdiagnosis (for example, diabetic polyneuropathy mistaken for radiculopathy), pre-operative psychological distress, insufficient rehabilitation, mechanical instability, impaired fibrinolytic activity, diabetes, obesity and hypertension.

The complication rate following microdiscectomy is 15–30%.

Intra-operative complications:

- Exploration of the wrong side or level
- Dural tears resulting in post-operative CSF leak, pseudomeningocoele
- Injury to the nerve root
- Retroperitoneal injury to great vessels and bowel
- Facet joint fracture
- Haemorrhage

Post-operative complications:

- Discitis (septic or aseptic)
- Arachnoiditis
- Soft tissue infection
- Failure of pain relief
- Recurrence of pain due to failed back surgery syndrome.

Minimally Invasive Spinal Surgery[16]

The traditional surgical technique of discectomy involves extensive resection of the posterior bone and muscular structures leading to increased post-operative

pain, intra-operative blood loss and morbidity. Extensive paraspinal muscle detachment from the midline osseous elements can cause weakness secondary to muscle denervation. Damage to the "tension band" consisting of the supraspinous and interspinous ligaments may lead to increased instability of the spine during lumbar flexion resulting in failed back syndrome. Hence, minimally invasive spinal surgical techniques have been developed with the idea of minimising tissue trauma without compromising the goal of a successful surgical outcome. Long-term prospective controlled data are lacking to establish the success rates of minimally invasive procedures on the spine compared with the traditional ones. Moreover, a learning curve is required to be familiar with these procedures.

Chemonucleolysis

Chemonucleolysis with chymopapain is based on the principle that depolymerisation of the proteoglycan and glycoprotein macromolecules of the nucleus pulposus reduces the water content of the extracellular matrix of the nucleus pulposus and reduction in the IVD height and bulge. In addition, chymopapain may also have an anti-inflammatory role in the nerve apart from the possibility of producing a total or partial neurectomy like effect by interacting with the sensory fibres of the annulus. It is reserved for patients with soft herniated disc as demonstrated by imaging. Contraindications include patients older than 60 years of age (poor response rate due to low mucoprotein content of the disc), migrated disc, canal stenosis, past history of discitis and allergy to papain. Success rates ranging from 82 to 87.2% have been reported. An inadvertent intrathecal injection results in hemiparesis, paraplegia, raised intracranial pressure, meningitis and haemorrhage.

Percutaneous Nucleotomy

The technique of percutaneous nucleotomy was first described by Hijikata in 1975 and popularised by Kambin and his colleagues. This procedure is most ideal for contained disc fragments. Sequestrated disc fragments, spinal stenosis, spondylolisthesis and past history of spinal surgery are contraindications. Success rates reported in literature range from 77.5 to 87% with a complication rate of 1%.

Percutaneous Laser Assisted Discectomy

It involves placement of a needle in the disc space coupled with passage of laser energy generated by carbon dioxide, Nd YAG, KTP laser or Holmium YAG laser. A 70–80% rate of long-lasting pain relief has been demonstrated with a complication rate of 3.5%.

Intradisc Electrothermal Coagulation

It is a therapeutic innovation specifically designed to treat discogenic pain.[19] Targeted thermal energy is delivered from an electrosurgery unit into the disc space by percutaneously threading a flexible heating electrode into the disc, such that the electrode passes circumferentially around the inner surface of the disc. The energy thus delivered is thought to reduce discogenic pain either by thermal coagulation of the nociceptors or by increasing the stability of the disc via contraction of type I collagen fibres. Successful relief of pain in up to 60% of the patients has been reported.

CONTROVERSIES IN MANAGEMENT

Surgery is recommended if symptoms persist after 6 weeks of supervised conservative management, although the optimal timing of surgery is still being debated. The major advantage of early surgery is quick pain relief, but the clinical results after 1 year are similar, which legitimates prolonged conservative treatment in selected patients.

The optimal treatment of patients with lumbar disc herniation and neurological deficit is not known. A study on recovery from paresis due to lumbar disc herniation has demonstrated no difference between surgically and medically treated patients.[3]

Post-operative physiotherapy was not recommended by 50% and 24% of British and Dutch surgeons respectively. These post-operative regimens are in contradiction to the literature, which has shown strong evidence in favour of active rehabilitation. However, the Cochrane review (2003) concluded that intense exercise programmes are more effective for functional outcome and lead to a faster return to work.[12] The same review also concluded that post-operative restrictions may not be necessary in most patients, and there is no evidence that it is harmful to return to activity immediately after surgery.

The spine patient outcomes research trial compared operative and non-operative care in patients with symptoms of lumbar disc herniation.[9,18] The conclusion drawn was surgery only shortens the duration of pain; if one can achieve the same with the use of analgesics, he or she can be better within 2 years without surgical risks. Numerous critics have pointed out fallacies in the study design and consider the conclusion of the randomised clinical trial invalid. One such fallacy was in the randomisation of patients in which, although treatment allocation in the trial was random, the actual treatment received was essentially stratified according to disease severity by the patient's choice.

The value of routine histopathological examination of IVD tissue has been questioned. The incidence of unexpected and important histopathological findings in tissue samples obtained during discectomy performed for a benign indication is approximately 1 in 1,000. Hence, routine histopathological examination of IVD specimens, especially those obtained in lumbar IVD procedures is justified and cost-effective according to some authors.[5]

RECURRENT DISC HERNIATION[15]

The rate of recurrent disc herniation after lumbar discectomy is 5–15% with an average pain-free interval of 8 years. The strict definition of recurrent disc herniation is the presence of herniated disc material at the same level, ipsilateral or contralateral, in a patient who has experienced a pain-free interval of at least 6 months after surgery. The clinically more appropriate definition, however, is disc herniation at the previously operated site and side. The current neuroimaging tool of choice in investigating a patient with post-discectomy recurrent symptoms is gadolinium enhanced MR imaging. The findings on imaging should be interpreted carefully and should not be confused with the post-discectomy changes. The nerve root should not enhance 6 months after the initial procedure.

Treatment options include observation and aggressive medical management (pharmacological therapy and physical therapy for rehabilitation) or operative intervention. Revision laminectomy and discectomy are the most commonly performed surgical therapies, starting at an area known to be intact, finding landmarks, beginning medially, and working out laterally to locate the pathological entity. Fusion is not routinely needed, unless spinal instability is demonstrated. There is no consensus on timing or optimal intervention in the treatment of patients with recurrent herniated discs. Higher recurrence rates and poorer outcomes have been documented in diabetic patients. Chymopapain, intradiscal electrothermal coagulation therapy and laser-assisted decompression are not options because the annulus is no longer intact in revision disc surgery.

RECENT ADVANCES

Artificial Disc Technology[1]

The two most common spinal surgery procedures, discectomy and fusion, are far from ideal for treating spinal disc degenerative disease. Although discectomy has a reasonably good short-term effect in relieving radicular pain, it causes disc height reduction in almost all patients[1] and further increases the instability of the treated disc. Scientifically, both physicians and industrial and academic researchers have been seeking better solutions for low-back pain treatment. Naturally, disc arthroplasty has been considered to be the "holy grail" of back pain treatment. The evolution of artificial disc technology is attested in part by experience in numerous patients as reported in publications over the past 50 years, especially the last 20 years.

One of the major reasons why artificial disc technology has been slow to develop is the structural and functional complexity of the disc, unlike hip and knee joints, which are composed mainly of a layer of cartilage tissue on each articulating surface. In IVD replacement, one can replace either the entire disc or only its nucleus, the former prosthesis is called an artificial total disc and the latter an artificial nucleus. Basic design concepts and component material(s) can be divided into three groups:

1. Metal
2. Non-metal
3. Metal in combination with non-metal.

The nucleus prosthesis approach has several obvious advantages over the total disc prosthesis. By replacing only the nucleus, it preserves the remaining disc tissues—annulus and end-plates—and therefore preserves their functions. Because the nucleus has a much simpler structure and function than the annulus and end-plates, the design of the nucleus prosthesis allows surgeons to leave the annulus and end-plates intact, making the surgical procedure much easier than that required to replace the entire natural disc. The major limitation of the nucleus prosthesis is that it can be used only in patients in whom disc degeneration is at an early or intermediate stage because it requires the presence of a competent natural annulus. Some of the artificial disc and nucleus available for use are the Charite device, prodisc and Raymedica implant.

Stem Cell Therapy[6]

Regenerative medicine and stem cells hold great promise for IVD disease. The therapeutic implications of utilising stem cells to repair degenerated discs and treat back pain are highly anticipated by both the clinical and scientific communities. Mesenchymal stem cells from adults are the best candidates for IVD repair. Although the avascular environment of the IVD poses a challenge for stem cell–mediated regeneration, neuroprogenitor cells have been discovered within degenerated discs, allowing scientists to revisit the hostile environment of the IVD as a target for stem cell therapy. Issues now under investigation include the timing of cell delivery and manipulation of stem cells to make them more efficient and adaptive in the IVD niche.

CONCLUSION

The complexity of the pain from the syndrome of degenerative disc disease and the fact that we do not fully understand the condition make it difficult to devise a common and effective treatment for every patient. Several controversies exist in the management of patients with herniated lumbar disc. Therefore, the treatment protocol varies from one centre to another. At the same time, newer methods like artificial disc replacement and stem cell therapy are being tried out as therapeutic options.

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115 Lumbar Canal Stenosis

Manas Kumar Panigrahi, Debabrat Biswal

Changes in the diameter of the vertebral canal as a cause of neurological disturbances was first reported by Antoine Portal in 1803 and focused attention on changes in the size of the vertebral canal as a cause of compression of its contents. He noted that the abnormal curvature of the spine might produce deformity of the canal and narrowing and the second cause of narrowing was due to swelling of the vertebral bodies towards the canal. Venereal diseases and rickets were thought to be the underlying disorder. In 1864, Jaccoud, in a chapter, quoted a case of paraplegia resulting from compression of the spinal cord due to a narrow canal. In 1910, Sumita for the first time described narrowing of the vertebral canal in cases of achondroplasia. In 1911, Bailey and Casamajor described five cases of osteoarthritis producing compression of the spinal cord due to diffuse osseous growths with canal narrowing. In 1924, Vittori Putti, an Italian orthopaedic surgeon, emphasised the relevance of anomalies or acquired degenerative alterations of the intervertebral foramina and lateral recess, for causing sciatica by causing an entrapment of the exiting root. In 1925, Parker and Adson described a series of cases with hypertrophy, vascularity and sponginess of the laminae causing canal narrowing in which no diagnosis was given and infection and trauma were considered the causative factors. In 1931, Town and Reichert reported two cases with cauda equina compression due to hypertrophy of the ligamentum flavum causing intermittent claudication. In 1937, Sparling et al. described seven patients with cauda equina deficits as a result of hypertrophy of the ligamentum flavum. In 1948, Van Gerderen described an orthotic caudal nerve root syndrome and the patient deteriorated on erect posture due to compression by the hypertrophied ligamentum flavum. In 1947, Sarpyener in an article discussed congenital stricture of the vertebral canal.[27]

In 1949, Verbiest also known as the "pope of spinal stenosis", described three cases of stenosis of the lumbar vertebral canal where the interpedicular distance was normal, but the AP diameter grossly reduced. This publication became the watershed literature from which the term lumbar canal stenosis (LCS) was recognised.

In 1959, Verbiest classified stenosis into absolute and relative. The absolute were cases in which the vertebral body caused the compression, while relative in which occurrence of minor deformities would cause compression. It took considerable time before developmental narrowing or stenosis of the lumbar canal and its frequent association with intermittent claudication gained general recognition. Freidman (1961) and Epstein (1962) were the first authors to confirm the existence of this entity and from then there have been several studies and published data about LCS and its manifestation.[27]

LCS most commonly affects the middle-aged and elderly population and is one of the most common diseases in elderly persons.[31] This refers to the degenerative changes or trauma of the lumbar spine, resulting in narrowing of the spinal canal and entrapment of the cauda equina roots by hypertrophy of the osseous and soft tissue structures surrounding the lumbar spinal canal. It is often associated with incapacitating pain in the back and lower extremities, difficulty in ambulating, leg paraesthesias and weakness and, in severe cases, bowel or bladder disturbances.[14,31] It is caused by a complex process of disc degeneration, facet arthropathy, ligamentum flavum hypertrophy and spondylolisthesis. The prevalence of LCS is between 1.7 and 8% in the general population as reported by Fraser et al.[9] With increasing longevity of our population and a continually rising proportion of middle-aged and elderly persons, the problem of LCS has shown a significant increase in the patient population as reported by Kazuo Nakanishi et al. in their study.[20] Low back pain resulting from degenerative disease of the lumbosacral spine is a major cause of morbidity, disability and lost productivity. Due to the slow progression of the disease, the diagnosis may significantly be delayed. Given the potentially devastating effects of this condition, early diagnosis and treatment are essential if patients are to be returned to their previous levels of activity.

NORMAL ANATOMY

The lumbar vertebral canal is roughly elliptical, rounded, triangular or trefoil in shape and is narrowest in its anteroposterior diameter in the axial plane. The average anteroposterior diameter of the lumbar canal in adults, as determined by anatomic and radiographic studies, ranges from 15 to 23 mm and a cross sectional area of about 77 +/– 13 mm.[2,20] The canal is anteriorly bounded by the posterior edge of the vertebral body including the posterior longitudinal ligament, which is closely apposed

to the posterior vertebral body surface, laterally by the pedicles, posterolaterally by the facet joints and articular capsules, and posteriorly by the lamina and ligamenta flava (yellow ligaments).[13] Coric et al. observed that the vertebral bodies and discs account for the majority of the axial load bearing capability of the spine. The disc absorbs load and stress, provides support and resists movement. The superior facet and associated ligamentum flavum form the roof of the lateral recess, where nerve roots exit the canal and enter the foramen. The lumbar facet complex is biplanar with the medial portion oriented in the coronal plane and the lateral portion in the sagittal plane. The medial portion (coronal) limits forwards translation and the lateral portion (sagittal) resists lateral rotation. Therefore, the total facet load consists of a component responsible for sharing axial load bearing with the disc as well as components for resisting anterior and lateral shear. Ligaments play a primary role in resisting flexion rotation and posterior shear. Biomechanical studies on cadavers demonstrate that the posterior ligaments, notably the supraspinous and interspinous ligaments, exert a significant effect on tensile stiffness. The neural foramen is bordered by the superior and inferior articular processes and pars interarticularis of the superior vertebra dorsally, sequential pedicles superiorly and inferiorly, and the intervertebral disc and the posterolateral surface of the vertebral body ventrally. The nerve root exists caudal to the pedicle, and the dorsal root ganglion lies in the superior and lateral portion of the foramen.[7,10]

Lumbar stenosis has been classified anatomically as central or lateral (or mixed) and developmentally as congenital or acquired.

Central stenosis involves narrowing predominantly of the spinal canal. Coric et al. subdivided lateral stenosis as entrance zone stenosis, mid-zone stenosis and exit zone stenosis. Lateral stenosis has also been referred to as lateral recess, foraminal canal, subarticular, subpedicular, intervertebral foramen and lateral gutter stenosis (Fig. 1).[10]

The classification system proposed by Verbiest categorises the multiple causes of lumbar stenosis into two types: conditions that lead to progressive bony encroachment of the lumbar canal (including developmental, congenital, acquired and idiopathic causes) or stenosis produced by nonosseous structures such as ligaments, intervertebral discs and other soft tissue masses.

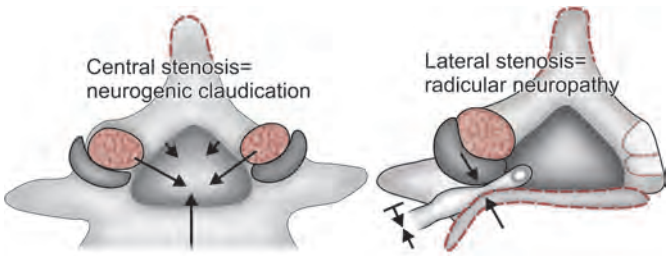

Fig. 1: Central stenosis versus lateral stenosis

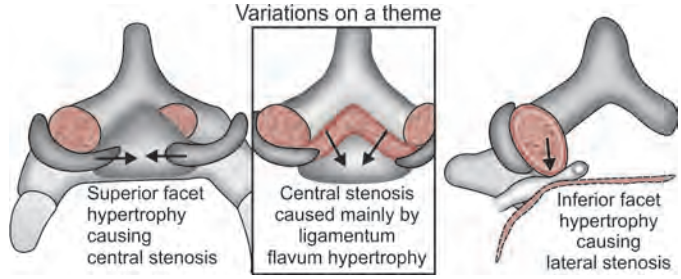

Fig. 2: Acquired stenosis due to hypertrophy of superior and inferior facets and ligamentum flavum

For practical purposes, however, the aetiologies of lumbar stenosis can be divided into congenital or acquired forms.[26,27] The two forms of spinal stenosis are described as follows:

Congenital stenosis which is primary and relatively uncommon is divided additionally into idiopathic and achondroplastic varieties. This condition is diagnosed more easily because patients are younger and usually lack other complicating medical problems such as diabetes or vascular insufficiency. Stenosis may develop at several levels of the vertebral column and may often lead to serious neurological deficits.

Acquired stenosis is a degenerative condition. The vast majority of patients present with acquired LCS. Patients generally become symptomatic at 50 years of age or older. Degenerative changes of the spine can include osteophyte formation, facet hypertrophy, bulging disks and hypertrophy of the ligamentum flavum. Any of these processes can result in canal or foraminal narrowing. Degenerative spondylolisthesis can further compromise the canal (Fig. 2).[1]

In some cases, the patient has acquired degenerative changes that augment a congenitally narrow canal,[29] which are classified as complex lumbar stenosis and present concurrently with other spinal deformities such as spondylolisthesis, scoliosis or lumbar kyphosis (flatback deformity). These lesions may be idiopathic, degenerative or surgery induced.[9]

PATHOPHYSIOLOGY

Nadalo reported that spinal stenosis results from progressive narrowing of the central spinal canal and the lateral recesses. The essential content of the spinal canal includes the spinal cord, the cerebrospinal fluid (CSF) of the thecal sac and the dural membranes that enclose the thecal sac. The spinal canal may become narrowed by bulging or protrusion of the intervertebral disc annulus, herniation of the nucleus pulposus posteriorly, thickening of the posterior longitudinal ligament, hypertrophy of the facet joints, hypertrophy of the ligamentum flavum, epidural fat deposition, spondylosis of the intervertebral disc margins, uncovertebral joint hypertrophy in the neck, or a combination of two or more of the above factors.[19]

The spine responds to physiological stresses with bone growth at the superior and inferior margins of the vertebral body (osteophytes). Osteophytes can form anteriorly or posteriorly. Posterior osteophytes narrow the intraspinal diameter and also cause lateral recess stenosis. This results in spinal cord or nerve root impingement. Furthermore, arthritic degeneration causes formation of synovial cysts and hypertrophy of the facet joints, which further compromise the patency of the spinal canal and the neural foramina.[13]

Fraser et al. noted that during ageing the discs dehydrate and can get compressed and bulge. This process can cause tilting, slippage or rotation of the vertebral bodies. The ligamentum flavum may also ossify and becomes hypertrophic. The compressed discs result in shortening of the spinal column, which causes the ligamentum flavum to buckle inwards and compress the spinal sac and nerve roots. Lumbar intervertebral disc degeneration represents a cascade of events involving bulging of the disc, disc herniation and ligamentum flavum into the canal, and resulting chronic facet arthrosis, sclerosis and osteophytic growth. Hypertrophy of the ligamentum flavum is also an important element in the development of spinal stenosis. Lumbar spinal encroachment induces ligamentum flavum hypertrophy, which further aggravates stenosis. Disease of the nerve roots and cord, however, does not typically result directly from compression of the nerves. Rather, the resulting stenosis causes decreased flow of CSF (which represents approximately 60% of the nutritional supply to the cauda equina) and increased venous pressure.[9]

SPINAL CLAUDICATION SYNDROME

The narrowing of the spinal canal leads to a compression of the cauda equina and its nerve roots. However, there is no direct relationship between the extent of the stenosis and the clinical symptoms. This finding remains unexplained. Furthermore, patients are usually asymptomatic when sitting and lying indicating a strong functional influence. There are the following two prevailing theories that try to explain intermittent claudication.

Neurogenic Compression Theory

Prolonged compression of a peripheral nerve followed by mechanical stimulation is known to produce abnormal electrical discharge,[12] thereby causing pain in experimental animal studies.[3] Long-standing direct mechanical compression of nerve roots leads to decreased CSF supply to the nerve root. Impaired nutritional supply results in microvascular changes, and causes oedema, accumulation of noxious substances, deterioration and fibrosis. The combination of these changes may explain neurological dysfunction. This theory does not explain all the functional aspects of neurogenic claudication.[22]

Vascular Compression Theory

The vascular compression theory suggests that spinal stenosis has pathological effects on the blood supply of the cauda equina. Particularly, multiple-level central stenosis is associated with spinal claudication. It is assumed that venous congestion between the levels of stenosis compromises nerve root nutrition and results in clinical symptoms. Additionally, the compressed nerve root arterioles may lose the ability to respond to exercise by vasodilatation. This compromise explains that walking produces back, buttock and leg pain as well as heaviness and discomfort in the lower limbs. During rest the vascular (nutritional) supply may suffice and the patient may be asymptomatic. However, a critical look indicates that some aspects of the clinical syndrome still are not explained well. This is particularly valid as patients with severe stenosis can be asymptomatic.[22]

CLINICAL PRESENTATION

Epstein, in her detailed article, noted that patients with severe congenital lumbar stenosis begin to show symptoms in their 30s and 40s, whereas those with acquired stenosis develop complaints in their 50s through 80s. Low back pain is often accompanied by asymmetrical, unilateral more than bilateral, radicular or claudication complaints. Standing and walking, which causes an acute increase in lumbar lordosis and infolding of the ligamentum flavum, precipitates claudication that can readily be reversed on flexion (by sitting or lying down).[6]

The characteristic syndrome associated with lumbar stenosis is termed neurogenic intermittent claudication. This condition must be differentiated from true claudication, which is caused by atherosclerosis of the pelvofemoral vessels.[13] Compression of the microvasculature of the lumbar nerve roots, resulting in ischaemia, is believed to be a major contributing factor in the development of neurogenic claudication. Wilson[11] classified neurogenic claudication into two major types based on the putative pathophysiological mechanism: postural or ischaemic. Postural neurogenic claudication is induced when the lumbar spine is extended and lordosis is accentuated, whether at rest or during exercise in the erect posture. With extension of the spine, degenerated intervertebral discs and thickened ligamenta flava protrude posteriorly into the lumbar canal, producing transient compression of the cauda equina. In the ischaemic form, it is theorised that transient ischaemia occurs in compressed lumbosacral roots when increased oxygen demand occurs during walking.[1]

Kobayashi et al. in their experimental study, observed that intermittent claudication in patients with LCS, which occurs during walking and subsides with rest, cannot be explained solely by mechanical compression of the nerve roots. These radicular symptoms associated with degenerative disease of the lumbar spine reportedly are attributable to a combination of mechanical nerve root

compression and resultant circulatory disturbance, but the dynamics of nerve root circulation are still poorly understood.[17]

It is not unusual not to find significant neurological deficits in patients with stenosis. Positive mechanical findings of entrapment are the Lasègue's sign and femoral stretch test and these can be elicited in 60% of patients with absolute and 43% of patients with mixed stenosis.[16] Mild motor dysfunction most frequently involves the extensor hallucis longus and peroneal muscle groups (L-5), and reflexes may diffusely be diminished or absent, mostly the ankle reflex. Sensory deficits, usually noted in the L-5 or S-1 distributions are rarely seen in more cephalad L2-4 or more caudad (sacral) distributions.[16] At the initial examination no neurological deficit may be elicited but a brief period of exercise often uncovers the deficit. Symptoms and signs are related to the age of the patient but not to the radiographic data (i.e. site and degree of the narrowest part or number of stenotic sites).[16] Patients with canal stenosis tend unconsciously to assume a style of gait that precludes the development of symptoms,[25] and this is one reason why the style of walking noted in these subjects immediately after they start walking is different from that in normal subjects.[10]

IMAGING STUDIES

Older patients in whom spinal stenosis is suspected should be examined using conventional spinal radiology, including AP, lateral, oblique and lower lumbar-centred views. Lateral views are most sensitive for central spinal stenosis, while oblique views of the cervical and lumbar areas demonstrate lateral stenosis syndromes better. Younger patients and all patients in whom conventional radiology findings are negative should be evaluated using either spinal CT scanning with reformatted images, spinal MRI, 3D CT or CT myelography.

Spinal MRI is the most suitable technique for the diagnosis of spinal stenosis. Spinal MRI should include imaging sets obtained in the axial and sagittal planes using T1-weighted, proton-density and T2-weighted techniques.

Plain radiographs of the lumbar spine reveal multilevel spondylotic changes with osteophytes, facet hypertrophy and disk space narrowing. Interpedicular and sagittal measurements of the canal on plain films are helpful in defining the stenosis. Flexion-Extension radiographs help demonstrate motion occurring at a potentially unstable segment.

CT scan helps in viewing facet hypertrophy, especially of the superior process, leading to constriction of the transverse diameter of the canal. Ventrally located osteophytes and hypertrophied laminae narrowing the canal in its AP diameter are readily demonstrated. Together, these changes narrow the lateral angles of the canal, diminishing the height of the lateral recess. The limitation of CT scan is in its poor demonstration of the ligamentous hypertrophy and disk protrusion (Fig. 3).[27]

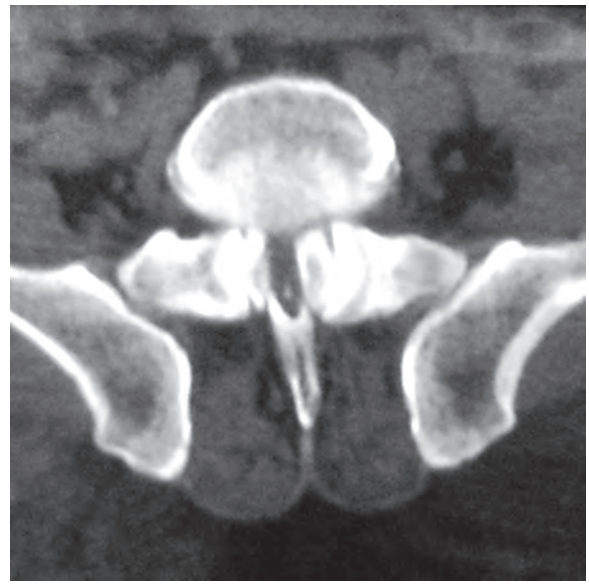

Fig. 3: CT scan axial cut showing the medialised hypertrophied facets causing canal narrowing

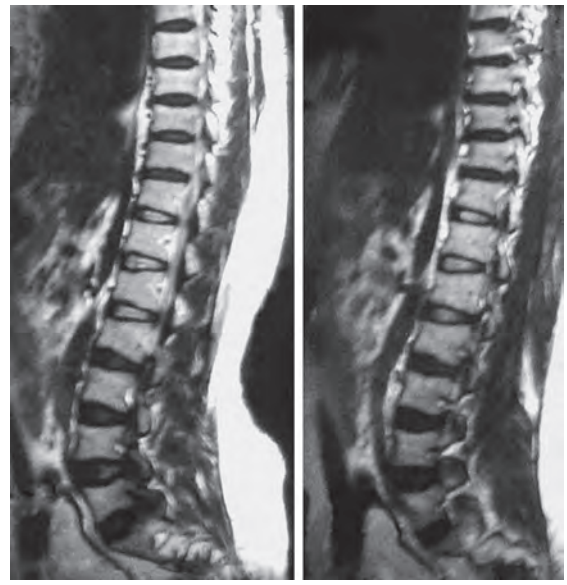

Fig. 4: MRI sagittal view of a patient of achondroplasia showing severe canal stenosis

Magnetic resonance imaging studies better delineate the soft tissue changes laterally, in the foramina and far laterally. MRI with Gadolinium DTPA affords a near myelographic view of the entire subarachnoid space. It also identifies tumours, demyelinating syndromes, adhesive arachnoiditis and infection. Compared to CT, MRI has a significant advantage because of its better soft tissue resolution (Figs 4 and 5).

CT Myelography

The benefits of CT over plain films are that it can provide greater resolution in terms of an increased ability to appreciate density differences. A second advantage of CT is its ability to image in different planes, either directly

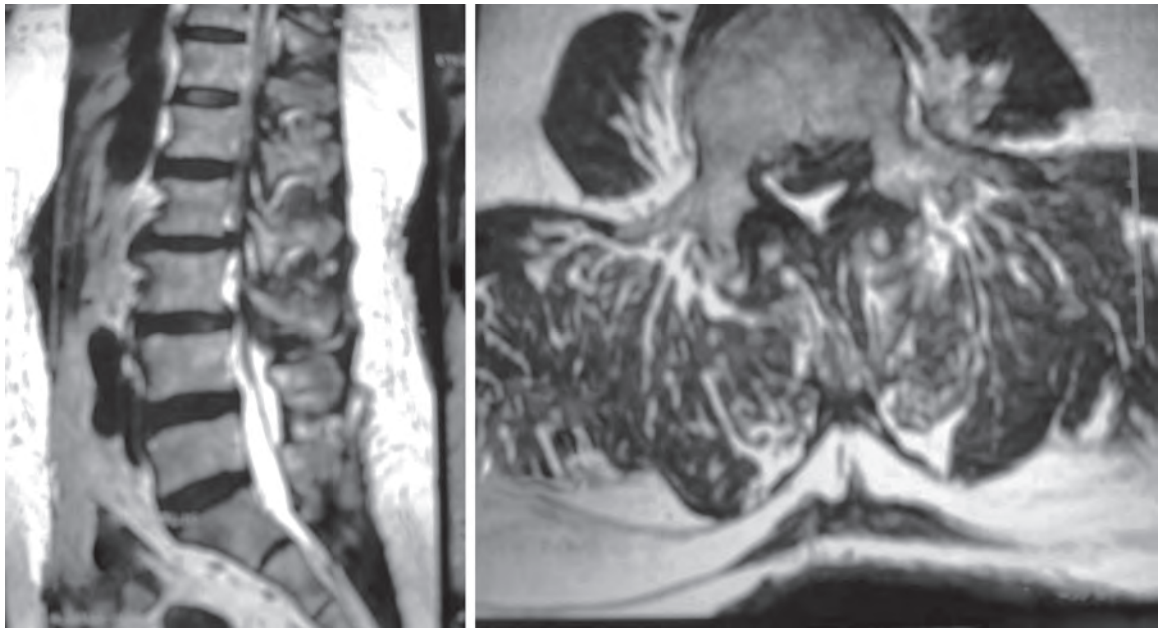

Fig. 5: MRI of the lumbar spine showing sagittal and axial view of a degenerative spine with ligamentum flavum hypertrophy, disc protrusion and facet hypertrophy causing severe canal narrowing

or by multiplanar reconstruction. On CT, midsagittal lumbar canal diameter less than 10 mm is regarded as absolute stenosis and midsagittal lumbar canal diameter less than 13 mm indicates a relative stenosis.[21]

Compared to MR imaging, the disadvantage of CT is that it does not allow good visualisation of the nerve roots and exposes the patient to radiation. If MRI is not possible (e.g. pacemaker, metallic artefacts), CT myelography provides the best alternative to confirm nerve root involvement. However, CT myelography may not display foraminal stenosis because the dural root sheath ends at the entrance of the foramen.

MANAGEMENT

Decompression of the spinal canal relieves the symptoms of lumbar stenosis in a considerable proportion of cases, but the results have been inconsistent. Patients must be chosen carefully for surgery, and success is likely if the clinical features conform to the typical syndrome, mainly pain that altered in various positions and is at least partially relieved by rest, with definite evidence of root compression by imaging.[28] Medical treatment alternatives, such as bed rest, pain management and physical therapy, should be reserved for use in debilitated patients or patients whose surgical risk is prohibitive as a result of concomitant medical conditions.[13]

Favourable indications for non-operative treatment would be mild claudication symptoms, concomitant back pain, mild to moderate radiculopathy, minimal interference with lifestyle and absence of motor deficits.

Conservative treatment options may consist of medication like analgesics, NSAIDs and muscle relaxants. The administration of calcitonin has been reported to improve the symptoms of neurogenic claudication.[23] Some patients may improve their function as a result of postural education and instructions for physiotherapy. As extension worsens the symptoms by reducing the size of the spinal canal, it is obvious that extension exercises must be avoided. Epidural injections anecdotally have a temporary beneficial effect and may be considered as a treatment in elderly patients in whom surgery would be too risky or who refused surgery. However, the therapeutic value of epidural injections in all lumbar spinal disorders and particularly in spinal stenosis remains controversial. The administration of intravenous infusion of PGE1 (60 mcg/d) for approximately two weeks has been found to be useful for treating intermittent claudication in patients with lumbar spinal canal stenosis. The effect of PGE1 was not related to the degree of stenosis obtained with images, age or claudication distance, but was correlated with baseline disease severity.[20]

However, studies comparing non-operative and surgical treatment demonstrated the better overall results of surgery.[30] Moreover, only one single randomised study compared short-term and long-term results of medical and surgical therapy. Amundsen et al.[2] concluded that an initial conservative approach is advisable for oligosymptomatic patients because those with an unsatisfactory result can be treated surgically later without impairment of the prognosis.

Surgery for lumbar spinal stenosis is generally accepted when conservative treatment has failed or if the stenosis substantially impacts on the patient's lifestyle. The general goals of operative treatment are to improve quality of life by reducing symptoms. Indications for surgery are moderate to severe claudication symptoms, significant interference with lifestyle, progressive neurological deficits and cauda equina syndrome. With the

exception of a cauda equina syndrome or progressive neurologic deficits, the indication for surgery remains relative and is dominated by the subjective interference with the patient's quality of life.

The surgical technique is largely dependent on the type of stenosis, which may be central, lateral recess or foraminal and the presence of concomitant back pain. The principal surgical options for decompression of central and/or lateral spinal stenosis are decompressive unilateral or bilateral laminotomy or laminectomy, decompression with non-instrumented fusion and decompression with instrumented fusion.

Laminotomy or Laminectomy

The objective of decompression is to create more space for the cauda equina and nerve roots by liberating the neural structures from compressing soft tissues such as disc herniation, hypertrophied ligamentum flavum, thickened facet joint capsules and osseous structures like hypertrophied facet joints and osteophytes. Until recently, total laminectomy was the standard method of decompression in central spinal stenosis. However, the recognition that total laminectomy may increase or cause segmental instability has led to a more conservative approach, preserving the lamina and only removing those parts which actually cause the stenosis.[15]

Selective decompression is the surgical technique of choice in patients presenting with neurogenic claudication without relevant back pain. A technical detail is related to the preservation of the facet joint capsules when an undercutting medial facetectomy is required to decompress the thecal sac. In selected cases, a unilateral approach suffices to bilaterally decompress the thecal sac (over-the-top technique) by undercutting of the laminae, preserving the interspinous ligaments and the contralateral muscles.[5]

Endoscopic interlaminar decompression in cases of lateral recess stenosis and its superiority over the microsurgical technique has been claimed in a study by Sebastian Ruetten. He concluded that the rate of complications and revisions was significantly reduced in the endoscopically managed group. Endoscopic techniques are advantageous in the following areas: operation, complications, traumatisation and rehabilitation.[24]

Total laminectomy is still indicated in cases in which the thecal sac cannot sufficiently be decompressed or the access to the foramen is obliterated (foraminal stenosis). In rare cases of cauda equina syndrome, total laminectomy is indicated to ensure adequate neural decompression. Laminectomy alone should be avoided in cases with pre-existing instability such as degenerative spondylolisthesis, isthmic spondylolisthesis with secondary degenerative changes and degenerative scoliosis.[4]

Inverse laminoplasty[32] is a canal enlargement technique with ligamentum flavum excision, foraminotomy and lateral recess decompression with preservation of the osseous structure. This leads to a more stable lumbar spine after re-enlargement of the canal than after laminectomy. The lamina is cut just medial to the facet joints with a high speed drill, and cuts are made in a caudal to rostral direction. The ligamentum flavum is cut and the lamina is elevated, separating it from the dura mater carefully. After excision of the laterally remaining ligamentum flavum, for decompression, widening of the lateral recess and excision of the foraminal roof and the medial rim of the facet are performed bilaterally. The removed laminae are then inverted and reattached with titanium mini plates in all patients. Disc excision is performed in patients who have disc protrusion or extrusion. Inverse laminoplasty has three advantages: (1) prevention of instability and re-construction of spinal osseous structures (2) enlargement of the spinal canal diameter and (3) prevention of neural elements from peridural scar formation.

Decompression and Spinal Fusion

The addition of fusion with or without instrumentation to surgical decompression is generally recommended when segmental instability is assumed. However, the radiological assessment of segmental instability remains a matter of debate. Decompression and fusion are considered by many spine surgeons in case of segmental instability like degenerative spondylolisthesis and scoliosis, concomitant severe back pain, necessity for a wide decompression and recurrent spinal stenosis. In patients who had a concomitant fusion, the results were significantly better with respect to relief of pain in the back and lower limbs.[8]

Use of instrumentation like pedicle screws and rod stabilisation may lead to a higher fusion rate, but clinical outcome shows no improvement in pain in the back and lower limbs.[6] However, Kornblum et al.[18] demonstrated the long-term (5–14 years) benefits of a successful fusion over non-union with respect to back and lower limb symptoms in patients with degenerative spondylolisthesis and spinal stenosis. There is no evidence in the literature that an additional interbody fusion by an anterior (ALIF) or posterior (PLIF, TLIF) approach improves outcome.[6] Newer techniques, such as interspinous spacer stabilisation, are still evolving and conclusions on clinical effectiveness are premature.[2]

Indications for implantation of the interspinous spacer are: (1) resistance to conventional medical treatment; (2) age older than 70 years or, if younger than 70 years, a high operative risk and inability to tolerate lengthy surgery; (3) lumbar stenotic symptoms of greater than moderate severity, especially intermittent claudication; (4) pain relief in flexed lumbar and exacerbation when in an extended position and (5) dural compression, primarily caused by the ligamentum flavum. The paraspinal muscle is dissected from both sides of the spinous processes to the level of the facets and laminae. The supraspinous ligament is preserved mostly to prevent posterior divergence of the spacer after surgery. The advantage of the spacer is its ease of insertion into the interspinous process space. After opening an appropriately sized window by using dilators of increasing size and insertion of the

spacer with the aid of a dedicated inserter and retainer, which are then removed, the surgery is completed. This manipulation requires little effort.[31] Many types of spacers are now in use, such as Titanium and Ceramic, and the overall results with them are early, but quite encouraging.[31]

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116 Spondylolisthesis

Ramakrishna Easwaran

TERMINOLOGY

Spondylolisthesis is defined as a displacement of one vertebra over the next lower vertebra in the sagittal plane. Since the superior vertebra is usually displaced anteriorly and, as the problem is most frequent in the lumbar region, the unqualified term of 'spondylolisthesis' generally, refers to forward slipping of a lumbar vertebra. The word 'spondylolisthesis' coined by Kilian in 1854 is derived from two Greek words 'spondylos' (vertebra) and 'olisthanein' (to slip). The etymologically correct abbreviated version should be 'olisthesis' and not 'listhesis'. Spondylolysis refers to an acquired defect in the pars interarticularis. Spondyloptosis is an extreme degree of spondylolisthesis, where the upper vertebral body appears to be not in contact and is placed anterior to the lower body.

CLASSIFICATION AND AETIOLOGY

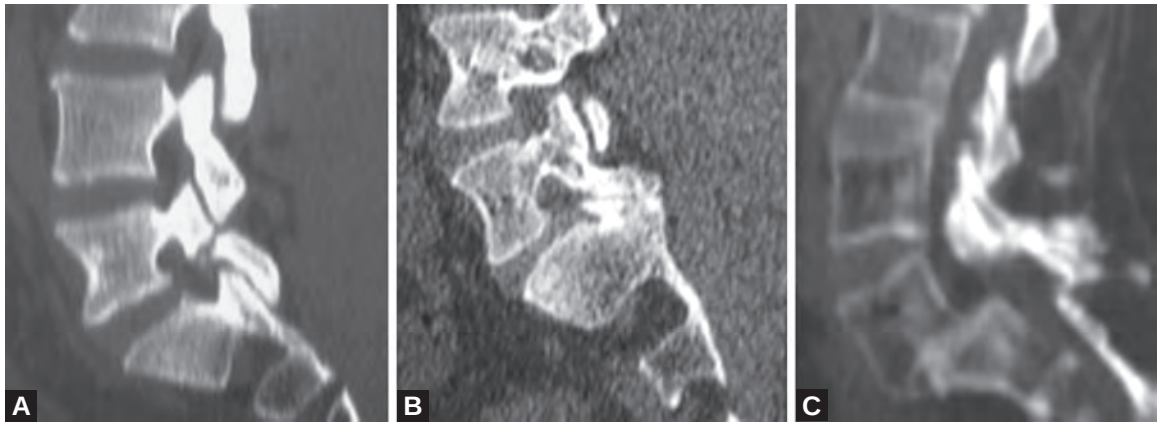
An aetiological classification that is widely accepted was proposed in 1976 by Wiltse, Newman and MacNab (Table 1).[65] Isthmic spondylolisthesis (ISO) is commoner in the 20–40 age group, while degenerative spondylolisthesis (DSO) is common above the age of 40. These two types are discussed in detail as they account for the majority of cases in clinical practice.

Isthmic Spondylolisthesis

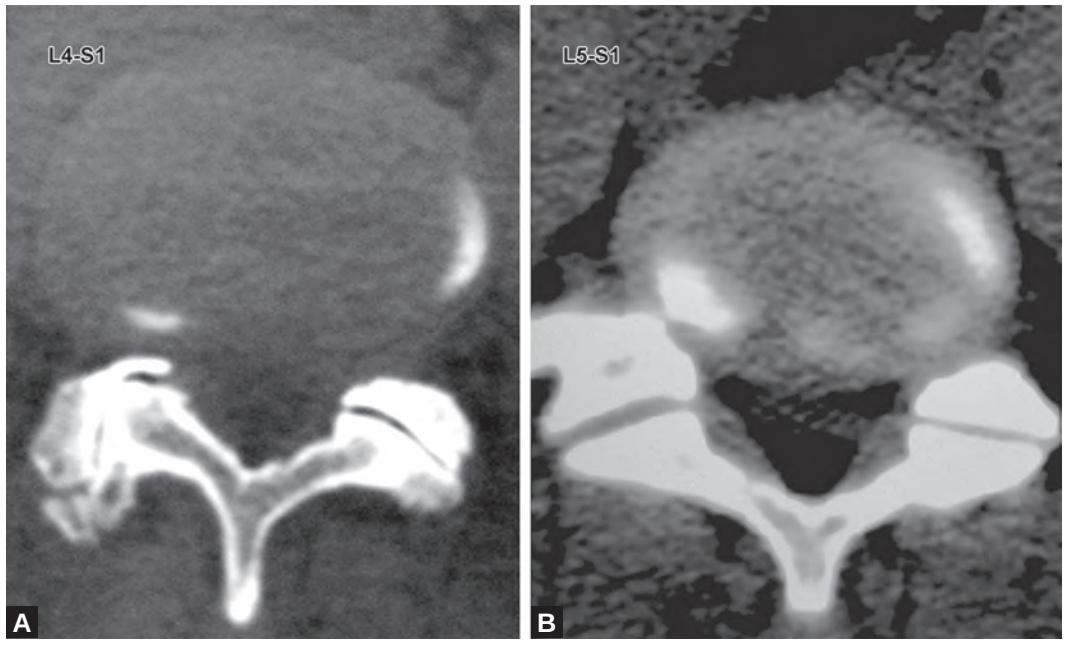
The pars interarticularis is an isthmus of bone that connects the superior and inferior facets. The pars appears to be the weakest point in the neural arch and yet it faces the highest stress.[23] Repeated stress fracture of the pars results in isthmic spondylolysis. Such stress fractures have been demonstrated by SPECT imaging and may be a cause of low backache in young athletes even without spondylolisthesis.[69] Right arm cricket pace bowlers tend to fracture their left isthmus.[9] Stress fractures start in the inferior or inferomedial cortex of the pars and propagate superiorly or superolaterally, as shown in a serial CT study.[13] A fracture that goes into non-union produces a wide smooth defect with edge sclerosis resulting in the subtype A of ISO. If there is healing and remodelling at the stress fracture site, the pars becomes elongated with alteration of the biomechanics of the motion segment, which leads to the subtype B of ISO (Figs 1A to C). These two subtypes are illustrated by sagittal CT reformation

Table 1: Wiltse-Newman-MacNab classification of spondylolisthesis[65]

Type	*Aetiology*	*Comment*
Isthmic	Defect in pars interarticularis (isthmus)	Commoner at L5-S1 level and in younger patients
Subtype A	Bilateral chronic spondylolytic defect in the isthmus	
Subtype B	Healed spondylolysis with elongated isthmus	
Subtype C	Acute bilateral fracture of isthmus	Type 4 of Aihara classification of lumbosacral dislocation (Table of chapter *Sacral Spine Injury* in this textbook)
Degenerative	Abnormal motion due to disc and facet joint degeneration	Commoner at L4-5 level and in older patients
Dysplastic	Congenital abnormality of neural arch such as malformed L5 inferior or superior S1 facet, abnormal sacral surface	Elongation of pars (mimicking isthmic subtype B) or fracture of the pars (mimicking subtype A) might occur secondarily. Horizontal orientation of L5-S1 facet joint and wedging of L5 body help distinguish dysplastic spondylolisthesis
Traumatic	Acute fracture of the neural arch at a site other than the isthmus	Type 1, 2, 3, 5 of Aihara classification (*see above*)
Pathological	A. Generalised bone disease	Example: Paget's disease, Marfan syndrome, achondroplasia, neurofibromatosis
	B. Localised bone disease disrupting the integrity of the neural arch	Example: Tuberculosis, metastasis. Fracture of the pars cephalad to a site of surgical posterior (laminar) fusion is also included (spondylolisthesis acquisita)



Figs 1A to C: Subtypes of spondylolisthesis (sagittal CT reformation). (A) Spondylolytic defect in the isthmus-subtype A of ISO. (B) Elongation of pars with normal orientation of the L5-S1 facet joint—subtype B of ISO. (C) High-grade dysplastic spondylolisthesis with pars elongation mimicking subtype B of ISO. Note the horizontal orientation of the L5-S1 facet joint and rounding off of the S1 body anteriorly



Figs 2A and B: Orientation of lumbar facets (axial CT). (A) Left facet joint has sagittal orientation which predisposes to DSO, whereas the right has a normal oblique orientation. Note the degenerative changes in the abnormally oriented joint. (B) Both the facet joints are coronally oriented and this predisposes to ISO

in Figures 1A and B. Acute fracture of the isthmus causing olisthesis constitutes the subtype C.

The roentgenographic studies of spondylolysis in the general population had suggested an incidence of 4.4% by age 6, increasing to 6% in adulthood. L5 was affected in 90% and L5 spina bifida was seen in 30%. Those with bilateral pars defects progressed to low-grade ISO but were not necessarily symptomatic.[22] A CT based Japanese study showed 6% incidence of spondylolysis in asymptomatic adults and a 2:1 male preponderance.[53] Females are however, four times more prone to developing symptomatic ISO. There is a five-fold higher incidence of spondylolysis in near relatives of patients with ISO suggesting a heritable tendency.[66] The lumbar facet joints appear to be more coronally oriented in patients with ISO (as opposed to a sagittal orientation which predisposes to DSO—see below).[11] Examples of abnormal facet joint orientation are shown in Figures 2A and B. A more horizontally oriented sacrum has been shown to increase the stress on the L5 pars from the repetitive stress due to daily activities such as standing or sitting.[46] ISO is a uniquely human disease and it is likely to be due to our bipedalism. The rare reports of spondylolysis in a 3.5-month-old infant and ISO in a non-ambulatory patient bespeak of yet other mechanisms at work.[6,23] ISO appears to increase in degree radiologically (although not necessarily in symptoms) until 25 years of age.[27] Older adults only rarely have worsening of the degree

Table 2: Factors predisposing to DSO (Reproduced with permission from *Progress in Clinical Neurosciences Vol. 23*)[14]

Female sex
• Oophorectomised women—3 times greater incidence
• Osteoporosis—leading to elongation of the pars
• Sagittal orientation of facets (sagittal facet angle > 45° increases risk 25-fold)
• Specific factors for L4-5 level DSO
• Narrow L4 inferior articular process
• Sacralisation of L5
• Horizontalisation of the lamina and the facets
• Specific factors for L5-S1 level DSO
• Slender L5 transverse process
• Greater inclination of sacral table
• Less deep location of the L5 vertebra in the pelvis

of slip but they progress more often to have symptoms.[19] Acute clinical and radiological progression of ISO in adults has been noted with trivial trauma.[58] When ISO occurs at L4-5, greater degree of progression has been noted and this has been noted also with a biomechanical study showing greater motion at L4-5 as compared to L5-S1 level ISO.[25]

Degenerative Spondylolisthesis

This was first described by MacNab in 1950, as 'spondylolisthesis with intact neural arch' or pseudospondylolisthesis.[39] DSO is found most commonly at the L4-5 level, followed with decreasing frequency by L3-4, L2-3, L5-S1 and L1-2 levels. Women aged 40–60 years exhibit slippage in a 2:1 to 10:1 prevalence compared with men.[15] Male patients are typically older, in the 6–8th decades. Table 2 lists the factors associated with an increased incidence of DSO.[14] DSO may be associated with translatory slips in the coronal plane or degenerative kyphoscoliosis.[21]

Dysplastic Spondylolisthesis

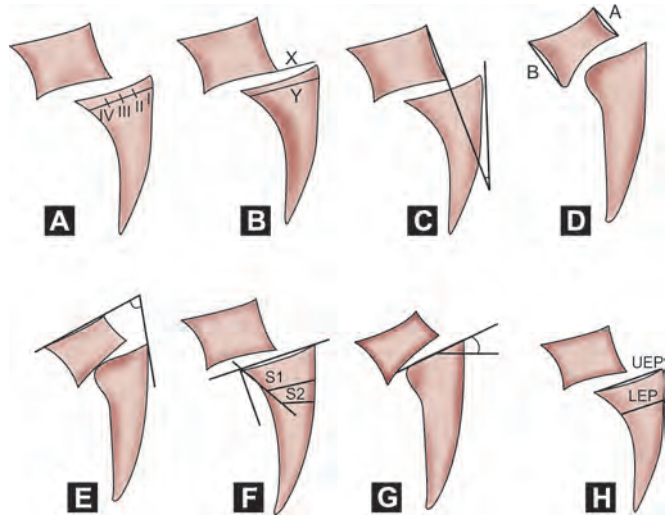
This spondylolisthesis occurs at L5-S1 level. If L5 is sacralised, dysplastic spondylolisthesis can occur at L4-5 level. Dysplastic spondylolisthesis needs to be distinguished from ISO subtypes A and B, as there might be a secondary isthmic defect or elongation in dysplastic cases too. The key is the horizontal orientation of the L5-S1 facet joint in dysplastic spondylolisthesis[66] (Fig. 1C). A higher incidence of associated spina bifida is noted with dysplastic spondylolisthesis.

Traumatic and Pathological Spondylolisthesis

Traumatic and pathological spondylolisthesis are mentioned in Table 1.

GRADING

Grading describes the severity of the vertebral slip. Meyerding, in 1932, divided the upper surface of the



Figs 3A to H: Measuring spondylolisthesis. (A) Meyerding grades. The upper surface of the lower body is divided into four equal parts to grade the forward slip: grade I: up to 25%, grade II: 26–50%, grade III: 51–75% and grade IV: > 75%. (B) Ratio X/Y represented as % gives the percentage slip. (C) The angle between the posterior borders of the bodies gives the sagittal plane rotation or roll. (D) The ratio A/B represented as % gives the lumbar index. (E) Lumbosacral angle of Boxall (normal = 90–110°) becomes more acute with high-grade olisthesis. (F) Sacral angle measures the inclination of the sacrum. (G) Sacral slope measures the sagittalisation of the upper surface of the sacrum. (H) The ratio between the width of the upper and lower endplates of S1 (called S1 index) is less than 1.35 in high-grade olisthesis

inferior vertebra into four equal parts and depending on the degree of slip of the superior vertebra, described four grades of spondylolisthesis (Fig. 3A). Grades 1 and 2 are considered low-grade and grades 3 and 4 as high-grade spondylolisthesis. This time-honoured grading system appears to have good inter-observer and intra-observer reliability.[60] What is striking on the lateral radiograph is the slip on the anterior border, but what is relevant to neural compression is the slip on the posterior border of the vertebra. Since radiographs are not always taken with parallel beams from a tube-patient distance of 6 feets, any system that relies on measurement by millimetres must not be trusted, because of non-uniform magnification of different structures within the same film and between two different films. It is necessary to specify the percentage of slip to describe slips of intermediate grades (Fig. 3B). When there is a sagittal plane translation (slip) there must be an accompanying sagittal plane rotation (roll), which becomes obvious in high-grade olisthesis. This rotation is measured by the angle between the posterior or the anterior surfaces of the two vertebrae (Fig. 3C). In high-grade olisthesis, there is rounding off of the anterior border of the upper surface of the lower body and sagittalisation of the disc space. The sacrum appears more inclined forward in L5-S1 olisthesis. The subpedicular posterior border in the slipping upper vertebra loses its height. This results in a wedge-like shape of the slipping vertebra. The ratio of the anterior and posterior heights

of the slipping vertebra is the lumbar index (Fig. 3D). The remaining measures used in studies on spondylolisthesis are shown in Figures 3E to H.

CLINICAL FEATURES AND THEIR BASIS

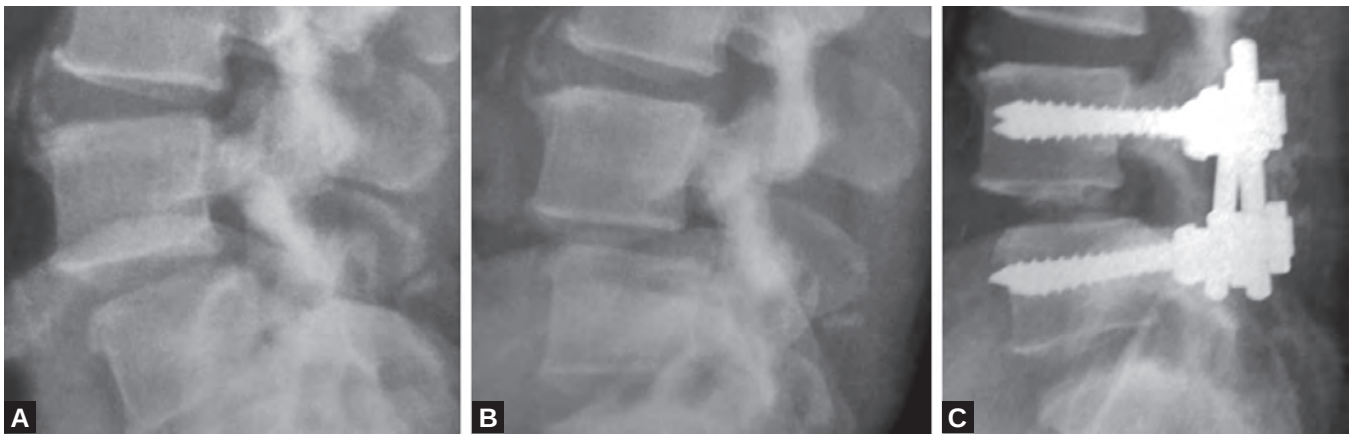
Spondylolysis and spondylolisthesis may entirely be asymptomatic. This is so in young low-grade ISO patients with good muscle tone and wide canals. Mild grade DSO might also behave similarly. Such patients do not have significant neural compression or instability. Their risk of progression is very low.[41]

Symptomatic spondylolisthesis presents with various combinations of low backache, restriction of back mobility, radicular leg pain (sciatica), neurogenic claudication, postural abnormality and neurological deficits referable to the caudal roots, roughly in that order of frequency. The back pain is poorly localised, central and sometimes is referred to the sacral and perineal region. It is worse on standing. It is believed to arise from the pseudarthrosis, ligamentous or facet joint strain or degeneration in the disc or facet joint. Many patients with ISO who have had minimal or no symptoms during young age, develop disablement only when spondylotic degeneration sets in.[19] Leg symptoms of sciatica and neurogenic claudication arise from compression or stretch on the spinal roots. In L5-S1 ISO the compression is on the exiting root, i.e. the L5 root that is stretched over the L5-S1 disc by the forward displacement. The root compression is at the foraminal level, the foramen having lost its height due to the loss of height of the L5 subpedicular body. The root is stretched by the undersurface of the L5 pedicle. The callus or pannus at the pseudarthrosis also contributes. The S1 roots and the central canal are usually free in L5-S1 ISO. Neurological deficits are rare in ISO but are seen in dysplastic spondylolisthesis.

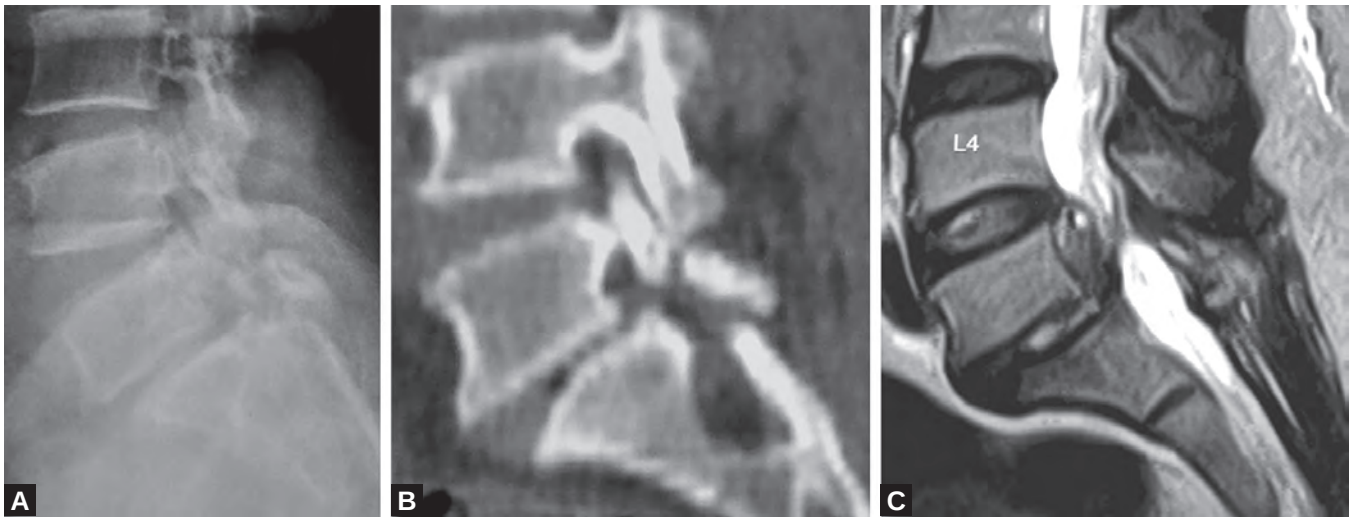
DSO is most common at L4-5 level and this again causes L5 root compression which is the traversing root. However, the compression is not, so much because of the slip as due to the lateral canal narrowing caused by the spondylosis deformans producing facetal bony hypertrophy, thickening of the facet capsules, synovial cysts from the facet joints and flaval ligamental hypertrophy. The bulging disc or a frank prolapse of the disc also narrows the space in the lateral canal. At surgery, one finds the medial enlargement of the L4 inferior facet narrowing the roof of the cranial part of the lateral canal over the L5 root and the hypertrophy of the upper part of the L5 superior facet biting into the undersurface of the L5 root, lower down in the canal. There is additional compression on S1 roots from the spondylosis deformans, even though this is not the level of slip. The symptoms do not improve on forward bending, unlike in the case of pure spinal stenosis. The patients tend to support the back of the trunk with their arms.[38] Clinical examination may show wasting of extensor digitorum brevis, weakness of toe-grip, sensory loss in the L5 and S1 segments and absent ankle reflexes. Acute worsening of pain and unilaterality of symptoms suggest an additional disc prolapse in both DSO and ISO (Figs 4A to C).

In high-grade L5-S1 olisthesis, the lumbar spine becomes hyperextended giving a foreshortened appearance of the trunk. The upper surface of the sacrum becomes vertical and the caudal sacrum juts out. The buttocks appear flat and there is a prominent transverse crease in the flanks and anterior abdomen. The hips and knees become flexed with tight hamstrings. The gait has a characteristic waddle. There may be an associated scoliosis.[43] The neurological findings are due to narrowing of the central canal where the caudal roots become pinched between the leading L5 lamina and the lagging upper posterior border of S1 body, even to the extent of producing sphincteric dysfunction. Understanding the basis for the symptoms helps the surgeon plan the decompression and stabilisation procedure better.

It is important in clinical examination to feel the leg pulses to rule out an additional vascular claudication. Neurogenic claudication is brought on by standing or walking; the pain is associated with numbness of the legs and is not felt while riding a bicycle. The "walk test" may bring about a new sensory, motor or reflex deficit that was not present at rest in a patient with neurogenic claudication. Vascular claudication is brought on by walking or cycling but not by standing.



Figs 4A to C: Large extruded disc in a patient with isthmic spondylolisthesis causing acute foot drop. (A) Lateral radiograph. (B) Sagittal CT reconstruction. (C) Sagittal T2 MR showing extruded, upmigrated L5-S1 disc prolapse



Figs 5A to C: Role of dynamic radiographs. (A) Lateral radiograph in extension shows hardly any spondylolisthesis. (B) Radiograph in flexion shows grade I L4-5 DSO. (C) Symptoms resolved with decompression and *in situ* instrumented PLIF (Reproduced with permission from *Progress in Clinical Neurosciences Vol. 23*)[14]

Additional diabetic neuropathy is common with DSO which causes overlapping clinical signs and will need to be ruled in or out prior to surgery with nerve conduction studies.

INVESTIGATIONS

Plain Radiographs

Plain radiographs tend to be overlooked in these days of high-tech imaging. It is humbling to see spondylolisthesis missed by MRI (done in the supine position) and picked up by a standing or dynamic lateral radiograph.[34] Figures 5A to C shows an example. The standard projections we use are: (1) anteroposterior view, which also covers the sacroiliac joints and both hip joints; (2) lateral view in the standing posture in neutral, flexion and extension. Since CT is much better at detecting the break in the pars interarticularis (Fig. 1A), we have stopped asking for oblique views to display the 'Scottie dog collar' sign. Worsening or appearance of the vertebral slip in flexion indicates a dynamic olisthesis. Around 15% of vertebral slips reduce on lying down.[38] Reduction, even if partial, in extension, suggests that such positioning of the patient is essential to improve the reduction during surgery. A forward movement of up to 2 mm in flexion is acceptable in normal persons.[28] There is often a retrolisthesis at a higher level, say L2-3 (Fig. 6). Lumbar scoliosis and degenerative disease at the adjacent levels are often found. These must be recorded to know, if the adjacent level disease seen during post-operative follow-up is a new development or not. Recognising the very common sacralisation of L5 or the much rarer lumbarisation of S1 is vital to prevent wrong level surgery.

Computerised Tomography Scan

CT scan is a *sine qua non* in our pre-operative planning. Multiplanar reconstruction of helically acquired data from a multi-detector CT done without intravenous or intrathecal contrast is our routine. Elongation of the pars and sclerosis/callus arising from healed pars defects are also seen (Figs 7A to D). CT shows spondylolysis better than oblique X-rays (Figs 1A, 7A to D and 8A to D). Our technique of CT pediculometry is shown in Figures 8A to D and it helps avoid nasty surprises on the operating table such as too narrow a pedicle or one with a very wide angle. Sagittal reconstruction can show the subtle slippage at the posterior vertebral border, without the overlap from the hypertrophic facets or iliac crests as would happen with a lateral X-ray. The sagittal reconstruction done at the levels of the facets bilaterally shows the spondylolytic defect that may be missed on lateral X-ray or MRI. This is vital in adult ISO as there is always an element of degeneration in the discs and facets, which might mislead one to think that the patient has DSO (Figs 9A to E). Coronal reconstructed images show any side-to-side translation but they are most useful for assessing the fate of the intervertebral bone graft in post-operative imaging of spinal fusion. Measuring the bone mineral density by volumetric quantitative CT can be done for osteoporosis assessment simultaneously.[37] This gives information about the osteoporosis in the vertebrae that are going to be operated upon rather than a generalised skeletal score as obtained with dual-energy X-ray absorptiometry. Intrathecal contrast CT myelography is used for those in whom MRI cannot be done (generally, because of metal artefact in the post-operative patient or severe scoliosis).

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) gives a wealth of information about the soft tissues such as intervertebral discs, synovium, ligaments and nerve roots. The ability to produce whole spine imaging is useful for picking up additional levels of disease and ascertaining the exact

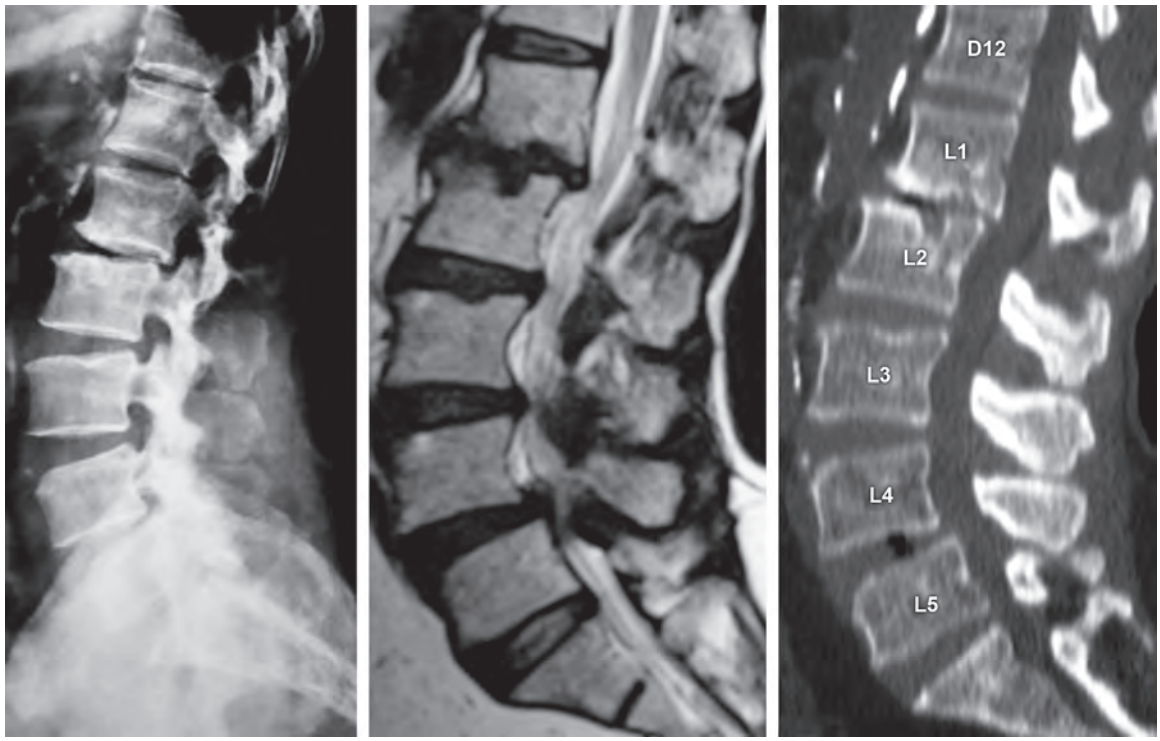
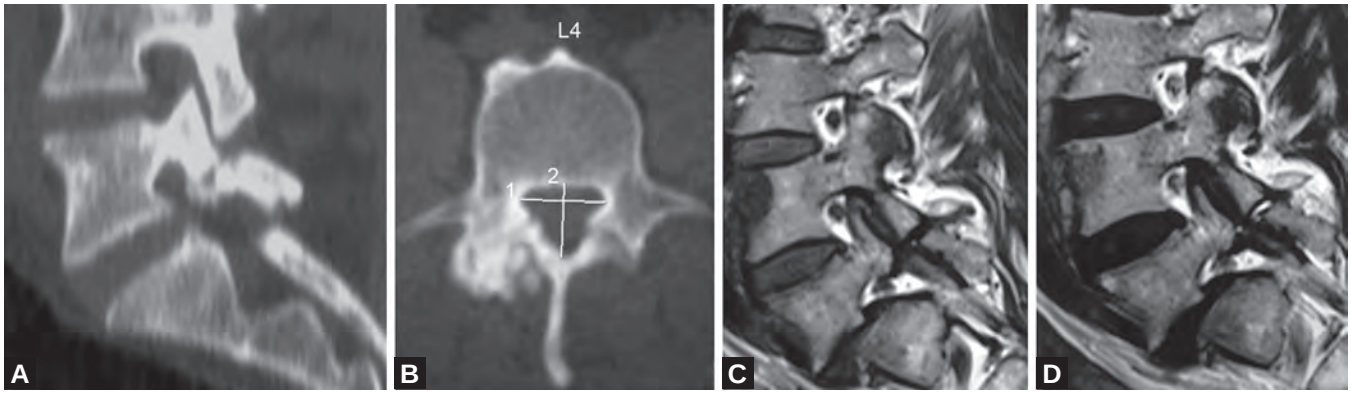
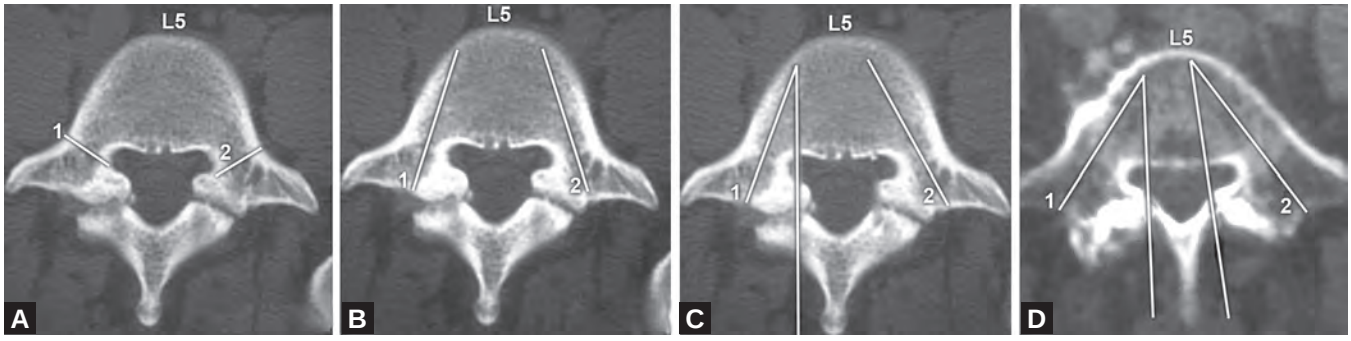


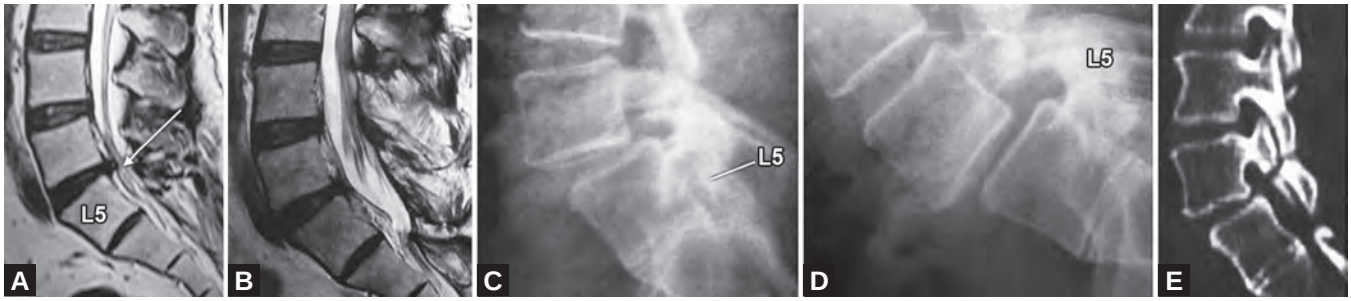
Fig. 6: Retrolisthesis at a higher level is often seen with anterolisthesis at lower level. In this patient L4-5 symptomatic anterolisthesis is accompanied by asymptomatic L1-2 retrolisthesis (lateral radiograph, MRI and CT)



Figs 7A to D: (A) Sagittal reconstructed CT showing pars break and callus. (B) Axial CT showing exuberant callus at spondylolytic defect. (C) Sagittal T2-weighted MR showing dark band at the site of spondylolysis due to loss of marrow signal. (D) Sagittal T2-weighted MR showing bright signal at the site of spondylolysis due to ingrowth of soft tissue



Figs 8A to D: CT pediculometry. (A) Pedicle width in axial plane gives the diameter of the pedicle screw needed. (B) Oblique length of drill channel gives the length of the screw needed. (C) The inclination of the pedicle to the sagittal plane (24° in this patient) gives the correct orientation for drilling. Note bilateral isthmic spondylolysis. (D) Unusually wide and varying angulation of pedicle at L5 in another patient: 29° (left) and 34° (right)



Figs 9A to E: Adult occult isthmic spondylolisthesis. (A) A 57-year-old man with L4-5 disc prolapse and canal stenosis. He underwent L3,4,5 laminectomy and L4-5 discectomy elsewhere but had worsening dynamic and static back pain and sciatica. (B) MRI 2 years later showed adequate canal restoration but did not show spondylolisthesis. (C) Standing radiograph in extension showed grade 1 L4-5 slip. (D) On flexion it increases to grade 2. (E) CT shows the defect in the L4 isthmus missed by MRI and radiographs (Reproduced with permission from *Progress in Clinical Neurosciences Vol. 23*)[14]

level by counting down from C1. Coronal plane imaging shows associated vertebral translation (Fig. 10). The distended facet sign has been described to be associated with position dependent spinal stenosis in dynamic DSO.[3] Axial loaded MRI and dynamic MRI can be done in a few centres only and unless this is done MRI will continue to miss subtle spondylolisthesis.[29] Normally, the marrow signal in the pars is uninterrupted from the superior to the inferior facet. Spondylolysis is suggested on sagittal MR images by a dark signal on all imaging sequences in the pars resulting from marginal sclerosis at the site of the break (Fig. 7C). If there is a gap at the site of the break then there will also be an increased signal in the gap resulting from the presence of soft tissue (Fig. 7D).[30] Presence of oedema in the pars indicates an acute stress fracture.[13] The wide canal sign on midline sagittal MR images is present in ISO but not in DSO (Figs 11A and B).[61] The paradiscal vertebral marrow changes described by Modic generally, indicate facetal instability.[47] These changes are discussed in greater detail in the chapter on the *Pathophysiology of Disc Degeneration* in this textbook. Large (>1.5 mm) facet effusions are predictive of L4-L5 DSO even though the slip is not seen in the MRI and only seen in erect dynamic radiographs.[7] Synovial cysts indicate disruption of facet joint function and were associated with greater progression of olisthesis after decompression in one study.[16]

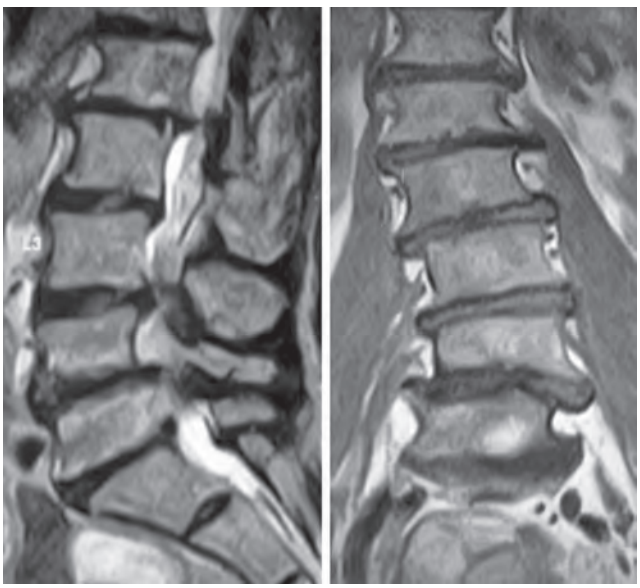


Fig. 10: Coronal plane translation in a patient with L4-5 DSO (MRI)

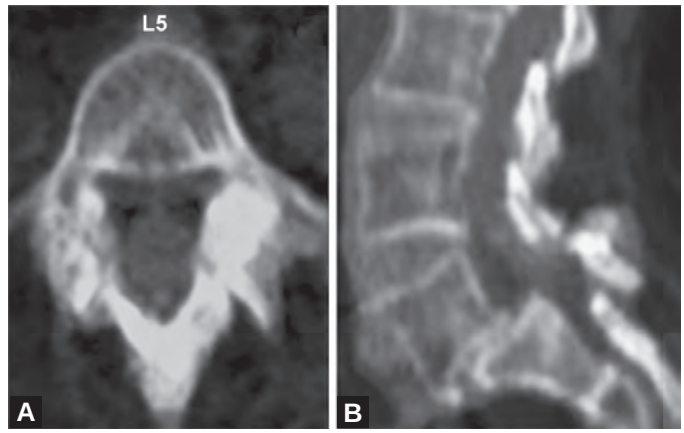
Discography

Discography is used to study the internal disruption of the disc by analysing the contrast diffusion patterns. It also aims to provoke the patient's pain. The invasiveness, rare chance of infection and poor patient acceptance of contrast discography have made many centres rely on MRI for the structural information. Modic type 1 MR changes have a high positive predictive value in the identification of pain generator and may help avoid discography.[59] Discography might help decide, if fusion surgery needs to be extended beyond the level of the olisthesis.[2]

MANAGEMENT

Conservative Management

Conservative management is indicated in patients with minimal or no symptoms. This is offered to young



Figs 11A and B: Wide canal sign is seen in ISO. (A) And is not seen in DSO. (B) Axial and sagittal CT reconstruction

patients with spondylolysis or low-grade spondylolisthesis and to the older patients with non-disabling DSO. The modalities consist of 3–5 days of rest till the acute episode of back pain resolves. Longer periods of bed rest are counter-productive. Oral analgesics, bracing, various physical therapies, epidural/facetal steroid injections and spinal flexion exercises are also prescribed but none of these have been validated by controlled trials. The wait-and-watch policy for patients without leg pain has been supported by a 10–18-year follow-up study of non-surgically managed patients with DSO.[41] Limitation of claudication producing activity is all that is needed for some elderly persons with DSO. Lack of medical fitness for surgery may rarely force one to settle for conservative treatment.

Surgical Management

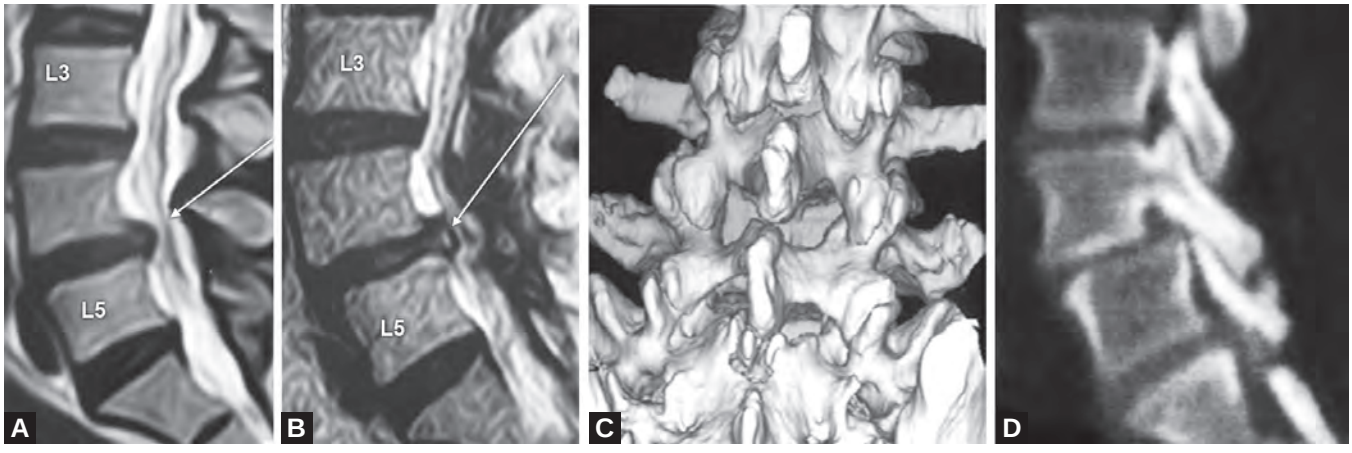
Surgical management is indicated in patients with disabling symptoms that are unrelieved by conservative management. Surgery could be offered to asymptomatic olisthetic patients with a high-risk of progression, if only we could identify that subset of patients. Unfortunately, there is no sure-shot method to do so. Factors such as spina bifida, younger age at detection, higher degree of slip at detection, female sex and dysplasia in the posterior elements have all been associated with symptom progression, but none of these are consistent markers.[8] Hence, it is prudent to wait and watch an asymptomatic patient. Clinical and/or radiological progression occurring during the observation period constitutes a strong indication for surgery.

The twin aims of olisthesis surgery are: (1) to relieve symptoms and (2) to prevent progressive worsening or recurrence of symptoms. One or more of the following is/are done at surgery for spondylolisthesis, so as to achieve these twin aims: (1) decompression; (2) reduction; (3) fusion and (4) instrumentation.

Decompression

Decompression of the nerve roots addresses the spinal stenosis and is traditionally the most important treatment for DSO and adult ISO. It may not be needed at all in young ISO patients as their neural canals are wide and they have no neural compression. In fact decompression without fusion (Gill's procedure) may be hazardous in the young patient with ISO as it leads to worsening of the olisthesis.[45] Figures 9A to E show an example of progression of adult ISO after decompression and Figures 12A to D show an example of progression in DSO after minimally invasive decompression. The decompression can take the form of unilateral laminofacetotomy, undercutting mesial facetectomy, foraminotomy, coronal hemilaminectomy (trumpet laminectomy of Kanamori) or complete laminectomy and facetectomy.[15] Partial pediculectomy, removal of osteophytes from the vertebral edges and excision of the ossified annulus may be needed.[56] Excision of thickened ligamentum flavum or hypertrophic synovium, drainage of synovial cysts, discectomy and epidural scar release are the soft tissue manoeuvres to relieve root compression. Restorative laminoplasty has also been described.[1] Over the years, decompressive surgery has become less invasive and more focused. Spinous process base osteotomy[64] and the ipsi-contra procedure[10] preserve the spinous processes and ligaments attached to it. Refinements, such as use of the operating microscope, endoscope[35] and high-speed drills, have enhanced the safety and added to operator ease. It is vital to find out what is being compressed by what and tailor-make the surgery so as to relieve it. This can be planned pre-operatively by correlating the clinical and imaging findings.

The arguments favouring a 'decompression-alone' strategy are summarised in Table 3. These are more fully discussed in an article in *Progress in Clinical Neurosciences*.[48]



Figs 12A to D: Progression of spondylolisthesis after laminotomy for DSO. (A) MRI of 61-year-old woman with L4-5 disc prolapse and grade 1 DSO. (B) Sagittal T2 MR 1 year after bilateral laminotomy/discectomy (done elsewhere)—the patient had unrelieved back and leg pain. (C) CT reconstruction to show the small laminar fenestrations and intact facets. (D) Parasagittal CT reconstruction clearly shows intact pars and grade 1 DSO. Note loss of foraminal height. Symptoms were relieved by instrumented PLIF (Reproduced with permission from *Progress in Clinical Neurosciences Vol. 23*)[14]

Table 3: Arguments favouring a 'decompression-alone' strategy in DSO

Arguments FOR performing non-fusion surgery (decompression alone)	*Arguments AGAINST performing fusion surgery (decompression + reduction, fusion instrumentation)*
Symptoms are due to nerve root compression alone and it is sufficient to relieve the compression	Spinal instability is a poorly defined entity
Decompression does not destabilise the spine	No proof that fusion gives better results
DSO is low-grade and does not progressively worsen to higher grades	Fusion surgery has more complications, has a steep learning curve and is poorly tolerated by the elderly. Convalescence is longer
Post-decompression progression of slip on radiographs may not be clinically symptomatic	A good post-operative X-ray does not equate to asymptomatic patient. On the contrary, even those with pseudarthrosis at a fusion site might be asymptomatic
Non-fusion surgery is simple, has low complication rate with shorter convalescence and is cheap	Even patients with radiologically successful fusion might have progression of spondylolisthesis
	Higher risk of adjacent level degeneration
	Higher cost and complications of instrumentation. No proof that instrumentation improves the clinical outcome. Instrumentation failure occurs
	Morbidity at iliac bone donor site is high

Reduction

Reduction of olisthesis is seldom necessary to achieve the twin aims stated above for patients with low-grade ISO or DSO. Complete (or at least partial) reduction is a fervently wished for goal in high-grade olisthesis, but it is rarely achieved in adults. Appropriate positioning of the patient on the operating table is vital for achieving reduction. The patient who has reduction on extension of the spine can be placed over bolsters under the chest and pelvis, allowing the weight of the hanging abdomen to force the lumbar spine in to extension. For others, some reduction occurs on breaking the operating table as in Figure 13. Reduction is easier to achieve and becomes neurologically safer when it is attempted after the decompression is completed, than before it. Manual traction on the vertebra applied to the neural arch or levering up the superior vertebra through the disc space can be done, but use of excessive force must be avoided. Achieving reduction is an important advantage of using metal instrumentation. Distraction force applied to pedicle screws can help achieve reduction (Fig. 14). Precontouring the vertical rod (or even better a plate) into lordosis can also force some reduction.[50] The vertical connector is fixed firmly to the caudal pedicle screw first and then the act of tightening the cranial (olisthetic) screw pulls up the slipped vertebra to at least some degree of reduction. Reduction pedicle screws bring about some additional reduction and also make it easy to place the rods through the screw heads which are at different depths due to high-grade olisthesis. It is acceptable to fuse *in situ* without making heroic attempts at reduction as long as the decompression is adequate.

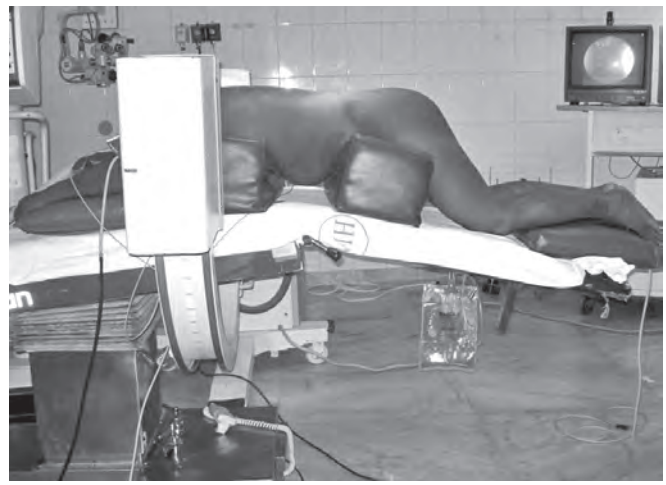


Fig. 13: Table position to maximise reduction in spondylolisthesis surgery

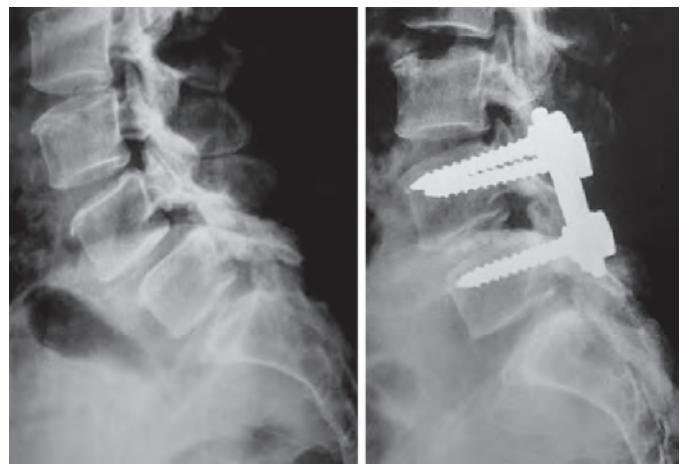
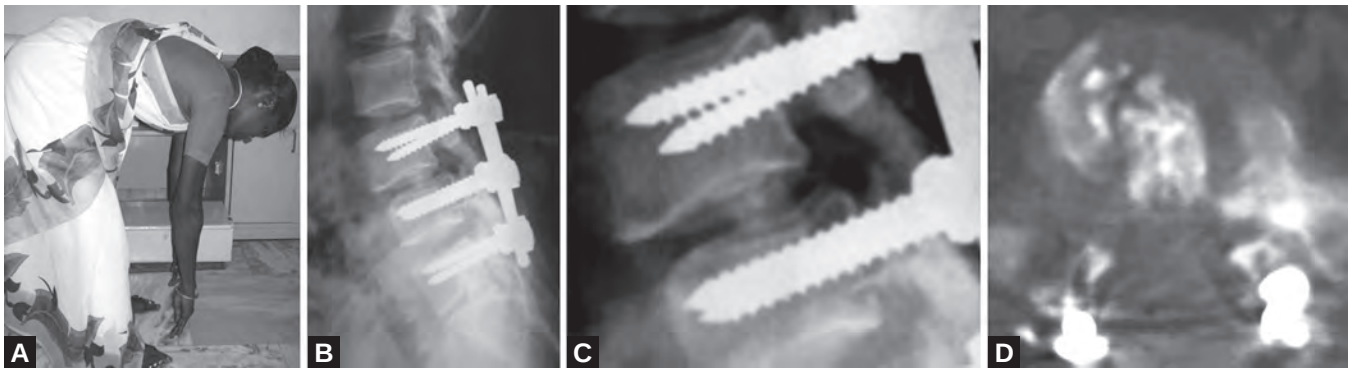


Fig. 14: Reduction of grade 1 DSO with pedicle screws in (pre- and post-operative radiographs)

Fusion

The aim of fusion is to obtain a stable spine and a pain-free patient. Fusion addresses the instability caused by



Figs 15A to D: Results 6 weeks after 2-segment instrumented PLIF for DSO. (A) Range of lumbar flexion. (B) Lateral radiograph. (C) Note onset of fusion of the chip PLIF grafts in L3-4 space. (D) Consolidation of graft in CT radiographs (Reproduced with permission from *Progress in Clinical Neurosciences Vol. 23*)[14]

the disease and aggravated by the decompression procedure. Successful fusion avoids motion at that segment and halts progression of degeneration. One or two level fusion does not greatly reduce the range of whole spine movements (Figs 15A to D). A variety of fusion procedures are available. These include intertransverse fusion (ITF), posterolateral fusion (PLF), posterior lumbar interbody fusion (PLIF), transforaminal lumbar interbody fusion (TLIF), anterior lumbar interbody fusion (ALIF) and circumferential (270° or 360°) fusion. Autografts, allografts (locally banked cadaveric bone or commercially available femoral rings) and xenografts (bovine bone) are used in various combinations. The autograft may be obtained from the lumbar spine during decompression or separately from the iliac crest. Morbidity at the iliac crest donor site is considerable. Persistent iliac pain was reported by a third of the patients 2 years after surgery in a recent prospective study.[54] This has prompted a switch to the use of local bone or cages. Cages for interbody fusion are made of titanium, carbon fibre, ceramic or polyethyl ether ketone. They come in various shapes such as threaded cylinders, spiked cuboids, tapered cuboids or the expandable variety. Anterior interbody fusion relies more on cages as the neural structures do not come in the way of implanting large cages. With instrumentation becoming nearly universal, it may not be necessary to get blocks of bone; morsellated chips obtained during decompression fuse just as well (Figs 15A to D). Good results have been reported with chip grafts in both PLF and PLIF.[33,57] Recombinant human bone morphogenic protein has been used to increase the chances of fusion and it might even obviate the need for a bone graft.[32] Progression of degeneration at the level adjacent to the fused segment is seen in about 15% of patients at 3–4 years at follow-up imaging.[17] It must be remembered that not all adjacent level degenerations are symptomatic.[42]

The arguments favouring fusion surgery are outlined in Table 4 and are fully discussed in an article in *Progress in Clinical Neurosciences*.[14] There is now evidence from 13 small randomised trials and comparative observational studies showing that a satisfactory outcome is more likely with fusion than with decompression alone for DSO.[52] A meta-analysis of retrospective series up to 1993 indicated success rates of 69%, 86% and 90% for decompression, non-instrumented fusion and instrumented fusion respectively for DSO.[40] Long-term (11–17 years) follow-up studies and patient satisfaction studies have also demonstrated superiority of fusion over non-fusion procedures in both DSO and ISO.[14] In 47 patients of DSO followed up for 5–14 years the clinical outcome was excellent to good in 86% of patients with a solid arthrodesis but only in 56% of patients with a pseudarthrosis.[36] Failed posterior surgery is an indication for anterior lumbar interbody fusion.[12]

Instrumentation

There is no consensus on the use of instrumentation in lumbar fusion. The reasons for performing instrumented fusion are summarised in Table 5. The fusion rate was higher (82%) with the use of instrumentation as opposed to the non-instrumented cases of DSO (45%) in a prospective randomised trial but it is not certain, if that automatically means better clinical outcome.[18] In a study of 44 patients of DSO followed for a minimum of 2 years, the rate of progression of spondylolisthesis was least with instrumented fusion, intermediate with non-instrumented fusion and highest with decompression alone.[5] The previously used posterior instrumentation using sublaminar wires and Luque rods or Hartshill rectangles is now supplanted by transpedicular screws.[44] Since they provide three column support, pedicle screws are the stablest of devices.[24] The vertebral slip can be corrected by distraction-lordosing. It is acceptable to obtain *in situ* fusion in low-grade olisthesis as long as the nerve root space is well-decompressed. The decompression and, therefore, the instrumentation and fusion might need to extend to adjacent stenotic levels in DSO (Figs 16A to C). The recent advances include use of neuronavigation for proper placement of the screw and percutaneous placement of pedicle screws.[20,51] Use of navigation helps minimise radiation exposure of the operating room personnel. Pedicle screw placement is an exacting technique with a steep learning curve. Complications of pedicle screws and ways to avoid them

Table 4: Arguments favouring fusion surgery in DSO (Reproduced with permission from *Progress in Clinical Neurosciences Vol. 23*)[14]

Arguments AGAINST performing non-fusion surgery (decompression alone)	*Arguments FOR performing fusion surgery (decompression + reduction, fusion instrumentation)*
Decompression adds to biomechanical weakening caused by established and ongoing degeneration, leading to worsening of symptomatic instability	Pain is not only due to static nerve compression, but mainly due to dynamic instability. Successful fusion relieves symptoms better and prevents further progression
Root pain may be relieved for sometime after decompression, but disabling back pain due to instability persists and root pain recurs	Recent advances make fusion surgery safe, simple and patient friendly. Increased experience reduces the complication rate
Surgeon hesitates to do the required degree of decompression for fear of inducing further instability. Inadequate lateral canal decompression is a common cause of failed back surgery syndrome	While adjacent level degeneration does occur after fusion, it is overestimated and not clinically relevant
Should the patient ultimately need a fusion, it is two operations, greater cost and longer convalescence	Literature evidence favouring fusion surgery
Not fusing an unstable or potentially unstable spine may be a ground for litigation	Use of instrumentation increases chance of good fusion
	Increased cost of instrumentation is offset by a quicker return to occupation
	Alternatives are available now to rigid fixation

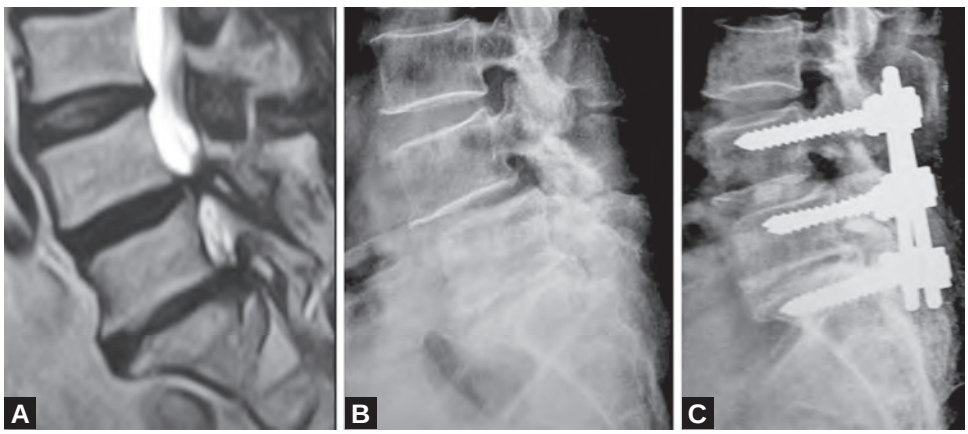
Table 5: Reasons for using instrumentation in lumbar fusion (Reproduced with permission from *Progress in Clinical Neurosciences Vol. 23*)[14]

- Immediate stabilisation
- Quicker ambulation and return to work
- Reduction of spondylolisthesis
- Correction of kyphosis or scoliosis
- Maximise chances of fusion
- Use in situations where fusion chances are lower (osteoporosis, smokers)
- Minimise the chances of recurrence of spondylolisthesis or stenosis
- Better clinical outcome

are listed in Table 6 but significant complications are rare in experienced hands.[31] In mild grade DSO, interbody cages might even obviate the need for pedicle screws (Fig. 17). There is a small randomised Chinese study that shows as good results with unilateral decompression and cage placement as with a bilateral procedure.[68]

Surgical Techniques

The details of the operative approaches, their merits, complications and results can be obtained from textbooks of operative techniques in spine surgery.[38] Only some salient facts are mentioned in this chapter. In our centre, the neurosurgeon and the orthopaedic surgeon perform spondylolisthesis surgery as a team. This has enabled us to bring together our unique training, attitudes and skills in managing spondylolisthesis. Thus, we are able to safely offer instrumented fusion for patients who have been denied surgery or offered only decompressive surgery elsewhere. Pre-operative percutaneous transpedicular external fixation has been tried in some centres to predict the response to fusion surgery, but we do not use it.[62] The obese patient is motivated to lose weight and the need for exercises to maintain back



Figs 16A to C: L4-5 DSO with L4-5 and L5-S1 canal stenosis. (A) MRI. (B) Erect lateral radiograph before operation. (C) The patient was relieved of back pain and claudication after canal decompression, partial reduction and pedicle screw instrumented PLIF. L5-S1 had to be included as there was significant degeneration and need for wide decompression at this level even though this level was not olisthetic

Table 6: Complications of and avoidance of complications in lumbar pedicle screw surgery

Intra-operative complications	*Avoidance*
Screw misplacement in pedicle Medial breach-dural tube injury, CSF leak Inferior breach-nerve root injury Lateral breach-screw loosening All walls—pedicle fracture Screw misplacement in body Excess screw length—aorta injury Insufficient screw thickness-loosening High placement-entry into disc space	Careful study of radiographs prior to surgery, CT pediculometry, correct identification of anatomical landmarks, precision drilling under lateral image intensifier control, checking of drill path position in AP view before tapping or screw placement, using paraspinous transmuscular approach rather than the midline approach, use of neuronavigation
Inability to mate the screw heads Sagittal plane-due to olisthesis Coronal plane-medial or lateral pedicle entry point	Use of reduction screws, contour the rod or plate, place screw in next higher level Use of polyaxial screws
Osteoporotic bone Screw loosening Iatrogenic fracture	Pre-operative bisphosphonate therapy, undertapping of pedicle, use of larger diameter screw, avoidance of excess force, PMMA bone cement in drill hole, inclusion of additional levels, use of transverse connectors, post-operative orthosis
Blood loss during exposure	Use of paraspinous transmuscular or percutaneous approach, avoiding too much transverse process exposure, lighting and magnification, use of bipolar cautery, hypotensive anaesthesia
Muscle and skin edge damage from retraction	Use of paraspinous transmuscular approach, releasing retraction from time-to-time
Post-operative complications	*Avoidance*
Screw back-out Small diameter or length of screw Lack of convergence Stress fracture, osteoporosis Infection Lack of bone fusion, progression of olisthesis	Choose correct screw dimensions Start drill path laterally for convergence Orthosis, avoid straining the back Antibiotics, meticulous technique Place adequate bone, bone morphogenic protein
Screw breakage	Use standard implants, ensure that threaded portion is fully in the bone
Slipping of rod	Adequate tightening of 'inny' nut and 'outy' bolt, avoid soft tissue interposition, use rod of adequate length
Neurological deficit	Avoid root injury
Wound infection	Antibiotics, meticulous technique
Chronic pain	Avoid root compromise, adequate decompression, additional anterior fusion
Interference with MR imaging	Use of titanium instead of stainless steel implants

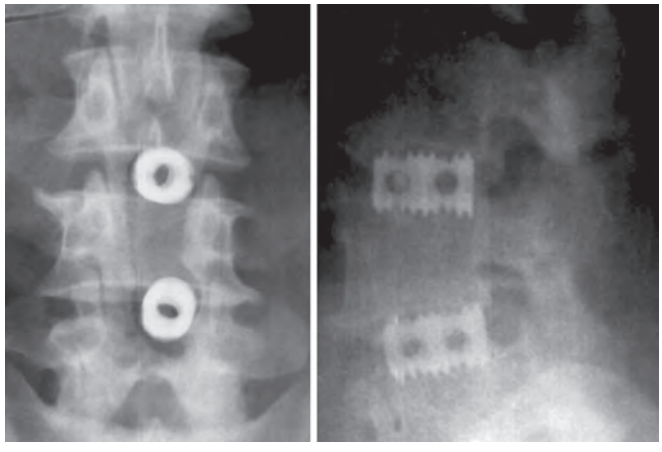


Fig. 17: Cages for lumbar fusion implanted through posterior approach (AP and lateral radiographs)

fitness is stressed repeatedly. Psychosocial issues must be sorted out before surgery. Poor general health, severe osteoporosis and extensive multilevel spondylotic disease contraindicate surgery.

Uninstrumented fusion: Intertransverse fusion using 'H' shaped grafts and posterolateral (facetotransverse) *in situ* bone fusion (PLF) using slivers of autografts were the standard techniques in the past. For the fusion to take well, adequate clearance of muscle and periosteum from the fusion surface was needed. This called for a paraspinous transmuscular (Wiltse) approach through a single midline or a horizontal incision (through which an iliac graft also could be harvested) or two paired paraspinous incisions. These procedures also entailed prolonged immobilisation, strict use of orthosis and restriction of activities. Our practice in the past was to

Table 7: Disadvantages of the conventional midline approach and advantages of the paraspinous transmuscular approach to open lumbar pedicle screw placement (Adapted with permission from *Progress in Clinical Neurosciences Vol. 23*)[14]

Disadvantages of the conventional midline approach	*Advantages of the bilateral paraspinous transmuscular approach*
Erector spinae muscle damage	Reduced muscle damage
Prolonged retraction	No prolonged retraction
Ischaemic damage	No ischaemia
Physical trauma	No physical injury
Bulk of muscle	No bulk of muscle
Prevents lateral starting of screw track	To prevent lateral starting of screw track
Convergence of screws difficult	Convergence of screws easy
Medial pedicle breach, risk to nerve root	Least possibility of breaching medial pedicle wall or damaging root
Poorer purchase, especially in osteoporotic bone	Good purchase even in osteoporotic bone
Needs cross-connector to prevent toggling	Cross-connector not needed for 1 level
Comes in the way of taps and wrenches	Does not interfere with taps and wrenches
Anatomical landmarks obscured, especially when facets are hypertrophic	Anatomical landmarks not obscured
Longer incision, skin necrosis from retraction	Shorter incision, no skin necrosis
Longer duration of surgery	Shorter time of surgery
Blood loss, need for drain	Minimal blood loss, no need for drain
Longer recovery time, pain	Shorter recovery time, less pain, analgesic need

do uninstrumented PLIF using iliac bone block autografts. When this procedure is done under the operating microscope through adequate laminofacetectomies, the risk to the nerve root is minimised. The bone grafts have a wider area of contact and are placed in compression between the bodies allowing early ambulation and ensuring adequate union.[49] PLIF also allows restoration of disc height. We should not forget that procedures like PLF and PLIF have a long history and have given good results in the hands of experts. An example is Yamamoto's series of 67 patients of DSO who had PLIF, nearly 2/3rd of them without pedicle screw augmentation.[67] The ultimate fusion rate was 94% (including delayed fusion and collapsed fusion) and 89% were reported to be in the excellent or good category. This is to be compared with the 64–80% good results reported by most series for initial decompression alone.[15]

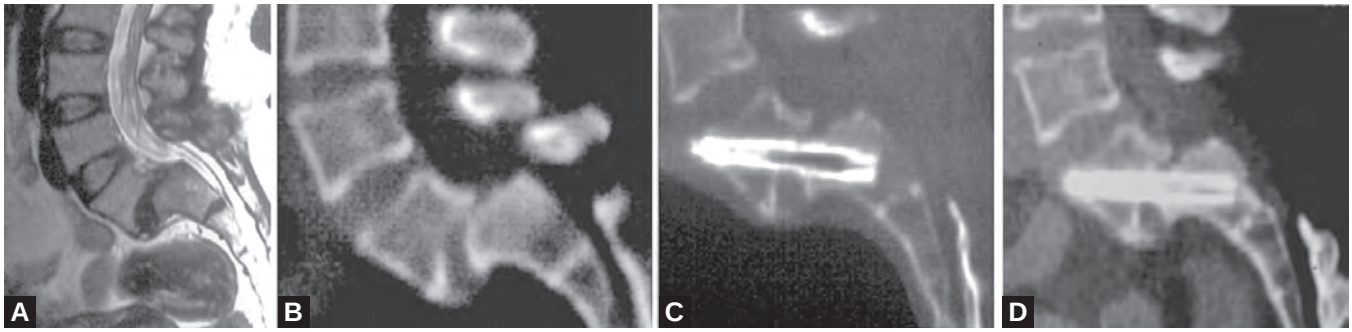
Anterior lumbar interbody fusion (ALIF) which used to be done through the transperitoneal approach was a major surgical undertaking.[26] We now, prefer the open mini-extraperitoneal anterior or anterolateral approach.[4] The results with ALIF have been demonstrated in 33 patients (including 13 with spondylolisthesis) with failed back surgery syndrome, in whom the back pain, leg pain and functional status improved significantly to 76%, 80% and 67% respectively. The complications related to the approach were iliac vein injury and ileus.[12] In cases of pathological spondylolisthesis where there is considerable destruction of the bodies, we prefer to do anterior debridement and fusion along with posterior pedicle screw instrumented PLF in a single session or as a two-stage procedure. Pyogenic spondylodiscitis, tuberculosis and tumours are common examples.

Instrumented fusion: Our standard procedure consists of pedicle screw instrumented posterior lumbar interbody fusion using bone chips derived from the laminofacetectomy. Since we encountered several disadvantages with the conventional midline approach (Table 7), we have switched to the bilateral paraspinous transmuscular approach in the last 5 years. This approach is akin to the Wiltse approach originally described for PLF.[63] Our technique of bilateral paraspinous transmuscular approach is described in an article in *Progress in Clinical Neurosciences*.[14] The advantages of the bilateral paraspinous transmuscular approach are listed in Table 7. This approach is ideal for patients with a midline scar from previous surgery. In patients with high-grade L5-S1 olisthesis, we have used trans-sacral fibular strut grafting, which can give a stable fusion without the need for pedicle screws.[55] Figures 18A to D show an example of such a procedure done through the posterior route.

Post-operatively, the patient is ambulated as early as possible, generally by day 2 or 3 and discharged by day 4 or 5. Back exercises are taught and activity gradually increased in the second week after the sutures are removed. Most patients resume low levels of activity in the 3rd to 4th week and unrestricted activity after 3 months. Corsets are not used routinely. Follow-up standing radiographs in flexion and extension are done at 3 months and at 1 year.

CONCLUSION

The key to success in managing lumbar spondylolisthesis is to know in whom, when and how to intervene. The best results are obtained in a symptomatic patient in good general health who does not have psychological overlay. The surgical team performing spondylolisthesis surgery must be conversant with more than one method of doing surgery but need not necessarily be capable of doing every conceivable procedure in the book. The



Figs 18A to D: High-grade dysplastic spondylolisthesis treated by posterior to anterior trans-sacral fibular strut graft fusion. (A) MRI. (B) CT (prior to surgery). (C) Immediate. (D) 1 year follow-up CT after fusion

wise surgeon would desist from trying out every new spinal implant introduced by a commercially motivated industry. Results improve when the team does the same procedure again and again over the years.

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117 Skeletal Fluorosis

Raja Reddy D, Srikanth R Deme

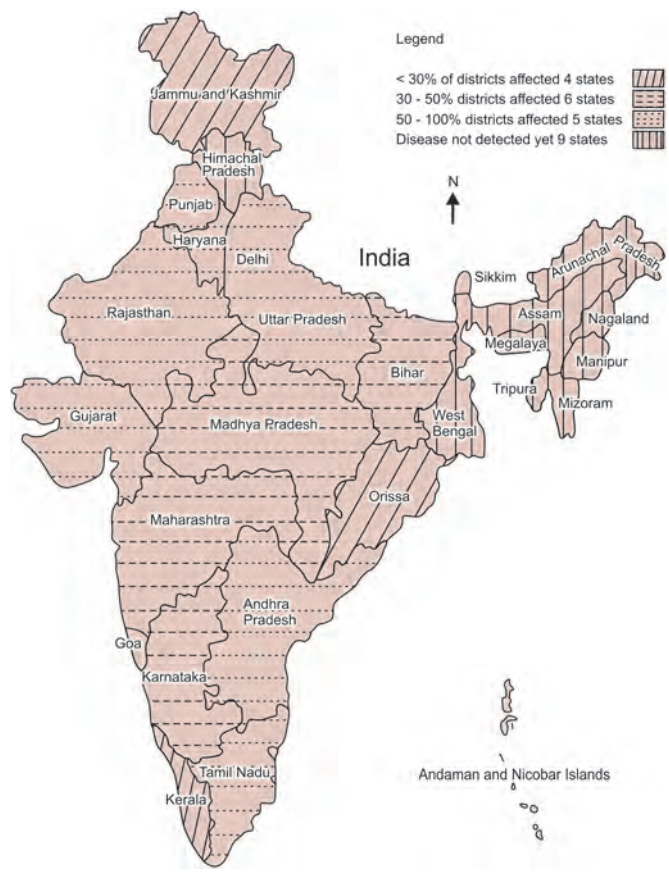
INTRODUCTION

Fluorine, a gaseous element, is a halogen which being electronegative and reactive of all elements does not occur in free form in nature. This element was isolated in 1886 by Nobel laureate Henri Moissan and it combines directly with most elements and indirectly with a few to form fluorides. Fluorides are ubiquitous in nature and are present in rocks, soil, water, plants, foods and even air.

The relationship between fluoride and dental caries was first noted in the early part of the 20th century when it was observed that residents of certain areas of USA developed brown stains on their teeth. These stained teeth, although unsightly, were highly resistant to dental decay and caries.[5] In 1930s, it was discovered that the prevalence and severity of this type of mottled enamel was directly related to the amount of fluoride in the water.[93] Subsequently, it was recognised that fluoride consumption in optimal amounts in the water supply imparted protection against the development of dental caries without staining the teeth.[13] Another benefit of fluorides is that the incidence of osteoporosis seems to occur less frequently in regions with high fluoride content in water than in those in which the inhabitants consumed little fluoride. Although, the importance of this element to normal mineralisation of hard tissues and formation of caries resistant enamel has been recognised, there has been as yet no conclusive evidence proving that it is an essential element for human health.[45] Indeed, a fluoride deficiency syndrome is yet to be described. This may be due to the fact that human body requirement of this micronutrient must be small which is met with naturally through food and water. Excessive ingestion of fluoride through water, food or dust causes acute toxicity or a debilitating disease called 'fluorosis', a term coined and first used by Cristiani and Gautier in 1925.[11] Acute fluoride intoxication is rarely seen and results most frequently from accidental ingestion of large amounts of fluoride compounds. The acute lethal dose of fluoride for a 70 kg man is 2.5–5.0 gm. Chronic fluoride poisoning is more common and can affect animals as well as humans. Excessive intake during the pre-eruptive stage of teeth leads to dental fluorosis and further continued ingestion over years and decades causes bony or skeletal fluorosis. Lastly, crippling disease produces neurological manifestations.

Feil first mentioned fluorosis in humans as an occupational disease in 1930.[16] This was substantiated when the occurrence of skeletal fluorosis in cryolite miners was reported in Denmark.[48] Skeletal fluorosis was next reported as a disease endemic to an area in India.[83] Their study led to the publication of first reports of neurological manifestations of fluorosis in the late stages. Subsequently cases of endemic and industrial fluorosis have been reported from various parts of the world.[61]

High incidence of endemic fluorosis in India is due to the fact that large areas of the country contain water supplies having high levels of fluoride. All states of India except the Northeast and Himachal Pradesh reported cases of fluorosis and 25–30 million people are exposed to high fluoride intake and half a million suffer from skeletal fluorosis (Map 1). In China, 300 million people are living in endemic areas of fluorosis out of which 40



Map 1: Incidence of fluorosis in different states of India

million have dental fluorosis and 3 million suffer from skeletal changes.[41]

METABOLISM OF FLUORIDE

Biological effects of fluoride intoxication are related to the total amount of fluoride ingested whatever the source, be it food, water or air.

Sources of Fluoride

Foods

Nearly all foods contain small quantities of fluoride and the total daily intake through any average human diet is small except in endemic regions. In certain endemic regions of India, the fluoride content of vegetables and food may be very high.[7] The contribution of food to the total daily intake of fluoride varies from region to region. Staple diets rich in Sorghum, *Ragia* or *Bajra* containing high silicon besides fluoride seem to aggravate fluoride toxicity in some endemic areas of India.[3,57]

Water and Beverages

In case of natural waters, the variation in the fluoride content from region-to-region is dependent upon such factors as the source of water, type of geological formation and the amount of rainfall. Surface waters generally have low fluoride while ground water may have high concentrations of fluoride as has been found in many parts of the world. The fluoride content of water in different parts of India is shown in Table 1. The highest fluoride concentration of 28.9 PPM was reported from India.[7] The fluoride content of seawater varies from 0.8 to 1.4 PPM, which explains why the fluoride content of diet rises when sea food is consumed. Among beverages, tea has an exceptionally high fluoride content which varies in different brands from 122 to 260 PPM or more. Each cup of tea may supply 0.3–0.5 mg of fluoride. Bottled beverages, which are increasingly being consumed around the world, have a variable content of fluoride and should be considered as additional sources of fluoride.

The fluoride intake dependent upon consumption of drinking water and beverages is determined by such factors as body size, physical activity, food habits and variations in atmospheric temperature and humidity.[22] That is why in tropical countries, like India, the daily fluoride intake is very high. Farm labourers drink a lot of water from wells and naturally have high fluoride intake and are at risk of developing fluorosis.

Table 1: Incidence of fluoride in water resources of India

States	*No. villages having maximum F > 2.0 mg/L*	*Fluoride level mg/L*
Andhra Pradesh	1245	28.9
Bihar	100	4.4
Gujarat	250	5.0
Haryana	360	11.0
Karnataka	300	8.0
Madhya Pradesh	150	7.0
Maharashtra	250	3.8
Orissa	200	4.0
Punjab	80	12.0
Rajasthan	450	28.0
Tamil Nadu	315	8.0
Uttar Pradesh	300	4.5

Optimum fluoride level in drinking water for a tropical country like India is < 0.5 PPM or 0.5 mg/L

Air

The atmosphere has very low fluoride content, and in 97% of non-urban areas fluoride is hardly detectable. The fluoride content of the atmosphere rises wherever there is volcanic action or industrial activity. Volcanic fumarole vapours have high concentration of fluoride, and industrial emissions from mining or manufacture of fluoride containing minerals may be hazardous. Low-grade coal has high levels of fluoride and smoke may be a source of fluoride pollution.

Total Daily Fluoride Intake

The fluoride contents from all the sources determine the human intake of fluoride. In the majority of endemic areas around the world, the main contribution is from water, and only in a few areas of India and China significant amounts come from food and, rarely, polluted air is the culprit. The estimated range of safe and adequate intake of fluorides for adults is 1.5–4.0 mg/day and it is less for children and those with renal disease. The daily intake of fluoride in endemic regions varies from 10 to 35 mg and can be even higher in summer months.

ABSORPTION OF FLUORIDES

Soluble inorganic fluorides ingested through water and food is almost completely absorbed and also those inhaled from the respiratory tract. Absorption of less soluble inorganic and organic fluorides varies from 60 to 80%.[10] Fluorides are absorbed from the gastrointestinal tract by a process of simple diffusion without any mechanism of active transport being involved. Various dietary components apparently influence the absorption of fluoride from the gut. It has been noticed that salts of calcium, magnesium and aluminium, when added to the diet, reduce the quantum of fluoride absorption on account of the formation of their less soluble compounds. This is the reason why waters with high calcium and magnesium content check the incidence of fluorosis, as indicated by epidemiological studies.[31] Therefore, it is to be expected that all other factors being equal, the incidence of skeletal fluorosis would be less where the calcium and magnesium content of drinking water is high.[62] It is noteworthy that administration of magnesium salts (serpentine and magnesium hydroxide) to patients

suffering from fluorosis and experimental animals has increased the faecal and urinary excretion of fluorides. Similarly, increased absorption of fluoride from the gastrointestinal tract ensues from the addition of substances, like phosphates, sulphates and molybdenum, to the diet and these can increase fluoride toxicity.[14]

DISTRIBUTION OF FLUORIDES

About 96–99% of the fluoride retained in the body combines with mineralised bones, since fluoride is the most exclusive bone-seeking element on account of its affinity for calcium phosphate.[4] But it has been noticed that there is no significant retention of it in the body, if very small quantities of fluorides are ingested.[46] In fact, there was no discernible retention of fluoride when up to 4–5 mg was ingested daily. But when more than 5 mg were ingested about half of it appeared to have been retained by the skeleton and rest excreted through urine. Observations show that after absorption from the gut fluoride enters the circulation, with plasma fluoride accounting for three fourths of the total amount of fluoride found in whole blood and the rest is in the cells. Fluoride in plasma exists in free ionic and bound forms, the latter bound to serum albumin forming about 85% of the total amount of fluoride in plasma.[98] Plasma fluoride in normal individuals in non-fluoridated areas ranges from 0.14 to 0.19 PPM and is higher in fluorotic patients.[88] Newer methods, which only measure the ionic component of plasma fluoride levels, show lower values which range between 0.004 PPM and 0.008 PPM when drinking water contained traces of fluoride and varied from 0.1 to 0.2 when water was fluoridated. Plasma fluoride concentrations tend to increase slowly over the years. It is seen that plasma levels of fluoride do not fluctuate widely despite a wide variation of fluoride levels in drinking water presumably due to the action of some regulatory mechanisms, which have not yet clearly been identified.[86] The sequestration of fluoride into the skeleton, urinary excretion and loss sustained through sweat helps in regulation of plasma fluoride. The levels of fluoride in most soft tissues of the body are lower than 1 PPM but are higher than those of plasma. The fluoride content of the brain is 0.4–0.68 PPM and the concentration in cerebrospinal fluid (CSF) is 0.1 PPM which is lower than that of plasma.[25]

The uptake of fluoride by the skeleton is very rapid and depends upon the vascularity and the rate of its growth. The fluoride uptake of young bones is faster than that of mature bones. The fluoride is incorporated more readily in the active, growing and cancellous areas than in the compact regions. It has been observed that skeletal fluoride concentration increases almost proportionately to the amount of fluoride ingested and the duration of its ingestion.[95] The amount of fluoride present in various bones of the same skeleton differs from bone-to-bone with the pelvis and vertebrae registering higher fluoride content than limb bones. Even in the limb bones, the amount of fluoride deposited in them depends upon the activity of muscles attached to them. In caged monkeys, the fluoride content of the upper limb bones is more than that in the lower limb bones. It is this increase in the fluoride content of the skeleton that provides the most reliable clue to excessive fluoride intake. The other indicators, such as urine and soft tissue levels which manifest wide fluctuations, cannot be relied upon. Once incorporated into the hard tissues, the fluoride is retrievable, although with difficulty, and entails an extremely slow process of osteoclastic resorption spread over many years.

EXCRETION OF FLUORIDES

Faeces

Fluoride present in faeces comes from two sources: (1) the ingested fluoride that is not absorbed and (2) the absorbed fluoride that is excreted into the gastrointestinal tract. About 10–25% of the daily intake of fluoride is excreted in the faeces.

Urinary

The elimination of absorbed fluoride occurs almost exclusively via the kidneys. Urinary fluoride in normal individuals fluctuates widely between 0 PPM and 1.2 PPM with an average of about 0.4 PPM when the fluoride content of drinking water is 0.3 PPM.[102] Urinary levels of fluoride are higher in individuals exposed to higher intake of fluoride. The renal clearance of fluoride is directly related to urinary pH and, under some conditions, to urinary flow rate. In alkaline urine, the fluoride is present in ionic form and hence its renal clearance is rapid. In acidic urine, on the other hand, fluoride is present in non-ionic form (HF) and hence it is rapidly reabsorbed by the renal tubules. The excretion of fluoride is much less if the person concerned is suffering from chronic kidney disease resulting in renal failure, which inevitably leads to high concentrations of fluoride in serum as well as bone.[111] In experiments on rats with renal insufficiency, increased intake of fluoride caused decreased glomerular filtration rate and increased blood urea nitrogen along with increase in serum and bone concentrations of fluoride. Since disturbed renal function predisposes to excessive retention of fluoride, individuals suffering from chronic renal failure may, therefore, develop skeletal fluorosis even at a considerably low level of 1 PPM of fluoride in drinking water.[52,68,106]

Sweat

Some fluoride is also lost from the body through sweat, and so, appreciable amounts may be lost in situations marked by excessive sweating. Sweat fluoride concentrations are similar to plasma.

Other Routes

The amount of fluoride in breast milk is low and the same is true of saliva.

CLINICAL FEATURES

Fluoride intoxication presents an extraordinary degree of uniformity in its clinical manifestations. It occurs in humans as dental and skeletal fluorosis. They are separated by a prolonged, relatively symptom-free interval during which the skeleton does not stop accumulating fluoride. In its advanced stages, skeletal fluorosis causes crippling deformities and neurological complications.

The effects of fluoride intoxication are related to the total amount of fluoride ingested, although earlier, only water was taken into account presumably because the supply of fluoride by food was deemed negligible. The safest minimum daily intake of fluoride is not known.[15] Earlier reports suggested that any daily ingestion of over 28 mg of fluoride would be harmful.[6] Subsequent studies cited 20 mg as the maximum safe limit,[26] but in endemic areas where the presence of local factors, like nutritional status and prolonged exposure, tend to aggravate the fluoride toxicity, the safe level of fluoride intake may be even lower. In India, balance studies of the cases of endemic skeletal fluorosis revealed an average fluoride intake of 9.88 mg and it is held that any intake of more than 8 mg would be harmful.[29] Kreptogorsky[37] suggested 3.2 mg as the highest level of fluoride intake, which could be deemed safe. It is true that in persons with normal functioning kidneys there is a wide margin of safety.

Dental Fluorosis

Dental fluorosis mainly involves enamel but severe intoxication may affect the dentine as well as the pulp. Enamel fluorosis occurs when fluoride concentrations in or in the vicinity of the forming enamel are excessive during its pre-eruptive development. Mottling of teeth is one of the earliest and most easily recognisable features noticed in the first decade of life (Fig. 1). Both sexes are equally affected. The permanent teeth are affected and they lose their normal creamy white translucent colour and become rough, opaque and chalky white. Pitting and chipping are other marks of fluorosis. Brown or black pigment gets deposited on the defective enamel and, once established, tends to remain there permanently. Incidence of dental fluorosis in endemic areas exhibits a linear relationship to the fluoride content of water, but it may also vary with other factors.[30] Dental fluorosis does not obviously occur when there has been no exposure to fluoride in the first decade of life.

Pre-Skeletal Stage

The duration of this stage may vary with the amount of fluoride ingested daily. Reportedly, it ranges from 10 to 30 years or even longer in endemic areas and from 10 to 15 years or longer in cases of industrial fluorosis.[19,89] In the early stages in endemic regions, generally, signs or symptoms do not appear. The persons concerned may occasionally complain of pain in the small joints of the limbs and back, which are often mistaken for rheumatoid arthritis or ankylosing spondylitis. However, various reports from Europe and America suggest that there would be symptoms corresponding to gastrointestinal, musculoskeletal, respiratory and visceral systems during this stage.[58,79,104] The majority of these visceral symptoms may be due to allergy to fluoride in susceptible individuals or the effect of fluoride on the various target organs, and these are non-specific.

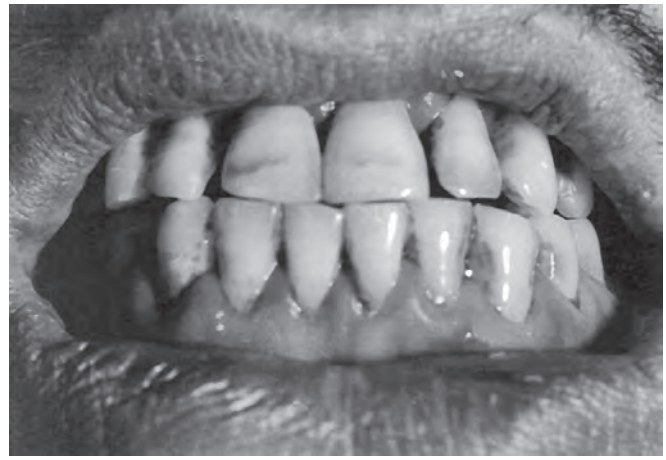


Fig. 1: Characteristic mottling of teeth with pigmentation

Skeletal Fluorosis

Early in the development of fluorotic changes in the skeleton, the patients often complain of a vague discomfort and paraesthesiae in the limbs and the trunk. Pain and stiffness in the back appear next, especially in the lumbar region, followed by the dorsal and cervical regions. Restriction of spine movements is the earliest clinical sign of fluorosis. The stiffness increases steadily until the entire spine becomes one continuous column of bone, manifesting as a condition referred to as 'poker back' (Fig. 2). In man, the spine is most likely to be affected first and severely due to its being required to sustain the erect posture.[49] When the condition becomes severe and chronic, various ligaments of the spine are involved and it soon spreads to various joints in the limbs owing to the involvement of the joint capsules, the related ligaments, tendinous attachments to the bones and interosseous membranes. The involvement of the ribs gradually reduces the movement of the chest during breathing, which finally becomes mainly abdominal. When that happens, the chest assumes a barrel shape. With the increasing immobilisation of the joints due to contractures, flexion deformities may develop at the hips, knees and other joints, which make the patient bedridden. Bony exostoses may also appear over the limb bones, especially around the knee, the elbow and on the surface of the tibia and ulna. Despite the fact that the entire bone structure has become affected, the mental faculties remain unimpaired till the last stages are reached.

Fig. 2: Marked rigidity of spine with restricted movements

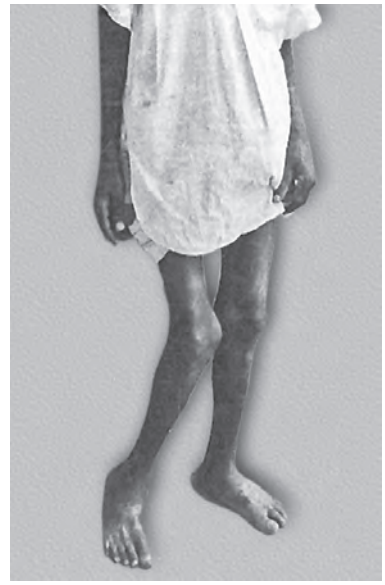


Fig. 4: Genu valgum deformities of the lower limbs

The stage at which skeletal fluorosis becomes crippling usually occurs between 30 years and 50 years of age in the endemic regions (Fig. 3). Newcomers to a hyperendemic region may sometimes develop symptoms of skeletal involvement within 4 years of their arrival.[83] Men suffer more than women from severe affects of the disease, presumably because their work is usually more strenuous than that of women.[30,83] The factors which govern the development of skeletal fluorosis are: (a) high levels of fluoride intake; (b) continual exposure to fluoride; (c) strenuous manual labour; (d) poor nutrition and (e) impaired renal function due to disease.[12,57,62] In regions with very high fluoride content, the disease may affect younger age groups including children. The longer the exposure to fluoride the higher will be its incidence. In tropical countries, skeletal fluorosis occurs even while drinking low levels of fluoride. It is the farm labourers who are prone to develop fluorosis rather than those engaged in sedentary occupations. Epidemiological observations revealed that nutritional status might influence chronic fluoride toxicity. Trace elements do play a role in fluoride toxicity. Aluminium, arsenic, selenium and strontium are known to aggravate fluoride toxicity, whereas calcium and magnesium have a beneficial role. Some of these elements are found in abnormal concentrations in drinking water supplies of endemic areas.[63] They may be responsible for the severe nature of fluoride intoxication in these regions.

Fig. 3: Crippling stage of skeletal fluorosis with deformities of limbs

Endemic Genu Valgum

Deformities occur most notably in weight-bearing lower limbs in children poorly nourished with a low calcium intake[38] in endemic areas (Fig. 4). There is increased calcium turnover in cases of endemic skeletal fluorosis. Diets poor in calcium provoke secondary hyperparathyroidism.[99] This in turn leads to osteoporosis and deformities of weight-bearing lower limb bones.

NEUROLOGICAL MANIFESTATIONS OF SKELETAL FLUOROSIS

The neurological sequelae in skeletal fluorosis manifesting usually as radiculomyelopathy arise principally due to the mechanical compression of the spinal cord and nerve roots brought about by osteophytosis and sclerosis of the vertebral column.[87] However, it is only in the later stages, owing to pressure on the radicular vessels in the intervertebral foraminae that vascular complications may supervene. Neural toxicity attributable to fluorides is yet to be established.

Neurological complications arise at a late stage of the disease in about a tenth of the patients with skeletal

Map 2: High endemic regions of fluorosis in India

fluorosis.[33] In 1937, Shortt and his colleagues from India reported on ten chronic cases with a history of 30–40 years intake of water containing 2–10 PPM of fluoride.[83]

Later there were similar reports from other parts of India.[9,33,50,67] The largest number of cases with neurological manifestations was reported from two endemic belts (Map 2): Punjab, Haryana, Rajasthan and adjacent Uttar Pradesh in North India and from Andhra Pradesh in South India. There have been few reports of fluorosis with neurological complications from countries other than India.[61]

The patients suffering from neurological manifestations varied in age from 20 to 70 years and the mean age of 74 cases reported by Jolly and his colleagues was 56 years. In the case of younger age groups, these complications may be traced to higher levels of daily fluoride ingestion. It was noticed that fluorosis occurred less frequently in areas having low levels of water fluoride, the lowest ranging from 1.2 to 1.35 PPM.[84] Men were reported to have been affected more frequently than women who formed only 6% of the cases reported by Jolly et al.[31] and who numbered 18 out of 70 cases described by Siddiqui.[85] Similar findings were reported by other investigators from India,[69] except for one lone report from Rajasthan where females slightly predominated over males and also developed fluorosis earlier than men.[97]

It is the cervical cord rather than the dorsal cord that is commonly affected by fluorosis. In the Punjab series, 70% of the cases had cervical spine involvement. Although the lumbar spine is usually the first to exhibit skeletal changes caused by fluorosis, compression of the cauda equina rarely occurs because its roots are so easily accommodated that by the time they are pressed upon, other parts of the spinal cord would have been affected. Although the disease develops slowly but relentlessly, the neurological deficits may sometimes be precipitated by a minor trauma.[43,77] Such cases present a wide spectrum of neurological deficits, which may be found manifesting as either lower motor neuron or upper motor neuron defects or both, which is more common. These may be found along with those caused by skeletal fluorosis resulting in restriction of spine movements. It is to be noted that in fluorosis higher cerebral function defects or cranial nerve palsies are rarely encountered.

Myelopathy

Patients suffering from fluorosis usually experience difficulty in walking due to the progressive weakness in the lower limbs. With the spreading of this weakness to the upper limbs, neurological disabilities occur that makes the patient bedridden. These disabilities are due to motor and sensory deficits, which are followed by sphincter disturbances. In such a condition, motor disabilities predominate over the others and sensory defects affecting touch, vibration, position and joint sense tend to be bizarre and widespread. When this happens, acroparaesthesiae may occur and a sensory level is hardly ever seen. What is striking is that due to the coexistence of crippling deformities at the hips, knee and other joints it becomes difficult to decide whether the disabilities are caused by neurological lesions or by skeletal deformities. Flexor spasms appear only at the late stage of the illness.

Radiculopathy

Nerve root compression leads to atrophy of various muscle groups in both the upper and the lower limbs. With the onset of fasciculations motor neuron disease may be mimicked. The upper limbs appear to be affected more than the lower limbs which may be traced to the commoner involvement of the cervical region or even the anatomical features of the cervical spine.[73] Sensory changes may not be as striking as disabilities of motor function and root pains do not usually occur. In advanced cases, marked cachexia develops on account of disuse atrophy of limb and trunk muscles.

Cranial Nerve Lesions

The skull is not much affected in fluorosis and basal cranial nerve foraminae are not encroached upon except in the advanced stages of the disease.[91] Of the cranial nerves, the most frequently affected, in a quarter of the cases investigated, has been the eighth nerve. In all cases calvarial changes caused by fluorosis are discernible. A progressive high frequency perceptive deafness is observed. Moreover, bone conduction is affected more

than air conduction. Nevertheless, total deafness rarely occurs. It is perhaps the compression of the nerve in the sclerosed and narrowed auditory canal that accounts for the deafness in fluorosis.[64]

Optic neuritis, however, is hardly ever seen in patients with endemic fluorosis, although administration of sodium fluoride in large doses as a therapeutic measure in osteoporotic patients was reported to have had a damaging effect on the optic nerve.[23] A higher incidence of myopia and optic pallor in a small proportion of cases of endemic fluorosis has been by seen us, which could be incidental.

Peripheral Neuropathies

Exostoses, which mainly develop around the knee, elbow and ankle, may press upon the median, ulnar or lateral popliteal nerves. Pain and paraesthesiae followed by weakness in the limbs may be caused by such bony growths. Even meralgia paraesthetica has been reported to occur in fluorosis.[9] Fluorotic patients may also manifest entrapment syndromes involving other peripheral nerves. Degenerative disc disease is very uncommon in fluorotic patients.

Cerebral Ischaemia

Involvement of the vertebrobasilar circulation caused by compression of the vertebral artery by cervical osteophytes may occasionally occur.[89] Increased calcifications of major vessels and disturbance of lipid metabolism that has been reported in fluorosis may lead to cerebrovascular accidents.

The occurrence of certain other neurological features, like headache, tetaniform convulsions, mental depression and electroencephalographic disturbances, have also been reported.[105] Several other complaints have been related to fluoride intoxication without adducing irrefutable ground for such conclusions.[81]

LABORATORY INVESTIGATIONS

General

A mild degree of anaemia and a decrease in erythropoietic activity of bone marrow are found in fluorosis, which may be due to associated nutritional factors or secondary to osteosclerosis and encroachment of medullary cavities. CSF analysis in cases of fluorotic spinal compression reveals a moderate rise of protein and the other constituents are normal. Balance studies have revealed the retention of phosphorus, magnesium, nitrogen and calcium, of which the latter has been markedly positive.[94] Evidence of impaired renal function was reported in a certain proportion of fluorotic patients.[83] The abnormalities included impaired urea clearance, decreased glomerular filtration rate and increased blood urea nitrogen. Singh et al.[91] found a generalised aminoaciduria in patients suffering from fluorosis, especially excessive tyrosine excretion, but investigations made by Srikantia and Siddiqui[96] did not bring out any abnormalities of amino acid excretion in urine. Alkaline phosphatase is often found elevated in fluorosis, which may be due to increased turnover rather than any specific effect of fluoride on the enzyme.[80] Fluorides are known to activate and inhibit enzyme systems. At low serum levels, fluorides are known to stabilise and activate several enzymes and, at higher levels, fluoride inhibits enzymes such as adenyl cyclase, pyrophosphatase, etc. In endemic regions, people with poor nutrition, especially those on low intake of calcium in their diets, develop secondary hyperparathyroidism.

Electrophysiological Studies

Neurophysiological experiments have revealed that sodium fluoride has anticholinesterase and anticurare like effects on muscle and nerve, although it has no effect on normal muscle membrane potentials even in the endplate region.[36] There are very few electrophysiological studies of muscle and nerve in endemic skeletal fluorosis.[73] Peripheral nerve conduction velocities in such cases are normal and compound action potentials are usually within normal range. These findings suggest that the nerve lesion in fluorosis is located either in the nerve roots or anterior horn cells in the spinal cord. Study of late responses, F wave and H reflex in cases of endemic fluorosis proved unequivocally that the nerve lesion is located in the root, which is responsible for the muscle involvement in fluorosis.[51] The nerve conduction velocities are found to be reduced to 30–35 m/sec in peripheral nerve entrapment on account of the pressure of exostoses or ligaments around the joints. In these cases both motor and sensory conduction velocities are affected, motor more than sensory.

Electromyographic studies in cases of endemic skeletal fluorosis have given unequivocal evidence of neurogenic atrophy, but no evidence of myopathy has been seen. The recognisable features which may be found singly or jointly in all such cases are the presence of fibrillation potentials, reduced interference pattern, increase in mean action potential amplitude and duration of surviving units. Some have shown polyphasia, which are of giant size. Other features noted in EMG studies are the upper limb muscle groups are more involved than the lower limbs and that the proximal muscle groups are more affected than the distal musculature. These changes are perhaps peculiar to the cases that were studied. In general, EMG findings endorsed those of clinical neurological examination, but muscle changes might sometimes be detected earlier through EMG studies than by clinical examination.

Fluoride Estimations

Diagnosis of fluorosis depends upon the estimation of fluoride levels of urine, serum and bone. Many methods are available for the determination of fluoride and the most widely used involve colorimetry or the fluoride

Table 2: Urinary fluoride levels in endemic fluorotic patients

		Urinary fluoride levels in PPM or mg/litre				
Name	*No. of days*	*Minimum fluoride level*	*Maximum fluoride level*	*Average*	*Variance*	*SD*
Yelliah	12	0.5	3.1	1.5183	0.5496	0.7413
Lingaiah	21	0.8	3.5	2.11	0.6242	0.790
Ramaiah	36	1.3	6.0	3.5486	1.1718	1.082
Ramnarasaiah	24	1.0	1.6	1.321	0.0431	0.2076
Mallaiah	12	1.3	2.1	1.625	0.077	0.277
Narasamma	26	0.6	1.5	1.1036	0.0508	0.225
RN	22	1.7	4.0	2.42	0.3564	0.5970
Veeraiah	7	2.8	4.1	3.4	0.2367	0.487
Narasaiah	28	0.9	13.0	5.4179	1.9763	3.158
Mallaiah	12	1.8	3.6	2.758	0.334	0.578
Kistaiah	12	1.2	10.0	4.258	4.959	2.2227
Narasaiah	7	1.0	5.0	1.70	2.167	1.472
Ramulu	10	1.350	6.516	3.0456	2.809	1.676
Sayanna	8	1.83	5.58	4.147	2.0244	1.4228
Hanumareddy	31	3.204	8.304	4.687	1.8330	1.3539
Laxmidevamma	24	4.48	10.01	6.095	2.492	1.5787

specific ion electrode. The latter is more popular than other methods because it is faster. Frant and Ross[20] introduced the selective electrode which gives an electrochemical response that is proportional to the fluoride ion activity in the sample.

Urine Fluoride Estimation

Urinary fluoride levels are the best indicators of fluoride intake. Since fluoride excretion is not constant throughout the day, 24-hour samples of urine are more reliable than random or morning samples for the estimation of fluoride content. In normal individuals urinary fluorides fluctuate widely between 0.1 PPM and 2.0 PPM with an average of about 0.4 PPM when the fluoride content of drinking water is 0.3 PPM. In general, urinary fluoride rises in relation to fluoride intake and it fluctuates widely from day-to-day and ranges from 0.5 to 4.48 PPM minimum and from 1.5 to 13.0 PPM maximum in cases of skeletal fluorosis (Table 2, Fig. 5). Urinary fluoride levels vary greatly in fluorotic patients unlike those of experimental animals, which are given a uniform diet.[74] In some highly endemic areas, urinary content of fluoride could be as high as 26 PPM or more.[91] A study on the excretion pattern of urinary fluoride in fertiliser workers showed an average of 4.2 PPM with a range of 1.5–7.5 PPM.[24] Urinary fluoride levels could be low in cases with renal disease. Fluorotic patients on a low fluoride regimen eliminate more fluoride than their intake.

Serum Fluoride Estimation

When chemical methods of estimating fluoride levels in serum and blood came to be employed by different research workers, wide divergence was noticed in their findings, but when fluoride ion electrode was used for

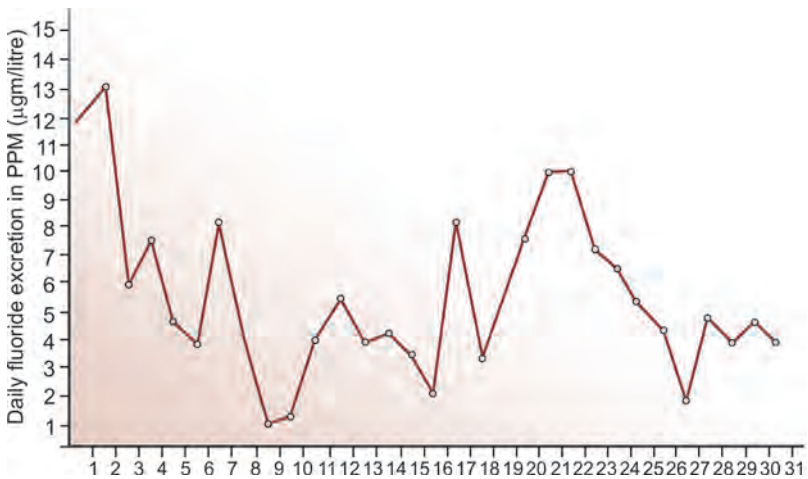


Fig. 5: Daily urinary fluoride level in a patient with skeletal fluorosis. Urinary fluoride excretion fluctuates widely, which makes it difficult to assess the effect of drugs

investigation, the fluoride levels in serum were found to be considerably lower: 0.4–0.9 PPM in fluorotic patients and 0.19–0.4 PPM in normal subjects. Normal values for blood in non-endemic regions varied between 0.002 mg/100 ml and 0.008 mg/100 ml. In endemic regions blood fluoride levels ranged between 0.02 mg/100 ml and 0.15 mg/100 ml whereas, in patients with skeletal fluorosis, they were 0.02–0.19 mg/100 ml.[91] Serum fluoride levels in 500 normal healthy adults ranged between 0.03 PPM and 0.13 PPM with a mean of 0.08 PPM and they were 0.04 and 0.28 PPM with a mean of 0.16 PPM in 17 fluorotic patients in our laboratory. The urinary levels of fluorides of these 17 fluorotic patients varied between 0.68 PPM and 7.80 PPM with a mean of 3.28 PPM.

Bone Fluoride Estimation

Measurement of bone fluoride content allows the determination of the extent of bone fluoride retention and is a useful complement to bone histology for the diagnosis of skeletal fluorosis and could be used for the management of fluoride treatment of osteoporosis. Bone samples are collected and prepared for subsequent analysis using the fluoride selective electrode. Roholm's study of industrial fluorosis revealed that bone fluoride content varied from 6000 to 8400 PPM in bone ash, whereas normal bones had a concentration ranging 500–1000 PPM,[79] but observations of fluoride content of bones in endemic areas are at variance with those mentioned above. For instance, the fluoride levels at which osteosclerosis was detected ranged 700–7000 PPM of fat-free dry bone in cases from Punjab[32] and from 1800 to 6280 PPM of fluoride in endemic areas of Sahara.[59] While reporting their findings, these authors commented upon the lack of correlation between the fluoride content of bones and the degree of osteosclerosis seen in radiographs. Weatherell et al.[109] hold the view that the rate of intake of fluoride is much more important than the amount of fluoride in the bones for the development of skeletal fluorosis. When the daily intake of fluoride is low, the skeleton may be accumulating enormous amounts of fluoride over a prolonged period without manifesting any alteration in its structure or function. When the rate of fluoride ingestion is high, as in endemic areas, the incidence of fluorosis is usually high. Weatherell and his colleagues suggested that, with high intake, a local increase in concentration of fluoride occurs at the site of active mineralisation along with high biological activity, which cause the changes that lead to fluorosis. Bone scintigraphic studies done by us in endemic fluorosis cases have shown a super scan appearance suggesting a very high metabolic activity in the bones. Electron probe microanalysis has confirmed that the newly laid bone has a higher content of fluoride than the bone existing before fluoride ingestion.[80]

Bone Biopsy

Histopathological changes of bone in fluorosis show that the haversian system is poorly formed and there

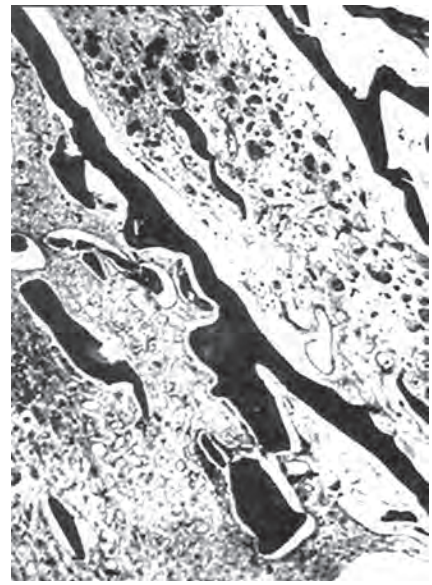


Fig. 6: Poorly formed haversian system and disordered lamellar orientation in the compact bone

is disordered lamellar orientation in the compact bone (Fig. 6). Osteoid tissue is found in the spongy bone and some of these irregular deposits of osteoid tissue extend into the attached muscles. In some of these cases, the osteoid tissue showed calcified muscular attachments. Ligaments show calcification and ossification. Crystals of fluoride material, which are described in cases of industrial fluorosis, were not seen in cases of endemic fluorosis.[69] Skeletal fluorosis involves mainly the spine, pelvis and long bones and it rarely affects the small bones of the hands and feet.

Pulmonary Function Tests

In fluorosis there is involvement of the rib cage, which causes restrictive lung disease. Vital capacity is reduced and the FEV1/FVC ratio is above 85% and the respiratory curve of flow-volume loop is flattened when the lungs are abnormally stiff in the late stages due to a restrictive ventilatory defect.

Scintigraphic Studies

Radionuclide bone scans using technetium labelled methylene diphophonate (99mTc-MDP) in fluorosis shows mostly a superscan appearance and in some cases joint abnormalities. Increased tracer activity between the forearm bones and the diffuse linear tracer activity along the ligamentous attachments were seen. Concentration of tracer may be noted in the joints such as sacroiliac and the anterior iliac spine where the inguinal ligament is attached. Hence, the bone radionuclide scan reveals the functional display of skeletal metabolism in fluorosis.

Radiology of Fluorosis

In fluorosis the radiological findings closely parallel those of gross pathological changes, but there is no

clear correlation between the degree of musculoskeletal changes and the osseous fluoride content. The mechanism of skeletal fluorosis has not been clearly demonstrated. It is difficult to assert that the density of bone is a result of reactive new bone and osteoid formation as a response to fluoride intoxication. All that can be said is that the density may be quantitative rather than qualitative owing to the increase in the matrix unaccompanied by any increase in mineralisation. Bone continues to be formed, but the thickened trabeculae with uncalcified borders are resistant to resorption and so they thicken.

In infancy and childhood, generally no definite radiological findings are demonstrable except in cases with malnutrition, especially calcium deficiency. Radiological changes usually manifest at puberty and in adulthood. However, in some young adolescents, osteopenia of a generalised nature may be seen along with sclerotic areas at the metaphyseal ends of long bones simulating renal rickets. In such cases, the epiphyses are also dense. The vertebral bodies may be prone to sclerosis of the endplates. Fluorotic poisoning does not materially affect growth, but the marks of fluorosis are discernable as growth lines at the metaphyses of long bones. In adults, the radiological findings could be set forth in three stages, each overlapping the preceding one.[8,76,79]

1. The findings are mainly confined to the axial skeleton. The primary trabeculae appear slightly rough due to sclerosis. This is clearly revealed in the iliac wings and the thoracolumbar vertebral bodies. In the secondary trabeculae, however, these are not prominent. The bones assume a ground glass appearance, an early manifestation.
2. In the next stage, the thick primary trabeculae merge with the secondary trabeculae to make the bone homogeneously dense (Fig. 7). The bone contours become uneven due to subperiosteal new bone apposition, which is prominently present in the ribs, pelvis and vertebral column. The skull demonstrates minimal changes in the base. The appendicular skeleton, however, is less affected, but the long bones of the limbs may show encroachment of the medullary cavities with endosteal new bone. The spongiosa bone manifests trabecular prominence and sclerosis. It may be noted that ligamentous calcification begins most frequently in the paraspinous, sacrospinous and sacrotuberous ligaments.
3. In the final stage, the bones of the axial skeleton demonstrate characteristic radiological features. The bones appear chalk like with an ill-defined trabecular pattern. With the loss of cortical and trabecular definition, the bone appears woolly (Fig. 8). The cortices of long bones are dense and thick due to amorphous subperiosteal new bone formation. The medullary cavities are encroached upon by endosteal new bone. In such cases, calcification in the para-articular ligaments is pronounced. Calcification is marked at the insertion of tendons and muscles and is seen in the interosseous membrane (Figs 9 and 10).

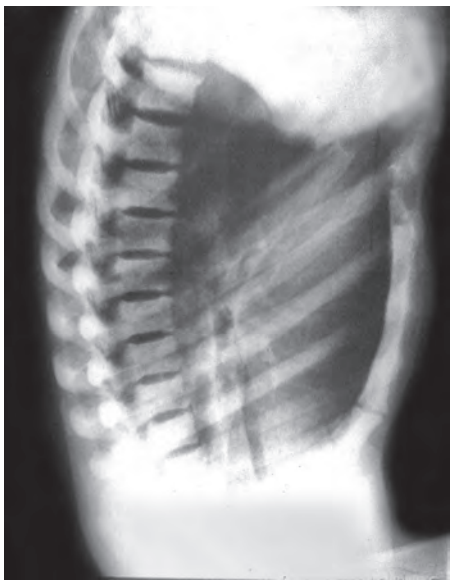


Fig. 7: Lateral view of dorsal spine showing uniformly dense vertebral bodies

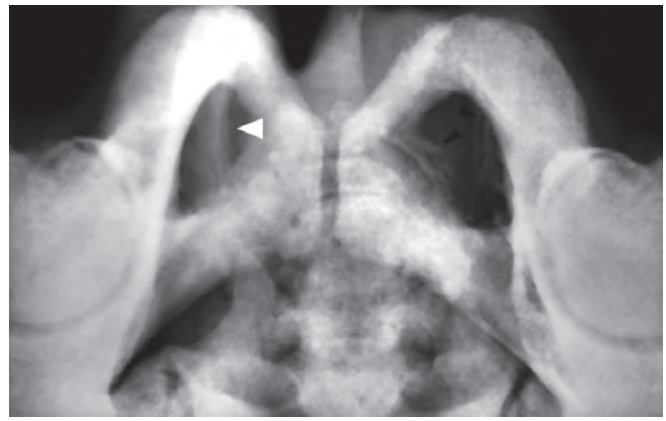


Fig. 8: Irregular calcification of sacrotuberous and sacrospinous ligaments and diffuse increase in the density of pubic bones

The articular ends of bones are less affected, but, in advanced cases, the condyles of long bones are prominent with irregularity of cortical bones. Osteophyte formation in the vertebral column is frequent (Figs 11 and 12). These osteophytes may encroach upon the intervertebral

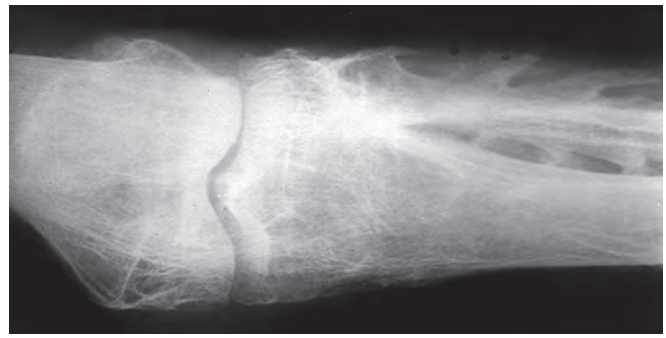


Fig. 9: Marked osteophytosis, extensive interosseous membrane calcification, ligamentous calcifications and degenerative changes in the knee joint

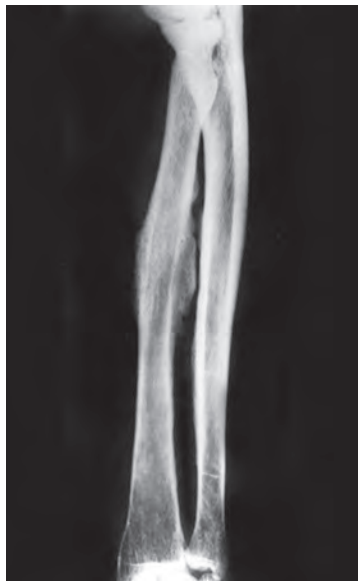


Fig. 10: The forearm bones are dense with calcification of a portion of the interosseous membrane

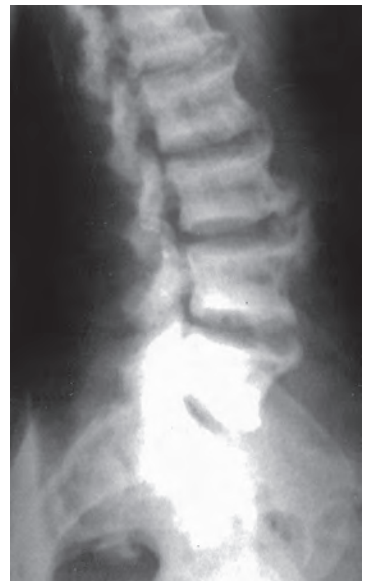


Fig. 12: Vertebral bodies are dense with haziness of the trabeculae and extensive osteophytes are seen

foramina, spinal canal and foramen magnum. The ribs are slightly enlarged with needle-like projections, which point to the advance of calcification into the intercostal muscles and membranes. There is extensive calcification of the costal cartilages. Subperiosteal resorption of bone and osteomalacia are found in some cases. The skull shows minimal changes in the calvarial bones. Sclerosis of bone at the sutural lines is one of the minor manifestations. However, the bones at the base show marked thickening. The petroclinoid ligaments show dense calcification. The occipital protuberance is very prominent and exostoses may occasionally be noted. Small osteophytes may encroach upon the foramina

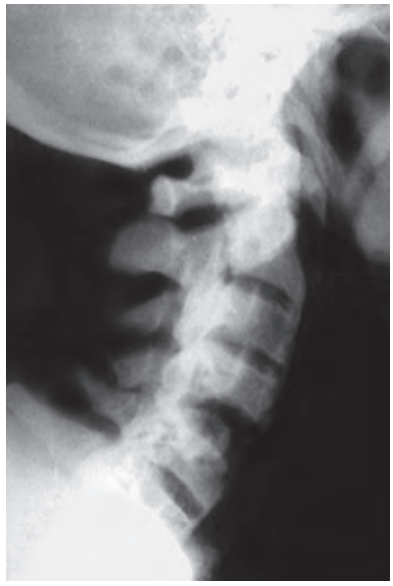


Fig. 11: Lateral view of cervical spine skiagram showing anterior osteophytes, syndesmophytes and calcified posterior longitudinal ligament

and produce cranial nerve palsies, as for instance the 8th nerve. A tendency towards calcification may be noted in the falx cerebri. Hypercementosis of the roots of the teeth is also encountered in some cases. Bony excrescences are present at the iliac crest, ischial tuberosities, condyles of long bones and other protuberances of bones. In such cases, there is a possibility of large calcareous spurs developing and the bones of the hands and feet show cortical thickening. Calcification of interspinous and intervertebral ligaments is noteworthy. In the differential diagnosis of radiological findings of fluorosis, several 'entities' should be taken into consideration. Paget's disease, which prevails in certain geographical areas and races, may produce diffuse sclerosis of bones and may closely mimic fluorosis. However, the enlargement of affected bones and the lack of calcification at the musculotendinous insertion and interosseous membranes and para-articular ligaments provide a clue, which should enable one to differentiate it from fluorosis.

Diffuse osteosclerotic lesions, such as myelofibrosis, osteoblastic metastases, myeloma, hypoparathyroidism and renal osteodystrophy, may pose a similar problem. However, a skeletal survey should help in differentiating them from fluorosis. Osteopetrosis, melorheostosis and similar congenital forms of diffuse sclerotic bone lesions should be identified and distinguished from skeletal fluorosis. Differentiation is also called for in the case of a high degree of metal intoxication such as phosphorus, vitamin D and radium. However, in most of these cases, the clinical history would be of great help in arriving at a proper diagnosis. Mastocytosis, tuberose sclerosis and, occasionally, syphilis, yaws and other infective lesions have to be differentiated from one another. To this long list may be added unusual lesions of Gaucher's disease, sickle cell anaemia and idiopathic osteosclerosis as well as other esoteric lesions caused by familial

hypophosphataemia, vitamin D resistant osteomalacia, Wilson syndrome, etc.

Osteosclerosis is a well-known effect of chronic fluoride intoxication, which can also cause osteoporosis and osteomalacia. It was Roholm[79] who, describing bone changes in industrial fluorosis, suggested that in certain cases osteoporosis could occur. Soriano,[94] while giving an account of 'wine fluorosis', made a mention of the development of osteoporotic and osteomalacic changes in the skeleton of individuals concerned. He pointed out that smaller doses of fluoride stimulated osteogenesis and new bone formation, while severe intoxication led to increased bone resorption and defective matrix formation. A significant observation in this regard has been that at high levels of fluoride intake there is reduced collagen synthesis in humans.[54]

Osteoporotic changes occurring in the bones of the legs in endemic skeletal fluorosis have been reported as Kenhardt bone disease from South Africa.[27] This usually affects children whose limb bones revealed demineralisation accompanied by thinning of the cortex and widening of the medullary cavities. The adult population of the area showed classical osteosclerotic changes of the skeleton. Cases similar to those in Africa were reported from various endemic regions of India and China. These changes in the appendicular skeleton of young individuals seem to be due to poor nutrition, especially low in calcium.[39,107] Liad and Wu,[42] describing the radiological features of endemic skeletal fluorosis from China, concluded that osteoporosis towards the ends of long bones is an early radiographic sign in individuals under the age of 40 years even among those with a good nutritional status. In high endemic regions with a very high intake of fluoride and diets being deficient in calcium there is a secondary hyperparathyroidism, which also adds to the radiological changes. Hence, a variety of radiological changes are seen in endemic regions with poor nutrition.

Computed Tomography

Computed tomography is the best imaging modality for visualisation of bony pathology and it provides more details than plain skiagrams. Besides proper appreciation of the morphological anatomy and density of the various parts of the vertebra, it shows the exact location and direction of the osteophytes compressing the various neural elements and thus helps in proper surgical planning (Figs 13 and 14). Spinal canal and root canal stenosis is also better appreciated with CT scan. The calcified ligaments are visualised earlier and with much more clarity than by plain roentgenology, so are the indentations of the epidural space and the alterations in the spinal canal. By reconstruction, CT provides exact dimensions of the ossified intraspinal ligaments such as the posterior longitudinal ligament and yellow ligaments (Fig. 15). The anterior osteophytes are seen to be most prominent in the thoracolumbar region. The facetal joints occasionally show significant hypertrophy. In delineation of ossification of the forearm interosseous membrane and ligaments of the pelvis in early cases of fluorosis CT is extremely sensitive.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI), being non-invasive, obviates the difficulties in performing myelography and, on the other hand, delineates the anatomy of the soft tissue structures and the spinal cord changes. It also demonstrates associated abnormalities, like psuedomeningocoele and cord changes, due to prolonged compression and secondary vascular compromise. It is useful to image the entire spine, which may

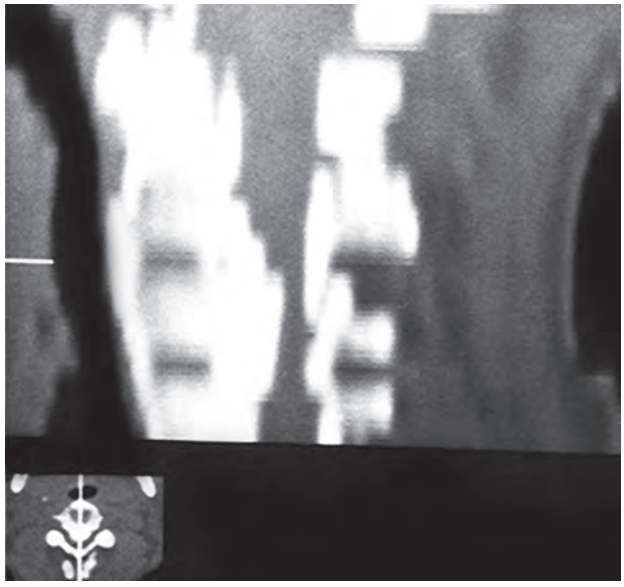


Fig. 13: Sagittal CT showing OPLL and calcified ligamentum causing severe compression of the cord

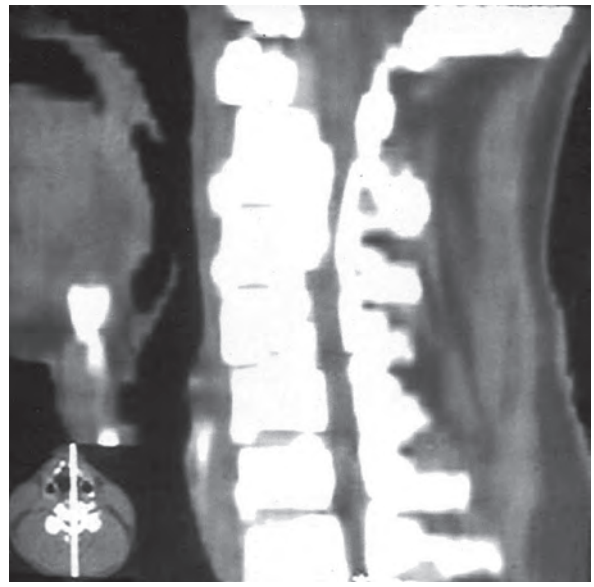


Fig. 14: Sagittal reconstruction of cervical spine in fluorosis demonstrating OPLL

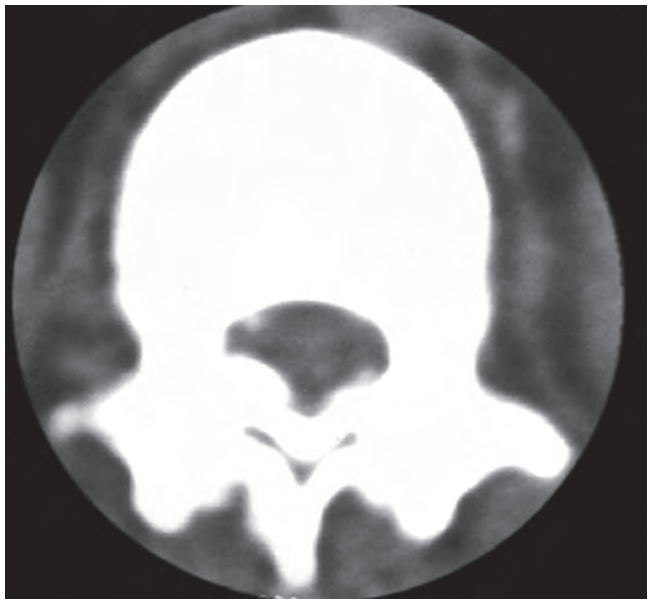


Fig. 15: Axial CT scan of dorsal spine showing bilateral dense flaval ligamentous ossification and increased density of bones

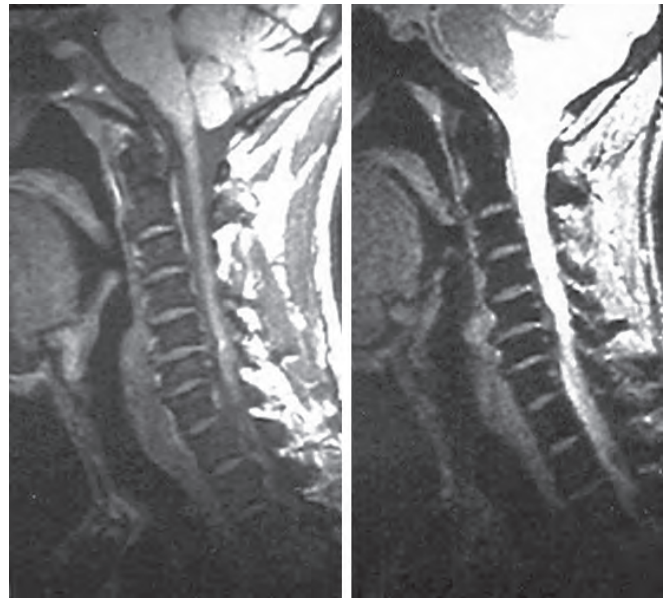


Fig. 17: MRI scan of the cervical spine in fluorosis. Note pronounced low intensity of bone marrow both on T1- and T2-weighted images, calcification of posterior longitudinal ligament and myelomalacia opposite C5

demonstrate incidental and interesting pathological lesions peculiar to fluorosis (Fig. 16). Fluorotic vertebrae are seen to be hypointense in both T1- and T2-weighted images (Fig. 17).[76] The localised areas of hypertrophy and ossification of ligaments are visualised clearly and these give a clue to the surgical approach. However, the differential diagnosis of cervical disc herniation, spondylosis and segmental OPLL is often difficult and plain radiography, tomography or CT can be complementary in this regard. MRI is superior to CT in the evaluation of the cervical and upper dorsal area due to shoulder girdle artefact on CT image, but in demonstration of minute ossification of ligaments and spinal canal stenosis, CT is more useful. As for spinal cord morphology, there is no better imaging modality than MRI. Evidence of chronic cord compression producing pathological changes, like myelomalacia, cavitation and necrosis, is seen as a high intensity signal in the spinal cord in T2-weighted images. This is frequent in cases of continuous OPLL since this type of ossification causes severe cord compression. Apart from these chronic changes, pathology of acute cord injury and its sequelae are visualised with clarity.

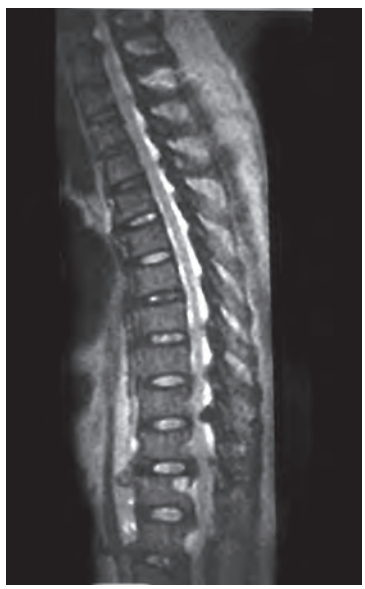


Fig. 16: MRI scan of dorsal spine, T2 sagittal showing low intensity marrow, ossified anterior longitudinal ligament and multiple levels of calcified flaval ligaments

Myelography

At advanced stages of skeletal fluorosis, lumbar and even cisternal punctures become difficult for obvious reasons, hindering the undertaking of myelographic studies. What is observable in the early stages is the localised epidural type of block, which is extensively found in the later stages (Fig. 18). For finer details, water-soluble contrast myelography coupled with computed tomography is far superior. However, following the advent of non-invasive MRI imaging, myelography is now seldom performed.

PATHOLOGY OF FLUOROSIS

Gross Changes in the Skeleton

Skeletal changes involving overall increase in bone mass, 2–3 times the normal is a characteristic feature of fluorosis.[69,90,108] The changes will be first noticed in the vertebral column and pelvis and, thereafter, in the rib cage and limb bones. The bones become whitish and, occasionally, mottled like the teeth. A clear indication of chronic fluorosis is the calcification and ossification of ligaments and interosseous fasciae occurring along

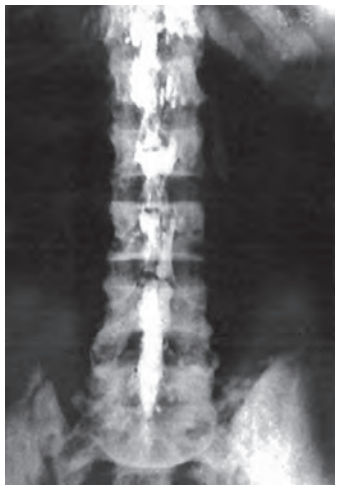


Fig. 18: Lumbar myelogram showing patchy epidural type of block

with periosteal new bone formation and development of exostoses on long bones and osteophytes in the spine (Fig. 19). It is in the muscular attachments and tendinous insertions that new bone formation occurs, as a result of which there is a thickening of the cortex and narrowing of the medullary cavity (Fig. 20). The effect on the vertebral column is seen in roughening of pedicles, laminae, and spinous and transverse processes. The osteophytes projecting into the spinal canal and intervertebral foraminae may press upon the cord and spinal roots and thus account for the radiculomyelopathic features in chronic fluorosis (Fig. 21). The spine is converted into a single rigid bone as a result of ossification of spinal ligaments and fusion of the adjacent bony structures (Figs 22A and B). The bones of the pelvis exhibit changes essentially similar to those found in the spine. The skull

Fig. 19: Photograph of macerated upper limb bones showing ossification of interosseous membrane and prominent landmarks of muscular attachments

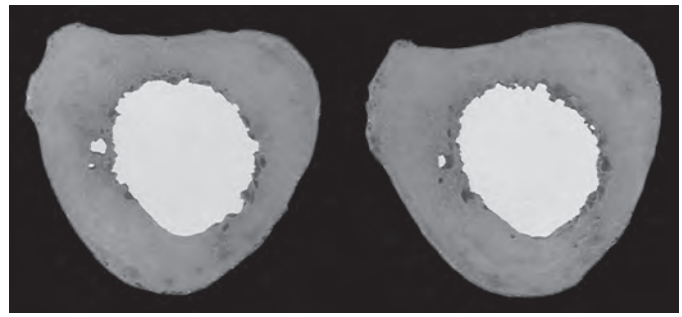


Fig. 20: Cross-section of mid-shaft of femur in fluorosis exhibiting dense cortex

is rarely involved, although there may be thickening of the calvaria and a roughening of the outlines of the foramen magnum. Other foraminae at the base of the skull are rarely affected, which is the reason why cranial nerve defects do not appear in fluorosis.

Histopathology of Bones

There have been few reports on the pathology of fluorotic bones and they present a confusing picture. These reports are unhelpful in that they are silent about the histogenesis and the mechanisms that bring about changes in bones. The work of Johnson et al.[28] on osteofluorosis is indeed outstanding because it spells out the mechanisms underlying the development of skeletal changes caused by fluorosis in animals and man. It was they who set forth three successive stages of development of fluorosis in bones, viz. fluoridation, mottling and abnormality. Bone fluoridation or chemical fluorosis is indicated if the fluoride content is less than 2500–5000 PPM. When this condition is reached, gross inspection and radiological examination will not reveal any abnormality but, when subjected to microscopic study, changes are seen such as mottled osteone. The mottled osteone is signified

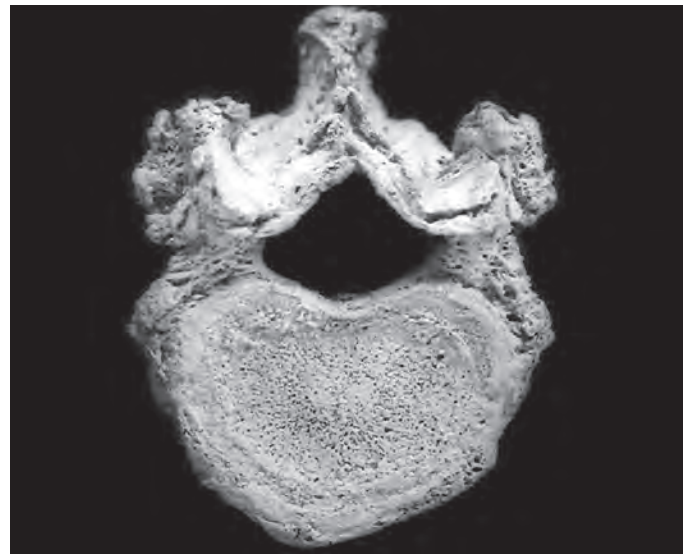


Fig. 21: Showing lumbar vertebral thickening and irregularity of its surfaces

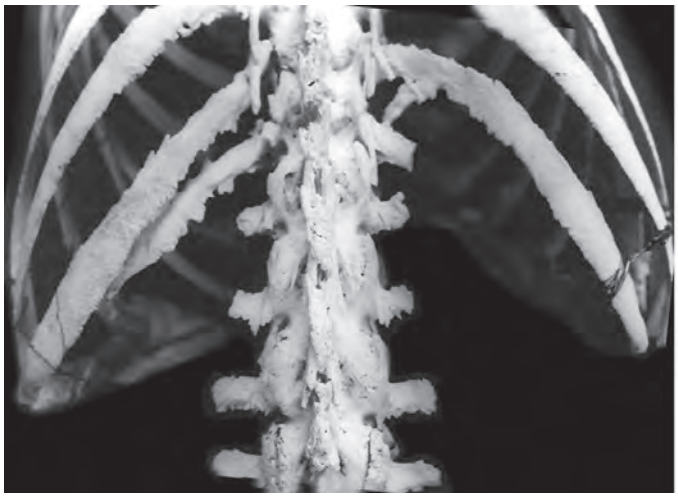


Fig. 22A: A segment of the vertebral column and the ribs showing typical changes of fluorosis (dorsal view)

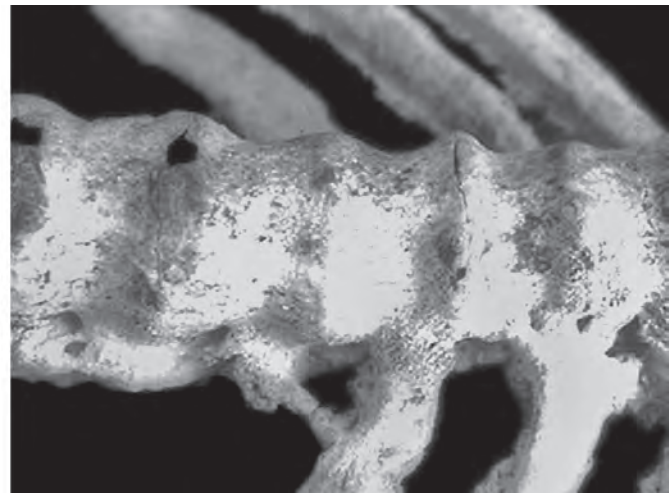


Fig. 22B: Anterior view of spine in fluorosis

by brownish discolouration and increase in the number of osteocytes found in a tangled mass on its periphery synchronising with a reduction of osteocytes in the rest of the osteone. What is further noticeable is the failure of these abnormal osteones to calcify although, in the other parts, abnormality is marked by calcification and in the formation of collagen matrix. Similar changes are also observable in the periosteal new bone. Indeed, mottling may be said to result from the action of fluoride on osteoblasts. The final stage is reached when the fluoride levels exceed 5000–6000 PPM, a stage at which even the naked eye could detect abnormality in the formation of the bone. These changes cause impairment of mechanical properties of bones.

Muscle Pathology

Neurological manifestations in skeletal fluorosis are secondary to compressive myelopathy. Franke[18] suggested that there could a direct toxic effect of fluoride on the spinal cord as well as on muscle based on a lone report of a study in a patient with industrial fluorosis who died due to glioblastoma multiforme. Similar myopathic changes were also reported in experimental studies by Kaul and Susheela.[34,35] Similar cardiac muscle changes have been reported in experimental animals and these might have been caused by the administration of very large doses of fluorides to these animals.[56,100] Our own detailed histochemical and histological studies on muscle in 22 patients suffering from endemic skeletal fluorosis have not revealed any muscle involvement due to toxic affect, but muscle changes were characteristic of denervating muscle pathology (Figs 23A and B).[78,82]

Nerve Pathology

Sural nerve biopsies were performed in 13 patients suffering from endemic skeletal fluorosis and processed for the study of: (a) myelinated fibre densities and diameter frequency distribution; (b) internodal lengths and diameter on teased fibre preparations and (c) histological changes.[78] Myelinated fibre densities were reduced indicating a dropout, probably due to axonal degeneration or demyelination, or both. It is, however, unusual that there was relative sparing of larger fibres, which is not the case in compression neuropathies. The data suggests that there is a selective damage to small myelinated fibres or their neurons with intact larger and fast conducting fibres (Figs 24 to 26). Hence, there was no significant reduction in conduction velocities in electrophysiological studies in fluorosis.

Spinal Cord Studies

There has been no report of spinal cord examination having been made in cases of fluorotic spinal compression. In a few cases in which autopsy was performed, the bones were macerated for studying the changes in

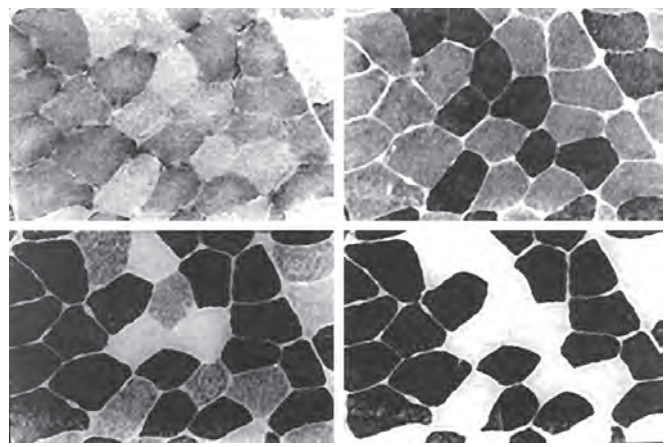
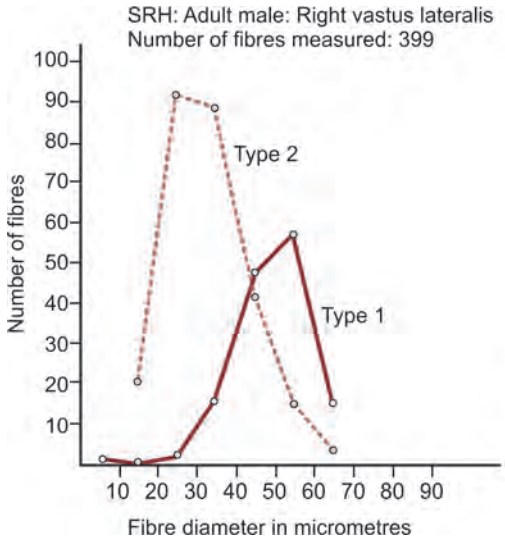


Fig. 23A: Muscle histochemistry (ATPase). Top left: pH 10.3; Top right: pH 9.4; bottom left: pH 4.6; bottom right: pH 4.3. Showing fibre type I predominance, grouping and type II atrophy



Parameters	Fibre Types I	2A	2B
Percentage ...	33.8	64.9	
M.D. (μm) ...	49.7	32.9	
S. D. ...	9.37	10.50	
V. C. ...	188	319	
A. F. ...	155	1285	
H. F. ...	–	–	

2C 1.3%

EMG : Deltoid and triceps–Mild denervation
Thenars, EDB and quadriceps–normal
MCV : 54 M/Sec SCV : 35 M/Sec

Fig. 23B: Type I fibre predominance is evident

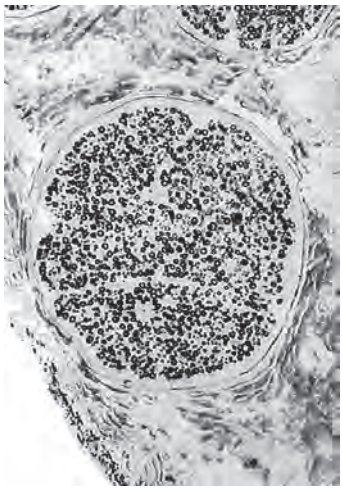


Fig. 24: Sural nerve. Cross-section (Kulchitsky-pal x 100) showing a drop in the myelinated fibre density

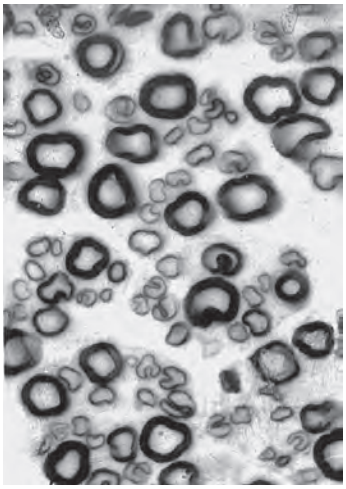


Fig. 25: Sural nerve. Cross-section (Kulchitsky-pal x 1000) showing predominance of large diameter myelinated axons and presence of axon clusters

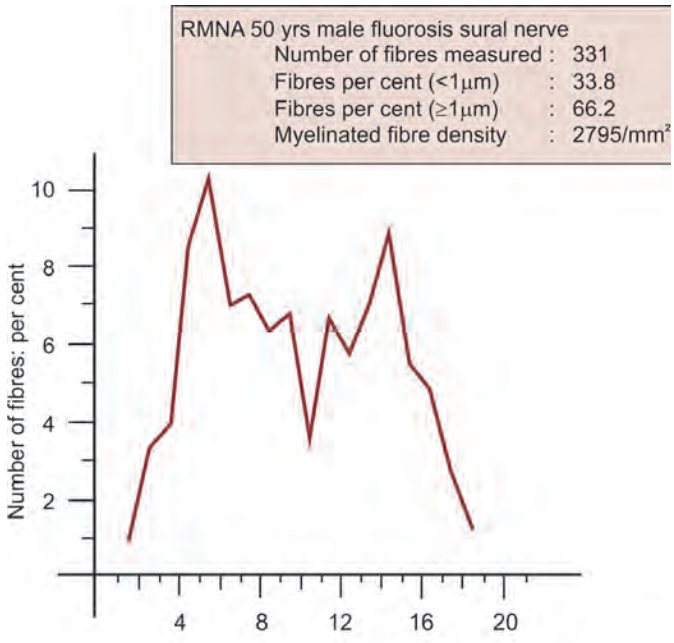


Fig. 26: The predominance of fibres larger than 7 microns is obvious

the vertebral column, but no attention was paid to the spinal cord and spinal nerves. Franke[18] reported anterior horn cell damage in the spinal cord without there being compression of the cord or nerves and it was attributed to the direct action of fluoride on these tissues. We studied spinal cord changes in fluorotic dogs from endemic regions without myelographic evidence of compression. The spinal cords revealed no abnormality histologically to suggest anterior horn cell disease.[7,75]

DIFFERENTIAL DIAGNOSIS

In areas of known endemicity, the diagnosis of dental and skeletal fluorosis does not present any problem. In

industries, where fluoride intoxication is a known hazard, skeletal fluorosis marked by restriction of spine movements can easily be diagnosed. In the early stages of skeletal fluorosis patients complain of arthritic symptoms, which have to be differentiated from those caused by such diseases as rheumatoid arthritis and ankylosing spondylitis. This is all the more important in the case of children residing in endemic regions in whom these symptoms need to be differentiated from those of rheumatic arthritis.[101] Diseases that are known to produce osteosclerosis in skiagrams should be taken into account while undertaking a diagnosis. In children and young adults genu valgum deformities have to be distinguished from those brought about by rickets and sometimes by osteodystrophies. When sclerosis of the vertebral column is not marked, calcification of the interosseous membrane in the forearm bones clearly indicates the incidence of fluorosis, which indeed is a very suggestive radiographic sign.[92]

Preskeletal stage of fluoride intoxication poses problems for diagnosis. In these cases, radiographs of the skeleton do not show sclerosis or calcification of the ligaments, nor will urinary levels of fluoride be found significantly elevated. Moreover, the symptoms that are manifested are so varied that they may be identifiable with those of various other system diseases.

Freitag and colleagues[21] state that for early diagnosis of skeletal fluorosis, microradiographic techniques are more helpful than conventional skiagrams. In doubtful cases, a bone biopsy and estimation of its fluoride content may have to be undertaken.[17] Mild trauma producing major neurological deficit is a known complication of skeletal fluorosis and in such situations in non-endemic regions one might overlook the diagnosis of fluorosis. MRI scans of the spine showing hypodensity of vertebrae in both T1- and T2-weighted images suggest that the underlying pathology is one caused by fluoride intoxication.[77]

TREATMENT OF FLUOROSIS

Prevention

In all cases of skeletal fluorosis, prevention is the aim, since no cure is possible through medical or surgical therapy, especially if it is allowed to develop to the stage when it becomes a crippling disease.

Prevention of Endemic Fluorosis

In India, which is highly endemic for fluorosis, over 50% of groundwater sources have excess of fluoride for a tropical country and it affects more than 150,000 villages. The supply of water with permissible levels of fluoride, although desirable, cannot obviously be made available to the vast number of people nor can they be shifted. That is why water purifying or defluoridation plants should be pressed into service in those areas. The plane of nutrition appears to play a crucial role in the incidence and severity of fluorosis and, hence, a balanced diet having adequate calcium and vitamins reduces the toxicity of fluoride.

Prevention of Industrial Fluorosis

Workers in industries and mining exposed to fluorides should be monitored and it should be ensured that their fluoride content of urine is below 5 PPM. It is said that skeletal fluorosis would not develop in well-nourished individuals, unless fluoride content of bones exceeds 5000 PPM.[47]

Medical Therapy

It is noteworthy that patients suffering from skeletal fluorosis, when kept off fluoride intake, register a negative fluoride balance while continuing to excrete large amounts of fluorides for years.[6,29,84] It should be obvious that excretion of fluorides mobilised from the skeleton through urine and faeces is a very slow and prolonged process lasting for many months or even years.[95] Attempts have been made to study the effect of various drugs on the binding of fluoride in *in vivo* studies and excretion of fluoride in *in vivo* experiments performed in animals and human beings. *In vitro* studies revealed that bone meal, serpentine, *dowex*, magnesium compounds, etc. could be effective in the reduction of the fluoride levels of water having a high fluoride content.[65,101] *In vivo* experiments with animals showed that salts of calcium, magnesium and aluminium acted as a check on fluoride absorption and also increased its excretion from the body.[2,103] The use of serpentine resorted to in recent times for increasing the excretion of fluoride in human fluorosis cases has been successful for clear reasons.[66] This naturally occurring mineral, which is chemically a magnesium metasilicate, seems to have an enormous capacity for absorbing fluoride at a wide range of pH and that is why it seems to hasten the excretion of fluoride from the body by mobilising it from bones. It has been observed during the administration of serpentine that the urine becomes markedly alkaline, which probably has the effect of increasing fluoride excretion from the body. An observation which tallies with the findings of physiological experiments of Whitford et al.[112] and which suggests that fluoride renal clearance is a pH dependent event. Since serpentine is impure and represents a group of minerals which comprise of chrysotile, antigorite, lizardite and a number of subgroups such as orthochrysotile, etc. having traces of many elements including fluorine, the use of active ingredients of serpentine, namely magnesium oxide and magnesium hydroxide, has been tried and found effective in animal fluorosis as well as in humans.[70,72] Magnesium hydroxide has been more effective than serpentine in both in-vivo and in-vitro studies of both animals and human beings,[60,70] but long-term studies have to be undertaken for gauging the effectiveness of these drugs in humans. Experiments conducted by Marier[44]

and Odell et al.[55] found a similarity between magnesium deficiency symptoms and those of fluoride intoxication which made them suggest that higher intakes of magnesium might prove beneficial to endemic fluorosis cases. Our own clinical and experimental studies confirm their observations and lend support to the view that, physiologically magnesium ion has a peculiar affinity for fluoride.

Surgical Management of Skeletal Fluorosis with Neurological Manifestations

Neurological manifestations of fluorosis are mainly mechanical in nature although, at advanced stages, secondary vascular changes may supervene. Surgery can obviously be of little help to the alleviation of neurological deficits in view of the extensive prevalence of the disease. Surgical decompression is only possible in such of those early cases in which the compression is confined to a small segment of the vertebral column. But management of even these cases bristles with problems due to the marked fixity of the spine and rigidity of the thoracic cage. Moreover, the markedly reduced expansion of the chest and the vital capacity of the lungs tend to create post-operative chest complications. Furthermore, intubation of the trachea during anaesthesia becomes problematic due to the rigidity of the cervical spine and positioning of the patient for surgery becomes difficult. That is why laminectomy, which has to be extensive in view of the disease being widespread, becomes difficult and burrs have to be used for removing the laminae.[1,40,53,71,110] However, the results of surgical decompression of the spine undertaken in a select group of cases were found to be encouraging in the cervical region, but discouraging in the dorsal region,[71] which might be attributed to the peculiarities of the anatomical features of these regions. Lumbar compression rarely necessitates surgical decompression as the roots get accommodated easily and by the time they are pressed upon, other parts of the spine become affected precluding surgery. It is on account of all these reasons that the attitudes towards the use of surgery in the case of spinal compression vary from those of cautious optimism to those of pessimism. In recent years, with accurate localisation of the compression in its extent in both vertical and axial planes by the MRI, fibre optic intubation and rigid fixation, better illumination and instrumentation during surgery for drilling and removal hard fluorotic bone and post-operative ventilatory support has made surgery safer and effective in alleviation of mechanical compression in fluorosis.

In recent years, the surgical approach to certain types of lesions of the cervical spine in fluorosis has changed. Fluorotic compression in the cervical region is due to: (a) cervical canal stenosis (Fig. 27); (b) localised calcified ligamentum flavum; (c) osteophytes causing compression anteriorly and lastly (d) ossification of the posterior longitudinal ligament or a combination of these lesions (Fig. 28). OPLL is very common in fluorosis and was found in 37 of 80 people over the age of 40 years in whom

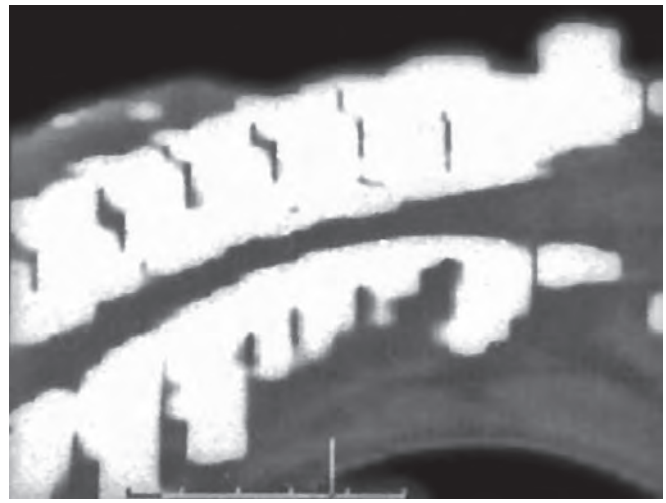


Fig. 27: Severe stenosis of the spinal canal in fluorosis. Note the markedly thickened laminae, spinous process and the osteophytes

cervical spine skiagrams were taken in an endemic village. The posterior approach is indicated in cases of canal stenosis and in lesions of the ligamentum flavum. Such of those cases in whom minor trauma causes major cervical myelopathy would also benefit from decompressive laminectomy. Ossification of the posterior longitudinal ligament, which could be continuous or segmental, is tackled through the anterior approach with better results than in the past when the posterior approach was used. Even when the posterior approach is undertaken in such cases, newer methods are followed such as canal expansive laminoplasty which obviates the complication of the anterior approach that immobilises the spine and destabilising problems following extensive laminectomy. Dorsal cord compression in fluorosis is of three types: (1) diffuse, extensive where surgery is not beneficial (Fig. 29); (2) localised posterior osteophytic or ossified ligamentous compression, wherein results are excellent (Figs 30A and B) and lastly (3) localised posterior osteophytes which are spread over many vertebral levels, although technically feasible to excise them, the

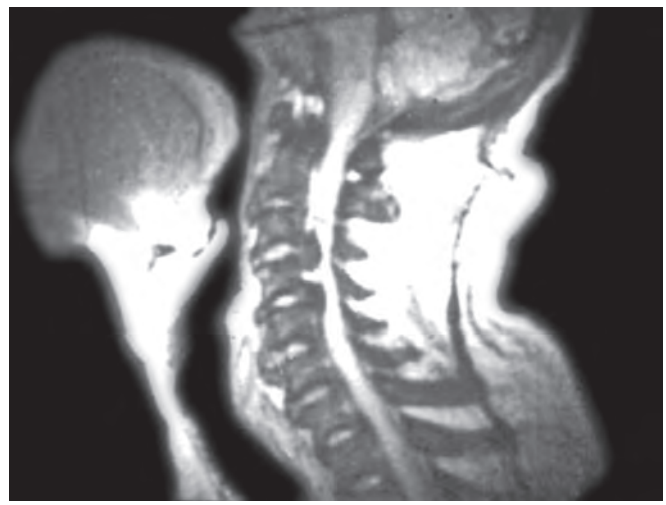


Fig. 28: Segmental OPLL in fluorosis

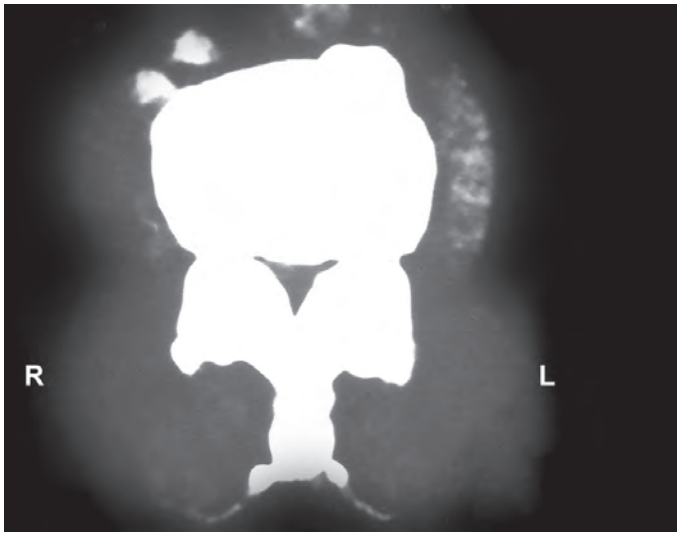


Fig. 29: Axial CT scan of dorsal vertebra in fluorosis showing severe compression of the cord

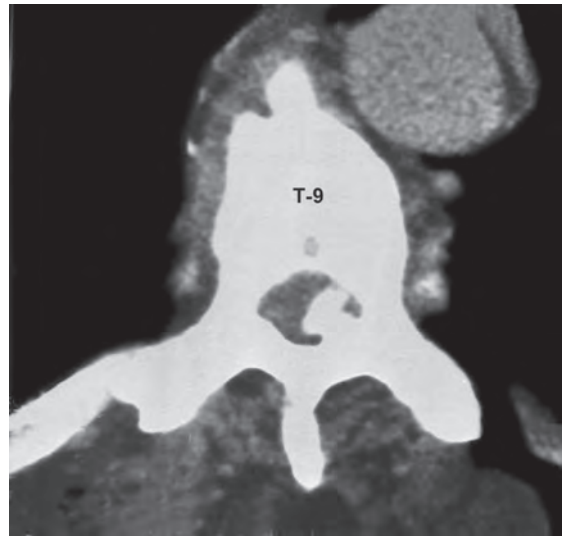


Fig. 30B: Axial CT scan of mid-dorsal spine showing increased density of vertebral body, anterior longitudinal ligament ossification and unilateral ossification of flaval ligament

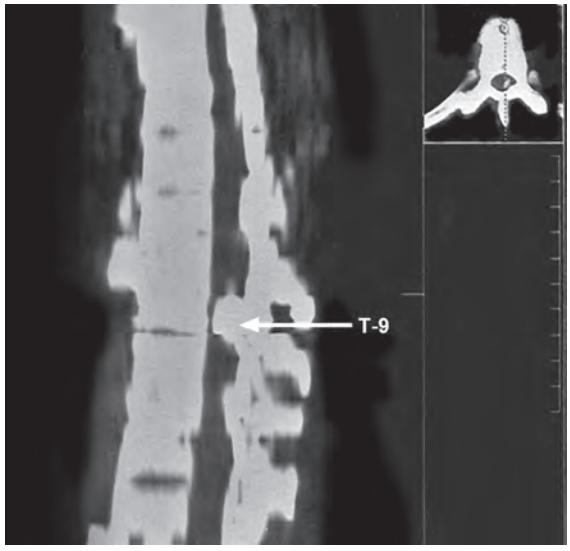


Fig. 30A: Sagittal reconstruction showing severe compression from ossified flaval ligament

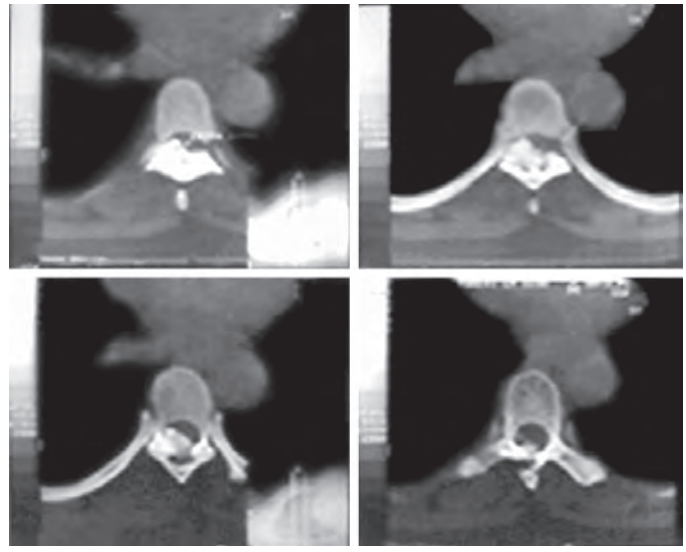


Fig. 31: Severe dorsal laminar and ligamentous compression of the cord extending over many vertebral levels

results obviously are not all rewarding (Fig. 31). It is also not known what happens to all those patients after surgery, when they go back to their endemic areas and again start to ingest high fluoride containing water and food.

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118 Osteoporosis

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INTRODUCTION

Osteoporosis is the commonest metabolic bone disorder. An estimated 61 million people have osteoporosis in India.[39] The aging of the population and changes in lifestyle or food habits are contributing to the increasing prevalence of osteoporosis. For a disorder that is so common, it is grossly under recognised. Vertebral compression fracture, which presents to the neurosurgeon is only the tip of the iceberg of the problem of osteoporosis in the community.

DEFINITION

Osteoporosis is defined as "a disease characterised by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk".[15] In addition to loss of bone mass or bone mineral density (BMD), other factors contribute to the loss of bone strength in osteoporosis (Table 1).

AETIOLOGY

Normal bone consists of organic (30%) and inorganic (70%) components. The organic osteoid component is mostly made up of type 1 collagen. The inorganic component is mostly made up of hydroxyapatite, $Ca_{10}(PO_4)_6(OH)_2$, a macrocrystalline mineral.[42] Bone is a dynamic tissue that keeps on remodelling during a person's lifetime. Osteogenetic and osteoclastic activities are continuous and are decided by local stresses, nutrition and hormonal factors. The peak bone mass which is a function of gender, race, genetic or familial factors, nutrition and exercise in adolescence is attained at 30–35 years.[10,62,72,74,84] Loss of bone mass begins after the age of 35 in normal men and women at the rate of 0.3% per year. At menopause, the rate of trabecular bone loss dramatically increases to 3% per annum for 10–15 years.[26] This postmenopausal (previously called 'type 1') osteoporosis appears to be mainly due to increased osteoclastic activity rather than insufficient osteogenetic activity.[42] Beyond the age of 70, the loss is slower and the rate of loss is the same in men and women. The age associated bone loss equally affects the trabecular and cortical bone. This age related bone loss (previously called 'type 2') osteoporosis appears to be mainly due to insufficient osteogenetic activity. Several factors, such as decreased absorption of calcium, reduced activation of vitamin D, a decline in the lifespan and function of osteoblasts and decreased concentrations of sex hormones, contribute to age associated osteoporosis.[48,78]

The reduction in bone mass and BMD is called osteopaenia when it is subclinical. When it is severe enough to produce symptoms or increase the fracture risk it is called osteoporosis. The World Health Organization (WHO) criteria (Table 2) based on the BMD give a quantitative definition of osteopaenia and osteoporosis.[86]

The fracture risk approximately doubles with fall in the BMD by each standard deviation below the normal as defined in the criteria.[51] The criteria based on BMD are only convenient clinical signposts. As is evident from Table 1, BMD must not be construed to be the *only* determinant of bone strength.

A new, yet-to-be-established, hypothesis proposes that the stress placed on the haematopoietic system due to menstrual blood loss influences the osteogenetic-osteoclastic system leading to osteoporosis in women.[29] Excessive mast cell activity has also been held responsible for osteoporosis.[12] Amylin, a peptide product of the pancreatic beta cells is similar to calcitonin and may be a factor in the osteoporosis of type 1 diabetes.[8] In a mouse model of osteoporosis, decreased spatial memory and hippocampal neuron number has been demonstrated,

Table 1: Factors weakening the bone in osteoporosis

Loss of bone mass and reduced mineralisation (reduced BMD)[86]
Reduced capacity to heal microfractures[57,81]
Altered bone turnover[69]
Alteration in bone microarchitecture[11]
Alteration in bone geometry[7]

Table 2: Criteria for osteopaenia and osteoporosis[86]

Category	*Criteria based on mean bone mineral density (BMD) of young adult reference population-t score*
1. Normal	Mean ± 1 standard deviation (SD)
2. Osteopaenia	1–2.5 SD below mean
3. Osteoporosis	< 2.5 SD below mean
4. Severe osteoporosis	< 2.5 SD below mean + any insufficiency fracture

Table 3: Aetiology of osteoporosis

Primary	*BF*	*BL*
Postmenopausal		↑
Age associated osteoporosis (OP)	↓	
Rare: Idiopathic juvenile OP, Transient hip OP, Regional migratory OP[81]		
Secondary		
Endocrine		
Excess of cortisol (Cushing), thyrotoxicosis, hyperprolactinaemia		↑
Deficiency of growth hormone, parathormone, gonadal hormones, insulin	↓	
Dietary		
Calcium/vitamin D deficiency, malabsorption, alcohol, scurvy	↓	
Systemic disease		
Inflammatory bowel disease, liver disease	↓	
Haemolytic anaemia, myeloma, leukaemia, mastocytosis		↑
Rheumatoid arthritis, chronic obstructive pulmonary disease	↓	
Drugs		
Glucocorticoids, antiepileptic drugs, anticoagulants, antiandrogen therapy	↓	↑
Genetic		
Osteogenesis imperfecta, Marfan syndrome, Ehlers-Danlos syndrome	↓	
Others		
Prolonged immobility, sedentary life style, smoking, HIV infection	↓	↑

Note: BF, Bone formation; BL, Bone loss; ↓, Decreased; ↑, Increased.

but one wonders if the common link is accelerated senescence.[49]

Several secondary causes of osteoporosis are seen in practice, especially among males with osteoporosis (Table 3). Neurosurgeons are likely to see osteoporosis due to glucocorticoid or antiepileptic therapy, Cushing syndrome, hypopituitarism and prolonged immobility.

CLINICAL FEATURES

Osteoporosis is essentially asymptomatic until a fracture occurs. Many patients, who are ultimately shown to have osteoporosis, complain of pain, especially over the low back or lower extremities. While this may be due to microfractures, the pain syndrome overlaps with the pain caused by degenerative lumbar spondylosis and osteoarthritis, which are common comorbidities. Fatigue and pain may also be worsened by the associated depression.[38]

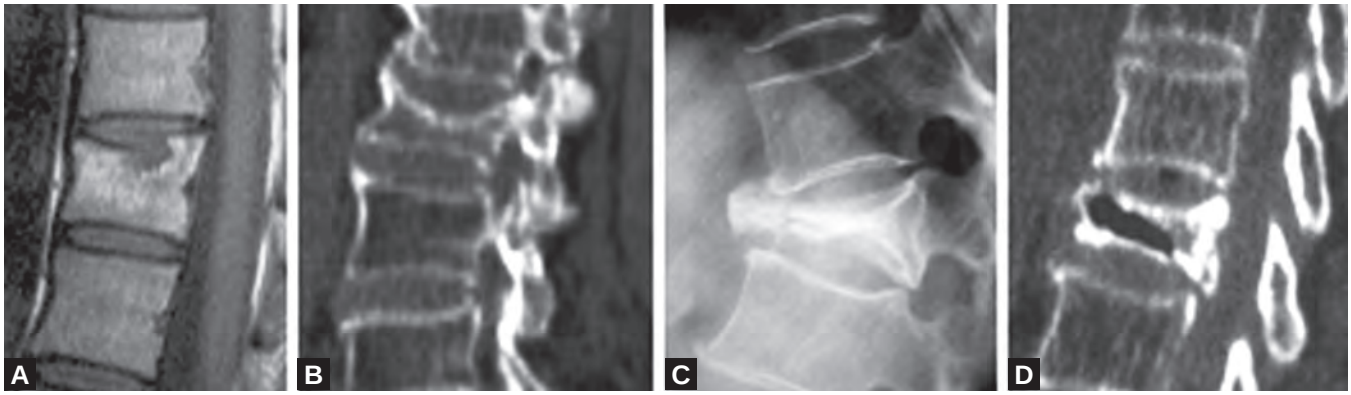
Vertebrae (50%), proximal femur (20%) and distal radius (15%) are the common sites of insufficiency fractures in osteoporosis.[53] The vertebral fracture may occur after being jolted during travel in vehicles or just with a minor fall. The elderly are more prone to fall because of visual impairment, dizziness or loss of co-ordination. The impact is of low energy. There may be no remembered fall, although many patients recall a pain of acute onset. The pain is localised to the site of the vertebral fracture and there is often a girdle pain. Patients with T12 or L1 fracture may complain of pain over the L5-S1 area. Radicular leg pain is rare and should suggest spondylosis or metastasis. The pain is worsened by sitting, spinal movement or coughing. Neurological deficits of spinal cord or cauda equina function are also not common except when there is a break in the posterior cortex of the vertebral body.[41] Painless deformity of the spine may occur due to one or more vertebral compression fractures. Often, the vertebral fracture is asymptomatic and is incidentally detected by X-ray, such as a routine chest radiograph. Reduction of body height of more than 2 cm should prompt a search for vertebral compression fracture.[76] Progressive kyphosis (Dowager's hump) is a consequence of multiple compression fractures.

History of fractures caused by minimal trauma (fragility fracture) elsewhere in the body is often elicited. Women with insufficiency fractures may recall their mothers being similarly afflicted. Intracapsular femoral neck fractures are mainly seen in postmenopausal osteoporosis while the intertrochanteric fracture is common in age-associated osteoporosis. The mortality and morbidity of osteoporotic hip fractures is higher than that of vertebral fractures. This is more so for men with osteoporotic fracture than women.[16] In patients with one vertebral fracture, the risk for a subsequent vertebral fracture is 33-fold higher in men and 11-fold higher in women.[54]

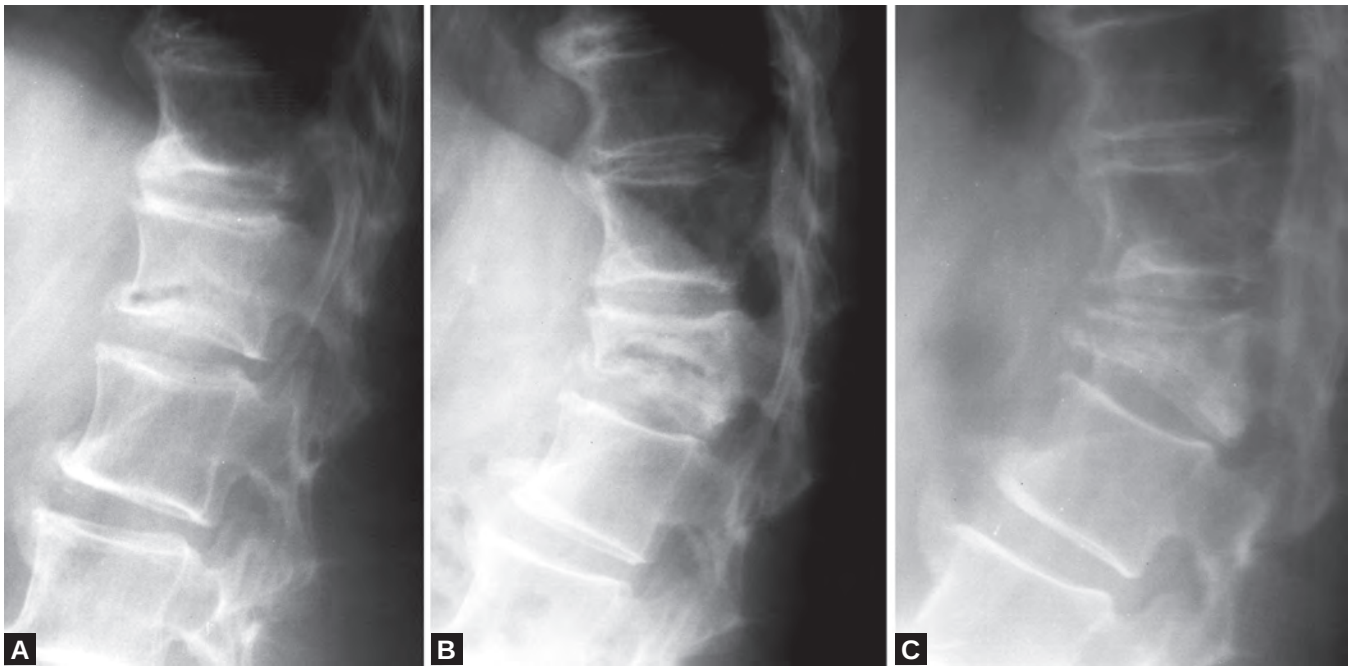
INVESTIGATIONS

Plain Radiography

Osteoporosis becomes evident on standard radiographs only when the bone mass diminishes to nearly 50% and, therefore, it is a poor and unreliable tool for assessing



Figs 1A to D: Various patterns of vertebral compression fractures. (A) MRI of superior endplate fracture. (B) Sagittal reformatted CT of "fish vertebra". (C) Lateral radiograph of vertebra that appears radiodense due to compaction of the bone in an anterior wedge compression fracture. (D) Sagittal reformatted CT of axial compression fracture with intravertebral cleft

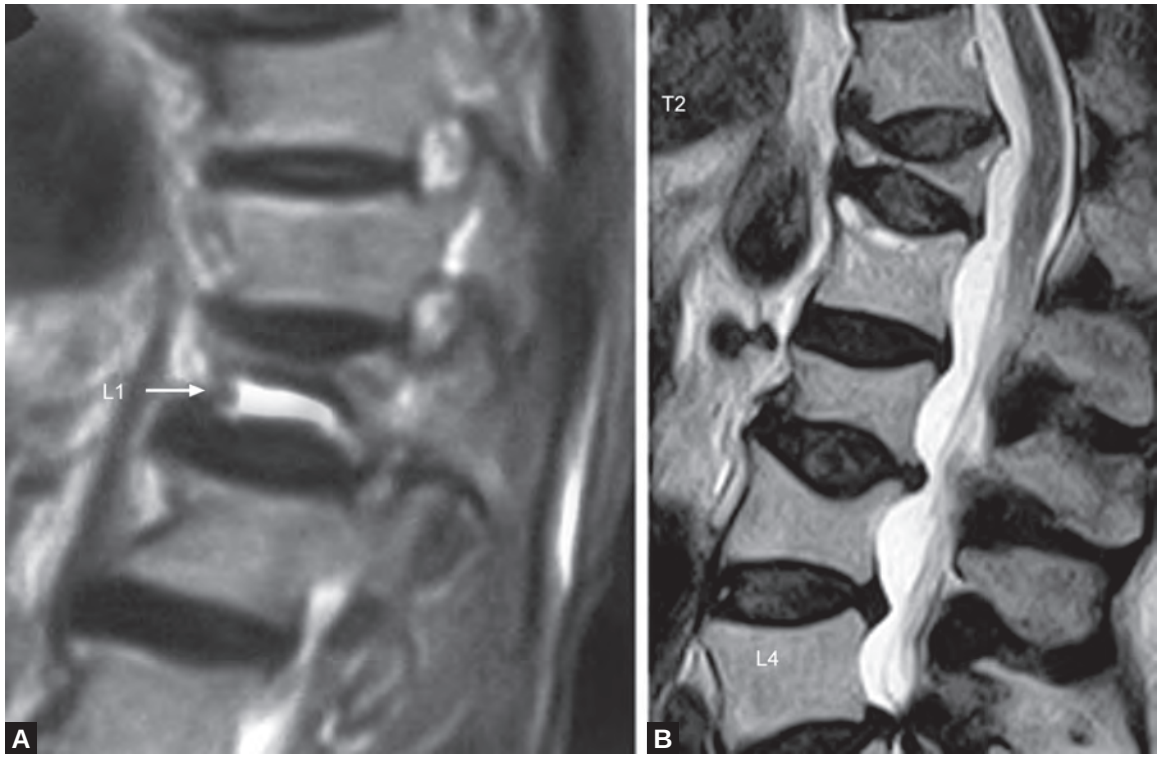


Figs 2A to C: Progression of osteoporotic wedge compression of L1 vertebral body in an 85-year-old man. (A) Note the cleft in the anteroinferior part of the body in the initial radiograph. (B) The cavity is bigger in the radiograph taken 2 months later and the vertebra has become wedged. (C) The kyphosis has worsened due to increasing anterior wedging in the radiograph taken after 3 more months. The cleft is less obvious due to collapse. The endplates and disc spaces are preserved in all films

osteoporosis. Prominent Schmorl's nodes may be seen. Breaks in the vertebral endplates are also seen (Fig. 1A). In the advanced stages, ballooning of the discs into the weak vertebral body may cause the end plates to appear biconcave (fish vertebra) (Fig. 1B).

Silent multiple vertebral compression fractures are the hallmark of osteoporosis. Therefore, it is mandatory to screen the entire vertebral column by imaging. A difference in height of the vertebra of greater than 4 mm between the anterior and the posterior borders should be taken as evidence of a compression fracture. The compression may involve the anterior and the posterior borders equally, sometimes to the extent of causing a vertebra plana. The compaction of trabeculae due to compression fracture may give a paradoxical radiodense appearance to the vertebra (Fig. 1C). It is usually not possible to assess the age of the fracture on radiographs. Although CT (Fig. 1D) or MRI may show the intravertebral cleft better, it is often seen on standard radiographs (Fig. 2A). Comparison with previous X-rays shows the progression of osteoporotic clefts and loss of vertebral height (Figs 2A to C).

Anterior wedging, preserved disc spaces and absence of vertebral displacement or paraspinous shadows are classical findings of the osteoporotic compression fracture. Fractures are generally in the thoracolumbar junction and usually not above T6 level. Posterior wedging and the 'wink sign' on anteroposterior radiographs due to loss of pedicle suggest metastasis or myeloma. A cavity in the vertebral body is seen, but the walls are



Figs 3A and B: MRI of osteoporotic compression fracture of vertebra. (A) Sagittal T2-weighted MR image of the same patient as in Figure 2. The absence of T2 hyperintense signal in the parenchyma of the bone in the chronic stage and the presence of hyperintensity in the cleft, the preservation of the posterior cortex with anterior wedging are characteristic. (B) Sagittal T2-weighted MR image of an 80-year-old woman with previous fracture (fish vertebra) at T12 level and a new superior endplate fracture at L1 level manifested by the T2 hyperintense signal. Note the ballooned discs

sclerotic rather than lytic, unlike those seen with metastasis (Figs 1D and 2A). The presence of a vertebral body cleft is a predictor of delayed collapse and subsequent neurological deficit.[37] Sacrum is a rare, but increasingly recognised, site for insufficiency fracture.[45] While the diagnosis of an insufficiency fracture can be made by plain radiography, further investigations may be needed to rule out metastasis or myeloma.

Computerised Tomography Scan

CT scan is mainly required to look for retropulsed fragments in the spinal canal and to demonstrate the intravertebral cavity (fluid content) or cleft (gas or vacuum) that can be targeted for vertebroplasty (Figs 1D and 3A). The reconstructed sagittal and coronal CT can detect subtle compression fractures missed by conventional radiography. The presence of callus may indicate an old fracture. CT is very useful to study the pedicle width and the integrity of the posterior cortex for vertebroplasty. Primary vertebral lesions, such as haemangioma, show up well on CT. *Micro CT* employs highly collimated beams from a Synchrotron to produce microarchitecture maps on micron thick sections of bone.[11]. This technique can at present be done only on *ex vivo* bone samples and is a research tool.

Magnetic Resonance Imaging

The presence of hyperintense oedema in the bone on T2-weighted images indicates a recent fracture. Hence MR is useful for picking up the recent fracture for treatment in a patient with multiple wedge compression fractures (Fig. 3B). The subtle infiltrates caused by tumours or infections are seen earliest with MRI. In the absence of a cavity, contrast enhanced MR has been found to show an area of non-enhancement that corresponds to the cleft which can be filled up during vertebroplasty.[64] Study of microarchitectural changes can be done with the help of thin section MRI.[11]

Radionuclide Imaging

The advantage of radiotechnetium imaging is the ability to look at the whole skeleton simultaneously. This is helpful for metastasis screening. Recent osteoporotic fractures appear as hot spots while the clefts may show up as cold spots. It is also a useful technique for imaging patients with pacemakers, who cannot undergo MRI.

Quantitative Assessment of Bone Mineral Density

Single photon or dual photon absorptiometry utilising radionuclides are now out of vogue. Since its introduction

in 1987, dual energy X-ray absorptiometry (DXA or DEXA) has become a rapid, reliable and cost-effective method of measuring BMD.[3] Low BMD predicts fracture better than elevated cholesterol levels predict coronary artery disease.[86] The lumbar spine and proximal femur are usually studied. The presence of osteophytes, compression fracture, deformities and presence of implants or aortic calcification may vitiate the results in the lumbar spine.[47] The *t* score is the number of standard deviations below the average BMD of a young adult of the same race and sex, while the *z* score is a similar measurement with reference to an age and sex matched control. Osteoporosis is defined as *t* score being at least –2.5 (Table 1).[86] Low *z* scores indicate a secondary cause for osteoporosis. About half of the fragility fractures occur in the group diagnosed to have merely osteopaenia by the WHO criteria.[75] Measurement of forearm BMD is recommended for hyperparathyroidism associated osteoporosis.[5]

BMD measurement in the hip may not necessarily predict fracture risk in the spine.[56] Spinal BMD measurements may particularly be important in younger postmenopausal women, since they may show osteoporotic values earlier than the hip,[68] while the hip measurements are more suited to the older men and women.[56] The normative data are different for each brand of DXA machine. BMD values in Indian population are approximately 15% lower than those in Caucasian women.[65] BMD measurement by DXA results in less radiation exposure than a chest radiograph (10 mrem as compared to 50 mrem).[68]

Quantitative Computerised Tomography

Quantitative computerised tomography (QCT) gives excellent three-dimensional (voxel) information on specific parts of the lumbar spine. The technique is more accurate, but it is expensive and carries a greater radiation exposure than DXA. The *t* and *z* scores for QCT are different from those determined by hip DXA because only trabecular BMD is measured by QCT.[44]

Quantitative Ultrasonography

Quantitative ultrasonography (QUS) is performed on the calcaneum. The technique measures either ultrasound transmission velocity or broadband ultrasound attenuation, but these parameters are affected not only by BMD but also by other factors such as bone architecture. The reproducibility of the results is low and the correlation between the BMD at the calcaneum and the osteoporotic fracture risk in the hip or vertebra is debatable. Therefore, QUS can at best be considered a screening tool. The low cost and portability of QUS are advantages for mass screening.

The indications for performing bone densitometric studies are given in Table 4 and are in keeping with the guidelines by the US National Osteoporosis Foundation.[60] Osteoporotic fractures occur 10–20 years earlier in Indians as compared to Caucasians and hence the age criteria have to be lower for the Indian population.[39]

Table 4: Indications for osteoporosis screening (BMD measurement)

All women > 65 years, (? All men > 75 years)
Postmenopausal women < 65 years with 1 additional risk factor
Premenopausal women or men with 2 risk factors
Risk factors: 1. Personal history of fracture (fragility or traumatic)
2. Family history of fragility fracture
3. Low body weight (< 57 kg), recent loss of > 5% body weight [22]
4. Amenorrhoeic women, early menopause, delayed menarche
5. Presence of any secondary cause for osteoporosis listed in Table 2, especially steroid/antiepileptic therapy, rheumatoid arthritis and inflammatory bowel disease
6. Smoking, alcoholism, sedentary lifestyle
7. Increased risk for falls
Monitoring osteoporosis therapy (usually 2 years after starting therapy)

Assessment of Bone Turnover

The markers of bone formation (bone specific alkaline phosphatase, osteocalcin) and bone resorption (deoxypyridinoline, collagen telopeptides) have been measured but are clinically not commonly done. They have been more accurate in the assessment of perimenopausal rather than postmenopausal women.[36] They may be measured in a serial manner for monitoring therapy.[69]

TREATMENT

Medical Treatment

The two medical strategies for treating or preventing osteoporosis are to reduce bone resorption and to increase bone formation. Table 5 summarises the drugs currently in use for treatment of osteoporosis. Only sodium fluoride (no longer in use) and synthetic fragment of parathyroid hormone (teriparatide) work by enhancing bone formation. All the other drugs in Table 5 act predominantly by preventing excessive osteoclastic activity. Strontium ranelate has a dual mode of action.

Bisphosphonates constitute the first line therapy in those who can tolerate the drug.[70] Bisphosphonates provide 7% increase in hip and spine BMD and 60% decrease in markers of bone resorption. Bisphosphonates also reduce the incidence of new vertebral fractures by 50%.[24] The fracture protection effect is seen even before the BMD starts improving and is always greater than the degree of rise in BMD.[18] These findings suggest that bisphosphonates may improve bone strength by means apart from improving bone mineralisation.[21,73] Oesophageal ulceration caused by bisphosphonates can

Table 5: Drug therapy for osteoporosis

Drug	*Dosage and route*	*Adverse effect*	*Proven efficacy in risk reduction*	*Recommended for*
Bisphosphonates				Prevention and treatment
Alendronate	5 mg daily or 35 mg weekly, oral, for prevention. Twice this dose for treatment	Esophagitis, myalgia	Vertebral, non-vertebral and hip fracture	
Risedronate	5 mg daily or 35 mg weekly, oral	Esophagitis incidence same as alendronate	Vertebral, non-vertebral and hip fracture	
Ibandronate	2.5 mg daily or 150 mg monthly, oral	Joint pain, fever with first dose of 150 mg	Vertebral fracture	
Strontium ranelate	1-2 gm daily at night, oral	Diarrhoea, venous thromboembolism	Vertebral and non-vertebral fracture	Prevention and treatment
HRT				
Low-dose oestrogen	Conjugated equine oestrogens 0.625 mg daily, oral	Venous thromboembolism, stroke, myocardial infarct, breast cancer	Vertebral, non-vertebral and hip fracture	Prevention and treatment
SERM				
Raloxifene	60 mg daily, oral	Hot flushes, leg cramps	Vertebral fracture only	Prevention and treatment
Calcitonin	100-200 IU, daily, subcutaneous or nasal		Vertebral fracture only	Treatment only
Teriparatide	20 µg/day	Hypercalcaemia	Vertebral, non-vertebral and hip fracture	Treatment (presently for 2 years)

be prevented by taking the dose on an empty stomach in the morning with 200 ml of water. The patient must be instructed to strictly avoid lying down or taking any diet for 30 minutes. Etidronate, a first generation bisphosphonate, was associated with necrosis of the jaw and is no longer used. Pamidronate is an intravenous alternative that can be used for those who cannot tolerate oral bisphosphonate therapy.

In a randomised controlled trial, alendronate was better than risedronate and was just as well tolerated.[71] The maximisation of bone mass takes 7 years and hence bisphosphonate therapy is always long term, possibly lifelong. There is no rapid fall in BMD after cessation of bisphosphonate therapy,[23] unlike that which occurs on withdrawing hormone replacement therapy.[28] Bisphosphonates offer protection against hip, spine and other fractures, unlike synthetic oestrogen receptor modulators (SERM, e.g. raloxifene) which mainly act on the vertebral trabecular bone.[25] Strontium ranelate therapy reduces the risk of vertebral fracture by 40% and is less effective for preventing other fractures.[55,63]

Hormone replacement (HRT) with either low dose oestrogen or a combination of oestrogen and progestin is no doubt an effective way to combat postmenopausal osteoporosis. The vertebral fracture incidence came down by 50% and hip fracture by 33% in two large studies.[72,85] However, the increased incidence of myocardial ischaemia, stroke, venous thromboembolism and breast carcinoma have led to the abandonment of HRT as the primary treatment for postmenopausal osteoporosis.[80]

Recombinant human parathyroid hormone (1–34) (teriparatide) stimulates bone remodelling by increasing bone formation. It afforded 50% risk reduction of all fractures in a randomised trial.[61] The combination of bisphosphonates and teriparatide in a concurrent, cyclical or sequential manner appears logical, but there is no evidence of a superior efficacy of such combinations in reducing fracture risk.[43] Salmon calcitonin is not used for prevention but is mainly useful for managing severe pain in patients with osteoporotic fractures.

Once a patient has a fragility fracture, drug therapy is naturally indicated. Preventive drug therapy is indicated in patients with *t* score of –2.5 or less. It is also indicated in patients with *t* score of –2 to –2.5 along with one additional risk factor listed in Table 4.[79]

General Measures

The importance of maintaining calcium and vitamin D intake throughout life cannot be overemphasised.[6] The recommended daily intake is summarised in Table 6. Calcium and vitamin D supplements are indicated when the diet alone cannot provide the recommended daily intake and when the patient is on bisphosphonate therapy.[74] Supplemental calcium must be given in 2–3 split doses. High oxalate containing vegetarian diets may prevent absorption of dietary calcium. For those without renal disease, alfacalcidol does not offer a significant advantage over cholecalciferol. Maintenance of body weight, regular weight bearing activity and physical exercise are also essential. Preventing falls is desirable. Hip protectors can be used selectively.

Conservative Management of Vertebral Compression Fracture

The pain of the recent vertebral compression fracture responds to bed rest and simple analgesic therapy. Prolonged bed rest is poorly tolerated by the elderly and hence the patients are mobilised early, usually within a week or two. Anterior spinal bracing may be used in the first 6–8 weeks after the fracture. Calcitonin helps the pain when other analgesics fail. All fractures that remain painful after 3 weeks, selected early fractures and chronic non-healing fractures greater than 6 weeks old are considered for percutaneous augmentation.

Percutaneous Intervention for Osteoporotic Vertebral Compression Fracture

Indications

Percutaneous injection of polymethylmethacrylate (PMMA) bone cement was first done in France for haemangioma of the vertebra in 1984.[19] Over the last 15 years, it has widely been applied to relieving the pain of osteoporotic vertebral compression fractures. The other indications include osteolytic metastasis and myeloma with or without pathological fracture,[31] vertebral histiocytosis and the painful fractures of osteonecrosis (Kummell's disease). The prophylactic augmentation of the osteoporotic vertebra before it gets fractured is a recent but debated indication.[2] Since 1999, correction of kyphosis by a balloon inserted percutaneously has been available as an adjunct to vertebroplasty. Kyphoplasty opens up the wedged vertebra by means of an inflatable bone tamp prior to injection of bone cement. This should ideally restore the vertebral height and correct the kyphosis. Even when the kyphosis correction is minimal, the compaction of the trabeculae that occurs during kyphoplasty allows a greater volume of cement to be injected under lower pressure, thus minimising the risk of cement leakage.[58]

Table 6: Recommended daily intake

Age (Years)	*Calcium (mg)*	*Vitamin D (IU)*
3–8	800	200
9–17	1300	200
18–50	1000	400
51–70	1200	400
> 70	1200	600

Mechanism of Pain Relief

Vertebroplasty has been proved by *in vitro* biomechanical studies to stiffen the vertebra.[52] Stabilisation of the microfractures is one mechanism of pain relief after vertebroplasty. The heat produced by the exothermic polymerisation of methylmethacrylate may damage the nociceptive nerve endings in bone. The unpolymerised monomer may directly damage the cells secreting pain mediators.

Contraindications

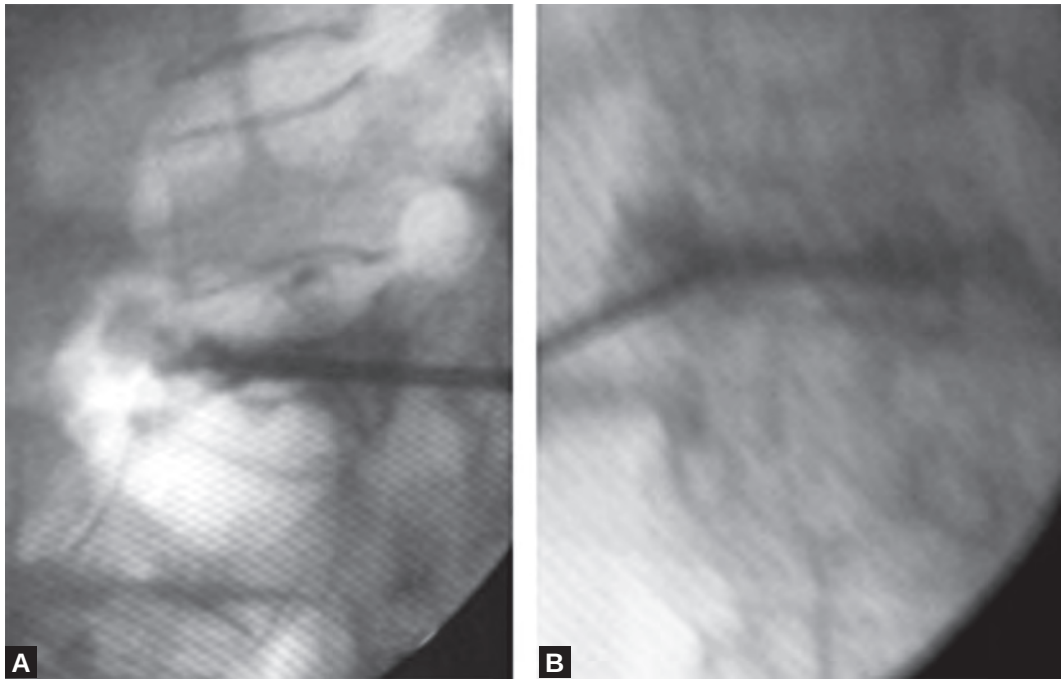
Systemic or local infection, bleeding diathesis and neurological deficits due to spinal canal compromise may contraindicate vertebroplasty and kyphoplasty. Disruption of the posterior vertebral cortex increases the chance of intraspinal cement leakage. The procedure may be rendered difficult by a totally (> 90%) collapsed vertebra but may still be done. The patient shown in Figure 1C underwent vertebroplasty with good relief of pain. In view of its minimally invasive nature, even patients who are not medically fit for major open surgical stabilisation procedures can be candidates for percutaneous vertebral augmentation.

Technique

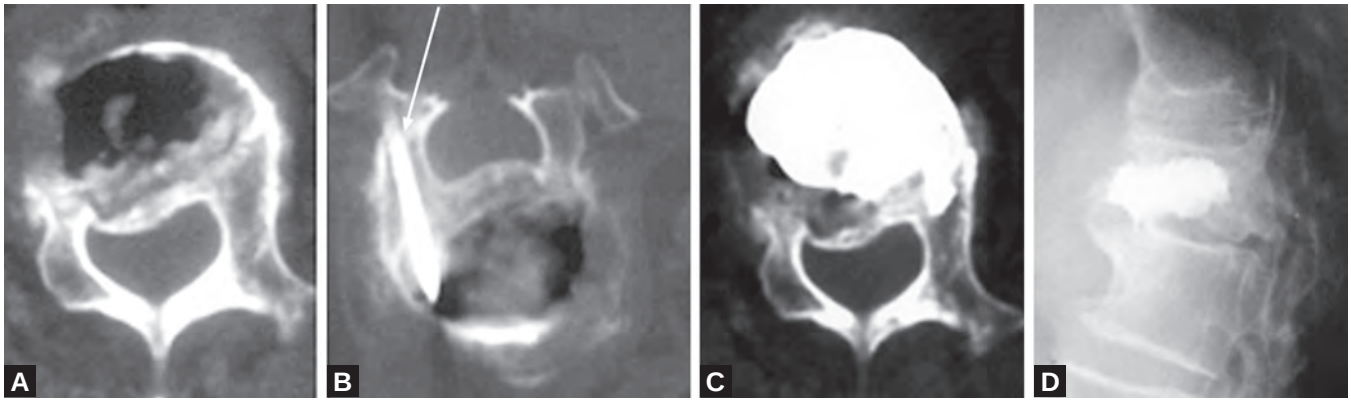
Vertebroplasty is done under local infiltration analgesia. Conscious sedation is useful. General anaesthesia is reserved for those who need to undergo multiple level augmentations in one session or when kyphoplasty is planned, but the patient must be medically fit. The patient is positioned prone for thoracic or lumbar fractures, on bolsters, with the spine in some extension to allow postural reduction.[13] The procedure is done on a radiolucent table with C-arm image intensifier screening. Rotating a single plane C-arm image intensifier to obtain anteroposterior and lateral projections is sufficient (Figs 4A and B) but a biplane image intensifier saves time. CT guided needle placement is used when the vertebrae or pedicle landmarks are difficult to visualise on radiography, when simultaneous lesional biopsy is planned and for procedures on the cervical vertebrae. We have used routine CT guided placement of the needle for the transpedicular approach (Figs 5A and B). Peri-operative systemic antibiotic may be supplemented by addition of tobramycin to the cement preparation.

Approach

Transpedicular approach is the classical route. The advantages are that the pedicle is a well-recognised radiographic landmark and that the long intraosseous path prevents nerve root injury minimising cement leakage



Figs 4A and B: Vertebroplasty. Needle position for C-arm image intensifier guided vertebroplasty by the transpedicular approach. (A) Lateral projection. (B) AP projection



Figs 5A to D: CT guided vertebroplasty. (A) Axial CT scan of osteoporotic wedge compression of L1 vertebral body (same patient as in Figure 2) Note the cavity in the body and the intact pedicles. (B) Percutaneous transpedicular needle placement was done. (C) Methylmethacrylate vertebroplasty was done. Note the bilateral filling in the post-procedure CT after unipedicular injection. The patient had excellent pain relief. (D) Follow-up lateral radiograph one year after vertebroplasty. Note the partial height restoration and reduction of kyphosis as compared to Figure 2C

into the soft tissues. In this approach, although the needle lies in one half of the vertebra, the entire vertebra often gets filled (Fig. 5C). In some cases, bipedicular injection may be needed to fill both halves of the vertebral body. In small pedicles, such as those seen in the upper thoracic region, the parapedicular approach may be chosen. For kyphoplasty, the inflatable balloon tamp needs to be placed in the middle of the vertebral body and hence the parapedicular approach may be preferred. Through a paraspinous stab incision, a 11G needle is placed in the vertebral body. The pedicle may be viewed either in a straight anteroposterior projection or may be seen 'end-on' by rotating and angling the image intensifier. Biopsy is obtained if needed. Injection of iodinated contrast confirms the correct placement and outlines the venous pattern but is not mandatory.[83] Despite venography, bone cement might enter the venous system.

Cement Injection

Chilling the bone cement components before the procedure extends the time for the cement to set. Since commercial preparations vary in their barium content and some may not sufficiently be radio-opaque, sterile barium sulphate is added to obtain 1:3 barium:PMMA mixture. Injection of bone cement in a thick soupy consistency is done with 1 ml syringes using hand pressure. Injection when the mixture is too thin encourages venous embolisation and must be avoided. The injection is done under lateral image intensifier screening to look for entry of cement into the spinal canal. The body opacifies with

cement in the anterior to posterior direction. The volume needed per level might be 2–6 cc. Cement injection is stopped when the posterior quarter of the body is filled or when it leaks beyond the vertebra. The patient must lie prone for 15–20 minutes until the cement hardens. The patient can be ambulated within hours. Pain relief is usually seen within a day and is lasting. The radiographical correction of kyphosis is also lasting (Fig. 5D), but loss of correction has been seen in some cases. Pain relief has been reported in up to 90% of patients undergoing vertebroplasty in various series done for different indications. Calcium phosphate cement has recently been tried for vertebroplasty.[59] Bioactive glass-ceramic reinforced material has also been introduced as an alternative to PMMA.

Technique of Kyphoplasty

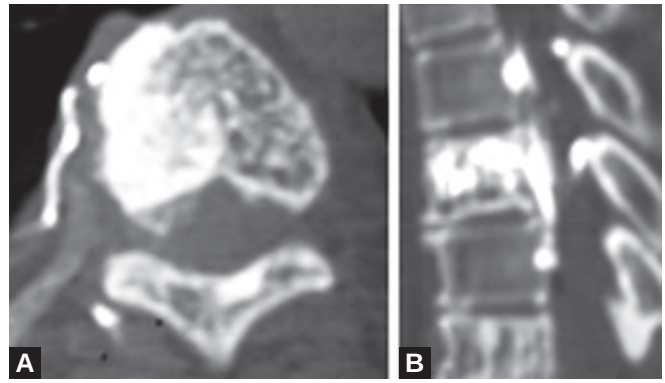
The initial steps are similar to vertebroplasty. The needle, placed in a similar manner, is exchanged for a cannula and introducer system over a guide pin. Through this the balloon tamp is introduced and inflated till the kyphotic deformity is corrected or the balloon reaches the cortical margin. The balloon is then deflated and bone cement is injected. More viscous cement can be injected under lower pressure into the cavity created. Kyphoplasty is generally done with bilateral approaches but unipedicular kyphoplasty has been reported.[34]

Results

A prospective but non-randomised study has shown that vertebroplasty for *acute* vertebral compression fracture can reduce the pain, disablement, hospital stay and improve quality of life as compared to medical management.[20] Small numbers of patients studied in the long term have shown efficacy of vertebroplasty to last 4 or 5 years.[66] Kyphoplasty has also shown similar efficacy in improving pain score and disability index in a prospective study.[17] An average of 68% restoration of anterior height of the vertebra was observed at 1 year in a study of balloon kyphoplasty, but there were also patients in whom there was no height restoration at all.[46] In another study, 58% of the fractures were partially reducible with kyphoplasty and mean Cobb angle correction was 14 degrees.[67]

Complications

Placement of the needle may engender root injury and might fracture the pedicle or rib. Cement leakage may be seen in 60% of patients[33] and is usually asymptomatic, especially when it occurs into the anterior or lateral paravertebral spaces, disc or the perivertebral veins (Fig. 6A). Small intraspinal leaks may also be asymptomatic (Fig. 6B). Symptomatic cement leakage may result in either radiculopathy or myelopathy, and occurs in only 1%.[33] The frequency of leakage is the same in those with or without the intravertebral cleft, but epidural leaks are more common in patients without a cleft.[40] Pain and minor deficits might improve with steroids and expectant therapy, while the serious deficits call for surgical decompression.[19] Pulmonary cement embolism is rare. Bleeding at the puncture site, transitory worsening of pain and fever in the hours following injection due to the heat generated during polymerisation and bone infection have been reported.[27] Complications are more common in patients with tumours undergoing vertebroplasty.



Figs 6A and B: (A) Asymptomatic entry and persistence of bone cement in the intercostal vein one year after vertebroplasty for haemangioma of T3 vertebral body. (B) Asymptomatic intraspinal leak of bone cement in a patient undergoing vertebroplasty for haemangioma

Concerns

The toxicity of PMMA to the personnel and the patient is an issue that needs to be clarified. Vertebroplasty and kyphoplasty have not yet been evaluated against best medical therapy or between themselves in prospective randomised, controlled trials. Cementing one vertebra in a very osteoporotic spine may promote fractures at the adjacent levels.[82]

Surgery for Osteoporotic Compression Fractures

The widespread availability of vertebroplasty has lessened the need for surgical intervention for osteoporotic vertebral compression fractures. Patients with demonstrable instability and significant neurological deficits may need surgery in the acute stage. Delayed neurological progression after initial fracture healing also calls for surgery. The techniques of stabilising and fusing the spine are similar to those used in non-osteoporotic vertebrae. The problems of instrumentation and fusion of the osteoporotic bone are dealt with in the next sections. Apart from these are the complications caused by the age and poor medical fitness of osteoporotic patients.

Instrumentation in Osteoporotic Spine

Instrumentation of the osteoporotic spine (Table 7) is rendered difficult by poor purchase of screws leading to screw pullout, wires cutting through the bone, greater tendency for settling of cages and proneness for iatrogenic fracture.[1,32] The weakest link in osteoporotic bone is the bone-metal interface. The less stiff segments adjacent to the rigid instrumented segment may fail.[82] These problems can be solved to an extent by: (1) increasing the points of

Table 7: Recommendations on the methods for internal fixation of the osteoporotic spine

Level	*Method of choice*	*Comments*
Odontoid fracture type 2	1. Anterior screw fixation[4] 2. Posterior transarticular screw fixation	Chance of wire cut through high in Gallie or Brooks wiring
Subaxial cervical spine	1. Anterior constrained plate-screw construct 2. Unconstrained plate with bicortical screw purchase (Caspar) 3. Rectangular cages sit on the peripheral thick cortical shell and are better than porotic autografts	Lateral mass fixation is prone to fail Interspinous wires may cut through
Thoracic spine	1. Multiple segmental fixation using pedicle screw or sublaminar wire construct, 2–3 levels above and below the injured level, supplemented by laminar hooks 2. Bicortical purchase and placement of screws as safely as possible near the end plates for anterior fixation 3. Claw or staple washers prevent the screw head from sinking into the soft vertebral body	Spinous process wire cut through, pedicle screw pullout, pedicle break after sublaminar wiring and hook failure due to break in pars-pedicle junction are likely[9,14]
Lumbar spine	1. Multiple segmental fixation using pedicle screw construct 2. Under-tapping or no tapping,[30] injecting carbonated apatite cement under pressure,[50] convergent screw paths, large diameter screws, expanding tip screws help achieve good pedicle screw placement 3. Placement of a good interbody construct (bone or cages) lessens the strain on the pedicle screw system	Lower the BMD, greater the chance of pedicle screw pullout. Pedicle screws cannot be used in spines with BMD < 0.3–0.4 gm/sq cm.[77] Placing bone graft in a stripped screw hole does not prevent screw pullout in osteoporotic bone

fixation to evenly spread out the stresses over many levels; (2) adding supplementary fixation as for example using laminar hooks, wires or transverse connectors along with pedicle screws; (3) using PMMA bone cement to augment fixation;[35] (4) using "escape" methods like larger screws to thwart loosening; (5) using larger cylindrical or rectangular cages which maximise the surface area of contact; (6) using implants which are less stiff and nearer to bone in elasticity; (7) using appropriate orthoses for longer periods and (8) by careful selection of the method of fixation in individual cases (see recommendations in Table 7).

Interbody Fusion in Osteoporotic Spine

Notwithstanding the generally poor autogenous donor bone quality, tricortical iliac crest autograft is still the best for fusing the osteoporotic spine. Cylindrical threaded cages, rectangular cages and femoral ring allografts are available. Cages made of steel, titanium, PEEK ceramic and carbon fibre are available. Material that is similar to bone in stiffness will give a better result, as subsidence of a hard interbody spacer is a real problem in osteoporotic bone. Cylindrical cages do not conform to the apposing surfaces in the disc space and rectangular cages seem to be better. The central portions of the vertebrae are softer than the peripheral cortical shells that are denser dorsally and ventrally. Rectangular cages or bone grafts supported by these rims are less likely to fail, especially in osteoporotic bones. End plate integrity must be maintained to prevent settling of cages or strut grafts. Bone morphogenic protein improves bone fusion but is very expensive.

SUMMARY

Osteoporosis epidemic is on the rise. Neurosurgeons should have osteoporosis in their minds when they see patients on long-term glucocorticoid or antiepileptic therapy. Simple supplementation of calcium and vitamin D, early diagnosis by BMD measurement, antiresorptive therapy and early pain relief with percutaneous augmentation will help to reduce the morbidity due to osteoporotic vertebral compression fracture.

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SECTION

11

Pathology of Intracranial Tumours

Sankar

119 Classification of Tumours of the Nervous System

Vani Santhosh

CLASSIFICATION

The earliest classification of central nervous system (CNS) tumours was that of Bailey and Cushing in 1926.[1] These authors studied the embryogenesis of the various cellular components of the CNS and then attempted to classify tumours based on cytogenesis after enumerating about 20 cell types in the nervous system. The next well accepted classification was that of the World Health Organization (WHO)[73] in 1979, termed 'International Classification of Central Nervous System Tumours'. This represents the initial consensus of opinion put forth by several independent groups. Essentially, it was derived from Bailey and Cushing's classification and, despite widely differing view points, has maintained uniformity on most of the commonly recognised tumour entities and their frequent variants.[72]

This classification was revised and, in 1993, the WHO proposed a new classification of tumours of the nervous system (2nd edition). This was based on the premise that a particular type of tumour occurs as a result of abnormal proliferation of a particular cell type. Since the behaviour of the tumour is determined by the basic cell type, it was clear that tumour classification dictates the choice of therapy and predicts prognosis.[29,36]

The 1993 classification reflects the progress and changes made since the publication of the first edition of nervous system tumour classification in 1979. Several new tumour entities were included, for example, pleomorphic xanthoastrocytoma (PXA), central neurocytoma, desmoplastic infantile ganglioglioma/astrocytoma (DIG/DAI) and dysembryoplastic neuroepithelial tumour (DNET). Histological variants of some of the tumour entities were included. More importantly, with the introduction of immunohistochemical techniques for assisting histological diagnosis, and with increasing morphological and molecular data on glioma progression, it was realised that glioblastoma (GBM) is synonymous with malignant astrocytoma Grade IV and was thus grouped with astrocytic neoplasms. The classification of embryonal tumours was largely retained and the term primitive neuroectodermal tumour (PNET) was used as a generic term for medulloblastomas and other neoplasms that are histologically indistinguishable from medulloblastoma and located at sites in the CNS other than the cerebellum.

The 3rd edition[31] of WHO classification of tumours of the nervous system was published in the year 2000. The format of this classification is different from the earlier two editions in that each tumour entity has been discussed comprehensively, which included the clinical, epidemiological and radiological aspects along with gross and histological morphology, molecular genetic features and predictive/prognostic factors for that tumour. This classification has been made to suit clinicians, pathologists, geneticists and clinical oncologists. The tumours also bear the International Classification of Disease for Oncology (ICD-O) codes, which can facilitate epidemiological analysis of neoplasms of the nervous system.

Some of the new tumour entities included in this classification are: chordoid glioma of third ventricle, cerebellar liponeurocytoma, atypical teratoid/rhabdoid tumour and perineurioma. Some of the histological variants of known tumour entities include; tanycytic ependymoma, large cell medulloblastoma, rhabdoid meningioma and teratoma with malignant transformation. The entity polar spongioblastoma has been deleted from the classification in this edition. In addition, the classification has extensively been revised for meningiomas. Further, this classification emphasises various genetic profiles of tumours and the role of the molecular diagnostic approach to tumour classification, which is considered to have a bearing on the prognosis and therapy, for example, the distinct subtypes of GBM, the clinically useful 1p 19q markers in oligodendrogliomas and 22q/1N11 for atypical teratoid/rhabdoid tumours. In short, the WHO 2000 classification of nervous system tumours was proposed to be used by the neuro-oncologist and the medical research community worldwide.

The 4th edition of the WHO Classification of the Nervous System (2007) is the latest published classification. The changes incorporated in this classification reflect the recognition of new tumour entities and additionally offers a better understanding of tumour behaviour. This classification lists several new entities like angiocentric glioma, papillary glioneuronal tumour, rossette forming glioneuronal tumour of the fourth ventricle, papillary tumour of the pineal region, pituicytoma and spindle cell oncocytoma. Some of the histological variants added are, pilomyxoid astrocytoma, anaplastic medulloblastoma and medulloblastoma with extensive nodularity (MBEN). The WHO grading scheme and the sections on

genetic profiles of CNS tumours have been updated. In the section of familial tumour syndromes, the entity of 'rhabdoid predisposition syndrome' has been included. On similar lines as the WHO 2000 (3rd edition), the classification is accompanied by comprehensive information with the clinicopathological and biological characteristics of each tumour.[5,38,39] Table 1 represents the current WHO classification of CNS tumours.

GRADING OF CENTRAL NERVOUS SYSTEM TUMOURS

The goal of any grading system is that tumour grade should predict the biological behaviour of a neoplasm. It should be sufficiently objective, so as to minimise interobserver variability and maximise reproducibility. Tumour grade is the key factor that influences and guides adjuvant therapy.

WHO has included a grading scheme in its classification and this has largely replaced previously published grading schemes. Most CNS neoplasms are included in the grading scheme except for some newer entities, since additional data and long-term follow-up of these neoplasms are required.[29,31,39]

Significance of Grading

In the CNS, tumours are graded from I to IV. Grade I tumours are those with low proliferative potential and could possibly be cured by surgical resection alone. Grade II tumours are usually infiltrative, have a lower proliferative potential, but often progress to higher grade malignancy and recur, for example, diffuse astrocytoma (DA) (Grade II) which can progress to anaplastic astrocytoma (Grade III) and GBM (Grade IV). Grade III tumours are malignant and these patients have to receive appropriate radiotherapy and/or chemotherapy. Grade IV tumours are cytologically malignant, with brisk mitosis, often associated with necrosis. These patients have a poor prognosis and a fatal outcome. Examples for Grade IV tumours are GBM and most of the embryonal tumours.

Predictive Value of Tumour Grades

WHO grades definitely predict response to therapy and outcome.[39] However, several studies have shown that, apart from tumour grading, other clinical parameters particularly age of the patient, Kernofsky performance status, location of the tumour, radiological characteristics, especially the contrast enhancement pattern, extent of surgical resection, tumour proliferation indices and genetic alterations are the factors that govern the biological behaviour of brain tumours and the prognosis of patients, particularly in gliomas. Despite all these variables, studies have shown that patients with WHO Grades II tumours survive for more than 5 years and those with Grade III tumours survive for 2–3 years. In Grade IV tumours, the prognosis largely depends upon the degree of response to effective treatment regimens. The prognosis for GBM patients is very poor with the mean survival period not exceeding 9–12 months.[33] However, in patients with medulloblastoma and germ cell neoplasms (Grade IV tumours) who have received adequate adjuvant therapy, the 5-year survival rate exceeds 67% and 80%, respectively.[39]

Grading of Astrocytomas

Astrocytomas are the most heterogeneous neoplasms varying in their grades of malignancy within the same neoplasm. Several grading schemes have been applied to this group of tumours, notably that of Ringertz,[56] St. Anne/Mayo[8] and the published WHO schemes.[39] Currently, the objective criteria taken into account for grading astrocytomas are: nuclear atypia, mitotic activity, microvascular proliferation and/or necrosis. Tumours with nuclear atypia alone are graded as II, those with nuclear atypia and mitosis are graded as III and tumours additionally showing microvascular proliferation and/or necrosis are graded as WHO Grade IV neoplasms. This grading scheme is comparable to the St. Anne/Mayo grading system with one major difference, i.e. Grade I astrocytoma. According to WHO, this term refers to pilocytic astrocytoma, which is a circumscribed tumour. However, according to the St. Anne/Mayo grading system, Grade I is designated to a rare DA without nuclear atypia. Currently, the WHO grading system is the one mostly used for ease and uniformity.

Nuclear atypia refers to variation in nuclear size or shape, multinucleation and hyperchromasia. Mitosis should be unequivocal but there is no importance given to their number and morphology. Sometimes it is difficult to differentiate a Grade II from a Grade III astrocytoma, when there is a solitary mitosis in a large tumour. Several authors advocate that MIB-1 labelling indices be used to distinguish accurately a Grade II from a Grade III astrocytoma.[23,48] The term 'endothelial proliferation' or 'microvascular proliferation' refers to 'heaping up' of endothelial cells rather than simple hypervascularity or glomeruloid vasculature. Necrosis can be either of the 'field' type or 'wreath' type with perinecrotic pallisading of tumour cells. It is important to know that these four objective criteria (e.g. nuclear atypia, mitosis in tumour cells, endothelial proliferation and/or necrosis) appear in a predictable sequence as the tumour grade increases.[39] Table 1 represents the current WHO grading of CNS tumours.

ASTROCYTIC TUMOURS

Among CNS neoplasms, astrocytomas are the commonest, comprising more than 60% of the primary tumours. They represent a wide range of neoplasms that differ in their location within the CNS, age and gender distribution, morphological features, growth potential, extent of invasiveness, tendency to progression and clinical course. Astrocytomas are divided into two distinct

Table 1: WHO classification and grading of tumours of the nervous system (Adapted from WHO 2007 classification of CNS tumours)[7]

Tumours of Neuroepithelial Tissue	*Grade*
Astrocytic tumours	
• Pilocytic astrocytoma	I
– Pilomyxoid astrocytoma	II
• Subependymal giant cell astrocytoma	I
• Pleomorphic xanthoastrocytoma	II
• Diffuse astrocytoma	II
– Fibrillary astrocytoma	
– Gemistocytic astrocytoma	
– Protoplasmic astrocytoma	
• Anaplastic astrocytoma	III
• Glioblastoma	IV
– Giant cell Glioblastoma	IV
– Gliosarcoma	IV
• Gliomatosis cerebri	III
Oligodendroglial tumours	
• Oligodendroglioma	II
• Anaplastic oligodendroglioma	III
Oligoastrocytic tumours	
• Oligoastrocytoma	II
• Anaplastic oligoastrocytoma	III
Ependymal tumours	
• Subependymoma	I
• Myxopapillary ependymoma	I
• Ependymoma	II
– Cellular	
– Papillary	
– Clear cell	
– Tanycytic	
• Anaplastic ependymoma	III
Choroid plexus tumours	
• Choroid plexus papilloma	I
• Atypical choroids plexus papilloma	II
• Choroid plexus carcinoma	III
• Other neuroepithelial tumours	
• Astroblastoma	I/II
• Chordoid glioma of the third vertical	II
• Angiocentric glioma	I
Neuronal and mixed neuronal-glial tumours	
• Dysplastic gangliocytoma of cerebellum (Lhermitte-Duclos)	I
• Desmoplastic infantile astrocytoma/ganglioglioma	I
• Dysembryoplastic neuroepithelial tumour	I
• Gangliocytoma	I

Contd...

Contd...

Tumours of Neuroepithelial Tissue	*Grade*
• Ganglioglioma	I
• Anaplastic ganglioglioma	III
• Central neurocytoma	II
• Extraventricular neurocytoma	II
• Cerebellar liponeurocytoma	II
• Papillary glioneuronal tumour	I
• Rosette-forming glioneuronal tumour of the fourth ventricle	I
• Paraganglioma	I
Tumours of the pineal region	
• Pineocytoma	I
• Pineal parenchymal tumour of intermediate differentiation	II/III
• Pineoblastoma	IV
• Papillary tumour of the pineal region	II/III
Embryonal tumours	IV
• Medulloblastoma	
– Desmoplastic/nodular medulloblastoma	
– Medulloblastoma with extensive nodularity	
– Anaplastic medulloblastoma	
– Large cell medulloblastoma	
• CNS primitive neuroectodermal tumour	
– CNS neuroblastoma	
– CNS ganglioneuroblastoma	
– Medulloepithelioma	
– Ependymoblastoma	
• Atypical teratoid/rhabdoid tumour	
Tumours of Cranial and Paraspinal Nerves	
• Schwannoma (neurilemmoma, neurinoma)	I
– Cellular	
– Plexiform	
– Melanotic	
• Neurofibroma	I
– Plexiform	
• Perineurinoma	I/II/III
– Perineurinoma	III
– Malignant perineurinoma	
• Malignant peripheral	
– Nerve sheath tumour (MPNST)	II/III/IV
– Epithelioid MPNST	
• MPNST with mesenchymal differentiation	
• Melanotic MPNST	
• MPNST with glandular differentiation	

Contd...

Contd...

Tumours of Neuroepithelial Tissue	*Grade*
Tumours of the Meninges	
Tumours of meningothelial cells	
• Meningioma	I
– Meningothelial	
– Fibrous (fibroblastic)	
– Transitional (mixed)	
– Psammomatous	
– Angiomatous	
– Microcystic	
– Secretory	
– Lymphoplasmacyte-rich	
– Metaplastic	
– Chordoid	II
– Clear cell	II
– Atypical	II
– Papillary	III
– Rhabdoid	III
– Anaplastic (malignant)	III
Mesenchymal tumours	I/II/III
• Lipoma	
• Angiolipoma	
• Hibernoma	
• Liposarcoma	
• Solitary fibrous tumour	
• Fibrosarcoma	
• Malignant fibrous histiocytoma	
• Leiomyoma	
• Leiomyosarcoma	
• Rhabdomyoma	
• Rhabdomyosarcoma	
• Chondroma	
• Chondrosarcoma	
• Osteoma	
• Osteosarcoma	
• Osteochondroma	
• Haemangioma	
• Epithelioid haemangioendothelioma	

Contd...

Contd...

Tumours of Neuroepithelial Tissue	*Grade*
• Haemangiopericytoma	
• Anaplastic haemangiopericytoma	
• Angiosarcoma	
• Kaposi sarcoma	
• Ewing sarcoma—PNET	
Primary melanocytic lesions	
• Diffuse melanocytosis	
• Melanocytoma	
• Malignant melanoma	
• Meningeal melanomatosis	
Other neoplasms related to the meninges	
• *Haemangioblastoma*	I
Lymphomas and Haematopoietic Neoplasms	
• Malignant lymphomas	
• Plastocytoma	
• Granulocytic sarcoma	
Germ Cell Tumours	IV
• Germinoma	
• Embryonal carcinoma	
• Yolk sac tumour	
• Choriocarcinoma	
• Teratoma	
– Mature	
– Immature	
– Teratoma with malignant transformation	
• Mixed germ cell tumour	
Tumours of the Sellar Region	I
• Craniopharyngioma	
– Adamantinomatous	
– Papillary	
• Granular cell tumour	
• Pituicytoma	
• Spindle cell oncocytoma of the adenohypophysis	
Metastatic Tumours	

categories—circumscribed astrocytic tumours and diffusely infiltrating astrocytic tumours.[55]

Circumscribed Astrocytic Tumours

The circumscribed astrocytomas clearly exhibit distinct clinicopathological features. Tumours in this group include: (a) Pilocytic astrocytoma (WHO Grade I) and its variant Pilomyxoid astrocytoma; (b) PXA (WHO Grade II); (c) Subependymal giant cell astrocytoma (SEGA) (WHO Grade I). These tumours are relatively circumscribed and generally tend to have a more favourable prognosis which is due to a reduced capacity for invasive spread and limited potential for growth and anaplastic progression. Therefore, clear recognition of these entities is important.

Pilocytic Astrocytoma (WHO Grade I)

Pilocytic astrocytomas typically arise in children and young adults are more often circumscribed, slowly growing and indolent neoplasms corresponding to

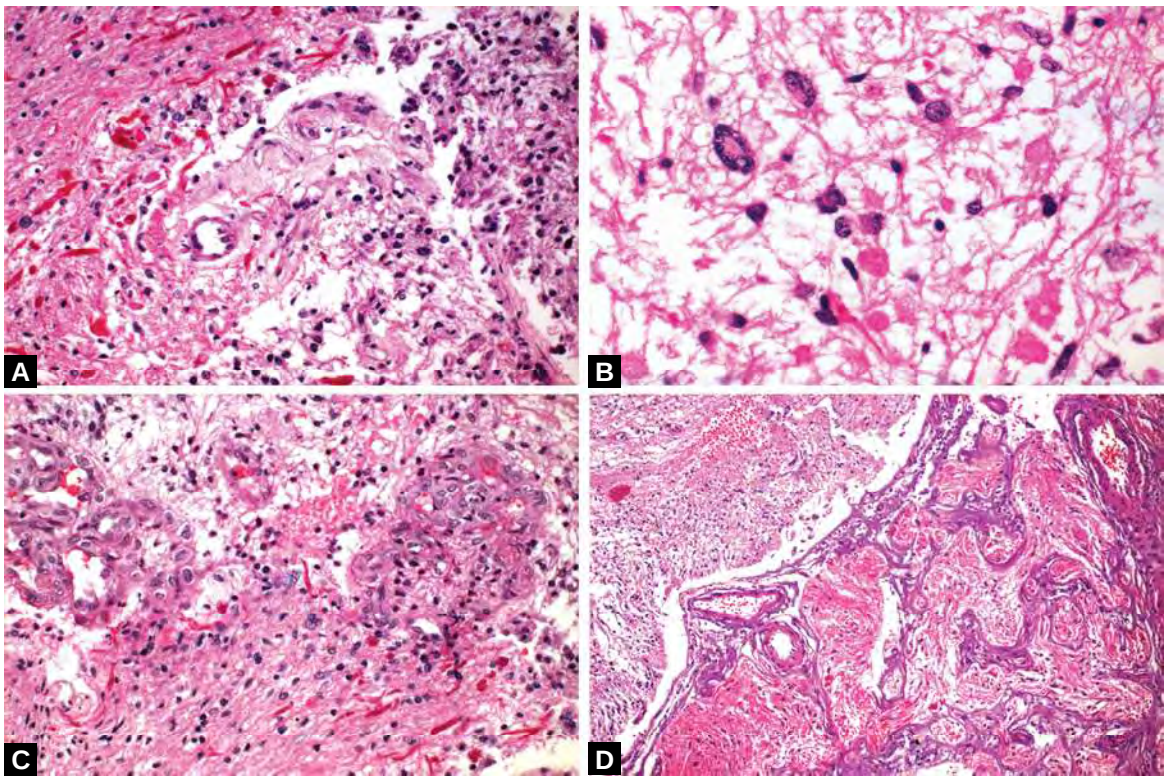
WHO Grade I. Unlike DAs, they have very little tendency for anaplastic progression.

Incidence and localisation: They comprise 3–6% of all intracranial neoplasms and 5–6% of all gliomas.[39] In children, pilocytic astrocytoma is the commonest glial neoplasm[18,33] with a predilection for the cerebellum,[20] optic pathway and the hypothalamic-third ventricular regions[59] and, hence, the synonyms: 'cerebellar astrocytoma', 'optic glioma', etc. Other regions in the neuraxis, like the brainstem, cerebral hemispheres, thalamus and basal ganglia, and spinal cord, can also be involved. In large hypothalamic and brainstem gliomas, when they occupy the ventricular cavity, it becomes difficult to determine their exact site of origin.

Clinical features: The clinical presentation of a pilocytic astrocytoma is that of a slowly growing lesion. Cerebellar tumours present in the first two decades clinically with clumsiness of movements and features of raised intracranial pressure. Brainstem tumours are usually of the dorsal exophytic type[60] and cause hydrocephalus or brainstem dysfunction. Optic pathway tumours present with visual loss and hypothalamic/pituitary dysfunction as is seen in patients with large hypothalamic tumours.[59] Tumours in the cerebral hemispheres produce focal neurological deficits or non-localising signs and in the spinal cord, present as an expanding mass.

Neuroimaging: By CT and MRI, these tumours are relatively circumscribed and the majority have a heterogeneously enhancing cyst with a mural nodule (Fig. 1A). The nodule is not hyperdense. These characteristics distinguish them from DA (WHO Grade II). Exceptionally, the tumour can be a solid lesion and calcification is seen in 5–25% of cases.[15]

Histopathology: Classically, pilocytic astrocytoma demonstrates a biphasic pattern of growth, consisting of compact portions composed of elongated, bipolar or 'piloid' astrocytes associated with Rosenthal fibres and microcystic zones being made up of multipolar cells, eosinophilic granular bodies (EGB) and hyaline droplets (Figs 1B and C). Several times, pilocytic astrocytomas show extensive degenerative nuclear atypia with pleomorphic and hyperchromatic nuclei (Fig. 1D). However, mitotic activity is not evident or a rare mitotic figure may be seen. Glomeruloid vascular proliferation is frequently observed in cerebellar and hypothalamic pilocytic astrocytomas. This is responsible for the contrast enhancement seen on MRI and can occasionally cause diagnostic confusion with high grade astrocytomas, particularly in small biopsies. However, endothelial hyperplasia, a feature of high grade diffuse astrocytic tumours, is not evident in pilocytic astrocytoma.[20] In pilocytic astrocytomas, vascular proliferation, mitotic activity and necrotic



Figs 1A to D: Histological features of pilocytic astrocytoma. (A) Compacted piloid cells with Rosenthal fibres and loose textured cells with microcysts (HE X 320). (B) Marked nuclear atypia in the absence of mitosis and presence of several eosinophil granular bodies (HE X 320). (C) Prominent glomeruloid vascular proliferation in the tumour (HE X 320). (D) Subarachnoid spread of the tumour (HE X 320)

foci, even when present, do not have the same ominous prognostic significance as in DAs.

Since pilocytic astrocytomas are slowly growing, indolent neoplasms, they can histologically show several regressive changes. One such feature is markedly hyalinised ectatic vessels which can at times resemble a cavernous angioma with piloid gliosis. Along with this, there can be haemosiderin-laden macrophages reflecting an old bleed. Other regressive changes include calcification, infarct-like necrosis and tumour infiltrating lymphocytes[39] and, occasionally, hyperchromatic large nuclei resembling a malignant cell.

Sometimes pilocytic astrocytomas (particularly those arising in the cerebellum and optic nerve) infiltrate the leptomeninges and impart a distinct lobular pattern to the tumour. This is not indicative of aggressiveness and malignant transformation, nor does it portend subarachnoid dissemination. In contrast, it is a characteristic and diagnostically helpful feature. Other histological features seen at times include oligodendroglioma-like cells seen particularly in cerebellar tumours and pallisading arrangement of cells that resemble what was termed as 'primitive polar spongioblastoma'.

Pilocytic astrocytomas are very indolent tumours with a low proliferative index. The MIB-1 labelling indices range from 0 to 3.9% (mean 1.1%) (Fig. 1C). Very rarely pilocytic astrocytomas undergo malignant transformation with high mitotic activity, endothelial proliferation and pallisading necrosis and have been termed anaplastic (malignant) pilocytic astrocytoma. It is presumed that such tumours occur as a result of radiotherapy given to a previous pilocytic astrocytoma.[10]

Histogenesis: It is presumed that pilocytic astrocytomas arise from radial glia which are present in the hypothalamus, cerebellum and the spinal cord during development, and the glial cells of the pineal gland. These astrocytes presumably have the capacity to form Rosenthal fibres and the hair-like 'piloid fibres'.

Prognostic and predictive factors: Pilocytic astrocytomas are very slowly growing tumours which stabilise during their course of evolution. Recurrence is rare and most often is a reflection of cyst reformation. Supratentorial neoplasms and delay in radiotherapy, when required, are associated with shorter survival.[28] Recurrent hypothalamic and brainstem tumours are known to have increased morbidity and mortality.[59] Pilocytic astrocytomas associated with neurofibromatosis-1 (NF-1) tend to be less aggressive and sometimes spontaneously regress.[61] The prognosis of these tumours labelled as 'atypical' or 'malignant' is not very clear.[39]

Pilomyxoid Astrocytoma (WHO Grade II)

Pilomyxoid astrocytoma is a recently recognised variant of pilocytic astrocytoma. These tumours manifest in very young children, below the age of 4 years (median 10 months), most often in the hypothalamus or 3rd ventricular region, but can occur at other sites common to pilocytic astrocytoma.[69] Distinct histopathological features include a monomorphic bipolar population of neoplastic pilocytes in a prominent myxoid background in an angiocentric arrangement (Fig. 2). Rosenthal fibres and EGBs are absent, mitotic activity is slightly higher and the MIB-1 labelling index ranges from 2 to 20%. Immunostaining demonstrates strong diffuse reactivity to GFAP, S-100 protein and vimentin. Some tumours are positive for synaptophysin.[39]

Histogenesis: The cell of origin is not known but some state that the tumour arises from radial glia in the proximity of the optic tract.

Prognostic and predictive factors: These tumours are more aggressive than pilocytic astrocytomas.[69] Local recurrence and craniospinal seeding have been observed.

Pleomorphic Xanthoastrocytoma (WHO Grade II)

This is another circumscribed variant of astrocytoma with a favourable prognosis, typically occurring in young adults and children, in the superficial cerebral hemispheres, in close association with the leptomeninges and often as a cystic neoplasm with a mural nodule.

Incidence and localisation: PXA accounts for less than 1% of all intracranial neoplasms. Typically, the tumour is located in the superficial cerebral cortex often involving the leptomeninges (therefore also called meningocerebral glioma). The tumour is most often located in the temporal cortex followed by the parietal and frontal cortex.[17]

Clinical features and neuroimaging: Most patients have long standing seizures given the superficial location of the tumour. By CT and MRI, these tumours are well circumscribed or cystic masses with an enhancing mural nodule. Peritumoural oedema is not pronounced owing to the slow growth of the tumour and calcification is uncommon.

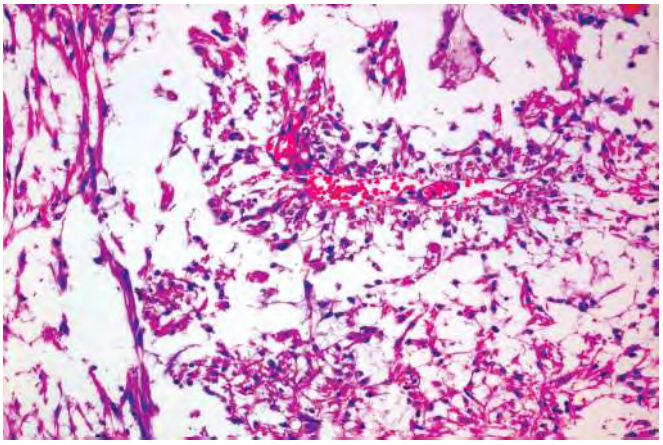


Fig. 2: Pilomyxoid astrocytoma: the tumour shows a monomorphic population of piloid cells in a homogeneously myxoid background. Angiocentric arrangement of tumour cells is also seen (HE X 320)

Histopathology: The tumour is circumscribed (Fig. 3A) and composed of closely packed, highly pleomorphic giant and lipidised cells. Variable xanthomatous change is seen in the cytoplasm because of intracellular accumulation of lipids. The astrocytic nature of the tumour cells is demonstrated by GFAP immunopositivity. Prominent EGB is a constant finding. A dense intracellular reticulin network and lymphocytic infiltrates are typical microscopic features. Necrosis and mitosis are usually absent. Another histological hallmark of PXA is the presence of intratumoural reticulin fibres, best seen using silver impregnation (Fig. 3B). By immunohistochemistry, the tumour cells are constantly positive for GFAP and S-100 protein. However, variable expression of neuronal markers has been reported.[25] The behaviour of PXA is generally that of an indolent tumour and most tumours have a MIB-1 labelling index of less than 1%. However, a small percentage of PXAs can recur and undergo malignant transformation. These tumours show higher mitotic activity (5 or more mitosis in 10 HPF) and are termed as 'PXA with anaplastic transformation'. On recurrence, the tumour might show histological features similar to the original tumour or increasing anaplasia.[39]

Histogenesis: It has been proposed that PXA arises from subpial astrocytes.[27] Ultrastructural studies have shown that both the subpial astrocytes and the tumour cells of PXA have a prominent basal lamina, which accounts for the rich reticulin network within the neoplasm. Some authors, however, state that PXA has a more complex histogenesis in view of the expression of neuronal and other markers by the tumour cells.[24]

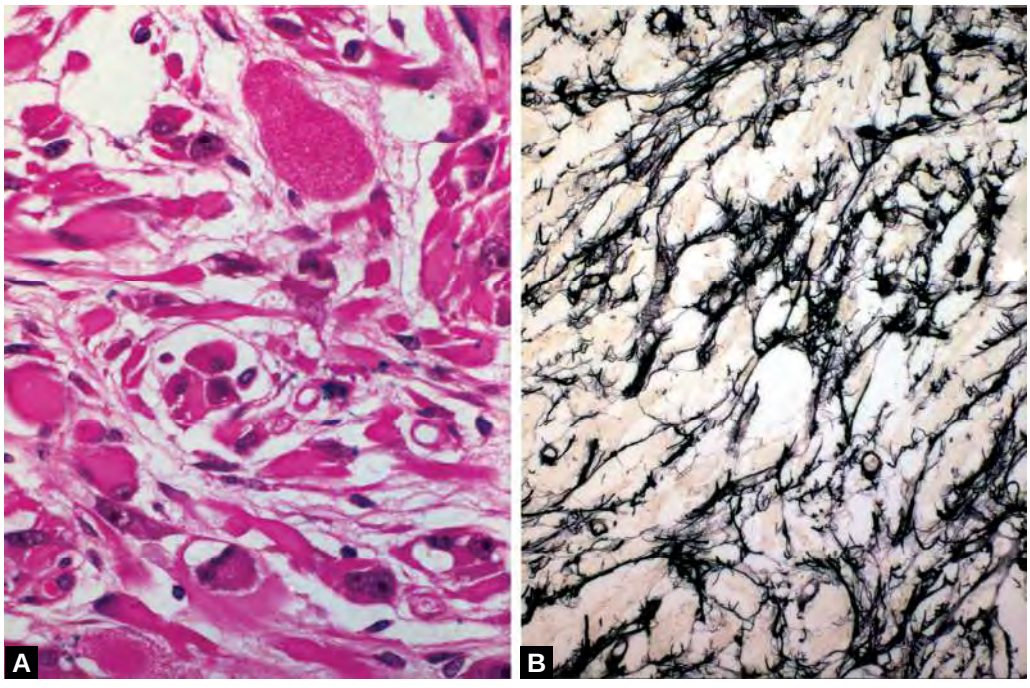
Prognosis and predictive factors: Despite its pleomorphic histomorphology, the prognosis of patients with PXA is favourable. Extent of tumour resection and a low proliferative index are definite prognostic factors. In one large series,[17] recurrence-free survival of 72% at 5 years and 61% at 10 years has been observed.

Subependymal Giant Cell Astrocytoma (WHO Grade I)

This is a benign, slowly growing tumour composed of large cells resembling gemistocytes and ganglion cells (ganglioid astrocytes), typically arising from the walls of the lateral ventricle.

Incidence and clinical features: SEGA is the most common CNS tumour in patients with tuberous sclerosis complex (TSC). Its incidence ranges from 6 to 14% in patients with confirmed TSC and it is one of the major criteria for the diagnosis of TSC.[58] The tumour manifests mostly in children and young adults and the patients often present with worsening of seizures or symptoms of raised intracranial pressure.[57]

Histopathology: SEGAs show a wide phenotypic spectrum of astrocytes ranging from polygonal and spindle shaped astrocytes to large polygonal cells resembling gemistocytic astrocytes with abundant glassy cytoplasm. In addition, characteristic giant pyramidal cells with a ganglionic appearance and nuclei with prominent nucleoli are also seen (Fig. 4). Occasional nuclear pleomorphism and multinucleated giant cells can be seen in SEGA. However, mitosis is absent or very rare and the proliferative index is generally low (mean 1.5–7.4%).The tumours are extremely vascular with numerous dilated vessels resembling cavernous spaces and this results in massive spontaneous haemorrhage in the tumour. Calcification is a common feature. By



Figs 3A and B: Pleomorphic xanthoastrocytoma. (A) Tumour shows highly pleomorphic astrocytes and eosinophil granular bodies. There is no mitosis (HE X 320). (B) Reticulin stain highlights the extensive intra-tumoural reticulin fibres (HE X 320)

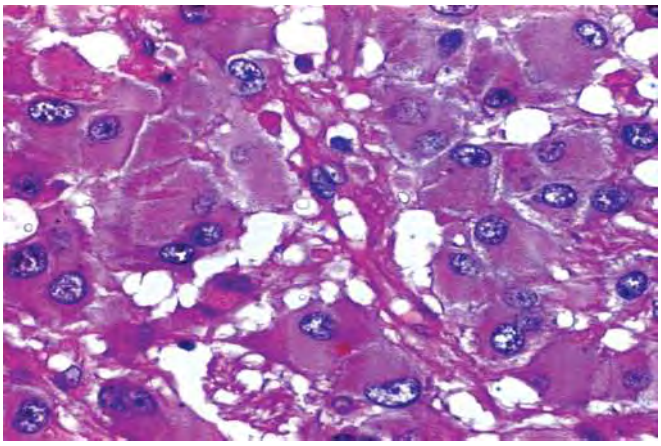


Fig. 4: Subependymal giant cell astrocytoma (SEGA) showing characteristic 'Ganglioid astrocytes' (HE X 320)

immunohistochemistry, the tumour cells express mixed glioneuronal markers. There is variable expression of GFAP and S-100 protein and some cells also express neurofilament protein and other neuronal markers including several neuropeptides. These findings suggest that SEGA contains cells with a capacity for divergent phenotypic differentiation including glial, neuronal and neuroendocrinal forms.[39]

Diffusely Infiltrating Astrocytic Tumours

This group encompasses at least 75% of the astrocytic tumours and termed as 'diffusely infiltrating astrocytomas'. This is further subdivided into: (a) DA/WHO Grade II; (b) Anaplastic astrocytoma (WHO Grade III) and (c) Glioblastoma (GBM-WHO Grade IV) and its variants such as giant cell GBM and gliosarcoma are currently also included in this group.[39] This category inevitably has a more ominous prognosis due to significant tendency for these tumours to undergo malignant transformation, infiltrate the surrounding brain and to invade the leptomeninges.

Diffuse Astrocytoma (WHO Grade II)

This is a diffusely infiltrating astrocytoma which is considerably differentiated, usually manifesting in young adults and most often supratentorial in location. It has an intrinsic tendency for malignant transformation, progressing to anaplastic astrocytoma and finally to GBM.[39]

Incidence and localisation: DA comprises 10–15% of all astrocytic neoplasms.[9] The peak incidence is in young adults between 30 years and 40 years of age. The tumour may be located anywhere in the CNS, but is mostly encountered in the cerebral hemispheres. Other common sites include the brainstem and spinal cord.

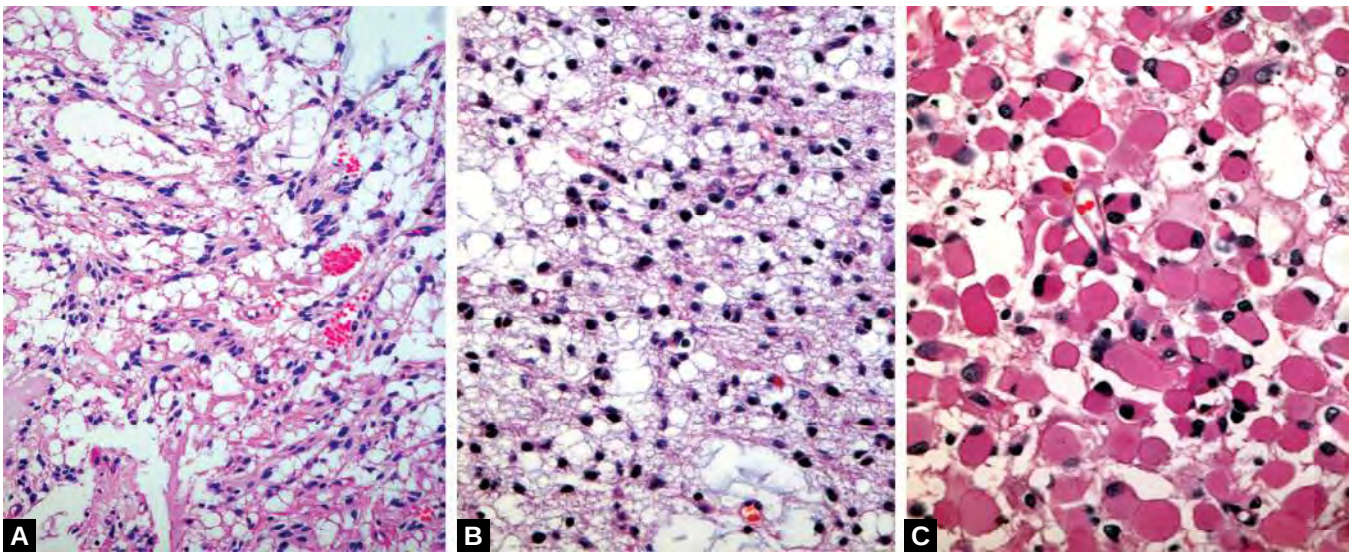
Clinical features and neuroimaging: Seizures are the most common presenting symptom. Others are subtle and include features of raised intracranial pressure, motor deficits, speech and cognitive dysfunction.[67] In contrast to pilocytic astrocytomas, on CT and MRI, these tumours are ill-defined, homogeneous masses of low density without contrast enhancement.[64]

Histopathology: DAs may be subdivided into fibrillary, gemistocytic and protoplasmic types based on the resemblance to the morphology of normal and reactive astrocytes (Figs 5A to C). In practice, most are fibrillary but mixed neoplasms, especially gemistocytic elements are common. These are mildly hypercellular tumours exhibiting a moderate degree of nuclear atypia. The cells are embedded in a loosely fibrillated, microcystic matrix. Mitosis is absent and infiltration of the cortex is seen. An occasional mitosis which can be seen at times does not allow the diagnosis of anaplastic astrocytoma.[39] The fibrillary variant is the most frequent type and is a mildly hypercellular neoplasm composed of well differentiated spindle to stellate cells with mild to moderate nuclear atypia, separated by a loosely fibrillated and sometimes microcystic matrix. Mitotic figures are absent or very rare. Some show prominent infiltration of the cortex. Protoplasmic forms are composed of small tumour cells with round nuclei and limited number of delicate cytoplasmic processes. Gemistocytic variants contain usually more than 20% of gemistocytes. These cells are plump, with glassy, abundant cytoplasm. Some studies indicate that gemistocytic astrocytomas are prone to undergo malignant progression to a higher grade more rapidly than ordinary DAs and accordingly warrant more aggressive therapy.[64] Perivascular tumour infiltrating lymphocytes are commonly seen. The MIB-1 labelling index is less than 4% in these tumours and this is an important tool which can be used to differentiate DAs from anaplastic astrocytomas.[62]

Prognostic and predictive factors: These tumours are known to progress to anaplastic astrocytomas within a mean period of 4–5 years. Malignant progression is determined by clinical and biological factors.[49,66] Some of the recognised clinical parameters that are associated with a favourable prognosis include age of the patient, seizures as the single presenting symptom and gross total resection of tumour. Among histopathological factors, tumours with a significant proportion of gemistocytes tend to progress more rapidly to anaplastic astrocytoma.[32] Some studies have shown that presence of tumour infiltrating lymphocytes and microcystic degeneration in the tumour are associated with a slightly better prognosis.[53] A MIB-1 labelling index of greater than 5% has been found to constitute a threshold value for early progression. The presence of p53 mutations has not been found to be useful in prognostication in these tumours.[37,39]

Anaplastic Astrocytoma (WHO Grade III)

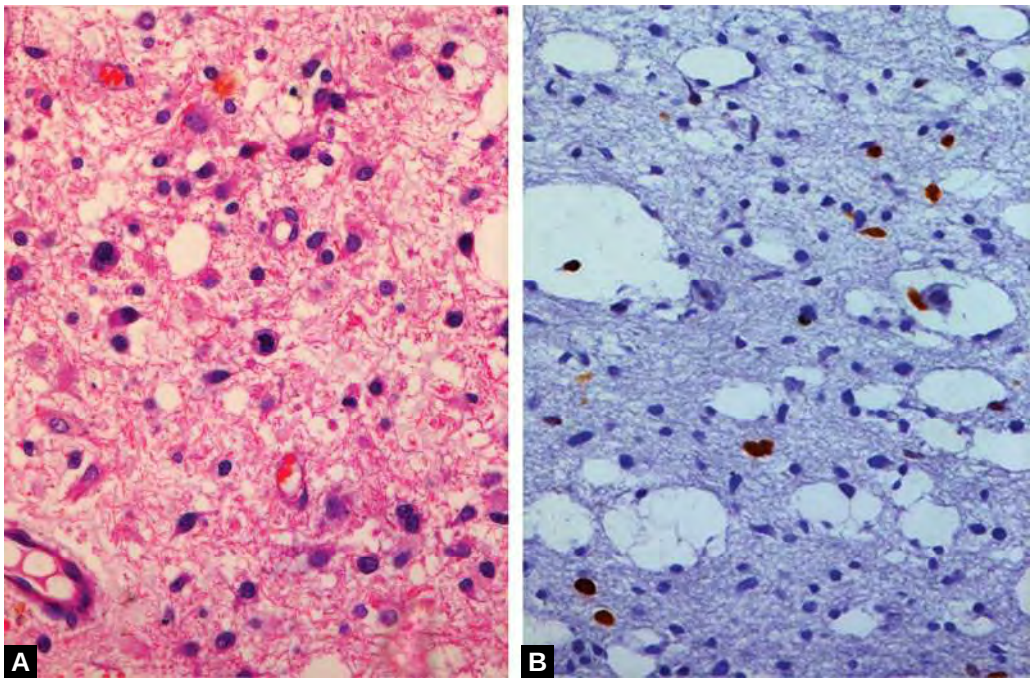
This is a more cellular, diffusely infiltrating tumour arising in the cerebral hemispheres and, apart from significant nuclear atypia in the tumour cells, show prominent mitotic activity. These tumours may arise from a pre-existing DA or *de novo*.



Figs 5A to C: Diffuse astrocytoma grade II. The tumour can be composed of fibrillary astrocytes. (A) Protoplasmic astrocytes. (B) Gemistocytic astrocytes. (C) Note the prominent microcystic stroma in A and B (HE, AX160: BX160: CX320)

Incidence, localisation and clinical features: The mean age at which the tumour is detected is 45 years.[51] Tumours are most often located in the cerebral hemispheres. Symptoms are similar to those of DA and in some patients, where the tumour arises from a pre-existing DA, the symptoms are of longer duration. Radiologically they show variable contrast enhancement and significant perilesional oedema.

Histopathology: Histologically these tumours resemble DAs. However, in addition to nuclear atypia, they exhibit increased mitosis (Figs 6A and B). Since anaplastic features may be focal, the prognostic value attached to grading minute fragments obtained by stereotactic biopsies depends on the representative sampling of the neoplasm. In such samples, presence of a single mitosis is significant and indicative of malignancy. However, if the sample is ample as obtained from open surgery, the presence of a single mitosis is not sufficient to grade the tumour as anaplastic. In such cases, MIB-1 labelling would definitely improve diagnostic accuracy.[23] The MIB-1 labelling index in anaplastic astrocytomas ranges from 5 to 10%.[39]



Figs 6A and B: Anaplastic astrocytoma-grade III. (A) The tumour is hypercellular and exhibits mitotic activity (HE X 320). (B) Nuclei of several cells show immunoreactivity for the proliferation marker MIB-1 (HE X 320)

Prognostic and predictive factors: These tumours are known to progress to GBM in a mean time interval of approximately 2 years. The clinical prognostic factors are similar to those in DAs.[39]

Glioblastoma (WHO Grade IV)

This is the most common and most malignant glioma arising in adults and despite advances in therapeutic strategies, these patients have a dismal prognosis.

Incidence and localisation: GBMs are the most frequent brain tumours accounting for about 12–15% of all intracranial neoplasms and more than 60% of all astrocytic tumours.[51] The peak incidence is between 45 years and 75 years.[39,51] The tumour occurs mostly in the cerebral hemispheres, affecting the subcortical white matter and spreading to the superficial grey matter. The tumour is known to spread across the corpus callosum to the contra lateral hemisphere and such tumours are referred to as 'butterfly gliomas' (Fig. 7A). The deep nuclear masses, particularly the thalamus and basal ganglia are also sites for GBM, especially in children.[39] Brainstem GBMs often affect children.[11] The cerebellum and spinal cord are rare sites for this neoplasm.

Clinical features and neuroimaging: Most patients present with features of raised intracranial pressure and focal neurological deficits. Extensive haemorrhage may occur within the tumour and produce stroke-like symptoms clinically. The duration of symptoms is short (less than 3 months) in the majority of patients, and these tumours are *de novo* or primary GBMs. In others, the tumour occurs as a result of progression from a lower grade astrocytoma and such patients have a longer duration of symptoms. Such tumours are referred to as secondary GBM.[52]

Imaging features: On imaging, GBMs often have a low density centre which is mainly due to variegated necrosis, and an enhancing rim due to enhanced neovascularity and a hypercellular, fleshy neoplasm. There is also a corona of oedema around the tumour (low density, hypointense on T1-weighted image and hyperintense on T2-weighted image). This is attributed to 'oedematous' white matter and areas of neoplastic infiltration.

Histopathology: The cellular morphology is highly variable and hence the term 'GBM multiforme'. The tumour usually contains highly pleomorphic cells with fibrillary astrocytes that are admixed with gemistocytic, lipdised and multinucleated giant cells and clusters of small undifferentiated cells. Occasionally, within the tumours large granular cells with PAS positive cytoplasmic granules can be present in small groups. Nuclear atypia is significant and mitosis is brisk with several bizarre mitotic figures. Some of these tumours, however, are composed of sheets of undifferentiated small cells that should be differentiated from de-differentiated anaplastic oligodendrogliomas or even lymphomas and primitive neuroectodermal tumours. Such tumours form a subset called 'small cell GBM'. Sometimes, there can be foci of large epithelial-like cells within GBMs with reduced expression of GFAP. These tumours are referred to as 'adenoid GBM' and are mostly seen in recurrent samples of GBM. A mucinous stroma and a 'mesenchymal' component (gliosarcoma) can also be present. Rarely GBMs may contain an oligodendroglial component and these tumours are currently being described as 'GBM with oligodendroglial component' and these tumours have been found to have a marginally better survival rate.[39]

Glioblastoma is a highly vascularised neoplasm. The tumour always shows extensive neovascularisation (sprouting angiogenesis). In addition, several large feeder vessels show marked sclerotic changes, abnormal branching and thrombosis.[39] One of the histological hallmarks of GBM is the presence of microvascular proliferation, which is characterised by heaping up of proliferating endothelial cells along with pericytes and vascular smooth muscle cells. These are called "glomeruloid tufts". These endothelial cells are mitotically active. Another fundamental feature of GBM is necrosis. Two types of necrosis can be distinguished, large ischaemic necrotic zones called 'field' necrosis and multiple irregularly shaped serpigenous pseudopallisading necrosis called 'wreath' necrosis. Compared to adjacent tumour cells, pseudopallisading cells show higher apoptotic and lower proliferative rates (Figs 7B to H).

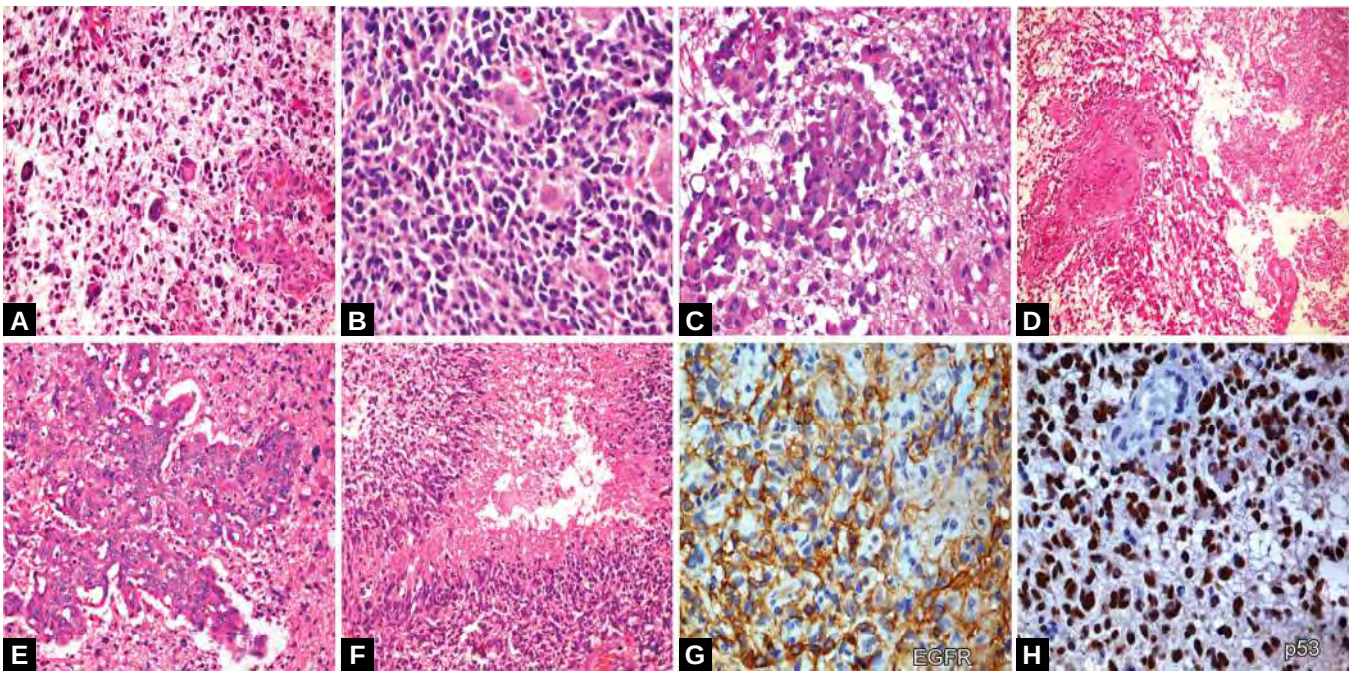
Glioblastomas are known to have extensive invasive capacity. They arise and spread in the white matter and diffusely infiltrate the grey matter. The pattern of spread is perineuronal (called 'satellitosis'), perivascular, subependymal and subpial, and spread along myelinated tracts is also seen. Such morphological patterns of spread are referred to as 'secondary structures'. They are highly diagnostic of diffusely infiltrative tumours such as GBM, oligodendroglioma and gliomatosis cerebri.[39]

Biology/Molecular Genetics/Predictive and Prognostic Factors

Molecular Genetics

Two interrelated concepts of molecular oncogenesis have been developed over the past three decades and it is now proposed that initiation and progression of astrocytomas, similar to several other neoplasms, are under the influence of tumour promoting oncogenes and tumour suppressor genes. Accordingly, two pathways have been defined in the development of classical GBM resulting in the formation of primary and secondary GBM.[63]

Primary GBM occurs in elderly individuals, presenting with a short clinical history and no clinical or histological evidence of progression from a lower grade astrocytic glioma as precursor. Molecular genetic studies have shown that the majority of these tumours have amplified oncogenes like the epidermal growth factor receptor (EGFR) gene on chromosome 7. They also possess deletion in the cell-cycle-related INK4a-ARF genes, $p16^{INK4a}$ and $p19/p14^{ARF}$. Mutations of the *p53* gene



Figs 7A to H: Glioblastoma grade IV. (A) The tumour is composed of pleomorphic astrocytes with increased mitosis. Note the microvascular proliferation (HE X 320). (B) Small cell variant of glioblastoma shows sheets of undifferentiated astrocytes (HE X 320). (C) Adenoid variant of glioblastoma with groups of cells having epithelial morphology (HEX160). (D) Large areas of ischaemic necrosis in the tumour. Also note sclerosed and thrombosed vessels adjacent to zones of necrosis (HE X 160). (E) Microvascular proliferation with formation of 'glomeruloid tuft' (HE X 160). (F) Characteristic pseudopalisading necrosis (HE X 160). (G) Cytoplasmic membrane labelling of EGFR, seen often in primary glioblastoma (Immunoperoxidase x 320). (H) Nuclear accumulation of *p53* in tumour cells and not endothelial cells, seen often in secondary glioblastoma (immunoperoxidase x 320)

(tumour suppressor gene on chromosome 17p13.1) are infrequent and noted in less than 10% of cases. However, the other tumour suppressor gene that is often mutated is the phosphate and tensin homology (PTEN) gene located on chromosome 10. On the other hand, secondary GBMs evolve from a lower Grade II or Grade III DA. They occur in younger individuals and show predominantly p53 mutations along with other genetic alterations such as amplification of CDK-4 or loss of Rb involved in cell cycle regulation. Tumours in this younger group of patients also tend to express a different signal transduction alteration-amplification or over expression of platelet derived growth factor (PDGF). It is not clear whether these two variants of GBM (primary and secondary) are different prognostically. However, understanding the pathways underlying their development would help in future to design novel therapeutic strategies.[30]

Epidermal growth factor receptor: The oncogene encoding EGFR is located on chromosome 7. EGFR is a transmembrane receptor that can sense extracellular ligands, like EGF and TGF-α, and subsequently transduce the proliferation signal. EGFR gene amplification is seen most often in primary GBM (in about 40% of cases), always associated with protein over expression. EGFR amplification is often associated with structural alterations of the gene forming truncated variants, like EGFR VIII,[2] leading to uncontrolled cell proliferation via the PI3-kinase, RAS and mitogen-activated protein kinase signalling pathways. In view of this, EGFR VIII is a promising target for therapy.[7]

The other forms of GBM include giant cell GBM and gliosarcoma. In contrast to classical GBM, these variants always develop *de novo*, and have a distinctly different molecular pathway compared to classical GBMs.

Phosphate and tensin homology: This gene is located on chromosome 10q 23.3 and plays a major role in the PI3K/EGFR/AKT pathway. In this pathway, EGFR, when activated after binding to its ligands, recruits PI3K (phosphatidylinositol 3-Kinase) to the cell membrane. PI3K converts PIP2 (phosphatidylinositol-4,5-bisphosphate) to PIP3 which in turn activates its downstream molecules such as AKT and mammalian target of Rapamycin (mTOR). This in turn leads to uncontrolled cell proliferation and survival. Normally PTEN inhibits the PIP3 signal and inhibits proliferation. It gets mutated in about 15–40% of GBMs, mostly primary GBMs.[70]

The p53 tumour suppressor gene that is located on chromosome 17p 13.1 encodes for a 53 kDa nuclear phosphoprotein which plays an important role in regulation of the cell cycle, and in cell response to DNA damage and other vital cellular functions.[4] This gene is mutated in several human neoplasms and notably in astrocytic glioma.[41] The wild type protein is not detected by

immunohistochemistry due to its short half-life and it is the mutated, thus highly stable protein that is detected.[7] p53 mutations are seen in more than 65% of secondary GBMs and are generally evident in lower grade astrocytoma.[30] Mutations occur less frequently (about 25%) in primary GBMs also. Another gene, the MDM2 (located on chromosome 12q 14.3), inhibits the actions of wild type p53. Interestingly, the transcription of MDM2 is induced by wild type p53.[3] In normal cells, this autoregulatory feedback regulates the activity of these two genes. MDM2-mediated degradation of wild type p53 is further regulated by $p14^{ARF}$ which binds to MDM2. Therefore, loss of function of the tumour suppressor gene p53 can occur when there are alterations of either the p53 gene itself or of MDM2 and/or $p14^{ARF}$ amplification. Over expression of MDM2 occurs in greater than 50% of primary GBMs and loss of function of $p14^{ARF}$ occurs both in primary and secondary GBMs.[52] Cell cycle control is also regulated by the $p16^{INK4a}$/CDK4/RB1 signalling pathway. Alteration of this pathway can also lead to neoplastic transformation. This pathway is disrupted in a variable proportion of primary and secondary GBMs. Loss of heterozygosity (LOH) of chromosome 10 occurs frequently in GBMs.[52] LOH of 1p and 19q are also noted in GBMs in varying proportions.[39]

Parameters of Invasiveness

DAs have the inherent property to invade brain parenchyma, which is largely independent of the histological grade. GBMs, however, have the highest invasive capability. These properties may be related to the capability of tumour cells to modify the various extracellular matrices (ECM) in the CNS which in turn facilitates invasion. Studies on several adhesion molecules, which play an important role in modifying ECM components, have begun to yield data which ultimately may be useful in diagnosis and prognostication.

Recent gene expression profiling studies have revealed subsets of GBMs with increased expression of ECM components and intracellular proteins that are associated with cell motility. Several molecular determinants of invasion have been described including activation of TGF-β and AKT pathways.[71] Since invasion due to protease activity is rather a late effect in tumourigenesis, it provides an attractive target for therapeutic intervention in established tumours. Several protease inhibitors are currently being tested in clinical trials.

Tumour Angiogenesis

Astrocytoma development and progression is always accompanied by the formation of new blood vessels. GBM is the most vascularised of all human neoplasms. The classical angiogenesis is the sprouting angiogenesis, in which there is recruitment of endothelial cells by neoplastic astrocytic cells, endothelial cell proliferation, migration and vasculogenesis.[12] Angiogenesis in gliomas is regulated by several factors. Hypoxia is the important underlying factor and this leads to accumulation of hypoxia-inducible factor 1-α (HIF-1α) which in turn leads to transcriptional activation of several genes that regulate angiogenesis, cellular metabolism, cell proliferation/apoptosis and migration.[12] An important downstream target of HIF-1α is vascular endothelial growth factor (VEGF). VEGF is mainly produced by the perinecrotic pallisading neoplastic cells in GBMs. Current evidence suggests that VEGF, which binds to VEGF receptors 1 and 2, is the most important regulator of vascular functions in glioma induced angiogenesis.[40] This is upregulated not only in all high grade astrocytomas, but also in a sub-set of low grade DAs which can progress to a malignant phenotype, suggesting that malignant transformation in low grade astrocytomas is at least partly based on their inherent angiogenic potential. This could form a basis in future for providing a rationale for therapeutic strategies directed at inhibiting the angiogenic process and, thus, tumour progression in patients with astrocytomas.

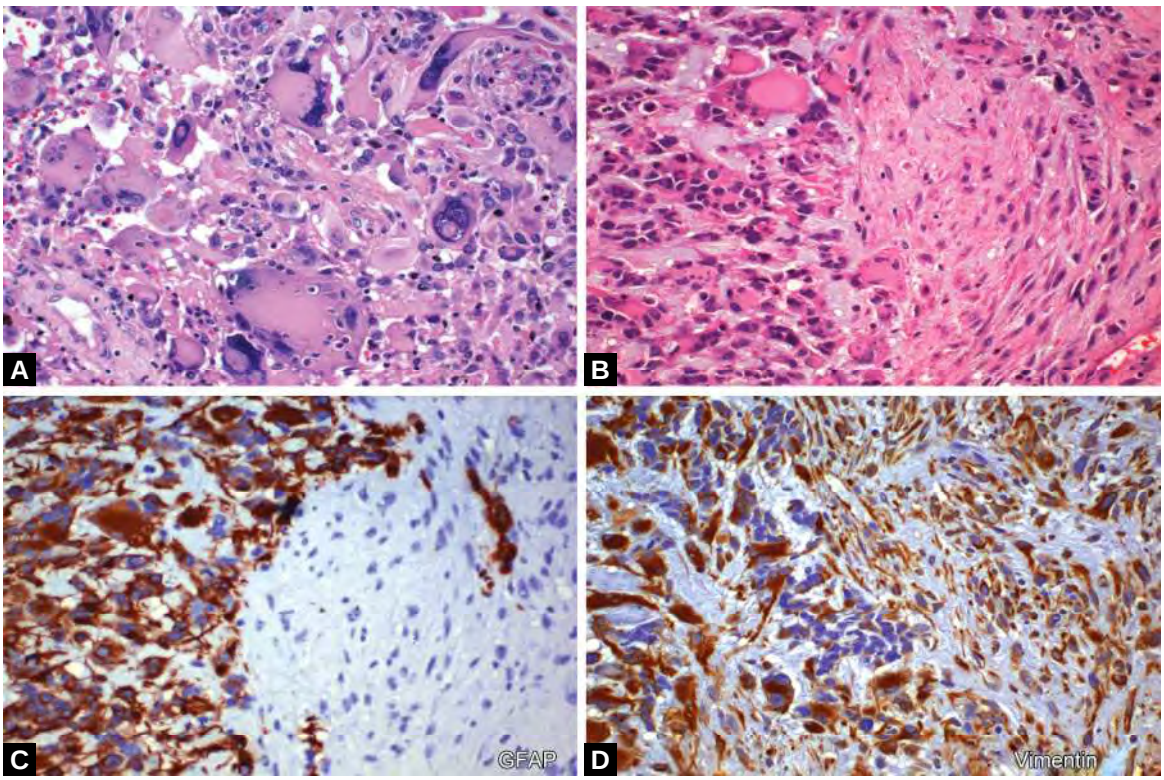
Gene Expression Profiles in Glioblastomas

Microarray expression profiling of GBM allows simultaneous analysis of thousands of genes and is likely to identify molecular markers associated with tumour subtype, progression and patient survival.[34] Through cDNA microarray experiments, several distinct gene categories of transcripts differentially expressed in different sets of GBMs have been currently identified.[68]

Prognostic and Predictive Factors

The prognosis of patients with GBM is dismal, with a mean survival of 10–12 months. Currently available treatment options are multimodal, which include surgery, radiotherapy and chemotherapy, but these have shown to improve survival only marginally in these patients.[33] Most multivariate studies have shown that age and Kernofsky performance score are strong predictors of outcome in patients with GBM. Younger patients are known to have a better prognosis in most studies.[6] On histology, the extent of necrosis correlated with poor prognosis in some studies.[21] There has been no consistent correlation between p53 mutations, EGFR amplification and patient survival.[50]

Temazolamide is one of the important alkylating agents currently used in the treatment of GBMs. It causes tumour cell death by forming cross-links between adjacent strands of DNA by alkylation of O^6 position of guanine.[47] O^6-methylguanine-DNA methyl transferase (MGMT) is the repair enzyme that removes the O^6 position in DNA and in turn protects cells from the effect of alkylating agents.[44] Hypermethylation of the promoter, CpG islands of the gene results in loss of MGMT expression thus enhancing susceptability to the alkylating agent. MGMT promoter hypermethylation in



Figs 8A to D: Giant cell glioblastoma and gliosarcoma. (A) Several bizarre tumour giant cells in giant cell glioblasoma (HE X 320). (B) Gliosarcoma with biphasic gliomatous (left) and sarcomatous components (HE X 320). (C) The gliomatous component shows strong GFAP immunoreactivity (Immunoperoxidase X 320). (D) Vimentin staining is seen in both the gliomatous and the sarcomatous components (Immunoperoxidase X 320)

GBM is seen in some patients and is associated with longer survival.[19]

A few biomarkers have currently been identified in the serum of GBM patients.[39] YKL-40 is one such marker. It is known to be over-expressed in GBM tissues and is a secretory protein. Its detection in the serum has been used to monitor GBM patients for early tumour recurrence.[22]

Giant Cell Glioblastoma

These tumours are characterised by the presence of numerous bizarre multinucleated giant cells (Figs 8A to D) which are sometimes lipidised, with an abundant reticulin network and, thus, can be mistaken for PXAs. They show high frequency of p53 mutations. It accounts for nearly 5% of all GBMs. They have a relative circumscription and are firm tumours. On imaging they can be mistaken for a metastatic deposit. Microvascular proliferation is exceptional. The cells are variably positive for GFAP, but constantly show reactivity to S-100 protein, vimentin, β-tubulin, p53 and EGFR. In view of their less infiltrative nature, patients with this tumour are reported to have a better prognosis than in classical diffusely infiltrating GBM.[43]

Gliosarcoma

This tumour is characterised by a dual population of glial and mesenchymal cells. It accounts for 2% of all GBMs.[39] In tumours with a predominant mesenchymal component, the tumour appears as a well demarcated hyperdense mass with homogeneous contrast enhancement mimicking a meningioma.[42] The demonstration of a distinct malignant mesenchymal component which is GFAP negative is necessary to distinguish gliosarcoma from desmoplastic response in a GBM with meningeal infiltration. Currently there is cytogenetic and molecular evidence of a monoclonal origin for both glial and mesenchymal elements of this malignant tumour.[45] Some studies have shown these tumours to have a better prognosis than classical GBM,[46] although not supported by other series.

Gliomatosis Cerebri

This tumour is defined as a diffuse glioma, usually astrocytic, showing extensive infiltration of the cerebral hemispheres, involving at least three cerebral lobes, usually with bilateral and/or deep grey matter involvement, and with frequent extension to infratentorial structures.[39] It corresponds to WHO Grade III. By CT and MRI, there is diffuse enlargement of cerebral structures without tissue destruction or focal tumour mass or 'epicentre'. T2 weighted or FLAIR MR sequences reveal the full extent of the tumour with significant signal hyperintensity. This spreading neoplasm produces minimal mass effect. Histologically, the tumour cells are most often astrocytic, but cases with oligodendroglial cells or

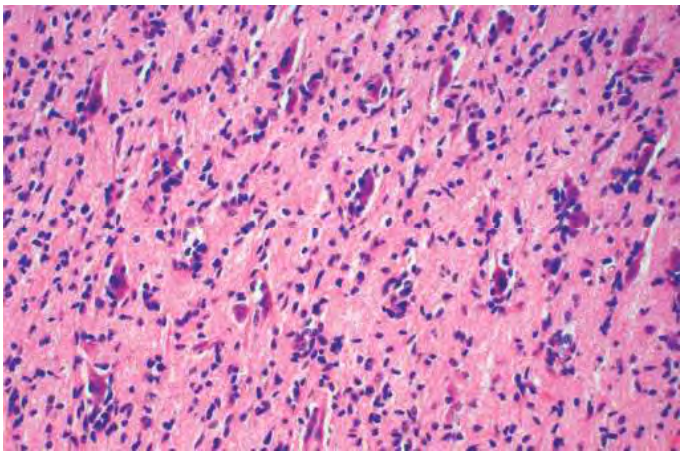


Fig. 9: Gliomatosis cerebri: there is a diffuse infiltration of the cortical grey matter by undifferentiated fibrillary astrocytes with preservation of neurons (HE X 80)

mixed oligoastrocytic cells are known.[65] Despite diffuse infiltration of the white and grey matter by the tumour cells, the anatomical structures are relatively preserved (Fig. 9). Two hypotheses regarding histogenesis of this tumour have been put forth. Some authors believe that gliomatosis cerebri represents a subset of diffusely infiltrating glioma with an extensive capacity to spread,[16] while others consider that it results from simultaneous neoplastic transformation in an extensive tissue field in the cerebral hemisphere termed as 'field transformation'.

Oligodendroglioma

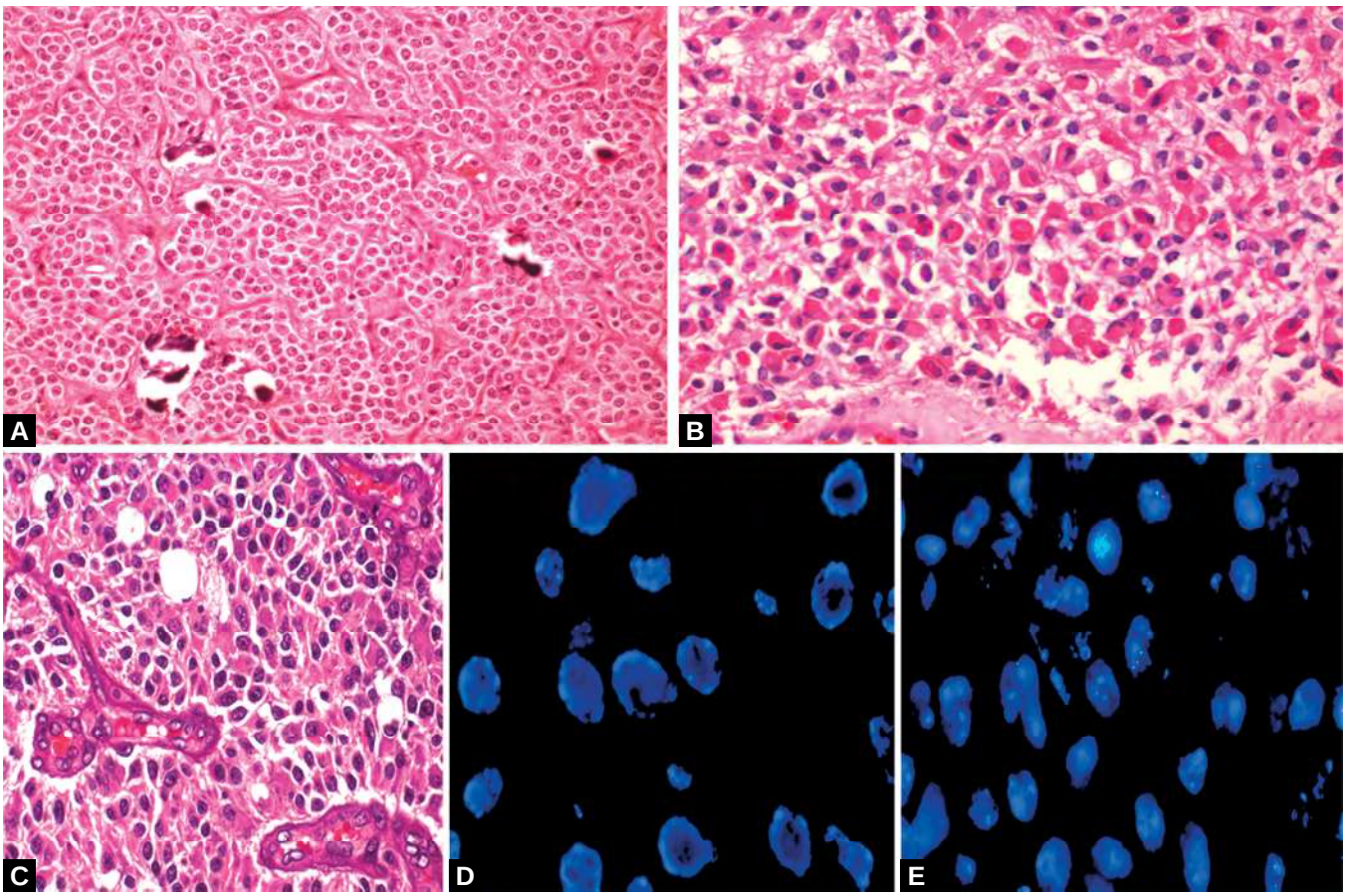
According to the World Health Organisation (WHO 2007) classification, oligodendrogliomas are well-differentiated, diffusely infiltrating tumours of adults, typically located in the cerebral hemispheres and composed predominantly of cells morphologically resembling oligodendrocytes. They constitute about 5% of all gliomas and the incidence varies from 5 to 18% in different series. Oligodendrogliomas are divided into two grades; oligodendroglioma (Grade II) and anaplastic oligodendroglioma (Grade III).

Incidence and localisation: They are predominantly tumours of middle age (range 35–55 years). Grade II are more common in individuals less than 40 years and Grade III neoplasm is seen after the age of 40 years. Six per cent of the oligodendrogliomas occur in children. The most common sites are the cerebral hemispheres involving the frontal, temporal, parietal and occipital lobes, respectively. Rare sites are cerebellar hemispheres, brainstem and spinal cord.

Clinical features and neuroimaging: The most common symptoms are seizures and headache. On CT scan, the tumours appear as hypodense or isodense lesions. Calcification is often seen. On MRI, a well demarcated hypointense lesion on T1-weighted images becoming hyperintense on T2-weighted images will be seen. Perilesional oedema is moderate and tumours can show haemorrhage and cystic change. Correlation of the status of 1p/19q with the pattern on imaging has shown that tumours exhibiting co-deletion of 1p/19q chromosomal deletion have mixed signal intensity on T1-weighted and T2-weighted images.[25]

Histopathology: Oligodendrogliomas show a patternless growth characterised by sheets of cells with round nuclei and swollen clear cytoplasm (honeycomb appearance or fried egg appearance). Microcysts filled with mucoid material, arcuate vascular pattern (chicken wire capillary pattern), focal areas of dystrophic calcification, loss of demarcation between grey and white matter, perineuronal satellitosis and subpial spread are the salient features (Figs 10A and B). Occasional mitosis can be present. In addition, some oligodendrogliomas contain cells referred to as "minigemistocytes" and "gliofibrillary oligodendrocytes". The minigemistocytes are smaller than the conventional gemistocytes and lack process formation (Fig. 10C). They have oligodendrocytic nuclei and plump hyaline cell bodies with abundant eosinophilic cytoplasm. The gliofibrillary oligodendrocytes also possess a moderate quantity of cytoplasm with well-defined cell borders, but their fibrillarity is less obvious and processes are sparse. Both these cell types are positive for GFAP, Hence, the term "transitional cell" has been used to refer to these cell types, because they form a cytological and ontological bridge between typical astrocytes and oligodendrocytes. Increased cellularity, pleomorphism, presence of necrosis, increased mitosis and vascular proliferation are the features of anaplastic (Grade III) oligodendrogliomas (Fig. 10D). Tumours with MIB-1 labelling index of greater than 5 are likely to be anaplastic and indicate an unfavourable outcome. There are no specific markers for oligodendroglioma and hence the diagnosis continues to rest on histological criteria. The cells of a well-differentiated oligodendroglioma are immunonegative for GFAP, but the transitional cells can be GFAP positive. Proteins such as myelin basic protein (MBP), myelin associated glycoprotein (MAG) and galactocerebroside (GaLC), which are specific proteins of mature and developing oligodendrocytes, are only inconsistently expressed in oligodendroglial tumour cells. Recently, two markers Olig-1 and Olig-2 encoding transcription factors expressed in early developmental and mature stages of oligodendrocytes have been seen in oligodendrogliomas.[35] However, other studies have shown their expression in astrocytic tumours also.

Molecular genetics: Deletions on chromosomes 1p and 19q identify anaplastic oligodendroglial neoplasms that are likely to respond well to some chemotherapeutic regimens and are associated with prolonged patient survival. Deletion of these chromosomal alterations is becoming increasingly important in evaluating these glial tumours. Interphase fluorescence *in situ* hybridisation (FISH) is one of the methods used for screening these tumours.



Figs 10A to E: Oligodendroglioma. (A) The tumour shows typical 'Honey comb' arrangement of oligodendrocytes. There are areas of microcalcification (HE X 160). (B) Sheets of minigemistocytes in the tumour (HE X 160). (C) Anaplastic oligodendroglioma with microvascular proliferation, nuclear atypia and mitosis (HE X 320). (D) FISH preparation showing 1-p deletion in anaplastic oligodendroglioma. Four cells clearly show one red signal as seen for 1p 36 test probe and two green signals are seen for the 1q 25 reference probe, indicating loss of one copy of 1p36 (X 800). (E) FISH preparation showing 19q deletion in the same tumour. Several cells show one or no red signal for the 19q13 test probe and two green signals for the 19p13 reference probe, indicating loss of one copy of 19q13 (X 800)

(Fig. 10E) These chromosomal alterations are found in 70–90% of oligodendrogliomas in different series.[26]

The frequent loss of heterozygosity (LOH) on 1p and 19q in oligodendrogliomas and oligoastrocytomas indicates that these chromosome arms harbour as yet unknown tumour suppressor genes, which are of paramount importance in their tumourigenesis. However, the oligodendroglioma-associated tumour suppressor genes on 1p and 19q are as yet to be characterised.

Allelic losses on 1p and 19q are linked to a favourable response to chemotherapy and longer survival in anaplastic oligodendroglioma patients treated with Procarbazine, Lomustine and Vincristine (PCV). In a recent study by Reifenberger et al.[54] combined LOH on 1p and 19q chromosomal loci was associated with late progression, longer overall survival, and a higher 5-year survival rate. Depending on the presence or absence of combined LOH on 1p and 19q, patients with anaplastic oligodendroglial tumours treated with adjuvant radiotherapy and/or chemotherapy showed a median time to progression of 86 months versus 39 months, a median overall survival of 91 months versus 46 months, and a 5-year survival rate of 80% versus 36%, respectively. Similarly, LOH on 1p and 19q was associated with longer survival in patients with low-grade oligodendroglial tumours (TTP: 57 months versus 47 months; OS: 172 months versus 105 months; 5-year survival rate: 92% versus 70%). Several other independent studies have confirmed these observations. Although all these studies are based on a retrospective analysis of relatively small numbers of patients, their results suggest 1p and 19q deletions as a genetic marker important in diagnostic and prognostic assessment of oligodendroglial tumours.

Oligoastrocytoma

Oligoastrocytomas are "tumours composed of a conspicuous mixture of two distinct neoplastic cell types morphologically resembling the tumour cells in oligodendroglioma and DA". They are subclassified into Grade II oligoastrocytoma and anaplastic Grade III oligoastrocytomas.

There is a high degree of variability in the morphological criteria used for the diagnosis of oligoastrocytomas. The diagnosis of oligoastrocytomas "requires the recognition of two different glial components both of which must be unequivocally neoplastic". However, the percentage of each component minimally required for diagnosis has not been specified in the WHO classification system. Oligoastrocytomas may be a biphasic compact variant or an intermingled diffuse variant. In the biphasic variant, the two areas are juxtaposed, (Figs 11A to D), while in the intermingled variant they are intimately admixed. No mitosis or necrosis is seen in Grade II tumours. Anaplastic Grade III oligoastrocytomas are characterised by nuclear pleomorphism, high mitotic activity, microvascular proliferation and necrosis. About 30–50% of oligoastrocytomas are characterised by loss of 1p and 19q in both the components, strongly suggesting a monoclonal origin of the two cellular components. Another 30%, however, carry genetic aberrations typically found in astrocytic gliomas, i.e. mutations of p53. Thus, oligoastrocytomas are genetically heterogeneous with one subset related to oligodendrogliomas and another to DAs.[41] From a clinical viewpoint, it has become increasingly important to differentiate between oligoastrocytomas and pure astrocytic tumours because a subset of oligoastrocytomas, like oligodendroglial tumours, appears to respond favourably to chemotherapy with PCV regime.

EPENDYMAL TUMOURS

These include Ependymoma (WHO Grade II), Anaplastic ependymoma (WHO Grade III), Subependymoma (WHO Grade I) and Myxopapillary ependymoma (WHO Grade I).

Ependymoma (WHO Grade II)

This is a slowly growing tumour arising from the ventricular walls and composed of neoplastic ependymal cells.

Incidence and Localisation

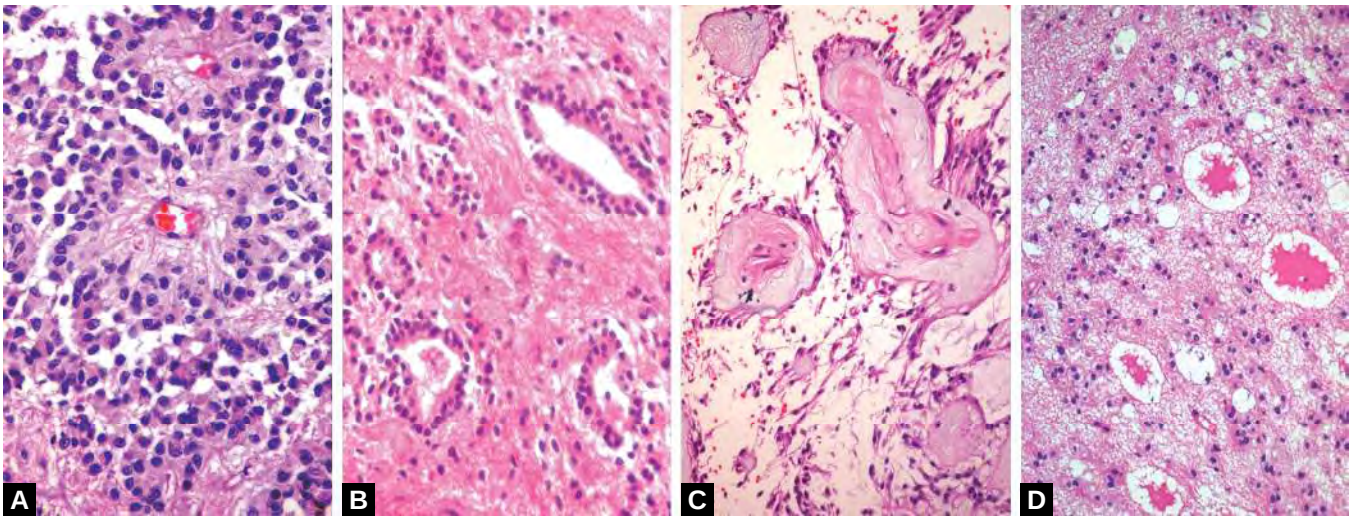
These tumours comprise about 2–9% of all intracranial neoplasms. Infratentorial ependymomas occur most often in children, while supratentorial tumours occur in children and adults. In the spinal cord, in adults, this tumour accounts for 50–60% of glial neoplasms.[39] Ependymomas occur most commonly in the spinal cord, fourth ventricle, lateral ventricle and third ventricle in that order of frequency.

Clinical Features and Neuroimaging

These depend on the neuroanatomical site of the neoplasm. Most fourth ventricular examples present with features of obstructive hydrocephalus and raised intracranial pressure. Tumours of the spinal cord present with motor and sensory deficits. On CT and MRI they are seen as well circumscribed tumours with a varying degree of contrast enhancement, focal cystic component, areas of haemorrhage and calcification.

Histopathology

Ependymomas are moderately cellular neoplasms composed of clusters of cellular zones containing cells with a monomorphic nuclear morphology ('salt and pepper' speckling of the nuclear chromatin), alternating with a cellular fibrillated glial stroma. Other histological features include perivascular pseudorosettes and ependymal rosettes. Perivascular rosettes comprise of cells arranged around vessels with long glial processes resting on the vessel walls. True ependymal rosettes and ependymal canals are composed of columnar cells arranged around



Figs 11A to D: Ependymoma. (A) Classical ependymoma with perivascular rosettes. (B) Ependymal canals (HE, A X 320; B X 160). (C) Myxopapillary ependymoma shows myxoid degeneration of the core of papillae that are bordered by ependymal cells (HE X 320). (D) Subependymoma shows clustered nuclei, fibrillary stroma and microcystic change (HE X 160)

a distinct central lumen. Calcification, cyst formation, fresh and old bleed can be seen. Usually, mitosis is absent or rarely present. Immunohistochemically, most of the ependymomas including papillary variants are immunoreactive for GFAP, which is predominant in the pseudorosettes. These tumours are also positive for S-100 protein and vimentin (Cytokeratin protein) is focally positive. A high percentage of ependymomas also express EMA. Synaptophysin is not expressed by the tumour cells.

Histological Variants

Cellular ependymoma: This is a variant with increased cellularity and absence of pseudo or true ependymal rosettes. Since other features of anaplasia are not evident and mitosis is rare or absent, this tumour belongs to WHO Grade II.

Papillary and myxopapillary ependymoma: This tumour is composed of well-formed papillae with round to oval monomorphic tumour cells around the blood vessels. Other histological features of ependymoma, such as pseudorosettes, ependymal rosettes and ependymal canal, could also be seen. Usually, mitosis is absent or rarely present. The papillary structures of ependymoma, a lack basement membrane, are in sharp contrast to the papillae of choroid plexus tumours. Myxopapillary ependymomas occur in the filum terminale region. Here the papillary core shows myxoid change.

Clear cell ependymoma: This variant contains clear cells resembling oligodendroglial cells. They occur most often in the supratentorial compartment. Recent data shows that this variant has a more aggressive behaviour than classical ependymoma.[14]

Tanycytic ependymoma: These tumours are often found in the paraventricular region of the infundibulum, fourth ventricle and spinal cord, where the brain-CSF barrier is not strong. They are composed of long spindly bipolar cells that poorly intertwine. These cells are presumed to be tanycytes or ependymoglial cells (paraventricular) with long processes recapitulating their development.[13] Perivascular rosettes are rare and ill-defined, and ependymal rosettes are not seen. They can be mistaken for astrocytic tumours but they have ultrastructural features of cells in ependymoma like intracellular cilia.

Predictive and Prognostic Factors

Children, particularly with posterior fossa tumours, have a far worse prognosis than adults (particularly with spinal tumours). The site of the tumour is an important prognostic factor. Posterior fossa tumours fare much worse than supratentorial tumours. Spinal tumours have a better survival. Extent of resection determines further progression and frank anaplastic change in the tumour is a known factor for poorer survival.[64]

Anaplastic Ependymoma (WHO Grade III)

This tumour is a malignant variant of ependymoma characterised by high mitotic activity, necrosis and microvascular proliferation. The tumour shows an aggressive growth pattern and is associated with a poor prognosis, particularly in children.

Subependymoma (WHO Grade I)

This tumour is characterised by clusters of isomorphic nuclei dispersed over fine glial stroma and with prominent microcystic change. They have a very low mitotic activity or none. Sometimes, these tumours can coexist with a classical or cellular ependymoma and such tumours are graded according to the ependymal component.[39]

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120 Pathogenesis of Tumours of the Nervous System

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Neurosurgical and radiotherapeutic management of human malignant intracranial tumours would greatly be facilitated by an understanding of the pathogenetic mechanisms which are responsible for the initiation and progression of the intracranial tumours as well as for their biological behaviour. Since the first classification of brain tumours by Virchow, who coined the term 'glioma', enormous efforts have been made in basic neurosciences towards an understanding of the morphology, behaviour, immunology and molecular genetics of central nervous system (CNS) tumours. Despite the exciting findings in these fields and the development of newer therapeutic approaches, the existing knowledge of the aetiopathogenetic mechanisms of spontaneously occurring human CNS malignant tumours still remains ill defined.

An overview of pathogenetic mechanisms that appear to be involved in the development of human CNS tumours is given, some of which are potentially significant, but not yet well characterised. The pathogenetic mechanisms in CNS tumours are discussed under the following heads: (1) Molecular pathogenesis (oncogenes and tumour suppressor genes); (2) Hereditary factors; (3) Oncogenic viruses; (4) Radiation; (5) Chemical carcinogens; (6) Immunosuppression; (7) Hormones and (8) Trauma.

MOLECULAR PATHOGENESIS OF GLIOMAS

The term 'glioma' refers to primary tumours of the brain originating from the major components of glial tissue, i.e. astrocytes, oligodendrocytes and ependymal cells. The first morphological consequence of anaplasia may be cell atypia, which, however, is not a hallmark. With anaplasia, the growth fraction increases and it is very likely that an oncogene activation or tumour suppressor gene deletion is involved in the passage of cells from the non-proliferating to the proliferating pool. The increase in cell density, enhanced mitotic response and nuclear pleomorphism are direct consequences of anaplasia, whereas other histological signs, such as nuclear pleomorphism, necrosis and endothelial proliferation, usually regarded as indicative of malignancy, represent indirect consequences only. Based on these four morphological characteristics, Daumas-Duport et al. published in 1988 a simple method of grading of gliomas.[18] Tumours are grade I if none of these criteria are met, grade II with one criterion, grade III when two are met and grade IV if three or four criteria are present in the sections. In fact, the World Health Organization (WHO) system is a three-tiered grading system, assigning grade II to astrocytoma (fibrillary, protoplasmic and gemistocytic), grade III to anaplastic astrocytoma and grade IV to glioblastoma multiforme.[37] Grade I tumours form a distinct category with tumours such as pilocytic astrocytomas and sub-ependymal giant cell astrocytomas. The described histopathological grading systems are not perfect since they often fail to provide essential information regarding invasiveness, malignant character and patient survival. In other words, detailed neuropathological analyses of biopsy specimens have not revealed morphological parameters that reliably predict the malignant progression of astrocytic neoplasms. Molecular genetic studies may hold promise for this vexing problem. Demonstrating the genes involved in the malignant progression of astrocytomas might identify subgroups in their well-known histopathological grades.

The initiation and progression of sporadically occurring human malignant tumours are a result of genetic alterations, mutation, deletion or rearrangement in one or more genes. Gross chromosomal aberrations in the form of both numerical and structural alterations are often demonstrated. Extra copies of the genetic material that encode an oncogene could increase the expression of the oncogene protein and tilt the balance towards uncontrolled DNA synthesis. The loss of genetic material that encodes a tumour suppressor gene could again favour uncontrolled DNA synthesis. Thus at least two types of genes have been implicated in the tumourigenic process of malignant tumours of the CNS: (1) Proto-oncogenes that promote cell growth and (2) Tumour suppressor genes (TSG), which negatively regulates cell growth.

Tumour Oncogenes

In 1976, DNA sequences almost identical to viral oncogenes were discovered in the genomes of all vertebrate and invertebrate cells.[78] These genes, named proto-oncogenes, encode growth factors, growth factor receptors and components of signal transduction mechanisms that mediate the cell cycle. In neoplastic cells, such genes are frequently found to be mutated or over expressed and

are, therefore, referred to as oncogenes. Earlier, it was believed that at least two oncogenes have to be active for malignant transformation of gliomas. Since then more than one hundred oncogenes are known to be involved in glial tumourigenesis. Two main groups of oncogenes will be discussed: one involved in growth factor pathways and the other in cell cycle control.

Growth Factors

Epidermal Growth Factor (EGF)

Several growth factors or their receptors have been found to be over expressed in gliomas. In particular, there is evidence for the amplification of the EGF gene and epidermal growth factor receptor (EGFR) gene.[43,47,89,92,94] The EGF, which is the protein encoded by the EGF gene, is a small polypeptide and has about 50% amino-acid homology with transforming growth factor-alpha (TGF-α).[69] The EGFR is a multifunctional allosteric transmembrane protein with an extracellular binding site for EGF, a single transmembrane region and an intracellular domain that exhibits tyrosine kinase (TK) activity.[75] Activation of this EGFR associated TK results in a number of cellular activities, including mitogenesis and migration of the cell. The EGFR gene has been localised on the short arm of chromosome 7, within 7p11-12. Amplification as well as over expression of the EGFR gene has been demonstrated in many histological types of brain tumours. Rearrangements at different places in the EGFR gene corresponding to the extracellular binding to EGF or to the cytoplasmic domains have also been recorded. The EGFR gene has been found to be amplified and over expressed in 1% of low grade astrocytomas, in a cumulative incidence of around 10% in anaplastic astrocytomas and in about 30–40% of glioblastoma (GBM) and is, therefore, considered to be a hallmark of malignant transformation in patients with gliomas.[20,31] When examining DNA on a cell-by-cell basis using the FISH method, it becomes clear that the percentage of amplification/over expression in GBM is even higher and reaches 60%.[74] Most individuals, whose gliomas carry an EGFR mutation or amplification, have a poor prognosis, even when the tumour is classified as a grade II astrocytoma.[20] An aberrant form of EGFR gene is present on the surface of the neoplastic cells and represents a tumour specific epitope that does not exist on the normal cell. Recently, the role of EGFR as a determinant by which GBM invades normal brain tissue has been demonstrated *in vitro*.[63] Invasion into the adjacent brain parenchyma could successfully be inhibited at much lower concentrations of TK inhibitors. Therefore, inhibition of these TK inhibitors might prove to be more successful than targeting their ligands or the extracellular domain of EGFR gene.

Vascular Endothelial Growth Factor (VEGF)

VEGF, a 46-kDa protein, is a dimeric growth factor. VEGF has two principal biological activities: (a) to promote microvascular permeability and (b) the ability to function as an endothelial cell mitogen and potentially stimulate angiogenesis. The ability to increase vascular permeability is independent of other inflammatory mediators such as cytokines. The effect of VEGF on endothelial cells is dependent on the activation of the receptor protein tyrosine kinase (RPTK).[60] There is strong evidence that VEGF plays a dominant role in the development of angiogenesis that accompanies the anaplastic progression of astrocytic tumours.[91] There is almost no expression of VEGF in the normal adult brain. There are also some indications of VEGF production when human malignant astrocytoma cell lines are stimulated with EGF and PDGF.[29] The current role of angiogenesis in malignant astrocytoma and the potential effects of VEGF on endothelial cells make this growth factor system an ideal candidate for therapeutic manipulation. Attempts have been made to abrogate angiogenesis and tumour growth, utilising specific antibodies directed against both N and C terminals of the VEGF molecule, and thus block both vascular permeability and endothelial mitogenic activity. It has been shown that a monoclonal antibody against VEGF significantly reduces tumour growth of a human glioblastoma multiforme cell line when transplanted into male mice. The growth inhibition was up to 80% and was associated with a marked reduction in tumour vessel density.[41]

Tumour Angiogenesis Factor (TAF)

This is another growth factor found to be present in high levels in glial tumours. It may play a role in the proliferation and possible subsequent transformation of vascular and perivascular mesenchymal elements to the development of an angiosarcoma. The mitogenetic properties of this factor have been determined *in vivo* and *in vitro* assays. The latter have included cultures of endothelial cells grown in the media conditioned by tumour cell lines of neuroepithelial origin such as C6 rat glioma, the C1300 mouse neuroblastoma and human neuroblastoma cell lines.[79] The other growth factors with potential mitogenetic activities include erythropoietin, found to be active in capillary haemangioblastoma; progesterone receptors in meningiomas and insulin-like growth factor receptors in glioblastoma.[72]

Other Growth Factors in Gliomas

Certain glioblastomas may also over express the transforming growth factor-alpha (TGF-α) gene, the protein product of which resembles EGF and binds to the EGFR stimulating TK activity.[56] Several studies demonstrated over expression of platelet derived growth factor (PDGF) and PDGF receptor in glioblastoma.[70] The oncogene encoding PDGF is located on chromosome 22. The basic fibroblast growth factor (bFGF) gene is known to exert a trophic effect upon a variety of cells of neural origin and is prevalent in the neural tissue. Human glioma cell lines binding the receptor proliferate in response to exogenously applied bFGF. It has also been suggested

that bFGF may promote glial tumour growth by the stimulation of angiogenesis or neovascularisation.[55]

The 12q Amplicon Including CDK4 and MDM2

Besides the growth factors, another important cell cycle regulator mechanism consists of the cyclin dependant kinases (CDKs) and their inhibitors. They regulate a number of target molecules by phosphorylation. Activation of these CDKs will lead ultimately to DNA replication and mitosis. The CDKs are activated by cyclins and inhibited by a still growing number of proteins that include factors named after their apparent molecular weights: p15, p16, p21 and p27, encoded by their respective TSG. The expression and interactions between these three types of molecules, CDKs, cyclins and CDK inhibitors account to a great extent for cell cycle control. The interaction between these molecules gives rise to different pathways, where many proto-oncogenes and TSG will have their own place. One such pathway involves cyclin D1, CDK4 and p16 as the inhibitor of retinoblastoma protein pRb1. pRb1 inhibits the progression from G1 to the S phase of the cell cycle, while CDK4 inhibits its function by phosphorylation. Over expression of CDK4, therefore, will indirectly stimulate cell growth (by controlling pRb1) and eventually lead to uncontrolled mitosis. Amplification of the CDK4 gene occurs in 30% of patients with anaplastic astrocytomas.[68]

Gene amplification in human tumour cells often involves large regions of genomic DNA, which can be several megabases in length. Such a large amplicon can be found in gliomas where a region on chromosome 12q13-14 [including CDK4 gene as well as the murine double minute (MDM2) gene] is often amplified. Reifenberger et al. analysed the MDM2 gene located on the same amplicon as the CDK4 gene in anaplastic astrocytomas and glioblastoma and found it to be present in 8–10% of patients.[68] The MDM2 gene product was shown to be a cellular regulator of *p53* activity. One copy of the p53 gene is frequently lost and the remaining copy is mutated in gliomas. An alternative mechanism for the loss of function of the p53 protein, if present, would be the over expression of genes coding for proteins known to bind to p53 and inhibit its function.

Besides the CDK4 and MDM2 genes, the 12q13-14 amplicon also harbours the genes SAS, GADD153, GLI and A2MR. The gene GLI, first found in a glioma, located on chromosome[12] (12q, 12-q14.3) has been found to be highly expressed and amplified in a human malignant glioma cell line. It is related to the oncogene of the 12q amplicon. However, it has so far not been shown to possess any transforming property and its precise role in tumourigenesis still remains unclear.

Tumour Suppressor Genes (TSG)

A second class of genes related to anaplasia is TSG. Indications for the existence of TSG came from observations made during the study of retinoblastoma, occurring both in sporadic and familial form.[39] The association of loss of genetic material with the development of cancer is consistent with the idea that the normal allele protecting against the formation of retinoblastoma must be dominant and, therefore, must be inactivated or deleted before the mutant, recessive retinoblastoma allele will give rise to the tumour. In the familial form, one mutation (first hit) is already present due to inheritance. The second hit (mutation or the loss of the other allele of a TSG) occurs somatically in the target tissue (retina). A high penetrance in the familial form that affects both eyes in very young children reflects the high probability of the second hit in these patients. In the sporadic form, two somatic events usually occur. Since the somatic mutation rate is low, only one eye is affected and the children are older before they develop retinoblastoma. This led to the two hit theory of Knudson[25] where inactivation due to loss of functional inhibition of both copies of specific allele on two homologous chromosomes may lead to tumourigenesis. In most instances of TSG inactivation, one allele carries a point mutation while the other is inactivated by a major structural alteration such as chromosomal deletion, inversion or translocation.

Retinoblastoma (Rb) Gene

The Rb gene is localised on chromosome 13q14 and has been isolated for the first time in 1986.[27] The Rb gene, which is the product of pRb1 protein, is involved in the transition of the cell from G0 or G1 to the S phase in the cell cycle. Inactivation of the Rb gene has been reported in about 20% of anaplastic astrocytomas and GBM, and it is concluded that the phosphorylated pRb1 is involved in the malignant progression of gliomas.[24] It was demonstrated later that 85% of a series of GBM had one or the other defect, thereby highlighting that the cell cycle growth control system determining their progression from G1 to the S phase by the phosphorylation of pRb1 is defective.

p53

Several intracranial tumours including gliomas with loss of chromosome 17 show partial chromosomal deletion with the common region of allelic loss involving *17p13*.[11,14] This region is known to encompass a candidate tumour suppressor gene encoding a 53-kilo Dalton nuclear protein known as p53.[6] The *p53* protein, which is the product of the p53 wild-type gene, is involved in cell cycle control. At least two stages in the cell cycle are regulated in response to DNA damage—the G1-S and the G2-M transitions. These transitions serve as checkpoints at which the cell cycle progress can be delayed to allow the repair of damage before entering either S phase or M phase. *p53* encodes a nuclear protein that suppresses this cell transformation. *p53* mediates this effect on cellular growth either by inducing apoptosis (programmed cell death) or through a transient cellular arrest at the G1 phase. Adenovirus mediated *p53* transfer

was reported to produce rapid and generalised death of human glioma cells via apoptosis.[30] The effect of *p53* on the transient cellular arrest at the G1 phase is mediated through the activation of the WAF-1 gene (also termed CDKN1), which results in the production of p21 protein, which in turn inhibits CDK4 and CDK6. The function of the *p53* protein is inhibited by the protein product of the MDM2 oncogene, which binds with *p53* protein. Thus, amplification of the MDM2 oncogene may result in excessive *p53* protein binding which in fact may have the same effect as mutation of *p53*. The mutant *p53* proteins analysed so far have a much longer half-life than that of the wild-type resulting in large amounts of the mutant protein which can transform cells to tumours.[34] Certain *p53* mutations result in the loss of the cell cycle control function and increase the transformation potential of cells. The description that *p53* is also involved in the angiogenesis of glioblastoma raises the interesting possibility that the lack of the wild-type *p53* may have a crucial and tumour cell-extrinsic impact on tumourigenesis.[84]

Somatic mutations of the *p53* gene have been reported to occur frequently in most of the human tumours including gliomas. Over 200 naturally occurring mutations have been described in different human tumours without identification of any brain specific mutations. p53 mutations are associated with 17p allele loss in low-grade astrocytomas as well as in glioblastoma multiforme.[85] Mutations of *p53* gene have been reported in all grades of gliomas, indicating that these mutations represent an early molecular event in the pathogenesis of gliomas. Until now, no grade-specific *p53* mutations are identified. Gliomas are observed with increased prevalence in association with Li-Fraumeni Syndrome (LFS of breast cancer, sarcomas, autosomal dominant patterns of inheritance), NF-1, NF-2, tuberose sclerosis and Turcot's syndrome. Gliomas occur in more than 10% of patients with LFS. Germ line *p53* mutations have been reported in a subset of LFS families as well as in non-LFS patients with gliomas.[52] The prevalence of inherited p53 mutations, a phenomenon that will render the individual more likely to develop the tumour (two hit theory of Knudson), has been estimated at 1% in the general population and at 20% in patients with a personal or family history of malignancy.[26] All these persons have a higher chance of developing gliomas. GBM in four siblings has recently been described without any *p53* mutations, indicating that a genetic event other than *p53* alteration can be responsible for the tumourigenesis of GBM in these patients.[21] The frequency of *p53* mutations was 64% in tumours with only one 17p allele, whereas it was 37% in patients with both *p53* alleles.[25] These mutations are often associated with a corresponding loss of the second copy of chromosome 17, thus meeting the classical paradigm of recessive tumour suppressor gene inactivation as described by Knudson et al.[39]

Sidransky et al.[76] analysed the *p53* gene in 10 primary brain tumour pairs, i.e. samples of tumours of the same patient but at different time points, to define the genetic events during tumour progression. The histological progression of brain tumours was associated with a clonal expansion of cells that have previously acquired a mutation in *p53* gene endowing them with a selective growth advantage. This data supports the clonal evolution model of tumour progression. It was found that the mutations of *p53* gene could be a reliable predictor for malignant transformation in a subset of gliomas.[26] On the contrary, recurrent astrocytomas have been investigated where progression of malignancy apparently occurs independent of *p53* mutation indicating that other genetic events promoting progression of glioma do occur. For glial tumours, *p53* is involved in the initiation as well as progression. *p53* alteration occurring in about 60% of low-grade astrocytomas might be important in the tumourigenesis of most, but not all gliomas.

p16

Until now, only p53 on chromosome 17p and Rb gene on chromosome 13q have been identified as major TSG that play a role in glial tumourigenesis, both these genes having a pivotal role in the cell cycle control mechanism. Another gene involved in the cell cycle progression located on the CDKN2 (MTSI, p16) gene on chromosome 9p is involved in the formation and progression of glial tumours.[61] Deletions involving chromosomal region 9p21 appear to be the most common molecular abnormality observed in grade III astrocytoma as well as in glioblastoma multiforme, where they have been reported to occur in 82% of glioma cell lines.[82] CDKN2 gene encodes p16, a cell cycle regulatory protein. p16 inhibits CDK4 and CDK6, thereby potentiating pRb1 as a cell cycle regulator. Inactivation of pRb1 may also occur through other mechanisms. Amplification of CDK4 gene inactivates pRb1 by phosphorylation. In total, about 85% cases of glioblastoma multiforme had one or the other defects demonstrating that cell cycle growth control systems determining progression from G1 to S phase by the phosphorylation of pRb1 is defective.[81]

LOH-10

Since the loss of alleles is in chromosome 10 in almost 80% of cases of glioblastoma multiforme, it is presumed that inactivation of a tumour suppressor gene on this chromosome is a critical step in the transition of astrocytoma grade III to glioblastoma multiforme. Despite considerable efforts, the common deletion region on chromosome 10 at molecular level remains poorly defined. For the present, this common deletion region is mapped at 10q25.[67] Others reported two independent suppressive regions on chromosome 10(10pter-q11 and 10q24-q26) that are involved in the progression of glioma.[77] A strong correlation between EGFR amplification and genetic loss of loci at chromosome 10 has been demonstrated, suggesting that co-operative mechanisms within such loci may underlie a subset of glioblastoma multiforme.

LOH-22q and 19q, 13.2-13.3

Allelic loss of 22q is detected in about 20% of gliomas regardless of their histopathological grades. There is also evidence to suggest that two or more than two TSG may reside on chromosome 19, one on 19p, important in the development of grade II astrocytoma and another on 19q, 13.2-13.3, important in the development of anaplastic astrocytoma.[69]

Genetic instability

Genetic instability has been suggested as a possible mechanism in the development of cancer. Initially this phenomenon was observed in hereditary non-polyposis colon carcinoma as well as in sporadic colorectal tumours. The genomic instability can be observed as a change in the length of microsatellite sequences in the tumour DNA as compared to constitutional DNA. The genomic instability is the result of replication errors. In hereditary non-polyposis colonic carcinoma, the observed replication errors are caused by mutations of the hMSH2 gene, which is located on 2p or by a mutation of the hMLH1 gene on chromosome 3p. Microsatellite instability has been found in many tumours including gliomas. It is present in low-grade astrocytomas, but more frequently in glioblastoma, and appears as a hallmark of a more generalised genomic instability.[83]

von Deimling et al.[86] suggested the existence of two different subsets of glioblastoma: one subset that has lost parts of chromosome 10 and 17p and another that might have arisen secondarily from a low-grade precursor, i.e. astrocytoma grade II and grade III. These patients are relatively younger and had a previous history of a low-grade astrocytoma (Type I). Another subset in which glioblastoma seems to arise *de novo*, may be characterised by the loss of parts of chromosome 10 and the amplification of the EFGR gene, without loss of heterozygosity for 17p (Type II). Patients with type II glioblastoma had no previous history of a low-grade astrocytoma and were significantly older than the patients with type I glioblastoma. These two subsets accounted for approximately two thirds of all investigated cases in their study.

HEREDITARY SYNDROMES

Familial clustering does not seem to account for a majority of brain tumours. However, a high incidence of brain tumours has been observed in up to 9% of families with at least one affected member with brain tumour, suggesting that tumour susceptibility may be inherited in these cases.[93] An analysis of tumour distribution among the relatives of 243 childhood brain tumours suggested that 4% might be attributed to hereditary factors.[7]

A number of hereditary syndromes, such as phakomatosis or familial cancer syndrome, are also associated with an increased risk for brain tumours. The phakomatoses (e.g. neurofibromatosis, tuberose sclerosis, von-Hippel-Lindau disease) are neurocutaneous disorders, characterised by tumours of ectodermal and mesenchymal origin, with vascular malformations of the skin, eyes and the CNS. Neurofibromatosis type I (NF-1) is characterised by café-au-lait spots, hamartomas of the iris (Lisch nodules) and multiple cutaneous and plexiform neurofibromas. Other neoplasms associated with NF-1 include schwannoma, phaeochromocytoma, rhabdomyosarcoma, optic glioma and astrocytoma. The NF-1 gene has been identified and mapped to chromosome 17q11.[57] It encodes the protein 'neurofibromin', which stimulates a ras-associated GTPase and may, therefore, exhibit its physiological role as a transducer for growth factor mediated signals. The NF-2 gene located on chromosome 22q11 encodes the proteins merlin/schwannomin, a cytochrome-associated protein.[80] The clinical triad of tuberose sclerosis (TSC) consists of adenoma sebaceum, seizures and mental retardation. The most frequently observed tumours are subependymal giant-cell astrocytoma and ganglioglioma.[42] Two genetic loci have been identified for this disorder, TSC1a on chromosome 9q34 and TSC2 on chromosome 16p. The disease-causing gene product has been identified only for TSC2, called 'tuberin' and it encodes a GTPase activating protein that may act in a similar fashion as the NF-1 protein.[71] Patients with Turcot's syndrome develop gliomas and adenomatous polyposis coli, which regularly progresses to colorectal carcinoma. The adenomatous polyposis coli (APC) gene has been cloned and mapped to chromosome 5. However, a recent survey of sporadic and Turcot's syndrome associated brain tumours failed to detect somatic mutation of the APC gene in the brain tumour tissue suggesting that other genetic alterations are responsible for the phenotype.[36] Li-Fraumeni's syndrome is caused by an inherited mutation of the p53 tumour suppressor gene. Affected patients display a variety of tumours, most commonly carcinoma of breast, sarcoma, leukaemia and brain tumours.[48]

Hereditary syndromes, such as the phakomatoses, provide phenotypically defined pedigrees for the diseases of interest that allows the identification of the relevant altered genes using molecular genetic approaches. If cytogenetic evidence implicates a specific chromosomal region, an investigative approach may be justified by screening candidate genes for mutations. In most cases, however, a detective approach is more effective, which employs the genome-wide screening of pedigrees for genetic markers. Linkage analysis then allows regional alignment of the disease causing locus to a minimal chromosomal region. Finally, the gene responsible for the phenotypes can be identified. Once the disease-causing gene has been identified, it can further be characterised as to its physiological and pathophysiological functions towards the development of rational treatment. In addition, genetic testing will help to identify individuals at risk, allowing early diagnosis and intervention. Thus an understanding of the genetic basis of hereditary disorders may also provide an insight to common pathogenetic mechanisms underlying the more frequent

sporadic brain tumours. Despite the great progress that has been accomplished towards the characterisation of genes underlying a hereditary tumour syndrome, no genetic risk factors predisposing to the development of sporadic brain tumours have been identified to date.

ONCOGENIC VIRUSES

Most available information regarding the role of oncogenic viruses in the causation of brain tumours are based on experimental and epidemiological studies. Several oncogenic viruses are known to induce a high incidence of brain tumours in rodents following intracerebral injection. Transgenic mice were used to identify the transforming viral genes responsible for the induction of brain tumours.[1] The type of brain tumour induced depends upon the transforming gene or the regulatory DNA sequence and the genetic background of the experimental model. Viral oncogenes have also been used in a grafting model in which retroviral vectors are used to transfect foetal rat brain cell line *in vitro*, which is subsequently injected into the caudoputamen of adult rats.[90]

A large number of oncogenic viruses have been implicated in the pathogenesis of human brain tumours and these include: simian virus, JC virus, Rous sarcoma virus, adenovirus, polyoma virus and papilloma virus. Among these, two to three oncogenic viruses are relevant to the pathogenesis of human brain tumours.

Simian Virus-40 (SV-40)

Experimental studies suggested that several oncogenic viruses are capable of inducing neuroepithelial and embryonal tumours in rodents. Primitive neuroepithelial tumours induced by 'simian virus-40 (SV-40) large T-antigen' are morphologically indistinguishable from that of human medulloblastoma. SV-40 large T-antigen binds and inactivates several tumour suppressive genes including p53 and Rb gene and is capable of transforming human cells *in vitro*.[8,9]

Historical Evidence

SV-40 virus was iatrogenically introduced on a large scale into the human population in North America and Europe between 1955–1962 through SV-40 virus contaminated polio vaccine.[9] SV-40 viral sequences have been identified in a variety of human neoplasms, raising the question of a possible aetiological role.[8] In brain tumours, SV-40 sequences have been detected at an overall frequency of approximately 35%[8] while the surrounding normal brain rarely contained SV-40 viral genetic material.[50] In another study, 25–50% of brain tumours of Swiss patients contained SV-40 sequence, which was not detected in a similar series of brain tumours from Finland, a country where SV-40 contaminated polio vaccine was not used.[58] This suggests an association between SV-40 viral infection and origin of human brain tumours. These observations also indicate that SV-40 is able to spread vertically in human populations to be present even today, 44 years after the cessation of the use of SV-40 contaminated polio vaccine. Because of the large population involved, the aetiological role of SV-40 in human brain tumours needs to be carefully assessed. Instead its presence may reflect a bystander infection due to an intra-tumoural microenvironment that favours viral replication in humans with a latent SV-40 infection.

JC Virus

JC virus has an extensive nucleotide sequence homology with SV-40 and also overlapping antigenicity, but the host range is definitely different. While SV-40 rarely infects human cells, latent JC viral infection is very common with a seroprevalance of 40–60% in most developed countries particularly in immunocompromised patients. In the brain, JC virus infection may cause progressive multifocal leucoencephalopathy. Most of the information regarding brain tumours due to JC virus infection is based on experimental evidence. Following intracerebral injection into newborn hamsters, JC virus causes brain tumours, mostly embryonal in nature, i.e. medulloblastoma and primitive neuroectodermal tumour.[87] Matsuda et al.[51] using *in situ* hybridisation, demonstrated that JC virus primarily infects cells of the external granular layer of the developing cerebellum, which then migrate to the internal granular layer where medulloblastomas are detected as early as 30 days following the inoculation. Following intracerebral inoculation of newborn rats with JC virus Tokyo-1, a strain isolated from the brain of a patient with progressive multifocal leucoencephalopathy, more than 70% animals developed brain tumours in the forebrain and cerebellum as seen in hamsters. Histologically, these tumours were undifferentiated neuroectodermal neoplasms probably originating from the subependymal matrix zones.[59] Two Colombian owl monkeys inoculated with JC polyoma virus derived from human PML cases developed brain tumours that closely resembled human astrocytomas.[44]

Adenovirus 12

Human adenovirus 12 has been shown to induce neuroblastoma and retinoblastoma in rodent models following intracerebral and intraorbital inoculation. Kolke et al.[40] established transgenic mice expressing the human adenovirus type 12 EIA and EIB genes under the control of the mouse mammary tumour virus long terminal repeat (LTR) and all the 12 homozygous mice developed neuroblastoma of the olfactory nerve between the ages of 6 and 9 months.

EFFECT OF RADIATION

Radiation has been implicated in the induction of human intracranial neoplasms for over thirty years. However, the exact incidence of intracranial tumour development following irradiation is still unknown. Meningiomas have

been reported to develop following radiation therapy for pituitary and glial tumours. Mann et al.[49] first reported the occurrence of malignant meningioma just six years after radiation to treat an optic nerve glioma. Lacono et al.[33] who reviewed 40 cases, noted that the latent period for the occurrence of meningioma in patients receiving less than 800 Rads was 31.3 years, while in the high dose-irradiated group (more than 2,300 Rads), the average latent period of development of tumour was 20.8 years. This data suggests that the higher the dose of irradiation, the shorter the latent period for the development of tumour. The most convincing evidence that radiation was associated with an increased incidence of meningioma was published by Modden et al.[54] They reviewed 11,000 children with *Tinea capitis*, who received radiation therapy to the scalp on an average 350–400 rad to each of the five scalp fields with a calculated brain dose of 140 Rads. Compared with a well matched control group, a four-fold increase in the incidence of meningiomas occurred in the irradiated group. A latent period of 16 years elapsed before tumour discovery in most of these children. From this data, it seems logical that these meningiomas were in some way related to the low-dose radiation, but conclusive proof is still lacking.

Fibrosarcomas are the next common type of tumours to develop after radiation therapy. Waltz et al.[88] reported two cases of fibrosarcoma developing after radiation therapy for pituitary adenomas. They also reviewed 13 previously reported cases. All these patients cited in the review received 3,500 Rads. The latent period was generally between 5 and 12 years.

Approximately 16 glial tumours have been reported following radiation. Chung et al.[12] reviewed these cases and emphasised that from the relatively few reported cases it is impossible to make a definite statement on the role of radiation in the development of glial tumours. However, the following criteria should be defined in order to incriminate radiation therapy in the development of intracranial tumours: (a) the tumour occurs within the anatomical territory of radiation; (b) an adequate latent period exists following radiation, commensurate with the dose of radiation given; (c) no factors predisposing to tumour development exists such as neurofibromatosis or multiple endocrine neoplasia syndrome; (d) the tumour would rarely occur spontaneously in a control group of non-irradiated patients.

Radio Frequency (RF) Radiation

In recent years, there is a rapid increase in the use of cellular phones. The question whether or not RF exposure following long-term usage of cellular phones causes brain tumours is not established. Data so far gathered is too limited to implicate the biological effects of radio exposure for the occurrence of brain tumour. However, exposure to higher frequency radio frequency fields is known to increase local tissue heat and vascularity and these may be expected to affect the blood-brain barrier.[2]

CHEMICAL CARCINOGENS

Several studies have been undertaken to test the assumption that N-nitroso compounds play a role in the evolution of human brain tumours, since some of these agents are potent neurocarcinogens in rodents, particularly when administered perinatally. Nitroso compounds have been detected in nitrite-preserved food and in beer, but they can also be formed in the stomach after the intake of their chemical precursor, nitrate/nitrite and secondary amines. The results of one multicentre analytical study suggest that the risk of developing a primary brain tumour may be higher in people with a high intake of meat, particularly cooked ham, processed pork and bacon.[5] Dietary habits during pregnancy are also suggestive of an adverse effect of food and are a likely source of nitroso compounds.[73] In some studies, an inverse association was noted with the intake of fruit and vegetables and vitamin C, which is known to block the endogenous formation of nitrosamines.[64]

Experimental data in animals provides evidence that chemical carcinogens, such as nitroso compounds and polycyclic hydrocarbons, can be used to induce brain tumours. Druckrey et al.[22] demonstrated that N-methyl-N-nitrosourea (MNU) selectively induced CNS tumours. Malignant gliomas developed in 90–100% animals within eight months after regular intravenous administration of MNU. Anaplastic and mixed gliomas along with oligodendroglioma are the commonest MNU induced CNS tumours. They occur preferentially in the subcortical white matter, hippocampus and periventricular regions. Ethyl nitrosourea (ENU) is another commonly used alkylating agent. Ivankovic et al.[35] found that a single ENU dose of 20 mg/kg body weight given to rats in the third trimester of pregnancy induced neural tumours in 100% of the offspring. Administration of ENU on the 15th day of gestation results essentially in CNS tumours, while exposure to ENU on the 21st day of gestation leads primarily to spinal cord and nerve sheath tumours. ENU has the advantage that a single dose of intravenous administration results in about 100% tumour formation, with low systemic toxicity and the morphological characteristics of the tumour are very similar to human oligodendrogliomas. The metabolism and mitogenesis of nitrosourea has been well studied. After intravenous administration, the nitroso compounds are widely distributed in the body and they cross the blood-brain barrier. They are rapidly hydrolysed and generally have a half-life of less than 10 minutes. According to Kleihues and Rajewsky,[38] the alkylating agents cause the formation of O-alkylated bases, especially O-alkylguanine. This molecular alteration results in mispairing of DNA bases, which can initiate the neoplastic transformation in the brain.

Despite sufficient experimental data suggesting that chemical carcinogens may have a role in animal models, so far no firm evidence of the carcinogenic effects of these elements in humans has been established. A link

between occupational exposure to nitroso compounds, polycyclic aromatic hydrocarbons, polyvinyl chlorides, synthetic rubber, acrylonitrile and other chemical compounds is still controversial.[4] This is likely due to the presence of several chemicals at any work place. Further, the number of patients studied is often too small for a given tumour entity to demonstrate a causal relationship between exposure to chemical carcinogens and development of brain tumours in the human.

IMMUNODEFICIENCY STATUS

Among all intracranial malignant tumours, association of congenital or acquired immunodeficiency disorders with primary central nervous system lymphoma (PCNSL) has been established. During the past two decades, the incidence of PCNSL has tripled.[46] The reason for this increased incidence of PCNSL in part is accounted for by the growing number of immunosuppressed individuals who have a well-known proclivity to develop these tumours. This susceptible cohort includes those with iatrogenic immunosuppression such as organ allograft recipients[53] and acquired immunodeficiency syndrome. Overall PCNSL occurs in as many as 6% of AIDS patients and may be seen in conjunction with other neurological complications such as cytomegalovirus or toxoplasmosis infection, or progressive multifocal leucoencephalopathy.[62] About 4% of the malignancies that occur in individuals with congenital immunodeficiency syndromes are PCNSL.[28] In particular, children with Wiskott Aldrich syndrome appear to develop these tumours.[32] The association of immunodeficiency disorder and PCNSL is further substantiated by the fact that these neoplasms occur much more at a younger age (mean group 31y) when compared to the occurrence of PCNSL in immunocompetent individuals.[23] The Epstein-Barr virus (EBV) is frequently found in lymphomas and in immunodeficient patients. This is thought to play a role in the pathogenesis. The EBV sequence has also been consistently found in AIDS-related PCNSL.[13] Regardless of its role in oncogenesis, the detection of EBV may occasionally be of diagnostic utility. Specifically, the presence of clonal viral sequences as detected by Southern blot hybridisation studies can be taken as evidence of neoplastic cell proliferation.[15] In addition, use of highly sensitive PCR to detect EBV genome in the CSF of AIDS patients may be diagnostic of PCNSL, providing a simple and non-invasive alternative to stereotactic biopsy.[19]

HORMONAL FACTORS

There is some evidence to suggest a role of hormonal factors in the development of meningioma and possibly acoustic schwannoma and pituitary adenomas. Steroid hormones can cross the blood-brain barrier and progesterone is thought to affect the growth of some intracranial tumours, especially meningiomas, gliomas and vascular tumours.[10] The female preponderance of meningioma and pituitary tumours has been well established in clinical and population studies,[16,17,45,66] an effect that was stronger in younger than older women.[16] Discrepancies between populations and clinical studies suggest that either some referral or health care bias may be overestimating female cases in clinical studies or that females are systematically under reported in population based incidences studies. This underscores the importance of having accurate incidence data on which to base hypotheses.

TRAUMA

An association between trauma and meningioma/glioma development has been proposed frequently. Based on their observations, Cushing and colleagues[17] suggested that one-third of meningiomas were related to previous trauma. More recent case reports of brain tumours associated with previous trauma sites were explained by the introduction of carcinogenic compounds into open wounds or by the activation of dormant tumourigenic cells during repair-related proliferation.[65] While repeated case reports keep the intriguing relationship in mind, sufficient data is not there to support an aetiologic role of trauma for primary brain tumours. Review of larger series did not detect a significant correlation between trauma and brain tumours.[3]

Precise pathogenetic mechanisms in the development of human malignant cerebral neoplasms are still not well defined. However, advances in basic neurosciences during the past two decades, especially in cellular and molecular genetics, biology and immunology, have produced a wealth of information on the pathogenesis of human brain tumours. Understanding of the processes such as cell-cycle control, programmed cell death and angiogenesis, together with the discovery of oncogenes and TSG have provided insight into the mechanisms of initiation, proliferation and progression of the tumour. Tumourigenesis is a multistep process caused by genetic changes that are either inherited or acquired. The identification of the genes responsible for hereditary syndromes associated with tumours such as p53, Rb and NF genes and the elucidation of their functional role have been extended to understanding the pathogenetic mechanisms underlying sporadically occurring brain tumours. In addition, analysis of genetic changes, such as gene amplification or loss of heterozygosity, allow the identification of markers that can be used as more accurate tools for diagnosis and the assessment of tumour prognosis. Finally, understanding of cellular and molecular processes involved in tumourigenesis may lead to more rational therapeutic approaches including the inhibition of angiogenesis, the replacement of tumour suppression genes with either gene transfer or the enhancement of specific immune responses. Many questions are still waiting to be answered. Therefore, the primary goal of the neuro-oncologist over the next decade will be to identify the many remaining TSG. The significance of recently identified epiphenomena, such

as telomere activation in tumours, DNA methylation and genetic instability in tumourigenesis, await further investigation, but may offer new therapeutic targets in the treatment of brain tumours.

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121 Germ Cell Tumours of the Central Nervous System

Vani Santhosh

Primary central nervous system (CNS) germ cell tumours are known to have a higher incidence in Far East Asia than in the West. In series from Japan, Taiwan and Korea, the reported incidence is about 8–15% of all primary CNS tumours in the paediatric age group[4] as against 3–4% in the Western series.[8] The majority of patients are below the age of 25 years and the peak incidence is 10–14 years. A distinct male preponderance has been observed.

They are classified as follows:

- Germinoma
- Teratoma—mature teratoma, immature teratoma, teratoma with malignant transformation
- Yolk sac tumour
- Embryonal carcinoma
- Choriocarcinoma

CLINICAL FEATURES AND LOCALISATION

These tumours preferentially affect midline structures. The majority of tumours arise from structures around the third ventricle-pineal region followed by the suprasellar compartment.[7] Other sites include: intraventricular; basal ganglionic; diencephalic; intramedullary and intrasellar. Germinomas have a predilection to arise from the suprasellar region while other non-germinomatous tumours arise from the other sites mentioned above.

Clinical symptoms depend on the anatomical site of the neoplasm. Those in the pineal region present with features of obstructive hydrocephalus and neuro-ophthalmic paralysis or Parinaud's syndrome due to infiltration of the tectal plate. They can also present with features of raised intracranial pressure. Tumours in the suprasellar region produce visual compressive symptoms. They disrupt the hypothalamo-pituitary axis and may produce diabetes insipidus and features of pituitary failure, which include retarded growth and sexual maturation. Some tumours that secrete human chorionic gonadotrophin (HCG) can cause precocious puberty. In general, the symptoms are more protracted in germinomas than in other germ cell tumours.

IMAGING FEATURES

On CT and MRI scans, except teratomas, all others are solid masses that are isointense to hyperintense relative to grey matter and show prominent contrast enhancement. Intratumoural cysts, areas of calcification and areas of low signal attenuation characteristic of fat are seen in teratomas.

PATHOLOGY

Germinoma

These are composed of large neoplastic cells that resemble primordial germ cells. The cells are round with a vesicular, centrally placed nucleus with a prominent nucleolus and abundant glycogen filled cytoplasm. Mitosis is frequent but necrosis is rare. The cells are disposed in sheets and lobules separated by a desmoplastic stroma. Infiltration of the tumour by a variable number of mature lymphocytes (T cells) is a characteristic feature (Fig. 1). Some tumours can have florid lymphocytic or lymphoplasmacytic infiltrates along with epithelioid granulomas and giant cells. In such tumours, it is important to identify primordial germ cell elements to avoid a misdiagnosis of a granulomatous lesion. Immunohistochemical markers for the germ cell component include cell membrane staining for placental alkaline phosphatase (PLAP), ckit and nuclear labelling for OCT4.[3]

Teratoma

These tumours contain ectodermal, endodermal and mesodermal elements.

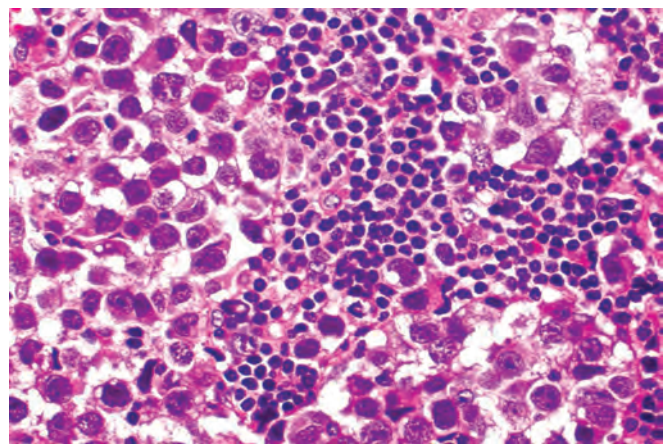

Fig. 1: Germinoma showing characteristic malignant germ cells admixed with mature lymphocytes (HEX320)

Mature Teratoma

These are composed of fully mature 'adult type' tissue elements. The common ectodermal elements include skin and neuroepithelial tissues. Mesodermal elements are represented by cartilage, fat, muscle and bone and the endodermal elements include respiratory or intestinal type of epithelium.

Immature Teratoma

This variant contains incompletely differentiated components resembling foetal tissues either as a minor portion of the tumour which is otherwise composed of mature elements or it can predominate in the tumour. The component that is often immature is the mesenchymal or neuroectodermal elements and these cells are mitotically active (Fig. 2).

Teratoma with Malignant Transformation

These are rare tumours exhibiting malignant transformation of one of the somatic elements. Commonly seen are undifferentiated sarcomas, or regions of squamous cells or adenocarcinomas within the tumour.

Yolk Sac Tumour

This tumour is composed of a loose myxoid matrix within which are primitive appearing epithelial cells (representing yolk sac endoderm). The cells can be in solid sheets, trabeculae or line delicate fibrovascular projections to form distinctive papillae known as Schiller-Duval bodies. They can also show a reticular or sinusoidal growth pattern. The diagnostic feature, although not always present, is the presence of PAS positive, diastase resistant hyaline globules located intracytoplasmic or freely in the myxoid stroma. The tumour cells exhibit high mitosis and cytoplasmic labelling of alpha fetoprotein (AFP) and this is characteristic. The hyaline globules are also AFP positive.

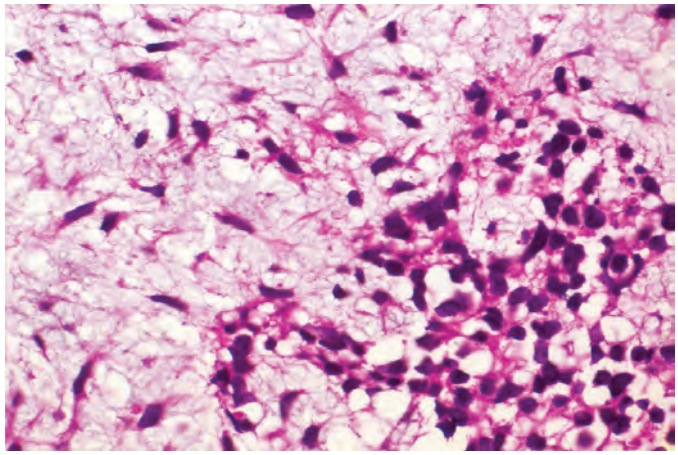

Fig. 2: Immature teratoma with embryonic mesenchyme like stroma and primitive neuroepithelial cells (HEX320)

Choriocarcinoma

These tumours contain cytotrophoblastic and syncitiotrophoblastic elements. Ectatic stromal vascular channels and large areas of fresh haemorrhage characterise this tumour. Cytoplasmic immunoreactivity for βHCG and human placental lactogen is diagnostic.

Embryonal Carcinoma

This rare tumour is composed of large cells arranged in abortive papillae, gland-like structures and can replicate an early embryo forming the 'embryoid bodies'. The tumour cells show cytokeratin immunoreactivity along with PLAP and OCT[4] labelling.

Often CNS germ cell tumours are encountered as mixed histological forms. In fact, only germinomas and teratomas are generally encountered as isolated tumour types.[1]

HISTOGENESIS

One of the hypothesis for the origin of CNS germ cell tumours is the neoplastic transformation of germ cells that either migrate in an aberrant fashion or 'home' to the embryonic CNS. However, immunohistochemical studies on foetal pineal gland for germ cell markers including PLAP expression have never shown this gland to harbour primordial germ cells.[2] An alternate hypothesis postulates an origin for CNS germ cell tumours in a variety of displaced embryonic tissues that can be sometimes incorporated in the developing neural tube.[6] Another speculation is the involvement of totipotent or pleuripotent stem cells in the origin of these tumours.[9]

PROGNOSTIC AND PREDICTIVE FACTORS

Prognosis depends on the histological sub-type of the tumour. Mature teratomas are curable by complete resection of the tumour. Germinomas are extremely radiosensitive and 10 year survival has been recorded after craniospinal irradiation.[7] The tumours most resistant to treatment are yolk sac tumours, embryonal carcinoma and choriocarcinomas. Immature teratomas and mixed germ cell tumours with predominant teratoma and germinoma components and containing non-germinomatous components occupy an intermediate position in terms of aggressiveness.[5]

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122 Embryonal Tumours of the Central Nervous System

Chitra Sarkar, Sharma MC

Embryonal Tumours of the CNS are highly malignant tumours (WHO grade IV) occurring predominantly in children. The following tumours are included in this group according to the WHO classification (2007):

1. Medulloblastomas (MBs)
2. CNS primitive neuroectodermal tumours (PNETs):
   - CNS/Supratentorial PNETs (SPNETs)
   - Medulloepithelioma
   - Ependymoblastoma
3. Atypical Teratoid/Rhabdoid tumours (AT/RTs).

MEDULLOBLASTOMAS

These are the most common malignant brain tumours of childhood accounting for approximately 12–25% of all CNS tumours in children. They correspond histologically to WHO grade IV and are subdivided into the following histological subtypes (WHO 2007):[48]

- Classic MB
- Desmoplastic/Nodular MB
- MB with extensive nodularity (MBEN)
- Anaplastic MB
- Large cell MB
- MB with melanotic differentiation (Melanocytic)
- MB with myogenic differentiation (medullomyoblastoma).

Clinical Features

The overall mean and median ages at diagnosis are 13 years and 9 years respectively with a peak age of occurrence around 7 years. Among the adult patients, 80% are in late adolescence or early adulthood (median 25 years).[48] MBEN typically occur in infants less than 3 years of age. The desmoplastic variant, however, shows almost equal distribution between children and adults. There is a marked male preponderance with approximately two-third of patients being males.[12,48]

MBs are tumours of the cerebellum with 75% of them arising in the cerebellar vermis. A hemispheric or lateral location is more common among adolescents and adults. The most common subtypes of MB in a hemispheric location are desmoplastic/nodular types.[12,48]

The presenting clinical features commonly include gait disturbances and truncal ataxia. These are often associated with features of raised intracranial pressure secondary to obstructive hydrocephalus. In the later stages, clinical manifestations may be related to the spread of tumour through the CSF pathways.

Imaging

Imaging (both CT and MRI) reveal most MBs as solid masses with intense enhancement on contrast injection. Striking "grape like" pattern on MRI is characteristic of MBEN.[12,48]

Histopathology

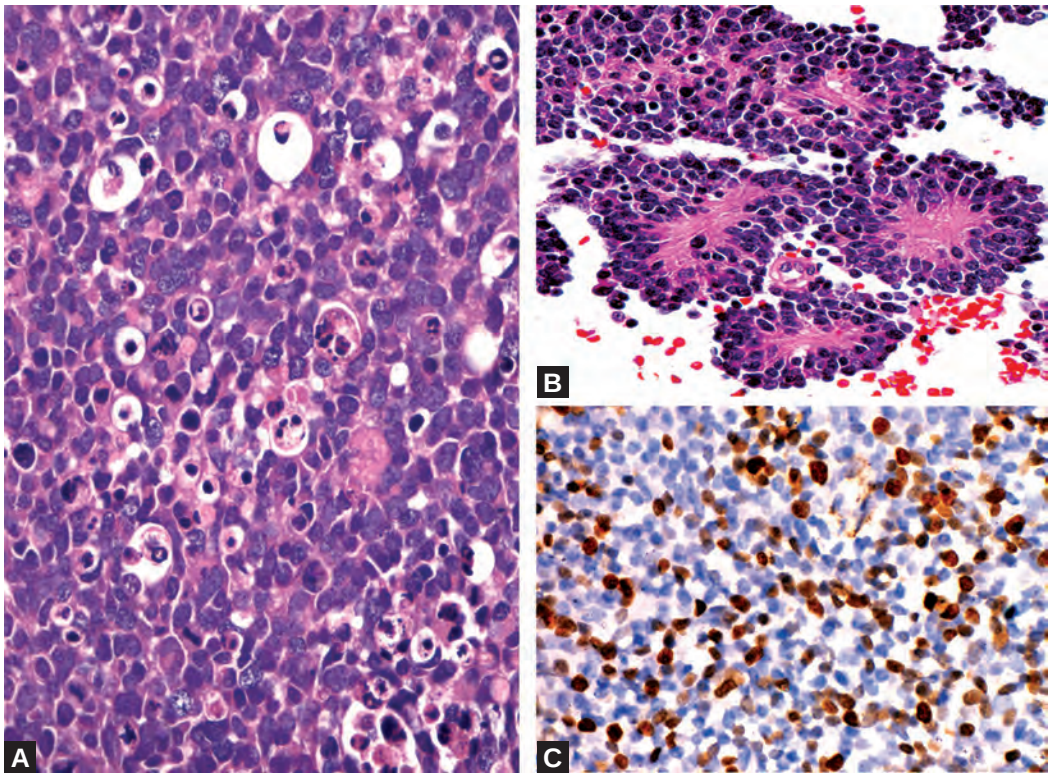
The majority of MBs arise in the vermis and appear as pink or grey masses that can project and fill the fourth ventricle. Foci of necrosis are generally small and extensive necrosis is uncommon.

Classic Medulloblastomas

Classic MBs are characterised by sheets of densely packed cells with hyperchromatic round to oval or carrot shaped nuclei, scant cytoplasm, numerous mitosis and conspicuous apoptosis (Fig. 1A). Homer-Wright rosettes are observed in less than 40% of cases (Fig. 1B). These rosettes are characterised by arrangement of tumour cells around a fibrillary centre. Varying degrees of neuronal and glial differentiation can be seen in these tumours. Areas of necrosis and vascular hyperplasia are uncommon. The tumour shows high mitotic activity (Fig. 1C).

Desmoplastic/Nodular Medulloblastomas

Desmoplastic/nodular MBs show a distinctive nodular architecture with reticulin free pale islands alternating with reticulin rich internodular regions (Figs 2A and B). The cells within the nodules have round uniform nuclei, with evidence of neuronal differentiation (synaptophysin +ve) and show low mitotic rate (low MIB-1 labelling index) but high apoptosis. In contrast, the cells in the internodular regions have hyperchromatic irregular nuclei, show evidence of glial differentiation (GFAP +ve) and have a high mitotic rate, but a low apoptotic rate. This characteristic pattern may be present either diffusely or focally throughout the tumour. It is important to emphasise that MBs showing only increased amounts of reticulin fibres and/or collagen, but lacking the nodular pattern, are not classified as desmoplastic/nodular

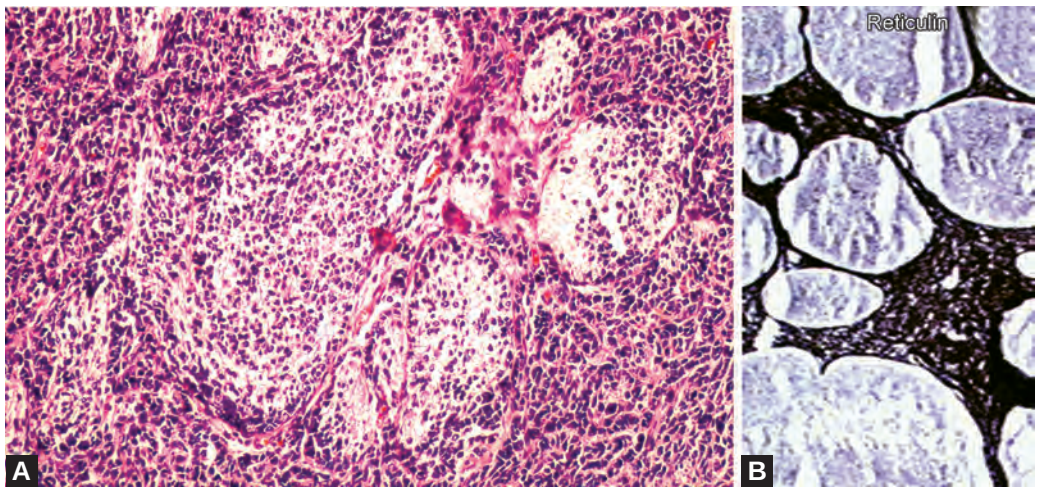


Figs 1A to C: (A) Classical medulloblastoma made up of sheets of undifferentiated cells with elongated, hyperchromatic nuclei interspersed with apoptotic bodies and cells in mitosis. (B) Focal areas show characteristic Homer Wright rosettes with central fibrillary neuropil representing neuronal differentiation. (C) MIB-1 immunostaining highlights high mitotic response [A:HE x 240; B:HE x 120; C:Immunoperoxidase x 120]

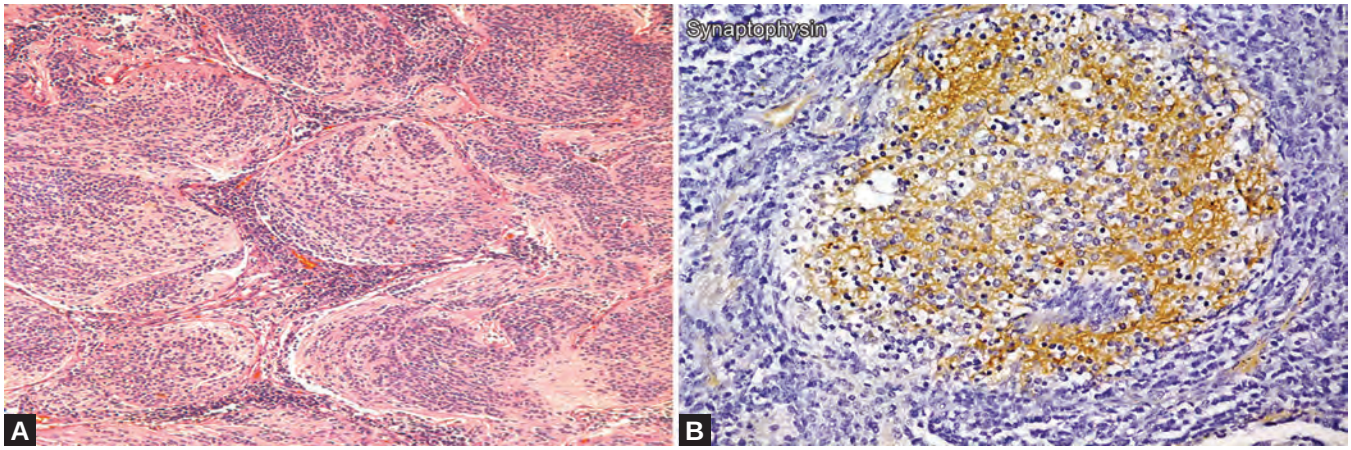
variant. The high reticulin/collagen content could be a secondary event to leptomeningeal invasion.

Medulloblastomas with Extensive Nodularity

MBEN comprise of nodules having round cells with uniform nuclei arranged in a laminar/streaming pattern with a fine fibrillary neuropil like matrix (cells resemble those of central neurocytoma) (Fig. 3A). These cells express synaptophysin (Fig. 3B) while the surrounding undifferentiated cells are negative. They possibly represent the most differentiated form of desmoplastic MBs comprising of well-delineated nodules with little or no internodular cellular component unlike desmoplastic MBs.



Figs 2A and B: (A) Desmoplastic medulloblastoma with pale nodular areas surrounded by islands of undifferentiated cells. (B) Nodular arrangement is highlighted by dense reticulin framework encircling the central reticulin free pale zones [A:HE x 100; B:Retculin silver x 60]



Figs 3A and B: Medulloblastoma with extensive nodularity (MBEN) shows characteristic pale neurocytic zones. (A) that strongly express synaptophysin. (B) in contrast to the surrounding undifferentiated cells [A:HE x 80; B:Immunoperoxidase x 120]

Anaplastic Medulloblastomas

Anaplastic MBs are characterised by marked nuclear pleomorphism, nuclear moulding, cell-to-cell wrapping, high mitotic activity (including abnormal forms) and high apoptotic rate (Figs 4A and B). The above changes have to be pronounced and widespread within a tumour to label it as an anaplastic MB. If these features are present only focally, then a tumour cannot be labelled anaplastic MB. Several studies have documented histological progression from non-anaplastic to anaplastic MB (similar to malignant progression in gliomas).

Large Cell Medulloblastomas

Large cell MBs comprise of monomorphic cells with large round vesicular nuclei, prominent nucleoli and variable amounts of eosinophilic cytoplasm with abundant mitosis and apoptosis. Large cell and anaplastic MBs show considerable histological overlap and, hence, in several studies, a combined large cell/anaplastic category (LC/A MBs) has been proposed.

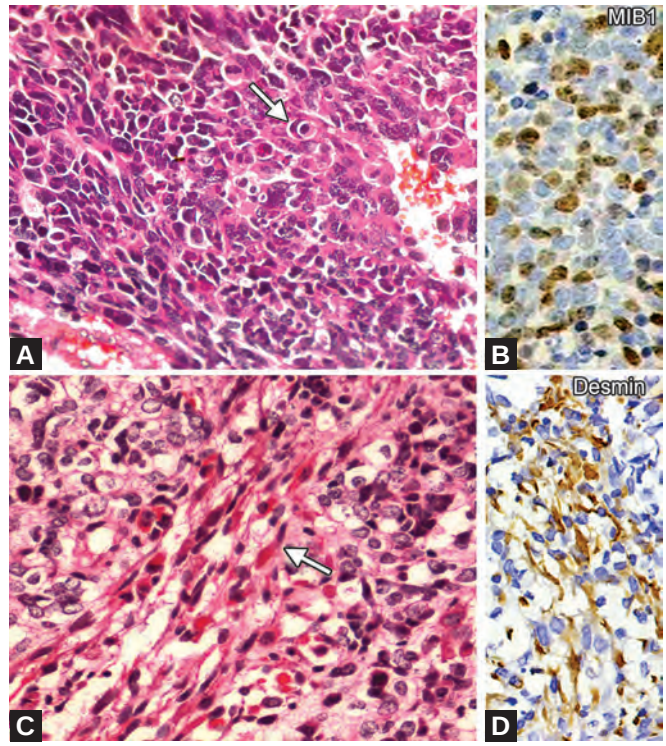
Melanocytic Medulloblastomas

Melanocytic MBs are characterised by the presence of melanin in scattered tumour cells.

Medullomyoblastomas

Medullomyoblastomas comprise of areas of classic MBs admixed with cells that show rhabdomyoblastic differentiation (spindle or strap cells with cross-striations of skeletal muscle and immunopositivity for desmin) (Figs 4C and D).

Most MBs are immunopositive for nestin and vimentin. Synaptophysin is also by and large positive, although its expression may take several forms (from completely negative to patchy positivity to diffuse positivity). The other markers that can be demonstrated, at least focally in many MBs, include class III beta tubulin, MAP-2, neuron specific enolase and neurofilament. Expression of all the above neuronal antigens indicates varying degrees of differentiation of MB along the neuronal lineage. The significance of immunopositivity for GFAP in MBs remains controversial. Most tumours contain GFAP positive reactive astrocytes but there are tumours in



Figs 4A to D: Large cell/anaplastic medulloblastomas showing. (A) Large pleomorphic cells with (B) High mitotic activity and at places showing characteristic cell-to-cell wrapping (A, arrow). High mitotic response is evident on MIB-1 immunostaining. Medullomyoblastoma. (C) Showing rhabdomyoblastic differentiation with elongated strap cells with bright red cytoplasm (arrow) admixed with undifferentiated medulloblastomas cells. (D) These cells are strongly positive for desmin. [A:HE x 240; B:MIB-1 x 280; C:HE x 240; D:Desmin x 240]

which unequivocal GFAP positivity is noted within the neoplastic cells. Varying degrees of photoreceptor differentiation (immunopositivity for retinal S antigen and rhodopsin) are also noted in some MBs.[12,48]

Tissue from the undifferentiated areas does not show any specific ultrastructural features. In the areas of neuroblastic differentiation (rosettes), the cells show neurite like cytoplasmic processes filled with microtubules. Dense core vesicles and synapse-like structures may also be seen. In areas of glial differentiation, abundant intermediate filaments are noted.

The histogenesis of MBs has remained controversial for over 80 years, since Bailey and Cushing first recognised it as a distinct clinicopathological entity in 1925. There are two main hypotheses. One view suggests that MBs arise from the cells of the external granular layer of the cerebellum. The second hypothesis states that MBs are derived from subependymal matrix cells, which reside throughout the embryonal CNS, including the fourth ventricle, which give rise to neuronal and glial cells.[11]

Perhaps, most likely, is a combined theory proposing that MBs arise from more than one cell type. Based on this theory it is suggested that classic MBs are derived from the periventricular primitive zone while nodular MBs arise from EGL cells. New candidate cells of origin continue to be proposed and one such recent hypothesis is the origin from CD133+ve stem cells found predominantly in the white matter of the postnatal cerebellum.

Molecular Genetics

Molecular and genetic alterations in MBs have been worked out extensively using various techniques. These have been divided into three main groups namely: (i) non-random chromosomal abnormalities; (ii) abnormalities in signal transduction pathways and (iii) altered expression of neural transcription factors.

Non-random Chromosomal Abnormalities

Chromosome 17: Partial or complete deletion of the short arm of chromosome 17 (17p) is noted in 30–50% of MBs and is the most frequent non-random chromosomal abnormality. The most common mechanism for 17p loss in MBs is isochromosome 17q. Interestingly, the well-known tumour suppressor gene (TSG) p53, although located on chromosome 17p, is rarely mutated in MBs (only in 5–10% cases).[1,58] This suggests that inactivation of other TSGs on 17p must be important in MB tumourigenesis, of which an important one is now believed to be hypermethylated DNA in cancer-1 (HIC-1) gene.

Other chromosomes: Loss of genetic material from chromosome 1q and 10q are demonstrated in approximately 20–40% of MBs. Other non-random chromosomal abnormalities detected in MBs include isolated examples of deletions of 3q, 6q, 9q, 10q, 11p, 11q and 16q and gains of 4p, 5p, 5q, 7q, 8q and 9p.[9,61]

Gene amplification: C-myc gene amplification occurs in 4–17% of MBs, followed by N-myc.[3,4,19] Large cell/anaplastic MBs, in particular, appear to have a high incidence of C-myc and N-myc amplification. Recently, Fan et al. noted amplification of the human telomerase catalytic protein subunit gene (hTERT) locus at chromosome 5p15 in 42% of MBs and other embryonal tumours.[26]

Abnormalities in Signal Transduction Pathways

Sonic Hedgehog SHH-PTCH signalling pathway: Sonic Hedgehog (SHH) is a family of ligands secreted by the Purkinje cells of the cerebellum, which promote the replication of granule cells, while PTCH is a TSG located on chromosome 9q.[74] SHH and PTCH function as part of a signalling pathway controlling normal CNS development.

Abnormalities in the SHH/PTCH signalling pathway was first suggested following the observation that 1–2% of patients developing MB have Gorlin's syndrome or Naevoid Basal Cell Carcinoma Syndrome (NBCCS) which are caused by mutations of the PTCH gene.[25] Subsequently, molecular studies on sporadic MB cases have shown alterations of the SHH/PTCH pathway in about 25% of cases, with a potential but not exclusive relation with the desmoplastic phenotype.[23,24,56]

'Wingless' (WNT/WG) signalling pathway: This is another signalling pathway that regulates cell proliferation and is essential for normal CNS development. Involvement of this pathway in MB was first suggested because of the association of some MB cases with type 2 Turcot's syndrome, a familial cancer syndrome, in which patients have adenomatous colonic polyps, predisposing to colonic carcinoma, in association with germ-line mutations of the APC gene (Adenomatous Polyposis Coli).[14] Disruptions in this WNT/WG signalling pathway have been found in about 13% of sporadic MBs.[23,24]

Neurotrophin signalling pathway: The neurotrophin signalling pathway comprises of the neurotrophin family along with the tyrosine receptor kinase family of receptors (Trk receptors A, B and C) and plays a major role in cerebellar development. Increased expression of Trk receptors, especially TrkC, has been noted in MBs, especially desmoplastic MBs.[7,54,71]

ErbB receptor signalling pathway: ErbB receptor signalling pathway is important in both cerebellar development and MB tumourigenesis. The ErbB2 receptor especially appears to play a central role in MB. In a study of more than 100 paediatric MBs, Gilbertson et al. reported ErbB2 protein expression in approximately 80% of MBs and co-expression of ErbB4 in 54%.[29,30]

Notch signalling pathway: Notch is a pathway that plays a critical role in regulation of neural stem cells. In the cerebellum, Notch 2 has been shown to promote proliferation of EGL progenitor cells. In MBs, elevated levels of Notch signalling have been found in about 15% of cases and this was caused by amplification of Notch 2 gene.

Altered Neural Transcription Factors

Many transcription factors involved in the development of CNS are deregulated in MBs, e.g. PAX5 and PAX6 mRNA (paired box containing gene transcription factors active in neural development) have been detected in 70% and 78% of MBs by *in situ* hybridisation. Other neural transcription factors found to be over expressed in MBs include ZIC (granule cell marker), NEUROD family of transcription factors, SOX transcription factors and REST (repressor of neuronal differentiation).

Molecular Differences between the Different Medulloblastoma Variants

Molecular genetic analysis studies reveal that large cell and anaplastic (LC/A) variants are particularly associated with myc oncogene (C-myc and/or N-myc) amplification and raised C-myc mRNA levels.[11] A recent study suggested that 17p loss/isochromosome 17q is also more frequent in LC/A MBs than in classic MBs. Abnormalities of chromosome 17 have been found more frequently in non-desmoplastic MBs than in the desmoplastic type.

Gajjar et al. reported ErbB2 expression most frequently in LC/A MBs. Further, increased aneuploidy in LC/A MBs was detected by several groups, suggesting that additional genetic changes are yet to be discovered.[27]

Deletions of chromosome 9q, PTCH gene mutations and mutations of other genes in the SHH signalling pathway occur preferentially, and in a significant proportion (30–40%) of desmoplastic MBs.[56] Eberhart et al. noted TrkA and TrkC in a high percentage of desmoplastic MBs, predominantly within their nodules.[21]

Treatment and Prognosis

Before 1970, the overall 5-year survival rate for patients with MBs was only 2–30%. Since then, with the advancements in diagnosis, imaging and management (both surgical and radio-chemotherapeutic) the 5-year survival has markedly improved to 60–70%.[18]

MBs spread via the CSF pathways with subarachnoid seeding occurring in up to one-third of patients at the time of diagnosis.[47] Recurrence, generally local, is unfortunately very common and mostly occurs within the first 2 years after initial treatment; however, late recurrences can occur sometimes 10–19 years after diagnosis. Systemic/extraneural metastasis is also described, the most common site being bone, followed by lymph nodes. They may manifest up to several years after initial treatment, within a median time of 12–32 months. The development of recurrence or metastasis carries a poorer prognosis with lowered 5-year survival rates. Patients with MB also have an increased risk for the development of second malignancies that is particularly attributable to the longer survival times as well as the use of RT and CT.[20,47]

Risk Stratification in Medulloblastomas (Prognostic Factors)

Clinical Factors

MBs have been stratified on the basis of age, extent of resection and Chang et al. metastasis staging into the following two risk groups:[15,75]

1. *Average risk:* Patients older than 3 years of age with non-metastatic disease and total or near total resection (<1.5 cm of residual tumour on post-operative imaging).
2. *High risk:* Patients less than 3 years, with incomplete surgical resection (>1.5 cm residual tumour) or with metastatic disease at presentation (Chang stages M1-4).

The major limitation of this stratification is that it does not differentiate high and low-risk patients within the same clinical stage. This is true, since there is wide discordance of clinical outcomes due to biological differences within a tumour. Therefore, the considerable shortcomings of the current clinical staging system are its inability to identify 20–30% of average risk patients with resistant disease or overtreated average risk patients.

These concerns have induced the search for stratification of MBs based on multiple parameters; this includes histology and new molecular markers. This will help in enhancement of the utilisation of existing therapies for MBs and minimise the hazards of suboptimal treatment and devastating side effects.

Histopathological Factors

The most important histopathological factors with a demonstrable role in prognosis of MBs are histopathological subtype, extent of nodularity and grade, and extent of anaplasia.

Histopathological subtypes: The best prognostic outcome is seen with MBEN[69] while large cell/anaplastic MBs have the worst outcome with high local recurrence, CSF and systemic metastasis and death within 1–2 years of diagnosis.[50] Prognosis of the desmoplastic variant still remains debatable. They have been inconsistently correlated with better outcome, worse prognosis or no relation with survival time. Other variants with poor outcome are melanotic MBs and medullomyoblastoma, with survival of 2 months to 2.5 years in the former, to less than 1 year in the latter.[22,33,34,44,46]

Anaplasia: It has been proposed as the criteria associated with aggressive behaviour and poor outcome.[11]

Differentiation: MBs have been shown to differentiate along glial or neuronal cell types. Different studies have shown variable prognostic significance for GFAP positivity ranging from better to poor to equivocal.[35,43]

Proliferation index and apoptotic index: Sarkar et al. have shown higher proliferation index and lower apoptotic indices in childhood as compared to adult MBs.[64] The overall significance of cell proliferation and apoptotic

index as prognostic markers is still debatable.[38] Ito et al.[42] have shown that MBs with a labelling index greater than 20% behave aggressively, while Schiffer et al.[66] showed no correlation of proliferation index in adult and childhood MBs.

Ploidy: Aneuploid tumours have been shown to respond favourably to treatment as compared to diploid tumours.[60]

Molecular, Cytogenetic Factors and Signalling Pathway Markers

It has been shown that combined analysis of molecular and clinical factors gives better risk stratification than clinical factors alone.

Loss of 17p/Isochromosome 17q

Poor outcomes, shortened survival and metastasis have been demonstrated with 17p deletions and/or isochromosome 17q. C-myc alterations in association with 17p alteration further promote their aggressive behaviour.[5,65]

C-myc and N-myc Amplification

Tumours with myc gene amplification have a significantly worse clinical outcome, shorter survival[57] and resistance to therapy. Therefore, it is important to identify myc gene amplification or myc RNA overexpression, since these parameters can act as independent prognostic criteria.

Gene Profiling

Gene expression profiling of MBs have been studied using oligonucleotide microarrays. Genes attributed to cerebellar differentiation and genes encoding extracellular matrix proteins have been correlated with a better prognosis. However, concomitant expression of genes related to cell proliferation and multidrug resistance are associated with poor outcomes.[57] Platelet derived growth factor receptor (PDGFR) and Ras/mitogen-activated protein (MAP) kinase signal transduction pathway show upregulation in metastatic disease.

TrkC Expression

TrkC is the single most important predictor of favourable outcome in MBs. Segal et al.[67] reported a high 5-year survival of 89% in MBs with high TrkC as compared to 46% for those with low TrkC. Also a 4.8-fold greater risk of death was reported in children with low TrkC mRNA expression.[37] Moreover, 100% progression-free survival was reported in PNET/MBs with combined low C-myc and high TrkC mRNA expression.[36]

ErbB2 Expression

Increased ErbB2 expression is associated with poor prognosis. Maintaining the cut-off of 50% for ErbB2 labelling of tumour cells, two different series have reported 10-year survival of 48% and 10% and 25-year survival of 46% and 17% respectively.[31,32]

Wingless (WNT/WG) Pathway

Nuclear accumulation of beta-catenin, a marker of activation in the WNT pathway, has been found to be an independent marker of good outcome.

The mainstay of treatment of MBs has been maximal surgical resection, whole neuraxis radiation and chemotherapy. However, only 60% of children with MBs are cured using the aggressive regimen and most of them suffer long-term side effects in the form of neuropsychological sequelae and neurocognitive decline.[39,53] Hence, new modalities of treatment aimed at lowering the dose of craniospinal axis irradiation (CSA-RT) combined with adjuvant chemotherapy (CT) are being tried. New treatment modalities being investigated include new techniques of three-dimensional conformal RT and intensity modulated radiation therapy (IMRT) which precisely direct RT to the desired site and minimise the neurotoxicity of conventional RT.[49,63]

New biological and molecular factors are also being targeted for novel therapeutic approaches. One of these is cyclopamine, a plant-derivative teratogen that inhibits the SHH/PTCH1 pathway by binding to and altering the conformation of SMO gene product. The recent finding that cyclopamine can reverse the effect of oncogenic SMO and PTCH mutations in murine cells *in vitro* suggest that this pathway may prove to be a future novel therapeutic target.[70]

A second class of potential molecular therapeutic agents for MBs is small molecule inhibitors of receptor tyrosine kinases like ErbB2 and PDGFR. Very recently, Erlotinib (TM), a dual specific ErbB1/ErbB2 inhibitor, was shown to selectively inhibit ErbB2 signalling, cell invasion and ErbB2-dependent prometastatic gene expression in MB cells *in vitro* and *in vivo*.[40] Further, the recent success of anti-ErbB2 monoclonal antibody Herceptin (TM) in the treatment of patients with advanced ErbB2 overexpressing breast cancer provides precedence for using such a strategy as a valuable target for novel therapy for MB.[16] A novel immunotherapeutic approach in the form of adoptive immunity by the T cells grafted with a HER2-specific chimeric antigen receptor has shown to induce sustained regression of established MBs in an orthotopic, xenogenic severe combined immunodeficiency model.[2]

Neural stem cells, retrovirally transduced with cytosine deaminase gene (CD-NSCs) treatment, followed by 5-fluorocytosine administration have shown to prolong survival periods significantly in experimental animals.[68]

The future of molecular therapies in MBs will, however, greatly depend on the continued co-operation between clinical and basic science disciplines.

ATYPICAL TERATOID/RHABDOID TUMOUR

This is a highly malignant CNS tumour in children, histologically corresponding to WHO grade IV.[45] It comprises about 1–2% of paediatric brain tumours and about 10% of CNS tumours in infants.

Clinical Features

AT/RTs most often present in children less than 3 years of age (mean age 2 years). They are rare in children older than 6 years and even rarer in adults. Male preponderance is noted.[41] AT/RTs occur both in the supratentorial and infratentorial locations (ratio of 1.3:1). Infratentorial tumours are commonly located in the cerebellar hemispheres, cerebellopontine angle and brainstem.[10] Supratentorial tumours are more often located in the cerebral hemispheres and less frequently located in the ventricular system, suprasellar or pineal region. About 2% of AT/RTs arise in the spinal cord. Variable clinical presentation is noted depending upon the age of the patient, location and size of the tumour.

Imaging

AT/RTs are isointense to slightly hyperintense with a variable degree of contrast enhancement, similar to MBs.

Histopathology

AT/RTs (Figs 5A to F) are soft pinkish and red bulky tumours with foci of haemorrhage and necrosis. Some regions of tumour may appear firm and grey-white.

AT/RTs are histologically heterogeneous lesions. The most conspicuous feature is the presence of rhabdoid cells with eccentrically placed vesicular nuclei, prominent eosinophilic nucleoli and abundant eosinophilic cytoplasm containing globular intracytoplasmic eosinophilic inclusions. In addition to these rhabdoid cells, most tumours contain variable components of primitive neuroectodermal, mesenchymal and epithelial cells (Figs 5A and B). Mitotic figures are abundant and necrosis is common.

AT/RTs show a wide range of immunoreactivity. Rhabdoid cells are consistently positive for vimentin (Fig. 5D) and epithelial membrane antigen (Fig. 5E). Expression of glial fibrillary acid protein, neurofilament protein, synaptophysin, smooth muscle actin (Fig. 5F) and cytokeratin are variably observed. Germ cell tumour markers are never expressed in these tumours.

Histogenesis and Molecular Genetics

The histogenesis of AT/RTs is not known. Various hypotheses suggested include origin from pluripotent foetal cells, neural crest cells, meningeal cells and germ cells.[10]

The genetic hallmark of AT/RTs is mutation or loss of the INI1 (hSNF5/SMARCB1) gene locus at 22q11.2 chromosome.[59] Consequent to the mutation, there is loss of INI1 protein expression in almost all AT/RTs. In normal tissue and in most tumours, INI1 is expressed as a nuclear protein; however, in AT/RTs there is loss of nuclear expression of INI1 in tumour cells. Immunohistochemical staining for expression of INI1 protein appears to be a sensitive and specific marker for diagnosis (Fig. 5C) of AT/RTs.[8,73]

Treatment and Prognosis

The overall prognosis of AT/RTs is very poor, mean survival being 11 months and median survival 17 months.[13] The majority of patients develop local recurrence and/or neuraxis dissemination, and die within a year of diagnosis.

CENTRAL NERVOUS SYSTEM PRIMITIVE NEUROECTODERMAL TUMOURS

This is a heterogeneous group of malignant tumours occurring predominantly in children and adolescents and which correspond histologically to WHO grade IV. The term CNS-PNET has been introduced in the new (2007) WHO classification and refers to all undifferentiated or poorly differentiated embryonal tumours that occur at any extra-cerebellar site in the CNS.[51] The following tumours are included in this category:

- Supratentorial PNET (sPNET)
- CNS neuroblastoma
- CNS ganglioneuroblastoma
- Medulloepithelioma
- Ependymoblastoma

Supratentorial Primitive Neuroectodermal Tumour

This is an embryonal tumour occurring in the supratentorial location, composed of undifferentiated or poorly differentiated neuroepithelial cells with the capacity for divergent differentiation along neuronal, astrocytic, muscular or melanocytic lines. Tumours of CNS/supratentorial PNETs with only neuronal differentiation are termed cerebral neuroblastoma while those with neuronal differentiation with ganglion cells are termed ganglioneuroblastoma. Since these are rare tumours, their precise incidence is difficult to determine.

Clinical Features

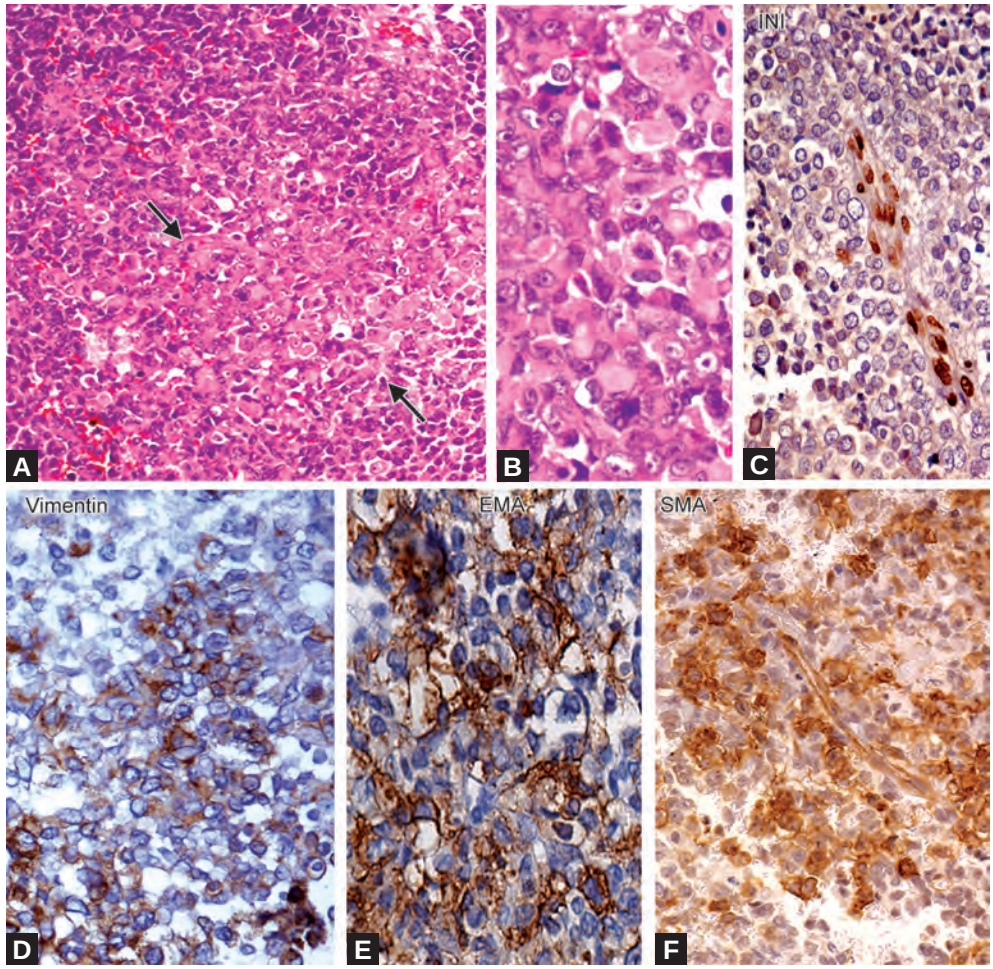
The mean age is 5.5 years with a range of 4 weeks to 20 years. Male preponderance is noted. These tumours are found most commonly in the cerebral hemispheres. Rarely, they have been reported from spinal cord and suprasellar regions. Clinical presentation is related to the site of origin of tumour.

Imaging

They are isointense to hyperintense and show enhancement on injection of contrast material.

Histopathology

These tumours appear as pink-red soft tumours with or without cysts and haemorrhage. These sPNETs are histologically similar to MBs, being composed of poorly differentiated round to oval cells with high nuclear cytoplasmic ratio and brisk mitosis. Fibrillary background may be seen in these tumours and Homer Wright rosettes can also be present. Calcification is a relatively



Figs 5A to F: Atypical rhabdoid/teratoid tumour showing conspicuous rhabdoid cells with vesicular nuclei, prominent nucleoli and eosinophilic globular cytoplasmic inclusions (arrows, A and B) admixed with undifferentiated cells. The tumour cells are negative for INI1 (C) and strongly positive for vimentin (D), epithelial membrane antigen (E) and smooth muscle actin (F) [A:HE x 160; B:HE x 300; C:INI1 x 160; D, E and F: x 240]

common feature within degenerated areas. Neuronal and glial cells, ependymal canals, striated muscle or melanin bearing cells, indicating divergent differentiation of tumours may be seen. These sPNETs express many of the neuronal markers, namely synaptophysin, class III beta tubulin and neurofilament protein. Variable degree of GFAP expression may also be seen.

Histogenesis and Genetics

Histogenesis of sPNETs is controversial. They possibly arise from primitive neuroepithelial cells. The genetic abnormalities in sPNETs are different from MBs. Although they are histologically similar to MBs, they lack many of the molecular genetic alterations characteristic of MBs. Thus, losses of 17p and isochromosome 17q abnormality are rarely seen in sPNETs.[13] In contrast, other genetic abnormalities seen in sPNETs are expression of neuroD family of basic helix-loop-helix transcription factors and RASSF1a promoter methylation. sPNETs also express Achaete-Scute, which is another neurogenic transcription factor with homology to neuroD genes.[62] Recent microarray studies have also revealed that MBs and sPNETs can be separated based on their specific pattern of gene expression.

Outcome and Prognosis

Children with sPNETs have a worse overall 5-year survival rate compared to children with MB. Infants less than 2 years of age have a poorer prognosis than older children.[28] CSF dissemination can be found in nearly one-third of patients. Extraneural metastasis to bone, liver and cervical lymph nodes have also been reported.[72]

Medulloepithelioma

These are very rare embryonal tumours, most examples being single case reports.

Clinical Features

They generally occur in neonates, infants and very young children aged less than 5 years (age range less than 1 month to 23 years with a mean of 45 months).

Medulloepitheliomas develop in both the supratentorial and infratentorial compartments.[52] The majority are located in the periventricular region and the remaining in the cerebral hemispheres. Isolated examples have been described in the cauda equina, presacral areas, posterior fossa and pons. Outside the CNS, these tumours occur intraorbitally.[55]

Most patients present with symptoms of raised intracranial pressure because the tumour is often large at the time of presentation. On imaging, they are similar to other embryonal tumours.

Histopathology

They are greyish-pink tumours with areas of haemorrhage and necrosis. Medulloepitheliomas have a cytoarchitecture closely resembling that of the embryonic or primitive neural tube. They are characterised by papillary, tubular and trabecular arrangements of the neoplastic pseudostratified neuroepithelium, having a PAS-positive external limiting membrane with the cells resting on a delicate reticulin framework. Mitoses are abundant and tend to be located more on the non-ciliated, reticulin-free luminal surface. Sometimes, multiple lines of differentiation, viz. neuronal, glial and mesenchymal elements can also be identified.

These tumour cells reveal extensive immunoreactivity for nestin, vimentin and microtubule associated protein type 5, similar to cells of the primitive neural tube. Other markers, like NF, CK and EMA, may be found in some cases. Positivity for GFAP and synaptophysin, if present, reflects the cell lineage of differentiation.

Genetics

Molecular genetics of medulloepitheliomas has not been well-characterised. In two cases, hTERT gene amplification has been reported, similar to that seen in MBs.[6]

Outcome and Prognosis

These are rapidly growing tumours and most children die within a year of diagnosis often with CNS dissemination, but rarely with systemic metastasis. Intraorbital medulloepitheliomas, which are different from their CNS counterparts in that they rarely metastasise, are effectively treated by enucleation and generally carry a favourable prognosis.[52]

Ependymoblastoma

These are rare embryonal tumours.

Clinical Features

They generally occur in neonates, infants and very young children aged less than 5 years. Males and females appear to be equally affected.

Ependymoblastomas are predominantly supratentorial and many appear entirely intraparenchymal without any obvious relationship to the ventricular lining, which is in marked contrast to typical ependymomas.

The most common presentation is with features of raised intracranial pressure and hydrocephalus. CT and MRI reveal contrast enhancing large tumours with extensive surrounding oedema.

Histopathology

They are generally well-circumscribed, grey-white tumours. The diagnostic features of ependymoblastomas are dense cellularity with distinctive multi-layered ependymoblastic rosettes or tubules. Unlike typical ependymal rosettes, these are formed by multiple layers of tumour cells, the inner ones often in mitosis. The outer layer of cells of the rosettes merges with the background of undifferentiated neuroectodermal cells. Immunohistochemistry (IHC) reveals positivity for vimentin and sometimes S-100 protein. Scanty GFAP positivity and absence of luminal EMA reactivity differentiate it from typical ependymomas. Unlike other embryonal tumours, ependymoblastomas do not show IHC evidence of neuronal differentiation.

Histogenesis

These tumours are presumed to arise from periventricular neuroepithelial cells.

Prognosis

These tumours grow rapidly with craniospinal dissemination and fatal outcome usually within 6 months to 1 year of diagnosis.[17]

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123 Tumours of Meninges

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MENINGIOMA

Meningiomas are generally slow growing benign tumours accounting for 13–26% of primary intracranial tumours. The tumours arise from the arachnoid cap cells.[41] Classification of the tumours arising from the meninges is given in Table 1.[40]

Primary Melanocytic Lesions

Diffuse melanocytosis, melanocytoma, malignant melanoma, meningeal melanomatosis.

Other Neoplasms Related to the Meninges

Haemangioblastoma.

Age and Gender

Meningiomas are tumours of adults with a peak incidence between 50 years and 60 years. They also occur in children and the elderly. They are twice as common in women as in men.

Site

Meningiomas occur in intracranial, spinal, orbital and ectopic locations (Figs 1A to F). The common intracranial locations include parasagittal, falx, cerebral convexity, olfactory groove, tuberculum sellae, sphenoid ridge, cerebellopontine angle, optic nerve, parasellar region and within the ventricles. Spinal meningiomas are more common in the thoracic region.[36,57]

Clinical Features and Associations

Meningiomas may present as space occupying lesions, with raised intracranial pressure, focal deficits or seizures. They may be incidental and asymptomatic. They can occur in association with neurofibromatosis 2 and may be multiple.

Radiological Features

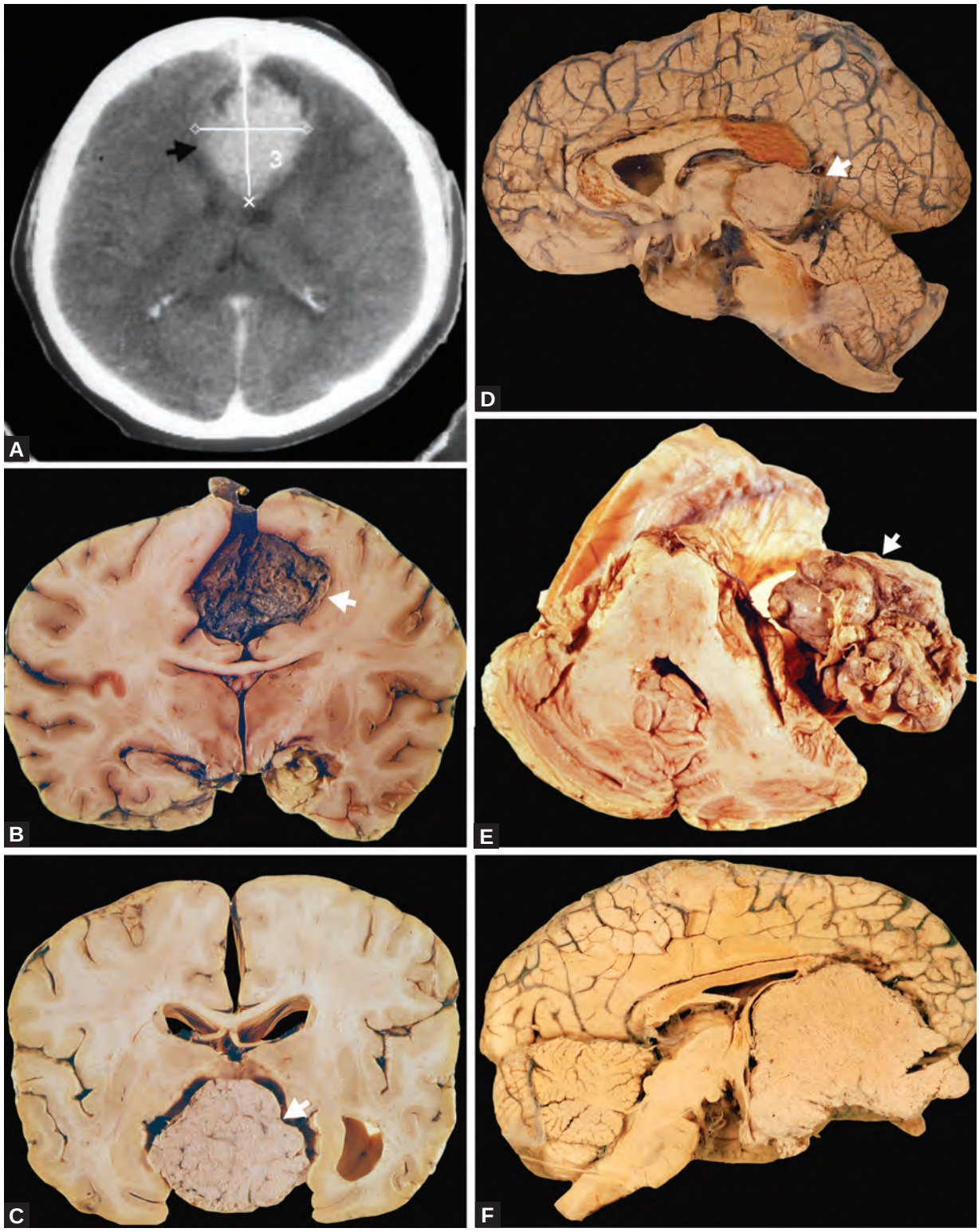
Meningiomas are isointense or hyperintense on the T2-weighted image and enhance with contrast. A short tapered peritumoural extension of contrast material along the inner surface of the tumour due to its attachment to the dura is called dural tail and is a helpful diagnostic feature of meningioma.

Gross Pathology

Meningiomas are lobulated, well demarcated tumours attached to the dura (which may not be obvious in all tumours) (Figs 1A to F). Some tumours are flattened and are called the enplaque variety. The tumours compress the adjacent brain parenchyma and may produce oedema. The peritumoural oedema is related to the size of the tumour, proliferative activity and histological subtype.[43] The overlying bone may show hyperostosis due to the presence of tumour cells in the diploic space. The tumour may infiltrate the dura, sinuses, bone, muscle, orbit, soft tissues and the brain. This infiltration is responsible for local recurrence even after complete resection.

Table 1: Tumours of the meninges (WHO 2007)[2]

Tumours of the meningothelial cells	
Meningioma (Figs 1 to 3)	
Meningothelial	*Metaplastic*
Fibroblastic	Chordoid
Transitional	Clear cell
Psammomatous	Atypical
Angiomatous	Papillary
Microcystic	Rhabdoid
Secretory	Anaplastic (malignant)
Lymphoplasmocytic-rich	
Mesenchymal tumours (Figs 4A and B)	
Lipoma	Chondroma
Angiolipoma	Chondrosarcoma
Hibernoma	Osteoma
Liposarcoma (intracranial)	Osteosarcoma
Solitary fibrous tumour	Osteochondroma
Fibrosarcoma	Haemangioma
Malignant fibrous histiocytoma	Epithelioid haemangioendothelioma
Leiomyoma	Haemangiopericytoma
	Anaplastic haemangiopericytoma
Leiomyosarcoma	Angiosarcoma
Rhabdomyoma	Kaposi's sarcoma
Rhabdomyosarcoma	Ewing's Sarcoma—PNET



Figs 1A to F: (A) Cranial CT scan showing a large uniformly enhancing lesion in anterior falcine region (arrow) with perilesional oedema. (B) Coronal slice of brain shows a large anterior falcine meningioma occupying the interhemispheric fissure compressing the cingulate gyrus and lateral ventricles corresponding to CT scan. (C) Large lobulated meningioma below the third ventricle, distending the ipsilateral temporal horn of lateral ventricle. (D) Sagittal view of brain showing a large meningioma in the pineal region, compressing the pulvinar of thalamus. (E) A large meningioma in the cerebellopontine angle (arrow) arising from free edge of tentorium compressing the pons and cerebellum and distorting the fourth ventricle. (F) A meningioma in the orbitofrontal area arising from the anterior cranial fossa. Patient presented with long standing dementia

Microscopy

Meningiomas exhibit a wide variety of histological diversity. The common histological varieties include meningothelial, fibroblastic and transitional forms. Psammomatous meningioma is more common in the spinal canal. However, they are benign and belong to WHO grade I (Figs 2 and 3).

Meningothelial Meningioma

This is composed of lobules of meningothelial cells with indistinct cytoplasmic margins and intranuclear pseudoinclusions. Cellular whorls and psammoma bodies are uncommon (Fig. 2A).

Fibroblastic Meningioma

This is composed of spindle cells in a fascicular architecture with intercellular collagen. Intranuclear inclusions and psammoma bodies are uncommon but calcification of the stroma is frequent (Fig. 2B).

Transitional Meningioma

This is characterised by cellular whorls usually around a central thin vessel and is intermediate between meningothelial and fibroblastic meningiomas. Psammoma bodies may be seen (Fig. 2C).

Psammomatous Meningioma

This type of meningioma shows extensive whorl formation and calcification along the concentric cellular whorls or central vessel forming numerous calcific psammoma bodies (Fig. 2D). These meningiomas are common in the spinal canal and olfactory groove.

Angiomatous Meningioma

Meningiomas rich in small vascular channels, some densely hyalinised, are called angiomatous meningiomas and they have no prognostic significance (Fig. 2E).

Microcystic Meningioma

This tumour arises from the arachnoidal trabecular cell.[24] The tumours are associated with peritumoural oedema, and large para and intratumoural cysts. Microscopically, there is accumulation of extracellular fluid with interconnecting cell processes. Whorl formation and psammoma bodies are infrequent.

Secretory Meningioma

This meningioma, in addition to a meningothelial and transitional pattern, demonstrates intracytoplasmic single or multiple brightly eosinophilic, periodic acid Schiff (PAS) positive globules which are called 'pseudopsammoma bodies'. Immunohistochemically, these globules are positive for epithelial membrane antigen (EMA), cytokeratin and carcinoembryonic antigen (CEA).[63] Serum or cerebrospinal fluid levels of CEA may also be elevated (Fig. 2F).

Lymphoplasmacyte Rich Meningioma

This type of meningioma is characterised by a dense infiltrate of lymphocytes and plasma cells, sometimes forming lymphoid follicles with germinal centres. This is associated with polyclonal hypergammaglobulinaemia. This lymphoplasmacytic response remits with tumour removal and reappears with recurrence.

Metaplastic Meningioma

These are meningiomas in which bone, cartilage, fat, myxoid tissue or xanthoma cells may be seen.

According to WHO 2007,[41] meningiomas are graded based on certain histological features (Table 2).

Certain histological types, like chordoid, clear cell, papillary and rhabdoid, and a few other histological features are associated with aggressive behaviour.

Clear Cell Meningioma (WHO Grade II)

These tumours have patternless sheets of polygonal cells with clear cytoplasm due to glycogen accumulation labelled by PAS stain (Fig. 2G). The vessels and stroma are hyalinised. Immunohistochemistry shows weak EMA positivity. These tumours, in spite of gross total removal, have aggressive behaviour with multiple recurrences, local spread and spinal metastases.[65]

Atypical Meningioma (WHO Grade II)

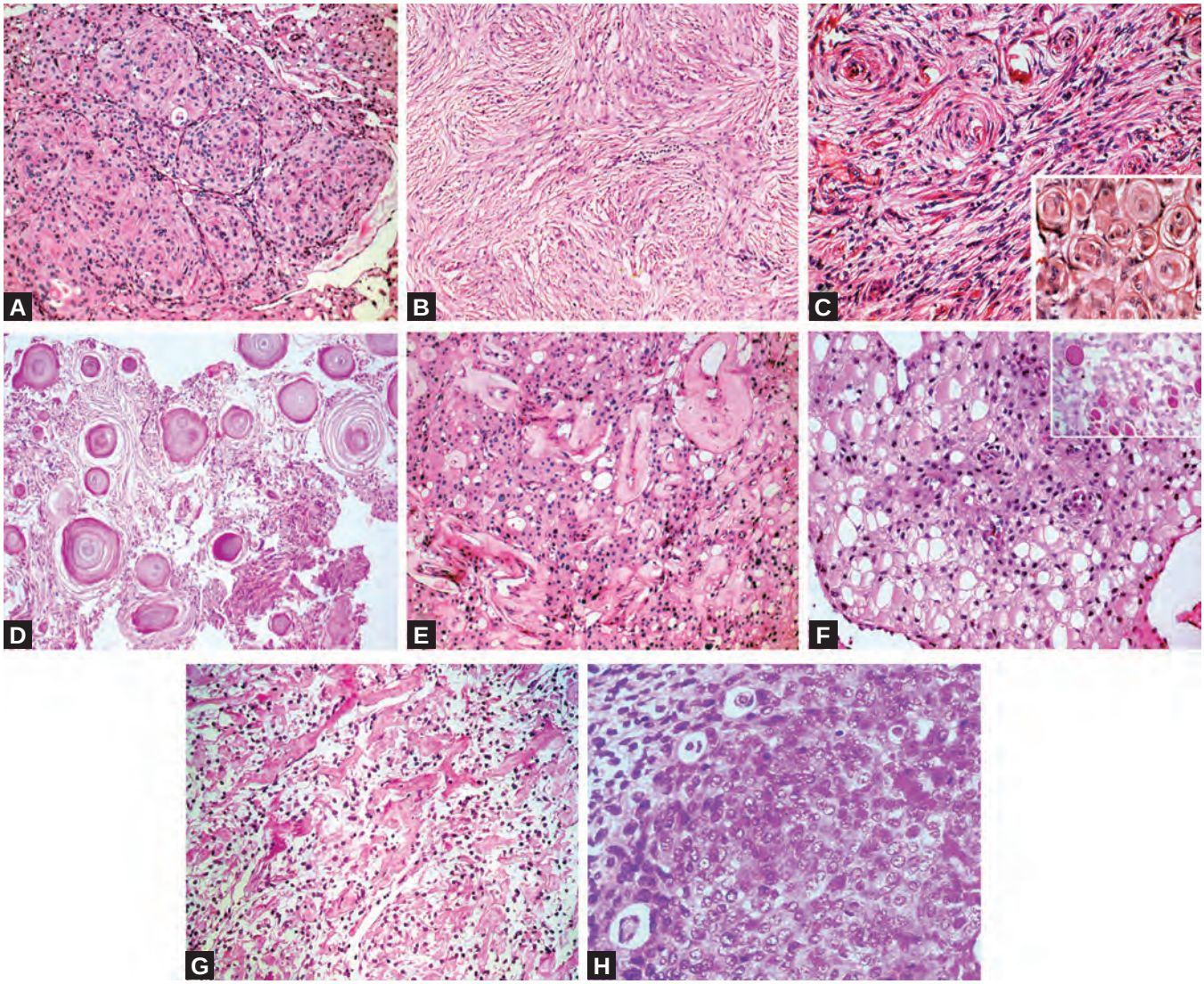
Any histological subtype of meningioma, which fulfils the criteria of WHO Grade II 2007 (Table 3), is associated with a greater chance of recurrence (Fig. 2H). Five-year recurrence rate may be as high as 50%.[43] MIB-1 labelling index is moderately high.

Chordoid Meningioma (WHO Grade II)

These tumours contain trabeculae of vacuolated or eosinophilic cells in a bluish matrix mimicking a chordoma (Fig. 3A). Meningothelial or transitional features may be seen in focal areas. Lymphoplasmacytic infiltrates are common.

Table 2: Histological grading of meningioma (WHO)[1]

Grade	*Criteria*
Grade II (Atypical meningioma)	Mitosis 4 or more/10 high power field or Three of the following five features: 1. high cellularity 2. loss of architectural pattern 3. small cells with high nuclear/cytoplasmic ratio 4. prominent nucleoli 5. necrosis
Grade III (Anaplastic meningioma)	Mitosis more than 20/10 high power field or Features of malignancy of a frank carcinoma or sarcoma or melanoma



Figs 2A to H: (A) Meningothelial meningioma showing lobules of meningothelial cells separated by thin compressed vascular septa (HE x 120). (B) Fibroblastic meningioma with fascicular pattern of spindle-shaped meningothelial cells arranged in interlacing bundles (HE x 120). (C) Transitional meningioma with areas showing fibroblastic morphology with spindled meningothelial cells and transitional zones with whorls. Inset: characteristic meningothelial whorl formation (HE x 200, Inset: HE x 300). (D) Psammomatous meningioma with numerous meningothelial whorls and calcified psammoma bodies (HE x 120). (E) Angiomatous meningioma with large vascular spaces separated by strands of meningothelial cells. Note prominent vascular hyalinisation (HE x 160). (F) Secretory meningioma with sheets of meningothelial cells dispersed in variably vacuolated stroma. Note the scattered eosinophillic hyaline bodies in stroma. Inset: highlights PAS positivity of secretory bodies (HE x 160, Inset: PAS x 200). (G) Clear cell meningioma with meningothelial cells having clear cytoplasm separated by hyalinised vascular channels (WHO Grade II) (HE x 160). (H) Atypical meningioma showing meningothelial cells in patternless sheets. Note cellular pleomorphism, nucleolar prominence and mitotic activity (WHO Grade II) (HE x 320)

Table 3: Aggressive meningiomas: grade, behaviour and histological type[2,4]

Grade	*Behaviour*	*Histological sub-type*
WHO grade II	Greater chance of recurrence	Atypical
WHO grade II (Brain invasive)	Greater chance of recurrence	Chordoid
		Clear cell
		Benign/Atypical
WHO grade III	i. Greater chance of recurrence	Anaplastic
	ii. Locally infiltrating growth	Papillary
	iii. Dissemination to systemic sites	Rhabdoid

Immunohistochemistry shows scant positivity for EMA and S100. These are rarely associated with Castleman's disease and other haematological conditions like iron refractory anaemia and polyclonal gammopathy.[30] Recurrence is nearly 100% after subtotal resection.[13]

Papillary Meningioma (WHO Grade III)

These are rare and tend to occur in children and young adults. They have a perivascular pseudopapillary pattern (Fig. 3B). The tumours exhibit an identifiable meningioma component and a variable papillary component. These tumours invade locally and into the brain parenchyma in 75%, tend to recur in 55% and metastasise in 20% of cases.[49]

Rhabdoid Meningioma (WHO Grade III)

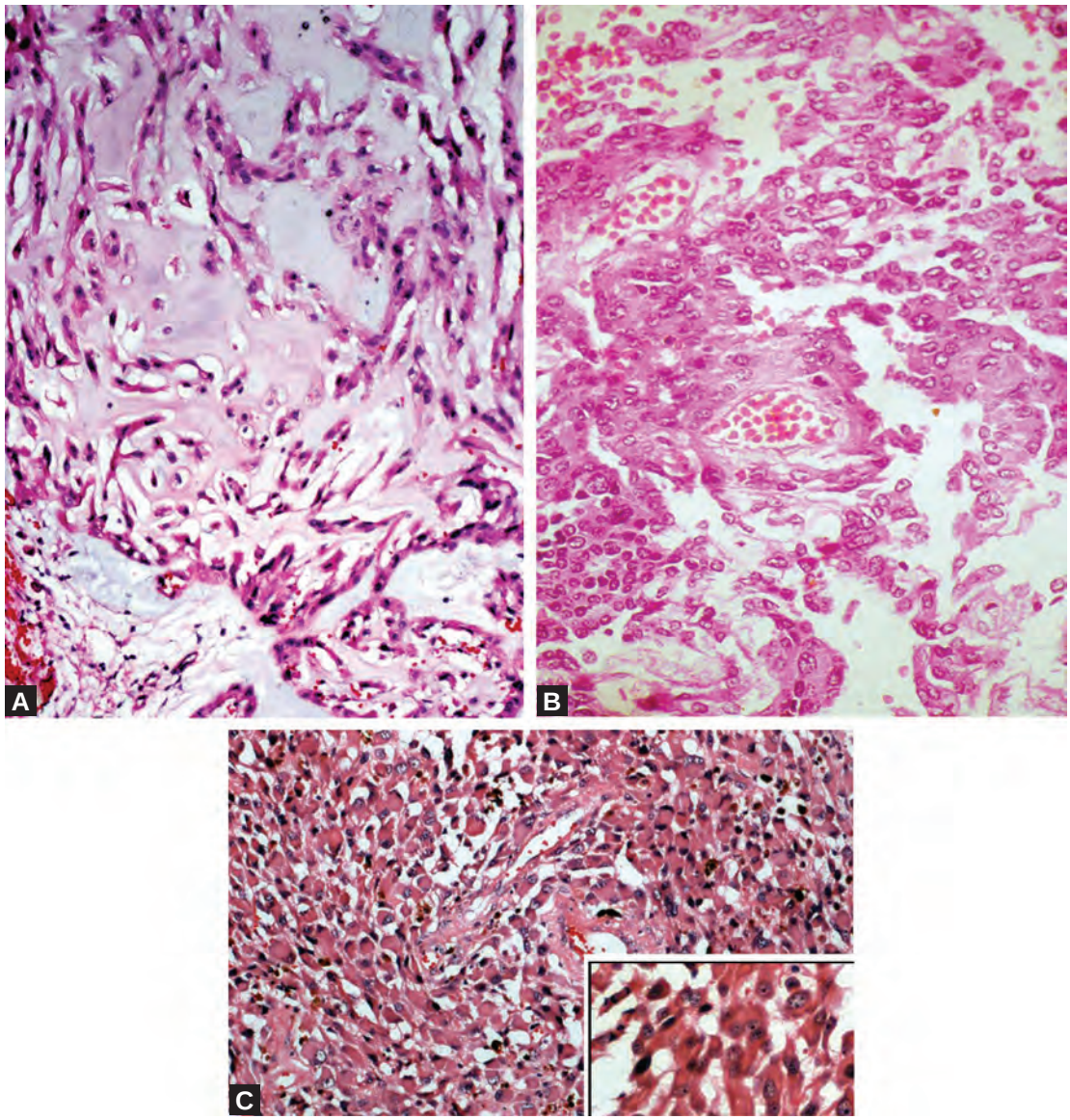
These tumours exhibit characteristic rhabdoid cells in diffuse sheets or focally (Fig. 3C). These rhabdoid cells have eosinophilic cytoplasm with eccentric nuclei and prominent nucleoli. The rhabdoid cells may be absent in the primary tumour and appear in recurrent tumours. MIB-1 index is high and recurrence is frequent.

Anaplastic Meningioma (WHO Grade III)

Meningiomas fulfilling the criteria of WHO 2000 of anaplastic features are usually fatal with a median survival of less than 2 years.[52]

Immunohistochemistry

The majority of meningiomas stain for EMA, but in atypical and anaplastic meningiomas, it is less consistent.



Figs 3A to C: (A) Chordoid meningioma with cords of meningothelial cells in a mucin-rich matrix resembling a chordoma (WHO Grade II) (HE x 200). (B) Papillary meningioma with meningothelial cells lining thick vessels resembling papillary structures (WHO grade III) (HE x 240). (C) Rhabdoid meningioma showing sheets of large tumour cells with characteristic eccentrically placed nuclei and deep eosinophilic cytoplasm as seen in inset (WHO grade III) (H&E x 2400; Inset: HE x 320)

All meningiomas show vimentin positivity. The S-100 protein is variably expressed. Secretory meningiomas are positive for CEA in pseudopsammoma bodies and for cytokeratins in the cells surrounding the pseudopsammoma bodies.[40]

Molecular Genetics

Chromosomal abnormalities have been described associated with the evolution of meningioma by Giemsa staining, fluorescent *in situ* hybridisation (FISH), comparative genomic hybridisation (CGH) and spectral karyotypic techniques.[56] The majority of sporadic and familial meningiomas are associated with abnormalities in chromosome 22. The Neurofibromatosis 2 (NF2) gene, on chromosome 22q12.2, a tumour suppressor gene, is believed to play a central role in the formation of meningiomas, in addition to schwannomas in cases of NF2 (Table 4). Meningioma sub-types show polymorphism in their rates of NF2 gene mutations, i.e. fibroblastic and transitional forms show 70–80% and meningothelial meningiomas 25% mutations.[62] Atypical and anaplastic meningiomas also show NF2 gene mutations in 70%, suggesting that NF2 gene mutations are probably involved with oncogenesis but not tumour progression.[37] The NF2 associated meningiomas are very few compared to sporadic meningiomas and the frequency of loss of heterozygosity (LOH) of chromosome 22 exceeds that of NF2 gene abnormalities. This led to the hypothesis that additional tumour suppressor genes on chromosome 22 are probably important in tumourigenesis in meningiomas. Search for other tumour suppressor genes resulted in the recognition of genes, BAM 22, LARGE, MN1 and INI1 as possible candidates.[38,39] LARGE gene mutations are implicated in recurrence and MN1 in multiple meningiomas.[38,54] Chromosome 1p abnormalities have been implicated in progression of meningiomas to higher grade and recurrence.[31,56] The other cytogenetic abnormalities that are noted in meningiomas include 6q, 7, 9p, 10, 14q, 18q, 19 or 20 chromosomes, but how these abnormalities aid in tumour progression is unknown.[3,4]

Production of vascular endothelial growth factor (VEGF) is associated with peritumoural oedema. Higher grade tumours are associated with a decrease in progesterone receptor staining and an increase in MIB-1 nuclear labelling.[56] Complex cytogenetic and molecular abnormalities including CDKN2A, CDKN2B, CDKN2C and PTEN gene mutations are identified in higher grade meningiomas.[27] Microsatellite instability is also described in meningioma.[55] Multiple meningiomas are clonal in origin and 50% exhibit NF2 gene mutations. Paediatric meningiomas, although rare, show NF2, 1p and 14q deletions and exhibit aggressive behaviour.[50]

Table 4: Genetic mutations, growth factors and association with meningioma tumourigenesis and progression

NF2 gene mutations	Tumour genesis
1p gene mutations	Tumour progression to high grade, recurrence
LARGE gene mutations	Tumour recurrence
MN1 gene mutations	Multiple meningiomas
Production of VEGF	Peritumoural oedema

Note: NF2: neurofibromatosis type 2, VEGF: vascular endothelial growth factor

Proliferation

Meningiomas exhibit increase in proliferative activity from benign to atypical to anaplastic varieties. This can be assessed by mitotic activity. The mean mitotic counts vary widely. The other markers of cell proliferation include nucleolar organiser regions (AgNORs), bromodeoxyuridine (BrdU) incorporation and MIB-1/Ki-67. Labelling indices are most commonly used and they show a highly significant graded increase correlating with progression from benign to atypical to anaplastic tumours.[14] The proliferation markers also show an increase in recurrent tumours. Table 5 depicts the increase in labelling index of different proliferation markers in meningiomas. Diploidy is more common in meningiomas, but the proportion of aneuploidy is higher in atypical and malignant meningiomas than in benign meningiomas. The proliferation index is high in aneuploidy than in diploidy.[47]

Recurrent Meningiomas

Although the majority of meningiomas are benign, recurrence after gross total resection still remains a problem. Risk stratification based on histological features alone has limitations. Various studies showed several parameters associated with recurrence. Extent of surgical resection, grade and sub-type of tumour, MIB-1/Ki-67 labelling index and loss of short arm of chromosome 1 (1p-) by *in situ* hybridisation are important parameters singly or in combination in predicting recurrence.[1,32] According to Maes et al.,[42] human telomerase catalytic subunit (hTERT) expression is a better predictor of recurrence in meningiomas than Ki67 labelling index.

Hormone Receptors

Meningiomas exhibit enhanced growth rate during reproductive life correlating with elevated sex hormone levels. There is an association with carcinoma of the breast also. Nearly 84% of meningiomas express progesterone receptors and it is influenced by histological grade, type and site.[9] Progesterone receptor levels are low in convexity, fibrous and atypical meningiomas and also associated with peritumoural swelling.[6,8] Lack of progesterone receptors is associated with large tumour size, atypia and anaplasia.[32] Androgen receptors reside in the nuclei suggesting a role for activating gene expression.[11]

Treatment and Prognosis

Surgery is the primary therapy. The extent of surgery affects the recurrence. Tumours in the cerebral

Table 5: Factors associated with recurrence of meningioma

I.	Extent of surgical resection:	
	a. Skull base	
	b. Parasagittal	
II.	Histological subtype	Chordoid, Clear cell, Papillary, Rhabdoid meningiomas
III.	Grade of tumour	Atypical, Anaplastic meningiomas
IV.	Invasion into adjacent structures	Muscle, dura, bone, brain
V.	Others	MIB-1 LI, ↓progesterone receptors, loss of expression of alkaline phosphatase receptors, loss of 1p gene, LARGE gene mutations

convexity and spinal canal can completely be resected, but tumours of the skull base, orbit and enplaque variety pose problems and hence recurrences are common. Five-year recurrence rate after gross total resection of benign meningiomas is 7–20%, for atypical meningiomas it is 29–40% and for anaplastic meningiomas it is 50–78%.[52,53] Factors associated with lung metastases include prior craniotomy, venous sinus invasion, local recurrences, histological malignancy and papillary morphlogy.[2]

HAEMANGIOPERICYTOMA

Definition and Grading

Haemangiopericytoma (HPC) of the central nervous system is a highly cellular and richly vascular neoplasm, histologically indistinguishable from its soft tissue counterpart. They correspond histologically to WHO Grade II, the anaplastic variant corresponding to Grade III neoplasms. However, the histological criteria for grading are not clearly established.

Incidence

These represent about 0.4% of primary brain tumours.[25] The ratio of meningeal HPC to other forms of meningiomas reported in the literature has ranged from 1:40 to 1:60.[21]

Age and Gender

Meningeal HPC are tumours of adults (mean age 43 years) and are more common in males (M:F = 1.4:1).[21]

Location

The majority are dural based and supratentorial with only occasional reports of an intraparenchymal location.[21,26] Multifocality has not been reported. Clinical and neuroimaging features that help in differentiating HPC from meningiomas are presented in Table 6.

Gross and Microscopic Features

Grossly these are lobulated, firm, well demarcated tumours with a fleshy, greyish to red brown cut surface. Microscopically, these are highly cellular tumours comprised of spindle shaped cells arranged around thin walled vascular spaces (Fig. 4). These vascular spaces have characteristic "staghorn" configuration (Fig. 4A). The degree of mitosis is variable.[46] These tumours lack cellular whorls, nuclear pseudoinclusions and psammoma bodies unlike those noted in meningiomas. These tumours are reticulin rich and have reticulin fibres enveloping individual cells (Fig. 4B).

Immunohistochemistry

The tumours are diffusely positive for vimentin, negative for EMA and express CD34 (Fig. 4A, Inset) in one third of the cases.[51]

Genetic Susceptibility, Cytogenetics and Molecular Genetics

There is no evidence of familial clustering in HPCs. Chromosomal rearrangements of 12q13 (common in HPCs), 19q13, 6p21 and 7p15 have been reported in HPCs.[44] NF2 gene mutations have not been reported in HPC.[29]

Treatment and Prognosis

These tumours are usually treated with surgery followed by local irradiation to the tumour bed. Haemangiopericytomas have a high recurrence rate (65%, 76% and 87% at 5-, 10- and 15-years, respectively). Another unique feature of HPC is their tendency to metastasise to extracranial sites like lung, liver and bone.[21] Histological features predictive of decreased survival include increased mitotic rate (≥ 5/10 HPF), high cellularity, nuclear pleomorphism, haemorrhage and necrosis.[46] These lesions correspond to WHO Grade III.

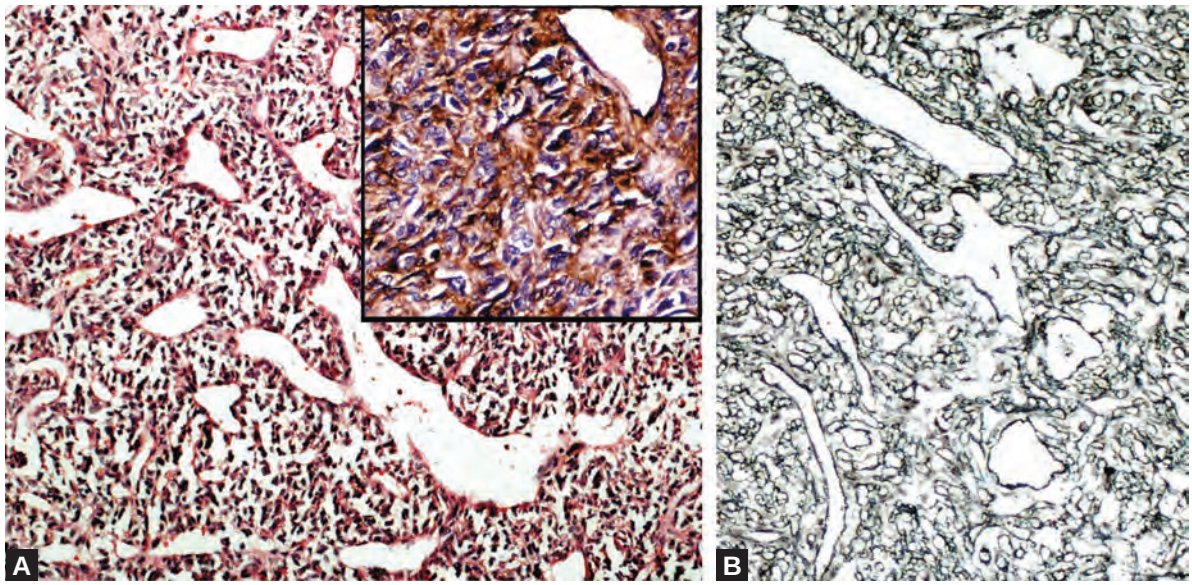
SOLITARY FIBROUS TUMOUR

Solitary fibrous tumour (SFT) is a rare tumour of the meninges, which is pathologically identical to similar tumours occurring in the pleura and other extrapleural sites. These tumours resemble meningiomas in terms of their age of occurrence and female predominance,[10] and can involve both the cranial and spinal meninges. The imaging features resemble those of meningioma.[10]

Grossly, these are firm, grey-white and circumscribed tumours. The size of the tumours ranges from 1 to 7 cm in the reported series.[28] Microscopically, the majority of the tumours show moderate cellularity with spindle cells arranged in fascicles between dense bands of collagen. There may be areas showing increased cellularity and reduced collagen as well as foci with a vascular pattern reminiscent of haemangiopericytoma. These tumours lack whorls, nuclear pseudoinclusions and psammoma

Table 6: Differences between meningioma, haemangiopericytoma and solitary fibrous tumour

	Meningioma	*HPC*	*SFT*
Incidence	13–20% of primary CNS tumours	0–4% of primary CNS tumours	Rare
Age in years	Peak incidence: 60–80 years	43 years (mean age)	57 years (mean age)
Male:Female	1:2	1.4:1	2:5
Location	Cranial-cerebral convexity, especially parasagittal spinal (11–12%)—mostly thoracic Intraventricular——most often lateral ventricle Multifocal tumours—16%	Cranial—most often involves tentorium and subtentorial space; 1/5th in posterior fossa Spinal—8% Multifocal tumours—not recorded	Falx, occipital and spinal dura, tentorium, and cerebellopontine angle Multifocal tumours—not recorded
Clinical features	Signs and symptoms referable to location and compression of adjacent structures	Indistinguishable from meningioma, but relatively shorter duration of symptoms	Indistinguishable from meningioma
Neuroimaging	Well demarcated dural based lesion Broad based dural attachment Dural tail sign adjacent to main mass Hyperostosis of adjacent bone Calcification	May resemble meningioma Narrow based dural attachment—more frequent Dural tail sign—50% Hyperostosis of adjacent bone—absent Calcification—absent Prominent vascular flow voids on MRI Angiography—cork-screw like vessels	May resemble meningiomas Hyperostosis—occasionally
Microscopic features	Wide range of histopathological appearance Fibrous type needs differentiation from HPC and SFT Lacks 'staghorn, vascular pattern of HPC Whorls, psammoma bodies and intranuclear inclusions seen Reticulin—Scarce, segregates tumour into lobules	Characteristic 'staghorn' branching vascular pattern Whorls, psammoma bodies and intranuclear inclusions—absent Reticulin—rich, envelope individual cells	Variable cellularity with intervening collagen bands Staghorn vessels—may be present in some Collagen sheathed vessels Whorls, psammoma bodies and intranuclear inclusions—absent
IHC	Vimentin—positive EMA—positive S-100—positive (80%) CD 34—positive (60%) Factor XIIA—positive (65%)	Vimentin—positive EMA—negative S-100—negative CD 34—positive (33%) Factor XIIA—positive (78%)	Vimentin—positive EMA—negative S-100—negative CD 34—positive (80–90%) Factor XIIA—positive (100%)
Genetic susceptibility, cytogenetics and molecular genetics	Familial clustering—present Association with NF2 NF2 gene mutation—60% of sporadic meningiomas del 22—most consistent abnormality	No evidence of familial clustering Rearrangements of 12q13 (common in HPCs), 19q13, 6p21 and 7p15 NF2 gene mutations—not reported	-
Recurrence and Metastasis	Recurrence rate: Benign meningiomas—7–20% Atypical meningiomas—29–40% Anaplastic meningiomas—50–78% Extracranial metastasis—extremely uncommon	Recurrence rate: 65% at 5 years 76% at 10 years Extracranial metastasis—64–68% at 15 years (bone, lungs and liver)	Recurrence rare



Figs 4A and B: (A) Haemangiopericytoma showing characteristic branching vascular pattern with intervening plump spindle cells (H&E x 120) Inset: Tumours cells showing CD34 positivity (Immunoperoxidase x 320). (B) Reticulin stain highlighting the vascular pattern and showing reticulin fibres enveloping individual tumour cells (Reticulin silver stain x 120)

bodies. Mitoses are sparse. Immunohistochemically these tumours show diffuse positivity for CD34 and are negative for EMA and S-100.[10,28]

HAEMANGIOPERICYTOMA AND SOLITARY FIBROUS TUMOUR—CURRENT CONCEPT

Stout and Murray[59] are credited with the first description of HPC, which they presumed to be a neoplasm comprised of pericytes exhibiting a characteristic well-developed 'staghorn' vascular pattern. Over the years it has been realised that the morphological features of HPC were not specific and can be seen in many benign and malignant soft tissue lesions. The literature review revealed that only about 30% of HPCs showed ultrastructural features and 10–20% immunohistochemical features of pericytic differentiation,[5,15] thus questioning the fundamentals on which this entity came into existence.

On the other hand, SFT was first described as a pleural based lesion of submesothelial origin.[33] Soon it was realised that SFT could also occur in extrapleural sites including soft tissues and visceral organs. Solitary fibrous tumours show a morphological spectrum ranging from fibrous to cellular forms, the latter being virtually indistinguishable from haemangiopericytoma. Hence, it is now suggested that HPC should be recognised as a cellular variant of SFT.[18]

Even in case of meningeal HPC, which is traditionally considered as a distinct entity, there is evidence that it belongs to the spectrum of SFT, representing its cellular variant. Based on their comparative study on fibrous meningioma, HPC and SFT, Perry et al.[51] concluded that in some cases it was impossible to make a distinction between SFT and HPC, morphologically and/or immunohistochemically. Tihan et al.[61] in their comparative study of SFT and conventional HPC of CNS, observed that two lesions which were initially diagnosed as conventional meningeal HPC recurred as SFT-like neoplasm, a finding that further supports the unifying concept. The current concept is that HPCs represent a cellular variant of SFT and not a distinct entity, at least in soft tissue locations and the same may hold true for CNS lesions as well.

In a seven-year study (2000–2006) at Nizam's Institute of Medical Sciences, Hyderabad, 571 meningiomas were diagnosed of which 538 (94.2%) were grade I, 24 (4.2%) were Grade II and 9 (1.6%) were grade III meningeal tumours. Atypical meningiomas were 19 (3.2%), clear cell 2 (0.4%), chordoid 3 (0.5%), rhabdoid 4 (0.7%) and papillary 1 (0.2%). The Ki-67 labelling index (LI) in grade I was 2.58 ± 2.61%, in grade II 9.7 ± 4.59% and in grade III 22.3 ± 9.8%. Brain infiltration was noted in 30 cases and Ki-67 LI was 4.71% in them. There were 22 recurrent meningiomas and Ki-67 LI was 5.04% in them. During the same period 14 haemangiopericytomas were diagnosed, of which 11 were grade II and 3 were grade III. The mean KI-67 LI in grade II tumours was 4% and that for grade III tumours was 8.5%.

HAEMANGIOBLASTOMA

Haemangioblastomas are WHO grade I tumours of uncertain histogenesis. They constitute 1.3% of intracranial neoplasms and 7.3% of posterior fossa neoplasms.[48] They occur both as sporadic tumours and in association with the inherited syndrome of Von Hippel Lindau (VHL) disease. Haemangioblastoma is a cardinal feature of VHL disease and about 30–40% of all cerebellar haemangioblastomas are associated with VHL disease.[52]

Location

Sporadic haemangioblastomas occur predominantly in the cerebellum but VHL associated tumours occur in brainstem and spinal cord. Supratentorial location is rare. They may be single or multiple, the latter often in association with VHL disease.

Age and Gender

The sporadic tumours have a peak incidence between 35 years and 45 years and VHL associated tumours occur earlier (mean age of 29 years).[12] There is no gender predilection.

Clinical Manifestations

Haemangioblastomas are slow growing tumours and present with symptoms of raised intracranial pressure. The tumours produce erythropoietins and hence cause secondary polycythaemia.

Neuroimaging

Magnetic resonance imaging (MRI) is the investigation of choice which has replaced CT and angiography. Various morphological patterns are described on MRI and CT. For example, (i) pure cystic, (ii) cyst with mural module, (iii) cyst with wall enhancement, (iv) solid and cystic areas and (vi) solid.[23]

Pathogenesis

Stromal cells, the neoplastic component of the lesion express high levels of hypoxia inducible transcription factors (HIF)-1 and HIF-2.[17] Normally, HIF-1 and HIF-2 are degraded by several enzymes, transcription factors and proteosomal complexes including VHL protein and pVHL.[34,45] Stromal cells also express receptors for growth factors like epidermal growth factor, transforming growth factor alpha, vascular endothelial growth factor (VEGF) and platelet derived growth factors (PDGF).[17,35] Inactivated pVHL due to a mutated gene or other factors lead to accumulation of HIF-1 and HIF-2 in stromal cells which in turn lead to upregulation of vascular endothelial growth factor and erythropoietin at transcriptional level.[35] This explains the elevated erythrocytosis and also the formation of vascular and cystic components of haemangioblastomas. Inactivation of the VHL tumour suppressor protein and subsequent loss of function in the VHL and Elongin BC Complex results in dysfunction in the ubiquitinisation of HIF which is an important step in the development of haemangioblastoma.[58] The stromal cell protein expression is characteristic and it has been shown that it is similar to the embryonic progenitor cells with haemangioblastic differentiation.[19] These studies suggest that a variety of autocrine loops may be initiated depending on the activation of HIF and the presence of protein in the stromal cells in different topographical regions of the CNS.[19]

Gross Pathology

Haemangioblastoma is a circumscribed mass but unencapsulated (Fig. 5A). It is reddish in colour due to its vascularity and sometimes yellow due to the lipid content in the stromal cells. It may be solid, cystic or partly solid and partly cystic (Fig. 5B).

Microscopy

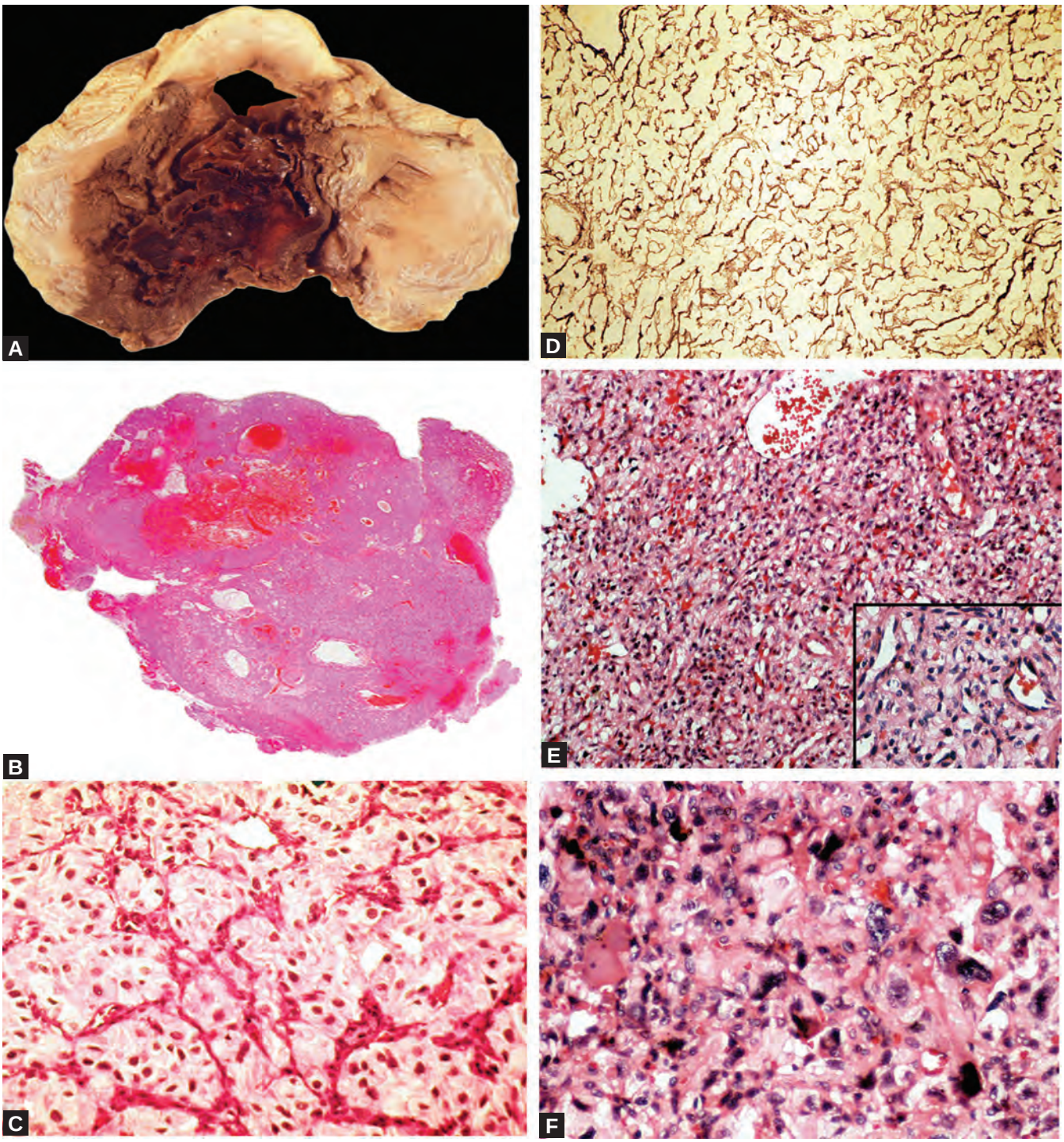
The tumour is composed of two components: The capillary sized blood vessels and the stromal cells. The stromal cells are the neoplastic component (Figs 5B to F). Based on the pattern of arrangement of stromal cells and capillary sized vessels, two patterns in the tumour are described—reticular and cellular patterns. When stromal cells are evenly distributed between capillary blood vessels it is called reticular pattern (Figs 5C and D) and when there are sheets of stromal cells with random vascular changes, it is called cellular pattern (Figs 5E and F).[22] The stromal cells have abundant cytoplasm with variable amounts of lipid and glycogen. The nuclei may show pleomorphism but mitosis is not a feature. The blood vessels are usually thin walled but sometimes thick walled vessels may be seen. Haemorrhages, haemosiderin laden macrophages, hyalinisation and microcyst formation may be seen. Reactive astrocytes with Rosenthal fibres at the periphery of the tumour may be seen. Infiltration into adjacent cerebellar tissue is rarely noted. Necrosis and calcifications are usually absent. Reticulin fibres are seen around blood vessels and groups of stromal cells. Stromal cells stain positive with oil red O reflecting the lipid content. The clear cell appearance of stromal cells may lead to a diagnostic problem mimicking metastatic renal cell carcinoma.

Ultrastructurally, the stromal cells contain electron-lucent cytoplasm containing lipid droplets and bundles of delicate filaments. Electron-dense bodies reminiscent of Weibel-Palade bodies of endothelial cells are also described in the stromal cells in some studies.[64]

Immunohistochemically, the stromal cells lack endothelial cell markers (von Willibrand factor and CD34) and endothelium associated adhesion molecule (CD31). Stromal cells express neuron specific enolase (NSE) and the neural cell adhesion molecule transthyretin. Vimentin is expressed and glial fibrillary acidic protein (GFAP) is not expressed by the stromal cells.[7,64] The stromal cells have no consistent antigen expression profile. The Ki-67 labelling index is less than 1%.

Prognosis

The outcome following surgical resection is favourable for sporadic tumours compared to VHL associated tumours. Mortality is low and permanent neurological deficits are extremely rare with improved microsurgical techniques in sporadic haemangioblastomas. In cases of VHL associated haemangioblastoma, haemorrhage is the most common cause of death. The histological sub-type



Figs 5A to F: (A) Horizontal sections through pons and cerebellum show a large cystic haemorrhagic lesion occupying the cerebellar vermis. The lesion shows sharp circumscription from surrounding parenchyma with brownish discolouration. The fourth ventricle is dilated. (B) Whole mount section through the cerebellar lesion shows a highly vascular lesion with foci of haemorrhage and focal cystic change (HE x 12). (C) High magnification highlights tightly packed stromal cells forming lobules and compressing the thin vascular channels (HE x 360). (D) Reticulin stain highlights rich reticulin framework and high vascularity of the tumour (Reticulin silver x 120). (E) Haemangioblastoma (cellular variant) with densely packed tumour cells and rich capillary network (HE x 120). Inset: Stromal cells showing foamy vacuolated cytoplasm (HE x 300). (F) Haemangioblastoma with stromal cells showing nuclear atypia and hyperchromasia. This feature is not indicative of malignancy (HE x 420)

of cellular variant is associated with more chances of recurrence.[62] Recurrence is common when it occurs in young age, associated with VHL syndrome and in multicentric tumours.[16] Solid tumours with less cystic spaces and tumours with lower proportion of lipid laden cells have higher chances of recurrence.[16,60] Risk of spontaneous haemorrhage is extremely low in haemangioblastoma of size smaller than 1.5 cm.[20] In VHL associated haemangioblastomas, neuroradiologic screening and lifelong follow-up are necessary for identification of new lesions before they become symptomatic.[12]

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124 Pituitary Tumours, Sellar and Suprasellar Lesions

Geeta Chacko

INTRODUCTION

The sella turcica in which the pituitary gland is housed is an intricate assembly of anatomical structures representing elements of neural, endocrine, vascular, osseous and meningeal tissues being in close proximity to the cavernous sinus, hypothalamus, and major blood vessels, nerves, bone and connective tissue. Lesions in the sellar region are, therefore, remarkably diverse, originating from varied tissues in the region (Table 1).

PITUITARY ADENOMA[8,55]

Pituitary adenomas are benign tumours that comprise 10% of all intracranial neoplasms and are a preventable cause of blindness. It is the most common neoplasm of the sellar region and may even be detected incidentally as frequently as 5–20%. They are derived from adenohypophyseal cells, are most often confined to the sella turcica, grow slowly, enlarge by expansion and are demarcated from the normal pituitary tissue by a pseudocapsule.[5] Pituitary adenomas can be a part of the multiple endocrine neoplasia syndromes. These tumours are monoclonal proliferations related to defects in oncogenes and tumour suppressor genes.[26]

Clinical features are related to mass effect and include visual symptoms, headache and hypopituitarism. In the case of secretory adenomas, the symptoms are related to the hormone secreted. Growth hormone (GH) excess is associated with acromegaly or gigantism; overproduction of prolactin (PRL) is associated with amenorrhoea, galactorrhoea, infertility, hypogonadism, decreased libido and impotence; increased secretion of adrenocorticotropic hormone (ACTH) causes Cushing's disease; follicle stimulating hormone (FSH) and luteinizing hormone (LH) oversecretion leads to hypogonadism or are clinically silent and hypersecretion of thyrotropin (TSH) leads to hyperthyroidism.

Radiographic Features

One sees a well defined tumour in the adenohypophyseal region (Fig. 1A).

Gross

The tumour is a well circumscribed brown-coloured mass in the sellar-suprasellar region (Fig. 1B).

Microscopic Features

The tumour is composed of sheets of monomorphic cells with uniform round to oval nuclei, evenly dispersed chromatin and moderate amounts of cytoplasm (Fig. 1C). The tinctorial properties of the latter vary from acidophilic to amphophilic or even basophilic. Cells within the same tumour have similar tinctorial properties, unless plurihormonal. A delicate capillary network traverses the tumour. A pseudorosette arrangement is seen if a papillary pattern is present.

Differential Diagnosis

Normal Adenohypophysis

A monomorphous population of cells is seen in adenomas, whereas the normal adenohypophysis has a mixture of cell types with different tinctorial properties (Fig. 1D). The acinar pattern of the normal adenohypophysis is disrupted in adenomas, which is best appreciated on a reticulin stain (Figs 1E and F).

Metastatic Carcinoma

These usually have brisk mitotic activity and show epithelial features with prominence of nucleoli.

Intra-operative diagnosis is rarely requested for the straight forward adenomas. In certain circumstances when the dura appears firm or abnormal, an intra-operative consult is sent to exclude other pathologies. It is imperative that the specimen be sent rapidly and preferably on moistened gelfoam or a smooth surfaced material so as to avoid drying. Gauze is not advised as the tissue tends to get impregnated into it and is difficult to remove.

Pituitary adenomas smear easily and hence, this method, smear or squash preparation of rapid processing, are preferred to frozen sections. Adenomas form cellular smears of uniform monomorphic cells. Differentiation from normal gland requires a reticulin stain and this is not optimal in an intra-operative setting. Hence, in the case of a microadenoma (such as in ACTH secreting tumours when the surgeon wishes to determine whether the entire tumour has been removed) it is preferable that all material be submitted for routine processing, so that, serial sections can be examined with both hematoxylin and eosin, as well as reticulin stains to detect the microadenoma.

Table 1: Lesions of the sella turcica

I. Neoplastic lesions of the sella turcica[1]	
Sellar, suprasellar region:	
Pituitary adenomas	Craniopharyngioma
Germ cell tumours	Spindle cell oncocytoma
Infundibulum and neurohypophysis:	
Granular cell tumour	Pituicytoma
Optic chiasm and hypothalamus:	
Astrocytoma	Ependymoma
Gangliocytoma	Ganglioglioma
Ganglioneuroma	
Bone and connective tissue:	
Post-irradiation sarcoma	Chordoma
Haemangiopericytoma	Chondroma
Chondrosarcoma	Fibroma
Fibrosarcoma	Lipoma
Plasmacytoma	Giant cell tumour of bone
Schwannoma	Paraganglioma
Vascular:	
Haemangioma	Glomangioma
Haemangioblastoma	Haemangiopericytoma
Olfactory groove:	
Meningioma	
Miscellaneous:	
Lymphoma[2]	Langerhan's cell histiocytosis
Leukaemia	Melanoma[3]
Metastatic tumours	
II. Non-neoplastic lesions of the sella turcica	
Sellar, suprasellar region:	
Pituitary hyperplasia	Rathke's pouch cyst
Empty sellar syndrome	Giant cell granuloma
Lymphocytic hypophysitis	Granulomatous hypophysitis
Xanthogranuloma	Rosai-Dorfman disease
Erdheim-Chester disease	Xanthoma disseminatum
Epidermal cyst	Dermoid cyst
Sarcoidosis[4]	Abscess[5, 6]
Tuberculosis[7]	Mucocoele
Infundibulum, neurohypophysis, optic chiasm and hypothalamus:	
Hamartoma	
Bone and connective tissue:	
Fibrous dysplasia	Cholesteatoma
Vascular:	
Aneurysms	
Miscellaneous:	
Malformative tumours and cysts	

ADENOMAS OF SPECIFIC CELL TYPE[21]

It is now generally accepted that light microscopic examination of pituitary adenomas based on staining characteristics of different secretory granules (chromophobe, acidophil and basophil) is inadequate to assess the clinical and endocrine status of the patients. Ultrastructural study of these tumours has led to a better understanding of their nature, but it cannot be fully relied upon particularly with respect to their secretory function. Although the size of the secretory granules gives a good indication of the nature of the hormone in a normal pituitary gland, in neoplastic conditions the size of the granules varies so widely that it has limited diagnostic value. Further, no adenoma including the clinically and biochemically inert null cell adenomas are agranular on ultrastructure.

Localisation of hormones in pituitary adenomas can be done quite accurately with immunohistochemistry and in conjunction with estimation of serum hormones, the functional status of pituitary adenomas can be better assessed. Hence, for a full evaluation of the endocrine status of pituitary adenomas, it is considered necessary to use a combination of currently available techniques such as light microscopy, electron microscopy, immunohistochemistry, and serum hormone analysis. This approach has led to a better understanding of the biological behaviour of pituitary adenomas including their clinicopathological correlation. Further, based on histological, immunohistochemical and ultrastructural studies of a large number of pituitary tumours, a new World Health Organisation (WHO) classification has been introduced. Tables 2 and 3 summarise the current WHO classification of pituitary adenomas along with their clinicopathological, immunohistochemical and ultrastructural features.

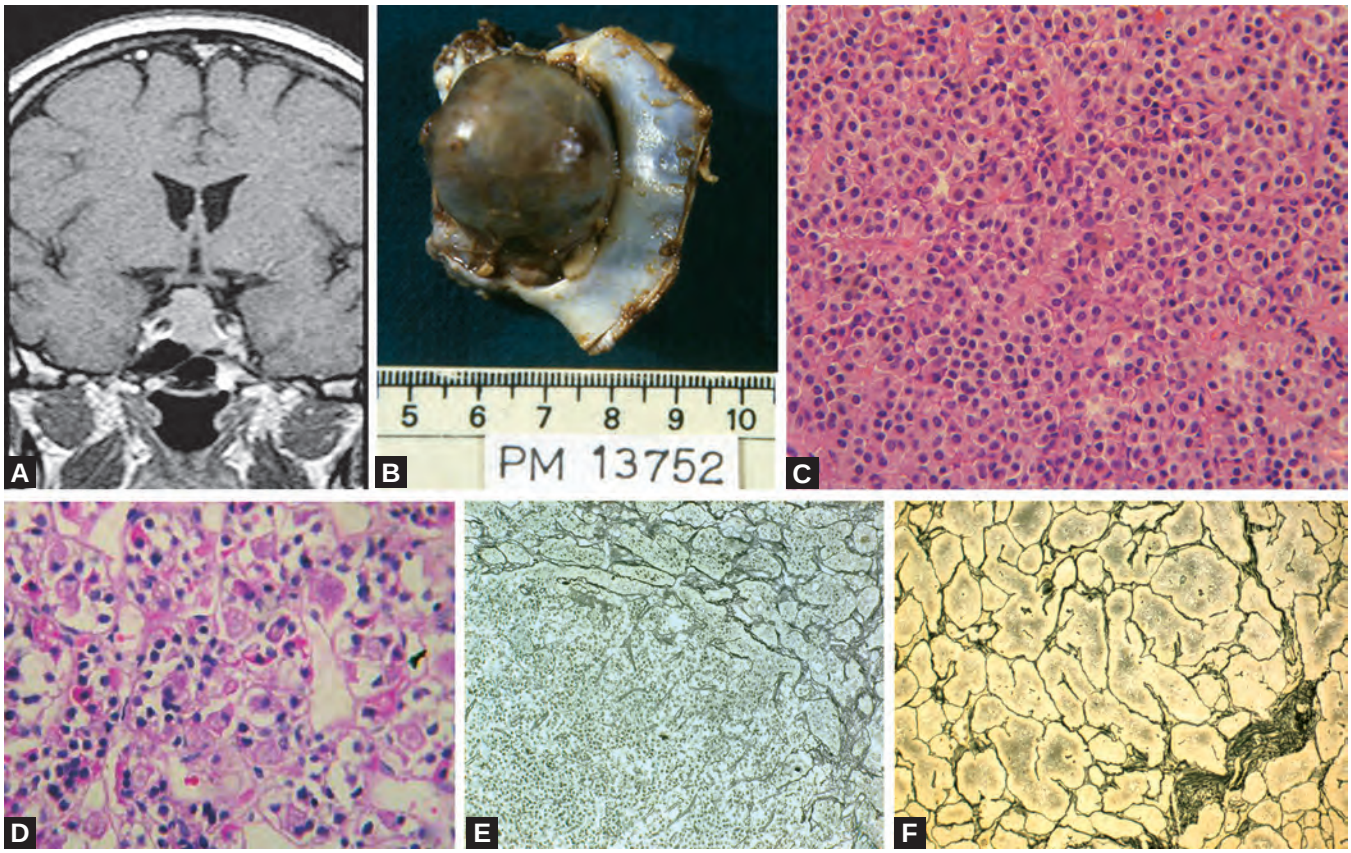
The salient features that are special to the different subtypes are discussed below.

Growth Hormone Cell Adenoma

GH tumours constitute 15–20% of pituitary adenomas. These tumours are often plurihormonal and show secondary immunoreactivity for PRL, alpha-subunit (α-SU), TSH, FSH and LH. Cytokeratin paranuclear dot-like positivity is seen in the sparsely granulated variant and corresponds ultrastructurally to paranuclear intermediate filament known as "fibrous bodies" (Figs 2A and B).[22]

The sparsely granulated variants are clinically aggressive. Growth hormone-releasing hormone (GRH) overexpression correlates with the level of GH as well as the aggressiveness of the tumour.[49]

The GH excess due to adenomas is not restricted to the sparsely and densely granulated variants of GH adenomas, but as described below, is also seen with mixed GH-PRL, mammosomatotrophic and acidophil stem cell adenoma, as well as with plurihormonal adenomas.



Figs 1A to F: (A) Magnetic resonance imaging of pituitary adenoma showing well defined tumour in the sella. (B) Large well circumscribed sellar-suprasellar macroadenoma. (C) Pituitary adenoma: sheets of monomorphic cells with uniform round to oval nuclei, evenly dispersed chromatin and moderate amounts of cytoplasm (H&E X 400). (D) Normal adenohypophysis—cells have varied tinctorial properties (H&E X 400). (E) Disrupted reticulin in the adenoma compared to retained reticulin in adjacent compressed normal pituitary (Gordon Sweet's Reticulin Stain X 90). (F) Normal acinar pattern of adenohypophysis highlighted by reticulin (Gordon Sweet's Reticulin Stain X 200)

Prolactin Cell Adenoma (Prolactinoma)

The frequency with which this tumour is seen by pathologists is on the decline as medical therapy with dopamine agonists is effective in the vast majority of cases obviating the need for surgery.

These tumours are seen in the reproductive age group. There is a female predominance, with females in the reproductive age group presenting with amenorrhoea and galactorrhoea, while they are functionally silent in post-menopausal women and in men.

Other causes of hyperprolactinaemia such as primary hypothyroidism and antipsychotic drug use need to be ruled out. Hyperprolactinaemia due to stalk effect needs to be recognised as distinct from that due to an adenoma. The latter usually results in biochemical values greater than 150 ng/ml.

Psammomatous calcification and amyloid deposition are features that are peculiar to prolactinomas. Immunoreactivity corresponds to the Golgi zone with secondary immunoreactivity for α-SU. Prolactinomas have abundant rough endoplasmic reticulum and the presence of "misplaced exocytosis", which is the presence of secretory granules between neoplastic cells (Fig. 2C). These tumours can be aggressive in both males and females in the post-reproductive age group.

Morphology after medical treatment: The dopamine agonist, bromocriptine, has a dramatic effect on the histology and ultrastructural features of prolactinomas with cells undergoing atrophy. There is significant stromal fibrosis (Fig. 2D). The changes are reversible and cessation of therapy results in regrowth of the adenoma.

Adenomas Producing Growth Hormone and Prolactin[36]

There are three principal subtypes of adenomas producing both GH and PRL

Mixed Growth Hormone Cell-Prolactin Cell Adenoma

These are rare indolent neoplasms that manifest with acromegaly and have serum PRL elevation. The bimorphous nature is evident on ultrastructure (Fig. 2E).

Table 2: WHO classification of pituitary adenomas: clinical and pathological characteristics

WHO classification–adenoma type	*Incidence*	*Clinical features*	*Staining characteristics*	*Hormone (localised by immunohistochemistry in tumour cells)*
Lactotropic adenomas:				
Sparsely granulated	25%	Amenorrhoea and/or galactorrhoea	C	Prolactin (PRL)
Densely granulated	1%	in females/impotence/non-functional Amenorrhoea and/or galactorrhoea in females/impotence	A	PRL
Somatotropic adenomas:				
Sparsely granulated	5%	Acromegaly or gigantism	C/A	Growth hormone (GH)
Densely granulated	5%	Acromegaly or gigantism	A	GH
Adenomas with combined lactotropic and somatotropic features	5%	Acromegaly or gigantism ±	A/C	GH/PRL
Mixed GH cell/PRL cell	3%	Hyperprolactinaemia	A	GH/PRL
Mamosomatotroph	1%	Acromegaly or gigantism ±	C	GH/PRL
Acidophil stem cell		Hyperprolactinaemia		
		Hyperprolactinaemia or "non-functional"; only occasional acromegaly		
Corticotropic adenomas:				
Cushing (densely/sparsely granulated)	10%	Hypercortisolism	B	Adrenocorticotropic hormone (ACTH), β-lipotropic hormone (LPH), endorphins and propiomelanocortin (POMC)
Nelson	2%	Pigmentation; mass symptoms	B/C	ACTH, β-LPH, endorphins and POMC
Crooke cell	<1	Hypercortisolism	B/C	ACTH, β-LPH, endorphins and POMC
Silent corticotropic	3%	Mass symptoms; hypopituitarism	B/C	ACTH, β-LPH, endorphins and POMC
Glycoprotein adenomas:				
Gonadotropic	7–15%	Hypogonadism; functionally silent; mass effects	C/B	Follicle stimulating hormone and luteinizing hormone
Thyrotropic	1%	Hypothyroidism or hyperthyroidism	C/B	thyrotropin (TSH)
Plurihormonal adenomas	10%	Usually acromegaly ± hyperprolactinaemia; glycoprotein hormone production rarely expressed	C/A	Usually GH, PRL and TSH, α – subunit; includes other unusual combinations
Silent sub-type 3	3%	Mass effects; hyperprolactinaemia or GH effects	C/A	No specific hormones
Null cell adenomas	20%	Visual symptoms; hypopituitarism;	C	None ± mild hyperprolactinaemia as a result of pituitary stalk compression
Non-oncocytic	14%	headache		
Oncocytic	6%	Visual symptoms; hypopituitarism; headache	A	None ± mild hyperprolactinaemia as a result of pituitary stalk compression

A—Acidophil, B—Basophil, C—Chromophobe

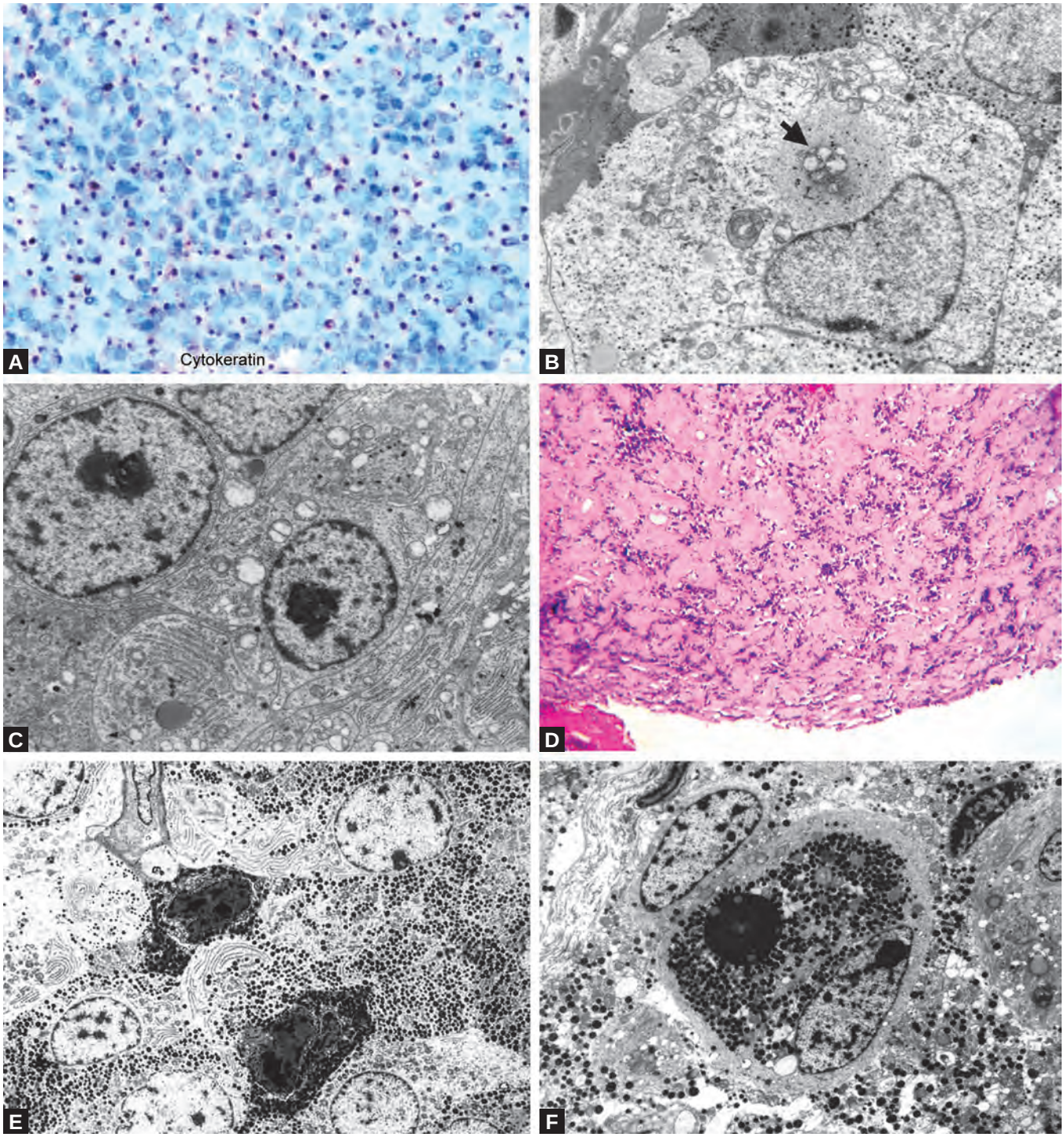
Table 3: Pituitary adenomas: ultrastructural features

Adenoma type	*Ultrastructural features*
Prolactin cell adenoma:	
Densely granulated adenoma	Cells round to oval with eccentric and oval to irregular nuclei. The RER in parallel stacks. Prominent ring shaped Golgi.
Sparsely granulated adenoma	Cells polyhedral with oval to irregular nuclei. The RER in "Nebenkern"(concentric whorl) formation. Golgi abundant, ring shaped or convoluted. Misplaced exocytosis present.
Growth hormone cell adenoma:	
Densely granulated adenoma	Round to oval cells with central, round to oval nuclei and prominent nucleoli. Peripheral parallel arrays of RER. Golgi prominent, spherical and numerous vesicles.
Sparsely granulated adenoma	Pleomorphic cells with single to multiple, eccentric and irregular nuclei. The RER in peripheral parallel rows or scattered. Abundant, ring-shaped Golgi. Paranuclear fibrous bodies may be present.
Adenoma with combined lactotrophic and somatotrophic features:	
Mixed growth hormone cell-prolactin cell adenoma	Variable proportions of sparsely and densely granulated growth hormone and prolactin cells with ultrastructural features as detailed above.
Mamosomatotroph cell adenoma	Polyhedral cells with oval to irregular nuclei. Well developed and prominent RER and Golgi. Two populations of secretory granules within the same cell—150–450 nm and 350–2000 nm size.
Acidophil stem cell adenoma	Elongated cells with irregular nuclei. Poorly to moderately developed RER and Golgi. Few secretory granules.
	Paranuclear fibrous bodies, misplaced exocytosis, abnormal/giant mitochondria and variable oncocytic change may be present.
Corticotroph cell adenoma:	
Densely or sparsely granulated Cushing adenoma	Round, angular, or elongated cells with round to oval nuclei. Abundant RER and prominent Golgi. Perinuclear and cytoplasmic microfilaments present.
Nelson syndrome	As above but with little or no microfilaments.
Crooke cell adenoma	As above but with marked accumulation of macrofilaments.
Silent corticotroph cell adenoma	Resembles densely or sparsely granulated Cushing adenoma.
Silent subtype 1	Small polyhedral cells with centrally placed nuclei. Numerous RER, prominent Golgi.
Silent subtype 2	No perinuclear and cytoplasmic microfilaments.
Glycoprotein adenoma:	
Gonadotroph cell adenoma	Small to medium cells with sparse RER. Golgi moderate, occasionally dilated. Vacuolar ("honeycomb") transformation of Golgi in adenomas of females.
Thyrotroph cell adenoma	Small; angular cells with elongated processes; irregular to oval nuclei. Poorly developed profiles of RER; moderate Golgi.
Plurihormonal adenomas:	
Silent subtype 3	Heterogenous group of adenomas which vary greatly in ultrastructural appearances; some tumours are monomorphous, whereas others consist of two or three distinct cell types.
	Irregular polar cells. Nuclei pleomorphic with spheridia. Moderate RER; prominent Golgi. Abundant SER.
Null cell adenoma:	
Non-oncocytic adenoma	Small polyhedral cells with irregular, indented nuclei. Sparse stacks of RER; moderate Golgi.
Oncocytic adenoma ("pituitary oncocytoma")	Large polyhedral cells with irregular, indented nuclei. Sparse stacks of RER; moderate Golgi. Abundant mitochondria—some dilated and some with inclusions.

RER—Rough endoplasmic reticulum
SER—Smooth endoplasmic reticulum

Mammosomatotroph Cell Adenoma

These tumours present with acromegaly and hyperprolactinaemia. The tumour has a single cell type with reactivity for both hormones. Key features include densely granulated cells resembling somatotrophes, but exhibiting both large granules and misplaced exocytosis, a feature of lactotrophes. By double labelling immunoelectron microscopy both hormones can be localised within the same cell and often within the same granules.



Figs 2A to F: (A) Sparsely granulated variant of growth hormone adenoma—cytokeratin paranuclear dot-like positivity (Avidin peroxidase X 400). (B) Sparsely granulated variant of growth hormone adenoma—paranuclear intermediate filament on ultrastructure, corresponding to the "fibrous body". (C) Prolactinoma: ultrastructure of a prolactin cell adenoma with well-developed rough endoplasmic reticulum and sparse secretory granules, with misplaced exocytosis. (D) Prolactinoma: stromal fibrosis following treatment with bromocriptine (H&E X 90). (E) Prolactinoma: ultrastructural appearance of a mixed GH-PRL adenoma displaying the bimorphous nature of sparsely granulated lactotrophs and densely granulated growth hormone cells. (F) Adrenocorticotropic hormone (ACTH) adenoma: electron dense secretory granules in a densely granulated ACTH adenoma

Acidophil Stem Cell Adenoma[13]

These tumours are rare and are usually non-functional. Hyperprolactinaemia may be present. Immunoreactivity for PRL generally exceeds that for GH. Secondary immunoreactivity is seen for α-SU and TSH. The cells show some features of both GH and PRL producing cells. Oncocytic change is a common feature due to the presence of numerous mitochondria, some of which are giant. The tumours show progressive growth and invasive behaviour.

Adrenocorticotropic Hormone Cell Adenomas

There are three principal subtypes of ACTH-producing adenomas:

Adenomas of Cushing's Disease

These tumours constitute 10% of all pituitary adenomas and are predominantly microadenomas. The male to female ratio is 1:5. The ACTH immunoreactivity is variable. These tumours are densely granulated with electron dense, teardrop secretory granules and perinuclear bundles of intermediate (cytokeratin) filaments (Fig. 2F).

Microadenomas can be difficult to diagnose and hence, samples submitted for histopathology have to be carefully handled with minimal wastage during sectioning. Reticulin and periodic acid-Schiff (PAS) stains are helpful in identifying the adenoma.

Crooke's hyaline change is a conspicuous finding in the non-neoplastic pituitary surrounding an ACTH-producing adenoma. It is seen surrounding the nucleus as a pale zone and consists of perinuclear accumulation of keratin microfilaments within the corticotroph. Rarely, Crooke's hyaline change affects the cells of an ACTH-producing adenoma.

Adenomas of Nelson's Syndrome

Adrenalectomy for undetected microadenomas was performed in the past to treat adrenocortical hyperplasia. This lead to unsuppressed growth of the microadenoma, with progression to invasive macroadenomas.[19] Nelson's adenomas underlie a significant proportion of pituitary carcinomas.

Silent Corticotroph Cell Adenomas

Approximately 5% of corticotroph cell adenomas are unaccompanied by elevations in ACTH or clinical evidence of Cushing's disease.[37] These are usually invasive macroadenomas. There are two subtypes of silent corticotroph cell adenomas:

1. Subtype I
2. Subtype II.

Glycoprotein Adenomas

These tumours produce hormones that have two amino acid chains. The α-SU is common to all these hormones and a beta that has functional specificity. They include gonadotropic (FSH-LH) and TSH adenomas.

Gonadotroph Cell Adenoma

These represent 10% of pituitary adenomas.[56] They are seen primarily in elderly individuals, most often in males. These are macroadenomas with a low invasion rate.

These adenomas show perivascular pseudorosette or ribbon formation (Fig. 3A). Oncocytic change is seen in approximately 50% of adenomas. Staining for FSH and/or LH and the α-SU is highly variable and patchy (Fig. 3B), with secondary immunoreactivity for PRL, GH and ACTH. These tumours have small (200 nm) secretory granules that are peripherally located. A "honeycomb" Golgi complex is seen in female patients.

Thyrotroph Cell Adenoma

These tumours are the least common (1%) of pituitary adenomas.[10] They manifest as hypothyroidism in individuals of all ages. There is an equal gender distribution.

The majority are invasive macroadenomas. TSH positivity and variable staining for α-SU, GH and PRL typify these adenomas. Secretory granules are few, small (200 nm) and peripherally located beneath the plasma membrane.

Plurihormonal Adenomas

Adenomas that produce both amino acid hormones (GH, PRL, ACTH) and/or glycoprotein hormones (LH, FSH, TSH, α-SU) are termed plurihormonal adenomas.[11]

Acromegaly is a common feature with GH, PRL or TSH. Other plurihormonal adenomas that are reported are: PRL-TSH; PRL-FSH/LH and ACTH-LH-α-SU.

Silent Adenoma, Subtype III

These tumours are clinically silent or non-functional and are seen in the second and third decades in females, and at any age in males. Immunoreactivity is seen for any of the pituitary hormones; however, some adenomas are entirely immunonegative.[14] The adenomas are aggressive in behaviour.

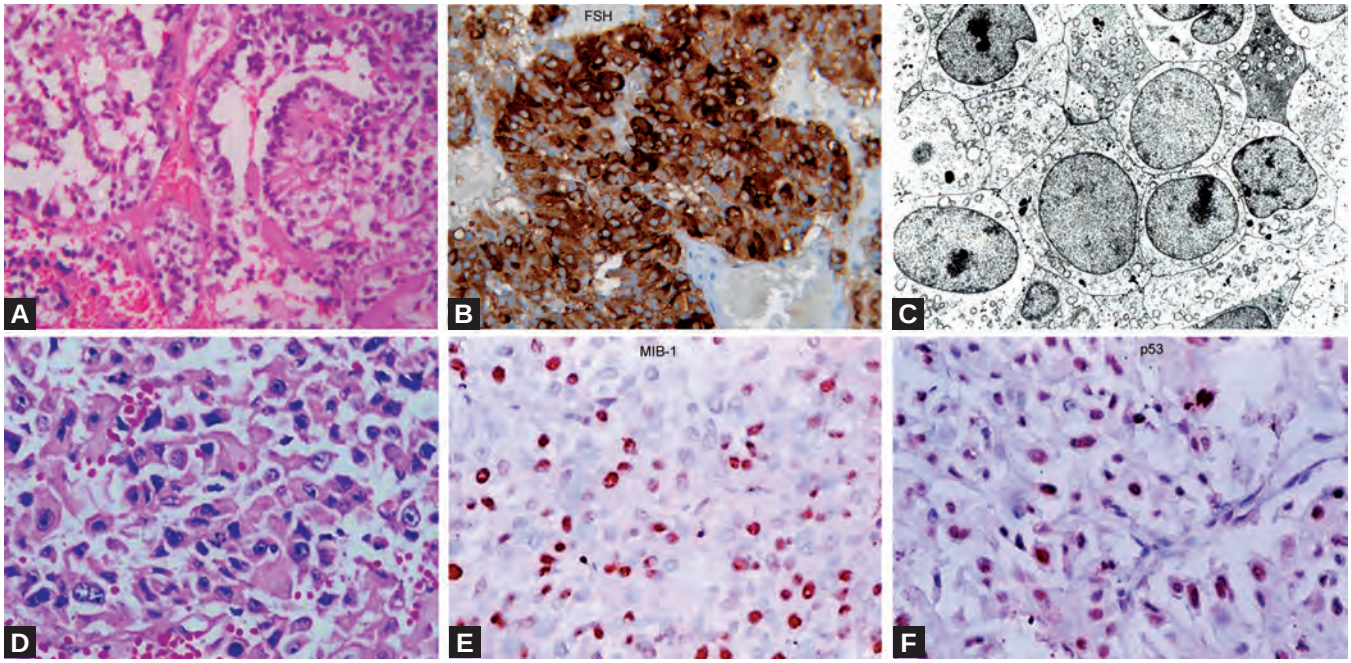
Null Cell Adenomas

These adenomas constitute one-fifth of all pituitary adenomas.[20] These tumours are clinically silent or non-functional and indolent in behaviour. They are macroadenomas with 40% being invasive. The tumours are negative for pituitary hormones, or show scant glycoprotein hormone or α-SU production. There is a paucity of organelles and only few small secretory granules (Fig. 3C) on electronmicroscopy.

INVASION AND MALIGNANCY IN PITUITARY ADENOMAS

Invasive Adenoma

A subset of tumours demonstrates a propensity for infiltrative and destructive growth.[41] Termed invasive adenomas they represent a group between the well-demarcated benign adenomas and the metastasising pituitary carcinomas.[50] Routine histological tests fail to reliably distinguish aggressive and locally invasive pituitary adenomas from those that are biologically indolent. Morphological markers of aggressiveness in most tumour systems, namely nuclear pleomorphism, cytological atypia, high cellularity, necrosis and brisk mitotic activity are of limited usefulness in pituitary



Figs 3A to F: (A) Gonadotroph adenoma with papillary configuration resulting in pseudorosette formation (H&E X 400). (B) Gonadotroph adenoma immunopositive for follicle stimulating hormone (Avidin peroxidase X 400). (C) Ultrastructural appearance of a null cell adenoma with small cells in which the cytoplasmic organelles are poorly delineated. (D to F) Atypical pituitary adenoma with pleomorphism, mitotic activity, a MIB-1 labelling index of greater than 3% and immunoreactivity for p53 (D: H&E X 400; E&F: avidin peroxidase X 400)

neoplasms, particularly in the assessment of their invasive tendency, growth rate, potential for recurrence and general biological behaviour. Several other biological markers have been studied to determine predictors of behaviour in adenomas and these are discussed later in this Chapter.

Atypical Adenoma

Atypical adenomas are adenomas that are in a category intermediate between benign adenomas and the pituitary carcinomas. These adenomas have mitotic activity, a MIB-1 labelling index of greater than 3% and immunoreactivity for p53[21] (Figs 3D to F).

Pituitary Carcinoma

This tumour is defined as one which has either craniospinal spread or metastasis to lymph nodes, liver or bone. These tumours are by and large functional, but may not show overt histological signs of atypia.[21,42]

Pituitary Apoplexy

Surgical specimens from cases of apoplexy can range from haemorrhagic material to infarcted tumour and combinations of these. On occasion there may be old haemorrhage as evidenced by the presence of cholesterol crystals and haemosiderophages. Viable tumour may also be present. In the absence of viable tumour, immunostaining is not advised as ambiguous results may be obtained.[6] The reticulin framework of an adenoma is usually preserved and, hence, a stain to highlight this is helpful in diagnosis.

MARKERS OF BIOLOGICAL BEHAVIOUR OF PITUITARY ADENOMAS

DNA Analysis

The clinical relevance of DNA analysis in pituitary tumours is still to be conclusively established, with variable results on secretors and non-secretors.[27]

Karyotypic studies on pituitary adenomas have shown abnormalities in chromosome 1, 4, 7 and 19 in functional tumours and numerical abnormalities in non-functioning tumours. There are no reported differences in karyotype between functional and non-functional tumours.

Proliferation Markers

It has been shown that pituitary adenomas with histologically proven dural invasion have a statistically significantly higher Ki-67 index compared with non-invasive adenomas.[18,48] In the study by Thapar et al.[48] the mean Ki-67 derived growth fractions for non-invasive adenomas, invasive adenomas and pituitary carcinomas were 1.34%, 4.66% and 11.91%, respectively. Establishing a threshold labelling index of 3% served to distinguish invasive from non-invasive adenomas with 73% sensitivity and 97% specificity. These findings are disparate from those of Gandour-Edwards et al.[9] and Lath et al.[25]

In the study by Lath et al.[25] the mean Ki-67 LI was 0.84% (+/− 2.08) with a range of 0–17.45%. The mean Ki-67 LI was higher in invasive tumours 1.33 +/− 3.232 than in non-invasive tumours. The difference in Ki-67 LI between invasive and non-invasive adenomas was, however, not statistically significant. Gandour-Edwards et al.[9] too failed to confirm the Ki-67 proliferation index as a marker of invasive pituitary adenomas involving the sphenoid sinus.

p53 Tumour Suppressor Gene

In a study by Thapar et al.[50] expression of *p53* gene mutation was present in 100% of pituitary carcinomas, 15.2% of invasive adenomas and none of the non-invasive adenomas. Data from other studies have, however, failed to confirm the validity of the p53 gene as a clinical predictor of the aggressiveness of pituitary adenomas.[3]

Apoptosis

Kulig et al.[23] reported a relatively low level of programmed cell death in a wide range of pituitary tumours. In this study the highest apoptotic index was present in pituitary carcinomas. The B-cell lymphoma-2 was moderately expressed in all groups of tumours and normal pituitary, and was much weaker in pituitary carcinomas. The Bax, Bad and Bcl-X were expressed in most pituitary tissues with less intensive staining in carcinomas, indicating that both pro-apoptotic and anti-apoptotic proteins are expressed concurrently in the same cells.

Angiogenesis

Pituitary adenomas show a lower microvascular density than normal pituitary tissue with the exception of invasive prolactinomas and pituitary carcinomas.[52,54]

Growth Factors

Many growth factors are expressed in normal pituitary and pituitary adenomas.[34] There is, however, no evidence for using the expression of growth factors or their receptors as prognostic markers.

MOLECULAR PATHOLOGY: ONCOGENES AND TUMOUR SUPPRESSOR GENES[29]

Amplification of oncogenes H-ras and c-Myc and inactivation of tumour suppressor genes Rb, p53, nm[23] has been thought to play a role in initiation and adenoma progression. C-erbB-2 staining was reported in 40% of invasive adenomas and 1.2% of the non-invasive tumours.[28] Pituitary oncogenes gsp, Cyclin D1 and PTTG are frequently found in pituitary adenomas.[57] Cyclin D1 is found more frequently in non-functioning and aggressive adenomas.[16,53] Cyclins A, B and E are expressed in all adenomas and are significantly higher in macroadenomas compared to microadenomas.[53] The allelic loss of a RB1 intragenic marker on chromosome 13q loss is more frequent in invasive adenomas.[31,45] The ZAC gene is highly expressed in the adenohypophysis, however, there is a reduction or absence of ZAC mRNA and protein expression reported in non-functioning pituitary adenomas.[30] GADD45 gamma mRNA is another suppressor found in the normal adenohypophysis, but in only a few clinically non-functioning pituitary tumours. Absence of the cyclin-dependent kinase inhibitor 2A/multiple tumour suppressor gene 1 (CDKN2A/MTS//p16) was demonstrated in 78% of non-functioning tumours.[44]

All cases of pituitary adenoma require a hematoxylin and eosin section and preferably reticulin and PAS stains. This together with the clinical and biochemical profile helps in diagnosis of most pituitary adenomas. *Reticulin* stain helps in detection of microadenomas. Immunohistochemistry is imperative in the detection of mixed GH-PRL adenomas, acidophil stem cell adenomas, silent corticotroph adenomas, gonadotrophic adenomas, and null cell adenomas and in confirming PRL production when serum PRL levels are not markedly elevated. Immunohistochemistry for the MIB-1 monoclonal antibody and p53 are helpful in diagnosing atypical adenomas. Electron microscopic examination is useful in the diagnosis of mixed GH-PRL adenomas, acidophil stem cell adenomas, female gonadotroph adenomas, null cell adenomas and silent subtype III adenomas.

Potentially aggressive adenomas are sparsely granulated GH adenomas, acidophil stem cell adenoma, PRL adenomas in the post-reproductive age group, ACTH adenomas associated with Nelson's syndrome and silent subtypes I and II, TSH adenomas and silent subtype III.

CRANIOPHARYNGIOMA[4]

These are epithelial neoplasms which arise in the sellar and/or third ventricle region.[2]

Clinical Features

Craniopharyngiomas manifest with hypothalamo-pituitary dysfunction and visual disturbances.

Histological Subtypes

There are two histological subtypes:
1. Adamantinomatous
2. Papillary

1. Adamantinomatous

The tumours are thought to arise from Rathke's cleft, squamous metaplasia of adenohypophyseal cells of the pituitary stalk or embryonic rests with odontogenic potential. These tumours are seen in the first two decades of life, although they can also be seen in adults.

They are cystic, contrast enhancing, partly calcified masses (Fig. 4A) in the sellar or third ventricular region.

Gross

The tumour is ill circumscribed with a poor interface with adjacent brain. They are partly cystic with calcific material and "machine–oil" fluid rich in cholesterol particles. Chemical meningitis results if the contents spill into the cerebrospinal fluid space.

Microscopic Features

They are similar to odontogenic tumours like adamantinoma of the jaw with anastomosing trabeculae of epithelial cells that exhibit peripheral palisading of columnar epithelial cells and enclose in their central portions loosely arranged epithelium known as "stellate reticulum" (Figs 4B and C). Amorphous masses of keratin (wet keratin) with secondary calcification are seen. The cyst contents incite an inflammatory reaction that is usually xanthomatous. Cholesterol granulomas are also a feature.

Behaviour

Adamantinomatous craniopharyngiomas have a propensity to recur owing to their infiltrative nature and, especially, if they are subtotally excised.

Sometimes biopsy material is scant and consists of the cyst contents or wet keratin without any epithelial elements. In such a case only a presumptive diagnosis of craniopharyngioma can be made.

Adamantinomatous craniopharyngiomas often infiltrate the adjoining parenchyma as nests and incite a rim of piloid gliosis (Fig. 4D). This may rarely be the first sample that reaches the pathologist for a frozen section. A mistaken diagnosis of a pilocytic astrocytoma arising from the optic pathway should be avoided by being aware of the clinico-radiological and intra-operative correlates as well as by the fact that gliosis is usually less cellular and lacks eosinophilic granular bodies and the biphasic appearance of pilocytic astrocytomas.

Differential Diagnosis

Epidermoid cyst: These cysts have lamellated keratin instead of wet-keratin nodules, gradual keratinisation of the epithelium and the presence of keratohyaline granules.

2. Papillary Craniopharyngioma

Papillary craniopharyngiomas are seen primarily in adults in the third ventricle or suprasellar space. The sella may hence, be normal.

Gross

They are solid tumours that have papillary fronds (Fig. 4E).

Microscopic Features

A discrete tumour with simple squamous epithelium covering fibrovascular cores without adamantinomatous features (Fig. 4F) typifies this tumour. "Wet" keratin, machine-oil fluid and calcification are not features of this neoplasm.

Behaviour

Complete excision is possible due to their well circumscribed nature. Reported recurrence rates are low after radical excision, however, more recent reports suggest that these tumours too have a propensity to recur similar to adamantinomatous craniopharyngiomas.

Differential Diagnosis

- Epidermoid cyst
- Adamantinomatous craniopharyngioma.

PITUICYTOMA AND GRANULAR CELL TUMOUR[4,8]

These tumours are seen in adults, usually in the fourth and fifth decades of life.

Their cell of origin is the pituicyte, which is a modified glial cell of the infundibulum, and neurohypophysis. They are well circumscribed contrast enhancing tumours, isointense on T1-weighted and T2-weighted images seen in the sellar/suprasellar region in relation to the neurohypophysis and infundibulum.

Gross

These are firm, tan-coloured masses that can be vascular.

Microscopic Features

Granular Cell Tumour

The tumour is composed of sheets of polygonal cells with granular, eosinophilic PAS-positive, diastase resistant cytoplasm with eccentrically placed round nuclei with uniform nucleoli (Fig. 5A). Perivascular lymphocytic infiltrates are sometimes present.

Pituicytomas

These tumours are composed of fascicles of spindle-shaped cells with an astrocytic morphology and fibrillary cytoplasm, uniform bland nuclei and distinct small nucleoli. Mitotic activity is sparse.

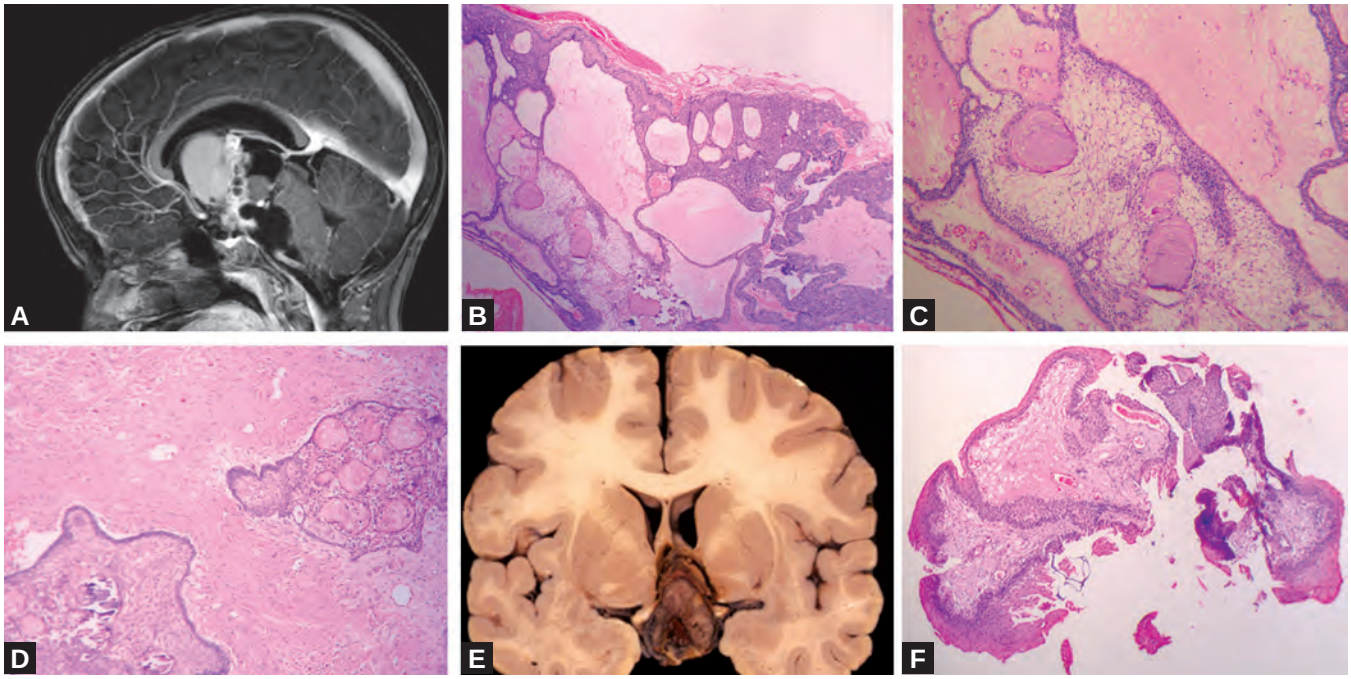
Immunohistochemistry

Granular cell tumours are CD68 positive and rarely S-100 protein and GFAP positive.

Pituicytomas are S-100 protein positive and variably reactive to GFAP.

Ultrastructural Features

Numerous intracytoplasmic lysosomes (Fig. 5B) are seen.



Figs 4A to F: (A) Magnetic resonance imaging of a partly cystic craniopharyngioma. (B and C) Adamantinomatous craniopharyngioma with cystic spaces and anastomosing trabeculae of epithelial cells that exhibit peripheral palisading of columnar epithelial cells and enclose in their central portions loosely arranged epithelium known as "stellate reticulum" (H&E: A X 40; B X 90). (D) Piloid gliosis surrounding islands of adamantinomatous craniopharyngioma (H&E X 90). (E) Papillary craniopharyngioma occupying the third ventricle. (F) Papillary craniopharyngioma: simple squamous epithelium covering fibrovascular cores without adamantinomatous features (H&E A X 40)

Differential Diagnosis

Pilocytic Astrocytoma

These are large tumours seen mainly in childhood with a biphasic histological pattern with rosenthal fibres and eosinophilic granular bodies.

Behaviour

These tumours are reported to have a variable prognosis with recurrences.

SPINDLE CELL ONCOCYTOMA OF THE ADENOHYPOPHYSIS[7]

These tumours arise from folliculostellate cells. They are seen primarily in adults who present with visual field defects and panhypopituitarism. They resemble pituitary adenomas on imaging.

Microscopic Features

These are tumours composed of spindle-shaped cells. Mitotic activity is absent.

Immunoreactivity

These tumours are positive for vimentin, epithelial membrane antigen and S-100 protein and are negative for all the pituitary hormones, synaptophysin, chromogranin and GFAP.

Prognosis

There are no recurrences reported to date.

POST-IRRADIATION SARCOMA[4,8]

These tumours are seen following irradiation to the sellar region after a latent period of about 10 years.

Microscopic Features

The histological features are those of a fibrosarcoma, osteosarcoma or a rhabdomyosarcoma, which is often admixed with a pituitary adenoma.

Behaviour

The tumours are locally aggressive.

NON-NEOPLASTIC LESIONS OF THE SELLA TURCICA[4]

Rathke's Cleft Cyst

They arise from Rathke's cleft rests. These cysts are rarely symptomatic.[47] They are often an incidental finding at autopsy or present as cysts that cause visual symptoms, hyperprolactinaemia, diabetes insipidus, growth retardation or other endocrinal dysfunction. They are intrasellar cysts with suprasellar extension with a high signal on T1-weighted images. Calcification is absent.

Microscopic Features

The cyst is lined by a single to pseudostratified layer of columnar, mucin-producing or ciliated cells with a few goblet cells (Fig. 5C). Squamous metaplasia is seen occasionally. They are rarely associated with adenomas.

Behaviour

Recurrences have been reported.[17]

Empty Sella Syndrome[15,46]

It is of two types, primary or secondary. In the primary form, arachnoid herniates into the sella through an incompletely formed sellar diaphragm resulting in displacement of the infundibulum and compression of the gland. In the secondary form the herniation is secondary to loss of the intrasellar contents, either secondary to surgical resection, apoplexy or necrosis.

Giant Cell Granuloma[4]

Giant cell granuloma is thought to be autoimmune in origin.

Clinical Features

They manifest with pituitary insufficiency and diabetes insipidus, occasionally.

Gross

In the early stages an enlarged gland is seen and later one sees a shrunken gland.

Microscopic Features

Discrete non-caseating granulomata containing several giant cells, with associated fibrosis (Fig. 5D) are seen within the adenohypophysis.

Behaviour

It is a self-limiting condition.

Differential Diagnosis

Tuberculosis, fungal infections and sarcoidosis. Necrotising granulomas are usually of infective aetiology. Sarcoidosis usually involves the neurohypophysis or hypothalamus.[24]

Lymphocytic Hypophysitis[1,4,33,51]

This is secondary to an autoimmune response which is both cellular and humoral, most often directed against pituitary hormones.

Clinical Features

These manifest with pituitary insufficiency and hyperprolactinaemia. There is a female predominance usually in late pregnancy or post-partum.

Radiographic Features

A symmetric enlargement of the pituitary is seen with contrast enhancement (Fig. 5E).

Gross

A firm gland is seen macroscopically.

Microscopic Features

Lymphocytic hypophysitis is characterised by pituitary acini extensively infiltrated by lymphocytes, as well as occasional plasma cells and histiocytes (Fig. 5F). Lymphoid follicles with germinal centres are seen. There is extensive fibrosis. An inflammatory infiltrate may also be seen in other endocrine organs.

Treatment

A biopsy is followed by hormone replacement as this can be fatal if untreated.

Pituitary Hyperplasia[4,12]

Pituitary hyperplasia occurs in response to stimulation by hypothalamic releasing hormones either as a physiological response to end-organ failure or due to a neoplasm.

Microscopic Features

Hyperplasia is either nodular or diffuse in pattern and usually involves one cell type. The reticulin stain plays a pivotal role in the diagnosis of hyperplasia. Nodular hyperplasia is seen as expanded acini. Cell counts are required for the diagnosis of diffuse hyperplasia.

Growth Hormone Cell Hyperplasia

It is seen with GRH-producing tumours, such as carcinoids and pheochromocytomas.[38] These cells are immunoreactive for GH.

Prolactin Cell Hyperplasia

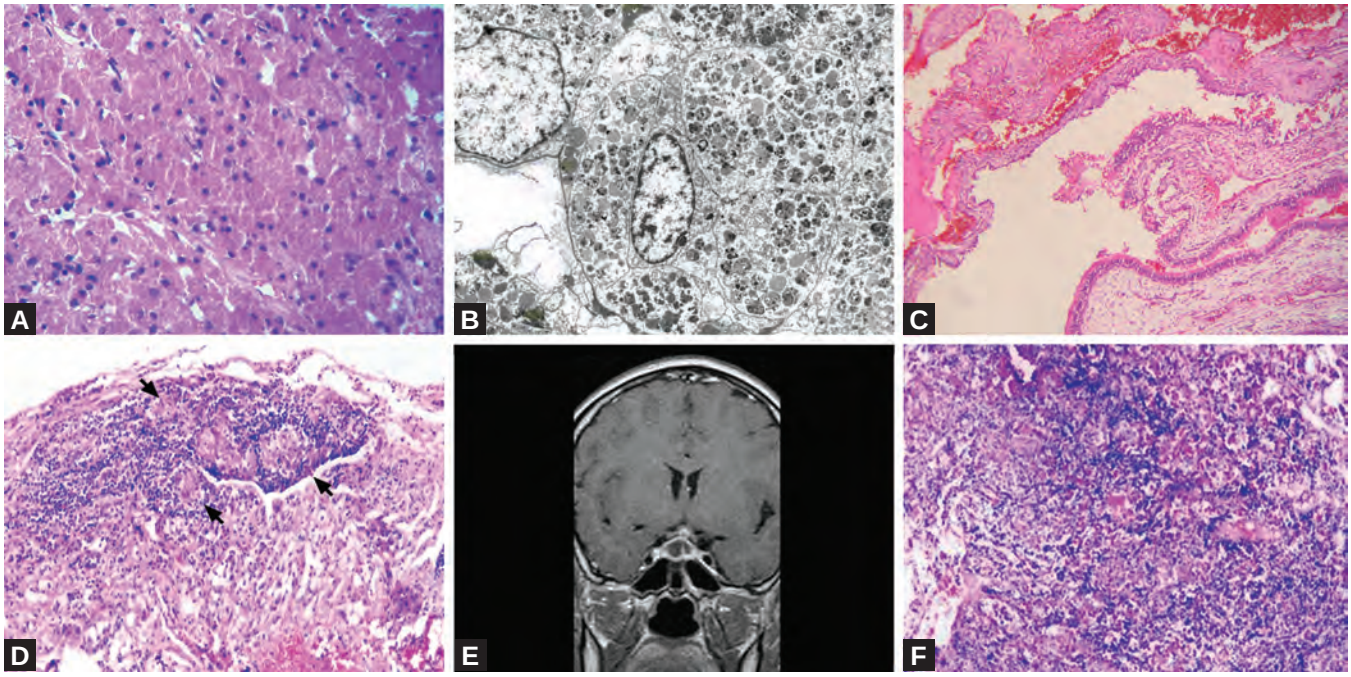
It is seen as a constant feature in association with pregnancy and lactation.[43] It is also seen in long standing cases of primary hypothyroidism, secondary to increase in TSH releasing hormone as well as in Cushing's disease.

Corticotroph Hyperplasia

Corticotroph hyperplasia is seen in the adenohypophysis adjoining a corticotroph adenoma. It is also seen in untreated Addison's disease as well as in association with tumours that produce corticotropin-releasing hormone.[40]

Gonadotroph Hyperplasia

It is seen in early onset primary hypogonadism such as in Klinefelter's or Turner's syndrome.[35]



Figs 5A to F: (A) Granular cell tumour: sheets of polygonal cells with granular, eosinophilic cytoplasm and eccentrically placed round nuclei (H&E X 400). (B) Granular cell tumour: numerous intracytoplasmic lysosomes. (C) Rathke's cleft cyst wall lined by single to pseudostratified layer of columnar epithelium (H&E X 90). (D) Giant cell granuloma: adenohypophysis with discrete non-caseating granulomas (H&E A X 40; B&C X 90; D X 400). (E) Magnetic resonance imaging of a case of lymphocytic hypophysitis: hypointense mass with peripheral enhancement. (F) Lymphocytic hypophysitis: dense infiltrates of lymphocytes and occasional plasma cells interspersed with adenohypohyseal cell clusters (H&E X 90)

Thyrotroph Hyperplasia

It is seen in patients with long-standing primary hypothyroidism.[32,39]

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125 Lymphomas and Metastatic Tumours of Nervous System

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LYMPHOMAS OF THE CENTRAL NERVOUS SYSTEM

Non-Hodgkin's lymphomas of the central nervous system (CNS) can be primary or secondary. Systemic lymphomas can spread to the CNS in about 10% cases, usually in advanced or relapsing phase. Certain primary sites, like testis, bone marrow, bone, paranasal sinus, are more likely to seed the CNS. High grade lymphomas spread to the brain more frequently than others, and the involvement is usually leptomeningeal.

Primary central nervous system lymphoma (PCNSL) is a non-Hodgkin's lymphoma that is confined to the brain, leptomeninges, eye or spinal cord without evidence of involvement of other parts of the body.[32,41]

Involvement of the brain is uncommon in Hodgkin's lymphoma and plasma cell dyscrasias. They can, however, present with spinal cord compression.

PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA

Epidemiology

Primary central nervous system lymphoma (PCNSL) was considered a rare neoplasm before 1980 and it constituted less than 1% of all intracranial neoplasms.[63] However, there were reports of increasing incidence of PCNSL from the West. There was a tenfold increase in the incidence of PCNSL from 1973 to 1992.[68] This was largely attributed to the epidemic of acquired immunodeficiency syndrome (AIDS)[18] and also to immunosuppressive therapy for patients with organ transplantation and other autoimmune diseases. However, increase in the incidence of PCNSL was observed in immunocompetent individuals also during the same period, for reasons not clear.[4] On the other hand, recent data suggests that the annual incidence of PCNSL may be stabilising or declining slightly.[36,59] There were a few hospital-based series of PCNSL reported from India, which did not show any significant increase in the incidence of PCNSL over the last 24 years.[53,65] Similar observations were made from Canada, Denmark and Scotland[30,33,46,51] suggesting significance of geographical domains for the incidence of PCNSL.

Predisposing Conditions

PCNSL occurs in both immunocompetent and immunosuppressed individuals.

The immunodeficiency states associated with PCNSL may be acquired or congenital. The immunodeficiency states include AIDS and immunosuppressive therapy for organ transplantation (especially cardiac and renal transplantations). The congenital immunodeficiency states include: Wiskott-Aldrich syndrome; severe combined immunodeficiency syndrome; immunoglobulin A deficiency; ataxia-telangiectasia; X-linked lymphoproliferative syndrome and Chediak-Higashi syndrome. PCNSL is diagnosed in at least 2% of human immunodeficiency virus (HIV) infected individuals and is an AIDS defining illness. The relative risk of PCNSL in HIV infected individuals was 3600 fold when compared to the general population before the use of highly active antiretroviral therapy (HAART). It has decreased after the introduction of HAART.[4,50] PCNSL is a late manifestation of the disease in AIDS when $CD4^+$ T cell counts are less than 200/μl.[41,49] In India, the majority of PCNSLs are reported in immunocompetent individuals. Clinical as well as autopsy studies of HIV related neurological diseases in India reported very low incidence of PCNSL.[8,28,45,53] This is probably related to early deaths in AIDS patients due to opportunistic infections.

Age and Gender

PCNSL occurs in all age groups, but age differs significantly depending on the immune status. In immunocompetent individuals, the mean age at diagnosis is 55.2 years while in immunosuppressed individuals, the mean age is 30.8 years.[29,69] The mean age of PCNSL in India varies from 39 years to 44 years in immunocompetent individuals, significantly lower than that reported from the West.[65]

There is a male predominance in both AIDS patients (> 95%) and in immunocompetent patients with PCNSL (2:1).

Clinical Presentation

The clinical features depend on the neuroanatomical location of the lesions. The patients present with focal

neurological deficits, neuropsychiatric symptoms, raised intracranial pressure, seizures or ocular symptoms.[4] The leptomeningeal lesions may be asymptomatic and spinal cord lesions are usually discrete intramedullary nodules.[47]

Pathogenesis

The pathogenesis of PCNSL is unclear as the CNS does not contain any lymphatic system. Three hypotheses have been put forwards but none of them can explain the pathogenesis completely:[37] (i) A systemic B cell lymphoma develops and spreads to all organs, but lymphoma cells are eradicated by an intact immune system in all organs. The CNS being an immunologically privileged site, the cells proliferate and develop neoplasia there. However, there is no evidence of concomitant lymphoma at other immunologically privileged sites like testis. (ii) B cell lymphomas that arise elsewhere in the body develop particular adhesion molecules permitting homing to the CNS, where such cells proliferate and develop into lymphomas in the absence of immune regulation. (iii) An intracerebral inflammatory lesion with polyclonal inflammatory infiltrate may progress to a neoplastic monoclonal B cell proliferation similar to MALT lymphoma evolving from gastritis induced by *Helicobacter pylori*. However, there is paucity of B cells even in inflammatory CNS disorders. Also, to date, no difference in cell surface expression of adhesion molecules have been found between PCNSL and systemic lymphoma.[37,59,60] Smith and colleagues identified a B cell attracting (BCA) chemokine (CXCL-13), which is responsible for homing of B cells to secondary lymphoid organs.[71] Both BCA-1 and its receptor CXCR-5 are expressed by B cells in PCNSL suggesting their possible role in homing of B cells in the CNS.[22] Recent evidence shows that BCA-1 and SDF-1 (both B cell chemokines) are expressed by retinal pigment epithelium in primary intraocular lymphoma.[38,64] Animal models of PCNSL show that lymphoma cells enter the brain preferentially through the choroid plexus and cranial nerves and then disseminate along the optic nerve sheath into eye. Recent studies suggest that the tumour arises in an extraneural environment with subsequent localisation to the CNS, possibly by virtue of a specific neurotropism. It is probably a late germinal centre or a postgerminal centre lymphoid neoplasm.[39]

In the majority of immunosuppressed patients, PCNSL is associated with latent infection of B cells by Epstein Barr virus. Virtually all PCNSLs in AIDS patients contain EBV DNA. Clinical or sub-clinical infection with EBV results in both humoral and cellular immunity and EBV persists despite the immune effector responses and results in latent infection of B cells. The proliferation of B cells is controlled by T cell immunity. In HIV and other immunosuppressed states, due to loss of T cell mediated immunity, there is proliferation of B cells which are latently infected with EBV. There is evidence that EBV infection of tumour clone is associated with CNS tropism[2,43,67,74] (Table 1).

Non-AIDS Related Molecular Pathology

PCNSL and primary intraocular lymphomas express BCL-6 which is a germinal centre cell marker suggesting that the tumour cells are derived from mature B-cells which are exposed to an antigen and undergone T cell dependent maturation in the germinal centre.[26,76] BCL-6 expression is associated with favourable prognosis.

Roychowdary et al. (2003)[6] developed a rat model of EBV related PCNSL which allows preclinical evaluation of antiviral therapy in EBV related PCNSL. Studies applying molecular genetic techniques provide information about molecular markers, which help understand pathogenesis and also predict prognosis.

Gross Pathology

Four forms of involvement have been described in PCNSLs: (i) discrete or diffuse intracranial mass lesions that are solitary or multiple, often in contact

Table 1: Comparison between PCNSL in the immunocompetent and AIDS PCNSL

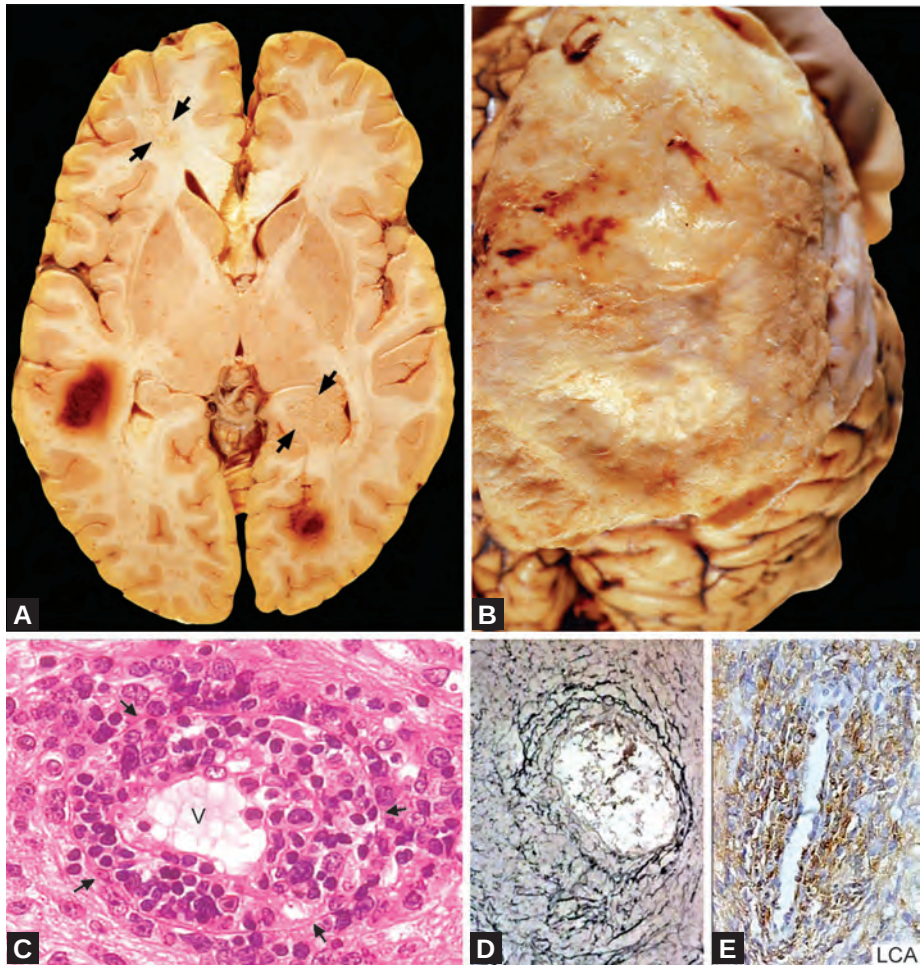
	PCNSL in immunocompetent individuals	*PCNSL in AIDS patients*	*References*
Median age at diagnosis	55.2 years	30.8	16, 17
	India 39–44 years	Indian data not available	7
Gender	M:F = 2:1	> 95% male	16, 17
Multifocality	25%	52%	16
Leptomeningeal involvement	7% at diagnosis, 4% by MRI, CSF cytology, autopsy	More common at diagnosis, almost 100% at autopsy	34
Haemorrhage into tumour	Uncommon	Common after surgery	19
Necrosis	Usually not seen	Extensive	40
Clinical features—change in mental status, seizures	Less common	More common	16
Clinical course	Weeks to months	Days to weeks	41
CD4 counts	Normal	< 200/μl	42
Ebstein Barr virus genome	0–20%	94–100%	40

with ventricular or meningeal surface; (ii) leptomeningeal lesions; (iii) ocular lesions with or without other lesions and rarely (iv) spinal cord lesions.[47] Majority of the intracranial lesions are supratentorial (85%) in the periventricular zone and areas in thalamus, basal ganglia and corpus callosum[4,10] and the lobar lesions in the frontal, parietal, temporal and occipital lobes in the descending order of frequency.[4] Primary leptomeningeal lymphoma, without parenchymal involvement (7%) and primary intraocular lymphoma (6%), are rare forms of PCNSL and spinal cord involvement is very uncommon (less than 1%).[44,62,68] Leptomeningeal involvement is common in PCNSL either in mass lesions or primary leptomeningeal form, but majority are asymptomatic. However, it provides an important aid in diagnosis by CSF cytological examination (Figs 1A and B).

Histology

PCNSL are most often high grade diffuse large B cell Lymphoma (DLBCL) according to REAL and WHO classifications.[3,52] All types of lymphoma including the rare ones with signet ring cell morphology or anaplastic large cell (Ki-1) type have been reported in the brain. The PCNSL in AIDS frequently include immunoblastic and small non-cleaved Burkitt-like cell type. Low grade PCNSL similar to systemic NHL as a subgroup are described recently.[48] The round to oval cells infiltrate the cerebral parenchyma diffusely and aggregate in the Virchow Robin spaces with infiltration of the vessel walls. The tumour cells are angiocentric, pleomorphic, discohesive and infiltrative. There is no associated endothelial proliferation or thrombosis. The cells show high mitotic index. The vessels show perivascular cuffing and the reticulin stain shows splaying of reticulin fibres (Figs 1C and D). The AIDS related PCNSL shows atypical features, areas of necrosis and EBV genome by *in situ* hybridisation, and EBV associated latent membrane protein by immunohistochemistry (Figs 1C to E).

More than 95% of NHL in the brain are of B cell lineage and show CD 20 and CD 79a positivity. A few reactive T cells can be seen in B cell PCNSLs. Other evidence of B cell lineage includes clonal IgH gene rearrangements, frequent alterations of non-coding regions of the BCL 6 gene and BCL-6 protein expression.[62] Primary T



Figs 1A to E: (A) Axial slice of brain shows pale, circumscribed lymphomatous deposits (arrows) in left frontal white matter and hippocampus, and haemorrhagic lesions in left temporal and right parieto-occipital white matter. (B) A large circumscribed pale lymphoma deposit on the dura resembling a meningioma. (C to E) Microphotograph of lymphomatous lesion shows characteristic. (C) Angiocentric distribution of lymphoma cells. (D) Splitting reticulin framework. (E) Immunohistochemistry shows positive labelling of tumour cells for LCA. (C:HE x 320, D:Reticulin silver x 160, E:Immunoperoxidase for LCA x 160)

cell lymphomas including anaplastic large cell variant, constitute a small minority of PCNSL, especially in the cerebellar and leptomeningeal examples.

In a study of PCNSLs at the Nizam's Institute of Medical Sciences, Hyderabad, 56 cases of PCNSLs were diagnosed from 1988 to 2006. The median age of presentation was 42 years, with male predominance. The PCNSLs have remained fairly constant through the years forming 1.07% of intracranial neoplasms. Of the 56 cases, 55 cases were immunocompetent and only one patient was HIV positive. Majority were large B-cell lymphomas and 19/19 cases were negative for E B Virus by *in situ* hybridisation.

Diagnosis

The diagnosis of PCNSL may be suggested by several radiological findings.[69] They are angiographically avascular. On CT scans, they are either isodense or hyperdense in relation to the normal cortex, as opposed to glial tumours and metastasis, which are hypodense. They tend to cause less oedema than gliomas. More than 90% are contrast-enhancing. The radiographical appearance of PCNSL differs significantly between AIDS and non-AIDS setting. In immunocompetent patients, PCNSL appears multifocal in one-third of patients, enhance uniformly with contrast, and lack ring enhancement, whereas in AIDS associated PCNSL, the lesions are multifocal in 30–75%, may be cortical or subcortical and enhance after contrast administration.[49] On MRI, PCNSL is typically hypointense or isointense on T1-weighted images with variable enhancement pattern on Gadolinium, especially ring enhancement.[49] It is difficult to reliably distinguish AIDS associated PCNSL from AIDS related infections, especially Toxoplasmosis on CT or MRI. Diffusion weighted MRI and metabolic imaging hold promise in this direction.

Cerebrospinal Fluid Examination

It should be performed in all patients with suspected PCNSL, unless contraindicated by a large posterior fossa mass lesion, elevated intracranial pressure or coagulopathy. Cytological examination may provide useful information and eliminate the need for surgery.[13,49] CSF shows raised protein, low sugar, may be positive for tumour markers such as β2 microglobulin and LDH. Cytology may be positive in a third of patients and detection rate increases after repeated sampling. Flow cytometry improves sensitivity of detecting occult leptomeningeal disease.[9] Polymerase chain reaction (PCR) for EBV DNA in CSF has a sensitivity of 80–100% and specificity for lymphoma of 93–100%.[42] It is also positive in EBV associated systemic lymphoma in AIDS patients. Combining CSF-EBV analysis with metabolic imaging improves the accuracy of diagnosis of AIDS-PCNSL.[63] In a recent review, Batchelor and Loeffler discussed the unique diagnostic, prognostic and therapeutic issues of PCNSLs in immunocompetent patients.[38]

Role of Stereotactic Brain Biopsy

Stereotactic Brain Biopsy (SBB) is the standard procedure for obtaining tissue for a pathological diagnosis of cerebral lymphoma. The centre of the suspected lesion should be targeted for biopsy. The advantages of SBB over open biopsy include minimal skin incision, option of local anaesthesia, short post-operative recovery period, and low rate of morbidity and mortality. Surgical excision of a parenchymal PCNSL confers no survival benefit. They may be associated with a worse survival along with a risk of seeding the leptomeninges with tumour cells.

The morbidity and mortality of SBB is higher in AIDS patients due to the high frequency of haemorrhagic complications. Stereotactic biopsy is particularly useful to obtain tissue in PCNSLs involving deep structures like thalamus, periventricular area and corpus callosum.[47]

Use of steroid therapy before biopsy can obscure histopathological features due to tumour cell apoptosis to the point that lesional cells disappear completely.[47] As most patients with PCNSLs have relapses if treated with steroids alone and there are difficulties in establishing subsequent diagnosis, corticosteroids should not be administered before biopsy.[39]

Prognostic Markers

Age more than 60 years, performance status more than one; elevated serum LDH, high CSF protein concentration and involvement of deep regions of the brain (periventricular regions, basal ganglia, brainstem and/or cerebellum) were significantly and independently associated with bad prognosis and low survival rate.[35]

PCNSL without treatment has a median survival of 1.8–3.3 months only. Combined modality approach with chemotherapy and whole brain radiotherapy has improved survival, but relapses occur in almost all PCNSL.

Spinal Cord Compression Due to Haematological Malignancies

Spinal cord compression due to haematological neoplasm is a serious complication requiring immediate diagnosis and treatment. It can occur due to involvement of spinal cord, spinal leptomeninges, dura or vertebra. The spinal involvement is common with multiple myeloma (MM),[66] followed by NHL,[7] but rare in Hodgkin's lymphoma,[73] leukemia[5] and extramedullary myeloid cell tumour (EMCT).[34]

Patients with myeloma or lymphoma have a good prognosis even if they present with cord compression, when treated appropriately and promptly.

Non-Hodgkin's Lymphoma

Cord compression has been noted at presentation in 2.2% of cases of NHL. Back pain and weakness are the commonest presenting symptoms.[7] All histological

grades of NHL have been reported. Surgery to provide a tissue diagnosis followed by combined radiotherapy and chemotherapy is indicated for all cases.

Hodgkin's Lymphoma

Hodgkin's lymphoma presenting with spinal cord compression is very rare and occurs in only 0.2% cases of Hodgkin's lymphoma.[73] The thoracic spine is the most commonly involved site. Histopathology of the lesion along with detailed clinical evaluation with history of previous biopsy, lymph nodal status and organomegaly is required to make a definitive diagnosis.

Multiple Myeloma and Solitary Plasmacytomas

Involvement of spinal cord and/or nerve root by myeloma is a serious complication and is secondary to involvement of vertebrae. It occurs in about 10% of patients of multiple myeloma and may be the initial manifestation.[7] Solitary plasmacytomas can also present with spinal cord compression.[20] Recognition of paraspinal mass by CT/MRI is useful in diagnosis and early recognition is important. Histology is diagnostic and immunohistochemistry for kappa and lambda light chains of immunoglobulins can be carried out. Associated amyloidosis carries a poor prognosis. Clinical, imageological and biochemical evaluation including serum and urine immunoelectrophoresis along with bone marrow examination is necessary for instituting therapy.

Myeloma involving skull bones of the vault do not usually produce neurological symptoms but those involving base of the skull can produce cranial nerve involvement. Meningeal involvement in myeloma is rare and intracerebral mass lesions are rarely reported.[75,16]

Solitary plasmacytomas are rare and account for less than 10% of plasma cell tumours and are morphologically indistinguishable from multiple myeloma on immunohistochemistry. Skeletal survey and bone marrow evaluation are necessary to rule out multifocal lesions. Although the prognosis for solitary plasmacytoma is significantly better than that of multiple myeloma, solitary plasmacytoma eventually progresses to multiple myeloma.

METASTATIC TUMOURS OF THE CENTRAL NERVOUS SYSTEM

Metastatic involvement of the brain and spinal cord is one of the most serious complications of systemic malignancy and its incidence seems to be increasing with improvement of therapies for systemic malignancies. It may be the initial manifestation of a systemic malignancy.

Epidemiology

It is difficult to determine the exact incidence of brain metastases. It is estimated that 5–20% of patients dying of systemic cancer will be found to have metastatic disease to brain at autopsy and about half to two thirds of them will have symptoms referable to metastasis.[25,54,72] Advances in neuroimaging and routine staging to assess CNS involvement will offer insight into the actual incidence.[31]

Pathogenesis

Brain metastases exhibit considerable clinical and neuropathological heterogeneity. This cannot be explained only by the pattern of regional blood flow. Tumour cells have marked genetic, biochemical and cytological diversity.

The metastatic tumour cells use specific adhesion molecules to attach to microvessel endothelial cells. They then respond to endothelial cell derived motility factors and invasion factors, like neurotrophins and basement membrane degradative enzymes, which facilitate brain invasion by metastatic cells locally destroying blood-brain barrier.[11]

The tumour cells proliferate in response to local paracrine and autocrine growth factors. Receptors to paracrine growth factor, like transferrin (a glycoprotein), are expressed in greater numbers on the surfaces of cells that are metastatic to brain. Transferrin-like factors are important for invasion, colonisation and growth of metastatic cells in CNS and probably explain why certain tumours, like melanoma, lung carcinoma and breast carcinoma, metastasise to brain.[11,20]

Spread of the Tumours

Systemic tumours spread to brain by three routes: (i) haematogenous; (ii) contiguous and (iii) perineural.[72] Haematogenous spread is the commonest route by which the tumour cells reach the brain and spinal cord. The tumour cells reach nervous system via systemic circulation through pulmonary vasculature or through a patent foramen ovale in the heart rarely. Metastases may occur anywhere in the brain, but in general, the distribution is proportional to the blood supply to specific areas of the brain. Hence, grey matter is more commonly involved than white matter, and metastases occur with equal frequency to both hemispheres. Eighty per cent occur in cerebral hemispheres, 10–15% in cerebellum, 2–3% in brainstem.[24] Multiple metastases are seen in 50% of patients and numerous military metastases are described as military carcinomatosis.[72]

Tumours in CNS that develop by invasion of a primary tumour in the adjacent structures, like paranasal sinuses or bone, are not actually considered as metastases because they remain in continuity with the primary neoplasm. Tumours that spread by contiguous invasion include carcinomas of nasopharynx, paranasal sinuses, skull bone and middle ear.[61] Of these, nasopharyngeal carcinoma is the commonest. Osseous tumours of the skull and vertebrae also spread by contiguous invasion. Metastases to skull bones can occur from primary

tumours-like neuroblastoma in children and tumours of prostate, breast, kidney, thyroid, lung and myeloma in the adult.[72]

Perineural metastases are the least common and this type of spread is supposed to be the mechanism for meningeal carcinomatosis.[14]

Tumours Metastasising to Brain

The incidence of brain metastases and the spectrum of metastasising primary tumours vary with patient's age. In general, brain metastases occur more frequently in adults than in children. In adults, primary tumours metastasising to brain include lung, breast, kidney, gastrointestinal tract and melanoma in descending order.[19,27] Apart from the cerebral hemispheres, cerebellum and brainstem, other intracranial sites of metastases include pituitary, pineal and choroid plexus. The metastases can also involve pre-existing lesions like glioma, meningioma, schwannoma, arteriovenous malformations and infarcts[1,12] (Figs 2A to C).

Metastases affecting the spinal cord may involve the epidural space, leptomeninges or intramedullary spinal cord. Epidural metastases are the commonest and usually present as the initial manifestation of malignancy.[58] They arise by extension from a metastatic deposit in the vertebra. Thoracic spine followed by lumbosacral and cervical spine are involved by the metastases. Lung is the most common primary affecting area followed by breast, prostate and lymphoma.

In children, leukaemia and lymphoma involve the leptomeninges. In children younger than 15 years osteosarcoma and rhabdomyosarcoma produce solid brain metastases, while in older children germ cell tumours produce metastatic deposits.[15,70]

Melanoma, although constitutes only 4% of all cancers, has the highest propensity to result in brain metastases. Genitourinary tumours and sarcomas do not frequently metastasise to brain. On the other hand, any tumour can metastasise to the brain and patients with no known history of cancer may present with brain metastases.[56]

Metastases from melanomas and lung carcinomas tend to be multiple while tumours from breast, colon and kidney tend to be single. Metastases from melanoma and choriocarcinoma are usually haemorrhagic (Fig. 2A).[72] Metastatic choriocarcinoma should be considered in the differential diagnosis of haemorrhagic intracranial masses in women of child bearing age and the surgically resected blood clots should be examined histologically for determining the aetiology.[40] Systemic lymphomas and leukaemias involve leptomeninges and do not involve parenchyma and leptomeningeal carcinomatosis is usually an adenocarcinoma.[72] Primary brain tumours, like germinoma and medulloblastoma, also spread by CSF pathway. Histology of primary tumour also influences the metastasising potential. Small cell carcinoma and adenocarcinoma of lung along with breast carcinoma are found to metastasise to brain twice more frequently than other histological types.[70]

Diagnosis

Following clinical evaluation, the size, location and number of metastases can be assessed by CT and MRI. The approach to evaluation of the lesions is given in the flow chart. High index of clinical suspicion is required to make a diagnosis of leptomeningeal involvement as the neurological manifestations can be protean (Fig. 2D). The diagnosis should be suspected when symptoms and signs suggest involvement of multiple anatomic sites in CNS. These include headache, altered sensorium, cranial nerve palsies, back or radicular pain, lower motor neuron weakness, sphincter incontinence and sensory abnormalities.[21] The cerebrospinal fluid examination has to be repeated two to three times with more volume of CSF (up to 10 ml) when the clinical suspicion is high to get a positive yield (Fig. 2D3) and it has to be supplemented with special stains and immunohistochemical stains. Gadolinium enhanced T1-weighted MRI complements CSF cytology in suspected leptomeningeal metastases.[23] Similarly, the tissue obtained after surgery should be subjected to special stains and immunohistochemical studies in addition to routine haematoxylin and eosin staining. The immunohistochemical panel should include pancytokeratin, leucocyte common antigen and HMB-45 and extended as per requirement.

Approach to evaluation of a patient with brain metastasis is represented in Flow chart 1.

Prognostic Factors

Outcome in patients with metastatic brain disease depends on four parameters that include; age less than 60 years, unknown or controlled primary cancer, Karnofsky performance scale score greater than 70 and metastatic spread limited to the brain. Patients with all the four favourable factors had a predicted 200 day survival of 52% while the patients with none of the favourable factors had a predicted survival time of 54 days.[57] Patients with carcinoma breast, who have CNS involvement, whether occult or symptomatic, have an impaired survival.[55]

The institution of systemic chemotherapy was a positive prognostic factor in patients with subarachnoid lesions detected by neuroimaging or with extra CNS tumour deposits.[10]

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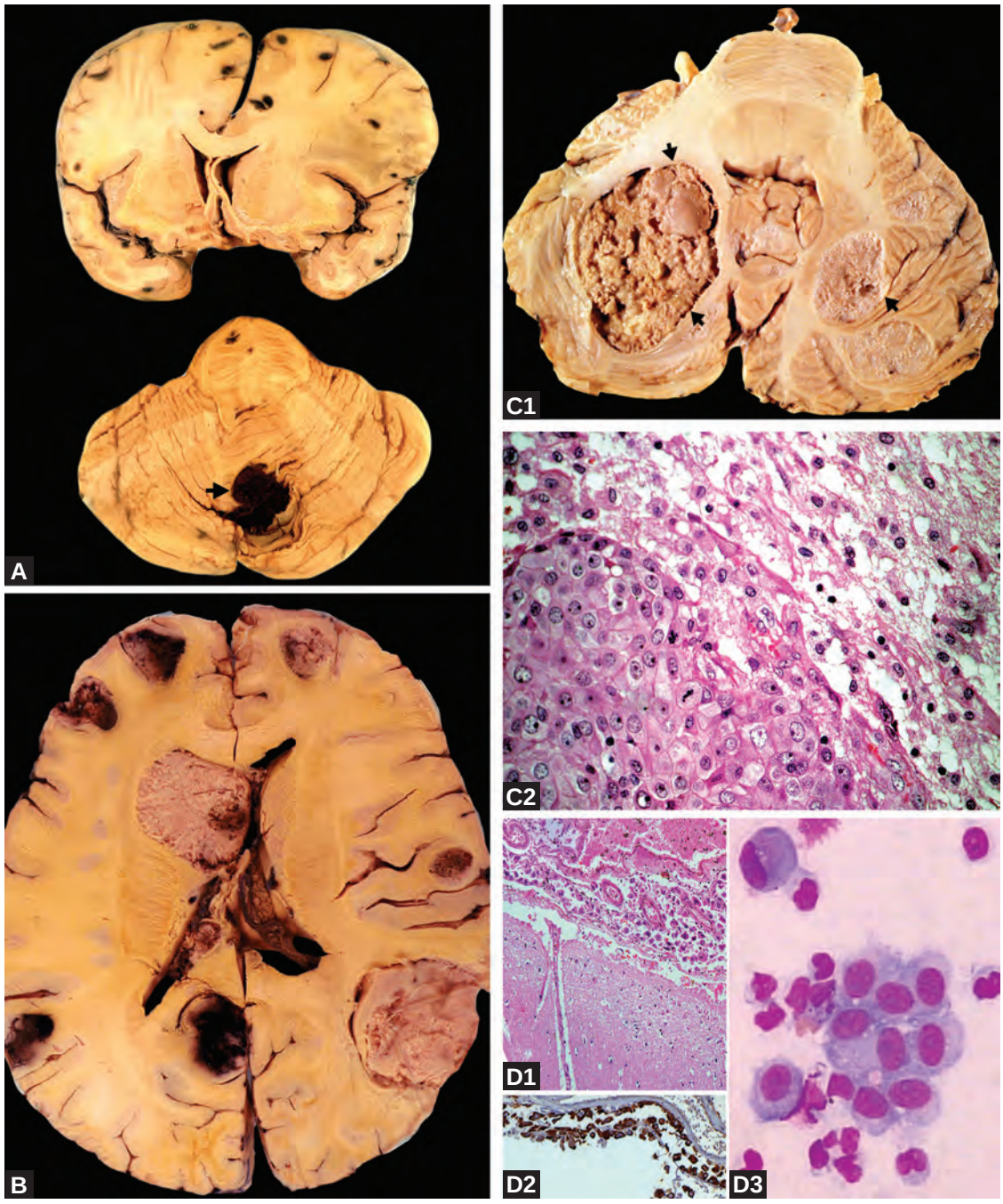
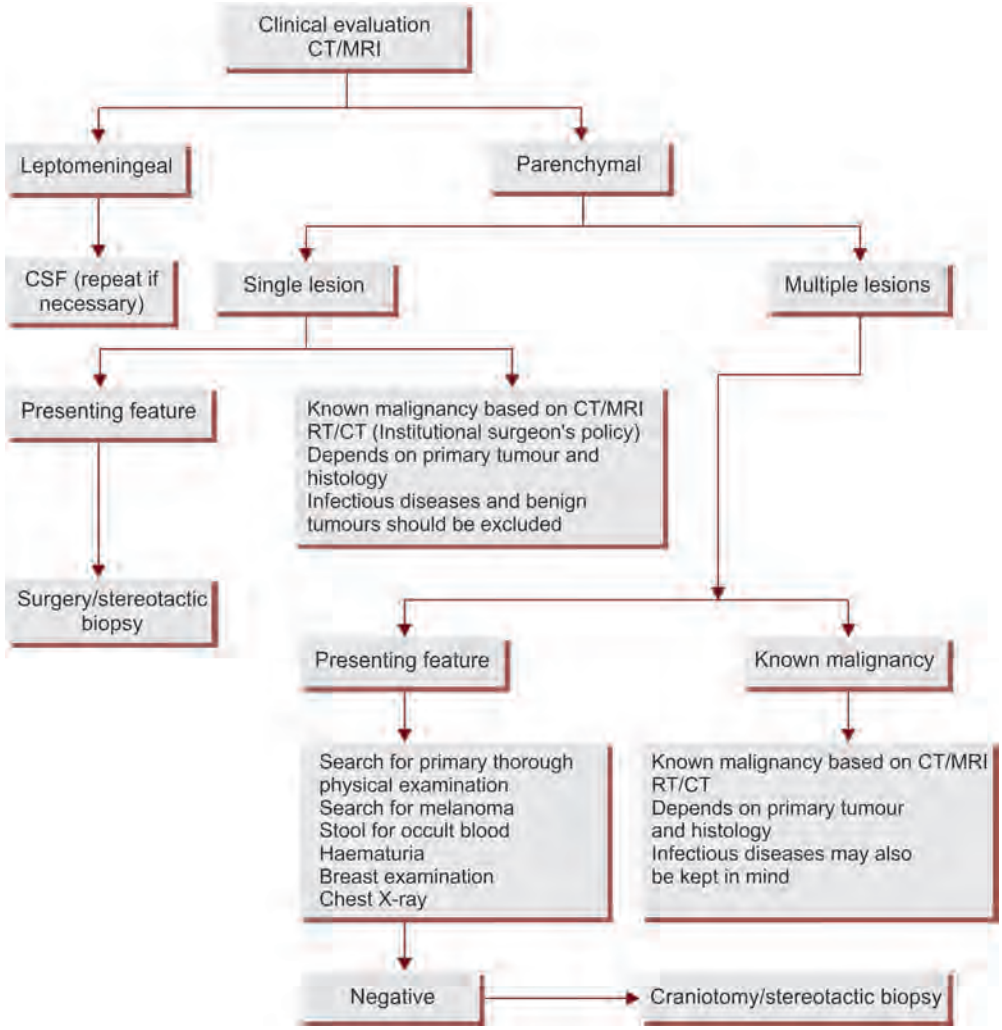


Figs 2A to D: (A) Coronal slice of brain showing multiple tiny haemorrhagic lesions in bilateral frontal and temporal lobes at grey-white junction in a case of choriocarcinoma. A large haemorrhagic lesion is also seen in the cerebellar vermis (lower panel) with small haemorrhagic lesions in pontine tegmentum. (B) Axial slice of brain showing multiple circumscribed solid lesions in bilateral frontal and parieto-occipital lobes involving the cortical ribbon and left caudate nucleus compressing ipsilateral lateral ventricle. Some of these lesions show haemorrhages. The patient was found to have bronchogenic carcinoma. (C) Horizontal slice through the brainstem and cerebellum shows large circumscribed lesions in bilateral cerebellar white matter compressing and distorting the dentate nuclei. The lesions appear tan with papillary configuration and tiny foci of cystic change on sectioning (C1). Histology shows metastatic squamous cell carcinoma in white matter (C2) (C2:HE x 320). (D) Subarachnoid space lined by malignant cells (D1) confirmed to be of epithelial origin on immunohistochemistry for cytokeratin (D2). Cytology of cerebrospinal fluid of the same patient showed tightly cohesive clusters of tumour cells with abundant basophilic cytoplasm and eccentric nuclei. Note small vacuoles in cytoplasm and cytoplasmic blebs (D3). The patient was an elderly male who presented with multiple lower cranial nerve palsies (D1:HE x 120, D2:Immunoperoxidase for cytokeratin x 200, D3:MGG x 400)

Flow chart 1: Approach to evaluation of a patient with brain metastasis



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126 Cerebral Oedema in Relation to Neoplasias of Nervous System

Shankar SK

A variety of mechanical effects and circulatory disturbances can be initiated by expanding lesions of appreciable size in the cranial cavity, which include tumours (primary and secondary), abscesses, large granulomas, massive subdural or intracerebral haemorrhage and also diffuse brain swelling. These circulatory disturbances involving the cerebral vasculature, brain parenchyma and CSF pathway result from inability of the adult cranium to expand under increased intracranial pressure. The disturbances are more proportional to the rapidity of growth of the mass (e.g. intracerebral haematoma, glioblastoma, metastasis) than the size (a large extra-axial meningioma), reflecting the accommodative compliance of the brain to slowly evolving pressure changes. In normal human adults, the intracranial volume includes intracellular (1100–1300 ml), interstitial (100–150 ml), CSF (75–100 ml) and blood (75–100 ml) spaces. Exchanges of fluid amongst these compartments take place in response to osmotic and hydrostatic forces at the interphase between:

a. Intracellular and extracellular compartments (cell membranes);
b. Blood-brain barrier (BBB);
c. CSF and brain (ventricular ependyma and glia limitans at the surface of the brain) and
d. Blood and CSF (choroid plexus and arachnoid granulations).

In addition, nearly 30 ml of water in brain is produced daily from glucose metabolism.[21] As the skull in the adult is rigid, any increase in brain parenchymal volume by tumour or haemorrhages would result in replacement of fluid from the low pressure CSF (approximately 10 mmHg in man) and venous (about 10 mmHg) compartments initially followed by the high pressure arterial compartment (approximately 100 mmHg mean), as enunciated in the Monroe-Kellie doctrine.[38] The volume of cerebrum and cerebellum, the space available in the supratentorial and infratentorial cranial cavity and the ventricular size cause differential pressure gradients by occlusion of the subarachnoid space at the tentorial incisura or between the intracranial cavity and the spinal subarachnoid space following the obliteration of communication at the level of the foramen magnum. This explains why, at times, the lumbar spinal fluid pressure may be within normal limits in patients with raised intracranial pressure. Other modifying factors could be elderly age of the patient with pre-existing cerebral atrophy and infants with pliable cranial fontanelle that provide compensatory capacity for accommodating a space occupying lesion.

The reciprocal relation between the volume of the space occupying lesion and the resultant increase in intracranial pressure is particularly important in causing clinical symptoms. In the later stages of growth of mass lesions, uniform increment of volume causes an exponential increase in intracranial pressure, rendering the patient vulnerable to minor changes in intracranial pressure with serious clinical consequences.[46] These pressure changes are the consequence of distribution of intracellular, interstitial, intravascular and intraventricular fluid volume manifesting as oedema, a subject of extensive clinical and experimental research.

The physiochemical properties of water enable it to act as a solvent for electrolytes and also influence the molecular configuration and hence the function, especially the enzymes and polypeptide chains in biological systems.[21] Association of water with electrolytes determines the osmotic regulation of cell volume and transmembrane ionic gradient essential for excitation and impulse transmission in the nervous system. The normal BBB is relatively permeable to water, but considerably less to ions and principal electrolytes. Brain fluid regulation takes place within the context of systemic fluid volume control, which depends on mutual interaction of osmotic, volume and pressure regulatory receptors in the hypothalamus, heart and kidney, hormones like vasopressin, renin-angiotensin, aldosterone, atriopeptins, immunoreactive substances and their respective sites of action. The concentration of Na^+, K^+ ATPase activity and the presence of Na^+ and K^+ antiporter at the abluminal (external) surface of cerebral capillaries than in other vascular beds in the body suggest that cerebral microvessels play an active role in brain volume regulation and ion homeostasis.[38] The normal brain extracellular space (ECS) amounts to 12–19% of brain volume and is markedly reduced following anoxia, ischaemia, metabolic poisoning and spreading depression of electrical activity. The asymmetric distribution and ionic gradient of Na^+, K^+ and Ca^{++} between the intracellular space (ICS) and the ECS underlie the role of these cations in nerve excitation, conduction and signal transduction.

Under normal conditions, the extracellular compartment within the brain has two fluids—the interstitial fluid and CSF and the ECS extending from the BBB, through a series of 100–150A° wide intricate intercellular spaces, anatomically continuous with CSF spaces. Following hydrocephalus, there is hydrodynamic distension of these collecting channels due to retrograde flooding of the extracellular compartment by the CSF with formation of periventricular oedema.[45]

To understand the pathophysiology of cerebral oedema in various pathological states, it is essential to have some basic insight into the normal structural and physiological elements involved in maintaining fluid homeostasis in the brain.

BLOOD-BRAIN BARRIER

The blood-brain barrier maintains a stable environment for neurons to function effectively. It excludes many toxic substances and protects neurons from circulating neurotransmitters, like norepinephrine and glutamate, following stress response. This exclusion is mediated by specialised anatomic barrier properties of cerebral capillaries. The brain in addition is considered a relatively immunologically privileged site, thereby abrogating the immune mediated and inflammation mediated oedema in contrast to extra CNS sites.[38] Specific examples of immunomodulatory factors include:[15]

a. Transforming growth factor-β (TGF-β) present in CSF, which endows macrophages with a capacity to induce antigen-specific suppression of delayed type hypersensitivity reaction.[23]
b. Low concentration of complement in extracellular fluid of brain reduces the possibility of antibody mediated inflammatory reactions in CNS that can cause oedema.[16]
c. The highly selective membrane at the capillary endothelium has low permeability to hydrophilic compounds and has a selective carrier mediated transport system instead of passive diffusion.
d. Factors produced in this immunologically privileged site on the contrary can distribute widely in the CNS microenvironment without significant diffusional loss into the capillary plasma because of an intact barrier.

In addition, the barrier membrane may control, by selective expression of homing receptors and other mediators of transmembrane passage, the movement of lymphocytes and macrophages in and out of the CNS.[5] Dynamic gradients may be superimposed by neoplasms and inflammatory mass lesions (abscess, granulomas) altering the equilibrium in both halves of the brain by local production of cytokines and immune mediators. Such a mechanism can explain the different immune responses between the normal side and the tumour-bearing side, manifesting with focal oedema or diffuse cerebral oedema even with a small focal lesion.

Anatomy of Blood-Brain Barrier

The structural blood-brain barrier is formed by specialised brain capillary endothelial cells and the astroglial processes that ensheath more than 95% of the abluminal (external) microvessel surface. The endothelial cells in the brain microvessels have tight junctions impervious to hydrophilic compounds (but permeable to lipophilic compounds, like alcohol, addiction forming drugs like morphine and anaesthetics) and relative lack of a pinocytic vesicular transport system.[54] In capillaries of peripheral organs and in sites of brain lacking BBB (circumventricular organs), blood borne polar molecules diffuse passively across vessels through interendothelial fenestrations and by passive fluid phase or receptor mediated endocytosis. The endothelial cells of the BBB are relatively deficient in vesicular transport and the interendothelial zone is not fenestrated but interconnected by a complex array of tight junctions with a resistance of 2000 Ω/cm^2 (normal interendothelial resistance 5–10 Ω/1 cm^2) and exclude even small molecules like K^+ ions.[14] With this barrier, the vessels are impermeable to poorly lipid soluble compounds like mannitol. Anticonvulsants, like phenobarbitone and phenytoin, bind to plasma protein and thus, reduce their delivery to the brain. Glucose, L-DOPA, large neutral amino acids and vinca alkaloids are delivered by non-energy dependent selective endothelial transport and enzyme systems, thus increasing permeability to them. Glucose is transported selectively by a hexose transporter (glucose transporter isotype-1 Glut-1 located on chromosome 1) which is facilitative and saturable and stereospecific glucose is driven across the luminal and abluminal surface of the endothelium, using a higher concentration gradient in the plasma. Glycine, glutamate and neutral amino acids are transported exclusively at the abluminal side of the endothelium by an energy dependent, Na^+ ion dependent carrier system, to limit accumulation of excitatory and inhibitory neurotransmitters in the CNS.[2] Multiple drug resistance (MDR) transporter, a transmembrane protein is found in the microvessels of the BBB, which is involved in delivery of chemotherapeutic drugs like vinca alkaloids, actinomycin D and steroid hormones. MDR genes expressed at the BBB interphase protect the brain from circulating toxins. The external membrane of brain capillary endothelial cells have a high concentration of Na^+ K^+ ATPase that exchanges intracellular Na^+ with extracellular K^+ in an energy dependent manner, thus removing the extracellular K^+ in conjunction with astrocytes following neuronal depolarisation. The catecholamine, vasoactive leukotrienes and glutathione bound products are inactivated by various enzyme systems of the barrier endothelium. These features represent the 'biochemical blood-brain barrier' in addition to the 'physical barrier'. Microvessels in the posterior pituitary, area postrema, subforniceal organ, lamina terminalis, subcommisural organ, pineal gland, median eminence and neurohypophysis lack the BBB.

Interendothelial fenestrations and many pinocytic vesicles account for easy transport across these vessels. The subforniceal organ is a chemoreceptive area that monitors blood angiotensin level to regulate water balance and other homeostatic functions.

During the development of the brain, not all capillaries develop the BBB at the same time, the barrier in the spinal cord forming earlier than in the telencephalon. The evolution of the barrier property is independent of endothelial proliferation.[54] The neural analogue of the brain is vascularised by invagination of proliferating vessels from an extraneural vascular plexus in the leptomeninges. Soon after penetration into neural tissue, the interendothelial fenestrations are lost and they mature into brain capillaries with a BBB. This BBB property is induced in the microcirculation by chemical signals from the brain. These barrier properties will develop in peripheral endothelial cells that invade the brain tissue, but are lost in the brain endothelial cells that invade the peripheral extraneural tissues. Astrocyte foot processes in conjunction with cyclic adenosine monophosphate agonists, specifically increase interendothelial tight junctions and their complexity, but not the neurons and oligodendroglia. This feature has an implication in the evolution of cerebral oedema and contrast enhancement on MRI/CT imaging and consequent clinical implications of respective tumours like oligodendrogliomas and gangliogliomas. Although the capillaries in the centre of the primary tumours (e.g. GBM, oligodendrogliomas) and metastatic tumours lack BBB, those vessels at the border between the proliferating edge of the tumour and the surrounding brain retain their impermeability. To deliver chemotherapeutic agents, the BBB can be opened by hyperosmolar mannitol. This opening of the BBB by mannitol is reversible after about 4 hours, but the major disadvantage is the breach of BBB is random and disseminated,[49] thus neurotoxic drugs cause widespread damage. In view of this, to deliver drugs, local muscle grafts which are richly vascularised and yet lack BBB property in the microvessels are tried. A similar phenomenon occurs following invasion of metastatic tumours and meningiomas into the brain with significant oedema at the interphase.

CEREBROSPINAL FLUID AND HYDROCEPHALUS

The CSF communicates with brain interstitial fluid and acts as a conduit for polypeptide hormones secreted by hypothalamic neurons that act at remote sites in the brain. The pH of CSF affects both pulmonary ventilation and cerebral blood flow. Small solutes diffuse freely between the interstitial fluid and CSF in the perivascular space (Virchow-Robin spaces) and across the ependymal lining of the ventricular system, the pia glial membrane at the surface facilitating movement of metabolites from deep brain parenchyma to the cortical surface and ventricular system. The total CSF volume is approximately 140 ml (lateral and third ventricle—12 ml; spinal subarachnoid space—30 ml, brain subarachnoid space and major basal cisterns containing most of the CSF), as measured by dynamic CT studies. Every day 500 ml of CSF is formed. The choroid plexus, which is structurally similar to the distal collecting tubules of the kidney produces CSF by capillary filtration and an epithelial secretory mechanism, and maintains the chemical stability of the CSF. The capillaries traversing the choroid plexus are freely permeable, but the blood-CSF barrier exists along the apex and sides of the epithelial cells of the choroid plexus. The barrier is responsible for carrier mediated active transport. The secretory capacity of the choroid plexus epithelium is bidirectional, facilitating continuous CSF production into the ventricles and active transport of metabolites out of the CNS into the blood. Under normal conditions, the blood plasma and CSF are in osmotic equilibrium, although CSF is low in K^+, Ca^{++}, bicarbonates and glucose and is more acidic than plasma. The normal pressure of CSF is 65–195 mm water (5–15 mmHg). The formed CSF is drained by a directional movement to the subarachnoid space and into the cerebral venous sinuses by hydrostatic gradient, passing through the arachnoid granulations functioning as unidirectional valves. In view of continuity between the ventricles and the interstitial space, a limited amount is drained into brain capillaries passing through the Virchow-Robin space and to the superolateral subarachnoid space traversing the pia glial membrane. Dynamic disturbances in the formation and drainage of CSF from the ventricles lead to accumulation of the fluid causing hydrocephalus with hydrodynamic sequelae. This hydrocephalus has the following three possible causes:[6]

1. Although rare, enhanced secretion is considered to occur in some functional tumours like choroid plexus papilloma, as resection of the tumour can relieve hydrocephalus. These tumours are usually associated with high CSF protein content, thus impairing the absorption as well.
2. Impaired absorption of CSF may result from conditions that raise intracranial pressure like parasagittal meningioma compressing the veins, thrombosis of cerebral veins and cortical venous sinuses or due to tumour associated hypercoagulable states. Impaired CSF absorption causing communicating hydrocephalus occurs following subarachnoid haemorrhage and bacterial meningitis clogging the channels. Impaired CSF absorption is believed to be the cause of normal pressure hydrocephalus.
3. Obstruction to CSF pathways can result from tumours like septal and medial thalamic gliomas, subependymal giant cell astrocytomas and ependymomas obstructing the foramina of Monro. An anatomical site vulnerable for all the three mechanisms is the narrow aqueduct of Sylvius. Tectal gliomas projecting into the pathway, gliosis due to intrauterine infections and haemorrhage, fourth ventricular ependymomas, choroid plexus papillomas

and medulloblastomas cause obstruction to free flow causing ventricular dilatation proximally.

The accumulated CSF in the hydrocephalic ventricles, due to transient or continuous hydrocephalic attacks with a raised hydrostatic pressure gradient, backtracks into subventricular brain tissue by breaching the ependymal barrier and the subependymal gliotic tissue by bulk flow. The periventricular nuclear zones offer resistance to the spread as also low-grade thalamic gliomas with a glial fibre mesh work.

AQUAPORINS IN THE BRAIN

Regulation of water permeability across the microvessels, between the blood and brain was initially considered to be a simple passive diffusion or by bulk flow across a pressure gradient, lower cerebral blood pressure retarding the formation and spread of cerebral oedema. With the recognition of water channel proteins (aquaporins, AQPs) in Xenopus oocytes for the first time in 1992,[53] the AQP family of at least 11 subtypes has been identified in biological tissue. The AQP family is grouped according to their selectivity characters: water selective channels (AQP 1, 2, 4, 5 and 8), channels transporting glycerol and small solutes (AQP 3, 7, 9 and 10) and channels transporting chloride at low pH (AQP6). Each subtype has its own cellular distribution and distinct regulatory mechanism in its expression.[2,46] AQP1 is expressed in the apical surface of choroid plexus epithelium facilitating CSF formation, capillary endothelial cells throughout the body and a few microvessels in the human brain,[56] in human astrocytoma and metastatic carcinoma. In the spinal cord AQP1 is involved in water recycling and neural signal transduction for pain. AQP4 is the predominant type in the brain, expressed abundantly in perivascular glial processes and ependymal cells, but absent in neurons, oligodendroglia and microglia. AQP4 is expressed also in the abluminal and luminal aspects of microvessel endothelial cells. This protein is anchored by α-syntrophin (an adapter molecule associated with dystrophin) and this interaction is essential for localisation of AQP4 on the foot processes of astrocytes in contact with the vessel for fluid transport. Water transport via AQP4 is essential for normal neural activity. These glial water channels may modulate brain excitability and the initiation and generalisation of seizure activity. In the hypothalamus, the astrocytes express AQP4 and have an osmoregulatory role.[4,48,69]

AQP9 is expressed in the ependymal lining of the ventricle and tanycytes of the mediobasal hypothalamus and less, so in astrocytes and endothelial cells, suggesting a role in extrachoroidal production and resorption of CSF.[18,68]

Upregulation of AQP4 is observed in the oedematous zones of cerebral contusion, bacterial meningitis, glioblastoma and reactive astrocytes around metastatic tumours.[51] Similar enhancement of AQP1 and AQP9 are also noted along the margin of a tumour and decrease in the centre.[3,31,36,37] After focal transient ischaemia, AQP9 expression is increased on AQPs in peri-infarct areas. These observations suggest that AQPs play a role in regulation of post-ischaemic oedema, clearance of lactate from the ischaemic tissue and water transport in tumours.[36] The AQP function in brain microvessels is regulated by the adrenergic innervation of microvessels.[36] It is recently found that AQP1 and AQP4 are also present in brain microvessel endothelial cells. Experimental studies indicate enhanced AQP4 expression following hyponatraemia, around the site of infarcts and after mannitol administration. Similarly, AQP1 expression is increased by dexamethasone in vascular endothelial cells, while testosterone upregulated AQP4 expression.[36,50] AQP4 inhibitors reduce cytotoxic oedema only, if administered early to slow down the entry of oedema fluid into the brain parenchyma but once formed or, at the resolution phase, there is no role. On the other hand AQP4 upregulation facilitates clearance of oedema, providing a low resistance transcellular route for oedema fluid to move out.

CEREBRAL OEDEMA

Cellular and hydrodynamic physiology and hydro-oncotic changes due to electrolyte and protein build-up occurring within the cells and in the ECS leads to obligatory movement of water and water logging, manifesting as oedema.[29,45]

Cytotoxic Oedema

This is the result of deranged cellular metabolism resulting in inadequate functioning of the Na^+ and K^+ pumps in the glial cell membrane. As a consequence, Na^+ and water are retained in the astrocytes. These swollen astrocytes accumulate in grey and white matter, secondarily affecting neuronal and oligodendroglial function and intracellular fluid homeostasis. Cytotoxic oedema is noted with various intoxications (dinitrophenol, triethyltin, hexachlorophene, isoniazide), Reye's syndrome and ischaemia. In this form of cerebral oedema, the BBB is intact still (intact barrier oedema). This needs to be distinguished from focal cytotoxic injuries or abnormal accumulation of metabolic substances (as they cannot be cleared) due to enzyme defects (inborn errors of metabolism).

Hydro-oncotic changes due to electrolyte and protein build-up accruing within the cells and in the ECS leads to obligatory movement of water and water logging. The cellular oedema occurs (cytotoxic brain oedema) through intracellular hyperosmolarity and extracellular hypotonicity and a deranged ATP dependent Na^+/K^+ pump at the cell surface.

Vasogenic Oedema

Disruption of the cerebral capillary barrier (BBB) mechanism by structural and functional alterations of the

cerebral capillary endothelium and astrocyte foot process forms the underlying mechanism for vasogenic oedema. This form of oedema is found in response to trauma, tumours, focal inflammation and the later stages of cerebral ischaemia. The amount of oedema is greater in the white matter than grey matter, with a widened ECS, accumulation of water and Na^+ and decreased K^+ and swollen astrocyte foot processes reflecting initial glial cytotoxicity (closed barrier progressing to open barrier oedema). The interendothelial fenestrations are widened and transendothelial vesicle trafficking is enhanced. Most of the time, combined cytotoxic and vasogenic oedema manifest, one progressing to the other or they can manifest together from the onset, based on pathophysiological events.

Hydrostatic Oedema

Vasogenic oedema has to be differentiated from two other types of brain bulk enlargement like vascular swelling caused by vascular dilatation and venous obstruction. Brain oedema can be the first event in the initial stages of intracranial hypertension. Following acute and transient systemic hypertension beyond 160 mmHg, the 'BBB' and 'blood-CSF' barriers are opened transiently due to hydrostatic pressure and transudation occurs through interendothelial fenestrations and transendothelial fluid trafficking occurs through vesicles. At this stage, initially, there is no significant change in Na^+ and K^+ content of the brain, CSF and muscle with no measurable cerebral oedema, but with progression, the tendency is enhanced. Following venous compression and stasis proximal to the compression, the water with plasma proteins move out as a transudate by hydrostatic pressure through veins and venules which are devoid of a barrier. Later, the extracellular protein accumulation causes an osmotic gradient, drawing the fluid out of the vessels.

Red blood lysis contributes to brain oedema formation after intracerebral haemorrhage. RBC haemolysate (oxyhaemoglobin) has been found to be spasminogen in subarachnoid haemorrhage. Lysed RBCs alter the blood-brain barrier more than packed RBC's in a haematoma. These effects are evident 72 hours after the event.[71]

The cellular mechanisms related to high altitude (mountain sickness) oedema is not clear. Nitric oxide (NO) induced vasodilatation and altered cerebral circulation as a response to hypobaric oxygen status is considered to cause cerebral oedema.[17,71]

Osmotic Oedema

The usually marginally higher osmolality of the CSF and extracellular fluid as compared to plasma is reduced by an abnormal hypo-osmolar oncotic gradient created in the circulation following SIADH, water intoxication and haemodialysis. As a consequence water flows into the ECS causing cerebral oedema. In this form, the BBB is relatively intact. In the dynamics of events this form resembles oedema due to venous stasis.

The extracellular brain oedema (interstitial) appears as a result of build-up of oedema fluid in the ECS and can be due to hydrostatic extracellular brain oedema (through enhanced ultrafiltration and formation of CSF), oncotical (osmotic) extracellular brain oedema (vasogenic oedema) and hydrocephalic extracellular brain oedema. Most of the times, combined brain oedema manifests, one progressing to the other or they can manifest together from the onset based on pathophysiological events.

Hydrocephalic Extracellular Oedema

This form of oedema is essentially paraventricular, following a breach in the ependymal barrier leading to backflow of CSF into the brain parenchyma. Subependymal gliosis and the nuclear areas around the ventricle resist this movement of fluid. The hydrostatic fluid accumulation in the ventricles could be due to the rare enhanced production of CSF by ultrafiltration by choroid plexus, or continuous and longstanding stasis due to defective drainage at different levels. In this form of oedema the BBB is intact till the late stages. The oedema is essentially due to hydrostatic pressure and without a significant oncotic gradient. The precise mechanism underlying such oedema-induced neuronal dysfunction is not clear. It is suggested that interstitial brain oedema impairs oxidative metabolism even at the early stage of hydrocephalus and there is a shift to anaerobic glycolysis in spite of normal cerebral blood flow.[35]

Brain Oedema Following Trauma

Brain oedema leading to expansion of brain volume has a critical impact on morbidity and mortality following traumatic brain injury (TBI). Two major types of traumatic brain oedema exist; vasogenic due to a breach in the blood-brain barrier and fluid accumulation in the interstitial space and, cytotoxic oedema due to sustained intracellular water accumulation. Following TBI, various kinins and mediators of inflammation are released, which enhance vasogenic and cytotoxic oedema. In addition, osmotic brain oedema is caused by extravasation of plasma products and thus, a local imbalance in blood and tissue products and hydrocephalic oedema occur due to obstruction of CSF outflow. Cytotoxic oedema is of decisive pathophysiological importance following TBI as it develops early and persists, while the BBB is gradually restored, reducing vasogenic oedema. Avoiding cerebral anaerobic metabolism and acidosis is beneficial to control lactate and H^+ ion. No definite compound inhibiting the mediators and ion channels showed beneficial results in clinical trials despite successful experimental studies. In therapy, both cytotoxic and vasogenic oedema need to be managed simultaneously in traumatic brain injury. This assumes greater importance when TBI compounds a pre-existing brain tumour/mass lesion in clinical practice.[67]

BRAIN TUMOURS AND OEDEMA

Oedema associated with a brain tumour often exceeds the mass effect induced by the tumour itself resulting in raised intracranial pressure, destruction of tissue homeostasis and neurological disturbances.[66] All aggressive brain tumours, like malignant gliomas, metastatic tumours and many benign tumours, like meningiomas, produce oedema regardless of the cell of origin. The lethal effect of tumour-associated oedema is illustrated by the nearly ten-fold reduction in brain tumour mortality following reduction of oedema by steroid therapy.[32] Vasogenic oedema is the archetypical example with brain tumours, produced by fluid flow into the ECS of the brain parenchyma through an incompetent BBB. All focal lesions, including primary and metastatic tumours, abscesses, encephalitides and radionecrosis produce cerebral oedema. Brain swelling associated with long-term therapy of tumours remains to be an important issue in cases of recurrent tumours and lesions treated by radio/chemotherapy and radiosurgery rather than resection. In contrast to perilesional oedema and reactive astrocytosis associated with meningiomas and metastatic tumours, oedema around high-grade gliomas is characterised by extensive infiltration by tumour cells, thus distinguishable by histological and clinical properties.

a. Metastatic and non-glial tumours produce angiogenic factors, promoting new capillary formation with significant ultra structural abnormalities like more frequent pinocytic vesicles in the endothelial cells, and an irregular basal lamina.

   In human glial tumours, the endothelial junctions are either short or elongated. The endothelial cells display hyperplasia, irregular basal lamina and a large extravascular space.[57]

   In malignant gliomas, the endothelial cells have defective tight junctions, fenestrations, increased pinocytic vesicles and incomplete ensheathment by the basal lamina.

   These structural abnormalities explain a defective or lost barrier function facilitating exudation of plasma into the surrounding brain.

b. The morphologically disrupted tight junctions in the newly formed vessels in malignant gliomas are associated with paucity or lack of occluding[26] claudins[19] and junctional adhesion molecules.[42] These transjunctional proteins, through ZO-1 and ZO-2 bind to cytoskeletal proteins in endothelial cells. The decreased expression or function of these proteins results in opening of interendothelial junctions and initiation of oedema, and this feature is found in high-grade gliomas (Grade III–IV).[39]

c. VEGF, a cytokine, has a mitogenic and chemotactic action on the endothelial cells facilitating angiogenesis and also enhances the permeability of the endothelium, which is more potent than histamine.[12] VEGF exerts its effect on venules and capillaries, but not on smooth muscle cells or fibroblasts of vessels. VEGF impairs the function of occludin and thus opens the tight junctions and enhances fenestration of the endothelium. Upregulation of VEGF is found in gliomas, meningiomas and metastatic tumours.[52] In meningiomas (WHO Grade I) the upregulation of VEGF is mediated by platelet derived growth factor (PDGF), epidermal growth factor (EGF) and oestrogens.[41,43,60] Transitional, meningotheliomatous and secretory meningiomas are associated with oedema.[20] The peritumoural brain oedema in cases of meningiomas is found to be related to pial blood supply following a breach in the arachnoid and adherence to the brain.[10] Secretory meningiomas and anaplastic meningiomas are frequently found to be associated with extensive pial blood supply, while fibrous and psammomatous meningiomas, either in the cranium or spinal canal are rarely fed by pial blood vessels and produce mild oedema. In terms of pathophysiology, small tumours with significant oedema and large tumours with minimal oedema appear to correlate with the amount of pial blood supply from the superficial cortex. This suggests that the cerebral microvasculature on penetration into an extracerebral meningioma looses inherent barrier properties and behaves like the leaky extracerebral vessels. The secretion of VEGF by the meningeal tumour cells could facilitate angiogenesis from the pial microvessels and their entry into the meningioma.[44]

   By serial analysis of gene expression (SAGE) in microvascular endothelial cells derived from human brain tumour specimens Carson-Walter et al.[11] found five unique markers confined to the tumour microvasculature. One of these genes, plasmalemmal vesicle associated protein-1 (PV-1) was identified in the transendothelial channels in the fenestrated endothelium. This protein is selectively induced in high-grade gliomas and in hypoxic conditions like stroke causing disruption of the BBB, but not in the normal brain with an intact BBB. In view of its location on the cell membrane and selective expression in tumour endothelium along with angiogenesis, PV-1 inhibition by molecular targeting (RNAi) is a therapeutic modality that is being explored in the treatment of gliomas.[11]

d. Microglia rich brain tumours, especially gliomas, are associated with peritumoural oedema, via arachidonic acid, prostaglandin E2, lipoxygenase derived biologically active metabolites and cox-2 produced by these activated cells.[7,62] Induction of nitric oxide synthase (NOS) following anoxia and the modulating role of NO in vasodilatation, peritumoural oedema and angiogenesis have been found more commonly with metastatic tumours than primary brain tumours. Serotonin, thromboxanes and platelet activating factors are the other vasogenic substances involved in the pathophysiology of tumour associated oedema, especially with a coexisting cerebral infarct adjacent to a tumour and associated macrophage response.[27,58]

e. The spread of vasogenic oedema fluid by hydrodynamic bulk flow is determined by anatomic barriers like the nuclear areas and long fibre tracts which can be splayed apart. In the white matter, because of low resistance, even a small pressure gradient can result in spread of oedema in finger like projections similar to a phenomenon observed following cortical venous thrombosis and resultant white matter oedema. This formation of oedema and its spread by bulk flow is more common in metastatic tumours, which lack a blood-brain barrier. Diffusion tensor imaging by MRI has provided an insight into this pathophysiology, but also opened a new avenue of convection enhanced (bulk flow of fluid against gradient) drug delivery as a therapeutic modality.[22]

Malignant thalamic gliomas with perilesional oedema use the ventricular surface to drain off the fluid by bulk flow, depending on cell density and intercellular spaces below the ependyma.

As a consequence of hydrocephalus and raised CSF pressure, spontaneous but intermittent cerebrospinal rhinorrhoea is seen in some cases. Spontaneous ventriculostomy-perforation of the ventricular wall at a point where it is thin like the lamina terminalis, median eminence, peripheral white matter, between the fornix and forceps major, is nature's diversion route to reduce ventricular hydrostatic pressure. Cisternography reveals alterations in the flow dynamics of CSF. Now CT and MRI can offer similar information. In normal individuals technetium labelled albumin injected into the lumbar subarachnoid space can be traced by a gamma camera up to the cortical convexities and the CSF may reflux into the ventricles only, if the pressure dynamics are altered.

The volume of cerebral oedema, especially peritumoural, is dependent not only on the rate of production but also the resorption of fluid away from the lesion via the channels in the interstitial space which drain into the ventricles and to a smaller extent into the subarachnoid space. The resorption of extravasated proteins by the reactive astrocytes in the white matter reduces the oncotic pressure and facilitates the resorption of oedema. The local venules and capillaries also participate in resorption of oedema. Dexamethasone has been found to act at the endothelial level by retarding oedema formation than by enhancing resorption.[30] The extracellular oedema distribution volume and capillary permeability rate constant are found to be higher in meningiomas than gliomas and metastatic tumours.[5] Dynamic perfusion weighted MR studies revealed lower regional cerebral blood flow volume and lower blood flow rate in zones of peritumoural oedema, which is modulated by dexamethasone.[8] Another interesting observation on analysing apparent water diffusion (ADC) and directionality of water movement (anisotropy) by Diffusion Tensor (DT) MR imaging is the greater apparent water diffusion and less restriction of anisotropic movement in high-grade gliomas. This suggests destruction of the extracellular matrix by invading tumour cells. Correlative studies between MR imaging and histopathological features have revealed greater concordance between T2 signal abnormality and fractional anisotropy by DT imaging with oedema propagation and tumour infiltration. This understanding of oedema fluid flow dynamics and tumour cell spread is of great interest not only to optimise oedema treatment but also to facilitate drug delivery and brain tumour therapy.[47]

Dexamethasone not only reduces VEGF expression but also interferes with the effect of VEGF on capillary endothelial cells, acting through a glucocorticoid receptor.[24,40] As thrombin, a protein involved in the coagulation cascade is implicated in angiogenesis, cell proliferation and oedema formation, thrombin antagonists, like argatroban, have been found to be useful in reducing oedema and the occurrence of tumour related neurological deficits.[28]

In view of oedema induction by the macrophage system in the brain through the cox-2 pathway, selective cox-2 inhibitor like Rofecoxib have been tried and found to be as effective as dexamethasone in experimental studies. Rofecoxib acts by reducing the production of VEGF.[70] To treat brain tumour related oedema and reduce dependency on corticosteroids, the phytotherapeutic agent, 'Boswellic acid' has been tried in Europe and found effective in inhibiting oedema formation and even growth of malignant gliomas.[61] In a physiological approach to control *in vivo* corticosteroid release, attention has been directed towards corticotropin releasing factors (CRF) and they have been found to be useful in reducing BBB permeability in patients with brain metastasis and in experimental models with gliomas.[64] To control both glioma growth and associated cerebral oedema through the VEGF pathway, the anti-angiogenic drug, Semaxanib (selective inhibitor of tyrosine kinase activity of VEGFR, Flk-1), has been tried and found efficacious in rats with gliosarcoma and nude mice bearing human GBM xenografts.[63] Pan VEGFR inhibitor (via tyrosine kinase inhibitor), AZD2171, has been found to alleviate oedema in patients with GBM.[9] As the oedema fluid clearance in the brain requires passage through aquaporin-4, modulation for enhanced expression provides a novel therapeutic option.[36]

SECONDARY EFFECTS OF CEREBRAL OEDEMA-RAISED INTRACRANIAL PRESSURE

Papilloedema

This is caused by compression of the central retinal vein as it traverses the subarachnoid space of the optic nerve sheath. The compression results in fluid exudation from the engorged veins and capillaries. The fluid accumulation is minimal in the optic nerve as the enhanced venous pressure is countered by the transmitted increased intracranial pressure around the nerve and the fluid accumulation is maximal in the unsupported

disc zone. Reduced blood flow in the region of the disc and lamina cribrosa further contribute to axonal swelling interfering with rapid axonal flow and increasing swelling.[44,65]

Intracranial Herniations

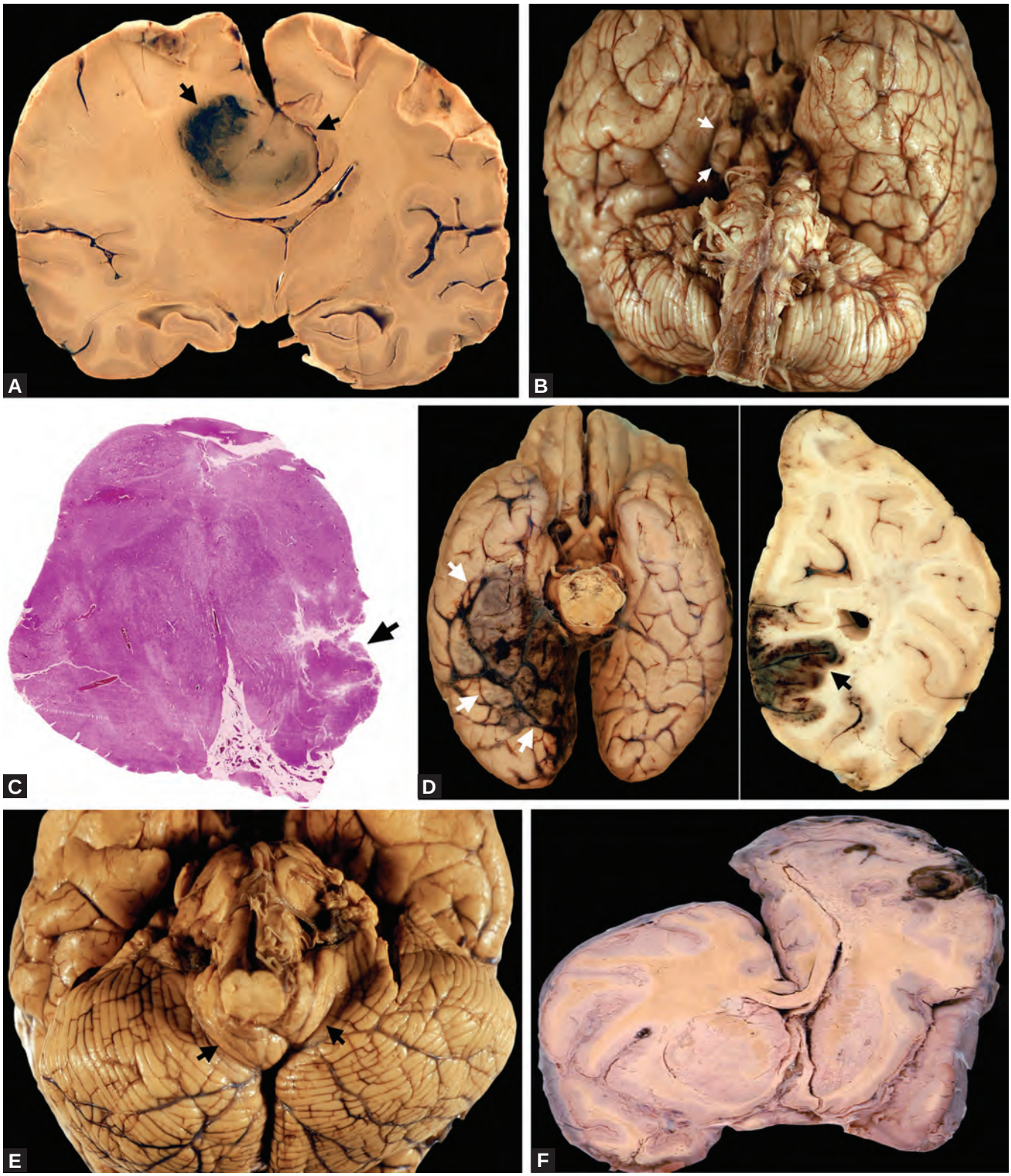
Laterally placed tumours in frontoparietal areas result in depression of the corpus callosum on the same side and herniation of the supracallosal gyrus beneath the free edge of the falx resulting in indentation along the medical surface of the cingulate gyrus (Fig. 1A). It may compress the branches of the anterior cerebral artery resulting in infarction.[59] With downwards displacement of the brain, the lesser wing of the sphenoid causes grooving on the inferior surfaces of the orbitofrontal lobes.

Raised intracranial pressure due to supratentorial tumours either in the midline or laterally placed, causes downwards displacement of the brain, impacting the uncus and parahippocampal gyrus through the tentorial hiatus (Fig. 1B). The characteristic early sign is the wedge shaped pressure necrosis in one or both parahippocampal gyri and in severe cases haemorrhagic necrosis occurs.[1] Rapidly growing temporal gliomas usually result in ipsilateral uncal herniation. More centrally located tumours cause bilateral herniation, compressing and deforming the mid-brain and aqueduct. Lateral displacement of the brain following unilateral herniation pushes the cerebral peduncle against the rigid free edge of the tentorium leaving a groove referred to as Kernohan's notch (Fig. 1C). Rarely, there may be bilateral lesions of this kind on the crura suggesting torsion and swelling of the brainstem. Obliteration of the lumen of the aqueduct by the herniation can result in raised intraventricular pressure supratentorially, but not transmitted to the spinal subarachnoid space, recording a normal spinal pressure paradoxically.[34] Decompression of the supratentorial tumour and lowering the pressure in the cranial cavity may cause caudal displacement of the brainstem either along the midline or laterally, thus stretching the paramedian or long circumferential perforators and causing their rupture or avulsion and pontine tegmental haemorrhages. The tentorial hiatus is of variable size in individuals, the tentorium enveloping the brainstem more tightly in some than in others and thus determining the form and degree of tentorial herniation and the related clinical features.[13] Kinking of the posterior cerebral artery along the tentorial free edge can cause necrosis of the medial occipital cortex, especially the calcarine cortex, with punctate haemorrhages. The venous component is usually associated with it to cause conspicuous congestion (Fig. 1D). Similarly, caudal displacement of the brainstem and kinking of the posterior cerebral artery can cause secondary compression of the ipsilateral oculomotor nerve. Following unilateral hippocampal herniation and concomitant lateral pressure on the tegmental part of the midbrain may cause circulatory disturbances in the third cranial nerve nuclei leading to 'paralysis like loss of upwards movement' of the eyes and pupillary asymmetry.[33] With cerebellar tumours, the roots of the sixth cranial nerve may get compressed against the anterior inferior cerebellar artery, causing sixth nerve paresis. Lateral displacement of the cerebrum may cause circulatory disturbances in the stalk of the pituitary with secondary hormonal disturbances.[33] Similarly, caudal displacement of the brainstem and the drag may cause bruising of the pituitary stalk against the dorsum sellae or avulsion.

Expanding lesions in the posterior fossa may cause upwards herniation of the cerebellar vermis through the tentorial hiatus and cause compression of the superior cerebellar arteries leading to ischaemic infarction. Similarly, a downwards thrust can cause compaction of the cerebellar tonsils into the foramen magnum with grooving and necrosis of the tonsils (Fig. 1E). Severe tonsillar herniation, especially sudden, can cause compaction of the medulla with fatal consequences, while a mild degree of cerebellar tonsillar herniation may not be of any clinical consequence.

The surgical opening in the vault of the skull provides an outlet for the oedematous brain to fungate out with necrosis due to compression of meningeal vessels along the edge of the bone. This is usually seen in herniation of the cerebrum through a burr hole or craniotomy wound in cases of glioblastoma (Fig. 1F). The herniated parenchyma is usually necrotic and haemorrhagic. Persistent intracranial pressure can cause erosion of posterior clinoid processes and enlargement of the sella and thinning along the lesser wing of the sphenoid and orbital plates. Ionising radiation and chemotherapy to brain tumours and haemopoietic malignancies cause damage to the vessel walls. The brain tissue contiguous to the neoplasm is more vulnerable to radiation injury than the normal CNS. The fibrinoid necrosis of the vessel walls and resultant exudation of the protein rich serum into the necrosed brain results in oncotic brain oedema. In addition, enhanced vascular permeability and an impaired blood-brain barrier causes exudation of fibrin into the white matter followed by oedema and demyelination.[55] Primary injury to the brain vasculature with an early effect on cerebrovascular endothelium is an important cause of oedema following radio/chemotherapy and radionecrosis, manifesting with a mass effect. Variable degree of fibrillary gliosis in the white matter in children treated for acute lymphoblastic leukaemia is considered to be secondary to reversible cerebral oedema.[25] In the areas of demyelination following radiation, the BBB is relatively intact in contrast to vasogenic oedema. Although radionecrosis and chemotherapy related necrosis do not elicit significant inflammation during the healing phase, intense microglial response may cause cytokine mediated oedema, which is usually steroid responsive.

Brain tumour oedema and the associated structural changes in the surrounding brain are a complex event and multifactorial. It is the result of imbalance between



Figs 1A to F: (A) Coronal slice of the brain at level of mamillary body showing a transfalcine herniation (arrows) caused by malignant glioma of the cingulate gyrus. (B) Uncal herniation on right side (arrows) caused by a supratentorial mass lesion displacing the brain downwards and laterally. Note the torsion of the brainstem as well. (C) Whole mount preparation of the brainstem of the pontomesencephalic junction showing destruction of the crus due to compression against the tentorial free margin (arrow)—Kernohan's notch. Note linear haemorrhages on the opposite side (LFB x 8). (D) Unilateral large calcarine infarct on the right side (arrows) and infarction of the basis pontis following unilateral downwards displacement of the brain and compression of right posterior cerebral artery against the tentorial free margin. A close-up view of coronal slice shows haemorrhagic infarction of the calcarine cortex extending to the adjacent gyri. (E) Marked bilateral tonsillar herniation with a groove caused by impaction against foramen magnum (arrows) compressing the medulla oblongata. (F) Upwards herniation of the frontal cortex with malignant glioma through craniotomy opening. Note the distortion of the ipsilateral ventricle and the corpus callosum

water moving in and out of the brain. Molecular abnormalities of tumour endothelial tight junctions enhancing blood-brain barrier permeability and identification of water channels, the AQPs and their molecular diversity have enhanced our understanding of pathophysiology. Many dynamic events are yet to be understood in order to optimise the therapeutic approach at the bedside.

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127 Tumour Markers in Tumours of Nervous System

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A tumour marker is defined as "any substance that makes possible either a qualitative diagnosis of neoplasia or a quantitative estimate of tumour burden".[7,39] Hence, a tumour marker is also broadly defined as any cell product related to any event during tumour formation and/or growth such as malignant transformation, proliferation, differentiation/cell lineage and metastasis.[62]

USES OF TUMOUR MARKERS

The following are the uses of tumour markers:[7,39,62]

a. Diagnosis: Improves diagnostic capability
b. Characterisation of tumour in terms of cell lineage/degree of differentiation and maturation
c. Evaluation of treatment response:
   - Success of surgery—complete/incomplete surgical resection of the tumour
   - Effectiveness of chemotherapeutic drug
   - Guide for selection of most effective drug for each case
d. Assessment of aggressiveness of tumour:
   - Helps selection of treatment strategies
   - Helps prediction of prognosis/outcome
e. Detection of primary tumour metastasising to nervous system
f. Detection of recurrence of neoplastic lesion
g. A tool for screening asymptomatic population—for early detection of malignant disease.

CHOICE OF TUMOUR MARKERS

The most important criteria for the selection and use of tumour markers are their high sensitivity and specificity to identify the neoplastic nature, cell of origin and molecular fingerprint of neoplasia.[7,62] Otherwise, given the low prevalence of brain tumours in the general population, the marker would have very little predictive value.

CLASSIFICATION OF TUMOUR MARKERS

- Markers detected in Serum/CSF as a screening modality
- Markers detected in cells/tissues (immunohistochemical markers) to identify tumour cell lineage (Table 1)
- Molecular markers.

Table 1: Immunohistochemical markers for identifying cell lineage in CNS tumours

Glial tumours	• Glial Fibrillary Acidic Protein (GFAP)
	• S-100 protein
Neuronal tumours	• Synaptophysin
	• Neurofilament
	• Beta-tubulin
	• Microtubule associated protein (MAP 2)
	• Neuron specific enolase (NSE)
	• Alpha-internexin
	• Peripherin
	• GFAP +/- (aberrant expression)
Choroid plexus tumours	• Cytokeratin
	• S-100
	• Transthyretin
	• GFAP (20%)
Meningeal tumours	• Epithelial membrane antigen (EMA)
	• Vimentin
	• S-100
	• Cytokeratin
Schwann cell tumours	• S-100
	• Leu 7
Melanocytic tumours	• S-100
	• HMB 45
	• Meland D
Lymphomas	• Leucocyte common antigen (LCA)
	• B and T Cell
	• B (CD-20) and T cell (CD 3)
Germ cell tumours	• Alpha foetoprotein (AFP)
	• Human chorionic gonadotropin (HCG)
	• Placental alkaline phosphatase (PLAP)
	• Human placental lactogen
Tumours of vascular origin	• Factor VIII
	• CD 34 (also stem cell)
	• VEGF
	• Ulex Europeus
Neuroendocrine tumours	• Synpatophysin
	• Chromogranin
	• NSE
Stem cell	• Nestin, CD-133

USE OF TUMOUR MARKERS DETECTED IN SERUM/CSF

Oncofoetal Proteins

The only group of CNS tumours wherein detection of tumour markers in serum/CSF is useful at present is the germ cell tumours[1,7,62] (Table 2). Detection of tumour markers, such as AFP, HCG, PLAP, CEA and HPL, in the serum/CSF is more reliable and sensitive for diagnosis than CSF cytology. Further, in this group of tumours, markers help to monitor response to therapy and to identify early tumour recurrence.

The only drawback is that the absence of tumour markers in serum/CSF does not exclude a diagnosis of germ cell tumours.

TUMOUR MARKERS IN CELLS/TISSUES (IMMUNOHISTOCHEMICAL MARKERS)

Diagnostic neuropathology has benefited immensely in the last two decades with the advent of immunohistochemistry on tissue sections.[14,35,40,61] The development of reagents to identify epitopes associated with cell lineage, cell cycle, cell activation, oncogene and tumour suppressor gene products have helped to clarify the nature of cellular maturation, tissue differentiation, tumour progression and metastasis. All this has resulted not only in improving diagnostic accuracy, but also in clarifying developmental pathways within and between cell lineages involved. It has also lead to revision of tumour classification, prognostication and prediction of clinical outcome.

Use of Oncofoetal Markers[5,8]

The use of oncofoetal markers is chiefly for the diagnosis of intracranial germ cell tumours, both primary and metastatic. The various immunohistochemical markers for the diagnosis of germ cell tumours are enumerated in Table 3.

Types of Tumour Markers in Cells/Tissues[15,16,34,36]

Tumour Markers for Diagnostic Use

1. Cell lineage/differentiation markers:
   a. Structural/cytoskeletal proteins, cytokeratin, glial fibrillary acidic protein (GFAP), neurofilament, desmin, vimentin, nestin, actin, tubulin, microtubule associated proteins (MAPs)
   b. Cell surface antigens: Lymphoid markers—leucocyte common antigen (LCA), T cell markers (CD3), B cell markers (CD20)
   c. Secretory products: hormones, Immunoglobulins
   d. Neuroendocrine markers: Synaptophysin, chromogranin, neuron specific enolase (NSE).
2. Oncofoetal markers
   – Alpha foetoprotein (AFP)
   – Placental alkaline phosphatase (PLAP)
   – Human chorionic gonadotropin (HCG)
   – Carcinoembryonic antigen (CEA)
   – Human placental lactogen (HPL)
3. Miscellaneous
   – S-100, epithelial membrane antigen (EMA)

Tumour Markers Useful for Prognostic Evaluation

1. Cell cycle/proliferation markers
2. Oncogene/tumour suppressor gene proteins
3. Growth factors/receptors
4. Hormones/receptors
5. Adhesion molecules
6. Angiogenic factors

Table 2: Immunoreactivity of some common CNS tumours

Tumour	*GFAP*	*S-100*	*Synaptophysin*	*NFP*	*EMA*	*CK*
Astro/Oligo/Ependymal	+	+	-	-	-	-
Neurocytoma	+/-	-	+	+	-	-
Neuroblastoma/medulloblastoma	+/-	+/-	+	+/-	-	-
Ganglioglioma	+	+	+	+	-	-
Choroid plexus	+/-	+	-	-	+/-	+/-
Meningioma	-	+/-	-	-	+	+/-
Schwannoma	+/-	+	-	-	+/-	-
Metastatic carcinoma	-	+/-	-	-	+	+

Table 3: Immunohistochemical markers of germ cell tumors

Diagnosis	*PLAP*	*AFP*	*β-HCG*	*HPL*	*CK*
Germinoma	+	-	+/-	-	10%
Teratoma	+	+/-	-	-	+/-
Embryonal carcinoma	+	-	-	-	+
Yolk Sac tumor	+/-	+	-	-	+
Choriocarcinoma	+/-	-	+	+	+

Cell Proliferation Markers

Various stages of cell proliferation in neoplastic cells can be detected to get an insight into cell biology and evolve methodologies in cancer therapy (Table 4).

Uses of cell proliferation markers: These are very useful to measure the growth rate of tumours and hence these are markers of prognostic significance.[43,61]

a. Correlate with histological tumour grades and indicate aggressiveness
b. Correlation with prognosis. It is essential to realise that some cells, like vascular endothelial cells, intestinal epithelial cells and germinal cells, have inherent high proliferative activity as a reparative process.

In astrocytic tumours, a positive association between MIB-1 LI (labelling Index) and five year progression free survival (PFS) has been noted in a series of 98 cases of paediatric high grade gliomas by Pollack et al.[43] Thus, in patients with LI of less than 18%, the five year PFS was 33+7% whereas, in those with LI greater than 36%, the five year PFS was 11+6%. Others, however, have not noted any such correlation. In atypical neurocytomas, with MIB-1 LI of greater than 2%, a good correlation with outcome has been described by many authors.

Thus, cell kinetic studies are more accurate and objective methods of assessment of tumour growth rate and biological aggressiveness of tumours lacking definitive histopathological features. Proliferation indices can be used as an important adjunct to histological grading for guiding patient prognosis and management. However, their usefulness in predicting of tumour behaviour in terms of recurrence and survival remain controversial and, hence, they cannot be used as standalone prognostic markers.[27]

Molecular Genetic Markers

The clinical significance of molecular parameters for diagnostic and prognostic assessment of gliomas is just emerging. Some are elaborated below:

Loss of 1p/19q and prognosis: Oligodendrogliomas are the first CNS neoplasms in which a genetic signature, viz. chromosomal segments 1p and 19q deletion has been associated with outcome and response to chemotherapy.[18,19,21,22,31,32,53,58] A 5-year survival rate of 95% has been observed for those with deletions of 1p and 19q versus 65% for those without deletions. Those with deletions also had longer overall survival of 172 months versus 105 months without deletions.[6,19] In a series of 39 patients with anaplastic oligodendroglioma nearly all of the 70% with positive response to PCV chemotherapy (procarbazine, CCNU and vincristine) exhibited loss of heterozygosity (LOH) of 1p/19q. Recently published data indicate a similar and better outcome in patients with LOH 1p/19q treated at the time of diagnosis with both PCV chemotherapy and radiotherapy or only by chemotherapy.[6,30] Other recently published studies also support this positive correlation between LOH 1p/19q and survival.[5,23]

Two recent phase III prospective clinical trials by Radiation Therapy Oncology Group (RTOG) 9402 and European Organization for Research and Treatment of Cancer (EORTC) 26951 have included correlative analyses of 1p and 19q deletions in tumour specimens of anaplastic oligodendroglioma and anaplastic oligoastrocytoma as prognostic markers. The RTOG 9402 study showed that LOH for either 1p or 19q was a significant independent prognostic variable correlating with the outcome ($p = 0.01$). In EORTC 26951, a significant difference in survival was also observed for patients with 1p/19q loss as compared with those without deletions ($p = 0.003$).[9,10,59] Thus, combined loss of 1p and 19q is identified as a favourable prognostic factor in both studies independent of the treatment arms. Thus, irrespective of whether a patient was treated with RT alone or with PCV and RT, the survival was better if the patient had 1p/19q deletions. However, at this time, there is insufficient information to allow therapeutic decisions or assignment of treatment to be made solely on the basis of 1p and 19q deletion status.

This molecular signature of oligodendrogliomas has also become very important in diagnostic assessment of these tumours, e.g. for differential diagnosis of oligodendroglioma from neurocytoma, DNET, etc. The presence of 1p/19q deletion supports a diagnosis of oligodendroglioma.[48]

Table 4: Methods of detection of cell proliferation on tissue sections

Marker	*Technique*	
Mitotic figure	Routine Histology	M phase
AgNOR staining	Silver stain	Nucleolar organising region
[^{3}H] – Thymidine	Autoradiography	S Phase
BrdU/IdU	Immunohistochemistry	S Phase
Ki-67/MIB-1 antibody	Immunohistochemistry	G1, S, G2, M Phase
PCNA antibody	Immunohistochemistry	G1, S, G2, M Phase
Topoisomerase II	Immunohistochemistry	G1, S, G2, M Phase
Fluorescent antibody labelling of cell membrane	Flow cytometry	All phases

p53 mutations and prognosis: TP53 is a tumour suppressor gene and in tumours it is expressed in mutated form. The prognostic significance of mutated TP53 over expression in diffuse astrocytomas is controversial. TP53 mutations were not associated with an overall change in the prognostic outcome in a series of 159 consecutive WHO grade II astrocytomas and oligoastrocytoma patients treated at a single neurosurgical clinic.[11]

In the GBM group also, there is conflicting evidence as to whether or not *p53* alterations independently correlate with patient survival, although they may indirectly impact prognosis in certain patient subgroups.[8,49,55] While some hospital-based studies showed no association between TP53 status and outcome in patients with a glioblastoma,[38,52] one study indicated that the presence of TP53 mutations was a favourable prognostic factor.[49] At the population level, univariate analysis revealed that the presence of TP53 mutations was predictive of longer survival.[38] However, age-adjusted multivariate analysis revealed no difference in survival between patients with or without TP53 mutations.[38]

Thus, the presence of TP53 mutations may simply indicate occurrence of the glioma in a younger age group and slow progression, and does not reflect the survival period and prognosis as commented by some studies.[45] These studies need to be critically evaluated before interpreting for prognostication.

Presence of *p53* mutations are of diagnostic help in a few situations, e.g. for differential diagnosis between grade II and pilocytic astrocytoma. If *p53* mutation is present, it favours a diagnosis of grade II diffuse astrocytoma as *p53* mutations are rarely seen in pilocytic astrocytomas.

EGFR amplification/overexpression and prognosis: The predictive value of epidermal growth factor receptor (EGFR) amplification has been unclear. In earlier hospital-based studies (40 cases), EGFR amplification was associated with poorer survival in patients with a glioblastoma.[28,57] In contrast, a meta-analysis of seven previous studies (a total of 395 glioblastomas) did not reveal a significant predictive value of EGFR amplification.[40] Several studies have suggested that EGFR amplification is predictive for certain age groups of glioblastoma patients.[3,50,52,54] Shinojima et al.[50] reported that EGFR amplification was a significant predictor of poorer overall survival in glioblastoma patients and that the EGFR gene status was a more significant prognostic factor in younger patients (<60 years). Simmons et al.[36] reported that EGFR overexpression was associated with poorer survival of glioblastoma patients younger than the median age, and that EGFR over expression was negatively associated with survival in cases without TP53 mutation. Other studies found EGFR amplification to be a predictor of longer survival only in older glioblastoma patients.[3,54] At the population level, EGFR amplification did not affect survival of glioblastoma patients at any age.[38]

Loss of 10q/PTEN mutations and prognosis: Second only to gains on chromosome 7, losses involving chromosome 10 are quite frequent in astrocytomas, limited mainly to high-grade tumours.[12,41] LOH 10 is the most frequent genetic alteration in glioblastomas and occurs in 60–80% of cases.[29,46]

The available data on PTEN alteration and survival of glioblastoma patients are heterogeneous. In several studies, PTEN mutations were not associated with prognosis of glioblastoma patients[2,49,54,63] and this was confirmed at the population level.[38] Terada et al.[56] identified LOH around PTEN as a predictor of less favourable prognosis in a set of 40 astrocytomas (grades II–IV).

Sano et al.[47] reported that the PTEN mRNA level is an independent prognostic factor for glioblastoma patients. Patients whose tumours had low PTEN transcript levels had significantly shorter survival times than patients with high PTEN mRNA expression.

Smith et al.[54] reported that PTEN mutations were a powerful independent marker for short survival in their group of anaplastic astrocytoma patients. PTEN mutations were detected in 11 of 62 tumours, with the median survival times being 4.4 months versus 34.4 months for cases with and without PTEN mutation, respectively.[54]

C-myc/N-myc amplification, Erb-B 2 overexpression and Trk-C expression in prognosis of medulloblastomas: Chromosomal gains of MYCC and MYCN locus has been identified in medulloblastoma in 4–17% of cases. The MYCC or MYCN amplification is associated with the aggressive large cell tumour variant and a poor clinical outcome. Over expression of ErbB2 receptors has been proposed as an independent indicator of aggressive behaviour, while high TrkC receptor expression indicates a favourable outcome.[33]

Genetic/Molecular Markers for Prediction of Response to Treatment

Temozolamide (TMZ): O6-Alkylguanine-DNA Alkyltransferase (AGT)

Temozolamide (TMZ) is an attractive therapeutic agent for brain tumour management through much work remains to be done to develop biomarkers that can reliably predict response among malignant glioma patients. One clearly important modulator of TMZ response is O6-alkylguanine-DNA alkyltransferase (AGT), a critical DNA repair protein also referred to as O6-methylguanine-DNA-methyltransferase (MGMT). This enzyme removes chloroethylation or methylation damage at the O6 position of DNA guanines, thereby protecting normal cells from exogenous carcinogens, and similarly protecting tumour cells from alkylating and methylating chemotherapeutic agents.[47] AGT levels vary significantly across and within tumour types.[13,51] Methylation of the AGT promoter can diminish AGT transcription and expression.[17] AGT levels can be most readily measured by either immunohistochemistry or by a methylation specific PCR assay.[26,44,60]

Friedman et al. initially implicated AGT in TMZ responsiveness among malignant glioma patients.[58] In

a series of 36 newly diagnosed patients (including 33 with GBM), the response rate to TMZ was 60% among patients with low-level of expression of AGT (detected by immunohistochemistry in 20% of cells) compared with only 9% among patients with high-level of AGT (present in 20% of tumour cells). Similarly, following Carmustine (BCNU) chemotherapy, a radiographically detectable response in 12/19 (64%) patients with malignant glioma was noted with methylated AGT compared to only 1/28 (4%) patients with unmethylated AGT.[20] Two subsequent prospective studies demonstrated that AGT methylation is associated with better survival among malignant glioma patients treated with TMZ.[24,25] Of note in these studies is that the Kaplan-Meier survival curves for patients with methylated and unmethylated AGT become particularly divergent after 12 months of follow-up. Furthermore, these studies suggest that tumour AGT status is an independent predictor of outcome following alkylator-based chemotherapy, because AGT status does not correlate with established clinical prognostic factors.

Therefore, a looming, fundamental question is whether tumour AGT status should ultimately direct treatment of newly diagnosed GBM patients at all. Although results to date suggest that AGT status is an important biomarker for TMZ responsiveness, these findings require further validation in additional prospective analyses.

Microarray Based Expression Profiling for Prognostication of Glial Tumours

In the past, the number of genes that could be evaluated at one time was limited. Because most cancers (including GBM) have very complex patterns of differential gene expression profiles, the study of single genes in individual tissues only provides limited information towards our understanding of the bigger picture of neoplasia. The advent of high throughput complementary DNA (cDNA) and oligonucleotide microarray technology allows comprehensive gene expression analyses and has presented a significant advance in neuro-oncology.[4,37]

Microarray expression profiling of gliomas has identified molecular subtypes as well as genes associated with tumour grade, progression and patient survival.[4,24,25,37,42] Reports that expression profiles predict outcome better than histological classification provide support for the hypothesis that neoplasms defined morphologically as anaplastic astrocytoma and GBM represent a mixture of molecular genetic subtypes.[4,37,42] For example, the study of Phillips et al.[42] on high grade gliomas revealed three subclasses—one high grade glioma subclass displaying neuronal lineage markers associated with longer survival while two other subclasses enriched for immature neural stem cell markers displaying short survival. Poor prognosis subclasses exhibited markers of proliferation or of angiogenesis and mesenchymal differentiation. Upon recurrence, tumours frequently shifted towards the mesenchymal subclass.

Thus, given the possibility that molecularly distinct disease entities may exhibit different clinical responses, a greater understanding of the behaviour of molecularly defined subsets of tumours may aid in better prognostication and development of more effective therapies. At present various tumour markers are utilised by many centres with a hope to improve the prediction of tumour biology and use it in prognosticating the clinical response and survival. For a neurosurgeon of the coming years, it is essential to be aware of the developments in basic science to translate these to bedside patient care and effective treatment.

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128 Tumours of Cranial and Peripheral Nerves

Sundaram C, Anita Mahadevan

Before the advent of advanced imaging techniques, tumours of the cranial nerves were detected only by looking at bony changes they produced in the skull base foramina (on plain radiographs) or invasive techniques such as cisternography and angiography. Current imaging techniques and advances in treatment modalities have completely altered the natural history of these tumours making these one of the success stories of modern neurosurgery. Further, new insights into the biology of peripheral nerve tumour growth and development have unfolded newer modes of oncogenesis. These molecular advances are opening up potentially new and exciting avenues targeted therapies.

This group of tumours shows diversity not only in the wide range of histopathological features but also in their anatomical location and clinical behaviour. More frequently than any other class of CNS tumours, they occur in the setting of familial tumour syndromes, in particular, the neurofibromatoses.

One of the long standing difficulties with nerve sheath tumours was the struggle to develop a universally accepted classification. The current WHO classification[16] is provided in Table 1.

Table 1: WHO classification of peripheral nerve sheath tumours

Benign tumours of peripheral nerve
Schwannoma
Conventional
Cellular
Plexiform
Melanotic
Neurofibroma
Cutaneous (diffuse/nodular)
Plexiform
Perineurioma
Intraneural perineurioma
Soft tissue perineurioma
Malignant peripheral nerve sheath tumours (MPNSTs)
Epithelioid
MPNST with divergent mesenchymal and/or epithelial differentiation
Melanotic
Melanotic psammomatous

SCHWANNOMA

Schwannomas are benign, slow growing neoplasms of the central and peripheral nerve sheath that arise anywhere distal to the oligodendroglial-Schwann cell myelination junction. They are defined by WHO as encapsulated benign tumours composed exclusively of Schwann cells. They have been variously referred to in literature as "neuromas", "neurinomas" (Verocay, 1910) and "neurilemmomas" (Stout, 1935).

The majority of schwannomas are solitary, sporadic tumours although syndromic associations are seen particularly when multiple.

Syndromic Associations

- Neurofibromatosis type 2 (NF2) is associated with bilateral vestibular schwannomas and multiple peripheral nerve schwannomas.
- Schwannomatosis, a rare genetically distinct disorder[18] is associated with multiple peripheral schwannomas in the absence of bilateral vestibular schwannomas.
- Carney's complex is associated with psammomatous melanotic schwannomas.

Incidence and Site

As neoplasms of the nerve sheath, they may arise intracranially, intraspinally or in the periphery. They constitute 5–10% of all intracranial tumours. Sensory roots are more often affected than motor or autonomic roots. The peak incidence is in the third to sixth decade although no age is exempt. The intracranial tumours have a female predilection.

Ninety per cent of intracranial schwannomas arise from the vestibular division of the eighth cranial nerve. Other cranial nerves combined account for only 10% of all intracranial schwannomas. Trigeminal schwannomas are the second most frequent and may take origin from the ganglion, root or rarely the divisions of the trigeminal nerve. Glossopharyngeal, vagal and spinal accessory nerve schwannomas are recorded while involvement of other cranial nerves, such as oculomotor, trochlear, abducens and hypoglossal, that are purely motor nerves are extremely rare. Intraparenchymal schwannomas (intracerebral and intramedullary) are extremely rare but have been reported.[4,14]

The clinical and radiographic features vary according to the parent nerve involved. In general, these tumours present as mass lesions, produce neurological dysfunction by distorting the parent nerve and compressing the surrounding cranial nerves, brainstem and cerebellum.

They cause widening of the bony foramina and scalloping or erosion of bone at the skull base that are recognised on plain radiographs. They arise as extra-axial masses in the subdural space and widen the cisterns within which they are located, which is how they are recognisable on cisternography or pneumoencephalography. Angiographically, they are detected to receive their blood supply from branches of the external carotid system. On CT, they appear as isodense to slightly hyperdense, well circumscribed lesions which enhance on contrast administration. On MRI, they remain slightly hypointense on T1W1 and hyperintense on T2W1 and enhance uniformly and intensely on contrast administration. Degenerative change, particularly cystic change, is readily detectable on MR imaging.

Gross Pathology

Schwannomas are typically discrete, solitary and well encapsulated. They tend to displace the parent nerve eccentrically and have a smooth lobulated appearance (Figs 1A to C). The cut surface is glistening and interrupted by bright yellow areas (xanthomatous change), cysts and haemorrhage. In tumours arising from the peripheral nerves, the parent nerve of origin can usually be identified.

Conventional Schwannomas

Microscopically, conventional schwannomas are classically described as being composed of alternating compact zones (Antoni A pattern) and less cellular, loose textured (Antoni B) regions. The Antoni A regions have well ordered arrays of elongated spindle shaped cells with tapering, buckled nuclei and eosinophillic cytoplasm. The nuclei may line up in palisades with intervening nuclei-free zones forming characteristic structures called Verocay bodies (Fig. 1D). The Antoni B regions are poorly organised clusters of large vacuolated cells with small round nuclei (Fig. 1E). Cystic change and xanthomatous change are common in these zones, as are hyalinisation of vessel walls with thrombosis and perivascular haemosiderin deposits (Figs 1F to H). The Antoni B regions, therefore, probably represent degenerative changes. The prominent vascular hyalinisation may be responsible for intense contrast enhancement on imaging. Cystic change in the tumour contributes to hyperintensities on T2W1. The classic histology is more prominent in intraspinal and peripheral tumours, while the intracranial tumours typically lack the prominent palisades and show more prominent Antoni B regions with prominent xanthomatous changes.

Attention has been focused on two microscopic variants—the ancient schwannoma and the cellular schwannoma that demonstrate histological features that could be mistaken for malignant change.

Ancient Schwannomas

This refers to large tumours of long duration that have undergone extensive degenerative changes. They commonly demonstrate bizarre pleomorphic nuclei that represent degenerative atypia and do not connote malignancy (Fig. 1I).

Cellular Schwannomas

These are defined as hypercellular schwannomas composed exclusively of Antoni A areas, and devoid of Verocay bodies (Fig. 1J). Mitotic activity is readily identifiable (not exceeding 4 per 10 high power fields). They are found most often in paravertebral sites in the pelvis, retroperitoneum and mediastinum. Intracranially, they are described in facial and trigeminal nerves.[5] A single report of multiple cellular schwannomas is on record.[26] The clinical presentation does not differ, but the finding of hypercellularity, fascicular growth pattern, nuclear atypia and mitosis may lead to a mistaken diagnosis of malignancy. The Ki-67 labelling index ranges from 5.6% to 6% and p53 staining is found in a significant proportion, although with only few positive cells.

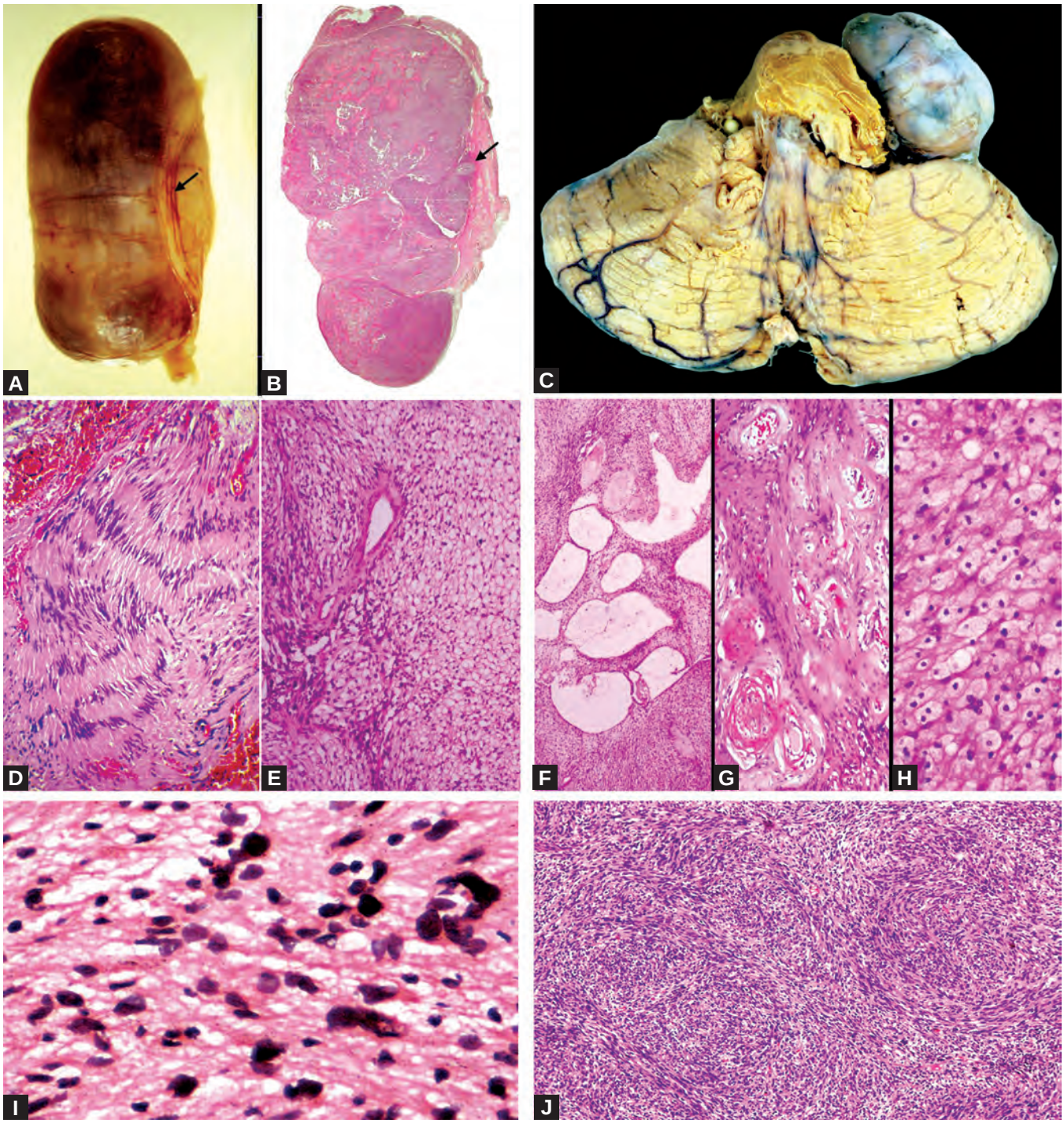
Cellular schwannomas are benign and may tend to recur, particularly the intraspinal examples, but no case has been reported to metastasise or show a malignant transformation.

Melanotic Schwannoma

These are grossly pigmented tumours that have cells that both ultrastructurally and immunophenotypically have schwannian characteristics but contain melanosomes and are reactive for melanoma markers. They are extremely rare and occur a decade earlier than conventional schwannomas. They may be psammomatous[3] or non-psammomatous.[11] The former involve nerves of the intestinal tract or heart and rarely cranial nerves. The majority of non-psammomatous tumours are seen in the spinal nerves. The distinction is of importance as approximately 50% of patients with psammomatous tumours have Carney complex[2] (that includes cardiac myxoma, lentigenous facial pigmentation and endocrine hyperactivity, most commonly Cushing syndrome with multinodular adrenal hyperplasia or acromegaly due to pituitary adenoma). Slightly over 10% of melanotic schwannomas follow a malignant course.

Plexiform Schwannoma

This refers to the growth of the tumour in a plexiform or nodular manner.[27] It is more often seen in the skin or subcutis of an extremity, head and neck or trunk where it arises from a nerve plexus. The cranial and spinal nerves are usually spared and the tumour is associated with NF2 (not NF1) or schwannomatosis.[9]



Figs 1A to J: (A) Gross photograph of an encapsulated schwannoma arising from a nerve (arrow). (B) The whole mount histology section shows encapsulation of the tumour and compressed fibrotic remnants of nerve (arrow) [HE x 5]. (C) Cerebellopontine angle schwannoma arising from vestibulocochlear nerve. The tumour is well encapsulated and compressing the pons. (D) Palisading of Schwann cells with cell free zones forming characteristic Verocay bodies in compact Antoni (type A) zones. (E) Loose textured microcystic Antoni (type B) zones. (F to H) Degenerative changes in a schwannoma with cystic change. (F) Vascular hyalinisation. (G) Xanthomatous change. (H) Marked nuclear atypia (degenerative nature) in an ancient schwannoma. (I) Is not indicative of malignancy. (J) Cellular schwannoma showing compact Antoni A areas with increased cellularity and low mitotic activity [D&E: HE x 120, F&G: HE x 80, H: HE x 240, I: HE x 320, J: HE x 120]

Immunohistochemistry

Tumour cells exhibit strong and diffuse positivity for S100 protein. They may also be positive for myelin-associated glycoprotein (Leu 7) and focally express GFAP. They are usually negative for myelin basic protein and EMA (marker of perineurial cell).

Ultrastructure

Ultrastructural features are diagnostic and demonstrate long entangled cell processes that enclose the intervening stroma analogous to normal axon-Schwann-cell-axon sheathing arrangement (pseudomesaxon). This is in contrast to a neurofibroma in which true axons are found within the tumour surrounded by Schwann cell processes (mesaxons). A well defined continuous basal lamina separates the cell processes from the stroma. The cells are devoid of pinocytotic vesicles and cell-cell junctions are rare.

Syndromic Association

Most schwannomas are sporadic but, when multiple, occur in association with two inherited tumour syndromes—neurofibromatosis 2 (NF2) and schwannomatosis. Bilateral vestibular schwannomas are pathognomonic of NF2 while multiple peripheral schwannomas in the absence of other NF2 features is characteristic of schwannomatosis, a newly recognised syndrome.[18] The gene product of NF2 Merlin/schwannomin is believed to perform a tumour suppressor gene function. Biallelic inactivation of the NF2 gene is identified in most sporadically occurring schwannomas as well as meningiomas.[25] Recent studies suggest that Merlin belongs to the protein 4.1 super family and is closely related to the ERM protein and provides a linkage between membrane-associated proteins and actin cytoskeleton. Being located on the membrane cytoskeleton, Merlin is not likely to directly control the cell cycle machinery. Merlin is probably a novel type of tumour suppressor that co-ordinates the processes of growth-factor receptor signalling and cell adhesion.

Psammomatous melanotic schwannomas are associated with Carney complex. Extensive genetic studies have implicated NF2 gene on chromosome 22 as a tumour suppressor gene integral to the formation of sporadic schwannomas also. Inactivating gene mutations are detected in up to 60% of schwannomas including the cellular variant. Loss of the protein merlin (or schwannomin) that the gene NF2 encodes has been demonstrated by immunochemistry or Western blotting as a universal finding in all Schwannomas.

NEUROFIBROMA

These are defined as well demarcated intraneural or diffusely infiltrative extraneural tumours that are composed of an admixture of neoplastic Schwann cells, perineurial-like cells and fibroblasts. Like Schwannomas they are most often single when sporadic but, when multiple, are associated with neurofibromatosis 1 (NF1).

There is no age or gender predilection. They have three distinct growth patterns: (1) localised; (2) diffuse and (3) plexiform. In the localised form, they present as cutaneous nodules (localised cutaneous neurofibroma) or as a mass arising from a peripheral nerve (localised intraneural neurofibroma). Unlike Schwannomas, they are occasionally seen in the spinal nerves[23] but are virtually unknown in the cranial nerves (Table 2). The diffuse growth pattern is rare and can present with localised involvement of skin and subcutis (diffuse cutaneous neurofibroma) or extensive involvement of soft tissue of an entire limb (elephantiasis neuromatosa). The diffuse form, despite its extensive involvement, never shows malignant transformation. The plexiform variant on the contrary is virtually pathognomonic of NF1 and, although rare (2–3%), is the most frequent form to show malignant transformation. They arise from large nerve trunks or plexuses.

The cutaneous tumours are either circumscribed or diffuse, and appear gelatinous and grey-tan on sectioning. Those confined to nerves are fusiform and well circumscribed while the plexiform variant that arises from nerve trunks or a plexus appears multinodular causing expansion and matting together of involved trunks producing a characteristic "bag of worms" appearance.

Table 2: Differences between neurofibroma and schwannoma

Features	*Neurofibroma*	*Schwannoma*
Cell of origin	Unidentified, mixture of Schwann cell, axons, perineurial-like cell and fibroblast	Schwann cell
Parent nerve	Fusiform enlargement/infiltration	Compressed
Capsulated	No	Yes
Growth pattern	Localised, diffuse, plexiform	Localised, plexiform (rare)
Degenerative changes	Uncommon	Common (cystic change, xanthomatous change, hyalinisation, haemorrhage)
Immunohistochemistry for S100	Focal	Diffuse
Ultrastructure	Mesaxons	Pseudomesaxon
Syndromic association	NF1	NF2 Carney's complex Schwannomatosis
Malignant transformation	2–3% (NF1)	Exceptional

Histological Features

Neurofibromas are characterised by both cellular and stromal components. The former is an admixture of neoplastic Schwann cells, perineurial-like cells and fibroblasts that typically proliferate in a haphazard fashion dispersed in a stroma rich in collagen and mucopolysaccharides (Figs 2A to C). If arising from a medium sized nerve, the tumour remains confined within the epineurium. If arising in small nerves, they spread diffusely into soft tissues. Large diffuse neurofibromas often show tactile differentiation with Wagner-Meissner like corpuscles and pigment containing melanotic cells. In the plexiform variant, the nerve bundles are matted together by tumour (Fig. 2D) and commonly demonstrate residual recognisable nerve fibres at the centre (Fig. 2E) and may infiltrate the dorsal root ganglia (Fig. 2F). Unlike schwannomas, degenerative changes (cystic change and xanthomatous change) as well as vascular hyalinisation are lacking. Immunohistochemically, S100 staining is present but less diffuse than in schwannomas. Variants of neurofibromas have been described.

Atypical Neurofibroma

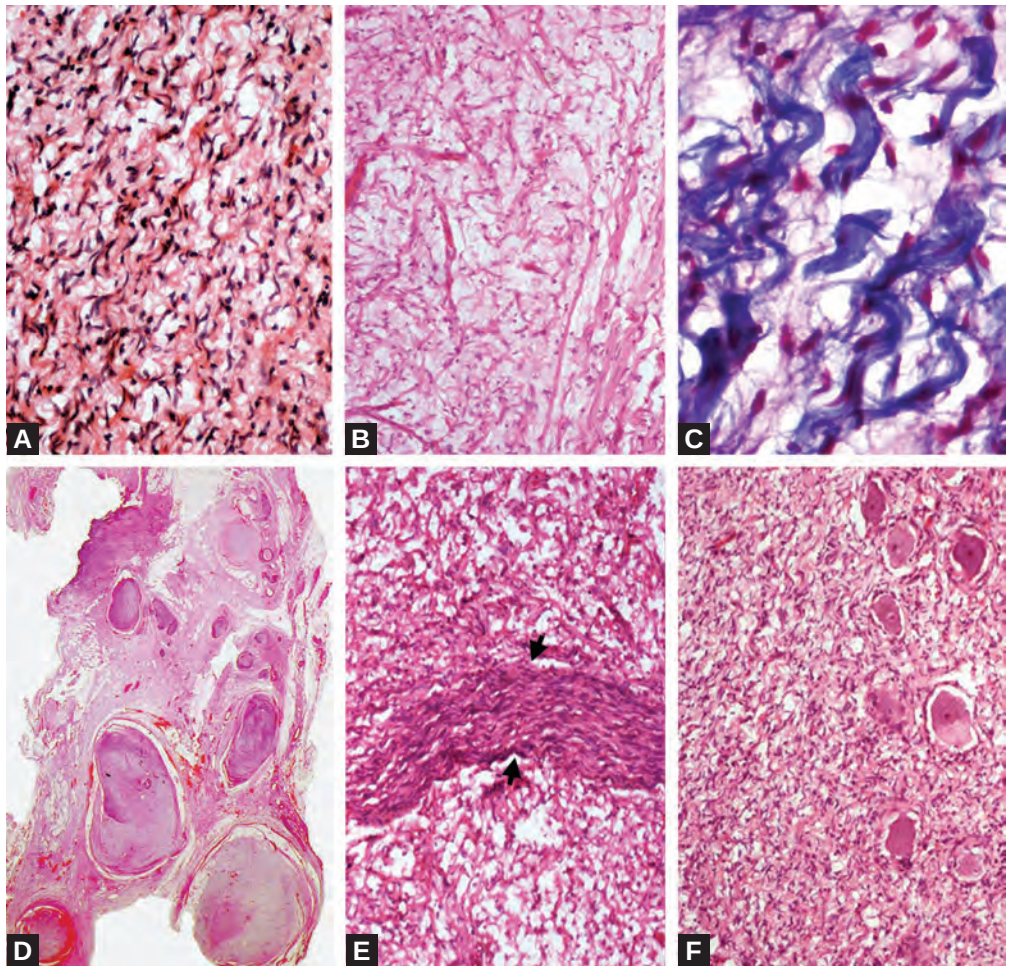
Presence of nuclear atypia (degenerative) in the absence of cellularity and mitotic activity in an otherwise typical neurofibroma is termed atypical neurofibroma. No risk of malignancy is identified in this variant.

Cellular Neurofibroma

Similar to cellular schwannomas, these demonstrate increased cellularity and appreciable mitotic activity, but do not connote malignant transformation. They need to be differentiated from malignant peripheral nerve sheath tumour (MPNST) by their low mitotic activity, lack of necrosis and absence of significant cellular atypia.

Cell Biology

Given the admixture of cell types, there has been a continuous debate as to whether neurofibromas represent a neoplastic or hyperplastic phenomenon. *In vivo* studies have convincingly demonstrated that Schwann cells from neurofibromas in contrast to normal Schwann cells



Figs 2A to F: (A) Neurofibroma showing characteristic wavy spindle cells dispersed haphazardly. (B) Myxoid degeneration with (C) collagen deposition in stroma resembling "shredded carrots" is common [A,B: HE x 120, C: Masson trichrome x 240]. (D) Whole mount view of expanded fascicles of varying sizes in a plexiform neurofibroma [HE x 5]. (E) Plexiform neurofibroma showing remnant of nerve twig in centre. (F) Infiltrating a dorsal root ganglion. (F) [HE x 120]

promote angiogenesis and invade the basement membrane[24] and, when grafted into nude mice, form neurofibroma-like tumours.[19] Recent studies have demonstrated that both NF1 associated tumours and sporadic neurofibromas show inactivation of NF1 gene.[20] The NF1 gene product, neurofibromin is a tumour suppressor and its inactivation in Schwann cells causes neurofibromas. The fibroblasts isolated from neurofibromas, however, demonstrate at least one normal allele and express NF1 protein.

Prognosis

The plexiform neurofibromas and those arising from major nerves are precursor lesions of MPNST. Malignant transformation is rare in the other forms of neurofibroma but, in the plexiform variant, malignant transformation occurs in 2–5%. It is more common in deep seated lesions and in cases where the duration of NF1 exceeds 10 years.

PERINEURIOMA

A benign tumour composed exclusively of neoplastic perineurial cells, they occur as intraneural lesions producing expansion of the involved nerve or as soft tissue lesions with no demonstrable origin from a nerve. They are extremely rare with just over 30 cases reported in literature.[15]

They are unassociated with any syndromes. Monosomy of chromosome 22 has been demonstrated in both types.[7,12] The intraneural perineuriomas most often affect peripheral nerves of the extremities causing nerve thickening, and progressive muscle weakness and atrophy closely mimicking hypertrophic neuropathies.

Intraneural perineuriomas are benign and do not show any tendency to recur or metastasise. Biopsy is sufficient for a diagnosis and resection should be avoided to retain neurological function.

MALIGNANT PERIPHERAL NERVE SHEATH TUMOURS

The term incorporates lesions that arise from specialised cells of the endoneurium and perineurium. It encompasses the previously used terms—malignant schwannomas and neurofibrosarcoma.

To define a tumour as MPNST it must satisfy one of the following criteria:[22]

- Arise from an identifiable peripheral nerve trunk and have histological features consistent with recognised types of MPNST.
- Arise in a patient with NF1 and have a histological type conforming to MPNST.
- Arise from a pre-existing benign nerve sheath tumour (schwannoma, neurofibroma or ganglioneuroma).
- Show histological features corresponding to a recognised type of MPNST with morphological evidence of Schwann cell or perineurial cell differentiation.

These types of MPNST recognised by WHO are depicted in Table 1.

Predisposing Factors

NF1 is the most important risk factor for MPNST and accounts for 50% of all tumours. Risk of a patient with NF1 developing MPNST varies in various series from 2–29%[21] with a lifetime risk of 10%. In general, patients with NF1 develop tumours a decade earlier. Tumours associated with NF1 show a loss of NF1 expression and high levels of Ras, but additional genetic events that inactivate key cell cycle regulators are required for malignant transformation. Radiation is another important risk factor seen in 10% of cases with a long latent period between exposure and tumour development.[6,10]

Incidence and Localisation

These are uncommon neoplasms and almost two thirds arise from neurofibromas, often of the plexiform type in the setting of NF1. Development from a pre-existing schwannoma is extremely rare.

MPNSTs occur most often in adults in the third to sixth decade. Large and medium nerves are more prone to involvement with the most common sites being the brachial plexus in the upper arm and the sciatic nerve in the buttock and thigh. They are large and often demonstrate foci of haemorrhage and necrosis on sectioning. Cranial nerve involvement is extremely rare with the fifth nerve being most frequently involved.[1,17]

Histopathology

MPNSTs grow within a nerve fascicle in fibrosarcoma-like pattern and commonly invade through the epineurium into the soft tissues. Large areas of geographical necrosis and brisk mitotic activity are common. Perivascular accentuation of tumour and haemangiopericytic growth pattern is a common feature. About 15% exhibit unusual histological features such as epitheloid morphology and divergent differentiation.

Epithelioid MPNST does not show any association with NF1 and carry a better prognosis. Divergent differentiation may produce glandular epithelium (Glandular MPNST), while neuroendocrine and squamous differentiation is uncommon. Association with NF1 in glandular MPNST is high as is the mortality.

MPNSTs showing rhabdomyosarcomatous differentiation (Malignant triton tumours) are more common than glandular MPNST and 60% of patients have NF1. Few cases from the cranial nerves are on record.[13,17]

Prognosis

The prognosis is extremely poor with overall 5-year and 10-year survival rates being only 34% and 23%.

Recent studies suggest that positron emission tomography and glucose analogue 18-fluorodeoxyglucose might be useful in presurgical differentiation between benign and malignant nerve sheath tumours.[8]

KEY POINTS

- Benign nerve sheath tumours include schwannoma, neurofibroma and perineurioma.
- Solitary tumours are often sporadic while multiple tumours are associated with familial tumour syndromes particularly neurofibromatosis 1 and 2 and a newly recognised entity, schwannomatosis.
- Schwannomas more commonly involve cranial and spinal nerves while cranial nerve involvement is very uncommon in neurofibromas.
- Sensory nerves are preferentially involved by schwannomas with the vestibular division of the eighth nerve and the trigeminal nerve being most frequent.
- Cellular schwannomas tend to recur with predilection for paravertebral regions (pelvis, retroperitoneum and mediastinum).
- Malignant transformation in schwannomas is exceedingly rare.
- The plexiform variant of neurofibroma has a higher risk of malignant transformation.
- Advances in imaging techniques (positron emission tomography and use of 18-FDG) allow presurgical detection of malignant transformation.
- Newer surgical options are being evolved in treatment particularly stereotactic radiosurgery allowing more precise treatment with retained function of the involved nerve.
- Molecular advances have revealed novel modes of tumourigenesis in producing sporadic tumours and development of neurofibromatosis that may have an implication in developing targeted therapies.

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129 Tumours of the Choroid Plexus

Yasha TC

Choroid plexus tumours (CPTs) are intraventricular neoplasms arising from the lining epithelium of the choroid plexus and comprise the following:[36]

Choroid plexus papilloma (CPP)	WHO Grade I
Atypical papilloma (APP)	WHO Grade II
Choroid plexus carcinoma (CPC)	WHO Grade III

INCIDENCE

Tumours of the choroid plexus are rare neoplasms forming 0.36–0.6%[39,43] of all intracranial tumours. They are more frequent in children and account for 2–3.69% in them.[39] Twenty per cent of patients present during the 1st year of life and 50% in the first decade.[43] In infants less than 2 years of age CPT are the third most common CNS tumours following medulloblastoma and ependymoma.[34] Papillomas occur approximately 3–5 fold more often than carcinomas,[28] and the latter are more common in children less than 2 years of age.

SITE

In children, CPT most frequently arise in the lateral ventricle, followed by the fourth and third ventricle,[4,7,43] while in adults the fourth ventricle is the commonest site followed by the lateral ventricle.[43] CPCs occur more often in the lateral ventricles of children less than 2 years of age.[30] CPT also present at the cerebellopontine angle as an extension of the tumour through the foramen of Luschka where they are often benign and rarely bilateral.[22] Diffuse hyperplasia of the choroid plexus[11] associated with communicating hydrocephalus is an entity now categorised as bilateral CPP.[8,12] Rare intra-parenchymal examples with no attachment to the ventricle have also been reported in the cerebral cortex[5] and in the brainstem.[33]

AETIOLOGY

Choroid plexus tumours are usually sporadic. They have been associated with Li-Fraumeni and Aicardi syndromes and a possible association with SV 40 virus has also been suggested.

Association with SV 40 Virus

Human polyoma viruses (e.g. BK and JC viruses) are tumourigenic in animal models and cause ependymomas and choroid plexus neoplasms in them. In humans, the presence of viral DNA signature of a closely related monkey virus, SV40 was noted in 50% of choroids plexus tumours and in almost all ependymomas.[3] Transgenic mice expressing SV40 large T antigen and SV11(+), develop spontaneous tumours of the choroid plexus.[38] The viral T antigen binds to cellular protein targets that favour tumourigenesis.

Role of p53

There is increasing evidence for the role of *p53* involvement in CPT tumourigenesis. CPTs are seen in patients of Li-Fraumeni syndrome (LFS) with *p53* germline mutations.[21] Loss of heterozygosity, other chromosomal alterations and possibly association with SV 40 virus are likely mechanisms of inactivation of wild type *p53*.[27]

Aicardi Syndrome

CPTs also occur in association with Aicardi syndrome, an X-linked dominant disorder with a triad of corpus callosal agenesis, infantile spasms and chorioretinal lacunae.[10,40]

Recurrent chromosomal abnormalities in CPT are gains of chromosome 7 and region 12q.[13] Gains of 9p and loss of 10q have correlated with a more favourable prognosis in CPCs.[37]

CLINICAL FEATURES

Choroid plexus tumours are usually slow growing and cause symptoms by mass effect and obstructive hydrocephalus. Occasionally, communicating hydrocephalus is caused by excessive CSF production by the functional tumour cells particularly in bilateral lateral ventricular CPP. Lesions in infancy may cause enlargement of the head. In children, the median age at presentation is 17 months (1-138) for CPP and 13 months (2-102) for CPCs.[28] Congenital tumours have also been identified on antenatal sonography.

A rare case of temporal lobe epilepsy caused by CPP in the temporal horn in a 27-year-old lady has been reported.[31]

NEUROIMAGING

On MRI, CPP are brilliantly enhancing intraventricular, lobulated masses, isointense on T1W and well-defined, and hyperintense on T2W images (Fig. 1A). CT scans

reveal isodense to hyperdense lesions. MR spectroscopy shows a higher level of myo-inositol in CPP compared to CPCs. On the other hand, markedly elevated levels of choline are noted in malignant tumours of the choroid plexus.[20]

MRI features commonly associated with CPC are a large intraventricular lesion (approximately 4–5 cm), with irregular enhancing margins; heterogeneous signal, oedema (73%), hydrocephalus and the presence of disseminated tumour (45%).[30] The latter is associated with a poor prognosis. Metastatic spread to lung and bone has also been reported.[9]

On occasion, CPP exhibit 'drop' metastases into the thecal sac[15,18] and rarely a more diffuse subarachnoid spread can be seen,[23] even after a long asymptomatic period.[45] Hence, total neuraxis imaging at the time of initial diagnosis as well as periodic follow-up examinations after resection is recommended.[45]

PATHOLOGY

Macroscopy

Papillomas are generally circumscribed, greyish red, soft tumours with a characteristic granular, cauliflower like surface (Fig. 1B), with focal gritty areas due to calcification. On sectioning, the tumour has variably compact and loose grey white areas with haemorrhage and cystic change.

Choroid plexus carcinomas can be infiltrative, less circumscribed and show areas of haemorrhage and necrosis (Fig. 1C).

Microscopy

CPP are benign papillary neoplasms resembling the normal choroid plexus and are composed of delicate papillary fronds with central fibrovascular cores lined by a layer of benign cuboidal to columnar epithelium (Fig. 2A). The vessels are thin walled or variably hyalinised. Histological features of anaplasia are not seen and mitotic activity is very low. Rarely, oncocytic change of the epithelial cells with abundant eosinophilic cytoplasm rich in mitochondria, focal clear cell, mucinous change or melanisation may be observed. These changes do not have any prognostic significance. Rarely, a mucinous adenoma pattern[35] or tubulo-glandular pattern may be noted.

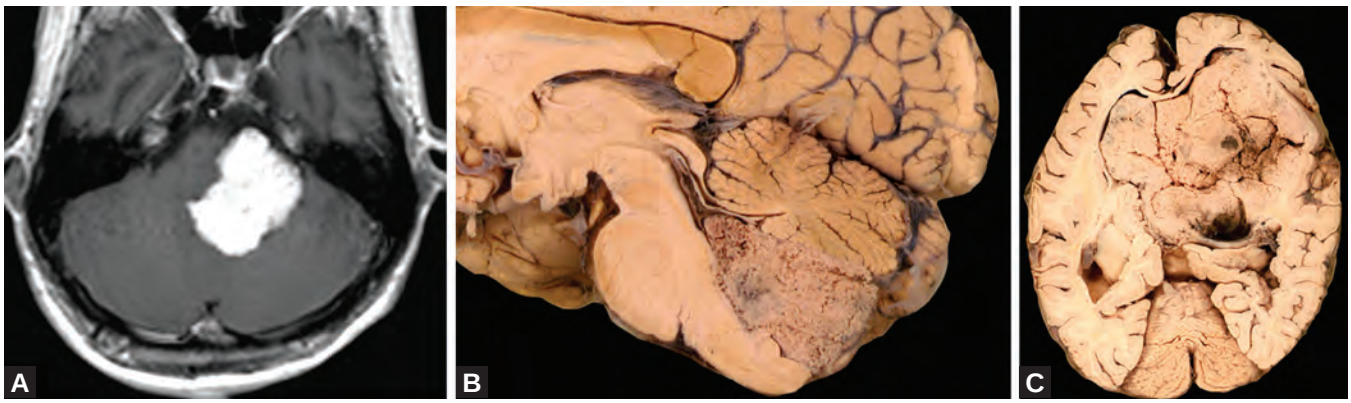
Psammomatous and non-psammomatous calcification, xanthomatous change, lymphocytic infiltrates in the stroma, cystic change and haemorrhage are often present. Extensive psammomatous calcification may be associated with aggressive behaviour and a higher proliferative index.[41] Cartilage, ossified bone (Fig. 2B) and, rarely, adipose tissue may also be seen as a metaplastic change.[6] Occasionally, large angioma-like aggregates of thin walled vessels can be observed in the core. Ultrastructurally apical microvilli, basement membrane, tight junctions and interdigitating cell membranes characterise the tumours.[26]

Atypical CPP

Tumours with one or more atypical features in focal areas, namely loss of papillary pattern, increased cellularity, necrosis and nuclear pleomorphism, but without frank anaplasia fall into this intermediate histological grade. Mitotic activity of greater than or equal to 2 per 10 high power fields is found to be the sole atypical feature associated with recurrence[17] and is the defining criteria for this grade in the WHO 2007 classification.[26]

Choroid Plexus Carcinoma

It is characterised by overt features of malignancy, namely solid growth with loss of papillary architectural



Figs 1A to C: (A) MRI brain: contrast enhanced MRI shows an intensely enhancing lobulated mass lesion within the fourth ventricle extending through the left foramen of Luschka. (B) Forty-year-old woman with an intraventricular choroid plexus papilloma filling the fourth ventricle, lifting up the cerebellum and obstructing the foramen of Magendie. (C) One-year-old child with a large intraventricular tumour filling the right lateral ventricle and causing CSF obstruction and mass effect. Areas of haemorrhage are seen within the tumour. Histology showed choroid plexus carcinoma. Seedings were seen along the ventricular lining in the occipital horn

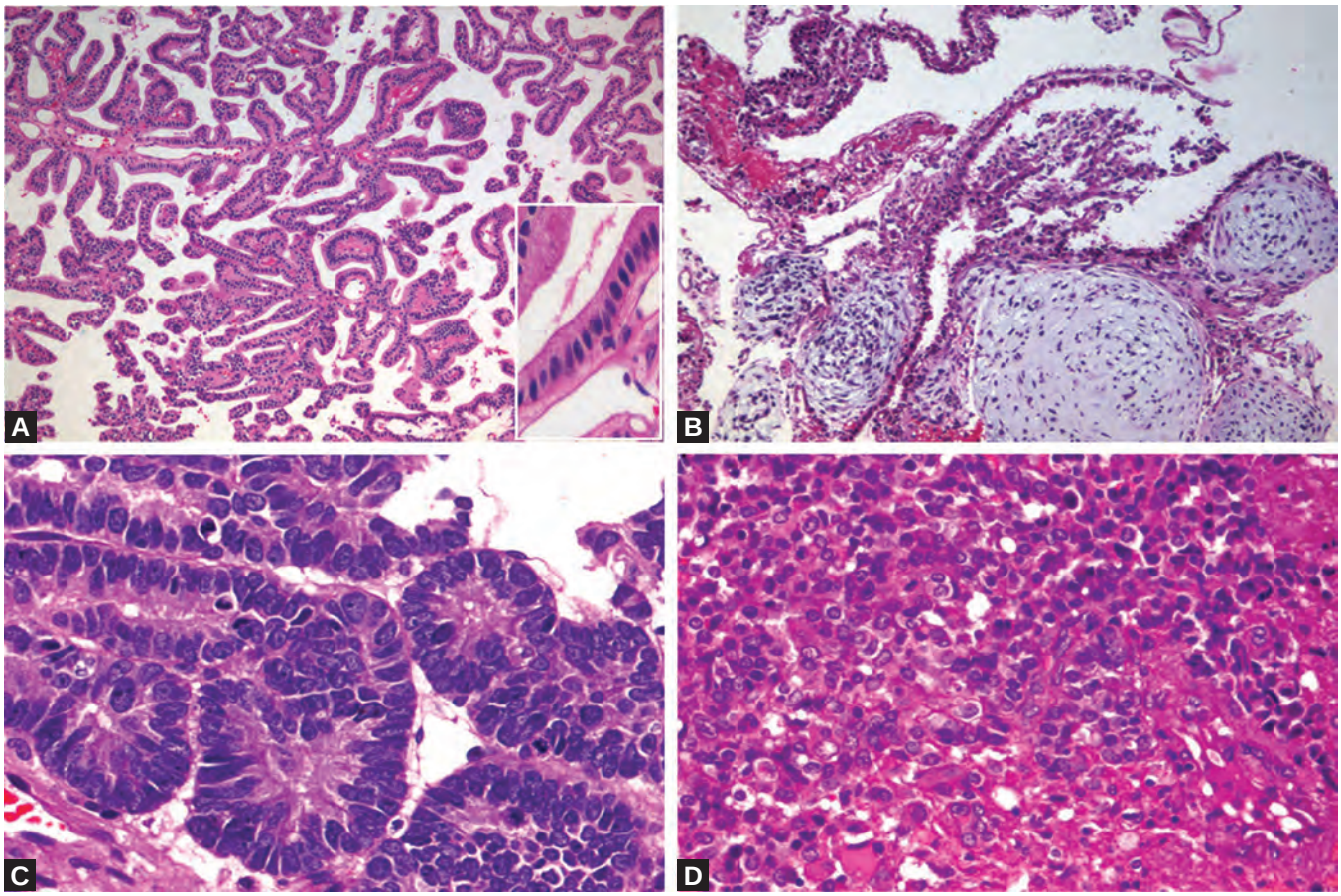
pattern, nuclear anaplasia, high mitotic activity (often more than 5 per 10 high power fields) and parenchymal infiltration (Figs 2C and D). The tumour may show both solid and papillary areas and necrosis is often present. Occasionally, cohesive clusters of tumour cells in otherwise typical choroids plexus papillomas have been noted within the adjacent brain parenchyma and their importance in prognostication is debatable since follow-up studies have not shown an increase in recurrence in them.[24] Infiltration by singly dispersed tumour cells has a more ominous connotation and is seen in CPC.

IMMUNOHISTOCHEMISTRY

Almost all choroid plexus neoplasms, both papillomas and carcinomas, express cytokeratin and vimentin. The majority (80–90%) of CPP and less frequently the malignant form are labelled by antibody to transthyretin (TTR) and S-100. Developmentally, the choroid plexus cells normally express GFAP, a glial marker, which persists in very few cells in adulthood. This is reflected in the plexus tumours, and GFAP is present in a small number of tumour cells in 25–55% of CPP and 20% of CPC.[36] Epithelial membrane antigen is generally absent.[26] Lack of or reduced S-100 staining has been associated with a poorer prognosis in CPC. Inconsistent expression of TTR in CPC and the finding that metastatic carcinomas also express TTR limits its utility as a diagnostic marker of CPC, especially in adults.[1]

A recent study using DNA microarrays and gene expression profiling of normal and neoplastic choroid plexus has identified Kir7.1 (inward rectifier potassium channel) and stanniocalcin-1 protein to be sensitive and specific markers for choroid plexus tumours.[14] Immunostaining for INI-1, a transcription factor expressed in nuclei, is retained[19] unlike atypical teratoid/rhabdoid tumours (AT/RTs) which are associated with INI/hSNF5 mutations and lack of staining. Survivin, a multifunctional molecule that inhibits cell death and is expressed exclusively in cells with high proliferation is localised to the ependyma and choroid plexus in the normal brain. In paediatric ependymomas and choroid plexus tumours, loss of nuclear survivin expression correlates with increasing cytologic atypia.[2]

The normal choroid plexus shows an MIB labelling index of 0.01–0.4%, while in CPP it ranges from 0.2% to



Figs 2A to D: (A) Choroid plexus papilloma with multiple papillary fronds composed of fibrovascular cores lined by cuboidal to columnar epithelial cells (inset: nuclei are oval and bland) [HE x 120, Inset: HE x 320]. (B) Islands of metaplastic hyaline cartilage are present in the stroma of a papilloma [HE x 120]. (C) Choroid plexus carcinoma. The papillae show increased cellularity and are lined by hyperchromatic, anaplastic cells with high mitotic activity [HE x 320]. (D) Choroid plexus carcinoma with solid growth of tumour cells and infiltration of brain parenchyma on the right [HE x 240]

6% (mean of 1.9%). CPC have a high LI of about 14% (range 7.3–60%).[26] Following chemotherapy, some CPC have shown a reduction in MIB-1 labelling index, suggesting that chemotherapy may work in part in reducing the proliferative potential.[4] Adhesion molecules, like CD44, markers for invasive growth and metastasis, are found in atypical CPP and CPC.[42] Altered p53 expression, a tumour suppressor gene, was found in all CPC and in one fourth of papillomas. In half of the positive cases, more than 70% of cells were labelled.[16] Mutations of *p53* gene, however, are present in less than 10% of cases of CPC and are absent in CPP.[26]

Immunolabelling for Aquaporin 1, a water channel protein, is seen in the normal choroid plexus and in CPP. Intense, diffuse staining correlated with a large hydrocephalus and the presence of tumoural cysts. It is negative in CPC.[25]

DIFFERENTIAL DIAGNOSIS

Typical benign CPP does not pose any diagnostic problem. On the other hand, CPC with their loss of architecture may mimic an embryonal AT/RT especially in the infratentorial compartment, metastatic carcinomas and rarely papillary ependymoma. Expression of INI-1 genetic marker is retained in CPC in contrast to its loss in ATRT. Metastatic carcinomas and CPC share many immunohistological features including reactivity for cytokeratin, and TTR, and currently there is no single marker that can reliably differentiate them. Two recently identified molecules, Kir7.1 (inward rectifier potassium channel) and stanniocalcin-1 are potential markers for choroid plexus tumours.[19] Aggressive papillary tumour of the endolymphatic sac or duct of the middle ear (also known as endolymphatic sac tumour, ELST) is histologically identical to CPP and explains the earlier reports of CPP in the temporal bone, close to the internal acoustic meatus. These tumours, unlike CPP, do not express TTR and are often a component of von Hippel Lindau (VHL) disease.[29] Anaplastic papillary ependymomas may mimic CPC. Perivascular pseudorosettes and strong perivascular GFAP fibre positivity serve to identify the former.

PROGNOSIS

For choroid plexus tumours histological features and complete surgical resection are the most important prognostic factors. In CPP, complete resection is more frequently possible (80.4–100%) than in atypical (61.5%) or malignant forms (39%).[28,44] Management is influenced by several factors like resectability, vascularity, presence of craniospinal spread and treatment of associated hydocephalus.[5]

After gross total resection in papillomas recurrences are rare and the functional outcome is excellent in 92%.[7] The median survival for CPP is 75.5 months.[28] In the small proportion of cases where resection of CPP is incomplete a wait-and-watch policy is advocated. In case of plexus carcinomas, gross total resection is possible in about 33% of cases and the median survival is only 6 months (range 1–90 months).[28] For CPCs, adjuvant chemotherapy and craniospinal radiation following surgery should be considered although its uniform efficacy in all cases remains to be established.[28]

The excessive vascularity of the CPT lends itself to peri-operative morbidity and mortality and infants have a higher risk of massive bleeding and coagulation disturbances.[32]

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130 Pineal Parenchymal Tumours

Vani Santhosh

Neoplasms occurring in the pineal region are very rare, comprising 0.5–1% of all intracranial neoplasms in adults. Among these, pineal parenchymal tumours are a small group, ranging from 15 to 30% of pineal region tumours. According to the revised WHO 2007 classification of central nervous system tumours, pineal parenchymal tumours (PPTs) are classified as pineocytoma (PC-grade I), pineal parenchymal tumour with intermediate differentiation (PPT-ID grade II/III) and pineoblastoma (PB-grade IV) and papillary tumour of the pineal region.[1] Papillary tumour of the pineal region is now recognised as a distinct entity in this group.

PINEOCYTOMA (WHO GRADE I)

Clinical Features and Localisation

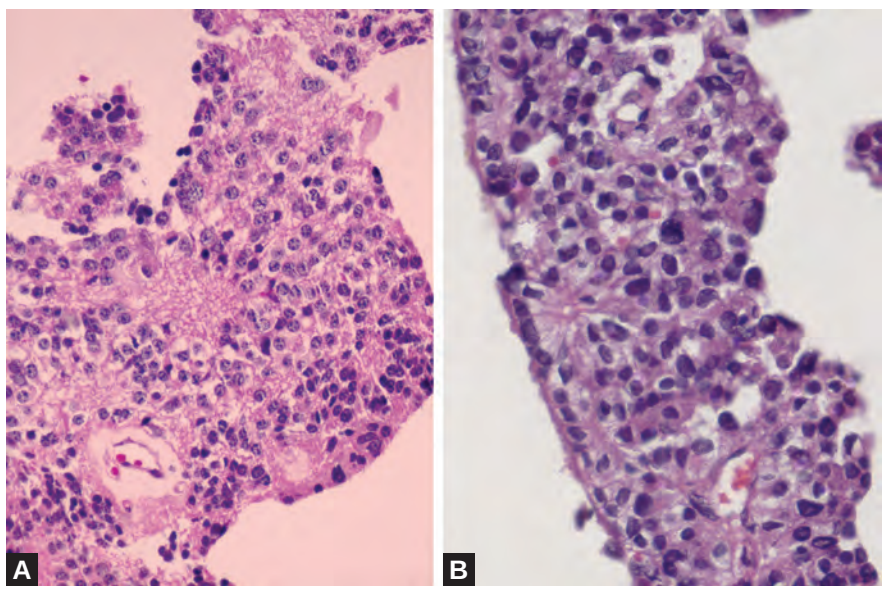
This is a slowly growing, relatively demarcated tumour occurring in the pineal region. Patients often present with neuro-ophthalmic paralysis or Parinaud's syndrome. They can also present with features of raised intracranial pressure.

Imaging Features on Computerised Tomography Scan

The tumour is relatively well demarcated with foci of calcification. It tends to be isointense on T1W images of MRI and hyperintense on T2W images. There is intense homogeneous contrast enhancement. Associated hydrocephalus is always seen.

Pathology

These are well differentiated neoplasms composed of uniform mature cells resembling pineocytes, arranged in sheets or ill-defined lobules (Fig. 1A). Mitotic activity is either absent or very low. Calcification is evident in some cases. Pineocytomatous rosettes are often seen. These are composed of pineocytic cells arranged around a fine meshwork of neuropil-like stroma (Fig. 1B). Occasional tumours exhibit foci of pleomorphic binucleate or multinucleate ganglionic cells and have been termed as pleomorphic variant of pineocytoma with ganglionic differentiation.[5] The tumour cells strongly express neuronal



Figs 1A and B: (A) Pineocytoma showing uniform mature cells amidst which are cell-free neuropil-like zones [HE x 320]. (B) Pineocytic rosette with cell-free space filled with a fine meshwork of cell processes [HE x 320]

markers such as neurofilament protein, synaptophysin, neuron specific enolase and others. They also express retinal s-antigen and rhodopsin indicating a photosensory differentiation of tumour cells.

PINEAL PARENCHYMAL TUMOUR OF INTERMEDIATE DIFFERENTIATION (PPT-ID; WHO GRADE II/III)

Clinical Features and Localisation

This is a pineal parenchymal tumour of intermediate grade malignancy which comprises about 20% of all pineal parenchymal tumours. The tumour occurs at all ages. The clinical features are very similar to that of pineocytoma and distinct imaging features are seen.

Pathology

The tumour exhibits varied histomorphological features. The majority are moderately cellular neoplasms exhibiting a lobular or sheet-like arrangement (Fig. 2). Some of the neoplasms exhibit a neuroendocrine or papillary pattern. There is a moderate degree of nuclear atypia and mitotic activity. There has been some attempt at sub-classifying these tumours according to the extent of mitotic activity.[3] Neuronal differentiation in the form of Homer-Wright rosettes or ganglion cells are seen occasionally. This tumour has a similar immunohistochemical marker profile as pineocytoma.

PINEOBLASTOMA (GRADE IV)

Prognostic and Predictive Factors

This is the most malignant of all pineal parenchymal neoplasms and is a form of primitive neuro-ectodermal tumour. The tumour most often affects children and has a predilection for CSF dissemination in view of its proximity to the CSF cisterns behind the mesencephalon.

Clinical Features and Localisation

The clinical presentation is similar to other pineal parenchymal tumours but the duration of symptoms is shorter than the others.

Imaging Features

On CT scan, pineoblastoma is a lobulated or poorly demarcated, homogeneous mass which is hyperdense after contrast enhancement. The tumour is hypointense to isointense on MRI scan and exhibits significant heterogeneous contrast enhancement. Calcification and extensive cystic change is rare. Infiltration of the surrounding structures and CSF dissemination is commonly seen.[8]

Pathology

Pineoblastomas are poorly differentiated neoplasms with features in common with other central primitive neuroectodermal tumours. They are composed of densely packed small cells with a hyperchromatic nucleus and scanty cytoplasm. Characteristic Homer-Wright and Flexner-Wintersteiner rosettes are seen (Fig. 3). The latter indicates a retinoblastic differentiation. Rarely fleurettes are also seen. All tumours exhibit a very brisk mitotic activity (more than 6 mitoses in 10 high power fields). In addition, apoptosis is also detectable on Hematoxylin and Eosin stained sections. Necrosis is also seen in several tumours. Rarely, a mixed tumour with alternating areas of pineocytoma and pineoblastoma can be noted. Pineoblastomas with mesenchymal or melanotic differentiation are referred to as 'Pineal anlage' tumours. The immunophenotype of pineoblastomas is similar to other pineal parenchymal tumours. The tumour exhibits a high MIB-1 index.[2]

HISTOGENESIS OF PINEAL PARENCHYMAL NEOPLASMS

The pineocyte is a cell with photosensory and neuroendocrine functions in lower animals and is believed to

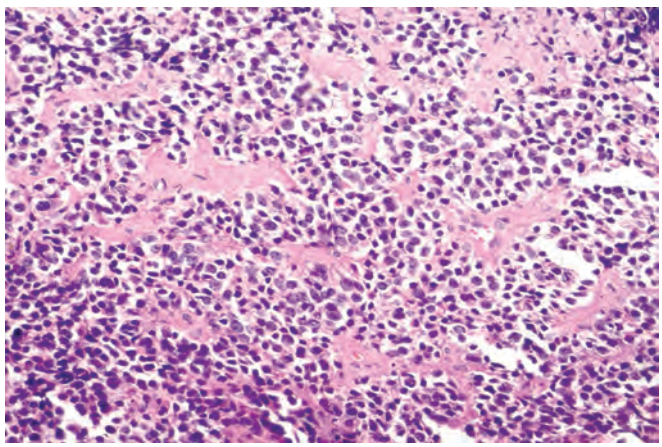


Fig. 2: Pineal parenchymal tumour of intermediate differentiation—the cells are arranged in a lobular manner separated by fibrovascular septa [HE x 160]

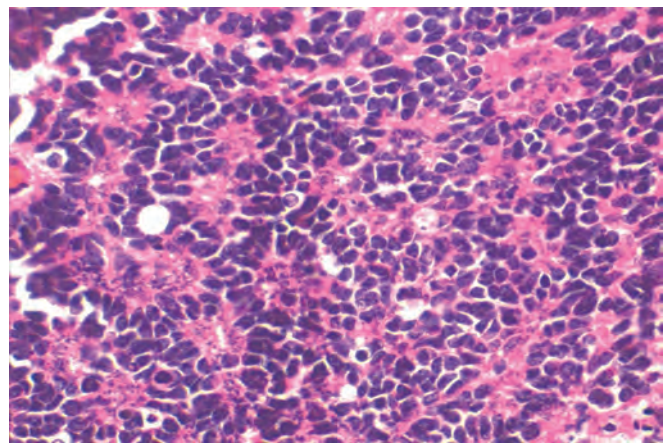


Fig. 3: Pineoblastoma—a highly cellular tumour with Homer-Wright and Flexner rosettes [HE x 320]

be the cell of origin of pineal parenchymal tumours. Ontogenically the pineal gland resembles the phylogeny of the human retina. During the late foetal gestational and early postnatal period, the pineal gland contains primitive cells arranged in small rosettes similar to developing retina. Later, the cells differentiate along neuronal lineage. The pineocyte is a differentiated cell and appears before 1 year age. To a large extent, there is a recapitulation of these developing events in the three groups of pineal parenchymal tumours.[6]

PROGNOSTIC AND PREDICTIVE FACTORS OF PINEAL PARENCHYMAL NEOPLASMS

Prognosis of patients with pineocytoma and PPT-ID after a gross total resection is variable. A 5-year-survival rate is noted in more than 75% of patients with pineocytoma and it ranges from 40 to 75% in patients with PPT-ID.[7] Pineoblastoma patients have a short progression-free survival. In general, some of the factors affecting survival in pineal parenchymal tumours are the morphological sub-type of the tumour, mitotic and MIB-I labelling index, presence of necrosis and neurofilament immunolabelling.[3]

PAPILLARY TUMOUR OF THE PINEAL REGION

This is an uncommon tumour of the pineal region in adults composed of cells with an epithelial morphology arranged as papillary structures. These cells exhibit cytokeratin immunoreactivity and ultrastructurally show features suggesting ependymal differentiation. The tumour grade is variable and may correspond to grade II or III. Only about 38 cases have been reported in literature thus far.[4]

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131 Neuronal and Mixed Neuronal Glial Tumours

Sharma MC, Chitra Sarkar

GANGLIOGLIOMA AND GANGLIOCYTOMA

These are well differentiated slow-growing neuroepithelial tumours consisting of neoplastic mature ganglion cells alone (gangliocytoma) or in combination with neoplastic glial cells (ganglioglioma). Both gangliocytoma and ganglioglioma correspond to WHO Grade I (Table 1) but, rarely, the glial component in ganglioglioma can be WHO Grade III.[4] The criteria for Grade II are controversial.[4,29] Ganglion cell tumours are found throughout the neuraxis, but the favoured sites are the cerebral hemispheres, especially the temporal cortex, followed by the cerebellar hemispheres, brainstem, spinal cord, optic chiasm, pituitary and pineal glands. Children and young adults are most commonly affected.[29] The most common presentation is with seizures but, sometimes, these lesions remain subclinical for decades.[6,9,47,71]

Neuroimaging

CT scan shows a well circumscribed mass lesion with a cyst and mural nodule. Calcification in the tumour and scalloping of the overlying bone can also be seen, but features of mass effect are absent. On MRI, this tumour is hypointense on T1WI and hyperintense on T2WI and the mural nodule will enhance.[29] The other brain tumours which show a cyst with mural nodule are pilocytic astrocytoma, pleomorphic xanthoastrocytoma, haemangioblastoma and, sometimes, papillary glioneural tumour (PGNT).

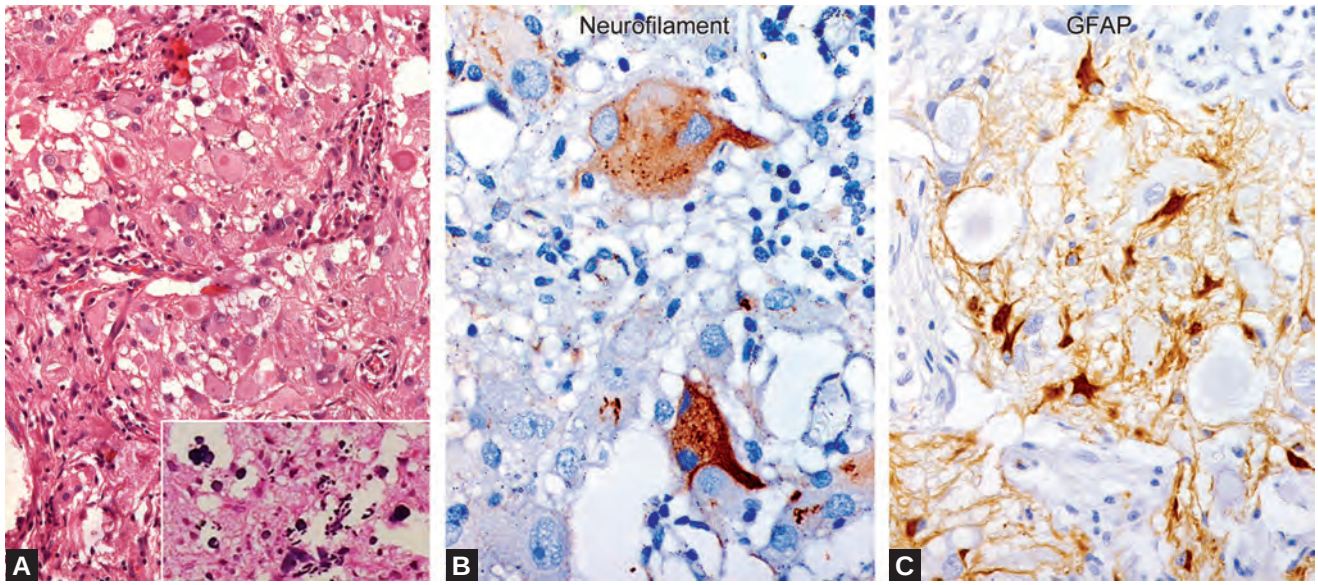
Histopathology

Ganglion cell tumours are typically well circumscribed with expanding margins, and infiltration of the surrounding parenchyma is unusual. Gangliocytoma is composed of nodular aggregates of ganglion cells in a fibrillary background. The individual cell has distinct cellular outlines, eosinophilic cytoplasm and large nucleus with prominent nucleolus. Cytoplasmic vacuolation, irregular distribution of Nissl substance, nuclear pleomorphism and binucleation differentiates a neoplastic cell from a normal neuron in the cortex. Perivascular lymphocytes are common and, sometimes, occur in large numbers to form a lymphoid follicle. Areas of dystrophic calcification are common. Mitosis, necrosis and vascular proliferation are typically absent.[29,47,71]

Gangliogliomas are composed of a dual population of cells consisting of neoplastic ganglion cells admixed with neoplastic astrocytic cells. These two elements may be admixed intimately, or be present separately, any of the two components dominating. The ganglionic component is composed of lobules of large cells with eosinophilc cytoplasm with vacuolation and paucity of Nissl substance (Fig. 1A). Nuclear dysplasia and binucleation favour the neoplastic nature of the cell (Fig. 1B). The glial component comprises of reactive looking astrocytes (Fig. 1C), at times a perfect caricature of pilocytic astrocytoma or oligodendroglioma. Perivascular lymphocytic inflammation and calcification is a frequent finding (Fig. 1A, Inset). Some cases show abundant eosinophilic granular

Table 1: The following tumours are included in the group of neuronal and mixed neuronal-glial tumours as per WHO classification (2007):

S.No.	*Name of the entity*	*WHO grade*
1.	Dysplastic gangliocytoma of cerebellum (Lhermitte-Duclos disease)	Hamartomatous/Grade I if neoplastic
2.	Desmoplastic infantile astrocytoma and ganglioglioma	Grade I
3.	Dysembryoplastic neuroepithelial tumour	Grade I
4.	Gangliocytoma and ganglioglioma	Grade I
5.	Papillary glioneuronal tumour	Grade I
6.	Rosette forming tumour of the fourth ventricle	Grade I
7.	Central neurocytoma and extraventricular neurocytoma	Grade II
8.	Cerebellar liponeurocytoma	Grade II
9.	Spinal paraganglioma	Grade I



Figs 1A to C: (A) Ganglioglioma showing biphasic pattern with lobules of large dysplastic neurons and peripherally placed neoplastic glial component. Note perivascular lymphocytic cuffing and focal calcification (inset). (B) Neurofilament immunostain highlights large binucleate cells with condensation of neurofilament [A:HE x 160, Inset x 100, B: Immunoperoxidase x 300, C: Immunoperoxidase x 240]. (C) GFAP labelled astrocytic component in the midst of ganglion cells

bodies and microcystic change as observed in pilocytic astrocytomas. Necrosis, mitosis or endothelial proliferation is not a common finding. The tumours which show frequent mitoses, necrosis or vascular proliferation in the astrocytic component are designated as anaplastic gangliogliomas of WHO Grade III.[4] The stroma with desmoplasia is commonly seen and this is better appreciated with a special reticulin stain or Masson trichrome stain. This feature is extremely useful in the diagnosis and differentiation from other tumours. Subarachnoid spread is not indicative of aggressiveness of this tumour and is commonly seen in benign CNS tumours.[6,47,71]

The surrounding brain may show areas of dystrophic calcification and neurofibrillary tangles, as seen in Alzheimer's disease. Focal cortical dysplasia (FCD), in the form of loss of laminar architecture or large dysplastic neurons, is seen in some cases.[9]

The ganglionic component is immunopositive for neurofilament proteins (NF), synaptophysin, MAP-2[7,10] and NeuN. CD34 positivity is demonstrated in 70% of the cases, especially in the temporal lobe tumours.[8,19,23,68] The glial component is positive to glial fibrillary acidic protein (GFAP), but is negative to MAP-2 protein. MIB-1 LI is low and sometimes can be spuriously interpreted as high, as infiltrating lymphocytes are also labelled. Grade III gangliogliomas show high MIB-1 LI. Under the electron microscope, the neuronal component shows neurosecretory granules and synapses.

Ganglioglioma needs to be differentiated from a large number of conditions like reactive neurons or glial cells, pilocytic astrocytomas, oligodendrogliomas and low grade diffuse astrocytoma infiltrating the normal brain. Sometimes, it is difficult to discriminate between normal reactive neurons in the cortex and neoplastic ganglion cells. However, loss of polarity, cytoplasm vacuolation, nuclear dysplasia or binucleation and CD34 immunolabelling of the cells favour a neoplasm. Focal clear cell change is seen in ganglioglioma, but diffuse change is likely to favour the diagnosis of oligodendroglioma, and positivity for neuronal markers in the clear cells excludes the diagnosis of oligodendroglioma. The tumours with predominant astrocytic component need to be differentiated from pilocytic astrocytomas and immunopositivity for neuronal markers coupled with negativity for MAP-2 favours the diagnosis of ganglioglioma. MAP-2 positivity is classically seen in true pilocytic astrocytomas but is surprisingly negative in the astrocytic component of ganglioglioma.[39]

Patients with neurofibromatosis-1 (NF-1) and Peutz-Jeghers syndrome are more prone to have ganglioglioma. Genetic abnormalities commonly found in ganglioglioma include gain of chromosome 7 and loss of chromosome 9p.[44]

The histogenesis of ganglioglioma remains unresolved. These tumours probably arise from dysplastic or malformative precursor glioneural lesions with neoplastic transformation of the glial component.[46]

Treatment and Prognosis

Surgical excision is the treatment of choice and curative. Good prognosis is associated with temporal lobe location, long history of epilepsy and complete resection. Seizures may persist in cases associated with cortical dysplasia. Anaplastic transformation is a bad prognostic indicator.[29]

LHERMITTE-DUCLOS DISEASE/DYSPLASTIC GANGLIOCYTOMA OF THE CEREBELLUM

It is a benign cerebellar tumour composed of dysplastic ganglion cells. The exact grade has not been assigned to this lesion in the WHO classification of tumours, as its exact nature is not clear.[4] This lesion was described by Lhermitte and Duclos and by Spiegel in the same year. This entity is also called cerebellar granular cell hypertrophy, diffuse hypertrophy of the cerebellar cortex and gangliomatosis of the cerebellum. Recently, it has been shown that it has a strong association with Cowden disease.

The majority of patients are adults at the time of presentation, although it may present in a range of 3–74 years. Most of the patients present with cerebellar dysfunction and obstruction of the CSF pathway. Mass effect, associated macrocephaly and seizures are common. MRI shows diffuse thickening of the cerebellar foliae.

Histopathology

Under low power magnification the cerebellum looks distorted and enlarged, and still maintains the architecture. The lesion causes diffuse enlargement of the molecular and internal granular layers of the cerebellum which are filled by large pleomorphic ganglionic cells. A layer of abnormally myelinated axon bundles in parallel arrays is observed in the outer molecular layer and extends from the granular layer through the molecular layer, and is better appreciated with myelin stains. Scattered small cells, morphologically consistent with granular neurons, are seen in the subpial region or in the molecular layer. This whole appearance is referred to as inverted cerebellar cortex. Purkinje cells are either absent or markedly reduced in numbers. The associated findings include abnormally ectatic vessels, calcification and vacuoles in the molecular layer or cerebellar white matter.[46]

The neurons are immunopositive for synaptophysin, chromogranin and neurofilament, but are negative for GFAP. Immunohistochemistry also shows loss of PTEN protein and increased expression of phosphorylated-Akt and S6 in the dysplastic neurons. Mitotic response in the cells is low.

This entity is likely to be mistaken for a ganglioglioma if the specimen is fragmented. The geographical confinement to layers of the cerebellum and widened cerebellar folial architecture on MRI are the most helpful in discrimination between the two conditions.

The exact origin of this condition is not known but a hamartomatous origin is favoured. If neoplastic, then it corresponds to WHO Grade I tumour.[46]

DESMOPLASTIC INFANTILE GANGLIOGLIOMA/ASTROCYTOMA

Desmoplastic infantile ganglioglioma (DIG)/astrocytoma (DIA) are large cystic tumours occurring in infants. They involve the superficial cortex, or leptomeninges, are often attached to the dura, show marked desmoplasia and correspond to WHO Grade I. DIG and DIA differ only with respect to the presence of ganglion cells in the former and their absence in the latter. Otherwise they have similar features.[14]

Clinical Features

Desmoplastic astrocytoma was variously described as meningocerebral astrocytoma attached to the dura with desmoplastic reaction or superficial cerebral astrocytoma attached to the dura. Desmoplastic supratentorial neuroepithelial tumours of infancy with divergent differentiation probably belong to the category of DIG.

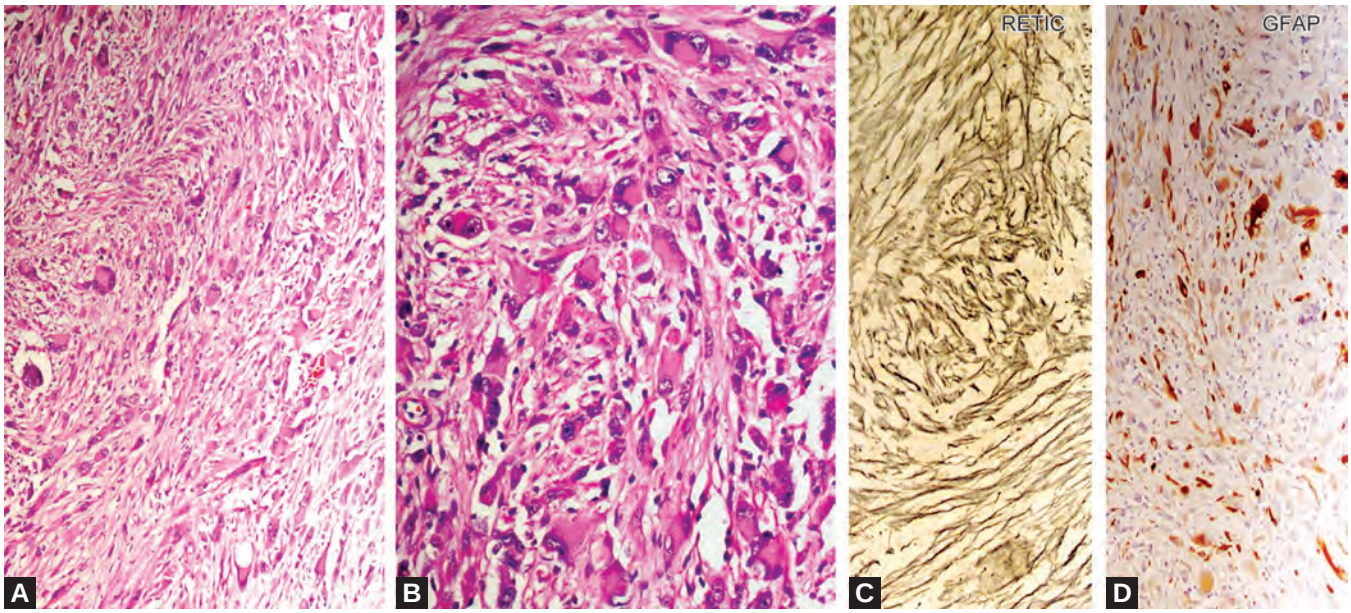
These are rare tumours of childhood, predominantly seen during the 1st year of life. Males are more commonly affected than females, but this male predominance is stronger when they occur between the ages of 5 years and 25 years. Most of the children present with marked enlargement of the head, bulging fontanelles, lethargy and 'setting sun' sign of short duration. Seizures and neurological deficits are uncommon.[14]

Neuroimaging

CT scan shows a large cystic lesion with a solid isodense or hyperdense superficial portion. MRI shows the cystic component to be hypointense on T1WI and hyperintense on T2WI, the superficial solid portion being contrast enhancing. Some authors have described five cardinal diagnostic signs namely: (1) massive size; (2) cystic architecture; (3) superficial position; (4) contrast enhancement and (5) dark desmoplastic component on T2WI, which are helpful in pre-operative diagnosis.

Histopathology

The most important feature of these tumours is desmoplasia (Fig. 2A) which varies in extent from region to region and from tumour to tumour. Some areas may be free of this feature. The lesions have three components: desmoplastic leptomeningeal, poorly differentiated neuroepithelial and cortical components. The leptomeningeal component is composed of fibroblast, like spindle shaped cells and pleomorphic cells, with an eosinophilic cytoplasm arranged in fascicles derived from the glial component (Figs 2A and B). These areas are reticulin rich (Fig. 2C) and mimic mesenchymal tumours. GFAP positive astrocytes are the sole component of DIA (Fig. 2D), but DIG, in addition, contains neuronal components ranging from small neurons to large ganglionic cells. The poorly differentiated neuroepithelial component comprises reticulin poor nodular aggregates of small cells with deeply basophilic nuclei and minimal pleomorphism. Mitoses may be seen in these cells. A multinodular cortical component with microcystic changes may be seen which is devoid of desmoplasia. Areas of calcification may be seen. There is sharp demarcation between the tumour and the underlying cortex, but



Figs 2A to D: (A and B) Desmoplastic infantile Astrocytoma (DIA) showing neoplastic astrocytes arranged in streams with marked desmoplastic components. (C) Reticulin stain demonstrates desmoplastic component encircling the glial components. (D) GFAP immunostain highlights the glial component [A:HE x 100, B:HE x 240, C:Reticulin silver x 120, D:GFAP immunoperoxidase x 120]

perivascular invasion along the Virchow-Robin spaces may be seen.

The desmoplastic component is immunopositive to GFAP (Fig. 2D), vimentin and rarely smooth muscle actin indicating a possible origin of this tumour from glial progenitors or subpial astrocytes. Neuroepithelial cells are positive for GFAP while the neuronal cells are positive for synaptophysin, NF and class III β tubulin. The poorly differentiated neuroepithelial component shows positivity for GFAP, vimentin, MAP-2 and rarely desmin. MIB-1 LI is generally low but may rarely be high, which does not connote aggressiveness.

The desmoplastic component can be mistaken for a mesenchymal tumour and the poorly differentiated neuroepithelial component for a high grade glioma, especially when mitoses are present. The younger age at presentation and radiological findings are important in these situations.[14]

CENTRAL NEUROCYTOMA AND EXTRAVENTRICULAR NEUROCYTOMA

WHO defines central neurocytoma as a neuronal tumour comprising of uniform round cells, typically located in the lateral ventricle in the foramen of Monro region and corresponds to WHO Grade II.[25]

The term central neurocytoma was coined in 1982 by Hassoun et al. They used this term to describe an intraventricular tumour which mimics morphologically an oligodendroglioma but after ultrastructural studies and immunohistochemistry was found to be of neuronal nature. Earlier these tumours were misdiagnosed as intraventicular oligodendrogliomas or ependymomas of the foramen of Monro.[21] Tumours which occur in the lateral, third or fourth ventricle are designated as central neurocytoma (CN), but those which are outside the ventricular system are designated as extraventricular neurocytomas (EVN).[13,16,37,40,57,58,62,64] They comprise about 0.1–0.5% of all intracranial tumours.[25]

Clinical Features

Central neurocytomas are typically located in the supratentorial ventricular system near the foramen of Monro in the lateral or third ventricle. The most common locations are the anterior portion of the lateral ventricle with attachment to the septum pellucidum with or without biventricular extension or extension into the third ventricle.

No gender predilection is noted and the majority of the tumours occur in the second and third decades of life. The duration of symptoms is usually long and patients present with headache, vomiting and visual disturbances. Rarely, an acute presentation due to haemorrhage has been reported.[50,55]

Imaging

Radiologically these tumours are isodense to hyperdense on CT scanning with cystic areas and contrast enhancing areas. Foci of calcification are commonly seen in about half of the patients and, sometimes, these tumours are densely calcified. On MRI, these tumours are isointense on T1WI but hyperintense on T2WI and uniformly to heterogeneously enhancing with contrast.

Histopathology

Intraventricular tumours are well demarcated, greyish and friable with areas of calcification.

On light microscopy, neurocytoma is a perfect caricature of an oligodendroglioma. Neurocytoma is a tumour of variable cellularity and classically shows cellular areas alternating with fibrillary areas. The cellular areas are composed of uniform cells with perinuclear clearing of cytoplasm, and a central, round to oval nucleus with speckled chromatin (Fig. 3A). The background shows a fine fibrillary neuropil-like matrix (Fig. 3B) and intervening thin walled blood vessels, at times hyalinised or dilated and congested. At places, the cells are arranged around the fibrillary areas giving the appearance of vague rosette formation. Rarely, large ganglionic cells are seen amidst them. The fibrillary areas, at places, project on to the blood vessels mimicking the perivascular rosettes of ependymomas. Mitoses are usually absent or occasional.[25,50,55] Increased numbers of mitoses, focal areas of vascular endothelial proliferation and necrosis are rarely seen and these tumours are designated as atypical neurocytomas.[42,61] Microscopic foci of calcification are seen in 50% of the cases (Fig. 3A). Some tumours with extensive ganglionic differentiation are labelled as ganglioneurocytomas.

Tumour cells are positive for synaptophysin (Fig. 3C) and neuron specific enolase (NSE), but negative for GFAP except for focal positivity mainly at the tumour periphery or around blood vessels. Nuclear positivity for NeuN is universally seen, but tumour cells are non-reactive to NF and chromogranin except in the ganglion cells.[50,55,69] MIB-1 LI is usually below 2% and tumours with more than 3% LI are atypical neurocytomas.[54,56]

Ultra structural examination shows dense core neurosecretory granules, microtubules in the cell processes and clear vesicles, but well formed synapses are rare.[28]

Morphologically central neurocytomas resemble oligodendrogliomas. Only by their immunohistochemical profile and ultrastructural characteristics, they can be differentiated from the latter. The striking feature of neurocytomas is the very fine neuropil-like fibrillary matrix as compared to the coarser glial fibrillary matrix of ependymomas. The alternating cellular and sparsely cellular or fibrillary areas, like ependymomas, do occur in neurocytomas, but synaptophysin positivity and lack of ependymal differentiation on ultra structure, differentiate them from ependymomas.[50,55]

The molecular pathogenesis of central neurocytoma is not known, but some genetic changes, like gain on chromosome 7, 2p, 10q, 18q and 13q, are commonly noted and TP53 mutations are not found in this tumour.[24]

Histogenesis

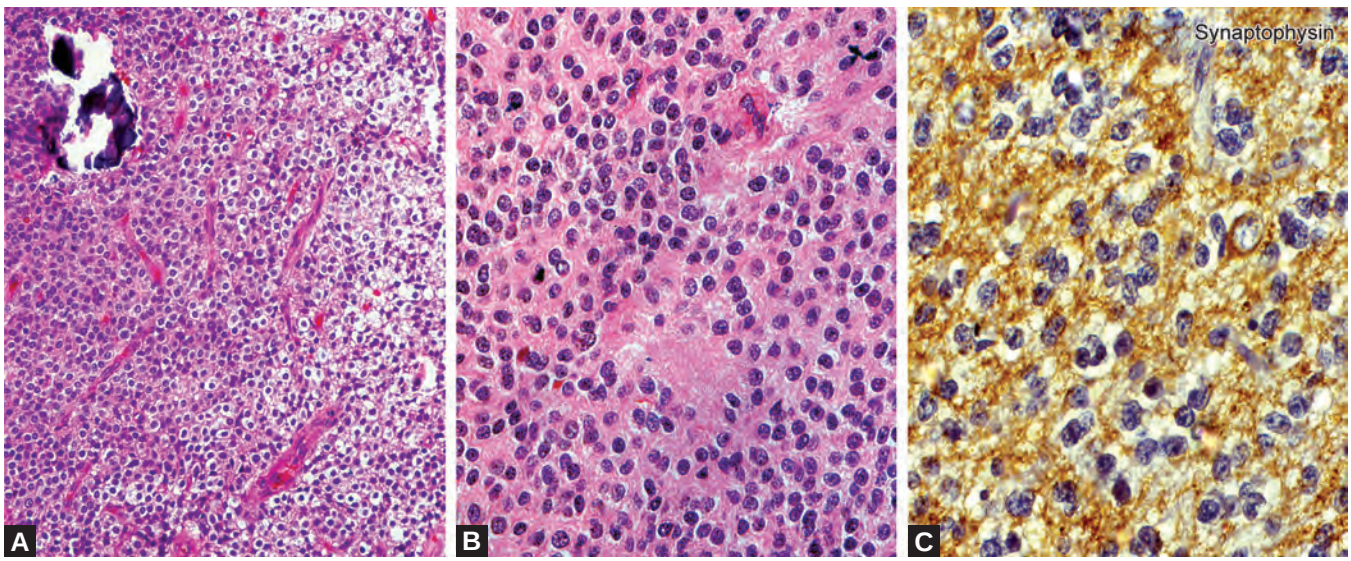
Central neurocytoma supposedly arises from the nuclei of the septum pellucidum and is of neuronal origin, but the presence of reactive looking astrocytic components in the tumour and tissue culture studies support the hypothesis that this tumour arises from primitive neuroglial cells with the capacity to differentiate towards both neuronal as well as astroglial lines.[70]

Treatment and Prognosis

Surgical excision is the treatment of choice but total excision may not be possible due to attachment to the surrounding structures. Some tumours remain stable even after partial excision. Radiotherapy should be reserved for recurrent or partially excised tumours or when surgery is not possible, or in atypical neurocytomas. Some studies have shown that radiotherapy is useful in local control of the tumour. Overall prognosis is good but recurrences are common in atypical cases with high MIB-1 LI. Craniospinal dissemination is rare.

EXTRAVENTRICULAR NEUROCYTOMA

These are neurocytic tumours which are remote from the foramen of Monro and are parenchymal in location, but



Figs 3A to C: (A) Central neurocytoma showing round cells with oligodendroglia-like appearance separated by thin vascular channels and focal calcification. (B) In many areas the cells are separated by intervening fibrillary matrix. (C) The tumour cells are immunopositive for synaptophysin indicating neuronal lineage [A:HE x 160, B:HE x 240, C:Synaptophysin x 300]

can impinge the ventricular system when located near the ventricle. Extraventricular neurocytomas resemble central neurocytomas with some differences.[25]

Clinical Features

The common sites of occurrence are the cerebral hemispheres, cerebellum and spinal cord. Children and young adults are commonly affected. Most of the patients present with mass effect or seizures. Radiologically, these lesions are discrete with frequent calcification and occasional cystic change.

Histopathology

Like central neurocytomas, they are composed of oligodendrocyte-like cells arranged in sheets in a variable fibrillary background. Ganglionic differentiation and areas of dystrophic calcification are common. These tumours are discrete, yet entrap neurons from the normal tissue which needs to be differentiated from ganglionic differentiation of the tumour.[13] The immunohistochemical profile is similar to central neurocytomas.

A radiologically discrete lesion with microscopic appearances of an oligodendroglioma and immunopositivity for synaptophysin favours the diagnosis of a neurocytic tumour rather than a tumour of glial origin.

Treatment and Prognosis

Like classic neurocytomas, extraventricular neurocytomas are expected to have a benign histology and an indolent clinical behaviour. Gross total resection is the treatment of choice. The residual tumour behaves in an indolent manner. Radiotherapy and chemotherapy should be reserved for recurrent or for atypical tumours. Neurocytomas of the spinal cord behave in an aggressive manner and can metastasise.

CEREBELLAR LIPONEUROCYTOMA

Liponeurocytoma is a rare cerebellar tumour of adults with consistent neuronal, variable astrocytic and focal lipomatous differentiation (WHO Grade II).[32]

Clinical Features

The presenting age range of this tumour is 25–77 years (mean age of 50 years) without any gender predilection. The most common location is the cerebellar hemispheres followed by the vermis and cerebellopontine angle. They are rarely seen in the supratentorial compartment. Most of the patients present with cerebellar signs, headache and signs and symptoms of raised intracranial pressure or obstructive hydrocephalus when they impinge on the fourth ventricle.

Neuroimaging

Radiological features vary according to the proportion of lipomatous tissue and, when abundant, can be suspected on imaging. On T1WI they are heterogeneously hyperintense. The adipose tissue corresponds to hyperintense streaks on T2WI and are heterogeneously enhancing.

Histopathology

Classically, this tumour is biphasic comprising of a variable admixture of neuronal and adipose tissue. The tumour cells resemble oligodendrocytes with a central round to oval nucleus surrounded by clear cytoplasm. Mitoses are absent or rare. The lipomatous component resembles mature fat cells but transition from cells with small vacuoles to large vacuoles imparting the signet ring cell appearance can be seen. Necrosis or vascular proliferation is classically absent.[43]

The tumour cells are immunopositive for synaptophysin, NSE and MAP-2. GFAP positive labelling can be seen both in neurocytoma and adipose cells. Rarely, the cells show myogenic differentiation and are desmin positive. MIB-1 LI is low both in the neuronal as well as in the lipomatous components.

The most important differentiation is from lipidised medulloblastoma and ependymoma. Medulloblastoma is a mitotically active small cell tumour, commonly occurring in children. In contrast, this tumour occurs in middle or old age with a low proliferation index. The lipidised cells of medulloblastoma are foamy macrophages rather than the mature looking adipose cells of this tumour. Rarely, medulloblastoma with lipomatous change, akin to this tumour, has been reported in children, but these are mitotically active with high MIB-1 LI. Some ependymomas do show lipomatous change which is focal but other features, like ependymal canals and perivascular pseudorosettes, are present when carefully examined. The clear cell variants of ependymoma are immunopositive to GFAP and show dot-like positivity for epithelial membrane antigen, indicative of intracellular micro lumina formation. Oligodendrogliomas are uncommon in the cerebellum and typically immunonegative to the neuronal markers.

Histogenesis

Immunopositivity for both neuronal and glial markers indicates that this tumour originates from precursor cells with a divergent differentiation potential and possibly arises from the external granular layer. TP53 mutations are common.[32]

Treatment and Prognosis

Surgery is the treatment of choice. The prognosis is favourable and survival varies from 5 to 16 years. Recurrences are common but malignant progression with recurrence has not been reported. No histopathological feature is predictive of recurrence.

PAPILLARY GLIONEURONAL TUMOUR

The WHO defines this entity as a relatively circumscribed, clinically indolent and histologically biphasic cerebral neoplasm comprising of astrocytic and neuronal components (WHO Grade I).[43,45]

Clinical Features

Papillary glioneuronal tumour is a new entity first described by Komori et al. in 1998 as a distinct entity, but tumours described earlier as pseudopapillary neurocytoma with glial differentiation and pseudopapillary ganglioglioneurocytoma probably belong to this category.[12] There is no gender predilection and the age of presentation ranges from 4 to 75 years (mean age of 23.1 years).[3,35,67] Occurrence in the young paediatric population is rare. The most common site of occurrence is in the cerebral hemispheres with a predilection for the temporal lobe, but any lobe can be involved. The most common clinical presentations included headache, visual disturbances, mood changes, gait disturbances and seizures of variable duration.

Neuroimaging

Most of the tumours present as well circumscribed solid and cystic masses, contrast enhancing and without much mass effect. Many of these tumours are cystic with a mural nodule and are close mimics of pilocytic astrocytomas, gangliogliomas, haemangioblastoma and pleomorphic xanthoastrocytoma in this aspect.

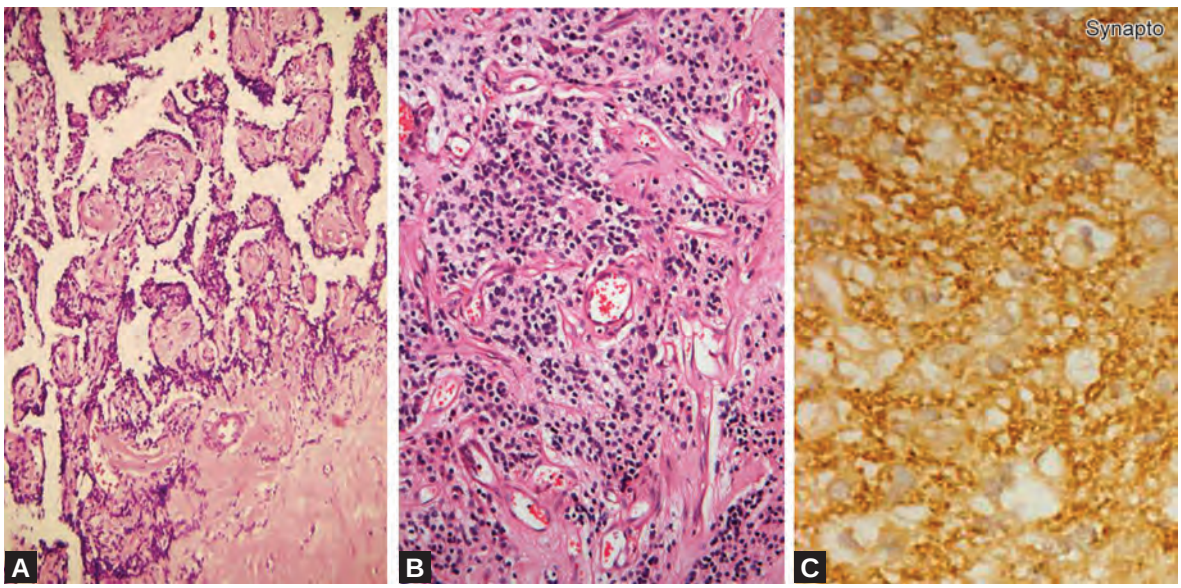
Histopathology

Radiologically as well as pathologically, these tumours are well circumscribed but, rarely, they can be infiltrative. These tumours have predominantly fibrovascular papillae with hyalinised fibrovascular cores, lined by a single to pseudostratified layer of cuboidal astrocytic cells along with sheets of neurocytes amidst papillae (Figs 4A and B). Some of the tumour cells in interpapillary areas are larger with abundant cytoplasm and vesicular nuclei with prominent nucleoli representing ganglion cells. The interpapillary neurocytes have round to oval hyperchromatic nuclei and scant eosinophilic cytoplasm without significant pleomorphism and necrosis. Mitotic activity is usually low. Immunohistochemistry shows diffuse positivity for glial fibrillary acidic protein in the cells along the hyalinised fibrovascular papillae, but the interpapillary cells are positive for synaptophysin (Fig. 4C), Neu N and NCAM. Only ganglionic looking cells are immunopositive for NF. MIB-1 LI is usually low but, rarely, can be high.[2,5,15,20,31,33,38,34,49,65]

The papillary architecture with GFAP positive cells lining these papillae is a helpful feature in the diagnosis of PGNT. Absence of nodular arrangement of ganglionic cells, perivascular lymphocytic collection, calcification and associated cortical dysplasia are helpful features to exclude other mixed glioneural tumours. Location of the lesion along with absence of staining for cytokeratin, epithelial membrane antigen, alfa-feto protein, transthyritin and c-kit (CD117) are helpful to rule out papillary metastatic epithelial tumours.

Histogenesis

The histogenesis of this tumour is not known. However, based on ultrastructural and double labelling immunohistochemical studies, it has been proposed that these neoplasms are neuroepithelial tumours which are capable of differentiating into glial as well as neuronal cells.[2]



Figs 4A to C: (A) Papillary glioneuronal tumour showing papillary gliovascular structures. (B) Higher magnification highlights clustering of small round neuroepithelial cells in interpapillary zones. (C) The cells in interpapillary zones are synaptophysin positive indicating neuronal lineage [A:HE x 80, B:HE x 200, C:Synaptophysin x 240]

Treatment and Prognosis

Surgical excision is the key for management, and chemotherapy/radiotherapy is not recommended if completely excised. Most of the PGNTs reported in the literature had a benign histology but recurrences are described. Cyst formation, hyalinisation of vessels, low mitotic activity and gross total resection of the tumour are indicative of a favourable prognosis.[11]

ROSETTE FORMING GLIONEURAL TUMOUR OF THE FOURTH VENTRICLE

Rosette forming glioneural tumours (RGNTs) are rare slow growing tumours of the fourth ventricular region, preferentially affecting young adults. They are composed of two distinct histological components consisting of neurocytes and a glial component (WHO Grade I).[27]

Clinical Features

RGNT is a rare tumour of young adults with female predominance. The range varies from 12 to 59 years with a mean age of 33 years. The most common location is midline fourth ventricle or aqueduct, but they can extend to involve the adjacent parenchyma of the cerebellar vermis, brainstem or pineal gland. Most of the patients present with signs and symptoms of obstructive hydrocephalus.

Radiologically, these tumours are well circumscribed and are hypointense on T1WI, hyperintense on T2WI with irregular contrast enhancement. Associated hydrocephalus is evident in most of the patients.

Histopathology

Although these tumours are well demarcated radiologically and macroscopically, some microscopic infiltration can be seen. This tumour is typically composed of a dual population of cells consisting of neurocytic and glial components. The neurocytic component consists of a uniform population of cells arranged in a ring-like pattern around a delicate eosinophilic neuropil. Perivascular pseudorosettes are seen. The neurocytic cells show scant amount of cytoplasm, spherical nuclei with fine granular chromatin and indistinct nucleoli. When observed carefully, fine delicate cytoplasmic processes are visible. Associated microcystic and mucoid change like in dysembryoplastic neuroepithelial tumours can be seen in some cases. The glial component looks like a pilocytic astrocytoma and may be the dominant component in some cases. At some places, this may resemble an oligodendroglioma. Mitosis and necrosis are absent, but glomeruloid vascular proliferation is seen in some cases in the astrocytic areas. Dystrophic calcification, eosinophilic granular bodies and haemosiderin deposits may be observed in some.[27]

The neuropil in the centre of the rosette and around the blood vessels is immunoreactive to synaptophysin. The neurocytes are positive to MAP-2 and NSE; the glial component is typically positive to GFAP and S-100 protein, but rosettes are negative to these markers. MIB-1 LI is typically low.[27]

Histogenesis

RGNT is classically seen in the fourth ventricle; therefore, its origin from the periventricular germinal matrix is suggested.

Treatment and Prognosis

Surgery is the treatment of choice, but inherent complications of the surgical procedure do occur due to the location of this tumour. Prognosis is favourable.

DYSEMBRYOPLASTIC NEUROEPITHELIAL TUMOUR

Dysembryoplastic neuroepithelial tumour (DNET) is a benign, usually supratentorial tumour, occurring in childhood or in young adults, characterised by a cortical location, drug resistant partial seizures and characteristic morphology (WHO Grade I).[17]

Clinical Features

In epilepsy surgery, the incidence of DNET is 12% in adults and 13.5% in children. Among all neuroepithelial tumours diagnosed in a single institution, DNET occurs in 1.2% of patients below 20 years of age and in 0.2% beyond 20 years of age with a male preponderance. Most patients present with pharmacoresistant partial seizures with or without secondary generalisation. The most common location is the temporal lobe, but it may occur in the caudate nucleus, septum pellucidum, lateral ventricle, floor of third ventricle, brainstem and cerebellum. Rarely, these tumours are multifocal.

Neuroimaging

MRI shows a well defined cortical lesion which is nodular or triangular in appearance with its apex towards the white matter. They are hypointense on T1WI and hyperintense on T2WI and show single or multiple ring enhancements on contrast injection. Scalloping of the inner table of the skull is a common finding.

Pathology

These tumours are located in the superficial cortex forming nodular expansions indenting the subcortical fibres (Fig. 5A). Extension into the underlying white matter is extremely rare. Grossly, they are mucoid in appearance.

The histological hallmark is the 'specific glioneuronal element' (SGE) described by Dumas-Duport. SGE shows columns formed by bundles of axons lined by oligodendroglial-like cells (OLC) (Fig. 5B), oriented perpendicular to the cortical surface. The lining cells are small with perinuclear clear cytoplasm simulating oligodendroglial

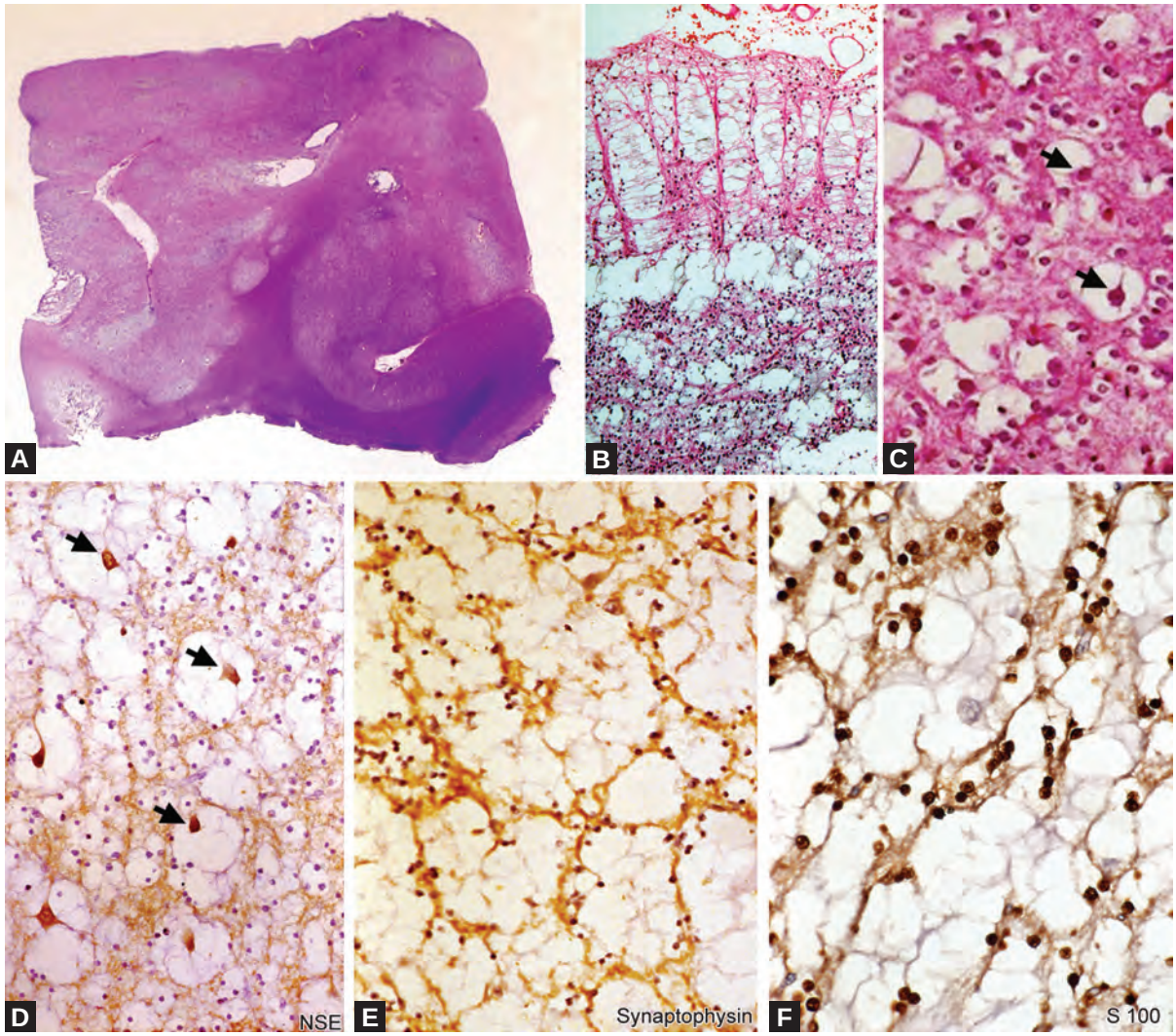
cells. Between these columns normal appearing neurons or large neurons float in a pale basophilic matrix (Fig. 5C) which is positive to alcian blue stain indicating its mucopolysaccharide nature. The scattered cells are positive for NeuN, NSE (Fig. 5D), synaptophysin (Fig. 5E), neurofilaments and class III β tubulin. MIB-1 LI is low.[55] GFAP positive astrocytes are seen between these cells. The small cells of DNT resemble oligodendroglia and are S-100 positive (Fig. 5F). On EM, neurosecretory granules and clear vesicles are seen in the OLC, but synapses are rare. Several morphological variants are described but the following two are well recognised.

Simple Form

This morphological variant shows a unique glioneural element which is focal and juxtaposed to a well recognisable normal cortex.

Complex Form

This variant is multinodular, the nodules containing either glioneuronal elements (SGE) or only a glial component juxtaposed to the cortex or nuclear areas. The constituent cells vary from each focus and from case to case. The 'glial alone' component resembles a low grade glioma, either as a nodule or in a diffuse form. Mitosis is low, but cellular pleomorphism and glomeruloid vascular proliferation resembling high grade gliomas can be present. In between, islands of calcified vessels or tetrangiectatic vessels resembling a vascular malformation can be seen. Cortical dysplasia (CD) of the surrounding cortex is seen in 80% of patients with DNT in the form of disorganisation of the laminar architecture, misaligned cytologically abnormal neurons or neurons in the white matter. A rare pigmented variant and, sometimes, association with a ganglioglioma is also reported.



Figs 5A to F: (A) Dysembryoplastic neuroepithelial tumour (DNET). Whole mount preparation of a lesionectomy specimen showing pale, nodular myxoid lesions expanding the cortical ribbon and indenting the subcortical white matter. (B) Characteristic glioneuronal element in a case of cerebellar DNET showing columns of axon bundles in a myxoid background with oligodendroglia-like cells attached to the columns. (C) Floating neurons in the midst of oligodendroglia-like cells (arrows). (D to F) NSE (D) Labels the floating neurons (arrows), while synaptophysin (E) S100. (F) Mark the glioneuronal element [A:HE x 8, B:HE x 100, C:HE x 240, D:NSE x 160, E:Synaptophysin x 200, F:S100 x 300]

Although DNT has a classical history as well as radiological and pathological features, these glial tumours are sometimes mistaken for other tumours, especially when biopsies are fragmented. The most common differential diagnoses include oligodendroglioma, low grade diffuse astrocytoma and ganglioglioma. Both oligodendrogliomas and DNT involve the cerebral cortex, often possess basophilic mucoid stroma and are composed of similar cells. Normal residual neurons may appear as floating neurons similar to that observed in DNT due to the infiltrating nature of the former lesions. The predominant involvement of white matter, unpatterned nodules, larger nuclei, neuronal satellitosis and presence of mitoses are common in oligodendrogliomas. Moreover, DNET are tumours of young age in contrast to oligodendrogliomas. Gangliogliomas can pose a problem in the differential diagnosis, but the presence of nodules of ganglionic cells, perivascular lymphocytic collection and rich reticulin are helpful in discrimination. Sometimes, DNT can be mistaken for a low grade diffuse astrocytoma, but the radiological appearance, infiltrative nature and absence of floating neurons helps in distinguishing them.

These tumours may occasionally occur in patients with NF-1 or XYY syndrome. No other abnormalities or mutations have been detected in these tumours so far.

Histogenesis

Association with cortical dysplasia, cortical location and young age at the onset of symptoms favours the theory of the malformative nature of this lesion, supposedly arising from the secondary germinal layers. A malignant progression in an occasional case indicates the neoplastic nature.[17]

Treatment and Prognosis

Surgical resection is the treatment of choice and is rewarding, as these tumours are benign and the prognosis is excellent. The tumours which are associated with diffuse cortical dysplasia may continue to produce seizures after surgery. Malignant progression has been described only twice in the literature and both of them presented with atypical features. In one patient, this malignant progression was seen after radiotherapy and chemotherapy.

SPINAL PARAGANGLIOMA

It is a unique neuroendocrine neoplasm, usually encapsulated and benign, arising from specialised neural crest cells associated with segmental or collateral autonomic ganglia (paraganglia) (WHO Grade I).[26,52]

Clinical Features

Earlier paragangliomas were classified as chromaffin and non-chromaffin based on their reaction to chromic acid, but this classification has been discarded as it does not reflect the true functional status. The current terminology is based upon their anatomical location, e.g. carotid body paraganglioma (chemodectoma), jugulotympanic paraganglioma (glomus jugulare tumour), spinal paraganglioma, etc. Usually, a description of functional status, e.g. functional or non-functional is also added.[26]

Paragangliomas of the CNS are rare, but most commonly the CNS is involved due to the intracranial extension of a glomus jugulare tumour of the jugulotympanic paraganglia. Although numerous other locations, like the sellar region, cerebellopontine angle,[18] cerebellar parenchyma, frontotemporal lobes, dura and pineal region, have been described, paraganglioma of the nervous system almost exclusively occurs in the cauda equina region comprising 3.4–3.8% of all tumours in that reg ion.[1,22,30,36,48,51,53,59,60,63,66] The other spinal levels involved are thoracic and cervical regions. The tumours in these locations are usually intradural in location with an intravertebral and paraspinal component.

These tumours are noted between the ages of 9–74 years, the peak age being the fourth to sixth decades with a male preponderance. The commonest clinical presentations are low back pain, followed by motor and sensory deficits in the form of paraparesis, sphincter disturbances and sciatica. Thoracic paragangliomas present with symptoms of spinal cord compression. Tumours producing excess catecholamine present with hypertension. Rarely, the patient may present with ataxia secondary to superficial siderosis following a bleed in the tumour. Patients with jugulotympanic paraganglioma present with pulsatile tinnitus.[30,59,60]

Neuroimaging

MR imaging typically reveals a well-circumscribed mass that is isointense relative to the spinal cord on T1WI and isointense to hyperintense on T2WI. Haemorrhage is common, and a low-signal-intensity rim (cap sign) may be seen on T2WI. Intense enhancement of these highly vascular lesions is virtually always seen after the administration of contrast medium. Serpentine flow voids are sometimes seen capping the tumour, which are believed to be caused by either hypervascularity of the tumour or compression of veins by the mass. Associated syringohydromyelia has been reported in some cases. Radiological features are characteristic and pre-operative diagnosis is possible.

Histopathology

Most spinal paragangliomas are well encapsulated and intradural in location, and are attached either to the filum terminale or caudal spinal nerves. They are sausage shaped reddish brown in colour and may show capsular calcification.

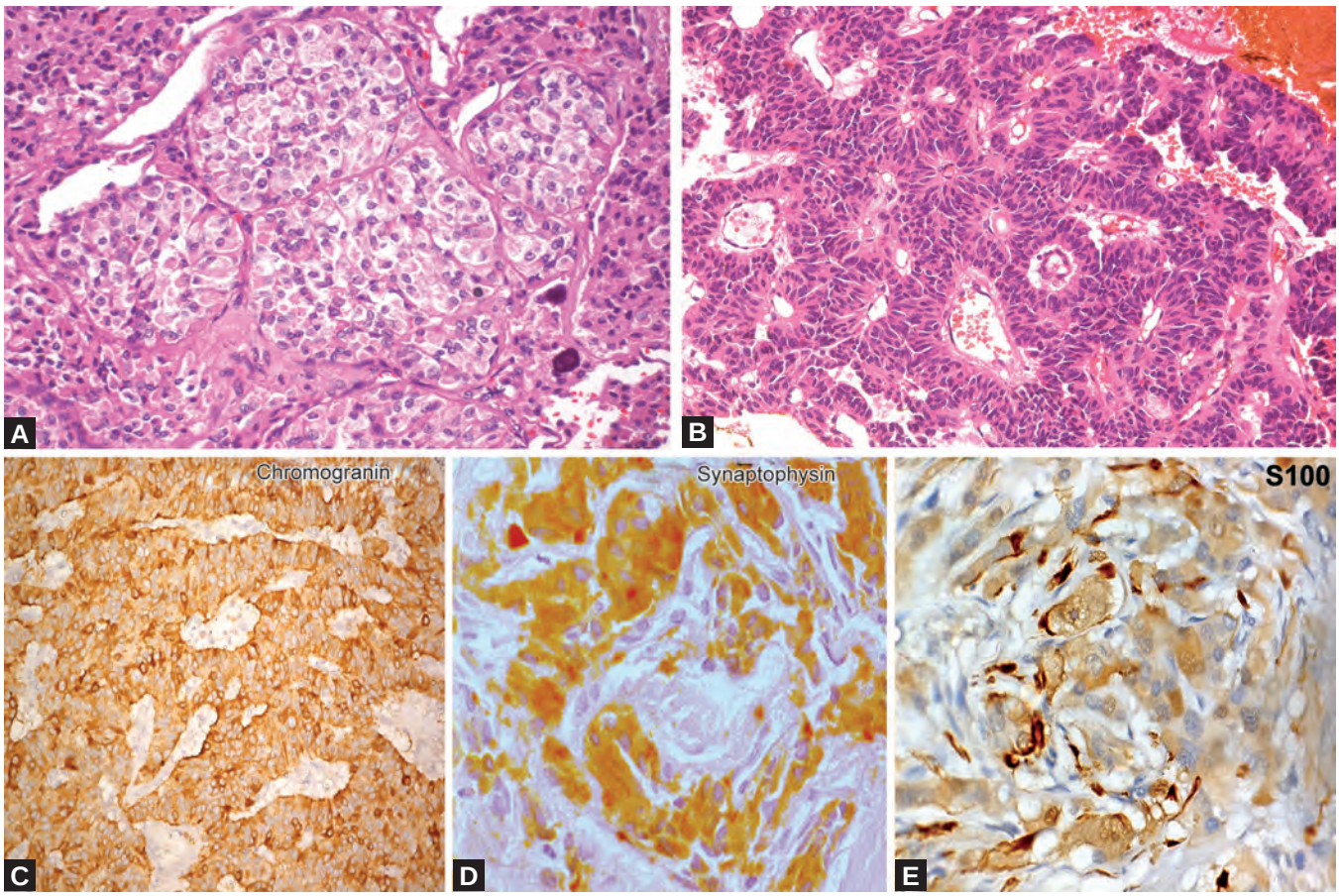
These tumours are composed of sheets and nests of chief (type 1) cells with a neuroendocrine nesting pattern to form "zellballen" (Fig. 6A). These lobules are separated by thin vascular channels with a fine endothelial

lining and occasional dilated sinusoids. There is usually a fine supporting reticulin fibre network separating the tumour islands. Individual cells are polygonal with moderate to abundant eosinophlic finely granular cytoplasm and a centrally placed nucleus. At times, the tumour cells are also seen to be arranged around small vessels reminiscent of pseudorosettes with papillary structures resembling ependymal tumours and are likely to be misdiagnosed as extra-axial ependymomas (Fig. 6B). The nuclear chromatin is fine and granular, and nucleoli are not prominent. The presence of mitosis or necrosis is not the usual feature in spinal paragangliomas, but nuclear pleomorphism secondary to degenerative changes can be seen like other endocrine tumours (endocrine anaplasia). Ganglionic differentiation is seen in some tumours. The sustentacular cells are interstitial spindle shaped cells that encompass the lobules of chief cells.[30,59,60]

The chief cells are immunoreactive to NSE, chromogranin (Fig. 6C), synaptophysin (Fig. 6D) and neurofilament (NF) proteins but negative for GFAP and EMA. Interestingly, dot like positivity for cytokeratin may be present in some cases of spinal paragangliomas. Sustentacular cells are immunopositive for S-100 protein (Fig. 6E) and rarely GFAP positive. Positivity for neuropeptides and serotonin is also reported in some cases. MIB-1 LI is usually low (< 2%) including in recurrent tumours.[30,41]

Ultrastructural examination shows electron dense neurosecretory granules, basal lamina at the interface of Zellballen and surrounding stroma. The sustentacular cells lack neurosecretory granules but contain abundant intermediate filaments.[30,60]

There are no distinct clinical and radiological features. In such a situation, it is difficult to differentiate these tumours from ependymomas or neurofibromas, or other potential causes of cauda equina syndrome. These tumours can even be mistaken for cavernous haemangioma due to the high vascularity at surgery. Even microscopically, these tumours may be misdiagnosed as an ependymoma, as perivascular pseudorosettes, epithelial cords and the papillary nature are a frequent occurrence. The most helpful differentiating features of paraganglioma include: (a) "zellballen" pattern; (b) granular argyrophilia; (c) immunoreactivity for S100 in sustentacular cells and (d) cytoplasmic immunoreactivity for chromogranin, synaptophysin and NSE. Spinal paragangliomas are non-familial.



Figs 6A to E: (A) Paraganglioma of cauda equina shows characteristic 'zellballen' arrangement of tumour cells with intervening thin vascular septa. Focal calcification is present. (B) Trabecular and pseudopapillary arrangement of elongated paraganglioma cells arranged around blood vessels resembling an ependymoma. (C to E) Immunostaining panel shows positive labelling of chief cells with (C) Chromogranin and (D) Synaptophysin. (E) While sustentacular cells are labelled by S100 [A:HE x 160, B:HE x 160, C, D and E:Immunoperoxidase x 240]

Histogenesis

Previously, this tumour was thought to be an unusual form of ependymoma. One school of thought is that these tumours arise from paraganglion cells associated with regional autonomic nerves and blood vessels, whereas others proposed its origin from peripheral neuroblasts normally present in the adult filum terminale which undergo paraganglionic differentiation.

Treatment and Prognosis

Surgical excision is the treatment of choice but the local anatomy may impose a restriction. Recurrences can occur even late following incomplete excision. Rarely, CSF seeding, CNS and bony metastases or metastases outside the CNS can occur. No histological feature is predictive of recurrence or metastasis.[51]

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Preface

Since the publication of the second edition of this Textbook in 1996, phenomenal advances have been made towards improved understanding of the pathophysiology of various neurosurgical disorders, their diagnosis and therapy. Advances in molecular biology and genetics on one hand, the refinements of imaging technologies, introduction of image-guided techniques for neuronavigation, and refinements in endoscopic and minimally invasive procedures on the other hand have markedly reduced the morbidity and mortality of neurosurgery. Simultaneously, better availability of radiosurgery and safer endovascular approaches have led to the development of non-surgical therapy for a variety of lesions.

Recent years have witnessed a rapid increase in the number of well-equipped neurosurgical departments across the country providing both state-of-the-art services to the patients and training to specialists in the diverse subdisciplines of neurosurgery. It has been our endeavour to meet their needs for an updated account of the current knowledge of the subject.

The third edition of the textbook includes a comprehensive account of all the recent advances succinctly provided by a galaxy of outstanding contributors especially selected on the basis of their expertise and experience. Care has been taken to include relevant published literature both from India and abroad.

As in earlier editions, special attention has been given to tropical disorders not often adequately covered in publications of the West. This may be an additional attraction for neurosurgeons in other developing countries as also to those in the developed ones who often encounter such conditions in their practice.

The present editors deeply miss the invaluable, wise and experienced guidance of the Senior Editor Prof B Ramamurthi who was the moving spirit behind the earlier editions. The editors would like to thank all the contributors, their associates and the secretarial staff for their co-operation. The Jaypee Brothers Medical Publishers (P) Ltd, New Delhi, India deserve our special thanks for the excellent quality of the publication.

PN Tandon
Ravi Ramamurthi

Caraka Samhita

The early medical writer Caraka tells us that when setting out to learn about Indian medicine, we should have certain criteria in mind for choosing the texts we wish to study (Caraka. 3.8.3):

"A discerning person who wants to become a physician should start by selecting a text based on a consideration of his ability to cope with hard or easy tasks, the results he is after, the likely aftermath, the place and the time. After all, there are numerous physicians' manuals in circulation in the world, so he should apply himself only to a text which is extremely famous, which is used by scholars, which covers a lot of topics and is respected by qualified people. It has to be good for pupils of all three levels of ability, and it should not be flawed by repetitiousness. It should be derived from the tradition of the saints. The connection and the sequence of the text and commentary should be well organised. It should be solidly based, and have no corrupt or missing words. It should be full of significance, its ideas should follow in sequence and it should give importance to the exactness of what ideas really refer to. Its ideas should be coherent and its topics should not be haphazard. It should have both definitions and examples.

This type of text is like a flawless sun; it dispels darkness and throws light on everything."

The Roots of Ayurveda
Dominik Wujastyk

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INTRODUCTION

The early and accurate diagnosis of intracranial space occupying lesions (ICSOL) and their skilful removal with minimal resultant neurological deficit is the most important aspect of a neurosurgeon's work. ICSOL are problems of concern for the neurosurgeons due to the associated increase in intracranial pressure (ICP) and the haunting spectre of a resultant permanent neurological deficit. Compared to some decades ago, widespread awareness of the incidence of intracranial lesions among the public and the profession, along with modern non-invasive diagnostic techniques, help us to diagnose early and adopt a safer surgical approach.[22] However, due to various social, economic and environmental factors, there will continue to be many patients who may seek neurological help late. Such cases need all our diagnostic acumen and surgical skill.

IMPORTANCE OF CLINICAL ASSESSMENT

Based on a precise knowledge of neural organisation in the brain and a careful assessment of the symptoms and signs of a patient with an intracranial tumour, it should be possible to accurately localise the majority of lesions. This is true for a large number of tumours, except in very early cases and in those occurring in the so-called silent areas of the brain. In the late stages, non-specific pressure effects result in false localising signs which complicate the clinical picture and create confusion in localisation.[85] Advances in neuroradiology and imaging techniques, like CT scanning and MR, have resulted in great reliance being placed upon these methods for localisation. This has led to the tendency to minimise the efforts spent over history-taking and careful neurological examination. In spite of all technical diagnostic advances, only careful recording of the history and clinical examination can lead to a proper overall evaluation necessary for the rational planning of investigations and treatment. Clinical wisdom lies in checking this tendency to rush the patient through a number of unnecessary investigations and in realising the importance of the clinical picture and its evolution.

Physical signs of derangement of neurological or mental functions provide the clues to the site of involvement in the nervous system and the answer to the question, 'Where is the lesion?' Careful elicitation of the history provides information about the mode of onset and the pattern and temporal profile of the progress of the disease. This is valuable for determining the pathology of the lesion to answer the question— "What is the lesion?" For example, the sudden onset of symptoms in a vascular lesion or the rapid progression of a highly malignant lesion, the slow progress of a benign neoplasm and the remission and exacerbation of symptoms in some special types of vascular lesions, in some varieties of meningiomas and some neurological conditions like multiple sclerosis.

The term 'intracranial tumours' includes, in a loose fashion, all space-occupying lesions within the cranial cavity including non-neoplastic lesions like cysts, granulomas, chronic abscesses and haematomas. This is because the pathogenesis and evolution of symptoms and localising features are common to many of these lesions, irrespective of their pathology. The term ICSOL is more acceptable.

ICSOL cause clinical symptoms by: (1) raising the ICP; (2) interfering with the function of the area involved by the lesion; (3) disturbing the function of neighbouring structures due to oedema or vascular disturbances and (4) by displacement and distortion of remote structures due to various herniations. As neural function has often a hierarchical organisation, damage to one region may, by removing its inhibitory control over the "lower" region, result in the manifestation of release symptoms and signs. One of the symptoms may manifest itself first or these may all begin to appear at the same time and progress at varying rates.

RAISED INTRACRANIAL PRESSURE— PATHOGENESIS

Except in infants and young children, the cranial cavity is not expansile and thus any addition of matter inside the cranial cavity results in an increase in pressure. In the early stages, some amount of adjustment may occur by displacement of a small quantity of CSF and venous blood. But this can accommodate only a small amount of extra matter. If the lesion increases in size, it has to accommodate itself by compressing the brain and the other intracranial structures with a resultant increase in ICP. The factors that determine the rise in ICP are: (1) the bulk of the tumour and the rapidity of its growth;

(2) associated cerebral oedema; (3) its effect on the CSF pathways with obstruction of CSF circulation and (4) compression of the major venous channels.

1. *The bulk of the tumour and rapidly of its growth*: A slow growing lesion, like a meningioma, may grow to a large size without manifesting any symptoms or signs of raised ICP. Over months and years, the tumour makes a bed for itself by compressing and indenting the brain slowly. On the contrary, a rapidly growing tumour, even when small in size, raises the ICP early in its evolution. Any event, like haemorrhage or cystic degeneration that may suddenly increase the size of a slow growing lesion, may also lead to decompensation and result in raised ICP.
2. *Associated cerebral oedema*: Some space occupying lesions have a tendency to break down the blood-brain barrier and cause extensive oedema, e.g. glioblastoma, some varieties of metastases, meningioma, tuberculoma, cysticercus and abscess. In these cases, the ICP may show a rapid rise, even though the tumour may be small in size.
3. *Proximity to CSF pathways*: Tumours occurring near the midline tend to obstruct the CSF flow and thus lead to hydrocephalus and increased ICP. Tumours arising in the medial temporal region, in the suprasellar region in the third ventricle and in the posterior fossa near the fourth ventricle are such examples. In these locations, even a small lesion may lead to an early rise of ICP.
4. *Compression of the major venous channels*: A tumour arising near a major venous channel may compress it and lead to venous stasis. This is rare, as generally other venous pathways open up rapidly and restore cerebral venous outflow.

EFFECTS OF RAISED INTRACRANIAL PRESSURE ON VARIOUS STRUCTURES

Increasing ICP causes varying effects on the different structures of the cranial cavity depending on their vascular supply and resistance.

1. *The skull and the scalp*: Due to the free communication between the scalp veins, the diploic channels and the dural and subdural veins, increasing ICP may be transmitted to the veins of the skull and scalp. The scalp veins may become dilated and prominent when the patient bends forward. They may appear especially prominent on the side of the tumour when the tumour is near the surface. The enlarged diploic veins become apparent on plain X-rays. The posterior clinoid processes get demineralised and may get absorbed and the pituitary fossa may get enlarged. In children and young adults separation of the sutures and beaten silver appearance are common.
2. *The dura mater*: As the ICP rises, the dura mater gets stretched. The basal dura being sensitive, the patient develops headache, which may be frontal, occipital or generalised. Stretching of either the falx cerebri or the tentorium may also result in localised or generalised headache. The dura, if stretched over the surface of a tumour, may get thinned out.
3. *Veins*: The intracranial veins are one of the earliest structures to suffer the effects of increased ICP. The walls of the veins near the tumour get stretched and compressed and the veins get obliterated leading to back pressure. As the ICP rises, a large number of veins get occluded but as the venous sinuses are enclosed in rigid dura, pressure on the sinuses is not common except when there is direct pressure by a tumour arising near the sinus. Pressure on the veins leads not only to retrograde congestion but also interferes with the absorption of CSF. Blockage of the venous flow from the orbit may result in a mild unilateral or bilateral proptosis. Tumours occurring in the middle cranial fossa or the temporal lobe may lead to a mild but perceptible proptosis on the side involved due to pressure on the veins draining through the superior orbital fissure.
4. *Cerebrospinal fluid*: The subarachnoid spaces along the base of the brain and over the convexity gradually get obliterated. A tumour adjacent to the CSF pathway may exude proteins into the CSF which may further increase the ICP. A spinal neurofibroma which elevates the protein levels in the CSF may raise the ICP and cause papilloedema.
5. *Major arteries*: In the initial stages, there are no alterations in the major cerebral arteries. However, as the tumour enlarges, local distortion of the neighbouring arteries may take place. The patient may complain of frontal headaches due to stretching of the vessels of the circle of Willis. In the late stages, the ICP may rise as high as the arterial pressure; this causes a reflex rise of blood pressure in an attempt to keep up the cerebral blood flow (CBF). In an acute and severe rise in ICP, when the ICP equals the arterial blood pressure, carotid and vertebral arterial flow into the brain may stop. At this stage, the patient is deeply unconscious and without spontaneous respiration. Angiography shows a 'carotid stop' or total circulatory failure. This phenomenon is more often seen terminally in cases of acute massive increase in pressure, as in sudden severe subarachnoid or intracerebral haemorrhage, fulminating post-traumatic brain swelling and only rarely in brain tumours. Reduction of ICP by diuretics or hyperventilation may help to restore the blood flow for a short while.
6. *Cranial nerves*: Owing to their pliability, the cranial nerves may get stretched without any apparent deficit. The nerves most liable to be involved in rising ICP are the sixth nerves, because of their long intracranial course and their angulation over the petroclinoid ligament and passage through Dorello's canal. Increased ICP may result in unilateral or bilateral external rectus palsy. In general, this is not of localising value. The third nerve is likely to be compressed in supratentorial lesions when there is transtentorial

herniation. The pupillary fibres being more superficial in the nerve, dilatation of the pupil is more frequently encountered than ptosis or ocular muscle weakness. Raised ICP can produce impairment of hearing, as has been documented in a series of studies from AIIMS.[86] The hearing deficit may be either conductive or sensorineural. Initially or predominantly, it may be unilateral, thus confusing the clinical localisation of the lesion. When the ICP rises further or in posterior fossa lesions when the cerebellar tonsils herniate through the foramen magnum, the first and second spinal nerves get stretched leading to spasm of the suboccipital muscles, as well as pain and paraesthesia over the occipital region. The effect of raised ICP on the optic nerve is dealt with elsewhere (refer Visual Field Defects). Besides paresis, stretching or pressure on the cranial nerves may result in positive phenomena. Thus, a tumour of the temporal lobe may produce trigeminal neuralgia by pressing on the Gasserian ganglion or a tumour in the CP angle may present with hemifacial spasm.

7. *Cerebral blood flow*: When the ICP is marginally raised, there is no change in the CBF. However, enlarging lesions may cause alterations in the blood flow of circumscribed areas depending on the local pressure and the pathology of the lesion. A very vascular growth or an arteriovenous malformation causes a considerable reduction in the blood flow to the surrounding areas due to the phenomenon of steal. As the ICP rises further, there is a gradual reduction in CBF leading to incipient cerebral anoxia. The rapid clinical improvement, often seen after the administration of diuretics or CSF diversion procedures, can be attributed not only to the reduction in ICP but also to improved CBF. On the other hand, when the ICP rises rapidly there may be a paralysis of autoregulation, resulting in a sudden increase in CBF which is responsible for the rapid deterioration in the condition of the patient.
8. *Effects on the brain*: The white matter is liable to be affected by a dilating ventricular system.[51] In long standing hydrocephalus, signs of pyramidal tract involvement appear due to stretching of the white matter of the corona radiata by the enlarging ventricles. In general, however, the brain substance suffers more from local pressure, venous congestion and oedema rather than from any general effect of raised ICP. This is true for both of the grey and white matter.

Secondary phenomena: Increasing pressure on the brain, the blood vessels and the CSF results in the secondary phenomena of herniations, false localising signs and systemic disturbances.

SIGNS AND SYMPTOMS OF RAISED INTRACRANIAL PRESSURE

These signs get modified according to age. The elastic skull of the infant and young child can accommodate the increase in intracranial contents by a slow expansion secondary to separation of the sutures. A tense fontanelle or a progressive increase in the size of the head may be the only sign of raised ICP for months. Percussion of the head elicits a cracked pot sound (MacEwen's sign) in some children. Young children often do not complain of headaches and the presenting symptoms may be abdominal discomfort, vomiting, irritability or listlessness. The optic fundus is often normal; papilloedema is uncommon but pallor of the disc may be seen in some children with raised ICP.

In old people, the brain shrinks a little due to atrophy and thus there is more space for the lesion to grow before causing an increase in pressure. Thus, slow growing lesions may attain a considerable size in elderly persons before pressure effects begin to appear.

Headache

Headache occurs frequently in patients with increased ICP and acquires special significance if it occurs in a person not previously subjected to headaches. The brain itself is insensitive to pain but the dura mater, especially at the base of the skull as well as the major blood vessels in the brain, are pain sensitive structures. Headache, in increasing ICP results from stretching of the dural coverings, shifting of the dural partitions and stretching and kinking of the major blood vessels. The headache may be frontal, bitemporal or occipital. The anterior parts of the dura are supplied by the trigeminal nerve and the posterior half by the second cervical nerve, frontal headache may indicate an anterior lesion and an occipital headache a more posterior tumour but this is often not true. Only occasionally the site of has headache any localising value. Anterior basal tumours often cause retro-orbital pain for months, before generalised headache appears. Pain over the vertex is uncommon, except in cases of parasagittal tumours arising near the vertex. Surface tumours, like meningiomas, may present with localised pain and tenderness.

Headache caused by raised ICP has certain features which may arouse suspicion of the possibility of a space occupying lesion. The headache is throbbing in character and gets aggravated by stooping, straining or exertion. It is common in the early hours of the morning and towards late in the evening. A characteristic feature of the headache due to raised ICP is its occurrence when the patient is sleeping. The throbbing headache often wakes the patient up in the early hours of the morning. Such headaches coincide with REM sleep (dream sleep) during which normally the ICP shows a tendency to rise due to cerebral vasodilatation. In patients whose ICP is already high, a further increase in pressure, during sleep, causes an increase in the severity of headache. Alcohol or other vasodilating drugs tend to increase this headache. A small percentage of patients (about 10%), for some obscure reason do not complain of headache in spite of severely raised ICP.

Pain in the suboccipital region has a serious import and requires urgent action. Suboccipital pain, occurring in a patient who has already been diagnosed as suffering from raised ICP, indicates tonsillar herniation. The herniating cerebellar tonsils irritate the C1 nerve root causing spasm of the suboccipital muscles which causes headache. The head may be tilted or rotated to one side and this is often seen in children. At a later stage, the C2 nerve root is similarly stretched leading to muscular pain. Such pain is often mistaken for upper cervical pathology both in children as well as in adults. Cough syncope may occur with herniated cerebellar tonsils.[48]

Localised Tenderness of the Skull

This has a localising value in tumours involving the cranium or the dura mater. More commonly, inflammatory lesions underlying these structures cause localised tenderness over the affected area. Some patients with cerebellopontine angle (CPA) lesions will give a history of transient severe ear ache or retromastoid pain on the side ipsilateral to the lesion.[22]

Vomiting

This is a frequent symptom of raised ICP and is caused by irritation of the vomiting centre in the medulla. While vomiting is prominent in some patients, it may be absent in others. Usually, vomiting occurs sometime after the headache sets in. Vomiting is a common and early symptom of increased ICP in children and may be the only symptom of a space-occupying lesion for a long time. Unexplained vomiting in a child has to be taken seriously and investigated.

Generally, the vomiting is described as projectile without any feeling of nausea but this is not always so. As the vomiting is not due to gastric causes, it is often possible to feed a patient with small amounts of nourishment soon after the vomiting. This must be remembered as otherwise the patient may get dehydrated and malnourished in a very short time.

Vertigo

This is often seen in intracranial tumours, especially in posterior fossa lesions. The patient will complain of an unsteady feeling and a disturbance of the sense of balance in space. This may occur with or without alteration in posture. Giddiness may be due to vestibular disturbances, pressure on the brainstem or visual disturbances like diplopia or transient blurring of vision.

Visual Changes[28,77]

When ICP has existed for sometime, the function of the optic nerves is affected. Ophthalmoscopic examination is essential in examining a patient suspected of harbouring a brain tumour.

Papilloedema

A blockage of the venous return from the retina results in papilloedema. This occurs in the majority of cases of raised ICP, except in young children[31], in whom raised ICP is compensated for a long period of time by separation of the sutures. Papilloedema is also late in appearance in benign low grade gliomas, epidermoids, meningiomas and in frontoparietal tumours, whereas posterior fossa lesions cause papilloedema early. Very rarely, papilloedema may not occur in raised ICP if the venous drainage of the retina is embryologically different, draining chiefly into the inframaxillary venous plexus. In pituitary and parapituitary lesions, the optic nerve gets compressed initially leading to primary optic atrophy; in such cases, even when the ICP increases later on, papilloedema does not develop in the eye with optic atrophy.

The earliest change in the optic fundus secondary to rise in ICP is loss of spontaneous venous pulsations (SVP). The presence of the pulsations indicates that the ICP is less than 200 mm H_2O. In about 10–20% of normal patients the SVP may be absent.[17]

The earliest indication of papilloedema is the enlargement of the blind spot. This is a useful diagnostic sign and should be carefully looked for whenever there is any doubt about the existence of papilloedema. The size of the blind spot corresponds to the area of exit of the optic nerve from the retina, i.e. the optic nerve head; hence the size of the blind spot increases when the optic nerve head begins to swell. Another early sign of increasing ICP is the enlargement and congestion of the retinal veins.

The normal optic disc is slightly pink and circular, with the temporal side being slightly paler than the nasal side. In papilloedema the disc projects forwards in relation to the retina, the projection being more obvious on the nasal side when seen through the ophthalmoscope. Normally, the optic nerve head is depressed below the surface of the retina by about two or three millimetres, thus forming the optic cup. From the centre of the depression, the retinal arteries and veins may be seen coursing in four directions. Pigment is often seen at the edge of the optic cup. An initial change that may often be observed in raised ICP is the obliteration of the optic cup, with the margins of the optic cup becoming ill defined. A little later, the origin of the retinal vessels from the optic cup cannot be visualised. As the swelling of the optic disc progresses further, the retinal vessels get narrowed and obliterated near the optic disc. At this stage, haemorrhages may develop and a generalised congested picture of the retina will become obvious. Even after such an oedema has occurred along with haemorrhages, the patient does not complain of diminution of vision except in some rare cases where a haemorrhage may have occurred over the macula.

A small cupless disc is vulnerable to anterior ischaemic optic neuropathy (AION). This is termed "disc at risk".[41] Measurement of dioptres with an ophthalmoscope is not worthwhile.[17]

Examination of the fields may show only a mild concentric contraction. In the late stages, when the papilloedema is advanced, there may be attacks of transient dimness of vision. Transient obscuration of vision may be complained of when the patient straightens himself after bending down or on getting up from bed. This is a danger signal and should be understood as a sign of impending visual failure. It is thus obvious that papilloedema may exist for weeks before visual failure occurs, and when it does, it may be sudden and the patient may say that the loss of vision has been acute.

This picture may be contrasted with that of optic neuritis. It is essential to differentiate between the two conditions, as early papilloedema may be mistaken for optic neuritis. In optic neuritis or retrobulbar neuritis, the changes in the optic discs are minimal compared to the degree of loss of vision. The failure of central vision occurring in optic neuritis leads the patient to complain of severe loss of vision, whereas the optic disc itself may be normal or may show mild congestion or slight pallor. It is uncommon to have retrobulbar pain in papilloedema. Papilloedema has also to be distinguished from pseudopapilloedema. Hypermetropia, congenital anomaly of the disc or deposits of Drusen may simulate papilloedema. Drusen is an inherited anomaly occurring in about 0.3% of the population. Deposits occurring deep to the disc give an appearance simulating disc swelling. There is no visual loss and the prognosis is good.

Papilloedma may occur in only one eye if the subarachnoid space around the optic nerve in the other eye is obliterated due to direct pressure by a tumour. In such cases, the patient presents with primary optic atrophy in the eye on the side of the tumour and papilloedema in the opposite eye (Foster Kennedy syndrome).

When papilloedema has been persistent for a long time, visual failure may occur even after the ICP has been reduced. In other words, onset of visual failure may occur after successful surgery for a tumour and the unfortunate patient may attribute this visual failure to the surgery.

The stages of papilloedema as graded by Frisen et al.[32] are as follows:

Grade 0: Normal
Grade 1: Minimal papilloedema characterised by a C-shaped halo
Grade 2: Mild papilloedema which is characterised by a complete halo
Grade 3: Moderate papilloedema which is characterised by obscuration of disc vessels off the disc
Grade 4: Marked papilloedema characterised by obscuration of vessels on the disc
Grade 5: Severe papilloedema characterised by mushroom disc with cup obliteration

Optic Atrophy

Long standing papilloedema leads to blindness with secondary optic atrophy. The disc becomes white, the vessels attenuated and the disc margins continue to be indistinct (as contrasted with primary optic atrophy). In the early days of neurosurgery in India and in the developing countries, a number of patients with intracranial tumours reported with blindness. Diagnosis of a brain tumour is possible and desirable before papilloedema sets in and the frequency of such diagnosis reflects the medical awareness of society and of the doctors.

Abducens Palsy

The patient may complain of diplopia and on examination show evidence of unilateral or rarely bilateral, external rectus paralysis. Owing to the long course of the VI nerve inside the cranial cavity, both in the posterior fossa as well as in the middle fossa, space occupying lesions and increased ICP tend to interfere with the function of this nerve more often than any other cranial nerve. Nathan et al.[58] have drawn attention to the anatomical variations in the course of the VI nerve. In some patients, they have seen two trunks arising from the brainstem and reaching the orbit separately. This may explain the partial involvement of the VI nerve seen in some instances. These variations explain why only some patients with raised ICP develop abducens palsy. Thus, abducens palsy occurring in raised ICP has generally no localising value. Diplopia may be a presenting symptom of intracranial tumours.

Proptosis

A mild proptosis may be seen in raised ICP.[84] Unilateral proptosis of a mild degree is of localising value. The lesion is often in the region of the lesser wing of the sphenoid bone or the middle cranial fossa of the concerned side.

Disturbance of Higher Functions

The higher functions of the brain, like concentration, judgement and memory, get impaired to a varying degree when ICP rises. In the early stages, the patient is often aware of these defects; occasionally the impairment may be reported by friends and relatives. Such changes occurring before the appearance of localising signs are often attributed to systemic disorders like arteriosclerosis. The general slowing of higher functions should not be mistaken as an indication of a frontal lobe tumour,[81] as it may occur with tumours in any part of the cerebral hemisphere. In elderly patients with neurodegenerative diseases, the great toe is upwardly pointing. This is called the striatal toe.[17] These patients also have a slow flexor plantar response known as the tonic flexor plantar response.[17] In frontal tumours such symptoms occur early, commonly preceding the signs of increased ICP. On the contrary, most children who develop raised ICP due to tumours are well behaved, quiet and remarkably mature in their actions.[14]

Generalised epilepsy may occur as a sign of raised ICP without localising significance. This has been attributed to anoxia, venous congestion or oedema in a brain with a low threshold for convulsions. Sleep rhythm is occasionally disturbed when ICP increases, the patient being restless and sleepy alternatively during the day and night.

Systemic Changes

Increased ICP may result in abnormal impulses being transmitted to the kidneys, resulting in renal ischaemia and leading to a rise in blood urea, non-protein nitrogen and extracellular potassium. The urinary output is normal. The patient becomes drowsy and irritable and may develop tachycardia, fits or generalised oedema. The urine may show albumin with marked decrease in sodium and chlorides. As the urine volume remains normal, the diagnosis may be missed.

Paroxysmal hypertension may be seen in the late stages of intracranial tumours, especially in posterior fossa lesions[16] Palpitation, perspiration and headache may be present with the acute rise in blood pressure and may be mistaken as due to a phaeochromocytoma. Bradycardia is a late sign of raised ICP and may also be caused by cerebral anoxia.

In the late stages, stupor, bradycardia and rising blood pressure are apparent along with respiratory depression. Rarely, neurogenic hyperventilation may be seen before respiratory depression ensues. Pulmonary oedema may be produced by increased ICP. The mechanism is mediated through the upper cervical cord.[26] The severe ICP leads to systemic vasoconstriction, systemic arterial hypertension, pulmonary venous hypertension and pulmonary oedema. Even in such a stage, a reduction of ICP by proper therapy leads to a reversal of the signs.

It will thus be noted that the non-specific signs of increased ICP may resemble systemic disease in their earlier stages. Hypertension may cause headaches similar to those of a brain tumour and in the late stages the ophthalmoscopic findings also may be similar.

Cerebrovascular disease also simulates the symptoms of brain tumour in elderly people, the convulsions and deterioration in personality being attributed to cerebral ischaemia. Toxic and metabolic encephalopathy, especially lead encephalopathy and also incipient uraemia may mimic symptoms of raised ICP.

Signs of Interference with Local Functions

Irrespective of the nature of the tumour, neurological signs appear depending upon the site of the lesion. Clinical localisation of a brain tumour is an exercise in neuroanatomy. After the demonstration, in 1870, by Fritsch and Hitzig[33] of the electrical excitability of the cortex, it was possible for Hughlings Jackson to vindicate his theory of cerebral localisation of function[57] MacEwen, in 1876, correctly localised a brain abscess[11] and in 1879, removed a meningioma localised on the basis of the onset of focal convulsions.[50] The first glioma was removed in 1884.[7] Thus, it became evident that recognition of the significance of early symptoms of either irritation or paralysis is possible,[88] depending upon one's knowledge of brain function and the meticulousness of the examination.

In early cases, various combinations of signs and symptoms or syndromes can be recognised. In late cases, secondary phenomena, like distant effects, neighbourhood effects and increasing ICP, confuse the clinical picture. Hence, a careful recording of the history of the onset and of early symptoms of the illness greatly contributes to localisation.

The local effects of the tumour may be either irritative or paralytic. Irritation results in abnormal increase of function, e.g. generalised or focal fits, flashes of light, tinnitus and in other bodily sensations. Depending upon the site of the lesion, paralysis of local areas of the brain manifests itself by negative signs like loss of motor power, sensation, speech and hearing. In addition, there may be positive signs of increased activity of the lower levels of the nervous system due to release phenomena, e.g. spasticity, grasp reflex.

Epilepsy and Brain Tumour

Epilepsy is a common symptom of intracranial tumours occurring in about a third of all patients with tumours. Supratentorial tumours, both extracerebral and intracerebral, manifest epileptic seizures as a symptom in about 50% of cases.[87] These may be focal or generalised, presenting as the initial symptom and remaining as the only symptom for a long time. Convulsions may also occur in the late stages of the disease due to increased ICP. When epilepsy marks the presence of a tumour, it occurs early in the course of the disease. It was the first symptom in 50% of temporal tumours, 78% of frontal tumours and 93% of central tumours.[49]

Focal epilepsy often suggests the site of the lesion. Postictal weakness (Todd's paralysis) is common and clears in a short time. When it occurs consistently and persists for a long time, the chances of an organic lesion being the cause of the fit are much higher.[69] General and focal convulsions may occur in the same patient. Variation in the pattern of the fits with passage of time or the occurrence of fits in clusters favours the possibility of a tumour. Sudden unheralded status epilepticus in an otherwise healthy individual may be the first symptom of a brain tumour. Oxbury and Whitty[63] found that the majority of such patients have a frontal tumour. However, this has not been confirmed.

About 1% of all patients with epilepsy have intracranial tumours. The onset of epilepsy in adult life above 35–40 years is more likely to be due to a tumour. Such patients should be carefully evaluated and advised frequent follow-up. Epilepsy as a symptom of tumours usually indicates a slow-growing tumour. Rasmussen and Blundell[72] found that many patients with seizures

as the first or the main symptom of the tumour harbour tumours with a low growth potential. A patient may have convulsions for a number of years before other symptoms of a tumour begin to manifest themselves. This is often seen in low grade gliomas and meningiomas. Glioblastomas are least likely to be accompanied by convulsions of a long duration.

Meningiomas cause convulsions by pressure on the cortex with the resultant local oedema and venous stasis. Sixty per cent of convexity meningiomas may have epilepsy as the first symptom. This is also true of tuberculomas, especially those involving the cortex.[68]

Regional Signs

Subfrontal Tumours

Tumours in the subfrontal region grow upwards into the under surface of the frontal lobe and may exist for a long time without causing any apparent neurological signs. In larger tumours, lack of inhibition and impulsive laughter or crying may occur, as also pointless silly joking (moria) associated with euphoria.[59] Rage attacks may also occur. There may be impairment of recent memory. Excitement or hallucinations may occur due to irritation of the frontobasal region. Epilepsy may be generalised or adversive in onset. Subfrontal midline lesions cause anosmia in the absence of rhinitis, as seen in olfactory groove meningioma. When the lesion extends posteriorly, optic atrophy results from pressure on the optic nerve or chiasma or there may be a Foster Kennedy syndrome.

Frontal Lobe Tumours

These may exist for a long time without any physical or mental sign or symptom, resulting in delay in diagnosis. The patient may be able to carry on routine work without impairment. When the lesion begins to spread posteriorly and involves the connections with the opposite frontal lobe, symptoms appear, commonly termed frontal lobe signs. The signs progress rapidly if the lesion is intra-parenchymal, whereas, with extrinsic tumours the symptoms progress more slowly. Lack of drive or reduction in initiative may be the first symptom and a failure to observe accepted social norms becomes obvious. There may be undue jocularity ('Witzelsucht'). There is an absence of inhibition naturally expected of a normal person in a particular social environment. This may manifest itself in an unnaturally familiar behaviour which may be mistaken for taking liberties or for impertinence. Later, the capacity for insight is impaired. These symptoms become more pronounced when the lesion extends backwards to involve the association fibres of the corpus callosum. Interference with memory is not a common sign in frontal lobe lesions, although occasionally, recent memory may be impaired. Visual inattention, confabulation and apathy may be observed.

There are three distinct prefrontal lobe dysfunction syndromes. They are: (1) Dorsolateral prefrontal lobe dysfunction which is important for working memory and adjusted behaviour; (2) medial prefrontal syndrome which is concerned with initiation of activity and causes akinetic-abulia syndromes and (3) orbital pre-frontal syndrome which is characterised by hyperactivity.[18]

A comparison of intelligence quotient scores between patients with frontal tumour and tumours elsewhere did not show any significant difference. But a comparison of the scoring between right and left frontal lobe tumours showed a greater loss of intellectual function in right handed individuals with left frontal tumours than in those with right frontal tumours.[8] Special psychometric tests can easily differentiate between frontal and temporal lobe dysfunction (as established by Brenda Milner of the Montreal Neurological Institute).

The motor signs of frontal lobe lesions are a manifestation of impairment of voluntary motor control, e.g. difficulty in performing serial alternating tasks, motor perseveration and ataxia of the contralateral leg. Apraxia of gait, occasionally seen in these patients, may be mistaken for ataxia. Dysphagia, as a presenting symptom in tumours of the posterior part of the inferior frontal region, has been reported by Meadows,[54] who attributed this to the involvement of the lowest part of the precentral gyrus or the inferior frontal gyrus.

Psychoses may be simulated by a long standing frontal lesion like a meningioma. Involutional depression or presenile dementia may be diagnosed when the patient has incontinence, apathy and dementia due to a frontal lesion. Basal frontal lesions may cause excitement or hallucinations which may lead to a mistaken diagnosis of hypomania or schizophrenia.[42] In advanced cases, the patient may have a leucotomy effect and may not even complain of severe pain, for example that of a strangulated hernia.[23]

When the lateral surface of the frontal lobe is irritated, adversive fits may occur with the head and eyes turning to the opposite side. In acute frontal lesions, conjugate deviation of the eyes to the opposite side occurs. In some chronic lesions, the eyes may tend to turn ipsilaterally. In frontal lobe lesions there is also difficulty in moving the eyes to the side on command, whereas follow-on movements are possible. When both the frontal lobes are affected, signs of dementia may be apparent.

Frontal lobe symptoms may be simulated by posterior fossa lesions and vice versa. When the anterior horns dilate due to hydrocephalus, the frontal fibres are compressed resulting in the production of frontal lobe signs. Intention tremor and other cerebellar signs may be seen in frontal lobe lesions. A variety of explanations have been given for this phenomenon.

Bilateral frontal lobe lesions may uncover primitive reflexes, e.g. grasp reflex in the hand or the tonic foot response. Lesions confined to the anterior part of the lobes on either side cause no symptoms, which become obvious only when the frontal lobes are involved more posteriorly. Posterior frontal tumours may rarely

produce contralateral or bilateral tremors simulating Parkinsonism. This may occur even when the basal ganglia are not directly involved. Incontinence of urine occurs when the medial surfaces of both the frontal lobes are involved or when the corpus callosum is affected. Frequency of micturition or urgency may be present in some patients. Incontinence occurring in an otherwise conscious patient has localising significance. As the lesion extends backwards, weakness of the contralateral limbs with exaggerated reflexes is seen.

Tumours in the Sensorimotor Region

Tumours involving the sensorimotor strip are more easily diagnosed because of the obvious impairment of motor and sensory function in the contralateral limbs. Epilepsy is a common symptom of such lesions. This may be focal motor or focal sensory with or without the Jacksonian march or generalisation. Loss of power or sensation, lasting for some time after a focal attack, is suggestive of local pathology. When the function is further affected, paralysis occurs which is more pronounced in one limb (monoplegia), or in one part of a limb. Isolated digit palsies may occur. Such circumscribed pareses are common in cortical lesions. Superior and medial lesions cause weakness of the hand or face, or dysphasia if the tumour is on the dominant side. Initially, this weakness may be flaccid with diminished reflexes but soon becomes spastic. When the lesion is deep seated, even a small tumour may cause hemiplegia with exaggerated reflexes. Primitive reflexes are unmasked, e.g. grasp reflex, the bulldog reflex, i.e. involuntary hold on an object placed between the teeth and the tonic plantar reflex. When the supplementary motor area of the dominant hemisphere is involved, the rare clinical phenomenon of dysphonia may be observed due to interference with the circuits linking the cortical speech area with the thalamus. Involvement of the sensory cortex is indicated by a feeling of tingling, dysaesthesia or numbness in the contralateral limbs.

Parietal Lobe Tumours

The cortical sensory area forms the anterior boundary of the parietal lobe. When the lesion spreads posteriorly, parietal lobe signs become more obvious. Discrete areas of sensory loss may be detected in small focal lesions. In anterior parietal lesions, tactile localisation, two point discrimination and light touch are affected, as also joint sense, vibration sense, stereognosis and appreciation of form and weight. Spontaneous pain and dysaesthesia of the opposite half of the body may be seen in some parietal lobe lesions and may resemble thalamic pain.[76] There will be difficulty in tactile localisation. The patient is not able to appreciate differences in texture of materials, e.g. between cotton and silk. There is also an impairment of appreciation of differences in temperature. While a normal person can appreciate differences between 2°C and 5°C, in parietal lobe lesions differences of 10°C may not be appreciated. There is difficulty in recognising numbers written on the skin (graphaesthesia), as also difficulty in appreciating differences in weight (abarognosia).

The joint position sense is impaired and thus, the posture of the limb is affected. This results in a drift of the outstretched arm and a pseudoathetotic posture. An early sign of a parietal lobe lesion is the fall of the outstretched arm. If the patient is asked to keep both his arms stretched out in front with the eyes closed, the arm opposite to the side of the lesion will slowly drift downwards and outwards. This is seen even when there is no apparent weakness of the arm. Occasionally, two or three fingers alone may drop downwards if a small lesion involves the concerned area.[40] The outstretched hand shows a peculiar hyperextended position of the fingers (pseudoathetosis). A left parietal lesion may produce a significant arm drift on the ipsilateral side in addition to the contralateral arm drift, whereas a right parietal lesion produces postural impairment on the left side only.[92] Trophic changes in the form of anhydrosis, or soft skin, along with muscle wasting may be seen.

In pure parietal lobe lesions, inattention is an early feature. This sensory inattention can be detected by simultaneous stimulation of identical areas on both sides of the body. On a simple command like, 'lift up your arms' the patient raises only the unaffected arm, even though there is no motor weakness on the affected side. In more extensive lesions, awareness of body image is lost. This may involve not only recognition of one's own body image but may extend to other persons also. As a part of this, the patient has finger agnosia, (an inability to identify the different fingers of his hand). Somatoagnosia leads to non-recognition of one half of the body, not shaving one half of the face or difficulty in dressing.[19] When the loss of the body image extends to outside objects, the patient is unable to identify parts in a human figure and also finds it difficult to draw objects, only one-half of the human figure or the face of a clock may be drawn. The patient also has difficulty in identifying familiar places or familiar routes.

Loss of awareness of the affected half of the body may also result in the patient denying his disability or asserting that the normal side of his body is the one that is diseased. As an extension of this, one may see the phantom limb phenomenon; the patient claims to have an extra limb or an extra half of the body which requires to be clothed or covered. When the lesion is near the parieto-occipital junction, the patient has difficulty in identifying faces. This may go to such an extent that he may not be able to recognise his own face in the mirror.

An inferior quadrantic hemianopia is often seen in such posterior lesions. Auditory neglect, similar to somatic neglect, has been observed in inferior parietal lesions.[24] The patient hears the sound in both ears but always reports that the direction of the sound is from the side ipsilateral to the cerebral lesion, i.e. neglecting stimuli from the contralateral side.

Apraxia is often seen, especially in lesions of the left side, leading to difficulty in writing (agraphia). Copying is not difficult. Apraxia of eye movements may be observed in bilateral parietal lesions. Apraxia of gait or apraxia of dressing may be an important manifestation. Voluntary fixation of gaze on an object is not possible although involuntary eye movements are full and normal. This apraxia is different from paresis of conjugate movement seen in frontal lesions. Rarely, parietal ataxia has been described.[2] All these symptoms are more prominent in intrinsic lesions. In right-handed people, right parietal lesions result in a greater disturbance of parietal lobe functions.

Gerstmann[34] described a syndrome with the chief components of: (1) finger agnosia; (2) agraphia-apraxia of writing confined to single letters or words, (while copying is not affected); (3) dyscalculia—difficulty in calculations; (4) right-left disorientation. Gerstmann believed that this syndrome was due to a lesion in the dominant (left) angular gyrus. However, the whole syndrome or a part of it may be seen in lesions involving the angular and supramarginal gyri and the contiguous area of the occipital lobe.[20]

Parietal lobe symptomatology may vary in extent and severity during different parts of the day, the difficulty being more prominent when the patient is tired. Epilepsy is common in lesions of the parietal lobe and often starts with a sensory aura. Occasionally, epigastric sensations may be present.

Parietal lobe dysfunction can be summarised as follows:

The dominant lobe is concerned with spatial motor skills while the non-dominant lobe is concerned with spatial orientation skills. Left superior parietal lobule lesions cause aphasia, agnosia, astereognosis and agraphaesthesia. Right superior parietal lobule lesions cause spatial agnosia, sensory neglect, astereognosis, agraphaesthesia and dressing apraxia. Left inferior parietal lobule lesions cause ideomotor/ideational apraxia and Gerstmann's syndrome (angular gyrus-Geschwind's area lesion—area 39) while right IPL lesions cause aprosody. Bilateral parietal lesions cause Balint's syndrome and movement agnosia.[18]

Temporal Lobe Lesion

Affection of the dominant temporal lobe leads to more pronounced disability than affection of the non-dominant temporal lobe. In the human, as speech and intellect are closely associated, early disturbance of speech may be mistaken for impairment of intelligence.

A careful study of the patient's difficulty is needed to diagnose early disturbances of speech. When the disturbance is more pronounced, the diagnosis is easier and the differentiation of aphasia or dysphasia into motor or sensory, serves a useful purpose. Cerebral speech disorders, resulting from lesions in different parts of the hemispheres, vary fairly significantly to be of localising value. Lesions in Broca's area (posterior part of the inferior frontal gyrus) result in non-fluent aphasia with difficulty in naming objects and with good comprehension. Lesions in Wernicke's area (posterior superior temporal lobe) cause fluent aphasia, with poor naming and impaired comprehension. In Jargon aphasia, the tone, inflection, etc. resemble speech but the words and phrases carry no meaning. Conduction aphasia (resulting from lesions in the arcuate fasciculus connecting Broca's area with Wernicke's area) resembles Wernicke's aphasia except that comprehension in these patients is good. Paroxysmal disturbances of speech may also be observed. Auditory disturbances are rare with unilateral temporal lobe lesions. When the medial temporal lobe is affected, the most common manifestation is complex partial seizures (temporal lobe epilepsy). The patient may have a cephalic or a visceral sensation as an aura. There may be psychosensory or psychomotor disorders like déjà vu phenomenon and a dreamy state. Hallucinations of taste or smell are a common feature of limbic lobe epilepsy and are more often seen in patients with tumours as compared to the more common medial sclerosis. Focal motor epilepsy starting in the face may occur in a small percentage of cases. The onset of temporal lobe symptoms, in an adult, without any preceding history of epilepsy, should arouse the suspicion of a space occupying lesion.

Lesions of the medial temporal region may lead to loss of memory, especially for recent events. The patient may be unduly irritable or aggressive and show emotional instability. When the lesion is in the more posterior part of the temporal lobe, the optic radiations are affected. As the optic radiation makes a loop (Meyer's loop) into the temporal lobe before proceeding to the occipital lobe, posterior temporal lesions result in a superior quadrantanopia. (Note inferior quadrantic defect in parietal lesions.) In more medial temporal lobe lesions, the optic tract could be affected leading to typical homonymous hemianopia.

Temporal lobe tumours, especially in the non-dominant side may exist for a long time and may even raise the ICP without any apparent localising sign. They show a greater tendency for uncal herniation than other tumours.

Occipital Lobe Lesions

The characteristic sign of an occipital lobe lesion is loss of vision in the opposite visual field, the extent of the defect varying with the site and size of the tumour (see chapter on Visual Field Defects).

Tumours compressing the outer surface of the occipital lobe usually spare the fixation area. These may also cause impairment of follow-on conjugate movement of the eyes. In occipital lesions causing homonymous hemianopia, the patient can detect moving objects but not stationary objects in the visual field.[40] Homonymous hemianopia is diagnosed at the bedside by the patient failing to look at persons on one side of his bed. During conversation the patient turns his head to one side to see

well. Thrusting a finger near the eyes on the hemianopic side fails to elicit the menace reflex.

Occipital lobe lesions may also show the phenomenon of visual inattention or extinction. When two objects are placed on either side simultaneously, the object in the defective field is not recognised. But as soon as the object in the normal field is removed, the object in the defective field becomes visible and is also recognised.

Seizures are less common in occipital lobe lesions compared to the other lobes. Seizures with uniform visual hallucinations like flashes of light may present as an early symptom of occipital lobe lesions and there may be an adversive element at the onset of fits. Unlike temporal lobe fits, these hallucinations are crude and not organised. Distortions of images and objects (metamorphopsia) may form the visual aura.

Lesions Near the Falx

These lesions compress the medial surface of the hemispheres and may cause bilateral signs. Spastic paraparesis occurs if the lesion is near the motor strip. Similarly, focal epilepsy irregularly involving either lower limb may be observed. Irritation of the supplementary motor area may result in focal seizures with adversion and tonic posturing of the limbs or generalised convulsions with loss of consciousness as the initial phenomenon. When the pressure is chiefly on the supplementary motor area of the dominant hemisphere, the patient may have the rare clinical phenomenon of spastic dysphonia.

Lesions of the Corpus Callosum

Being an extensive structure connecting the two hemispheres, the corpus callosum is involved in about a third of all cerebral gliomas. In an autopsy analysis of 200 cases of cerebral gliomas, Bull[15] found that the corpus callosum was involved in 36%. Being essentially a commissure between the two hemispheres, symptoms of corpus callosum involvement depend upon the areas of the brain that are 'disconnected' by the lesion. In discrete lesions of the corpus callosum or in experimental situations, specific disconnection syndromes may be established by special tests.[35,65] In tumours, however, the signs and symptoms depend upon the part of the hemisphere the lesion predominantly involves. In anterior lesions, frontal lobe symptoms appear more pronounced. In this area, the tumours may extend into both the hemispheres as a butterfly growth. Lesions in the middle of the corpus callosum result in impairment of sensory and motor functions. Posterior lesions cause early pressure on the third ventricle and the brainstem. Pressure on the colliculi may result in symptoms simulating a pineal tumour.

The common sign of callosal dysfunction is a unilateral left tactile anomia. The subjects are unable to name objects placed in the left hand although they are able to describe their features. There is also a difficulty in the cross replication of finger positions.[52]

Assessment of Lobar and Higher Cognitive Functions—Brief Outline

The routine neurological examination evaluates only the Rolandic lobe. Often, patients may have a normal gross neurological examination. It is in these cases that higher cognitive functions are indicated to aid lesion localisation. In clinical parlance right frontal and temporal lobe signs of dysfunction are subtle. An important feature to note is that higher function assessment cannot be done in patients who have a decreased attention span or have sensory dysphasia.

The basic initial step in the assessment of higher functions is the mini-mental state examination (MMSE).[29]

Score	Feature
	(a) Orientation:
5-	*Ask the patient to state the date, month, season, year.
5-	*Location—country, state, city, hospital, floor of the hospital.
	(b) Registration:
3-	*Name three objects—1 point for each object. Ask the patient to repeat all the names. Continue the repetition until all three names are registered.
	(c) Attention and calculation:
5-	*Serial 7s subtraction. One point for each correct answer. Stop after five answers. Alternatively a word can be spelt backwards.
3-	(d) Recall: Ask for three objects. Repeat all the words. Give one point for each correct answer.
	(e) Language:
9-	#1 name a pencil and watch (2pts) #2 repeat the following: No ifs and buts- (1pt) #3 three stage commands: Take a piece of paper in your right hand, fold it in half, put it on the floor (3pts) #4 read and obey the following: Close your eyes (1pt) #5 Write a sentence (1pt) #6 Copy a design

The MMSE is 80% sensitive and 98% specific. The average score adjusted for age and level of education is 25–30.

Frontal Lobe Dysfunction

Frontal lobe dysfunction is not easily picked up on psychological testing. The patients may have a normal MMSE. The Luria fist-edge-palm pattern repetition test is of value.[17] Digit repetition is the best test for attention span.[83]

Parietal Lobe Dysfunction

The clock drawing test which tests for constructional apraxia is a very sensitive test for detecting cognitive disturbance. It is based on the principle that to draw a

clock showing a particular time, one must know what a clock is and should have the motor co-ordination to draw the object and also have an ability to understand the examiner; which in effect tests the frontal, temporal, parietal and occipital lobes in one test. Those with left parietal dysfunction are unable to get the form right and those with right parietal lesions are unable to place the numbers in the correct spatial orientation.[30,83]

Temporal Lobe

Language and memory are important functions to be tested. The Babcock sentence (nonsense sentence) is useful for assessing language. Wertheim's test is useful for assessing non-dominant temporal lobe function-non-verbal language.[17] Lesions of the dominant temporal lobe result in impairment of intelligence quotient (IQ) while those in the non-dominant side affect the performance quotient (PQ).

Lateral Ventricle Tumours

These lesions are often silent till they grow to a large size. Meningiomas, ependymomas, choroid plexus papillomas and epidermoids occur inside the lateral ventricles. Cushing and Eisenhardt[21] described the syndrome produced by tumours in the lateral ventricles, which is characterised by headache on the side of the tumour, contralateral homonymous hemianopia, often with macular splitting, contralateral hemiparesis with pronounced sensory loss sometimes associated with trigeminal numbness, cerebellar symptoms and paralexia when the tumour is on the left side (as it commonly is).[38,46] All or any of these symptoms may be present. Posterior hemispheral signs are pronounced, because the majority of lateral ventricle tumours occur in the trigone. Signs due to raised ICP may occur alone without any of the above lateralising signs. The most common false localising signs are those that point to a posterior fossa lesion.

Lesions Involving the Basal Ganglia

These may result in abnormal movements, rigidity or tremors. Unilateral tremors may closely resemble those of Parkinson's disease. Chorea, athetosis and dystonia have been reported as the presenting symptoms of basal ganglia tumours in children.[5,55,61,64] Such symptoms are seen only when critical pathways are involved and not in all basal ganglia tumours. It is seldom possible to clinically suspect extension of hemispherical gliomas to the basal ganglia, a fairly common occurrence.

Due to the close association with the internal capsule, these tumours often cause contralateral motor, sensory or visual field defects. Pupillary inequality and impairment of conjugate movements have been described[53] and are due to pressure on the midbrain. Seizures may occur as drop attacks, with or without accompanying disturbances in the eyes and limbs. Loss of mirror movements is considered to be an early sign of basal ganglia dysfunction.[62]

Middle Cranial Fossa Lesions

These may be divided into sellar lesions, parasellar lesions, lesions near the cavernous sinus and lesions of the temporal fossa.

Sellar lesions: See Chapter "Pituitary Tumours".

Parasellar lesions: The common parasellar lesions are meningiomas, carotid aneurysms and tumours of the base of the skull. In medial lesions, obstruction of the cavernous sinus leads to a mild proptosis. A complete or incomplete ophthalmoplegia follows due to involvement of the III, IV and VI nerves. Often, the pupillomotor fibres are not affected and thus the pupils may remain normal. Involvement of the ophthalmic division of the trigeminal nerve causes hyperaesthesia or anaesthesia of the forehead. Anterior parasellar lesions in the carotid region (aneurysms) press on the optic nerve leading to loss of vision and optic atrophy.

Temporal fossa lesions: This being a fairly large fossa containing numerous structures, various disturbances may arise depending on the location and direction of growth of the tumour.

Anterior lesions of the middle cranial fossa may be asymptomatic for a long time and attain a large size (meningioma). Fits due to irritation of the cortex may be the only sign, followed much later by papilloedema. Of these lesions, the medial ones cause pressure on the optic nerve, while lateral lesions may cause early bony changes, at times visible and palpable externally. Lesions in the middle may cause only a mild proptosis for a long time, due to obstruction of the venous outflow from the orbit through the orbital fissure.

In posterior lesions of the middle cranial fossa, the motor division of the trigeminal nerve is affected with resulting weakness of the masseter, temporalis and pterygoids on the affected side. Pain and paraesthesia may be present over the trigeminal distribution. Raeder[67] described, in 1924, a paratrigeminal syndrome which included pain or numbness over the ophthalmic division and Horner's syndrome without facial anhydrosis. The latter is due to oculosympathetic paresis. This syndrome, accompanied by weakness of the III, IV, V or VI cranial nerves, is indicative of a mass in the middle cranial fossa. This closely resembles the syndrome of painful ophthalmoplegia commonly seen in India. A similar syndrome, without cranial nerve signs, may accompany vascular headaches.

The optic tract may be affected by lesions extending medially, resulting in visual changes. All middle cranial fossa lesions, if they extend superomedially, may cause temporal lobe seizures. Large lesions compressing the temporal lobe may produce temporal lobe signs in the later stages.

Midline Lesions of the Brain

Tumours of the third ventricle region can be conveniently divided into five groups: (1) anterosuperior; (2) anteroinferior; (3) inferior; (4) posterior and (5) lateral.[13]

The onset and progress of symptoms vary in these groups, although there may be a lot of overlap in the latter.

Anterior third ventricle tumours (e.g. craniopharyngioma or a colloid cyst) extending superiorly, often block the foramen of Monro. This blockage is usually intermittent in the case of a colloid cyst and thus the patient may suffer from intermittent bouts of headache, which in a few, gets dramatically relieved by a change in the position of the head. The dilating anterior horn may lead to dementia in adults. In children, anterior third ventricle tumours may be associated with mental retardation, memory loss, weakness of the lower limbs and occasional somnolence.

Anteroinferiorly, the lesions compress the hypothalamus and cause endocrine symptoms. Hypersomnia, diabetes insipidus and hyperthermia have been noted[82] and are more common in infiltrating tumours of the third ventricle.[60] Pressure on the chiasma leads to field defects in such inferior lesions. Disturbances of micturition or defaecation may occur in anterior diencephalic lesions.[1]

Posterior Third Ventricle Tumours

These infiltrate the thalamus and cause symptoms of contralateral pain, tremors, rigidity or weakness. Laterally placed tumours may simulate an early case of Parkinsonism. Pinealomas and posterior third ventricle tumours may present with the classical sign of difficulty in conjugate upward deviation of the eyes with or without other ocular nerve paralysis (Parinaud's syndrome). This is seen only in about 50% of the cases and is due to pressure on the superior colliculi by the tumour. Pressure on the inferior colliculus may cause tinnitus. Posterior pressure on the cerebellar peduncles may cause incoordination and ataxia, simulating a cerebellar tumour.[71] Cysts of the third ventricle have been reported to result in to and fro movement of the head and trunk in children: 'bobble-head doll syndrome'.[5,8,9,25,78,90] Pubertas precox, a rare clinical entity seen in association with third ventricle tumours, is due to interference with the hypothalamus.

Tumours Involving the Hypothalamus

Hypothalamic signs may be seen in patients with posterior fossa tumours due to pressure on the hypothalamic nuclei by the dilating third ventricle. Thus, children and adolescents with posterior fossa lesions may present with symptoms suggestive of hypothalamic involvement. A chubby child, too well behaved for his age, may be the early clinical picture of a posterior fossa lesion.[12]

The hypothalamus may also get compressed by tumours of the third ventricle and adjacent lesions like a craniopharyngioma and other sellar lesions. An increase in the subcutaneous fat, docility leading on to lethargy and lack of growth of hair over the body may be seen. Puberty is delayed in both boys and girls. In adults, libido is decreased and amenorrhoea may occur. These symptoms often simulate hypopituitarism.

Intrinsic lesions arising from or including the hypothalamus may cause signs of irritation or deficiencies of hypothalamic function. Precocious puberty is one such sign and is due to destruction of the posterior hypothalamus, leading to uninhibited action of the anterior hypothalamus on the pituitary and the gonads. Precocious puberty due to hypothalamic involvement is characterised by excessive development of the penis and testes, adolescent body contours and adult levels of 17 ketosteroids; whereas in adrenal precocity, the testis is immature, the body contours are that of a child and the 17 ketosteroids are greatly in excess of the adult values.[56]

Other signs of serious interference with function may also occur like diabetes insipidus.[6] The syndrome of inappropriate ADH secretion (SIADH) may occur. In some cases, fat metabolism is disturbed leading to fat depletion, resulting in marasmus or progeria (premature ageing). A typical diencephalic syndrome characterised by marasmus, euphoria and nystagmoid eye movements has been described in infants. The failure to thrive is obvious, the child is cachectic, but the sensorium is normal and the child remains active and playful. In other cases, hyperphagia and obesity may be seen as well as a lowered threshold for aggressive behaviour.[75]

Lesions of the Midbrain

Being situated in a strategic area between the edges of the tentorium, the midbrain is often involved in tumours of the cerebral hemispheres due to brain shifts and herniations. Intrinsic tumours may extend into the midbrain from the hemispheres above or from the pons below. When the lesion arises in the ventral part of the midbrain, the oculomotor nerve is affected as well as the crus. This leads to an ipsilateral ptosis with contralateral hemiparesis (Weber's syndrome). The signs become bilateral as the tumour spreads to the opposite side. Involvement of the tegmentum may result in coarse tremors on the contralateral side; occasionally, when the subthalamic nucleus gets affected, hemiballismus may result. Dorsal tumours will involve the superior colliculus leading to disturbances in upward gaze and pupillary reaction. This is also seen in tumours dorsal to the midbrain, e.g. pineal tumours. Intrinsic lesions of the brainstem occurring lower down will cause internuclear ophthalmoplegia. Occasionally peduncular hallucinosis can occur.[18]

Tumours of the Posterior Fossa

Posterior fossa lesions may be situated in six different locations: (1) posterior midline; (2) laterally, in the cerebellar hemisphere; (3) anterolaterally, in the cerebellopontine angle; (4) anterior midline, in front of the pons and the medulla; (5) intrinsic, inside the brainstem or (6) inside the fourth ventricle or aqueduct.

Cerebellar functions may be affected by lesions of the vermis, of the cerebellar hemispheres or of the cerebellopontine angle. Cerebellar disturbances may also be seen in brainstem lesions if the fibre connections passing

through the cerebellar peduncles get involved.[3,10] All the manifestations of motor cerebellar dysfunction, whether of the lobes or of the vermis, are attributable to asynergia, ataxia, dysmetria and hypotonia of the muscles. Based on these basic disturbances, many symptoms and signs appear, and numerous tests have been devised to reveal early dysfunction.

Posterior Midline Lesions

The vermis of the cerebellum occupies the posterior midline and is involved in lesions of this region, e.g. vermian astrocytomas, ependymomas, medulloblastomas, a dilating fourth ventricle, posterior midline cysts, tuberculomas and dermoids. The vermis of the cerebellum is concerned mainly with the control of the muscles of the trunk and the muscles of posture, whereas the cerebellar lobes exert control over the muscles of the ipsilateral limbs, chiefly of the upper limb. In lesions of the vermis an early symptom is truncal ataxia and difficulty in controlling the lower limbs. The first evidence of such a disability in a child may be its tripping over steps which it could previously negotiate easily.

This may be followed by mild unsteadiness of gait,[91] leading to an inability to walk or stand. At the same time it will be apparent that the child can use its upper limbs effectively, e.g. while sitting it can take its hand or a spoon to its mouth. The finger-nose test is normal. Such pure midline vermis syndromes are seen in early cases, before the tumour extends to the cerebellar lobes. Nystagmus is usually absent, but when seen, is rapid, fine and symmetrical.

Large tumours of the vermis extend into the cerebellar lobes producing signs in the upper limb. They also compress the fourth ventricle resulting in increased ICP, headache and vomiting. When extending higher up, functions of the fourth cranial nerve may be involved. Parkinsonism like tremors have been described.

Cerebellar Hemisphere Lesions

Both in man and in birds, the cerebellar lobes are developed, indicating the importance of the function of the upper limbs in man and the wings in birds. The common symptom of a cerebellar lobe lesion is the difficulty in using the ipsilateral upper limb, although the lower limb may also be involved. The patient complains of clumsiness of movement of the upper limb. In a right handed individual, this may manifest itself early as difficulty in writing. The letters become bigger than usual (macrographia). There is difficulty in picking up objects or in holding them steady. On examination there is a drift of the outstretched hand. The cerebellar disturbance is obvious only when the limb is put to action (action tremor) and disappears if the limb is supported or is resting. The finger-nose test reveals intention tremors and past-pointing. In early cases, an involuntary closure of the eyelid as the finger reaches the nose may indicate a cerebellar dysfunction.[70]

There is an inability to make rapid alternate movements of the limb (dysdiadochokinesia). The heel-knee test is impaired. The knee jerk is pendular and all the deep tendon reflexes are intact. Hypotonia is evident on testing the muscle tone. If the forearm is jerked quickly up and down, the hand will flap, indicating lack of tone in the forearm muscles. In an unconscious patient, the way in which an upheld limb drops on the bed can indicate hypotonia. Until the lesion begins to invade the vermis or the brainstem all the symptoms are confined to the ipsilateral limb.

Asynergia of the pharyngeal and tongue muscles leads to slurred (words running into each other) or staccato or scanning speech (words split syllable by syllable). Nystagmus, evidence of asynergia of eye muscles, is seen in cerebellar lesions only when the vestibulo-cerebellar connections (dentate nucleus) begin to get affected. Nystagmus is not seen in laterally placed cerebellar hemisphere lesions. In unilateral cerebellar lesions, the nystagmus is slower and coarser when the eyes are directed towards the side of the lesion than towards the opposite side. Such nystagmus disappears in a few weeks. If persistent, it will indicate pressure on or invasion of the vestibular nuclei.[36,40]

The cerebellum has a role in cognition as well. Diseases of the cerebellum are known to cause attention deficits and disturbed executive function, visuospatial disorganisation and impaired visuospatial memory, personality change and linguistic difficulties such as dysprosodia, agrammatism and mild anomia. So, the attention span must be assessed in all cerebellar lesions.[17] Lesions of the cerebellum in children have been reported to produce mutism.

Cerebellopontine Angle Tumours

This region is a frequent site of occurrence of space occupying lesions which exhibit a characteristic symptomatology. The structures in this region are the V, VII and the VIII nerves anteriorly, the cerebellum posteriorly, the brainstem medially and the lower cranial nerves inferiorly. Any one or all these structures get involved gradually as the lesion enlarges. When the tumour arises primarily from the eighth nerve, tinnitus and impairment of hearing are early symptoms. Disturbances of vestibular function, like giddiness or vertigo, are usually transient phenomena, compensation taking place very early.

An early sign of trigeminal affection is the loss of corneal sensation as shown in a diminution or abolition of the corneal reflex. This is elicited by touching the cornea gently with a wisp of cotton wool. The examiner's hand with the wisp of cotton should approach the cornea from the lateral side to prevent blinking due to the menace reflex. As the cotton wool touches the cornea, there is a brisk closure of the eyelid. If there is a fully established seventh nerve palsy preventing closure of the ipsilateral eyelid, the efficacy of the corneal reflex is judged by observing the rolling up of the ipsilateral eyeball (Bell's phenomenon) and closure of the opposite eyelid (see chapter on "Acoustic Neurinoma").

Prepontine or Clival Tumours

Anterior midline tumours, especially when slow growing, may exist for a long time without any apparent clinical signs. Unprovoked, uncontrolled laughter is a characteristic symptom of prepontine tumours. Pressure on the anterior aspect of the brainstem may lead to bilateral pyramidal or bilateral cerebellar signs. Other long tract signs are not obvious. However, as the tumour enlarges, multiple cranial nerves may be involved bilaterally. The lesions located anterior to the brainstem are chordomas, chondromas, clivus meningiomas, nasopharyngeal growths and basilar aneurysms).

Intrinsic Lesions of the Brainstem

The most common lesion is a glioma, rarely a metastatic lesion or an angioma may be seen. In India, the possibility of a brainstem tumour being a tuberculoma must always be kept in mind. These constitute more than 10% of all brainstem tumours. Likewise, it must be remembered that tuberculous meningitis may mimic a brainstem tumour. Headache is uncommon in brainstem gliomas, whereas it is a predominant symptom in tuberculous meningitis. Exacerbations and remissions of symptoms have been noted in some brainstem gliomas, thus mimicking multiple sclerosis.[79] Rarer symptoms of brainstem gliomas include continuous facial spasm[45,80] and hyperventilation.[47]

Gaze palsy, multiple cranial nerve involvement, cerebellar signs and bilateral long tract signs, in various combinations, constitute the clinical features of brainstem lesions. An early sign of an intrinsic brainstem tumour is external rectus weakness in one eye followed by facial palsy, swallowing difficulty and unsteadiness. Examination shows a combination of multiple lower cranial nerve palsies and motor and sensory long tract signs. This is specially seen in exophytic brainstem tumours. Unilateral or bilateral horizontal conjugate gaze palsy is characteristic of a lesion at this site. Internuclear ophthalmoplegia due to involvement of the medial longitudinal fasciculus, when seen, is diagnostic of an intrinsic brainstem lesion. On attempted gaze towards either side, there is paresis of adduction and an associated nystagmus of the abducting eye. Another ocular phenomenon seen in brainstem lesions is vertical nystagmus. This sign is always indicative of nervous system involvement, especially of the caudal brainstem, as labyrinthine disease cannot produce vertical nystagmus. Papilloedema is seen in only 15% of cases.[73,74] With modern imaging techniques and early suspicion of brainstem lesions, the incidence of papilloedema has become less. This combination of a variety of neurological symptoms of the brainstem, without apparent increased ICP, points to an intrinsic involvement of the brainstem. Periodic disturbances of the level of consciousness may be seen.

Tumours of the Fourth Ventricle

These tumours usually grow to a large size and fill up the ventricle before causing signs and symptoms of increased pressure. Small tumours may obstruct the aqueduct early. A common and early symptom, especially in children, is vomiting unassociated with abdominal discomfort or nausea. An otherwise healthy child that begins to vomit without reason and falters in its gait must immediately be suspected of harbouring a midline vermis lesion encroaching onto the fourth ventricle. Unsteady gait, giddiness or vertigo, nystagmus and lower cranial nerve palsies become evident much later.

Tumours at the Craniovertebral Junction

These are difficult to diagnose, being in the borderline between the brain and the spinal cord.[66] In the absence of symptoms and signs of raised ICP, lesions at the CV junction may masquerade as disseminated sclerosis, amyotrophic lateral sclerosis or spinocerebellar degeneration. They may mimic the clinical picture of craniovertebral anomalies. Lesions at this level may exist for a long time without causing any apparent neurological deficit. A large cisterna magna provides a lot of space for the growth of such tumours. Those arising intracranially cause obstruction to the CSF flow and raise the ICP without producing localising signs. They may also cause lower cranial nerve palsies. Occasionally, the hypoglossal nerve may be involved leading to wasting and weakness of one-half of the tongue. Pressure on the brainstem may lead to bilateral pyramidal signs. Cerebellar signs are occasionally seen. If the tumour is inferior, occipital neuralgia with a stiff neck, often mistaken for a long time for tension headache, may be the only symptom. Numbness over the occipital nerve distribution with signs in the upper and lower limbs that occur later, give a clue to localisation. Varying degrees of signs and symptoms of upper cervical cord involvement confuse the clinical picture.

Neighbourhood Signs

In addition to the local signs, neighbourhood effects are often seen in ICSOL. As the lesion grows in size, the neighbouring structures get compressed or infiltrated, the resulting symptomatology depending on the direction of growth of the lesion. The neighbourhood effects may also be caused by secondary phenomena, the most common being oedema. Oedema surrounding a space-occupying lesion varies in its intensity and severity depending upon the nature of the original lesion. Oedema around a tuberculoma, a glioblastoma or a metastasis could be pronounced and thus lead to neurological symptoms far more extensive than could be caused by the actual size of the tumour. Neighbouring structures may also suffer from a steal of blood supply as may happen in an arteriovenous malformation or in a highly vascular tumour.

Herniation

Owing to the softness and compressibility of the brain a growing tumour is able to displace the brain substance.

This displacement modified by the presence of dural partitions inside the cranial cavity results in brain herniations. Depending on the site of the tumour and the direction of the pressure, the herniation may take place under the falx, through the tentorium or the foramen magnum. In very acute and severe rise of ICP, brain matter may herniate through the exit foramina of the cranial nerves.

Subfalcine Herniation

In supratentorial space occupying lesions, the ipsilateral cerebral hemisphere is compressed and pushed against the falx cerebri. The portion nearest the dural partition, namely the cingulate gyrus, herniates under the free edge of the falx. Although, on rare occasions, this may result in occlusion of the anterior cerebral artery, such herniation does not cause any serious problem. Transtentorial and tonsillar herniations are more significant as they may threaten life.

Tentorial Herniation

As the supratentorial lesion grows in size, the brain not only gets pushed across the midline but herniates downwards through the tentorial hiatus. The structures (close to the tentorial edge) that herniate are the uncus and hippocampal gyrus which insinuate themselves between the brainstem and the tentorial edge. On the other hand, instead of the temporal lobe, the brainstem may itself be pushed down.

Depending on the site of the causative lesion and the direction of the pressure, tentorial herniation may chiefly be in its anterior or posterior part and in advanced stages may be complete. In anterior herniation, the third nerve and the crus are involved leading to a dilating pupil and a contralateral hemiplegia. In some cases, when the brainstem is pushed against the opposite tentorial edge, an ipsilateral hemiplegia may result (Kernohan's notch). The shift of the brainstem also leads to a kinking of the aqueduct with secondary blockage of the CSF flow, which further aggravates the supratentorial pressure. A complete bilateral tentorial herniation may block the CSF pathways around the brainstem and further disturb the CSF flow and absorption. In rare instances, the posterior cerebral artery may get compressed, resulting in occipital infarction and hemianopia or cortical blindness if both arteries are involved.

In posterior lesions, the anteromedial portion of the occipital lobe (the precuneus) herniates into the cisterna ambiens and presses on the colliculi and the midbrain. This may lead to varying degrees of oculomotor palsy, progressive deafness and decerebrate rigidity. There may also be paralysis of upward gaze, as well as hemianopia.

Cerebellar Herniation (Tonsillar Herniation)

In generalised increased ICP, as well as in posterior fossa lesions, the ICP may force the posterior fossa structures down through the foramen magnum. The cisterna magna gets obliterated. The tonsils of the cerebellum, which are situated near the margin of the foramen magnum, are pushed down through it and may reach the level of the second cervical vertebra. The crowding of structures in the foramen magnum aggravates the ICP by a secondary blockage of the exit of CSF.

Pressure on the upper cervical nerves leads to neck rigidity and torticollis. In the presence of a persistent herniation, a sudden rise in ICP precipitated by coughing or sneezing may quickly squeeze the medulla resulting in rapid respiratory failure followed by cardiac failure and death. Usually the stage of respiratory failure lasts for some minutes before cardiac failure sets in. Even at this stage, it is possible to save the patient by energetic treatment to reduce the ICP. Mild degrees of tonsillar herniation are seen in most cases of increased ICP. In unilateral cerebellar lesions, only the tonsil of the affected side may be found herniated.

Retrograde Tentorial Herniation

In some cases of posterior fossa tumours, when the pressure in the posterior fossa is much higher than the pressure in the supratentorial compartment, the structures near the tentorial hiatus may be pushed upwards. This may cause secondary pressure on the brainstem. Such an emergency sometimes arises as a consequence of a CSF diversion procedure for hydrocephalus. The patient may suddenly go into decerebrate rigidity with autonomic disturbances, followed later by respiratory failure.

Distant Signs

These are caused by obstruction to the CSF pathways, a disturbance of blood supply to distant areas or by shifts and changes in the position of various structures as the lesion grows in size. These lead to false localising signs.

False Localising Signs

Neighbourhood or distant effects may present themselves as primary symptoms, before any localising sign of the tumour becomes obvious. In such cases the primary presenting symptom may mislead the clinician to localise the lesion to a wrong part of the brain.[27] Practically, all possible neurological signs have been reported as false localising signs. Only a few common ones are mentioned here.

1. Ipsilateral hemiplegia lateralising the lesion to the wrong side. Gould[37] explained, in 1926, this false lateralising sign as due to a mechanical compression of the crus on the side opposite to the tumour against the lateral edge of the tentorium. This was confirmed, in 1929, by Kernohan and Woltman,[44] who demonstrated the notching of the crus in pathological specimens. Ipsilateral hemiplegia may also occur due to: (a) direct pressure acting on the opposite internal capsule due to the configuration of the falx cerebri; (b) longitudinal stretching of the opposite internal capsule;[39] (c) dilatation of the opposite lateral ventricle, especially when there

is a block of the foramen of Munro and (d) uncrossed pyramidal tracts.[89]

2. The presence of frontal lobe signs in cerebellar tumours and cerebellar signs in frontal lobe tumours have already been mentioned.
3. A highly vascular lesion of the temporal lobe may steal blood from the frontal region leading to the appearance of frontal lobe localising signs.
4. Cerebellar signs in a craniopharyngioma.[4,43]

In summary, therefore, a patient with an intracranial space occupying lesion may present with one or more of the following:

1. Symptoms and signs of raised ICP
2. Focal neurological deficit
3. Focal or generalised epilepsy
4. Psychiatric symptoms
5. Endocrine disturbances
6. Visible deformity of the head
7. A combination of any or all of these

The evolution of the illness, generally characterised by an insidious onset and a progressive course, may be occasionally apoplectic or rarely intermittent.

It is obvious from a study of the various phenomena described above that early diagnosis gives the best chance for good results to the patient and the neurosurgeon. This is not always possible in developing countries, where awareness of the existence of intracranial tumours as well as the facilities available to deal with them may vary widely.

It is important to quantify the extent of disability a patient with a brain tumour has. For brain tumours, it is the Karnofsky score which is as follows:

Score	Feature
100-	Normal, no complications.
90-	Normal activity is pursued with minimal signs or symptoms.
80-	Normal activity is pursued with effort and the patient has some symptoms.
70-	The patient is able to care for self but is unable to work.
60-	The patient requires occasional assistance but is able to cater to most of his needs.
50-	The patient needs continuous assistance and frequent medical care.
40-	The patient is disabled and requires special care.
30-	The patient is severely disabled and requires hospital care.
20-	The patient is very ill and is in hospital and requires supportive care.
10-	Moribund.
00-	Dead.

Early referral of patients leads to better localisation of the lesion due to the absence of secondary phenomena, and to better results of treatment, due to the minimal increase of ICP. With advanced imaging techniques and surgical expertise, the outlook in neurosurgery is far more optimistic than five decades ago.

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133 Supratentorial Astrocytomas

Ramakrishna Easwaran

INTRODUCTION

Gliomas are the most common group of intracranial neoplasms. They consist of a heterogeneous variety of tumours, with varying grades of malignancy. At one end of the spectrum is the well-behaved juvenile pilocytic astrocytoma and on the other, glioblastoma multiforme with a dismal prognosis. In between, there is a whole range of tumours with hoverlapping morphological and biological characteristics. Almost every area of "gliomology" is mired in controversy, be it the basic biology, classification, grading or the need for aggressive resection. After more than a century of a love-hate relationship with gliomas, the neurosurgical community is now closer than ever to evolving a consensus on these issues. This chapter deals with supratentorial gliomas and the focus is on astrocytomas and glioblastomas. Oligodendroglioma and ependymoma are dealt with in other chapters.

HISTORY

The term 'glioma' was coined by Virchow in 1863. Rickman J Godlee removed a glioma from the motor area on 25th November 1884 after the tumour was localised clinically by A Hughes Bennett. Thus was born glioma surgery and indeed neurological surgery. Gliomas accounted for 42% of the 2,000 brain tumours operated upon by Harvey Cushing and the proportion remains the same today. The difference since Cushing's times is the 20-fold drop in the peri-operative mortality of gliomas.[20] Corticosteroids, safer neuroanaesthesia and improved intensive care must take the credit for this falling mortality. Advances in biology (immunochemistry, cell cultures, immunology and genetics) have kept pace with the advances in imaging and surgical technology (computed tomography (CT), magnetic resonance (MR) imaging, operating microscope, stereotaxy, neuronavigation and functional localisation). While these developments have contributed to mitigating the morbidity, they have done little to improve the ultimate prognosis of the scourge that is glioblastoma.

INCIDENCE

Overall Incidence

Gliomas constitute 35–50% of all intracranial neoplasms. There are only minor variations in the total incidence of gliomas in intracranial tumour series reported from different centres in the world. After excluding granulomas, the incidence of gliomas among intracranial tumours in various Indian neurosurgical series is similar to that in the rest of the world.[45] The correct incidence has to be judged from population-based studies. The annual incidence of glioma per 100,000 persons has been reported as 2.2 in Japan[11 7] and 5.4 in the United States (US).[46] The incidence of primary malignant brain tumours was reported to be increasing until 1990, significantly so in the elderly, in a Florida study. This is not merely because of better detection with neuroimaging as the increase has been detected between two time periods after CT became available.[257] The incidence of glioblastoma was also reported to be increasing in Canada in a 1991 study.[134] However, in the last 20 years the incidence seems to have decreased in the US.[54]

Frequency of Subtypes

In a consecutive series of 500 verified supratentorial gliomas at the All India Institute of Medical Sciences (AIIMS), New Delhi, the distribution of various histological types was as given in Table 1.[240] This table also compares the incidence of the histological types from the Central Brain Tumour Registry of the US (CBTRUS) for the period 1998–2002.[27] The higher incidence of glioblastoma in the Western countries is apparent. Since glioblastoma incidence tends to peak at a later age, the higher proportion of the aged in the Western population may account for at least a part of this difference.

Table 1: Distribution of various histological types of supratentorial gliomas

Histological type of glioma	*AIIMS, Delhi N=500%*	*CBTR, US N=25539%*
Astrocytoma	37	13
Malignant astrocytoma	23	14
Glioblastoma	21	50
Mixed glioma	10	7
Oligodendroglioma	5	9
Ependymoma/Malignant ependymoma	3	5
Others	1	2
	100	100

Age and Incidence

Gliomas are seen at all ages from the just born to the nonagenarian. Congenital glioma, producing symptoms at birth or shortly thereafter, though rare, is well reported.[94] Nearly two-thirds of all cases of supratentorial gliomas occur in the third to fifth decade. In the AIIMS series 44% of the astrocytomas occurred below the age of 30 years. In contrast to this, 72% of glioblastomas occurred above the age of 30 years.[240] The mean age for astrocytomas was 37.4 years, for malignant astrocytomas 45.8 years and for glioblastomas 52 years in one report.[141] The relative risk of brain cancer is 3.18 for elderly persons as compared with young adults.[54]

Gender and Incidence

With the exception of meningioma, all brain tumours occur more frequently in males. About 74% of the 500 gliomas in the AIIMS study were in males.[240] The relative risk of brain cancer was 1.48 for men as compared with women.[54] In the CBTRUS data, 56% of all gliomas occurred in men. The increased incidence in men is mainly due to increased frequency of malignant astrocytoma and glioblastoma.[46]

Other Epidemiological Factors

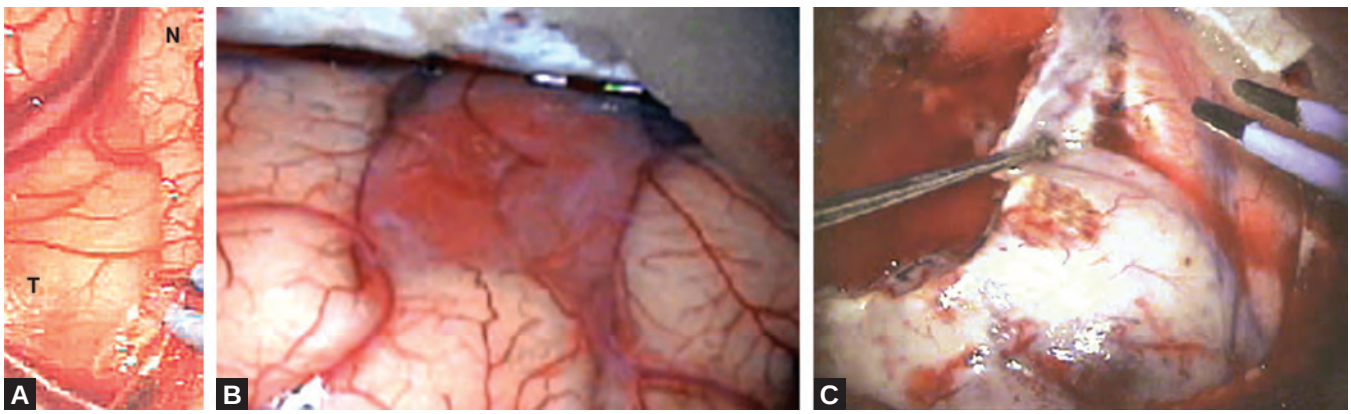
Malignant gliomas occur more frequently in Caucasians than in African-Americans, the relative risk being 1.86. The incidence is 1.35 times greater in the urban areas as compared to rural ones.[54] Most of the Northern Europe, North America and Israel are considered as high-incidence regions while Africa, India, China and Japan are considered low-incidence areas for malignant nervous system tumours in the age group of 35–64 years.[46] Those born in winter have been shown to have a higher risk of developing a glioma in later life. This was particularly so for left handed individuals in a case-control study.[25] Familial gliomas of the non-genetically determined type are extremely rare. The small number of cases does not permit us to conclusively say if relatives of the index glioma patient are at a greater risk of developing a glioma.[19]

Children of mothers residing within a mile of certain toxic chemical factories during pregnancy have been shown to have a risk of brain cancer.[37] Ionising radiation exposure (therapeutic, occupational or accidental) has been proved to increase the risk of malignant glioma (see section "Aetiology and Pathogenesis"). Less clear is the effect of diagnostic X-ray examinations, cosmic radiation in frequent fliers and high electromagnetic field exposures.[46] Recently, concern has been expressed about the radiofrequency exposure from cell phones. It was suggested in a Swedish study that gliomas were more frequent on the side of habitual use of mobile phone.[77] But in a recent British case-control study, the overall odds ratio for regular phone use was only 0.94 indicating that cell phone usage did not increase the chance of developing a glioma. There was no relation between risk of glioma and time since first use, lifetime years of use, and cumulative number of calls and hours of use of mobile phones.[81] There have been criticisms of the methodology of studies showing a negative correlation of cell phone use with glioma occurrence.[78] The last word on the matter has not yet been said.

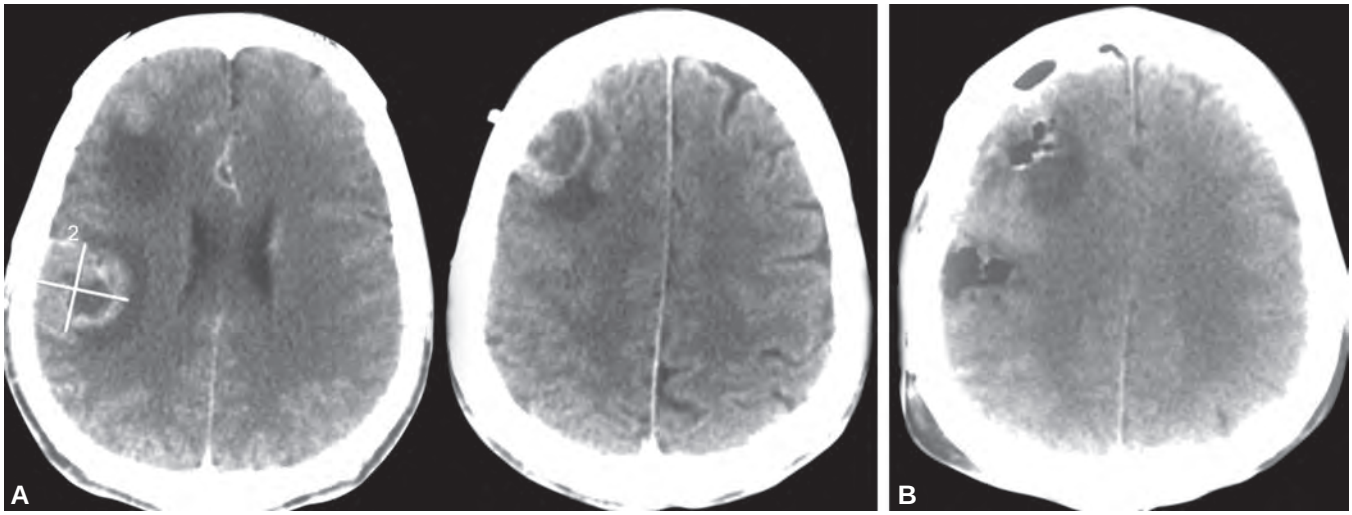
PATHOLOGY

Location of Gliomas

The majority of cerebral gliomas are located in the frontal, temporal and parietal lobes and the incidence is proportional to the size of each lobe. Tumours often transcend anatomical boundaries, though in the early stages many tumours are confined to the area of the gyrus and grow in size expanding the gyrus. Tumours that extend to the surface are easily identified at surgery. The distinction from the normal brain surface is subtler in lower grade tumours and more obvious in glioblastoma (Figs 1A to C). In subcortical tumours, the expanded gyrus can be identified at craniotomy. Two gyri, distant from one another in the same lobe may



Figs 1A to C: Surface appearance of gliomas at surgery. (A) Surface appearance of grade 2 astrocytoma. Note the glazed distended appearance of the tumour (T) as compared to the normal cortex (N). (B) Surface appearance of grade 3 astrocytoma. (C) Surface appearance of glioblastoma



Figs 2A and B: Two foci of gyral glioma. (A) Contrast enhanced computed tomography (CECT) of astrocytoma (grade 3) arising independently in two different gyri of the frontal lobe. The lesions were approached through a single craniotomy flap and excised through two gyrotomies. (B) Post-operative CECT (right) showing the two resection cavities

separately harbour a glioma each (Figs 2A and B). In a CT study from India, 20% of gliomas crossed the midline and 5.5% involved the basal ganglia.[240] The corpus callosum is often invaded by a lobar tumour but it may be the site of origin too. The thalamus, corpus striatum, pineal gland and pituitary fossa are the less frequent sites of origin. Rarely, gliomas are multicentric in origin or may occur in the same patient at two different sites after a long time interval. In an imaging and histology based study, 51 cases of multicentric glioma have been reported.[120] In 26 cases, the tumours were multicentric at presentation while in the rest, it developed during the course of treatment. In 14 cases, no pathway of dissemination could be found and these were the true multicentric gliomas. Bilateral synchronous tumours are reported from India in the frontal lobe[18] and in the thalamus.[145] Figure 3 shows an example from the author's personal collection. Consecutive cerebellar and cerebral astrocytomas have been reported.[17]

Gross Pathology

This is the pathology relevant to the surgeon as it can be readily seen and felt during the operation. The low-grade tumours tend to be poorly demarcated from the surrounding brain. They are relatively less vascular and appear grey. There is hardly any oedema in the surrounding white matter. In fibrillary astrocytomas, the consistency is tougher than the normal white matter. The subtle colour difference between the tumour and the normal brain is more apparent under the lighting and magnification of the operating microscope than to the naked eye. The difference in consistency is better appreciated by the tactile feedback the surgeon gets from the dissectors or bipolar forceps than from the use of the ultrasonic aspirator. A single large cyst or a honeycombed appearance due to multiple small cysts may be seen. The more malignant tumours may be more granular, pinkish and vascular. As the tumour grows, the central part becomes necrotic. The term "angioglioma" is used to describe a low-grade tumour with vascularity mimicking a cavernous angioma or arteriovenous malformation. Figures 4A and B show an example. They do not represent a distinct clinicopathological entity and the behaviour is no different from the less-vascular low-grade tumours.[127] The "angioglioma" is not to be confused with the recently described angiocentric glioma (see below).[186] Calcific foci are common in mixed glioma but profuse calcification along axonal pathways has been observed.[72] Though radiologically and histologically the calcification is impressive, the tissue feels only slightly gritty and never as hard as the calcification in a meningioma or craniopharyngioma (Figs 5A and B).

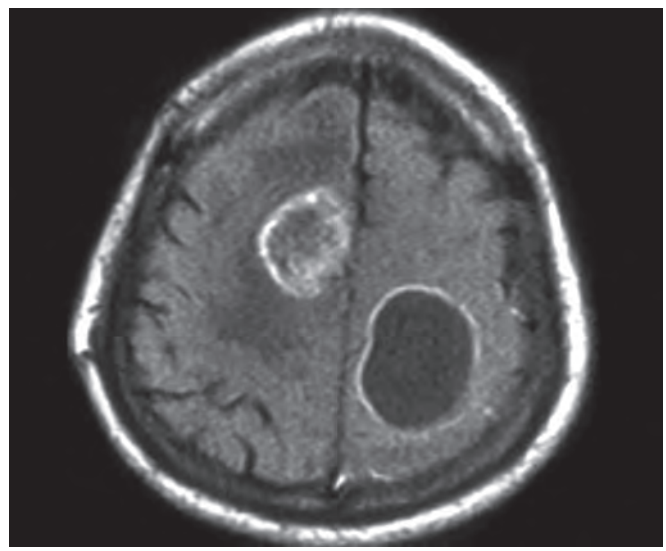
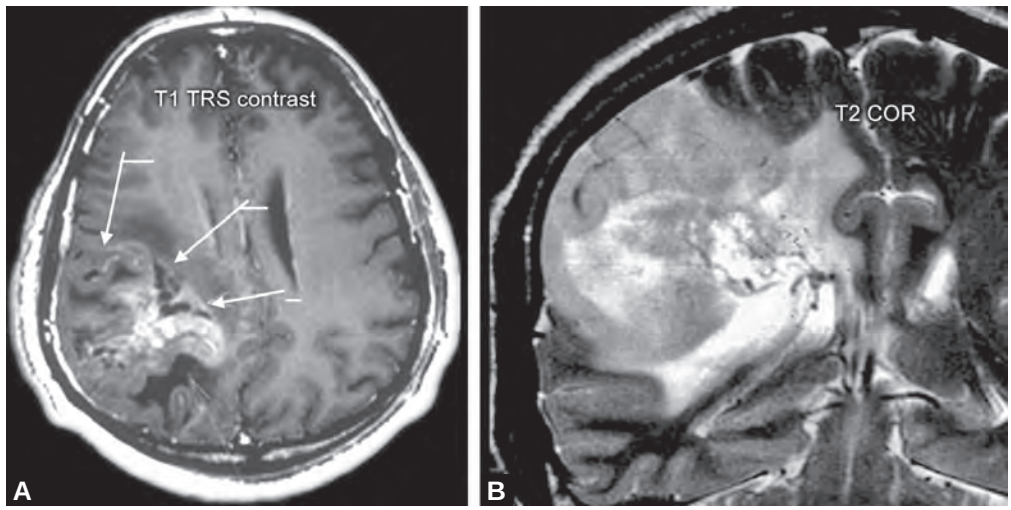


Fig. 3: Synchronous bilateral astrocytoma. Contrast magnetic resonance imaging. The tumour on the left was non-cystic and grade 2, while the tumour on the right was grade 3 by computed tomography guided stereotactic biopsy

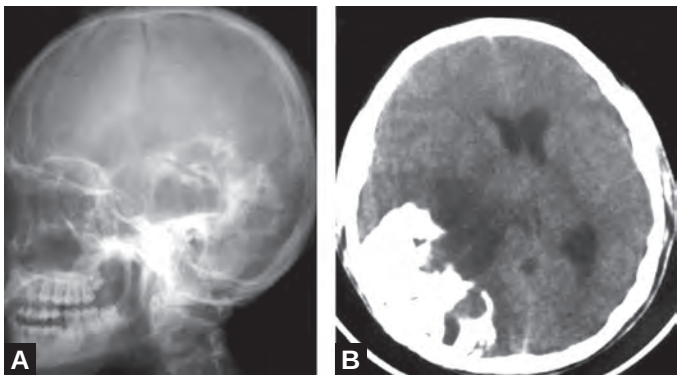


Figs 4A and B: "Angioglioma". Magnetic resonance of tumour in the parietal lobe. Note the multiple flow voids in the tumour. This patient presented with seizures and when the seizures became refractory 4 years later, consented to resectional surgery. The tumour was a mixed glioma with extreme vascularity. The patient remains without deficits or tumour progression, free of seizures on medication 5 years after surgery

The glioblastoma shows a variegated appearance, true to the tag of "multiforme" in its name. Pale yellow areas of necrosis or lipid accumulation, black areas of old haemorrhages, purple thrombosed vessels and cystic areas containing bright yellow fluid are interspersed in a soft pinkish-grey mass that is deceptively well circumscribed. The swelling and peritumoural oedema are disproportionately more for the size of the tumour. Involvement of an entire frontal or temporal lobe is characteristic. A glioblastoma that starts *de novo* and grows rapidly is called primary glioblastoma. A pre-existing low-grade astrocytoma may turn anaplastic and this gives rise to the secondary glioblastoma.

Spread

Gliomas spread within the neuraxis through the subarachnoid, subependymal, intraventricular or direct brain penetration routes in the descending order of frequency.[120] Superficial gliomas may invade the meninges.



Figs 5A and B: Calcification in mixed glioma. Lateral skull radiograph and unenhanced computed tomography of a young man with mixed glioma with mostly oligodendroglial component. Despite the extensive calcification in the tumour, the feel of the tumour was merely firm with only rare gritty areas

This invokes a fibroblastic proliferation and the tumour then simulates a meningioma at surgery. Biopsies from the superficial part of such a tumour may mistakenly be reported as meningioma. Gliomas are also known to arise from heterotopic glial rests in the leptomeninges.[143] Spread along the subarachnoid cerebrospinal fluid (CSF) pathways as happens in an ependymoma or a medulloblastoma is rare. If extensive, such a spread is called "leptomeningeal gliomatosis".[71,50] From the meninges, there may be a re-invasion of the parenchyma at a different site.[120] Glioblastomas are seen to spread subependymally along the walls of the third or lateral ventricle.

Periaqueductal gliomas are usually low-grade pilocytic tumours that block the aqueduct. They are amenable to endoscopic biopsy and ventriculostomy. These indolent tumours may even spread to the ventriculostomy site and block it.[138] A rare case of grade 2 astrocytoma occupying all the ventricles has been reported from Chennai as "holoventricular glioma".[82] Dissemination in to the posterior fossa from primary supratentorial glioma and its treatment is the subject of a recent paper.[223] The case of vermian spread reported from Vellore is unusual because it was from a grade 2 oligoastrocytoma and it occurred 4 years after the primary frontal tumour was treated.[231] Low-grade tumours tend to spread along fibre tracts without infiltration. The patterns of spread can be studied with magnetic resonance imaging (MRI).[22]

Extracranial Metastases

Extracranial metastases of brain tumours are uncommon because of the absence of lymphatic drainage. They may occur after a craniotomy that opens paths of exit from the brain. Extracranial metastases in the absence of a previous craniotomy have been reported in a few cases. In these cases, tumour cells were seen in the lumen of venous channels.[84] A case has been reported in which lymph node metastasis was the first manifestation of a

glioblastoma, the intracranial signs becoming manifest 3 weeks after the biopsy of the lymph node.[57] Tumour spread through ventricular shunts to the pleural and peritoneal cavity is well known for medulloblastoma, but is also reported with glioblastoma.[163] Spread to the lungs, liver and bones is rarely seen.[67,174]

CLASSIFICATION AND GRADING

Bailey and Cushing (1926) put forth the classification of gliomas on the basis of possible histogenesis. Penfield, Cone and Elvidge (1931) retained some of the 14 terms from this terminology (such as medulloblastoma) but replaced others (e.g. spongioblastoma multiforme was changed to glioblastoma multiforme). Since their time, the lumpers and the splitters among neuropathologists have modified the classification systems.[45]

The criteria of a grading system of gliomas are:

- The grade should predict clinical behaviour
- The system must be objective and should not allow inter-observer variation

There may be a small focus of malignancy in a well-differentiated tumour, but it is that tiny focus that would decide the prognosis. Any grading system can work only if the sampling has been representative and adequate. Grading is not of mere academic importance, but it is the basis on which therapy is recommended. The ideal grading system would allow easier organisation of prospective multicentre trials and help compare retrospective results from various centres meaningfully. It is to be remembered that grades are merely arbitrary stations in an oncological continuum.

Kernohan at Mayo Clinic divided astrocytomas in to grades 1 to 4 in the increasing order of malignancy (Table 2). The problem with Kernohan grades was that it placed the pilocytic astrocytoma and the low-grade fibrillary astrocytoma in grade 1, though they have widely differing behaviour and prognosis.[143] Follow-up studies also showed no prognostic difference between grade 3 and grade 4 in this scheme.[65] Ringertz in Stockholm recognised pilocytic astrocytoma as a distinct entity and placed the remaining astrocytic tumours in a three-tier system (Table 2). This system was shown to correlate better with clinical behaviour and prognosis.[143] Daumas-Duport made the scheme more objective so as to reduce inter-observer variability (Table 2). The mean survival time was 45 months for grade 2 tumours, 16 months for grade 3 tumours and 8 months for grade 4 tumours according to this scheme in a follow-up study.[100] However, the three-tier system is not without its detractors.[70] The inter-observer (and indeed the intra-observer) variability is so much that a computer aided morphometric analysis may be needed to classify the malignancy.[214]

Table 2: A comparison of grading systems of astrocytomas in the ascending order of malignancy

Kernohan (1949)	*Ringertz (1950), Burger (1982)*	*Daumas-Duport (1988)*
Astrocytoma grade 1 Hypercellularity No pleomorphism or mitotic figures or nuclear atypia (Includes pilocytic and low grade fibrillary)	Pilocytic astrocytoma Fibrillary astrocytoma	Pilocytic astrocytoma Astrocytomas-classified based on following features: 1. Pleomorphism 2. Mitotic figures 3. Vascular proliferation 4. Necrosis
Astrocytoma grade 2 Hypercellularity Nuclear hyperchromasia No mitosis or necrosis Minimal endothelial proliferation	*Astrocytoma* Hypercellularity Slight pleomorphism No necrosis or vascular proliferation	*Astrocytoma grade 1* None of above features *Astrocytoma grade 2* Any one of features 1 to 3 above
Astrocytoma grade 3 Many but not all cells appear astrocytic Pleomorphism Mitotic figures Necrosis in places Endothelial proliferation	*Anaplastic astrocytoma* Pleomorphism moderate No necrosis Vascular proliferation +	*Astrocytoma grade 3* Any two of features 1 to 4 above
Astrocytoma grade 4 Only few cells are recognizably astrocytic Severe pleomorphism Mitosis (numerous, bizarre) Widespread necrosis Marked endothelial proliferation	*Glioblastoma multiforme* Pleomorphism marked Necrosis Vascular proliferation ±	*Astrocytoma grade 4* 3 or 4 features listed above

Zulch (1979) authored the World Health Organization (WHO) classification of brain tumours. The Russell and Rubinstein school slightly modifies the 1993 WHO revised scheme of Kleihues, Burger and Scheithauer. The term "glioblastoma" is retained, as its morphology may be so bizarre that the origin from the astrocyte may be obscured. Astroblastoma is placed with the ependymal tumours as it shows tanycytes.[53] The less commonly seen histological subtypes are also included in this scheme (Table 3). The fourth edition of the WHO classification (2007) adds several new tumour types and recognises genetic profiling.[130] The new glial-neural tumours added in this edition are pilomyxoid astrocytoma, papillary glioneuronal tumour, angiocentric glioma and pituicytoma.[24] The future of grading will lie in identifying molecular signatures of the genetic subsets of histologically similar tumours that have differences in outcome.[51,129]

Table 3: Classification of central neuroepithelial tumours (the variants mentioned in parenthesis)

I. Tumours of neuroglial cells
II. Tumours of neuronal cells and primitive cells
1. Astrocytic tumours
A. Medulloepithelioma
Astrocytoma (protoplasmic/fibrillary)
B. Medulloblastoma (cerebellar neuroblastoma)
Anaplastic astrocytoma (gemistocytic)
C. Neuronal/Mixed neuronal-glial tumours
Glioblastoma multiforme
i. Cerebral neuroblastoma
Others
ii. Central neurocytoma
Pilocytic astrocytoma (adult/juvenile)
iii. Gangliocytoma
Pleomorphic xanthoastrocytoma
iv. Ganglioglioma
Desmoplastic infantile astrocytoma
v. Desmoplastic infantile ganglioglioma
Subependymal giant cell astrocytoma
vi. Dysembryoplastic neuroepithelial tumour
Gliomatosis cerebri
2. Oligodendroglial tumours
III. Tumours of specialised neuroepithelial tissues
Oligodendroglioma
A. Neurohypophysial tumours
Mixed oligoastrocyoma
i. Astrocytoma
Anaplastic oligodendroglioma
ii. Granular cell tumour
Ependymal tumours
B. Pineal parenchymal and glial cell tumours
Ependymoma
i. Pineoblastoma
Anaplastic ependymoma
ii. Pineocytoma
Astroblastoma
iii. Glioma
Subependymoma
C. Choroid plexus epithelial tumours
Ependymoblastoma
i. Papilloma
ii. Carcinoma

MICROSCOPIC PATHOLOGY

The histological features of astrocytic tumours are dealt with in detail in this textbook. Only certain variants and recent findings are highlighted here.

Types of Specimens

The squash or frozen section biopsy has been proved to be a reliable method of diagnosing glial tumours.[192,210,220] Discrepancies between the frozen section diagnosis and the final diagnosis arise in distinguishing astrocytoma from oligodendroglioma, in differentiating reactive astrocytic changes from tumour and in grading.[181] Stereotactic biopsies are small but usually accurate.[189] The low-grade tumour and glioblastoma are readily distinguished, but there is an inter-observer variation in grading anaplastic astrocytomas in stereotactic biopsies.[150]

Histological Variants

Pilocytic Astrocytoma

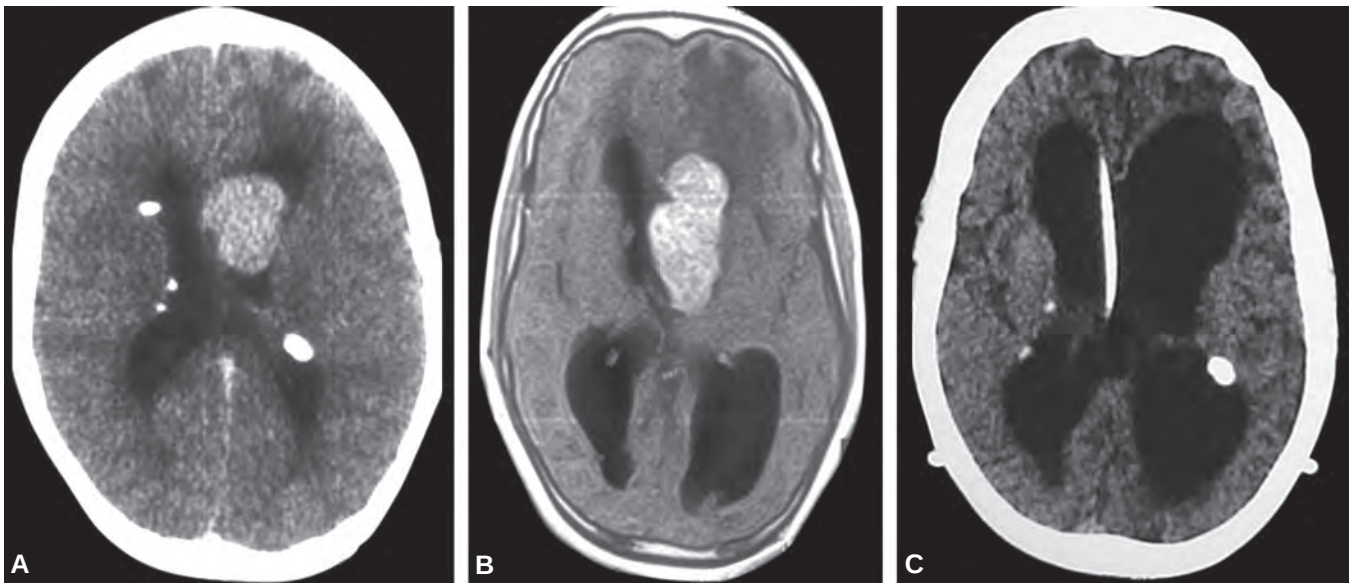
It occurs in the cerebellum and hypothalamus-optic pathway and it is described in the relevant chapters. Pilocytic astrocytomas with identical radiological appearance, histological findings and good prognosis are seen in the temporal and parieto-occipital lobes in the first three decades of life.[95] Adult pilocytic astrocytomas might recur frequently and may not behave in a benign fashion unlike the juvenile cases.[228]

Protoplasmic Astrocytoma

It has not been accorded a separate status in the recent classification. It is composed of process-poor astrocytic cells and a microcystic background. It is a rare variant occurring in about 5% of low-grade astrocytomas affecting mainly young males. Complete excision may be beneficial, but adjuvant therapy appears to have no effect on outcome.[185]

Subependymal Giant Cell Astrocytoma

This type of astrocytoma is characteristic of tuberose sclerosis (Figs 6A to C). The lesions arise in the lateral ventricle near the foramen of Monro. The CT and MR appearances are stereotyped as in the example shown.[38] Cellular pleomorphism, mitosis and foci of necrosis are seen, but do not indicate a worse prognosis in this tumour. Immunohistochemistry often (but not always) shows negativity for glial fibrillary acidic protein (GFAP) and surprisingly, positivity for neuron specific enolase (NSE) or synaptophysin. Adjuvant therapy is not needed and recurrence free survival is long.



Figs 6A to C: Subependymal giant cell astrocytoma. Computed tomography and magnetic resonance imaging of a boy with tuberose sclerosis who had a slow growing intraventricular tumour. Note the calcific and non-calcific tubers causing candle-drip appearance. The patient underwent a transfrontal total excision followed by ventriculoperitoneal shunting and endoscopic third ventriculostomy later on. Contrast enhanced computed tomography shows no recurrence 3 years after resection

Desmoplastic Infantile Astrocytoma

It appears to arise from the subpial astrocyte. The tumour is seen in the frontal or parietal lobe and grows to a large size with a big cyst. The cyst wall, even if enhancing, does not contain tumour.[13] Additional neuronal differentiation is possible and then it is called *desmoplastic infantile ganglioglioma*. They are usually resectable and the prognosis is favourable.

Angiocentric Glioma

It has been recently included in the WHO classification. It occurs in the cortical-subcortical areas of the temporal or parietal lobes and presents with refractory epilepsy from childhood. The characteristic is prominent perivascular tumour cell arrangements with features of astrocytic/ependymal differentiation, but lacking neoplastic neuronal features. Mitosis, necrosis and vascular proliferation are not seen. Resection provides long-term cure.[186]

Pilomyxoid Astrocytoma

It is a recently described solid, circumscribed tumour occurring in the hypothalamic region of young children. It is composed of a monomorphous population of bipolar tumour cells within a rich myxoid background, with a conspicuous angiocentric arrangement. This tumour is graded as WHO grade II.[24] It behaves more aggressively than pilocytic astrocytomas in the same location.[102]

Chordoid Glioma

It is an uncommon low-grade tumour arising in the third ventricular region, in middle-aged women. It shows chordoma-like histologic features including lymphoplasmacytic infiltrates and Russell bodies. Immunohistochemically, the tumour cells are positive for GFAP, neurofilaments and NSE, suggesting a divergent neuronal and glial differentiation. The Ki-67 index is low.[26]

Pleomorphic Xanthoastrocytoma

It is seen in the second decade. Most are in the temporal lobe and involve the cortex, accounting for their presentation with epilepsy. The radiological findings are similar to the cystic pilocytic astrocytoma. Their well-circumscribed nature allows total excision. The tumour shows a high degree of cellular pleomorphism. The characteristic yellow colour is due to lipid accumulation. Therefore, it needs to be differentiated from the lipidised glioblastoma.[116] An abundant reticulin network is produced due to infiltration of the meninges. The GFAP positivity proves its astrocytic origin. Demonstration of a basal lamina by electron microscopy suggests that the tumour might arise from the subpial astrocyte. The clinical behaviour is like a low-grade astrocytoma in spite of the pleomorphic and strikingly "malignant" histological appearance. Recurrences with malignant transformation are exceptional, but reported.[83]

Gliofibroma

It is a rare glio-mesenchymal tumour composed of astrocytic and benign mesenchymal components, usually seen in the first two decades of life. It has not been accorded a separate status in the recent classification. On imaging and at surgery it mimics a meningioma. The clinical behaviour correlates with the degree of anaplasia in the glial component.[48]

Gemistocytic Astrocytoma

Gemistocytic astrocytoma, recognised for long, is not a separate entity. It consists entirely of large astrocytes

with short, thick or no processes called gemistocytes. The cell bodies rather than the processes are GFAP positive. Often they are only a component within a fibrillary astrocytoma. If gemistocytes constitute more than 20% of the cells, the tumour is to be graded as an anaplastic astrocytoma independent of other features used to assess grading.[112]

Giant Cell Glioblastoma

It is a variant of glioblastoma that seems to have a better prognosis than the garden variety glioblastoma multiforme.[218] A few multinucleated giant cells may be seen in any glioblastoma, especially after radiotherapy. In the giant cell glioblastoma variant practically every cell is a giant cell.[135] The giant cells are GFAP positive and sometimes they are lipidised.

Gliomatosis Cerebri

It involves a whole hemisphere or even both hemispheres and spinal cord. This can be looked upon as a diffuse astrocytoma in an extreme form. The MRI is more sensitive than CT in detecting gliomatosis.[216] The areas of enhancement are the foci of higher grade of malignancy. Gliomatous change occurring simultaneously over a wide field and extreme motility of the transformed cells has been held as the cause of a very wide area of involvement. Stereotactic biopsy and initial temozolomide therapy have been recommended to delay radiation therapy in those patients who are often young children.[124]

Gliosarcoma

It is a rare malignancy consisting of gliomatous and sarcomatous elements (Figs 7A to C). They formed 2.4% of 748 glioblastomas in one report.[66] It shares the aggressive clinical behaviour and genetic similarities with glioblastoma. The tumour is reported to invade outside the dura directly.[197]

Table 4: Classification of low and high-grade gliomas

Low-grade gliomas (WHO grade)	*High-grade gliomas (WHO grade)*
Pilocytic astrocytoma (grade 1)	Anaplastic astrocytoma (grade 3)
Fibrillary astrocytoma (grade 2)	Anaplastic oligodendroglioma (grade 3)
Oligodendroglioma (grade 2)	Anaplastic oligoastrocytoma (grade 3)
Mixed oligoastrocytoma (grade 2)	Anaplastic ependymoma (grade 3)
Ependymoma	Glioblastoma multiforme (grade 4)
Subependymal giant cell astrocytoma (grade 1)	Gliosarcoma
Pleomorphic xanthoastrocytoma	
Desmoplastic infantile astrocytoma	
Pilomyxoid astrocytoma (grade 2)	
Angiocentric glioma	

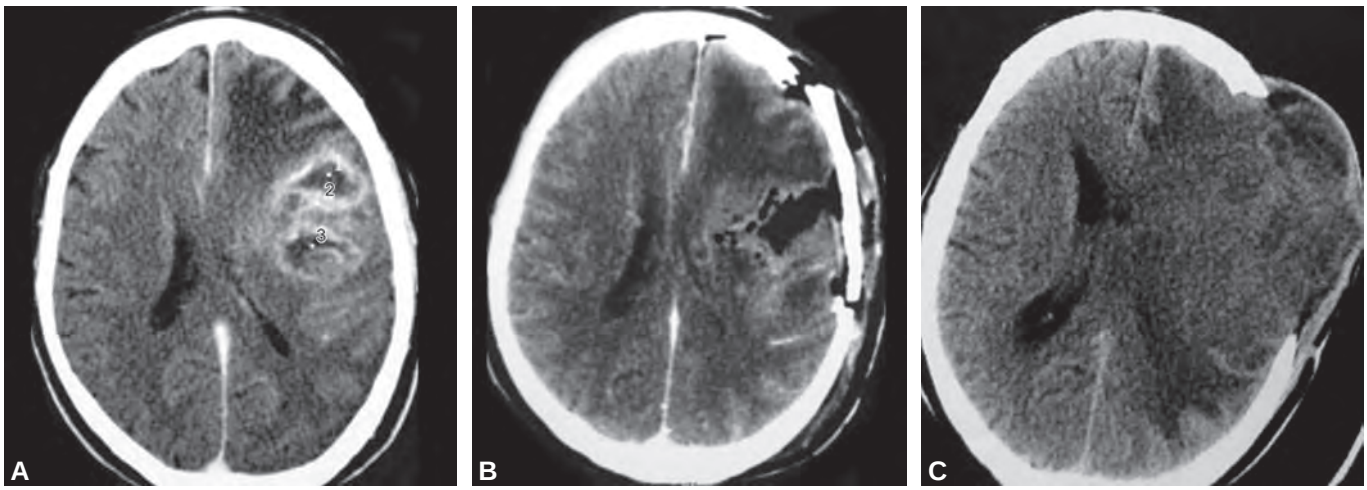
It is convenient to group gliomas in to low[128] and high-grade neoplasms based on usual clinical behaviour (Table 4).

AETIOLOGY AND PATHOGENESIS

The aetiology of the majority of gliomas is not known. The known causes include exposure to ionising radiation and genetic predisposition, but these are rare. Viral aetiology has been suggested but not proved. Glioma arising at the site of traumatic cerebral contusion has been reported and criteria for diagnosing a post-traumatic glioma have been set out.[153]

Radiation Therapy Induced Gliomas

(see above "Other epidemiological factors") Radiotherapy for other scalp, brain or head and neck lesions has been



Figs 7A to C: Gliosarcoma. Contrast computed tomography of a 42-year-old man with gliosarcoma. Despite an apparent complete excision there was residue and rapid regrowth in 3 months even while he was undergoing radiotherapy and chemotherapy. (A) Pre-operative. (B) Immediate post-operative. (C) 3 months later

reported to cause glioma. They generally arise after a latency of 8–25 years and are within the previous field of radiation. They are generally anaplastic and carry a poor prognosis. In one study of 305 irradiated pituitary tumours, four developed a secondary glioma. Their risk of developing a glioma was 16 times higher than the rest of the population.[245] Sellar radiation for craniopharyngioma also carries this risk.[146] Children treated for acute lymphoblastic leukaemia with craniospinal irradiation have been reported to develop malignant glioma. One wonders if chemotherapy also had a potentiating role in such tumours.[211] There are now reports of patients developing malignant glioma after stereotactic radiosurgery (SRS) for acoustic tumours or AVMs.[5]

Hereditary Syndromes and Glioma

There are five hereditary neurological tumour syndromes associated with gliomas. Table 5 gives the type of glial tumour, the gene mutation and chromosomal site in each of these syndromes.[34]

Children with trisomy 21 (Down's syndrome) have been reported to have a higher incidence of gliomas.[201] Though rare, the heritable neurological tumour syndromes are important, as they throw light on glioma genesis.

Cytokinetic Studies and Labelling Index

The factors determining the growth of the tumour are the cell cycle time, the growth fraction, tumour doubling time and cell loss. The parameter most commonly studied is the labelling index (LI), which reflects the proportion of cells in the DNA synthesis phase. The initial studies showed LI < 1% in low-grade glioma and LI > 5% in glioblastomas. The malignant tumours show greater degree of aneuploidy or polyploidy and greater proportion of cells in S phase of mitosis.[122] Increasing values of Ki-67/MIB-1 LI with increasing grade of malignancy in astrocytoma has been noted.[89] Combined Ki-67 and p53 indices higher than 15% indicate a worse outcome than suggested by the histologic grading in diffuse astrocytomas.[243]

Genetic Abnormalities in Non-Syndromic Glioma

The glioma cells show many altered genes leading to over-expression or under-expression of their products. Tumour results when tumour promoter genes are over-expressed or when tumour suppressor genes are under-expressed. The genetic alterations are recognised from the losses or gains in the chromosomal arms and loss of heterozygosity (LOH). Glial tumours are genetically heterogeneous. Primary glioblastoma, which occurs predominantly in elderly males, has a short evolution and a rapidly fatal course. The secondary glioblastoma that arises from a previous low-grade astrocytoma is seen in younger patients, has no gender predilection, presents with a longer history and runs a slower course. Though histologically the primary and secondary glioblastomatous areas are indistinguishable, their genetic makeup is quite different. The primary glioblastoma shows LOH on chromosome 10q, epidermal growth factor receptor (EGFR) amplification, $p16^{INK4a}$ deletion, and phosphatase tensin homology gene on chromosome 10 (PTEN) mutations. The secondary glioblastomas show p53 mutations and LOH on 10q.[168] There seems to be a difference in the chromosomal imbalances seen in adult and paediatric malignant gliomas of similar grade.[191] Patients with malignant gliomas demonstrating a chromosome 1q gain show longer survival and good response to chemotherapy.[234] Genetic subgroups of pilocytic astrocytomas, depending on loss or gain on 19q, might explain their diverse clinical behaviours.[233] The 1p/19q codeletion predicts a favourable response to chemotherapy in low-grade gliomas.[92]

The tumour suppressor gene p53, located on chromosome 17p, is known as the "guardian of the genome". The normal (wild) p53 product is a protein that has a very short half-life and cannot be detected routinely. The abnormal (mutated) p53 product is stable and can be detected. Hence, immunoreactivity to p53 product (TP53) indicates a mutated abnormal gene. The p53 protects cells from cancer by preventing cells with damaged DNA from proliferating wantonly. This is achieved by cell-cycle arrest, which facilitates cell repair; and apoptosis, which ensures the death of cells too severely damaged to be repaired. The p53 also has an important role in angiogenesis and tumour invasion, processes fundamental to malignancy. It is no wonder that TP53 is commonly seen in astrocytic tumours, except pilocytic tumours.[199] Over-expression of p53 has been correlated with adverse prognosis in childhood malignant glioma.[183] Another important gene is the Bc12 proto-oncogene located on

Table 5: Hereditary neurological tumour syndromes

Syndrome	*Glial tumour*	*Gene mutation and chromosomal site*
Neurofibromatosis 1 (NF1)	Optic pathway glioma, astrocytoma elsewhere	NF1 gene, chromo 17q
Neurofibromatosis 2 (NF2)	Astrocytoma, ependymoma	NF2 gene, chromo 22q
Tuberose sclerosis (TS)	Subependymal giant cell astrocytoma	TS1 gene, chromo 9q TS2 gene, chromo 16p TS3 gene, chromo 12q
Turcot syndrome	Malignant glioma	APC gene, chromo 5q
Li-Fraumeni cancer syndrome	Malignant glioma	p53 gene, chromo 17p

Note: p = short arm of the chromosome; q = long arm of the chromosome; APC = adenomatosis polyposis coli

chromosome 18. The Bc12 product is antiapoptotic. Over-expression of Bc12 gene product found in primary central nervous system tumours is known to make tumours resistant to chemotherapy or radiotherapy.[245] Aurora kinase family proteins are related to mitosis. Aurora B over-expression correlates with aggressive behaviour in glioblastoma.[267] Telomerase confers cell immortality. It has been found to be over-expressed in secondary glioblastomas.[76] Gains at the 1p36 chromosomal region are associated with symptomatic leptomeningeal dissemination of supratentorial glioblastomas.[105]

Role of Growth Factors

The mutations in glioma cells cause amplification and over-expression of epidermal, platelet derived and fibroblast growth factor receptors. In addition, the vascular endothelial growth factor (VEGFR) amplification causes angiogenesis. On the other hand, the inactivation of brain angiogenesis inhibitor also promotes angiogenesis.[96] The LOH in 10q causes inactivation of PTEN, a gene downstream of focal adhesion kinase, which controls cell migration and invasiveness. Neural cell adhesion molecule is down-regulated in the development of the malignancy of astrocytic tumours and its expression is inversely correlated to the degree of malignancy.[200] There is high degree of correlation between vascular endothelial growth/permeability factor (VEG/PF) expression by gliomas and the occurrence of peritumoural vasogenic brain oedema or tumour-associated cysts, irrespective of tumour grade, thus supporting VEG/PF's pivotal role as the common pathophysiological link between these processes.[227] Cyclo-oxygenase 2 (COX-2) is an enzyme that is over-expressed in glioma cells as compared to normal astrocytes. This over-expression is associated with angiogenesis and resistance to apoptosis.[162]

Role of Stem Cells

The malignant gliomas retain a small number of brain tumour stem cells (BTSC), which are derived from the neural progenitor/stem cells. These are responsible for recurrence of tumour. The BTSC progresses in to tumour due to changes in signalling and control pathways such as ras, retinoblastoma (Rb), Notch and sonic hedgehog (Shh). For further details the interested reader is referred to a review article.[265] It appears that dysregulation of the cadherin/catenin (cell adhesion molecules) assembly contributes to the malignant transformation and increased motility and migration of glioma cells into the parenchyma.[7]

Role of Environmental Factors

Recently, human cytomegalovirus (HCMV) antigen and DNA have been demonstrated in glioma cells. This herpes virus exhibits glial tropism. The higher grade tumours have a larger fraction of HCMV infected cells indicating a possible aetiological connection.[204] Patients with HIV infection developing a glioma are rarely reported.[250] Tumour hypoxia is known to promote tumour recurrence and decreases the efficacy of radiotherapy or chemotherapy.[88] This effect may be mediated by erythropoietin.[152] Vitronectin in CSF promotes glial tumour cell mobility.[64]

Glioma Models

Our knowledge about the basic biology of gliomas has come mainly from analysis of material obtained from patients. Teratogen (ethylnitrosourea) induced animal gliomas and established human astrocytoma cell lines have been used to study gliomas. Transgenic mouse models have recently been introduced. Models are essential to identify the molecular aberrations and the molecular targets that will eventually be therapeutically exploited. For further details the interested reader is referred to a review article.[56]

Several pieces of the jigsaw puzzle of glioma genesis have now been fitted in[260] (Flow chart 1). Active research is being done to devise molecular therapies for stopping the signalling pathways that promote tumour and enhancing those that suppress tumour (see section "Emerging Therapies").[244]

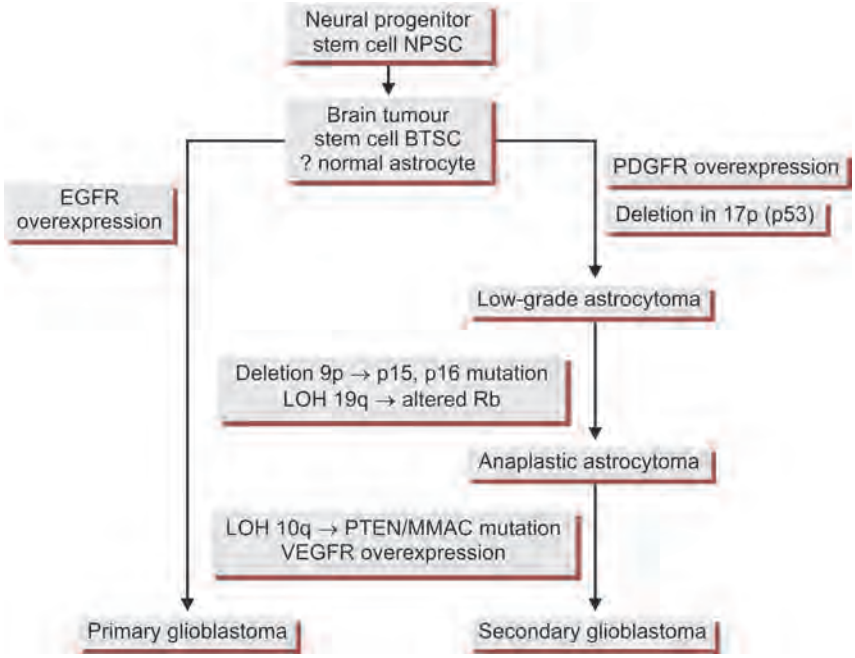
CLINICAL FEATURES

The signs and symptoms of supratentorial glial tumours depend upon the site, the size, the histological nature and the rate of growth of the tumour. The onset of symptoms is usually insidious and the course progressive.

Duration and Progression

The duration of symptoms is usually 2–3 years for low-grade tumours, 1–2 years for the intermediate grades and a few months or weeks for glioblastomas.[141] It is much longer for oligoastrocytomas and oligodendrogliomas. Stepwise deterioration may be observed with anaplastic astrocytomas. Sudden deterioration may set in during an otherwise gradual course, due to haemorrhage in the tumour or rapid necrosis or onset of oedema. These are seen more frequently in glioblastomas. A slow growing astrocytoma may suddenly change its character and turn into a glioblastoma, resulting in a rapid downhill course in a patient with an otherwise slow course. Slow growing tumours in the so-called silent areas of the brain, (the frontal lobes and the non-dominant temporal lobe) may acquire a large size without producing any symptoms and then show rapid deterioration and present with a short history due to decompensation of the intracranial pressure (ICP) dynamics. On the other hand, a small strategically located astrocytoma may, by manifesting an epileptic attack or early focal deficit, be associated with a short history. Thus, the duration of the illness may not provide a true indication of the histological nature.

Flow chart 1: Possible molecular pathways in astrocytoma and glioblastoma



Note: EGFR = epidermal growth factor receptor; PDGFR = platelet derived growth factor receptor; VEGFR: vascular endothelial growth factor; Rb = retinoblastoma gene; PTEN = phosphatase tensin homology gene on chromosome 10; MMAC = mutated in multiple advanced cancers; LOH = loss of heterozygosity, p53, Rb and p16 are tumour suppressor genes.[33]

Supratentorial gliomas may manifest themselves by symptoms and signs of raised ICP, epilepsy, progressive neurological deficits and cognitive/behavioural dysfunction.

Raised Intracranial Pressure

Headache and vomiting are the initial symptoms in about one-third of patients with supratentorial gliomas.[141] The headache is generalised and progressive, sometimes lateralised to the side of the tumour. The frequency and severity of symptoms of raised ICP is greater in patients with more malignant tumours and with gliomas situated nearer the midline. Signs of ICP like papillo-oedema and abducens palsy are less common nowadays, due to earlier diagnosis with the widespread use of imaging.

Epileptic Seizure

Two-thirds of patients with a supratentorial glioma are likely to get a seizure sometime during the course of their illness. In an Indian study, seizure history was present in 61% of patients before the operation and seizures were the only symptom in about 10% of patients. Seizure was the first symptom in 45% of patients. The incidence of seizures was higher (65%) in slow growing tumours and lower (29%) in glioblastomas.[239] Low-grade tumours also tend to present with seizure as their only manifestation. Adult onset focal seizures, changing character of seizure over time, prolonged postictal (Todd's) paralysis, and onset with status epilepticus have been traditionally held to arouse the suspicion of a tumour. Postictal paralysis may be prolonged or may not recover fully and may increase with every seizure. Generalised epilepsy of long duration and seizure history in childhood do not rule out the possibility of an underlying tumour.

Simple partial seizure, with or without generalisation, is the most frequent type accounting for 47% of patients with glioma presenting with seizure. Generalised tonic-clonic seizure was seen in 35% of patients and complex partial seizure in 10% of patients.[239] Tumour is the most likely cause in patients with olfactory or gustatory aura. The recurrence of attacks after a long seizure free interval in a treated patient generally indicates recurrence of tumour. There is a suggestion that glioblastomas presenting with seizures have a slightly longer survival, probably because the seizure brings them to medical attention earlier.[172] The occurrence of seizures at diagnosis was a strong predictor of subsequent seizures, and in many patients, seizures prove to be refractory to standard anticonvulsant therapy.[154]

Focal Neurological Dysfunction

Neurological deficit is not a common initial symptom, since a large percentage of hemispheric gliomas are located in the "silent" frontal and temporal lobes. It is predominantly a feature of tumours located in or near the sensorimotor cortex. Here, it generally starts as postictal deficit. Comprehension dysphasia is often overlooked or confused with memory impairment or a psychiatric illness. Patients developing hemianopia are often unaware of the deficit but bump in to objects on the hemianopic side. Similarly, the patient also ignores

sensory symptoms due to parietal lobe involvement. Dressing apraxia or the neglect of the contralateral half of the body or visual field may be observed by others rather than the patient. While a neurological deficit, as the initial symptom, is observed in 3% of cases only, nearly 60% of patients have some deficit at presentation. Motor weakness is more common with malignant glioma than low-grade glioma. Incontinence, when awake, may be the presenting symptom in frontal or midline tumours.

Cognitive Dysfunction

Apathy, change in personality, impairment of memory, inattention, inappropriate social behaviour, irritability, verbal-motor perseveration and psychomotor retardation are common symptoms. This is especially true for tumours of the frontal lobe and temporal lobe. Basal frontal tumours present with pseudomania, lateral frontal tumours with pseudodepression and medial frontal lesions with pseudodementia and akinetic state.[193] Impairment of memory is seen with frontal and temporal lobe tumours. Some of the mental changes are due to the raised ICP, but others are directly due to neurological dysfunction at the location of the tumour caused by compression or infiltration. Neuropsychological testing helps localise the lesion and aids post-operative follow-up.

Uncommon Presentations

Enlarging size of the head, irritability and a delay in achieving developmental milestones may be the presenting features of gliomas in children. Temporal lobe tumours may present in to the orbit or infratemporal fossa.[111,197] Cranial nerve involvement (other than the VI cranial nerve) has been reported rarely.[235] Hemiatrophy of the contralateral half of the body (seen in slow-growing parietal lobe tumours occurring at a young age) is a rare manifestation. "Man-in-the-barrel" syndrome, with disproportionate weakness of the arms as compared to the legs, has been reported with multicentric glioma.[18]

INVESTIGATIONS

Imaging

The CT and MRI are the only investigations used in clinical practice today for the diagnosis of supratentorial gliomas. The CT is generally the first investigation done for a patient with a suspected intracranial mass lesion, as it is more rapid, less expensive and more available. The CT can be done more easily than MRI in demented, restless or intubated patients. It can also be done in claustrophobics and patients with pacemakers. Calcification, fresh haemorrhage and bony anatomical landmarks are well made out in CT. Contrast CT study may be avoided if gadolinium enhanced MRI is going to be done. The MRI is more sensitive to pathological changes in the tissue and superior in assessing tumour volume or tissue characteristics. Patients presenting with seizures alone are generally investigated directly with MRI.

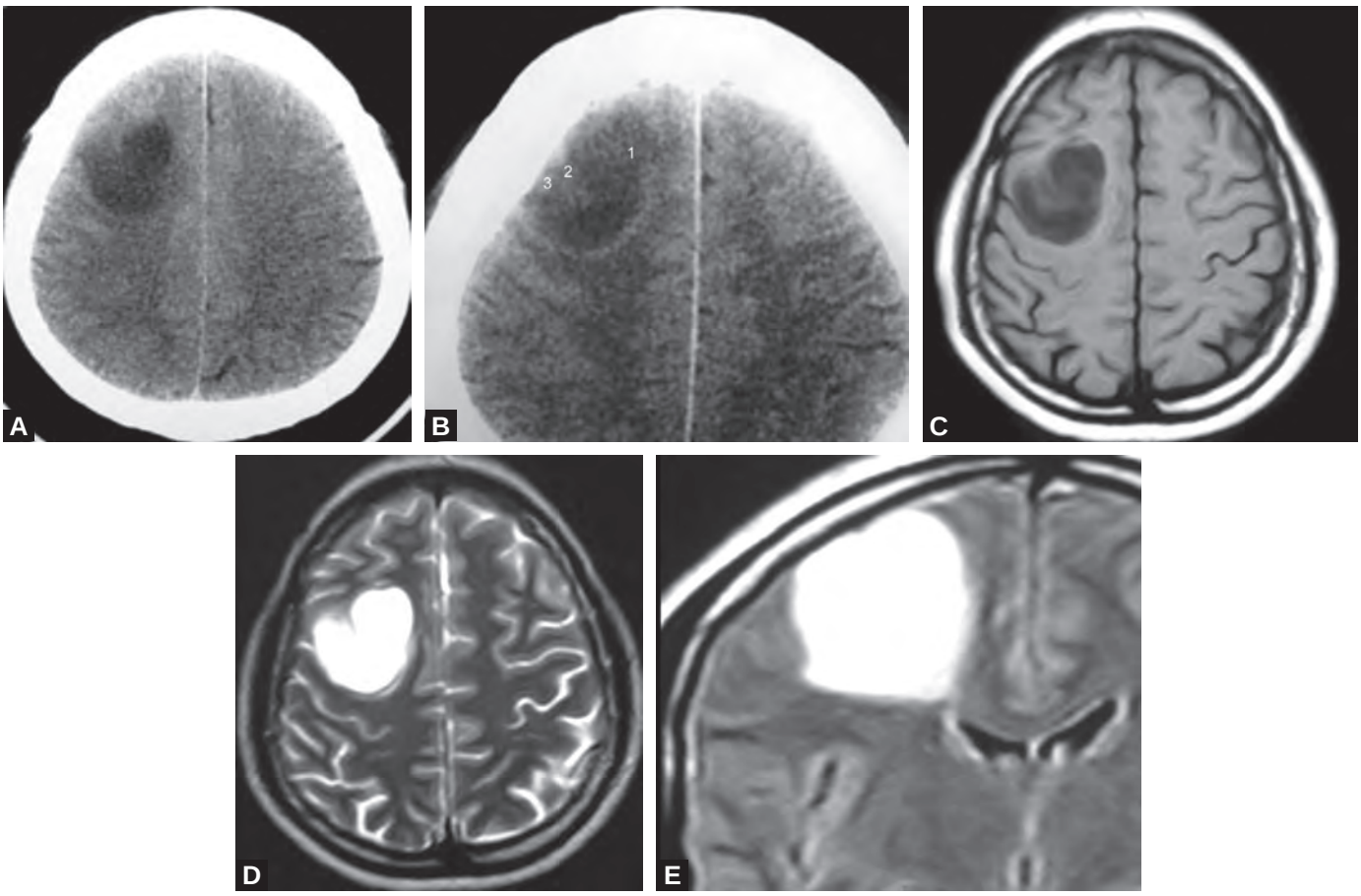
Low-Grade Astrocytomas

Low-grade astrocytomas take on one of two morphologies on imaging. The diffuse infiltrative low-grade astrocytoma is seen as a homogeneous hypodense (about 20 HU) area with indistinct borders on non-contrast CT (Figs 8A to E). They are hypointense in T1W and hyperintense in T2W, PD and fluid-attenuated inversion recovery (FLAIR) MR images. There is little or no peritumoural oedema. Since both the tumour and the oedema appear hypodense on CT, the judgment about the absence of oedema is made from the lack of much mass effect. There is usually no contrast enhancement. Focal hyperdensities on CT may be due to calcium or blood. Calcification is seen in about 20% of astrocytomas. It is better appreciated on CT and generally indicates slow growth (Fig. 5). Haemorrhage is seen if there is an oligodendroglial component. Attenuation values approaching that of water may indicate a cystic area, but even such hypodense tumours may be solid. This is because the "solid" area is in fact made up of microscopic cysts containing fluid. The isodense non-enhancing tumour is invisible on CT (about 5% of low-grade gliomas) and requires MRI for diagnosis. The closest imaging mimic is infarction.

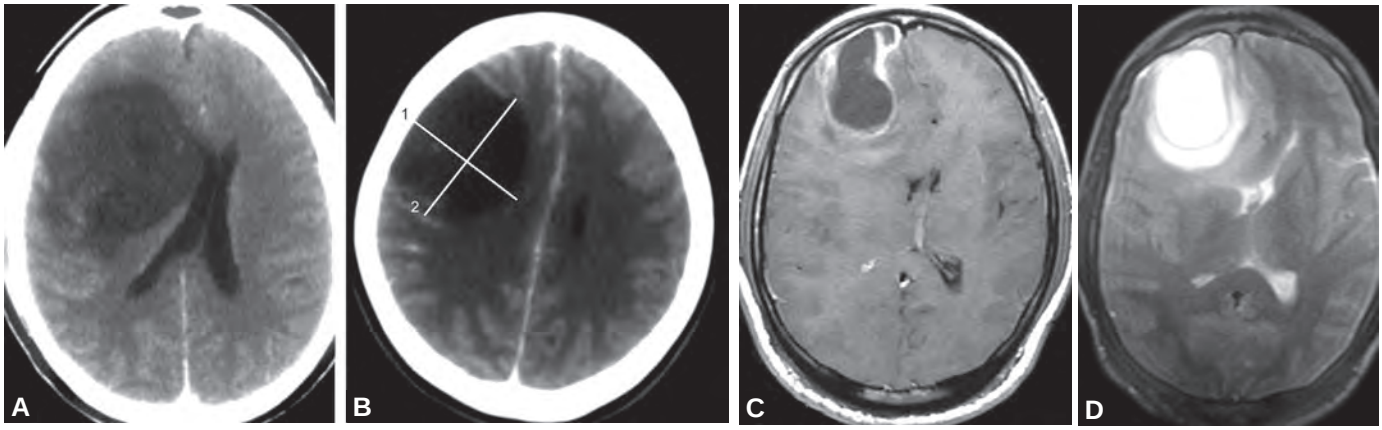
The other imaging variety of low-grade astrocytoma is the circumscribed one (e.g. pilocytic astrocytoma), which is sharply marginated. The circumscribed astrocytomas show contrast enhancement as globular masses or thick irregular rings on CT or MR (Figs 9A to D). Macrocystic change is common in these tumours. As mentioned in Table 1 in the chapter on cerebellar astrocytoma, the tumour can be true cystic (no tumour or enhancement in the wall) or false cystic (there is tumour and enhancement in the wall).

Anaplastic Astrocytoma

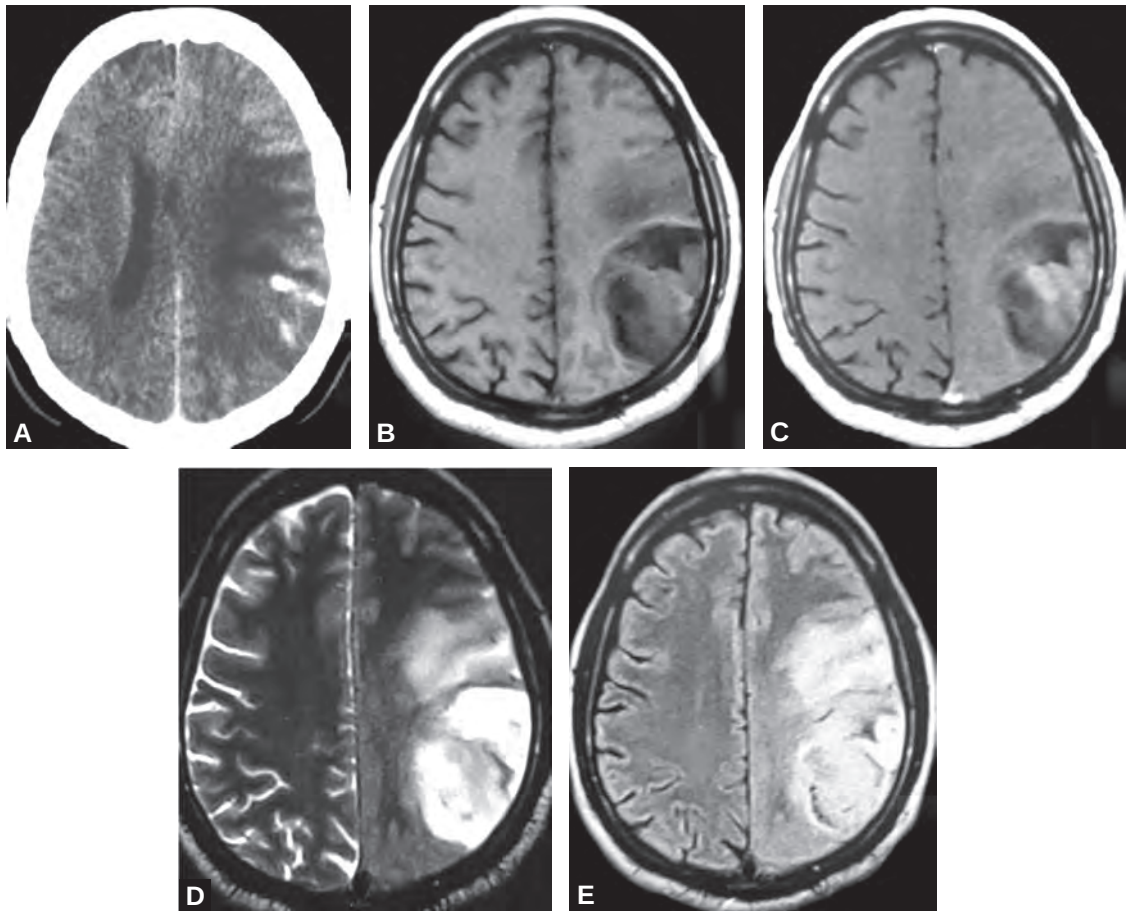
It is marked by the heterogeneity in appearance on imaging. There are areas of low density, isodensity and even areas of hyperdensity on non-contrast CT. Similarly, on MR, variations in intensities in the various imaging sequences are noted (Figs 10A to E). The cystic and necrotic areas both appear hypodense in CT. Delayed contrast CT may show contrast-fluid levels in cysts while this sign is absent in necrotic areas. The border of the lesion may be apparently better defined than in a low-grade tumour. The enhancement on CT or MR takes the form of a thick ring or a nodule. There is more oedema than in a low-grade tumour. This lesion needs to be distinguished from granuloma, abscess and metastasis. It has been found that an abscess appears hyperintense on diffusion-weighted MR images, whereas a tumour is hypointense. The apparent diffusion coefficient (ADC) values are lower in an abscess than tumour cysts.[73] The size of the lesion may increase in a few months (Figs 11A and B). Enhancement alone does not predict



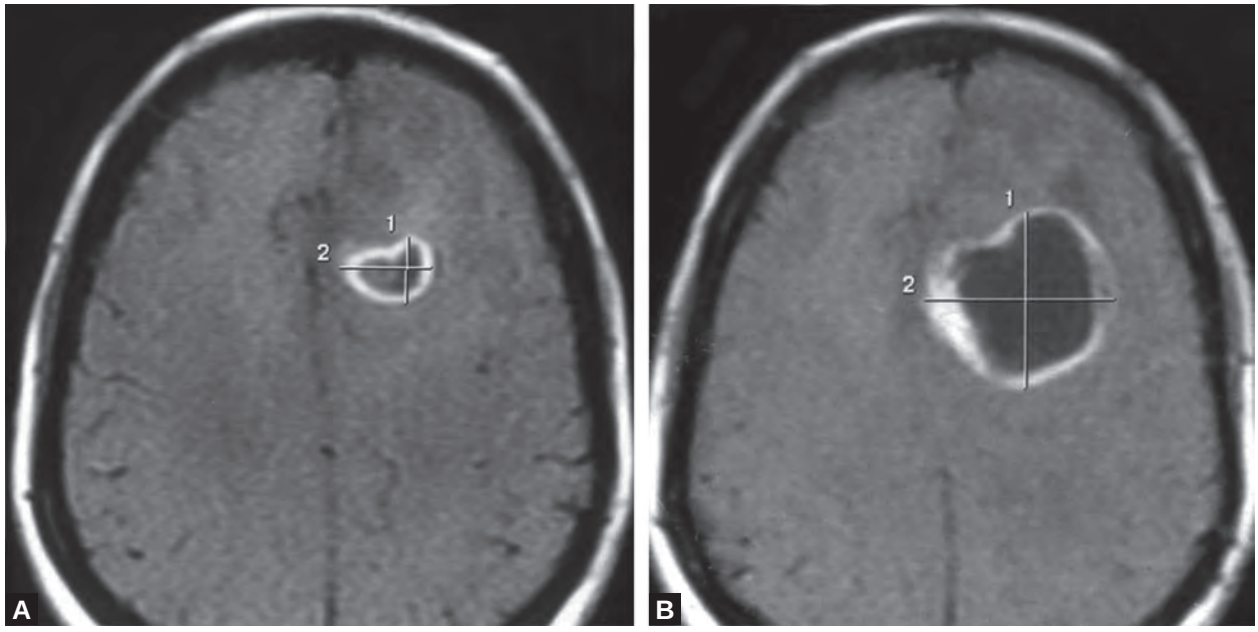
Figs 8A to E: Imaging characteristics of grade 1 astrocytoma. Note the absence of mass effect or oedema. (A) Non-contrast computed tomography. (B) Contrast-enhanced computed tomography. (C) T1-weighted image. (D) T2-weighted image (E) Fluid-attenuated inversion recovery (FLAIR)



Figs 9A to D: Imaging characteristics of grade 2 astrocytomas. Note the mass effect in the computed tomography scans of one patient on the left and lack of enhancement. In the magnetic resonance imaging of another patient on the right, the lesion is more circumscribed and enhances irregularly in the periphery. The T2-weighted images show the hyperintense central necrotic portion, the hypointense cellular part of the tumour and the hyperintense surrounding oedema. (A) Non-contrast computed tomography. (B) Contrast-enhanced computed tomography (C) Post gadolinium T1-weighted image. (D) T2-weighted image



Figs 10A to E: Imaging characteristics of grade 3 astrocytoma. The non-contrast computed tomography on the left shows areas of calcification in the tumour. The variegated intensity is well appreciated in T1-weighted magnetic resonance but the calcification is not seen. The enhancement with gadolinium is variegated. The surrounding oedema and the tumour can be differentiated in T2-weighted imaging but not in the proton density weighted images. The calcification is seen as intensely hypointense areas. (A) Non-contrast computed tomography. (B) T1-weighted image. (C) Post gadolinium T1-weighted image. (D) T2-weighted image. (E) Proton density (PD) image



Figs 11A and B: Rapid growth in an anaplastic astrocytoma. The size of the contrast enhancing mass on magnetic resonance imaging has increased in 5 months

the malignant nature. Enhancing tumours may have a benign histology (e.g. desmoplastic infantile astrocytoma)[13] and one-third of non-enhancing tumours may be malignant.[207] Absence of contrast enhancement on CT is observed in 54% of anaplastic astrocytoma and in 4% of glioblastomas.[30]

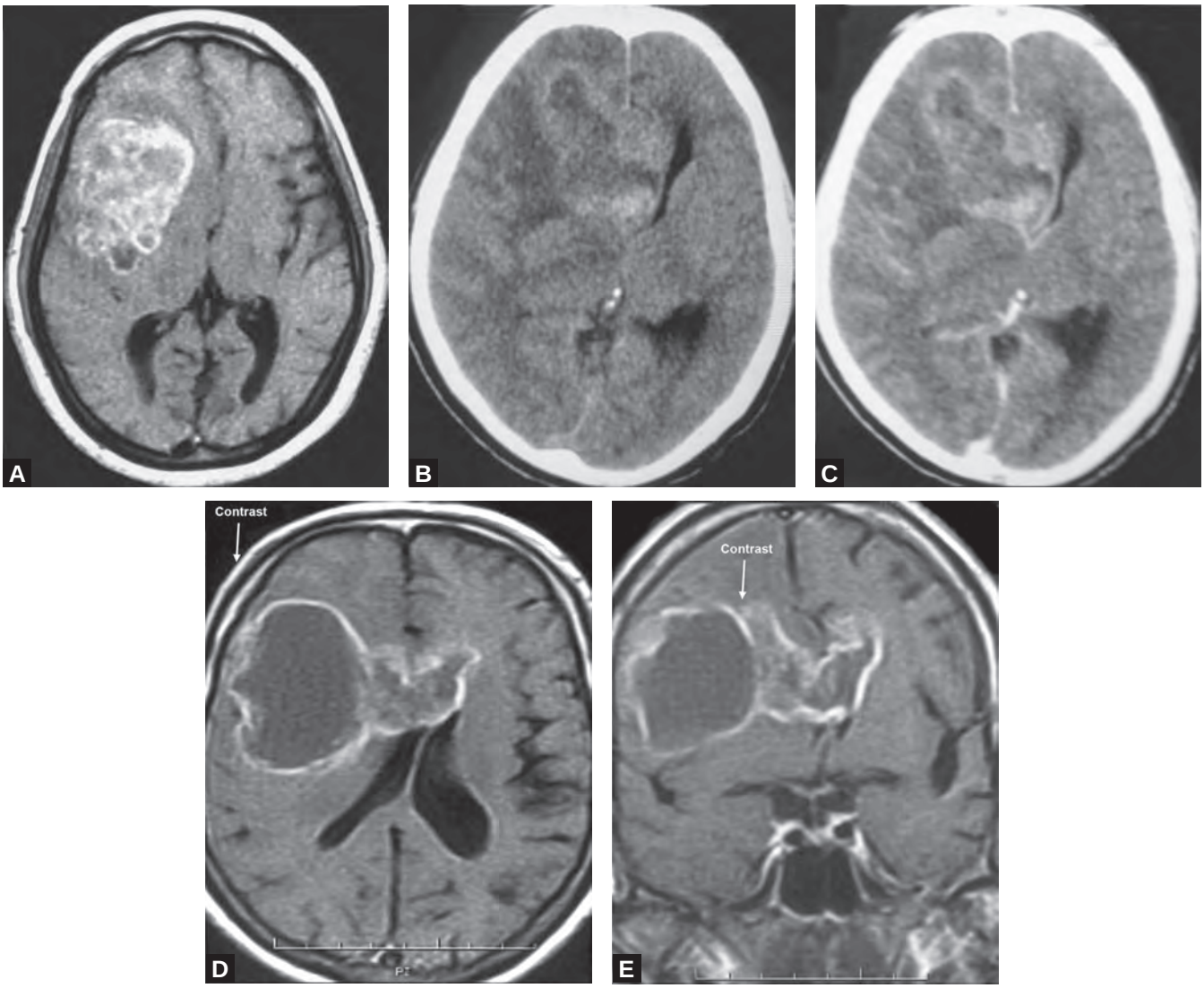
Glioblastoma Multiforme

It is marked by its variegated appearance and mass effect (Figs 12A to E). The secondary glioblastoma retains the imaging characteristics of the low-grade tumour from which it developed and adds the imaging features of neovascularity, haemorrhage or necrosis. The primary tumours on the other hand show a thick, shaggy and serpigenous pattern of enhancement all over the tumour. Infiltration of the opposite frontal lobe through the corpus callosum produces the famous "butterfly" glioma. In glioblastoma, and to some extent with anaplastic astrocytomas, the tumour cells have been detected in radiologically normal brain around the tumour. Though the MR gives a better estimate of the tumour volume, it must be remembered that there is tumour beyond the imaging edge.[98] Recently, it has been reported that glioblastomas with high p53 positivity show a ring enhancement pattern and well-defined borders in T1W imaging.[156]

Recent Trends in Imaging

Proton Magnetic Resonance Spectroscopy

Proton magnetic resonance spectroscopy (MRS) has been employed to predict tissue characteristics. The molecules



Figs 12A to E: Imaging characteristics of grade 4 astrocytoma and glioblastoma multiforme. The gadolinium enhanced T1-weighted (T1W) magnetic resonance (MR) (left) of a patient with grade 4 astrocytoma shows variegated rich enhancement and multiple necrotic areas. The computed tomography (CT) scans (centre) of another patient with glioblastoma. Note the hyperdense appearance of the growing edge in plain CT and the serpigenous but moderate enhancement. The infiltration of the corpus callosum is characteristic. The contrast MR (right) of another patient showing the "butterfly" appearance. (A) Post gadolinium-T1-weighted image. (B) Non-contrast computed tomography. (C) Contrast-enhanced computed tomography. (D) Post gadolinium-axial image. (E) Post gadolinium-coronal image

studied are N-acetyl aspartate (NAA), that reflects loss of neuronal integrity; creatinine (Cr), a measure of energy stores; lactate (Lac), that reflects anaerobic metabolism; and choline (Cho), that is elevated in tumours and inflammatory processes, reflecting rapid cell turnover. Generally, in highly metabolic tumours, including glioblastoma, the levels of NAA and Cr are decreased, and the rapid growth results in elevated Cho and Lac levels. Thus, in comparison with normal tissues, glioblastoma demonstrates an increase in Cho/Cr and Cho/NAA peak ratios, an increased Lac/Cho peak ratio, and a decreased NAA/Cr ratio.[85]

MRS is useful for distinguishing infarcts or inflammatory lesions that mimic a glioma on MR imaging.[114] Cho appears to correlate best with the degree of tumour infiltration. MRS appears more accurate than conventional MRI in defining the tumour boundary and quantifying the degree of tumour infiltration.[41] The relative levels of Cho and NAA correlated with the cell density in grade 2 and grade 3 gliomas. The association was irrespective of the presence of contrast enhancement. MRS can be used to identify regions of aggressive growth in presumed grade 2 or 3 gliomas that would be suitable for biopsy.[142] The role of MRS in distinguishing recurrent tumour form radionecrosis is mentioned below (See section "Imaging of Recurrence").

Perfusion and Diffusion Magnetic Resonance

The blood flow in the tumour can be assessed with perfusion MRI. Glioblastoma shows higher regional cerebral blood flow (rCBF) than lower grade tumours or lymphomas.[256] A high correlation between degree of contrast enhancement on dynamic contrast-enhanced images and regional cerebral blood volume (rCBV) values as measured by T2W imaging in high-grade glial tumours has been noted. This indicates that the areas of enhancement have high rCBV.[187] The pre-operative ADC in diffusion-weighted MR has emerged as a prognostic factor. Low ADC carries a poor prognosis.[155] Diffusion tensor imaging is a new modality that can delineate fibre tracts and depict their displacements or infiltration by gliomas. It can also be used for delineating accurately the tumour margin and oedema from the surrounding healthy white matter.[222]

In spite of the sophistication of neuroimaging, it must be stressed that imaging cannot substitute for tissue diagnosis. In one study of 20 patients thought to have a low-grade astrocytoma, nine had anaplastic astrocytoma and one had encephalitis when subjected to stereotactic biopsy.[103] In a more recent study, MRI was found to have high specificity but variable sensitivity for grading of glial tumours.[90] Pre-operative MRI and even positron emission tomography (PET) may underestimate or overestimate the grade.[4]

Positron Emission Tomography

Thus far a research tool, PET is now available to the clinician in some centres in India. Its spatial resolution is poor but, since it can be combined with CT, the resolution is improving. The advantage is that it is able to show the areas of active tumour growth by demonstrating hypermetabolism. PET using 18 F-fluorodeoxyglucose (FDG) has been shown to correlate with survival in anaplastic astrocytomas, those with higher uptake succumbing earlier.[175] PET studies using L-(methyl-11C) methionine have shown that methionine uptake was heterogeneous even among the homogeneous tumour areas demonstrated on MRI. Malignant pathological features were detected in the areas with the highest methionine uptake.[159] The combination of MRI and PET improves the accuracy of targeting and the diagnostic yield of biopsy, but does not replace histological diagnosis.[137] Increased[18] FDG uptake on PET may not necessarily reflect malignant transformation as similar changes can be induced by seizures.[166]

Serum and Cerebrospinal Fluid Markers

GFAP has been detected by enzyme linked immunosorbent assay test in serum samples of 80% of patients with glioblastomas. The levels are higher in those with larger tumours, larger areas of necrosis and greater tumour cell positivity for GFAP. It is not detectable in healthy controls or those with non-glioblastoma tumours.[91] Though CSF cytology may prove positive for tumour cells in glioblastomas, it is not advisable to obtain lumbar CSF in patients with large mass lesions. Ventricular CSF may be obtained during shunt surgery or endoscopy.[35]

TREATMENT

Goals of Therapy

There is no complete cure for gliomas, nor is one as yet in sight, notwithstanding the intense research efforts. As long as no other effective treatment is available, surgery will continue to be central to the management of gliomas. In spite of this, there is no unanimity in the approach of neurosurgeons as to the extent or nature of surgery. The lack of consensus adds to the difficulty in decision-making. The goals of management of an individual patient can be summarised as:

- To establish an unequivocal diagnosis
- To determine the degree of malignancy
- To relieve distressing symptoms
- To prolong useful survival without inflicting unacceptable neurological deficits
- To achieve as complete an excision of the tumour as possible
- Improve the effectiveness of adjuvant therapy like radiotherapy, chemotherapy and immunotherapy by cytoreduction.

To achieve these objectives the following alternatives are available:

- Image guided stereotactic biopsy (frame based or frameless)
- Tumour removal: partial; subtotal; macroscopically total; lobectomy

- Procedures for relieving ICP: drainage of cyst; CSF diversion (shunt or ventriculostomy); craniectomy for external decompression
- Procedures to facilitate adjuvant therapies (implanting catheters for intralesional therapy, radioactive material for brachytherapy, etc.).

Biopsy

Need for Biopsy

It is not always possible to ensure that the lesion seen on imaging is a glioma and not some other lesion such as infarction, abscess, granuloma or demyelination by imaging alone. Even if the imaging characteristics strongly suggest a glioma, its grading can only be suggested but not confirmed by the most sophisticated neuroradiological technique.[103] Hence, in all cases, it is necessary to obtain a histological diagnosis before deciding on further therapy. If the tumour is in a resectable region and the patient is fit for surgery, there is no need to do a preliminary biopsy before proceeding with tumour excision. Similarly, in a patient who needs a resectional procedure for relieving symptoms, there would be no need for a preliminary biopsy.

Indications for Biopsy

Biopsy-alone approach will be indicated in the following cases:

- Deep-seated lesions
- Small lesions
- Lesion associated with a large cyst
- Lesions affecting eloquent areas
- Multiple lesions
- Lesions where there is a differential diagnosis with a medically treatable lesion such as tuberculoma
- Patients who are not fit to undergo major surgery.

Accuracy

Stereotactic biopsy is generally accurate. About 80% accuracy on comparing with the subsequent resection specimen has been reported. More importantly, it leads to the correct treatment in about 96% of cases.[140] Small samples do not decrease the diagnostic yield when there is an expert team that does and interprets the biopsy.[80] The CT is usually used for stereotactic biopsy while MRI has proved to be as accurate in the axial plane coordinates and may be used for lesions not seen well on CT.[69] It is possible to obtain accurate samples with frameless stereotaxy also.[15] A better yield with frameless image-guided stereotactic biopsy in comparison to conventional frame-based CT-guided stereotactic biopsy and ultrasound-guided biopsy was noted in a study from AIIMS, Delhi.[87]

Rationale of Biopsy

Several surgeons have favoured the biopsy-followed-by-radiotherapy approach for malignant tumours.[39,132] Their argument is that there is no survival difference between those who undergo biopsy alone and those who undergo major resections for malignant gliomas as long as the patient undergoes radiotherapy.[160] They also point to the morbidity of major resections.[106] However, in the recent years, the safety of resectional surgery has increased and resection has been shown to confer a survival advantage (see below). While most radiotherapists believe that cytoreduction is a prerequisite for radiation therapy, some have cast a doubt on the role of cytoreduction in glioblastoma.[109] The resectionists feel that a limited biopsy may fail to reveal tumour heterogeneity and thus give an erroneous impression about its grade of malignancy. In one study, the stereotactic biopsy diagnosis and the diagnosis on the subsequent resection specimen differed in 49% of cases.[86] It must be remembered that the basis of the argument on both sides of the issue rests mainly on retrospective studies.[196] Patients with large tumours who have marked increase in ICP are obviously not suitable for this line of management.

Technical Issues

Conventional free hand biopsy is now passé, except in an emergency where the patient has already coned and prompt drainage of a cyst is aimed at. Image guided minimally invasive biopsy is the current standard. Open biopsy is nowadays seldom required. Wherever possible, the biopsy should be obtained separately from sites that appear different on imaging. It is erroneous to assume that it is sufficient to biopsy the enhancing portion alone as the non-enhancing portion also may show anaplastic areas.[207,159] Cyst fluid obtained during biopsy may be subjected to cytology. The trajectory must be planned so as to avoid ventricular entry to ensure that there is no shifting of the target. It is ideal to have the pathologist at hand to do a squash preparation and judge the adequacy of the sample before the biopsy procedure is completed. The post-procedure imaging can be done with the stereotactic frame on the patient to check the appropriateness of targeting and the procedure can be redone in the unlikely event of a miss. Tumours visible in the ventricular system are best biopsied with the endoscope. In that situation, additional tumour debulking to open a blocked foramen of Monro or a CSF diversion procedure such as third ventriculostomy/septum pellucidotomy also can be combined in the same sitting.

Safety and Risks

Stereotactic biopsy is generally a safe procedure. The minor morbidity (3%) and mortality/major morbidity (3%) are lesser than for major resections.[16] Haemorrhage is less if biopsy cannulae or 1 mm biopsy forceps are used. The haemorrhage related morbidity is hardly 1%.[108] An increased risk of morbidity is associated with the pre-operative use of antiplatelet agents, deep-seated lesions, malignant gliomas and a greater number of biopsy attempts.[203] Seeding along the track of biopsy is possible but rare.[226]

Tumour Removal

This section describes resectional surgery for anaplastic astrocytoma and glioblastoma. Low-grade astrocytomas are dealt with in a separate section (see below).

Differences Between Radical Cancer Surgery Elsewhere and in the Brain

Radical cancer surgery in other areas of the body has aimed at complete en bloc excision with surrounding normal tissue to assure a tumour free margin. None of these goals is possible to achieve in malignant brain tumours. The technique of neurosurgery involves intralesional decompression before piecemeal excision and so en bloc excision is not generally possible.[236] The en bloc removal technique using spoon retractors[119] may not ensure prevention of tumour spillage. It is important to recognise that a malignant glioma, even if it appears to be well circumscribed, is an infiltrating tumour. During surgery, the bulk of the tumour can be differentiated from the normal brain tissue by its colour, consistency and texture. However, even when using microsurgical techniques, it is impossible to be sure of the precise extent of tumour infiltration. Thus, the microsurgical limit of the tumour is well within the histological limits revealed by pathological examination.[98] Resection of surrounding brain to assure a tumour free margin is only rarely possible in small tumours in silent areas of the brain. Hence, though gliomas may be resectable, they are not amenable to oncologically radical excision. "Radical" or "aggressive" glioma removal is tantamount to a gross or macroscopic total removal. It should be considered a cytoreductive procedure and as the first step in a multimodality treatment regime.

Impact of Maximal Tumour Removal on Survival

The champions of resectional surgery hold that gross total resection of supratentorial glioblastomas and anaplastic astrocytomas is feasible and that it is directly associated with longer and better survival when compared to subtotal resection or mere biopsy. In one early study, the mean survival was 90 weeks for the gross total excision group and 43 weeks for the subtotal or partial resection group.[2] The Glioma Outcomes Project reports near doubling of mean survival time for patients undergoing resection as compared to biopsy.[123] Resection of the contrast enhancing mass alone in grade 4 gliomas prolonged the survival to 50 weeks as compared to 33 weeks for those undergoing biopsy.[55] Gross total excision has been shown to improve not only the length of survival but also the quality of life.[44] Benefits of resection have been demonstrated at all ages. In children with malignant gliomas, radical tumour resection (greater than 90%) is the only therapeutic variable that significantly improves the progression-free survival rates.[263] In 102 elderly patients with glioblastoma, those who underwent gross total resection had median survival of 69 weeks while it was only 20 weeks for those undergoing biopsy and radiation.[151] The volume of residual tumour after resection has been found to strongly correlate negatively with outcome.[1,97] This residual tumour assessment is not to be based on the surgeon's estimation but on contrast MR done within 72 hours of surgery. Totality of resection was associated with greater survival though the level of statistical significance was lower than that of the influence of age or pre-operative Karnofsky performance status (KPS) in a recent single institution study of 267 patients with glioblastoma.[225]

The enthusiasm for aggressive excision must be tempered by the sobering fact that none of the foregoing constitutes Class I evidence. In fact a Cochrane report in 2001 could not draw any conclusion as there was insufficient randomised data.[147] Only the Radiation Therapy Oncology Group's studies provide at least Class II evidence but this was in the early 1990s. The extent of surgery did not reach statistical significance in multivariate analysis even though it was significantly correlated with survival in univariate analysis.[43] The Glioma Outcomes Project also gives Class II evidence that extent of resection is a significant factor but no effort was made to quantify the degree of excision.[123]

Strategies to Maximise the Resection

These have been summarised in Table 6. Knowing the exact extent of the tumour by pre-operative MRI in all three dimensions is a *sine qua non*. The value of three-dimensional (3D) image reconstruction has been stressed.[29]

Use of a 7–10 MHz ultrasound probe can show up the higher echogenicity of the glioma tissue (irrespective of its contrast enhancing property) and can help in detecting residual tumour in the bed of an apparently complete excision. The more anaplastic areas are variegated in their echogenicity but always more echogenic than normal brain tissue.[75] The intra-operative ultrasound characteristics of malignant tumours as opposed to low-grade tumours have been well-described using a 3–4 MHz probe.[28]

Stereotactic craniotomy involves performing the craniotomy in the stereotaxy frame. The extent of resection

Table 6: Strategies to maximise the resection of malignant glioma

Accurate pre-operative imaging with magnetic resonance imaging (MRI)
Three-dimensional image reconstruction
Intra-operative ultrasonography (IOUS)
Stereotactic craniotomy
Non-volumetric
Volumetric, computer assisted
Neuronavigation
Intra-operative MRI
Intra-operative electrocorticography (for excising the epileptic foci around the tumour)
Fluorescence guidance
Strategies aimed at saving neurological function

can be physically verified by matching the coordinates obtained during surgery with the pre-operative stereotactic data in the simple and non-volumetric system.[9] With the sophisticated system developed by Kelly, it is possible to place tumour volume interpolated from the CT and MRI-defined boundaries into a 3D computer image matrix. This information can then be used for surgical planning for interactive volumetric stereotactic removal of the lesion.[125]

Neuronavigation [image guided resection (IGR)] achieves the same purpose and has been demonstrated to result in more complete excision and longer patient survival as compared to conventional microsurgery without navigation at least in univariate analysis.[118] A recent study shows that the apparent prolongation of survival with IGR might be because of selection bias. Those with favourable prognosis such as younger patients, smaller tumours and pathology other than glioblastoma are over-represented in series that report longer survival with IGR.[126] Addition of PET data to the MR data for IGR improves the extent of resection.[137,179] The problem with neuronavigation is the shift of targets that occurs after CSF drainage, brain shrinkage, displacement during removal of large lesions or ventricular opening. Frameless stereotactic technique is accurate for tumour volume of less than 30 ml and for lesions not near the ventricle.[11] Intra-operative MRI can address this deficiency of neuronavigation.

Intra-operative MRI to assess completeness of excision is logical, but is expensive and available in a very few centres only. The operating room needs to be dedicated to suit the magnetic environment. A low-field strength permanent magnet or an open short bore high-field strength magnet is used.[136] Contrast enhancement in the intra-operative MR has to be interpreted carefully as it may not be specific for residual tumour alone. Is intra-operative MRI a technical overkill or the future of brain tumour surgery? Only time will tell.[208]

5-aminolevulinic acid is a non-fluorescent prodrug that leads to intracellular accumulation of fluorescent protoporphyrin IX in malignant gliomas. This fluorescence, visible under violet-blue light distinguishes tumour from normal tissue and results in a better resection than with conventional white light. This requires appropriate modifications to the operating microsope.[229]

The strategies to save neurological function (see below) also help in clearing tumour from eloquent areas. Therefore, these strategies also help maximise resection of tumour.

Risks of Aggressive Resection

The risk of neurological worsening is foremost in the mind of the neurosurgeon attempting radical excision of gliomas. This fear is profound in dealing with lesions of the dominant hemisphere and in the eloquent (motor, sensory, speech or visual) areas.[237] Damage to the surrounding structures that may result from manipulation, excessive retraction or damage to important vessels (arteries or veins) in and around the tumour is likely to cause the deficit. Though the risk of neurological worsening is real it is often overestimated. In a series of 200 cases of supratentorial gliomas excised radically, hemiparesis became worse in four patients or developed post-operatively in three patients only. Similarly, dysphasia became worse in two patients and appeared post-operatively in six patients. In short, a new deficit developed in about 10% of cases. On the other hand, pre-operative hemiparesis recovered or improved in 41% of cases and pre-existing dysphasia recovered or improved in 12% of cases.[241] The Glioma Outcomes Project did not show any difference in the survival or functional outcome in the dominant and non-dominant hemispheric high-grade gliomas.[182] In a prospective study with aphasia measurement, left hemispheric tumour resection significantly improved language function in dysphasic patients, and was unlikely to impair language functions in non-dysphasic patients.[258] The same group reported worsening of language function in 9% of patients who were not aphasic before surgery and high risk of worsening of speech function in those already aphasic after stereotactic biopsy.[242]

Vascular damage is an important cause of morbidity in certain locations. The sites of tumour where the vessels are at risk are the medial surface of the frontal lobe (anterior cerebral branches), insular-opercular areas (middle cerebral branches)[113] and the medial temporal lobe (posterior cerebral branches). Venous damage is likely in the parasagittal region where the draining superolateral surface veins are vulnerable. A vein sparing excision may be done by performing multiple gyrotomies (Fig. 13). Vasospasm may occur after two or three days and cause ischaemic neurological deficit.[33] Peri-operative infarcts after tumour excision might mimic

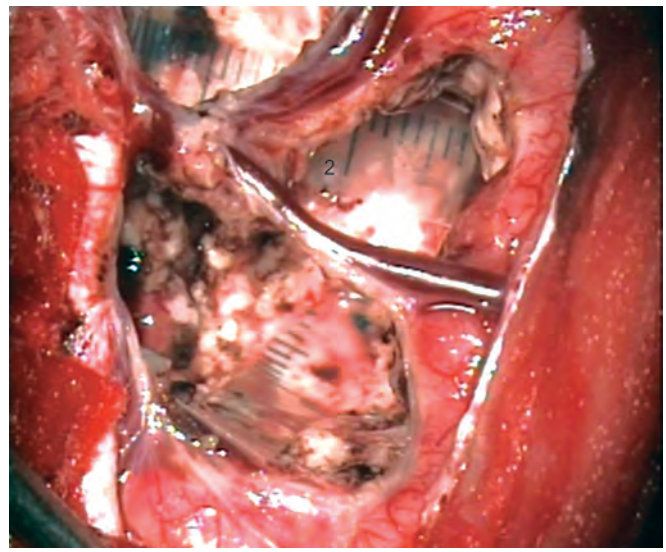


Fig. 13: Vein sparing glioma excision. This patient had a medial frontal astrocytoma grade 2. All the draining cortical veins were saved by making three transgyral approaches anterior, lateral and posterior to the veins. The exposures met at the depth. The lesion was excised totally

tumour residue or recurrence on enhanced MRI.[247] The tendency of brain surgery to set off a local version of consumption coagulopathy contributes to post-operative haemorrhage in the tumour resection bed or elsewhere in the brain. Such haemorrhage occurring in the unoperated tumour in a patient with multiple tumours is known by the fanciful name of "distant wounded glioma syndrome".[101] The incidence of venous thrombosis and pulmonary embolism is higher in patients with malignant glioma and they contribute to mortality.[209]

Strategies to Minimise the Risk to Neurological Function in Glioma Surgery

These have been summarised in Table 7. Broadly, they may be looked upon as anatomical or physiological methods.

Blood Oxygen Level Dependent imaging is known as functional MRI (fMR) and it can be used to map the eloquent areas pre-operatively. The increase in blood flow occurs after repetitive 12–30 seconds tasks (motor, sensory, visual or verbal). Artifacts are introduced by veins in the neighbourhood and by patient motion. In the ideal case, the spatial localisation accuracy is 5 mm, which is better than the 10 mm accuracy of stimulation methods (due to current spread). The fMR can detect areas deep within a sulcus, which can be missed by surface stimulation studies.[99] The fMR is best used with intra-operative neuronavigation. In one study no patient out of 19 had increased motor deficit after surgery on lesions near the motor area by the combined use of these two techniques.[262]

Motor pathway monitoring with motor evoked potentials (MEP) is especially needed for insular glioma surgery. Unchanged MEP or reversible deterioration of MEP indicates a good motor function while irreversible change indicates dense deficit.[161] Awake craniotomy, which is popular in epilepsy surgery, is less commonly used for glioma surgery. Resecting tumour just up to the point of producing deficit allows good functional recovery.[148] Awake language mapping shows much variability in the "language area".[198] The combination of fMR, neuronavigation and cortical stimulation during awake craniotomy has helped achieve excision of gliomas from Broca's area without producing any speech deficit in a Moroccan series of seven patients.[12] Pre-operative MR tractography to identify the pyramidal tract, integration of fibre tracking data with neuronavigation and MEP monitoring helped avoid motor deficit in removing tumours up to 1 cm of the pyramidal tract.[149] Intra-operative navigated 3D ultrasound angiography identifies hidden blood vessels and helps save them during resection. Ultrasound data can be easily updated and hence brain shift is not a problem in using ultrasonographic navigation.[195]

Table 7: Strategies to save neurological function in glioma surgery

Identifying veins, arteries, sulci with pre-operative imaging	A
Pre-operative functional magnetic resonance imaging	A
Awake craniotomy with or without cortical mapping	P
Intra-operative ultrasound angiography	A
Stereotactic/neuronavigation recognition of motor strip	A
Intra-operative evoked potential monitoring (motor, sensory)	P
Combinations of above techniques	

A—Anatomical methods
B—Physiological methods

Technical Aspects of Glioma Resection

Peri-operative dexamethasone therapy is now routinely used and it can be used for most diabetics also. Mannitol can be used if glycaemic control cannot be obtained on dexamethasone. In the past, generous flaps were advocated to allow for brain swelling and to identify normal structures. Nowadays, the recommendation is to tailor the craniotomy to the size of the lesion, thus minimising the exposure of the normal gyri and to ensure that the tumour is in the centre of the flap. Lesions close to the surface of a gyrus are approached through a gyrotomy and lesions at the depth of a sulcus are approached by the trans-sulcal approach. For lesions in the eloquent brain, a short (2 cm) cortical incision perpendicular to the axis of the gyrus directly over the tumour causes less damage than a far away incision on adjacent non-eloquent brain. This is because the dissection from a distant area would involve retraction, which is potentially more deleterious than incision. Oblique approaches also mean poor visualisation of tumour, less complete excision and difficulty in obtaining haemostasis. Self-retaining brain retractors must be used judiciously. Any cystic part is decompressed early to allow for brain relaxation.

Tumours up to 2–3 cm in diameter are best removed as a whole. Tumours larger than this will usually require internal decompression with suction-dissection, ultrasonic aspiration, evaporation with defocused CO_2 laser or shaving with diathermy loops depending on the consistency and vascularity. This should be followed by dissection in the apparent cleavage plane with the white matter. The dissection is best done with the spreading action of the bipolar forceps, while drawing the tumour towards the cavity of decompression. The developed plane is maintained with moist, tailed cottonoid patties. Often the decompression and peripheral dissection have to be done alternately. Ventricular entry during surgery does not necessarily promote CSF seedling.[61] Tumours involving a whole lobe may be approached by an anatomically defined lobectomy. The vessels to watch out for and protect have already been mentioned (see section "Risks of Aggressive Resection"). At the end of the resection, there must be crystal-clear haemostasis and the brain should be lax. Dural closure must be performed and, if needed, with a pericranial graft. The bone flap is replaced except in the rare case where the brain is not lax enough. Peri-operative anticonvulsants are necessary even in patients who have not had a seizure. Our practice is to obtain a non-contrast CT within 12 hours in all patients, even those who are

neurologically intact. Contrast MR is done within 24–72 hours to assess any residual tumour. Later than this, there can be enhancement of the resection margin due to the surgical trauma that might persist for several weeks. Enhancing residue predicts recurrence.[1]

In conclusion, for malignant gliomas, if tumour removal is decided upon, the aim should be to achieve maximal removal without risking damage to the surrounding normal brain. There has been an attempt at stratifying the risk and balancing it with the benefits of aggressive excision by pre-operative staging.[217] The pros and cons of resective surgery for glioma are summarised in Table 8.

Low-Grade Gliomas

Low-grade glioma presents a therapeutic dilemma. The patients are often in the prime of life. The sole symptom is seizures in about two-thirds of patients. The lesion might not show growth over several years. Early complete excision gives a reasonable chance of cure without any adjuvant therapy and avoids progression to an anaplastic tumour. Such an anaplastic progression has been found to occur in about 40% of patients.[128] But the catch is they often occur in functionally eloquent areas. In fact 82% of low-grade gliomas (compared with 54% of glioblastomas) were situated within functional regions in one study. The supplementary motor area and insula alone accounted for 52% of the sites for low-grade gliomas.[58] Injudicious surgery in these critical areas might make the patient worse off. Total excision is sometimes not possible because of the difficulty in defining the edge of the tumour from normal brain. The key questions that the neurosurgeon faces in dealing with a supratentorial non-optic pathway, non-enhancing lesion that is consistent with a non-pilocytic astrocytoma are:[131]

- Should the patient be observed without a tissue diagnosis?
- Should biopsy be done?
- Should tumour resection be done? If so should it be subtotal or gross total?
- Should radiation therapy be given?

Table 8: The pros and cons of resection of gliomas

Pros	*Cons*
Cytoreduction to facilitate adjuvant therapy	Oncologically curative resection not possible
Improves the existing neurological deficit	Neurological worsening after resection
Reduces intracranial pressure	Resection does not change the outcome substantially
Improves seizure control	No randomised trial showing resection is better
Avoids sampling error of stereotactic biopsy	Studies reporting superiority of resection have flaws (not multivariate analysis)
For certain low-grade tumours, adjuvant therapy is not effective	Extent of resection not objectively controlled with imaging in some studies

Observation

Observation seems to be a reasonable option with smaller non-enhancing lesions in neurologically intact, young patients who are imaged immediately after a seizure. This option is often exercised when the lesion is in an eloquent area. The possibility of a postictal evanescent imaging lesion necessitates that a repeat imaging is done in 3–12 weeks. Only if the lesion persists, one can be sure that it is not a mere postictal change. The observation period can be extended to years in patients who remain neurologically normal with adequate seizure control and have no increase in tumour volume on follow-up. This conclusion is bolstered by a retrospective comparison of "wait" and "no wait" groups of patients with suspected low-grade glioma. The rate of malignant transformation from the time of diagnosis and the survival or quality of life is no different in the two groups.[188] The patient must be made aware that 30% of lesions appearing to be low-grade gliomas might turn out to be anaplastic tumours or non-tumour lesions on biopsy.[103] The MRI occasionally discloses an entirely asymptomatic brain glioma (not even a single seizure) while looking for cervical spine disease. Such patients are also best managed by watchful expectancy.

Biopsy

It is an essential requirement before radiotherapy without resection. The rationale, the benefits and risks are similar to that discussed under malignant tumours (see above). The tendency would be to choose biopsy for lesions in eloquent or deep areas and resection for silent areas. The biopsy related morbidity and mortality is much less (near-zero) for low-grade tumours than for the malignant ones.[261]

Resection

Resection has been shown to give a survival advantage. The 5-year survival was 80% for total resection, 50% for partial resection and 45% for biopsy in low-grade astrocytomas.[178] The seizure control is also better after resection.[32] In a critical study of tumour volume, no recurrences were detected in those who had 100% resection in mean follow-up of 4.5 years. There was an inverse correlation between the residual tumour volume and the time for progression. The incidence of anaplastic transformation was also higher in those with larger pre-operative tumour volume and larger post-operative residual tumour volume.[14] The current practice is to choose early surgical resection for patients presenting with raised ICP, the older patients, those with enhancing or large lesions and tumours in non-eloquent areas. The strategies to maximise the excision and minimise the collateral damage (explained above) are all the more

relevant to low-grade gliomas. The Low-Grade Glioma Guidelines Team Members have evolved practice parameters based on evidence for adults with suspected or known supratentorial non-optic pathway low-grade glioma.[131] In general, age below 40 years, good KPS, seizure as a presenting symptom, imaging findings of circumscribed or homogeneous enhancement, hypometabolism on PET and microcystic or pilocytic histology predict a good prognosis.[128]

Radiotherapy

External Radiotherapy

While surgeons might disagree on how much tumour is to be removed, there is no question about the use of radiotherapy for malignant gliomas. This is in spite of the low radiation sensitivity of gliomas as compared to lymphoma or germinoma. Radiotherapy has the advantage of tackling the "unseen" tumour infiltration inaccessible to the surgeon's tools. The value of radiotherapy was documented three decades ago in the Brain Tumour Study Group's prospective randomised trial of malignant gliomas. It showed prolongation of median survival from 17 weeks for those who had no radiotherapy to 37 weeks for those given at least 50 Gy of radiation. The addition of nitrosourea chemotherapy did little to improve the survival.[254] The mean survival time was 48 months in those receiving greater than 60 Gy as compared to 21 months in those receiving less than 60 Gy in a recent study of 170 anaplastic astrocytomas.[165] Conventionally, 40 Gy of whole brain radiation (20 fractions in 4 weeks) has been followed by 20 Gy (10 fractions in 2 weeks) of booster to the tumour site. Radiation planning for the booster is ideally done with a mid-treatment T2W MRI as the tumour might have changed in size by then.[219] Avoiding whole brain radiation in favour of localised field radiation has been shown to improve the KPS without adversely affecting recurrence rate or time.[213] Accelerated hyperfractionation (1.2 Gy twice daily) allows the treatment to be completed faster. Hypofractionation (5 doses) is the standard technique of stereotactic radiotherapy. Though doses up to 90 Gy have been administered by conformal therapy techniques using micro-multileaf collimators and computerised treatment planning, there is no clear survival advantage.[157] Treatment planning with MRI is better than that with CT.[184] Intensity modulated radiotherapy has at least enabled reducing the irradiation to the normal tissues, if not enhancing the delivery to the tumour area.[158]

The efficacy of radiotherapy for low-grade tumours is less certain. For tumours such as pilocytic astrocytoma that are totally excised there is no need for radiotherapy. Short-term studies show no difference in outcome between irradiated and non-irradiated patients. The long-term studies show improvement in the 5-year or 10-year survival rates in the irradiated patients who have residual tumour and these studies demonstrate a dose related positive effect. Early radiotherapy (immediately after surgery) is preferable to delayed radiotherapy (at the time of demonstrable progression).[215] In eloquent areas, radiotherapy is the usual option for low-grade astrocytomas.[212]

Brachytherapy

It has been used along with external radiotherapy in an effort to increase the glioblastoma dose without increasing normal brain dose. Radioactive iodine (^{125}I) seeds and temporary iridium (^{192}Ir) wires have been used to improve the survival by about 6 months.[104] In low-grade astrocytomas brachytherapy has been tried, but not found to be a factor in determining outcome.[107] Since it requires a second operation for implantation, it can be considered an option for recurrent glioma requiring surgery. Methods to enhance radiation response have been surgical cytoreduction and the use of radiosensitisers. Most attempts with misonidazole and paclitaxel as radiation sensitisers have failed to improve the prognosis in glioblastoma. The COX-2 inhibitors are being tried now to enhance apoptosis induced by radiotherapy.[162]

Risks of Radiotherapy

Risks of radiotherapy that need to be highlighted are radiation necrosis and cognitive dysfunction. Radiation necrosis typically appears 1–3 years after therapy. Its incidence is reported as 5–24%, being higher at autopsy.[115] The risk increases significantly with higher radiation dose, fraction size and the subsequent administration of chemotherapy.[194] Radionecrosis has a predilection for the periventricular white matter and may be distant from the original tumour site. The imaging findings of radionecrosis can mimic enhancing tumour regrowth.[115] The MRS, PET and pMRS may be useful in distinguishing tumour from radionecrosis (see Table 8). The differential diagnosis might need stereotactic biopsy.[63] Radionecrosis might cause enough mass effect to warrant surgical excision if it does not respond to steroid therapy. Radionecrosis and tumour recurrence can coexist.[59]

Stereotactic Radiosurgery

SRS involves delivering the radiation dose on a single day with stereotactic precision to the tumour and its margin. The radiation can be from gamma ray sources (gamma knife radiosurgery) or from a linear accelerator (X-knife radiosurgery). SRS is a potential alternative in the management of small-volume low-grade astrocytomas in unresectable areas. It avoids the risks of larger-field fractionated radiotherapy.[74] Ten-year survival of 65% after SRS for low-grade astrocytoma has been reported.[255] Morphological redifferentiation in a case of grade 3 astrocytic tumour after gamma knife radiosurgery in to a grade 2 tumour, proved by methionone-PET, histology, Ki-67 labelling index and p53 expression is of importance from the glioma biology viewpoint.[232] Glioblastomas have also been treated by SRS. While the

small single institution studies showed some efficacy, the only randomised trial that has been done failed to yield any benefit for patients with glioblastoma who were treated with radiosurgery.[42] SRS has been done before and after external radiotherapy.

Chemotherapy

The initial attempts at chemotherapy with nitrosoureas [parenteral bischloroethylnitrosourea (BCNU) or oral chloroethyl-cyclohexyl-nitrosourea (CCNU)] did not add much to improve the bleak outlook of malignant glioma and posed significant toxicity risks.[254] BCNU has been re-evaluated for recurrent glioblastoma.[23] Combination therapy with procarbazine, CCNU and vincristine (PCV regime) was the next to be tried. There is a high incidence of haematotoxicity with this regime used for recurrent glioblastoma.[205] Carboplatin-vincristine therapy has been used for low-grade gliomas in children who cannot be given radiotherapy.[173] In order to reduce the systemic toxicity, intra-arterial chemotherapy and interstitial therapy have been tried. Intra-arterial cisplatin-etoposide chemotherapy (with or without osmotic opening of blood-brain barrier) administered prior to radiotherapy appears to be better than concomitant radiation and chemotherapy.[133] "Gliadel" is a BCNU impregnated wafer, implanted surgically in to the tumour resection bed that provides interstitial chemotherapy.[176] This approach carries the risk of brain oedema.

Temozolomide

It is an oral alkylating agent that received Food and Drug Administration approval in 1999 for recurrent anaplastic astrocytoma and in 2005 for newly diagnosed glioblastoma. The publication of the phase III randomised trial comparing radiotherapy alone and radiotherapy plus temozolomide for glioblastoma by the European Organisation for Research and Treatment of Cancer—Brain Tumour and Radiotherapy Groups and National Cancer Institute of Canada Clinical Trials Group was a landmark.[230] The dose used was daily temozolomide (75 mg/m^2/day, all seven days of the week from the first to the last day of radiotherapy), followed by six cycles of adjuvant temozolomide (150–200 mg/m^2 for 5 days during each 28–day cycle). This resulted in prolongation of median survival time from 12 months with radiation alone to 14.6 months when temozolomide was added. More significant was the rise in the 2-year survival rates (from 10 to 27%). Severe haematotoxic side effects occurred only in 7% of these chemoradiotherapy patients. Several other dosing schedules have also been tried. Methylguanine methyltransferase (MGMT) promoter hypermethylation (detected by a polymerase chain reaction test on frozen tissue) may be used as a predictive factor in selecting patients most likely to benefit from temozolomide.[52] The efficacy and relative safety of temozolomide has been shown in children[164] and in elderly patients.[36] Since children and the elderly tolerate radiation poorly, temozolomide alone has been used in these groups. The role of temozolomide in recurrent anaplastic astrocytoma is mentioned later (see section "Treatment of Recurrence"). Chemotherapy-alone approach has been used for low-grade gliomas in the hope of avoiding long-term side effects of radiotherapy. Temozolomide has been tried as sole adjuvant therapy for the chemosensitive low-grade tumours with 1p/19q deletion.[92] Topotecan, a topoisomerase inhibitor, has been used with some success in childhood high-grade gliomas.[253]

The adverse effects and costs are the real deterrents to the widespread use of chemotherapy. Results are better when chemotherapy is administered by a medical oncologist according to strict protocol.

PROGNOSIS

The prognosis of glioblastoma and anaplastic astrocytoma remains poor despite significant recent advances. A recent study showed that, although the tumours are being diagnosed earlier as compared to three decades ago and that the peri-operative mortality and morbidity have come down, there was no difference in the post-operative survival time in high-grade gliomas over the decades.[167] In retrospective studies reporting multivariate analysis, the universally agreed predictors of prognosis are the age of the patient, pre-treatment Karnofsky performance score and the use of radiotherapy for both glioblastomas and anaplastic astrocytomas.[121] The less consistent predictors are sex (females carry better prognosis), extent of surgical resection, pre-operative seizure as a symptom, imaging variables, histological grade, proliferation index and molecular markers.[100,123,128,155,172,199,218,240] These factors have already

Table 9: Compilation of data from the literature on outcome of astrocytomas, anaplastic astrocytomas and glioblastomas

Tumour	*OS*	*MST*	*PFS/TTP*	*Survival percentage*			
				1 year	2 years	5 years	10 years
Astrocytoma		118 months[132]	13% at 5 years[14]	-	-	50-80%[128,178]	39[215]-65%[255]
Anaplastic astrocytoma	22–42 months[98]	21–48 months[39,165]	27–35% at 5 years[263,183]		14–84%[155]	17–54%[165]	?
Glioblastoma multiforme	14 months[23]	13 months[121]	7.2 months[23]	53%[217]	14%[217]	5%[218]	Rare[266]

Note: OS = Overall survival; MST = Median or mean survival time; PFS/TTP = Progression free survival/Time to progress

been mentioned in the relevant sections. Table 9 gives a general idea of the outlook in astrocytomas and glioblastoma. It must be remembered that the figures from various studies are not directly comparable due to the differences in selection criteria, treatment methods and outcome measurement parameters.

A six-tier grading scheme has been proposed to stratify the surgical risk and outcome in gliomas. This scheme identifies the five most significant risk factors of age, preoperative KPS score, previous radiation therapy, depth of tumour invasion and location in eloquent regions.[252] It is traditional to measure the overall survival, median or mean survival time, progression free survival and survival percentage as a function of time. It is important that we include quality of life parameters in the assessment.[6] Cognitive changes can be not only due to tumour or surgery but also due to radiotherapy, and only a few patients are capable of fully independent living.[3]

Although the median survival in glioblastoma multiforme is about 1 year, 3–5% of patients survive for greater than 3 years.[110] Young age, presence of oligodendroglial foci, giant cells, low proliferative index, p53 expression and MGMT promoter hypermethylation have been observed in the long term survivors.[49,110] Two cases of glioblastoma surviving for a decade have been reported.[266]

RECURRENCES

The most common cause of death of a patient treated for a supratentorial glioma is recurrence. For a given patient, irrespective of histology, there is an uncanny uncertainty regarding the time of recurrence. It is easy to imagine a glioblastoma recurring, but even low-grade tumours may recur after imaging proved complete excision and after a considerable time lag.[206] Recurrence generally occurs at the site of the original tumour or within 4 cm from it.[68] This clinical finding correlates well with the experimental fact that glioma cells have been cultured from the histologically normal brain within 4 cm of the tumour margin.[221] Occasionally, the tumour may spread along the CSF pathways and present at a different site in the neuraxis. In such cases, genetic profiling of the first and second tumour may help establish if the second tumour is a distant recurrence or a new tumour.[248] Technically, a tumour might be deemed to have recurred only when there is evidence of complete excision in the early post-operative contrast imaging study. If there had been a residue, the more appropriate term is re-growth or progression. In clinical parlance, the two terms are often used interchangeably. Some studies have stipulated a 25% increase in tumour area or volume on imaging to be deemed as recurrence.[85] In some patients, a small residue that had not shown any progression over time on serial imaging surveillance might start proliferating all on a sudden and take on all the characteristics of a recurrent tumour. In most cases, the recurrent astrocytoma is more anaplastic than the initial tumour. Indian series of recurrences of supratentorial gliomas was published in 1997.[238]

Clinical Features of Recurrence

A recurrence manifests with recurrent seizures, symptoms of raised ICP or progressive neurological deficit. Epileptic fits occurring for the first time following treatment, or recurring after a seizure free post-operative period, indicate a recurrence.[239] Recurrence of neurological deficits that had improved post-operatively or appearance of new neurological deficits should arouse suspicion of tumour recurrence. Clinical deterioration does not necessarily imply tumour recurrence. In one-third of the patients clinically suspected to have a recurrence, there may be other factors such as reactive oedema following chemoradiotherapy, postictal weakness, infection, haemorrhage or radionecrosis that mimic symptoms of tumour recurrence. Equally, not all recurrences produce symptoms as some are detected only on imaging surveillance.[85]

Imaging of Recurrence

The MR is better than CT in investigating a possible recurrence. Most recurrent tumours are more T1 hyperintense than the original tumour and enhance with gadolinium. In one study, in nine out of 32 patients, the first post-radiotherapy MRI showed progressive enhancement that would suggest recurrence. In three of these nine, the MRI improved or stabilised for 6 months without additional treatment, thus ruling out recurrence.[47] PET demonstration of hypermetabolism indicates recurrence, but this is not as infallible as it was thought to be.[166] The MR and CT signs of radiation necrosis may be indistinguishable from recurrent tumour. The similarities and differences are enumerated in Table 10.[85] The difficult case might require stereotactic biopsy.[63] It has been recently found that increased CSF matrix metalloproteinase (MMP-9) activity could be a marker of recurrent malignant glioma, before any changes are detectable on MRI.[264]

Treatment of Recurrence

The choices for recurrent glioma are re-operation, radiosurgery, radiotherapy, chemotherapy and comfort therapy.

Re-operation

Re-operation is considered under the following conditions:

- Young age
- Low-grade of initial tumour
- Progression free survival of at least 1 year or longer
- KARNOFSKY performance score greater than 70
- Tumour causing a mass effect
- Tumour in non-eloquent area.[85]

Biopsy is occasionally required for differentiating true recurrence from imaging mimics. Except in this situation, the surgery is always resective and it aims at maximising tumour removal without provoking new neurological deficit. Surgery also allows interstitial chemotherapy and brachyradiotherapy. In a study of

Table 10: Imaging comparison of recurrent glioma and radionecrosis

Modality	*Recurrent/residual glioma*	*Radionecrosis*
Location	At previous tumour site, rarely at distant site	At previous tumour site, not uncommonly distant or contralateral side
Contrast enhanced Computed tomography or contrast enhanced Magnetic resonance	Ring enhancing	Ring enhancing, soap bubble or Swiss-cheese appearance
Oedema and mass effect	Present	Present
Central necrosis	Present	Present
Serial imaging	Growth	Growth, stabilisation or regression
Magnetic resonance spectroscopy- N-acetyl aspartate/creatinine ratio	Decreased	Increased
Perfusion magnetic resonance-regional cerebral blood flow	Increased	Decreased
Positron emission tomography	Hypermetabolism	Hypometabolism

46 patients undergoing re-operation for glioblastoma, 28% improved, 49% were stable and 23% experienced decline in Karnofsky performance levels. The median survival after re-operation was 36 weeks while, it was only 23 weeks in those who did not undergo re-operation.[8]

Radiosurgery

Radiosurgery is usually reserved for small recurrences and it can be done for those who have already had external radiotherapy. It resulted in median overall survival of 10 months in a group of 32 patients with glioblastoma.[40] Most radiotherapists would desist from giving a second course of radiation to the same brain field. In cases where the recurrence occurs after 1 or more years of the initial therapy and for those in whom an adjacent field needs radiation, re-radiation therapy may be considered. Re-irradiation therapy gave 10 months of median overall survival and clinical response in one-third of 42 patients.[251]

Chemotherapy

It is offered to patients who have recurrence within the 1st year of initial treatment and those in whom re-operation is not a choice (older age, poorer Karnofsky performance score, location in eloquent area, lack of mass effect). Temozolomide is the choice for those who have not had this drug earlier. Higher doses and one week on/one week off temozolomide schedule have resulted in median progression-free survival of 5 months in glioblastoma.[259] Cyclophosphamide has been used for temozolomide resistant recurrences.[31] Multi agent chemotherapy does not confer an advantage and poses a significant toxicity.[205] It is hoped that the emerging therapies (see below) might improve the bleak outlook of recurrent glioma.

EMERGING THERAPIES

Molecularly Targeted Therapies

The past decade has seen a spate of novel approaches to treating malignant gliomas. Broadly, they target growth promoting factors or stop the signalling pathways. These include EGFR tyrosine kinase inhibitors (gefitinib and erlotinib), mammalian target of rapamycin (mTOR) inhibitors (temsirolimus and everolimus), and VEGFR, protein kinase C-beta, and other angiogenesis pathways inhibitors (vatalanib, bevacizumab and enzastaurin).[171,244] These are generally not useful as sole strategies, but are used in combination with conventional methods. There are phase 2 studies of some of these agents (e.g. bevacizumab and irinotecan) that are promising, but randomised studies are needed to prove the efficacy of molecularly targeted therapies.[202] Notch activation contributes to Ras-induced transformation of glial cells and glioma growth. This pathway may be a new target for glioblastoma therapy.[93] Thalidomide has potent antiangiogenetic properties and it has been combined with temozolomide therapy.[10] Anti mutagenic therapy with chloroquine has been added to conventional regimens with good effect.[224]

Convection Enhanced Delivery

Convection enhanced delivery of therapeutic macromolecules through a stereotactically implanted catheter in to the tumour ensures coverage for a 2 cm margin of brain around the tumour. This is far more than the 2 mm penetration of drugs from implanted wafers. The chimeric macromolecule delivered is a conjugate consisting of a monoclonal antibody that specifically attaches to the tumour cells in preference to normal cells and another portion that is tumouricidal. The attachment may be to partly specific receptors such as transferrin or interleukin-13 receptors or highly specific tumour receptors.

The tumouricidal portion may be a biotoxin (modified pseudomonas/diphtheria toxin or plant derived ricin) or a radioisotope (^{131}I). This delivery method circumvents the blood brain barrier, provides high local drug concentrations and minimises systemic exposure.[246,249] Using biodegradable polymer microspheres is another approach to deliver therapeutic macromolecules in to the tumour. BCNU and interleukin-2 have been tried in the experimental setting in this fashion.[190] 5-fluorouracil has also been delivered using this vehicle stereotactically in the clinical setting.[144]

Gene Therapy

It has been explored for malignant gliomas. One concept is to deliver a cytotoxic gene in to the tumour cell through a viral vector. Retrovirus, adenovirus and herpes simplex virus have been tried as the vectors. The virus can be redirected in such a way as to specifically attach to tumour specific sites such as fibroblast growth factor receptor on the tumour cells and the endothelial cells in the tumour. The cytotoxic effect can then be increased with the antiadenoviral drug, ganciclovir.[268] The interested reader is referred to a review article for details of genetic therapy in gliomas.[139] Use of neural stem cells (NSCs) as delivery vehicles for therapeutic tumour-toxic molecules is aimed at targeting disseminated tumour pockets as NSCs possess tropism for infiltrating tumour cells.[60]

Other Drugs

Matrix metalloproteinase (MMP) activity in tumour cells controls the invasive nature of the tumour. This can be blocked by cannabinoids which downregulate the MMP-2 gene.[21] Doxycycline also blocks MMP-9 activity.[264] Another novel approach is the use of COX-2 inhibitors (celecoxib) and peroxisome proliferator-activated receptor-gamma agonists (pioglitazone) to enhance the chemosensitivity and enable low-dose chemotherapy.[79]

Immunotherapy

It has had a long but unsuccessful history. Non-specific therapy using Bacillus of Calmette and Guerin (BCG) vaccine or interferons has failed. Adoptive immunotherapy using activated lymph node derived T cells was an early approach.[180] Only recently, specific glioma associated antigens have been identified. These include EphA2, IL-13Ralpha2 and Survivin.[170] Vaccinations with autologous fibroblasts retrovirally transfected with TFG-IL4-Neo-TK vector admixed with irradiated autologous glioma cells or with type-1 dendritic cells loaded with autologous tumour lysate have been tried. The problem is the time taken to produce these vaccines from the patient's own cells.[169] Another approach is using whole-cell vaccine comprising autologous tumour cells genetically modified by a transforming growth factor-beta2 (TGF-beta2) antisense vector. Blocking secretion of the immunosuppressive molecule TGF-beta in this manner should inhibit one of the major mechanisms by which tumour cells evade immune surveillance and should lead to clinically effective antitumour immunity.[62] The efficacy of such treatment approaches need to be proved in larger studies.

The benefits of surgery, radiotherapy and chemotherapy for malignant gliomas seem to have hit a plateau. While phase I and phase II trials of emerging therapies appear promising, many do not pass muster in phase III testing.[177] The neurosurgeon has to decide on the extent of aggressive excision based on several factors such as age, pre-operative Karnofsky performance score and location of the tumour. The non-availability of sophisticated technology to the surgeon is a limiting factor, especially in third world nations, that drives management decisions. Protocol driven management should not lose sight of the individual patient's needs, aspirations and affordability. The neurosurgeon must keep abreast of the newer treatment modalities to face the inquisitive patient's relatives, who have learnt of the "latest" therapy from the Internet.

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134 Cerebellar Astrocytomas

Ramakrishna Easwaran

INTRODUCTION

"The cerebellar astrocytoma offers the best prognosis for normal survival of any brain tumour in any age group"—so said Matson in his monograph on Paediatric Neurosurgery.[37] Pilocytic cerebellar astrocytomas of childhood especially the cystic variety behave in a rather benign manner with several reports of long survival even after incomplete resection.[34] The same is not true of other histological types and in tumours that arise in adults.

INCIDENCE

Mishra et al. reported the incidence of cerebellar astrocytomas to be 23% out of 419 cases of childhood brain tumours seen at All India Institute of Medical Sciences, New Delhi, India.[39] Cerebellar astrocytomas constituted 11.6% of 482 intracranial gliomas reported from Christian Medical College and Hospital Vellore, India.[12] In a recent population based study from Switzerland, the incidence of pilocytic astrocytoma was 4.8 per 1 million per year, with 40% occurring in the cerebellum.[10]

Cerebellar astrocytoma is predominantly a tumour of childhood, 75% occurring in the first two decades of life. The youngest reported case of cerebellar astrocytoma was in a 5-week-old infant, which raises the possibility of origin *in utero*.[21] The average age at presentation was 13 years in Cushing's series and many patients were then blind with chronic papilloedema at presentation. The median age at presentation has dropped to 6–8 years in most modern series, indicating that these tumours are being diagnosed earlier, thanks to advances in imaging.[13,47] Cases have been reported in the sixth decade too, but these have often been recurrences after several decades, or histological variants such as xanthoastrocytomas.[24,49]

PATHOLOGY

Gross Pathology

Cerebellar astrocytoma is described classically as arising from one cerebellar hemisphere with a well-defined cyst containing yellow-brown fluid and a mural nodule. In two different series, the location was 28% in the cerebellar hemisphere, 30% in the vermis and the rest were tumours involving both the hemisphere and the vermis.[12,25] The tumours can be divided into the true cystic, false cystic and solid types.[25] The differences between the two cystic types are set out in Table 1 and Figures 1 to 3.

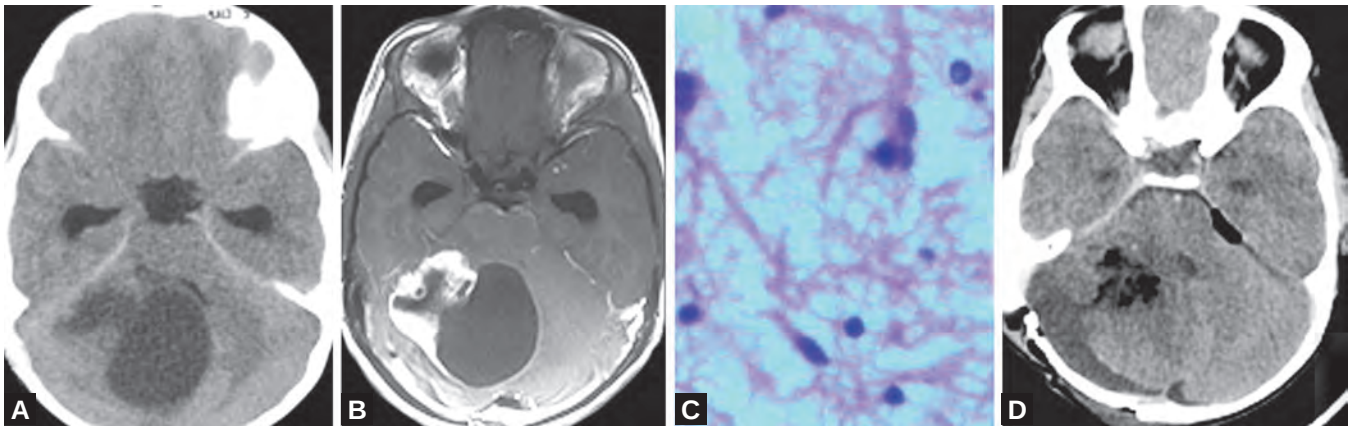
However, a recent report suggests that enhancing cyst walls, which appear smooth and shiny at surgery, may be non-tumourous.[6] There may not be a mural nodule at all, the entire tumour being in the cyst wall. Even the so-called solid tumours may have microcystic areas. Brainstem infiltration is more common in the solid and midline tumours, a reflection of their more malignant histology.[59] A rare case of benign cerebellar astrocytoma with extensive leptomeningeal spread has been reported.[46]

Microscopic Pathology

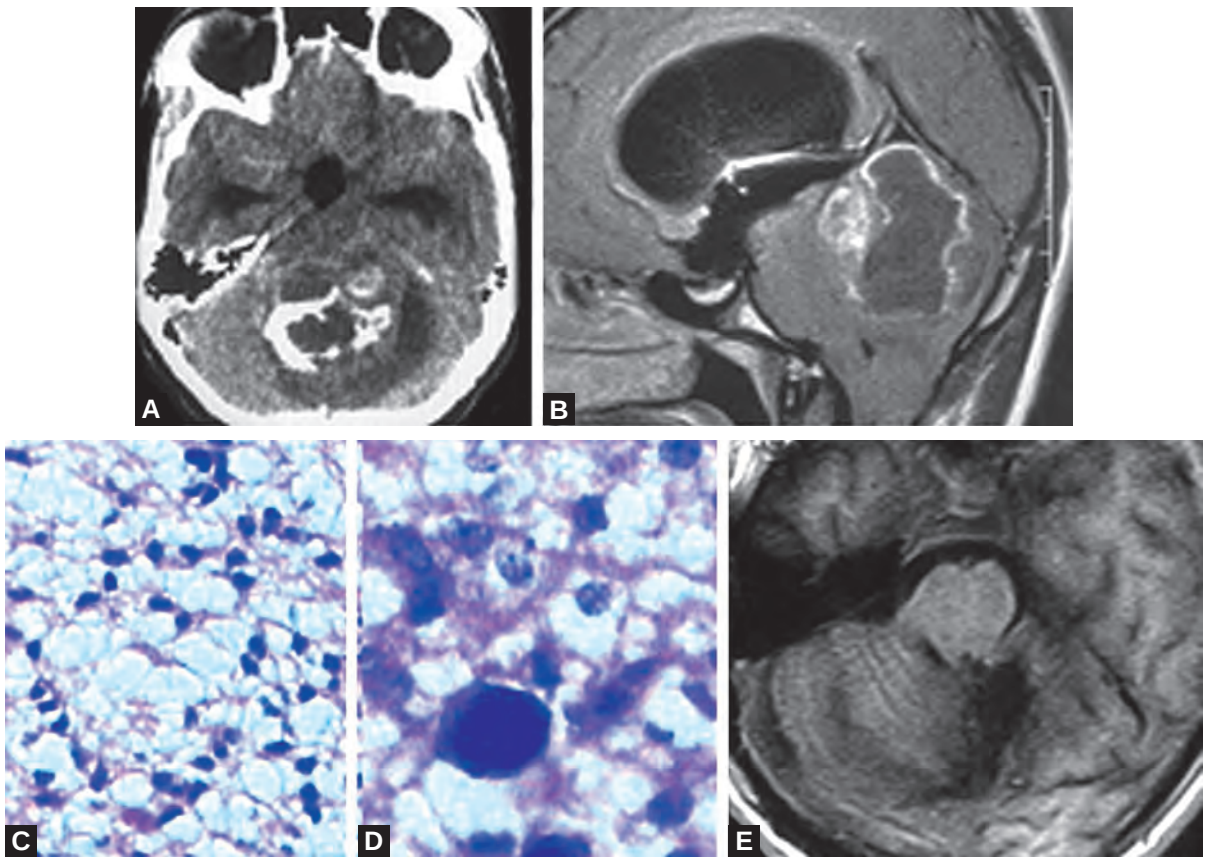
Pilocytic astrocytes, which are "hair-like" elongated bipolar astrocytes, are the histological hallmark of the paediatric cerebellar astrocytoma.[50] However, the most abundant cells in these tumours are the fibrillary astrocytes, arranged in alternating compact and loose areas resembling a honeycomb. Rosenthal fibres, the stout eosinophilic cytoplasmic rods made of heat shock protein, are more common in the compact zones. The absence of nuclear pleomorphism, mitotic figures, endothelial proliferation, necrosis and haemorrhage ensures that these tumours are graded as World Health Organisation (WHO) grade 1 (Fig. 1C). The tumour cells are positive for glial fibrillary acidic protein. About 20% of the paediatric cerebellar astrocytomas are histologically

Table 1: True and false cystic cerebellar astrocytoma

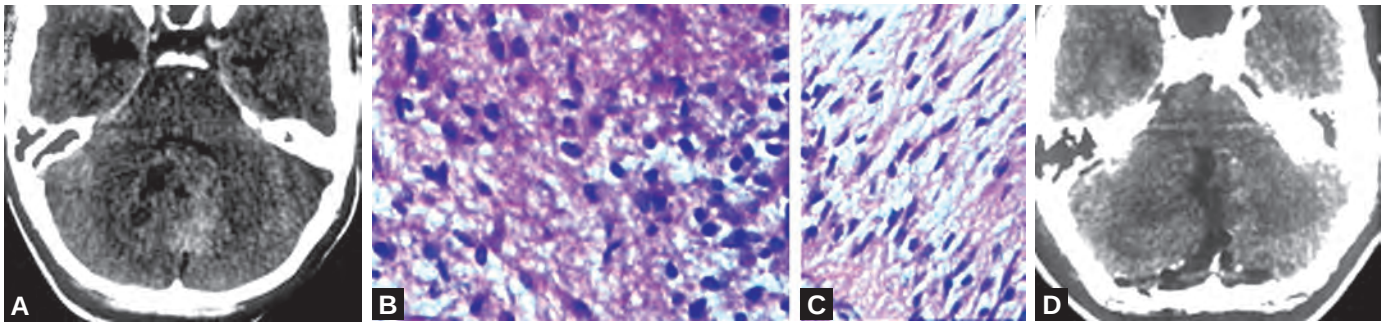
True cystic	*False cystic*
Mural tumour nodule within a glial cyst	Tumour lining the wall of the cyst
No tumour in the wall, which is thin	Wall is thicker, varies in thickness from part to part
Wall does not enhance with contrast	Wall enhances with contrast but to a varying degree
Wall shiny and translucent	Wall shaggy and opaque
Cyst content clear	Cyst content not always clear, usually xanthochromic



Figs 1A to D: (A) Non-contrast computerised tomography (CT) and (B) Gadolinium-enhanced magnetic resonance imaging of a 2-year-old child with cystic and solid hemispheric cerebellar tumour. Note the lack of enhancement in the wall of the cyst. The tumour was approached through a lateral suboccipital craniotomy in the prone position. Though the cyst wall appeared shiny, since it peeled off easily, it was excised along with the entire solid portion. (C) Histologically, there was only reactive gliosis in the wall while the solid part was a low-grade astrocytoma. Thus, this tumour may be described as a true cystic tumour. The child had a smooth post-operative course with no deficits. (D) The post-operative contrast CT done within 24 hours showed no enhancing remnant. Note the restoration of the fourth ventricle, reduction in the hydrocephalus as evidenced by the size of the temporal horns and the replacement of the craniotomy bone flap. The child did not need any shunting or ventricular drainage



Figs 2A to E: (A) Contrast computerised tomography (CT) and (B) Gadolinium-enhanced sagittal magnetic resonance imaging (MRI) of a 20-year-old male with cystic and solid midline cerebellar tumour. Note the calcifications in the tumour on CT and the crinkled enhancing nature of the wall of the cyst in MRI. The tumour was approached through a midline suboccipital craniotomy and vermiotomy in the prone position. The cyst wall appeared shaggy and did not peel off easily. The wall was excised completely along with the entire solid portion. (C) Histologically, the tumour showed astrocytic elements in the cyst wall. (D) The calcifications and "poached egg" appearance of oligodendroglioma in the solid part. Thus, this tumour may be described as a false cystic tumour. The patient had a stormy post-operative course with supratentorial extradural haematoma within 6 hours needing evacuation. By the 3rd day he required ventriculoperitoneal shunting for persistent hydrocephalus. He then had cerebellar mutism. Delayed supratentorial subdural hygroma appeared in the 6th week and was evacuated. (E) The post-operative MRI done in the 6th week showed no remnant tumour. The patient showed modest improvement with bromocriptine therapy over the next 4 months



Figs 3A to D: (A) Contrast computerised tomography (CT) of an 18-year-old female with poorly demarcated solid midline cerebellar tumour. Note the focal hypodense areas that appear to be cysts within the solid tumour. The tumour was approached through a midline suboccipital craniotomy and vermiotomy in the prone position. There were no cystic areas and the tumour had variable demarcation with the surrounding white matter. (B) Histologically, the tumour was a high-grade astrocytoma with compact cellular areas with cellular/nuclear pleomorphism. (C) Loose areas of recognisable astrocytes. (D) The post-operative contrast CT showed complete excision. The patient had self-limiting aseptic meningitis (in spite of dural closure and bone flap replacement) and mild residual ataxia but was otherwise well. She was given radiotherapy

classified as the diffuse fibrillary astrocytoma (Table 2). This group was reported by some to have a poorer prognosis than the juvenile pilocytic astrocytoma.[19] Others feel that there is no difference in prognosis between the two varieties as long as the lesion is totally excised.[4,34]

Malignant Astrocytomas

Anaplastic (WHO grade 3) astrocytomas account for 9–12% of cerebellar astrocytomas.[50,59] Malignant astrocytoma (Figs 3B and C) may either arise *de novo* or may result from malignant progression of a pilocytic astrocytoma.[2] Such a progression may occur even after three decades of original diagnosis.[9] Anaplasia may be localised to a focal region within the pilocytic astrocytoma and this focus appears radiologically distinct.[33] The solid nature and the tendency to infiltrate the brainstem or peduncle limit the extent of resection of anaplastic astrocytomas. Malignant astrocytoma has been reported to occur at the site of a previously treated medulloblastoma.[43]

Other Histological Types

Primary oligoastrocytoma is recognisable by the calcification pattern (Fig. 2D). Oligoastrocytoma metastasising from the frontal lobe to the cerebellum has also been reported.[55] Pleomorphic xanthoastrocytomas are rare in the cerebellum, but have been reported in a wide range of ages.[32,49] The surgeon should be aware that these tumours are harder in consistency (due to desmoplasia) and that they may involve the overlying dura or venous sinus. Glioblastoma multiforme is rare in the cerebellum, but carries as poor a prognosis as its supratentorial counterpart.[22] A case report of a patient who had a normal computerised tomography (CT) scan 2 months before the diagnosis of a large vermian glioblastoma suggests that the tumour arises *de novo* and grows rapidly, even in children.[31] Dysembryoplastic neuroepithelial tumour of the cerebellum is very rare.[30]

Table 2: Histological subtypes of cerebellar astrocytic tumours

Histological subtypes of cerebellar astrocytic tumours
Pilocytic astrocytoma (juvenile)
Diffuse fibrillary astrocytoma (low-grade)
Oligoastrocytoma
Anaplastic (malignant) astrocytoma (high-grade)
Glioblastoma multiforme
Lipidised glioblastoma[32]
Pleomorphic xanthoastrocytoma

Tumour Biology

Vascular endothelial growth factor expression and changes in the blood-brain barrier have both been proposed as mechanisms for the cystic change in pilocytic cerebellar astrocytomas.[35,36] In one study of 78 cases, none of the novel parameters such as MIB-1 labelling index, flow cytometry, *p53* immunoreactivity or apoptosis rate significantly predicted recurrence or survival, but they indicated substantial biological variation among cerebellar pilocytic astrocytomas.[23] The occurrence of cerebellar astrocytoma in association with ataxia-telangiectasia, Albright's disease, von Hippel-Lindau disease and neurofibromatosis suggests a genetic mechanism of causation, quite unlike the sporadic cerebellar astrocytoma.[29,40,45,54] The gene expression profiles of pilocytic astrocytomas differ significantly from those of diffusely infiltrating low-grade gliomas and their benign biologic behaviour may be related to up-regulation of immune defence-associated genes.[26]

CLINICAL PRESENTATION

The symptoms and signs vary with the age of the patient and the site of the tumour. In infancy, cerebellar tumours present with enlarging head size due to hydrocephalus, irritability and vomiting. The tense fontanel, rather than papilloedema, indicates raised pressure at this age. Older children and adults complain of headache, seen in about 80% of patients.[13,59] The headache is usually frontal, but

may later become generalised. Localised headache in the occipital region is rarely an early symptom. Headache occurring in the early morning hours has been attributed to sleep induced hypoventilation causing hypercarbia and postural cerebrospinal fluid (CSF) accumulation in the intracranial compartment during recumbency. The headache may be accompanied by vomiting, diplopia or irritability. Vomiting relieves the headache, probably due to the associated hyperventilation. Amaurosis fugax, especially on rising from the stooped posture, is a symptom of advanced papilloedema and may indicate impending loss of vision.

Vomiting alone, without headache, is also seen, though this story is more typical of a fourth ventricular tumour such as ependymoma. "Robin's rule" states that if the vomiting occurs before the headache, it is an ependymoma but, if the headache occurs before the vomiting, it is a medulloblastoma or astrocytoma.[60] Many children have undergone gastroenterological investigations for persistent vomiting before their posterior fossa tumour is detected. Some children arrive at the emergency department with brief episodic loss of consciousness and tonic stiffening of the limbs during the height of the headache—the so-called "hydrocephalic fit". Torticollis to the side of the tumour may be a symptom, sometimes a sole symptom.[58] This symptom indicates tonsillar herniation. Presentation with a spontaneous haemorrhage into the tumour cyst is known, but rare.[38]

The mean duration of symptoms before presentation was 2 years in Cushing's series (1930s) for childhood cerebellar astrocytoma. It came down to 11 months in the 1950s and is down to about 6 months in most modern series.[13,21,59] Clinical examination reveals signs of raised intracranial pressure (ICP) (80%) and those of cerebellar dysfunction (70%).[13,59] Neck stiffness without Kernig's sign in an afebrile patient indicates tonsillar herniation. Gait and stance ataxia denote a vermian lesion while unilateral appendicular ataxia is seen in the deeper hemispheric masses. Horizontal nystagmus is found in midline or lateral cerebellar lesions while vertical nystagmus or gaze palsy is caused by anterior vermian lesions compressing the collicular region. Acute concomitant esotropia, unilateral hearing loss mimicking an acoustic schwannoma and peduncular hallucinosis have been other reported rare presentations.[15,42,56]

NEURORADIOLOGY

While magnetic resonance imaging (MRI) has superseded CT in the detection and characterisation of posterior fossa tumours, a good quality CT may often yield the necessary information for management of the patient. Dilatation of the third and lateral ventricles is seen in the majority of patients, as the tumours tend to be large enough to cause compression of the fourth ventricle at the time of diagnosis. Periventricular lucencies suggest high intraventricular pressure. The solid part of the tumour is hypodense in non-contrast CT as compared to the cerebellum. The cystic part is hypodense compared with the cerebellum or the solid part, but it shows a higher attenuation coefficient as compared to the CSF due to its protein content (Fig. 1A). The tumour shows a varying degree of demarcation with the surrounding normal tissue. Calcific foci are uncommon, being reported in about 15%.[61] Calcification is displayed more graphically by CT than MRI and extensive calcification should suggest oligoastrocytoma (Fig. 2A). Pilocytic astrocytomas enhance well, while the more fibrillary variety may not. The enhancement may be non-uniform due to the presence of microcysts in the solid part of the tumour (Fig. 3A). The cyst wall enhances in the false cystic tumour due to the presence of tumour in the wall (Fig. 2B).

The cystic and solid parts of the tumour appear hypointense in T1-weighted magnetic resonance images and hyperintense in proton density or T2-weighted images. The solid part is hyperintense to the cerebellum in T2-weighted images and the cystic part slightly hyperintense to the CSF in T1-weighted images.[3] Presence of haemosiderin causes a rim of hypointensity in the cysts suggesting an old bleed. Gadolinium enhancement patterns are similar to CT contrast enhancement. Haemangioblastoma, ependymoma, medulloblastoma, dermoid tumour, choroid plexus papilloma, metastasis, tuberculoma and cerebellar abscess must be considered in the differential diagnosis. Magnetic resonance spectroscopy (MRS) may help in narrowing the differential diagnosis. Taurine detection by short-echo proton MRS is present in medulloblastoma and absent in cerebellar astrocytoma.[41]

MANAGEMENT

In the past, it was a routine practice to place a ventriculoperitoneal shunt a week or so before resecting cerebellar astrocytomas. The current opinion is against pre-operative routine shunting for all the disadvantages given in Table 3.[34]

Table 3: Pre-operative shunting for cerebellar astrocytoma

Advantages	*Disadvantages*
Rapid symptom improvement	Upward transtentorial herniation[17]
Life/vision saving in an emergency	Tumour dissemination through the shunt[28]
Lax brain during resective surgery	Shunt block/infection prior to resection
Luxury of converting an emergency into an elective operation	Increased risk of infection after posterior fossa surgery
	Supratentorial subdural haematomas
	Shunt no longer necessary in the long-term[14]
	Higher cost
	A rare patient may refuse resectional surgery, as the patient is relieved of symptoms by the shunt

Pre-operative dexamethasone preparation suffices in most cases. Peri-operative external ventricular drainage has been employed by some.[14] Endoscopic third ventriculostomy seems to be a better option when relief of hydrocephalus is needed before or after posterior fossa tumour extirpation.[51]

Surgery

Goal

Total excision of the tumour is the goal of cerebellar astrocytoma surgery. It used to be advocated that removal of the mural nodule in case of a cystic astrocytoma was all that was necessary if the cyst wall was thin and transparent. However, the uncertainity of tumour growth along the cyst wall makes it desirable to excise the tumour completely. Recurrence is likely to occur if tumour is left behind.[4,23] However, long-term survival following subtotal resection is well known. Invasion of the brainstem by the tumour is the only reason for partial or subtotal excision in current neurosurgical practice.

Approach

The surgical approach to a cerebellar astrocytoma is decided by the location of the tumour as summarised in Table 4. Positioning of the patient is a matter of the surgeon's preference. The sitting position, which could be a viable alternative to any of the positions advocated in Table 4, is not favoured in many departments nowadays due to its inherent complications such as air embolism, tension pneumocephalus, supratentorial haematoma, etc.

Exposure

Preparation is made for placing an occipital burr hole for ventricular drainage even though this is required only occasionally. The availability of powered bone tools helps in fashioning a craniotomy flap in the posterior fossa as opposed to craniectomy. This is especially easy in children (Fig. 1D). Apart from the obvious cosmetic and psychological value, the incidence of pseudomeningocoele and pain at the operation site are less on replacing the bone flap at the end of the tumour excision.[20] Should a re-operation be needed later, the planes are easier to define if the bone has been replaced. The posterior rim of the foramen magnum can be removed with the bone flap and replaced. Removal of the posterior arch of the atlas is not routinely necessary. It is generally safe to cross above the transverse sinus or torcula with a craniotome. Titanium ligating clips are preferred to sutures or bipolar coagulation for controlling the bleeding from the occipital and circular venous sinuses while opening the dura. The cystic component can be tapped transdurally to relax the brain before formally opening the dura. Cyst drainage causes the cerebellum to collapse and this may lead to intra-operative or post-operative subdural bleeding from the bridging veins. Such a complication must be foreseen and prevented. Placement of wet gelatine sponge, head elevation and patiently waiting are effective in controlling the bleed from the bridging veins. Desperate blind bipolar coagulation only worsens the bleeding. Wide opening of the arachnoid of the cisterna magna is avoided to prevent tumour spread along the subarachnoid space.

Tumour Excision

For midline tumours a vertical vermis incision through the avascular midline is well tolerated and does not worsen the gait ataxia permanently. A paravermian vertical incision is to be avoided as it carries a higher risk of post-operative mutism.[11] For lateral tumours, it is preferable to incise the cerebellar hemisphere horizontally along the direction of the folia. The mural nodule, all solid parts and contrast enhancing or shaggy cyst walls are excised under the magnification of the operating microscope. Small mural nodules can be excised as a whole. The bigger solid masses may require internal debulking (done elegantly with ultrasonic aspirator) before dissection of the plane between the tumour and the surrounding normal cerebellar tissue. The plane is well defined in pilocytic astrocytomas but may not be so in the fibrillary or, the rare malignant varieties. Shiny, thin, translucent cyst walls need not be excised even if they are enhancing.[6] Attachment to the pons or major invasion of the middle cerebellar peduncle may limit the completeness of excision.

Closure

After ensuring perfect haemostasis, the dura is closed. The dura always shrinks and primary closure is often not possible. Pericranium, fascia lata or dural substitutes are needed. Complete dural closure, replacement of the bone flap and meticulous layered wound closure reduce the incidence of, but do not totally eliminate the occurrence of aseptic meningitis, pseudomeningocoele or external CSF leak (Fig. 3). If the lateral ventricle had

Table 4: Choosing the surgical approach according to the location of cerebellar astrocytoma

Location	*Approach*	*Position*
Inferior vermian, medial hemispheric	Midline suboccipital	Prone
Lateral hemispheric	Lateral suboccipital	Prone
Cerebellopontine angle	Retromastoid	Lateral
Superior vermian	Infratentorial supracerebellar	Concorde
Anterosuperior	Occipital transtentorial[53]	Sitting

been tapped during surgery, the catheter may be left behind for post-operative ICP monitoring and control. The patient is observed in the intensive care setting until a CT is done within 24 hours.

Complications

The CT must be done emergently if the patient becomes less responsive or drowsy or complains of severe headache in the post-operative period. Possible causes include tumour bed haemorrhage, supratentorial subdural or extradural haemorrhage, infratentorial subdural haemorrhage, unrelieved hydrocephalus, pneumocephalus and venous or arterial infarction in the cerebellum. As with any posterior fossa surgery, complications such as pseudomeningocoele, aseptic or infective meningitis and external CSF leak can occur.

A complication that requires special mention is *transient cerebellar mutism*.[7,18] In this condition, the child or young adult, who has a relatively normal speech for 1 or 2 days after posterior fossa tumour surgery, becomes mute. These patients, additionally, may have long tract signs or behavioural abnormalities. Routine imaging fails to reveal any specific abnormality that can explain the deficits. The deficit is not nearly as transient as the name suggests; recovery is a slow and incomplete process taking several months. Bromocriptine has been anecdotally reported to be of help.[1] Many patients are left behind with speech and cognitive abnormalities.[27] The cause is believed to be damage in the region of the dentate and interpositus nucleus. The finding of contralateral cerebral hemispheric hypometabolism (diaschisis) by F^{18} fluorodeoxyglucose positron emission tomography study in a patient who had undergone cerebellar astrocytoma excision suggests that such vascular events may also be responsible.[44]

Adjuvant Therapies

Radiotherapy is not indicated for pilocytic astrocytoma as these can be "cured" by total excision. Even when a tumour residue has been left behind, radiotherapy may not prevent regrowth.[4] In case a residue has to be left behind, it can be observed with periodic imaging. Re-operation or adjuvant therapy can be advised for remnants documented to be progressing. Stereotactic radiosurgery has been used for remnants and those pilocytic astrocytomas exhibiting progression.[24,52] Though it is appealing to the patient, those advocating and practicing stereotactic radiosurgery must remember that it has its own complications, sometimes serious.[57] The more malignant varieties must be subjected to adjuvant radiotherapy and/or chemotherapy. Chemotherapy is the only possible adjuvant method for children younger than 2 years.

PROGNOSIS

The extent of surgical resection is the strongest determinant of prognosis.[13,23,47] In a study of 102 childhood cerebellar astrocytomas from Mumbai, India, the survival was 94% at 2 years, 87% at 5 years and 73% at 10 years.[13] Even after complete excision, recurrence can be seen several decades later.[8] Re-operation and total excision again is feasible in such cases. The recurrence may be malignant.[2] While the surgeon may think that the tumour has been excised completely, post-operative MRI may show residual tumour. The recurrence/progression rate was 19% in a study and 14% had stable size of the remnant or actual regression.[16] Previous studies had focused only on tumour progression and survival, but recent studies show increased cognitive and adaptive dysfunction in children operated upon for low-grade cerebellar astrocytomas.[5,48]

Cerebellar astrocytomas often behave in a benign fashion and total surgical excision has been the mainstay of therapy since Cushing's times. CSF shunting is less often needed in today's practice. Hopefully, future work would show us why certain tumours behave more aggressively than others.

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135 Brainstem Gliomas

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INTRODUCTION

Intrinsic brainstem tumours are common in childhood, comprising approximately 20% of all paediatric brain tumours, but are not uncommon in adults.[8] Pool,[2] as early as in 1968, reported useful long-term survival following surgical and X-ray treatment for verified brainstem gliomas. He suggested that if a brainstem tumour is suspected an exploratory craniotomy is generally advisable, otherwise a benign lesion might be overlooked. Magnetic resonance imaging (MRI) has completely changed the management of brainstem tumours; it not only accurately localises the tumours, but also identifies those subgroups, which may be subjected to radical surgery. The term "brainstem glioma" is an imprecise description as it suggests that all such tumours behave in the same manner. It is now appreciated that brainstem tumours are not a homogeneous group with regard to their clinical, pathobiological or histological features and that their prognosis may be directly related to tumour type and location.[2,3,24,38,41] The advent and the use of the operating microscope, the ultrasonic aspirator, laser or tissue vapouriser, and intra-operative evoked potentials and brain mapping has led to a more aggressive surgical approach to lesions in the brainstem.[14,16,23]

In the pre-computerised tomography (CT) scan era and the early CT scan era, all tumours between the thalamus and the cervicomedullary junction were called brainstem gliomas and were regarded as one entity. The traditional treatment of these tumours consisted of irradiation, often preceded by a biopsy, and sometimes followed by adjunctive chemotherapy.[35] This has met with little overall success. In part, this is because previous reports vary in their definition of "brainstem" tumours.[1-3,8,24,38,41] Some authors regard lesions of the midbrain, pons and medulla oblongata all as brainstem lesions, whereas others make a distinction between the thalamic and midbrain lesions on the one hand and pons and medulla lesions on the other. In addition, many studies include patients from the era before CT scans,[1,12,21] as well as cases of brainstem tumours that were not histologically proven.[1,12,21]

CLASSIFICATION

A number of classifications have been provided based on location, imaging and histopathology, but most of them obscure the fact that there exist basically two categories of brainstem tumours:

1. Focal, discrete and sometimes exophytic lesions associated with a favourable prognosis.
2. Classic diffusely infiltrative lesions known for their relentless growth, resistance to radiotherapy and chemotherapy, and a bleak prognosis.

Many authors[2,3,14,16,19,23,24,38,41] believe that the former mostly consist of pilocytic astrocytomas and the latter belong to a family of fibrillary astrocytomas, anaplastic astrocytomas and glioblastoma multiforme. The focal tumours are particularly amenable to total excision, and the patients have a good prognosis provided the surgery has been performed by an experienced surgeon who has had enough exposure in operating upon such lesions.

A number of classifications are available. Brainstem gliomas have been classified by site, imaging and pathology.

Location: The terms applied include midbrain tumour,[4,13,18] tectal tumour,[5,18,40] pontine glioma,[7,32] focal medullary tumour[17] and cervicomedullary tumour.[7,17]

Imaging: Diffuse gliomas,[17,20] intrinsic gliomas,[15] pencil gliomas,[43] exophytic tumours (dorsal; ventral and lateral),[7,17,20] focal and cystic tumours.[15]

Histopathology: Low grade or benign tumours (pilocytic and grade II) and high grade tumours (World Health Organization Grades III and IV).[7,15,17,20,32]

These classification systems by various authors are mentioned in greater detail in Table 1.

Currently, the most commonly used classification in clinical practise is based on imaging and location. This includes focal (solid or cystic), diffuse, exophytic (ventral, lateral or dorsal), tectal plate and cervicomedullary. However, as mentioned above, for practical purposes there are two categories of tumours:

1. *Focal*: discrete sometimes exophytic lesions.
2. *Classic*: diffusely infiltrative lesions known for their relentless growth and resistance to radiotherapy.[1,19] It is the former category of tumours that need to be tackled aggressively.

The description of "intrinsic" brainstem gliomas has been somewhat neglected in the literature. By the term "intrinsic" the authors mean tumours which are within the brainstem axis and are surrounded by normal parenchyma. One of the main reasons could be perhaps that

these tumours are difficult to access surgically and only surgeons with significant experience could perhaps do a radical decompression without producing any major morbidity. The present classifications (Table 1) with regard to this have several shortcomings:

- The surgical plan is still difficult to decide in many cases as most of the classifications are usually based on their anatomical location only. In this aspect the classification by Choux et al.[9] perhaps comes closest in helping to define a surgical plan.
- The difference between a diffuse brainstem glioma and large focal intrinsic brainstem glioma is not clearly differentiated in most of the classifications. Thus, it is sometimes possible that a large focal intrinsic tumour, which is actually a benign lesion is not subjected to surgery and sent for radiotherapy directly.
- It is usually not possible to determine radiologically whether the tumour is benign or malignant. A stereotactic biopsy too may not provide a holistic representative picture [e.g. may pick up a benign portion of a malignant tumour or vice versa].

Table 1: Different forms of classification systems

Author	*Classification system*
Epstein[14,16]	Intrinsic Diffuse Focal Cervicomedullary Exophytic Anterolateral into cerebellopontine angle Posterolateral and into pontine brachium Disseminated Positive cytology Positive myelography
Epstein and McCleary[16]	Diffuse Focal Cervicomedullary
Stroink et al.[46]	Group I—dorsal exophytic glioma Group IIA—intrinsic brainstem glioma Group IIB—intrinsic brainstem glioma, hyperdense, contrast enhancing, exophytic Group III—focal cystic tumour with contrast enhancement Group IV—focal intrinsic isodense, with contrast enhancement
Barkovich et al.[4]	Location (midbrain, pons, medulla) Focality (diffuse or focal) Direction and extent of tumour growth Degree of brainstem enlargement Exophytic growth Haemorrhage or necrosis Evidence of hydrocephalus
Allbright et al.[1]	Focal (midbrain, pons, medulla) Diffuse
Fischbein et al.[18]	Midbrain Diffuse Focal Tectal Pons Diffuse Focal Medulla Diffuse Focal Dorsal exophytic
Choux et al.[9]	Type I—diffuse Type II—intrinsic, focal Type III—exophytic, focal Type IV—cervicomedullary

In this respect, the authors feel that a more prudent method would be to classify the "intrinsic" brainstem gliomas in the categories given below. This is based on the senior author's personal experience of 40 cases (managed between Jan 1998–June 2007).

Expanding variety: These tumours have the following characteristics:

- Well delineated as seen on gadolinium contrast MRI, located posteriorly, posterolaterally or ventrolaterally.
- They have a slow progression of neurological deficits with a relatively long clinical history (here a period of 6 months was considered).
- Motor function is usually well preserved with the patient being independent for all activities of daily living.

Infiltrating diffuse variety: Here, the margin between the tumour and the brainstem parenchyma is not well defined. Patients usually have a short clinical history and there is a rapid progression of symptoms.

Ventrally located tumours: Here, the tumour is located completely ventrally without any lateral or posterolateral extension. They have been included in a different subset because of the "very difficult to access" surgical location. It has been felt by the authors that these tumours should not be operated upon as surgical intervention may cause more complications.

According to the authors only the "expanding variety" should be subjected to surgery. If surgery is undertaken, a radical removal should be done. Radiotherapy is given only if the tumour is found to be malignant on histology. Thus, a more important approach would be to try to remove the tumour as radically as possible, yet remaining within the tumour, provided the radiological image reveals such a possibility. A word of caution, however, that such pathology should be dealt with only by surgeons who have sufficient experience in this area. It should be remembered that this is a surgical strategical classification only for "intrinsic" brainstem gliomas. Surgery is anyway indicated for all exophytic tumours (Table 2).

PATHOLOGY

Most astrocytomas of the brainstem are infiltrative tumours of the fibrillary type, similar to diffuse cerebral astrocytomas. Macroscopically, they are usually characterised by a symmetrical enlargement of the pons (diffuse hypertrophy). The expanding lesion encroaches posteriorly and superiorly upon the fourth ventricle. Occasionally, there may be anterior enlargement. The

Table 2: The classification proposed by the authors for intrinsic brainstem tumours. Note that classification for exophytic tumours are same as proposed by earlier authors, but has been included here to provide completeness

Type of brainstem glioma	*Features*	*Comparison with other classifications*	*Surgery*
I. Intrinsic only	The tumour is well within the brainstem axis without any breach of the parenchyma		
A. Expanding variety	• Well delineated on gadolinium-magnetic resonance imaging (Gd-MRI)	Epstein et al. [1985]:[14] Focal (< 2 cm)*, cervicomedullary	Yes Radical excision
	• Slow progression of clinical symptoms (> 6 months)	Stroink et al [1987]†:[46] Group III, IV	
	• Well preservation of motor function with independent activities of daily living	Choux et al§ [2000]:[9] Type II, IV	
	• Size may be > 2 cm		
B. Diffuse infiltrative variety	• No margin of delineation on Gd-MRI	Epstein et al. [1985]¶: diffuse	No
	• Rapid progression of symptoms	Stroink et al. (1987)**: IIA Choux et al. (2000): Type I	
C. Ventrally located	Pure ventral location	May be kept as focal in other classifications, but authors prefer not to operate in view of the difficult location and associated high risk of complications	No No
II. Exophytic brainstem glioma	The tumour breaches the bordering brainstem parenchyma to become exophytic		Yes
A. Focal with exophytic	Has a well defined focal component with a dorsal or dorsolateral exophytic component		The exophytic portion removed radically. The intrinsic part may or may not be removed radically
B. Diffuse with exophytic	The intrinsic component is not well defined and the tumour has a dorsal or dorsolateral exophytic component		The exophytic portion removed radically. The intrinsic part may not be removed radically

*Tumours > 2 cm could still be expanding variety.

†Based on contrast enhancement and radiology only; clinical features not taken into consideration.

§Based more on anatomical localisation, clinical features not mentioned again.

¶Tumour looking focal but > 2 cm is still considered diffuse.

**Clinical features not taken into account.

medulla is often spared. Sometimes, however, it originates from the medulla and may spread to the upper cervical region.[42] Histologically, there is a diffuse replacement of nerve tissue by small and large astrocytic cells (stellate, pilocytic and gemistocytic), either randomly dispersed or arranged in small or large groups. This morphologic diversity reflects the cellular heterogeneity even in the absence of anaplasia. In some cases there may be frank features of anaplasia, necrosis and endothelial proliferation as seen in glioblastoma multiforme.[42] Depending on the macroscopic appearance, brainstem gliomas have been divided into the following categories.[34,42,47]

Diffuse

This is a classical example of brainstem tumours that have been recognised since the beginning of neurosurgery. These neoplasms present with a short history and with multiple cranial nerve palsies along with involvement of long tracts. The MRI is virtually diagnostic of these lesions. The tumour is invariably malignant and the only form of therapy advisable is radiotherapy or chemotherapy. Surgery is not indicated. Even stereotactic biopsy is not advised as the procedure may cause additional morbidity, and the biopsy may not contain representative tissue.

Focal

These more commonly involve the medulla and are often associated with a relatively long clinical history. Neurological examination usually reveals focal deficits, i.e. either a VI or VII nerve palsy. These neoplasms are

commonly low-grade astrocytomas and are amenable to surgical excision.

Cervicomedullary Tumours

These are usually low-grade astrocytomas and gangliogliomas and amenable to radical excision. Furthermore, they have well defined tumour margins and are thus amenable to a radical excision.

Cystic Tumours

These are usually low-grade pilocytic astrocytomas and highly amenable for surgical excision.

Exophytic Tumours

These tumours are characterised by exophytic growth either ventrally, laterally into the cerebellopontine (CP) angle or dorsally into the fourth ventricle. Of these, the dorsally exophytic tumours have the best prognosis, are amenable for radical excision and are associated with long-term neurological recovery. The other variants have a poor prognosis.

Tectal Plate Gliomas

These are uncommon in the paediatric age group. They have been reported to be one of the commonest causes for adult hydrocephalus in the Western literature. The main presenting feature is hydrocephalus. These are diagnosed on MRI with gadolinium contrast and are managed by performing a ventriculoperitoneal shunt.[40] These may be simply followed up and if they increase in size may be subjected to radiotherapy. Radiosurgery has also been used recently. We have performed endoscopic stenting of the aqueduct along with simultaneous biopsy in 12 cases. Endoscopic third ventriculostomy or aqueductal stenting may be a better alternative to shunt surgery.

Histology from a series of 40 cases of brainstem gliomas revealed pilocytic astrocytomas in 10 cases, grade II in 17 cases and grade III in 13 cases.

CLINICAL FEATURES

Albright et al.[2] stated that approximately 70% of children with diencephalic tumours live 5 years after diagnosis, whereas only 30% of children with brainstem gliomas survive for that long. However, it is now widely recognised that brainstem tumours are a very heterogeneous group with regard to their clinical, histopathological and biological features, and it is essential that they be therefore regarded as distinct entities.

Vomiting is a common symptom and is usually due to involvement of the area postrema and the other medullary nuclei by the tumour. Ataxia is usually due to involvement of the cerebellar peduncles. Motor weakness due to involvement of the pyramidal tracts is common. Extraocular motor palsy is characterised by squint usually noticed by the parents or school teachers. Additional signs include nystagmus, skew deviation and internuclear ophthalmoplegia.[14,16,19,23] The latter sign is a hallmark of intrinsic brainstem involvement characterised by failure to adduct the eye on the side of the lesion and presence of nystagmus of the abducting eye on the opposite side. This occurs due to involvement of the medial longitudinal fasciculus. Other signs of cranial nerve involvement include facial weakness, dysarthria and swallowing difficulties. Features of raised intracranial pressure may occur due to obstruction of cerebrospinal fluid (CSF) pathways in dorsally exophytic tumours. Focal intrinsic tumours from the tectum can cause obstruction of CSF pathways early in the course of illness.[40] The following features are characteristic of an intrinsic brainstem neoplasm:

- Internuclear ophthalmoplegia
- Horner's syndrome
- Cranial nerve involvement with crossed motor involvement, e.g. ipsilateral III nerve paresis with contralateral hemiparesis (Weber's syndrome)
- Combination of certain cranial nerve nuclei, e.g. VI and VII cranial involvement on one side indicates an intrinsic pathology
- Partial involvement of some large sized cranial nerve nuclei, e.g. III cranial nerve nucleus. This has many components, so a diffusely infiltrative tumour may cause bilateral ptosis (involvement of bilateral levator palpabrae superioris), or bilateral superior rectus palsy (involvement of unilateral superior rectus nucleus can still cause bilateral superior rectus palsy as the tract of the opposite superior rectus crosses contralaterally and passes through the opposite superior rectus nucleus) or unilateral complete III nerve palsy and opposite partial III nerve palsy.

Patients with tumours at the cervicomedullary junction exhibit lower cranial nerve dysfunction and pyramidal tract signs, similar to those occurring in the upper cervical spinal cord. In these patients, radical excision is possible with little morbidity, and usually a very protracted clinical course. Histopathologically, the vast majority of the tumours are low-grade gliomas.[14,16,19,23]

Intrinsic tumours of the pons are infiltrative in nature and are mostly malignant. Symptoms at the time of admission are usually cranial nerve palsy, pyramidal tract signs and ataxia. It is characteristic for these tumours to progress to an advanced stage without the development of increased intracranial pressure.[33] The course of the disease is steadily progressive, and most patients die within 2 years, even after radiation therapy. Epstein[13,14,16] refers to this group of tumours as "diffuse" and strongly advises against surgical intervention because this in no way alters the ultimate outcome. Even biopsy is not recommended by many authors, as it may not show the representative tissue due to the heterogeneous nature of the tumour and it poses a high risk to the patient. However, in the authors' experience, focal tumours even in the pons, if associated with

paucity of neurological signs, may be benefited from radical surgery.

However, it is important to differentiate these tumours from diffuse brainstem swelling which may occur in neurofibromatosis type 1 (NF-1).[7,10,26,36] Among patients with NF-1, histological confirmation, when available, is consistent with low-grade glioma in the majority of cases. These two entities, diffuse pontine glioma in patients without NF-1 and diffuse brainstem enlargement in children with NF-1, are different in their natural histories and may represent different pathophysiological processes. A recent study has demonstrated the use of magnetic resonance spectroscopy (MRS) in differentiating the two entities. The MRS neuronal marker (NA) peak was preserved in patients with NF-1, but significantly decreased in diffuse gliomas. They hypothesised that this finding reflects preservation of brainstem neuronal elements in the NF-1 group, consistent with their minor or absent symptoms of brainstem involvement. In contrast, patients with diffuse gliomas show significantly decreased NA and have major neurological deficits attributable to neuronal damage from their brainstem tumours.

A subgroup of benign brainstem gliomas, identified by Hoffman et al.[24,25] is the dorsally exophytic transependymal benign brainstem glioma. The duration of the onset of symptoms is longer in this group, and these children often have hydrocephalus (75%). Ataxia is also common, whereas cranial nerve deficit and long tract signs are relatively rare. These tumours are very amenable to surgical resection, frequently requiring no further therapy.[29,30]

Focal midbrain astrocytomas form a special entity. About 50% of all tumours occur predominantly in the tectal region, giving rise to obstructive hydrocephalus in 83% of cases.[14,16,23,41] Most patients with hydrocephalus exhibit headaches, vomiting and florid papilloedema as a result of increased intracranial pressure. The other 50% of focal midbrain tumours occur predominantly in the tegmentum and cause either long tract signs, due to compression of the cerebellar peduncles, or cranial nerve deficits, and signs and symptoms referable to the eyes (up-gaze paresis, Parinaud's syndrome) caused by pressure on the nuclei of the oculomotor nerves and their connecting pathways.[7,14-16,23,41,43]

In our series, the clinical features and demographical data are mentioned below as per our classification scheme.

Expanding variety: The ages of the patients ranged from 4 to 55 years with a mean of 19.2 years and a male:female ratio of 3:2. The majority of the patients were within 21–40 years [13] followed by 11–20 years [11], less than 10 years [10] and greater than 40 years [6]. The commonest clinical feature included cerebellar signs [28], followed by pyramidal involvement [27] [10 cases had hemiparesis and 5 quadriparesis, but ambulatory; 12 others had pyramidal involvement in the form of brisk deep tendon reflexes/upgoing plantars], ocular palsy [19], V nerve involvement [13], facial palsy [12], lower cranial nerve palsy [9], Horner's syndrome [4] and sensorineural deafness [2]. Prolonged headache was present in 9 patients. One patient lapsed into altered sensorium a day earlier; underwent an emergency shunt for obstructive hydrocephalus and returned to his pre-operative clinical status. The duration of clinical features ranged from 2–96 months with a mean of 13.6 months.

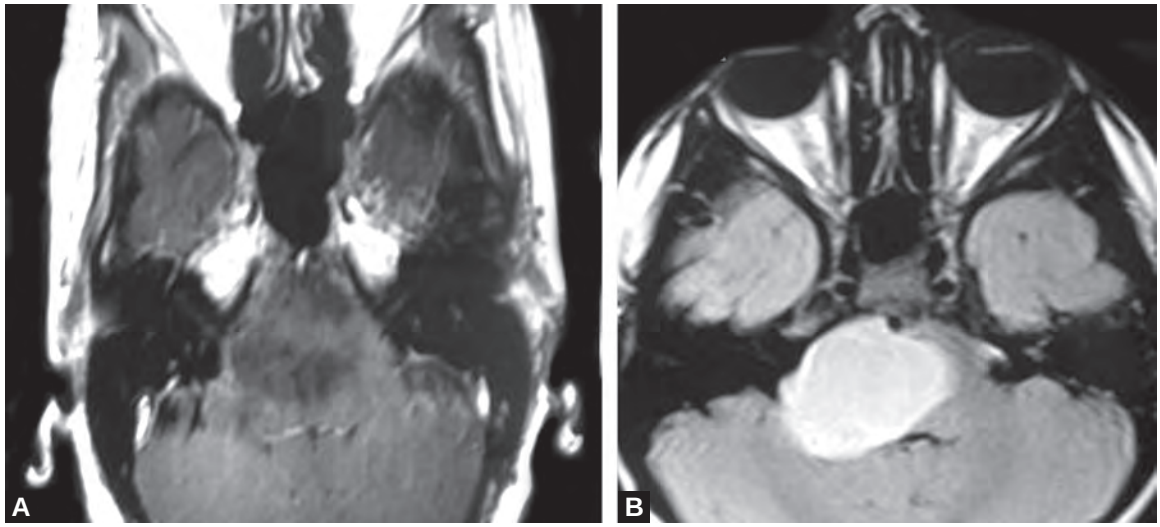
Diffuse infiltrative and pure ventral variety: The age of this group of patients ranged from 0.9–16 years with a mean of 5.2 years. Out of 32 patients, 17 had onset of symptoms in less than 3 months. Onset of symptoms in 12 patients was within 6 months. The remaining two patients had onset of symptoms between 6–12 months. The commonest clinical features in this group included pyramidal signs in 26 cases [16 hemiparesis, 10 quadriparesis; 11 were dependent for all activities of daily living], and cerebellar signs in 16 cases.

NEURORADIOLOGY

The advent of the MRI scan, with its readily available sagittal and coronal planes of imaging, has facilitated accurate localisation of pathological lesions within the brainstem. Tumours should be assessed for location, signal intensity, focality, extent of infiltration, degree of brainstem enlargement, presence of cyst, necrosis or haemorrhage, or an exophytic component. Following this the morphology should be categorised, whether it comes under focal, diffuse, cervicomedullary or exophytic type. The MR imaging should be always correlated with the clinical history. Finally, it is important to identify the benign subgroup of brainstem gliomas. Epstein et al.[14,16,23] have retrospectively analyzed 88 cases of brainstem gliomas and have proposed that the more benign tumours tend to displace rather than infiltrate the secondary structures like the pia, fibre tracts and the ependyma, the characteristics of which may be identified on good quality MRI's. As mentioned earlier, we prefer to first categorise whether the tumour is "intrinsic" or a "tumour with an exophytic component". In the former, we then identify whether the tumour is an "expanding variety", "diffuse infiltrative" or a "pure ventral type" of tumour (Figs 1A and B). Exophytic, cystic and expanding tumours should be subjected to surgery, while direct radiotherapy and/or chemotherapy is preferable for diffusely infiltrative and pure ventral type of tumours.

MANAGEMENT

The surgical approach should be according to the location and projection of the tumour. Most of the tumours in the pons, medulla and cervicomedullary junction can be approached through a midline suboccipital craniectomy/craniotomy in the prone position with or without vermian splitting. Tumours in the midbrain are approached by the authors in the sitting position through a midline suboccipital craniectomy/craniotomy through a vermian splitting approach. Tumours with an exophytic



Figs 1A and B: Magnetic resonance imaging axial sections showing: (A) "Diffuse infiltrating type" as compared to. (B) "Expanding type" of brainstem glioma. In the latter, the tumour is well differentiated from the surrounding parenchyma and even though is well beyond the cut-off size of 2 cm (to be classified as a focal tumour) would be (according the authors) still amenable for surgical excision

component laterally are preferably removed through a paramedian or a CP angle approach. Surgery in our 40 cases were performed in sitting [20], prone [9], lateral [7], and supine [3] positions. The sitting position was preferred for dorsal midbrain or upper pontine lesions. The prone position was used in dorsally situated lower pontine, medullary or cervicomedullary lesions. The lateral position was preferred in ventrolateral lesions of the lower pons, while the supine position was used for ventrolateral midbrain or thalamic lesions. A midline suboccipital approach with or without vermian split was most commonly preferred [27] followed by the retromastoid suboccipital CP angle approach [7], subtemporal approach [3], and the supra-cerebellar infratentorial approach was performed in 2 cases.

Mapping of the Cranial Nerve Nuclei

Because the rhomboid fossa and the brainstem are densely packed with cranial nerve nuclei and neural tracts,[6,45] surgery in this area carries a substantial risk of new or increased neurological deficits. For the same reason, neurosurgeons have long considered lesions in this so-called "no-man's land" at least among the most difficult to manage and even inoperable. However, new diagnostic and surgical techniques have reduced the risk of neurological deficit resulting from such surgery, and surgeries are being performed more frequently to treat intrinsic brainstem lesions.[6,11,37] Recent anatomic studies have identified safer approaches to the brainstem via the fourth ventricle,[25] but because disease often distorts the anatomy, landmarks may be difficult or impossible to identify with the aid of the operating microscope alone. Thus, electrophysiological techniques need to be developed to help distinguish the neural structures so that surgeons can avoid manipulating or injuring these structures. Two kinds of monitoring methods are commonly used.

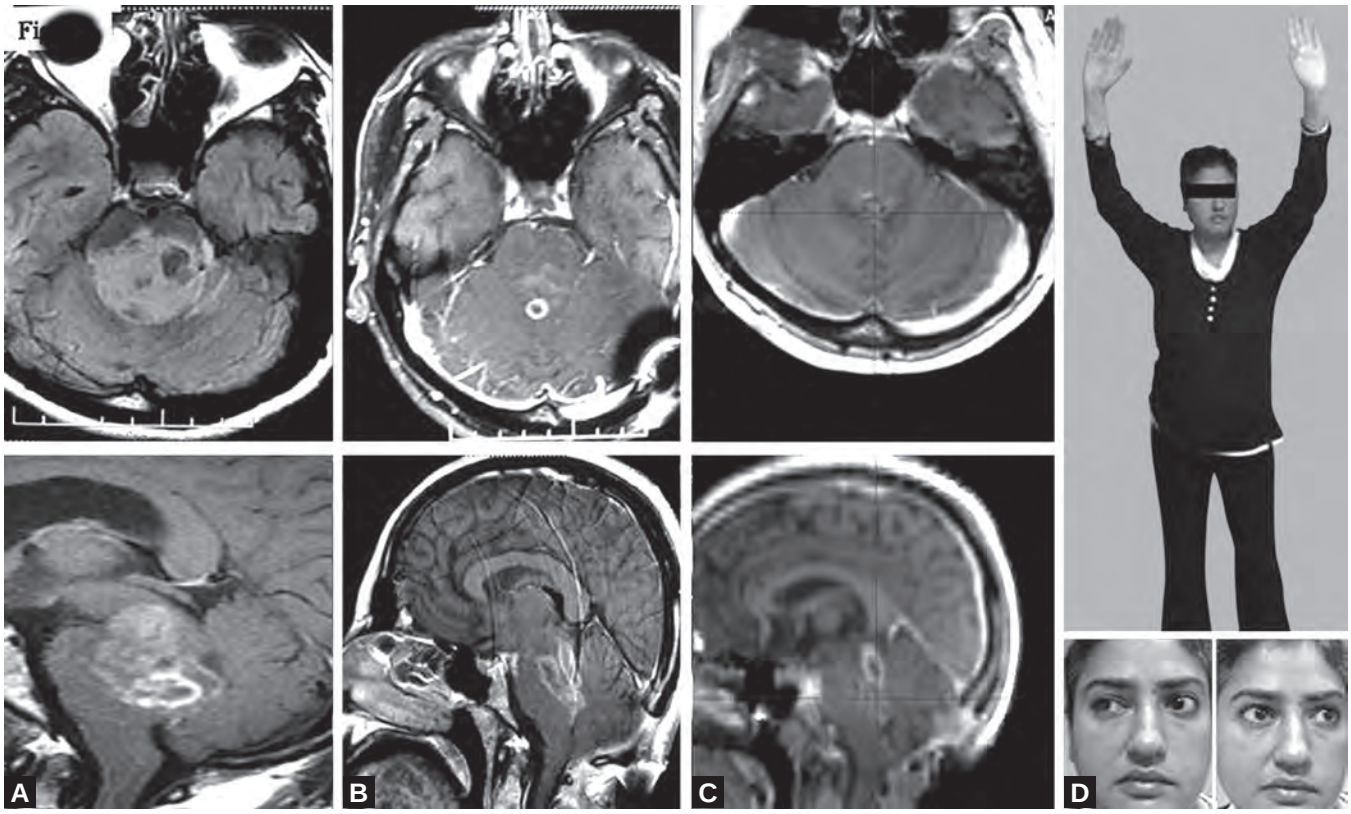
Intra-Operative Motor Nucleus Mapping

During motor mapping in the brainstem, electrical stimulation of the hypoglossal or the vagal triangle elicits continuous motor action potentials (CMAP) from the tongue muscles and the soft palate, respectively. Stimulating the facial colliculus, which contains facial and abducens nerve fibres, elicits CMAPs simultaneously from the lateral rectus and facial muscles. Stimulating other ocular motor pathways elicits CMAPs from corresponding extraocular muscles.

Continuous Intra-Operative Electromyographic Monitoring

Because muscles amplify the electrical activity in the individual motor units, continuous monitoring of the electromyographic (EMG) activity from certain muscles of the head can provide information about the status of the respective motor cranial nerves. Use of this technique has been described for monitoring the motor function of the facial nerve[22,28] and other motor cranial nerve nuclei.[44]

The prognostic value of these manipulation-evoked discharges is based on empirical information, rather than on the results of controlled studies or on a detailed understanding of the pathophysiological mechanisms involved. However, for practical purposes, the continuous recording of the EMG activity seems to provide a reliable way for the surgeon to identify the exact location of various cranial nerve nuclei to plan the incision on the brainstem. For dorsally located lesions, we usually use electrodes connected to the orbicularis oris, orbicularis oculi and the tongue muscles with either intermittent or continuous stimuli. A single stimulus of



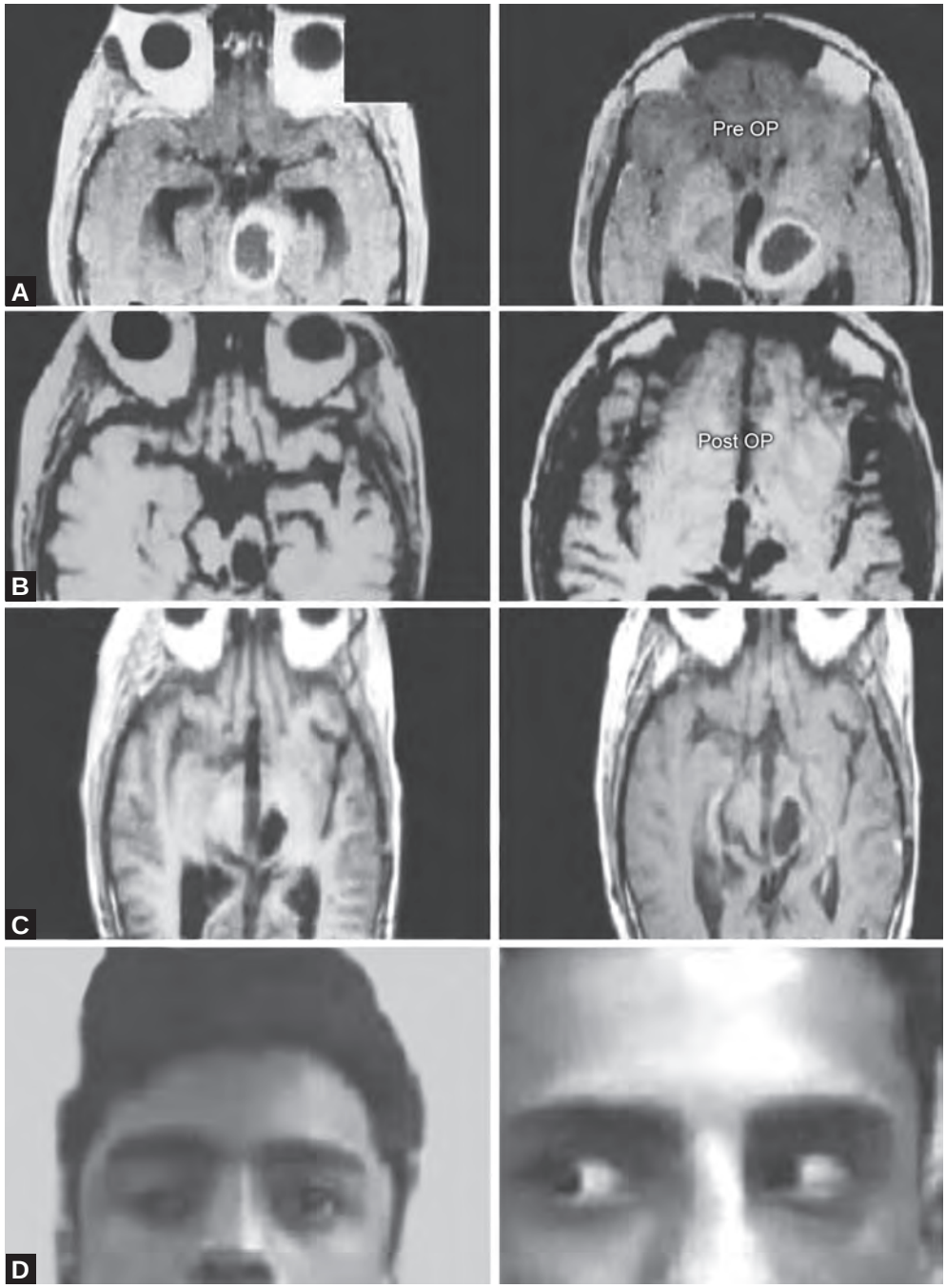
Figs 2A to D: (A) Magnetic resonance imaging showing a large "expanding type" of tumour situated dorsally, heterogeneously enhancing with contrast with a cystic component. Note the well-defined margins and the size well beyond 2 cm. The patient underwent a radical excision. Histopathology showed a grade II tumour with a low MIB labelling index of 8%. (B) Post-operative imaging at 3 months showed a small residual tumour. In view of the relatively higher MIB labelling index, the patient underwent radiotherapy. (C) The tumour was still of the same size at year of follow-up. (D) The patient at 6 months of follow-up shows preserved oculomotor movements with a grade I facial palsy. There has been no deterioration of the patient's clinical status, and like most of the patients with "expanding type" of tumours was independent for all activities of daily living before surgery

0.1–1 mA or a continuous stimulus of 10 Hz (50–400 mS) is generally used.

Surgical Approaches

Surgery is indicated for focal solid or cystic tumours, cervicomedullary tumours and exophytic (particularly dorsal) tumours.[13,14,23,27] The patients need to be followed up with regular neuroimaging. Patients with focal cystic tumours may undergo decompression of the cyst, which is a fairly easy procedure. However, focal radiotherapy may be required to prevent recollection of the cyst. In patients with dorsally exophytic tumours, decompression may be carried out till the tumour is shaved off flush with the floor of the fourth ventricle. It is advisable not to remove a thin carpet of tumour if it is not coming off easily from the floor, to prevent serious morbidity. A large number of patients with low-grade astrocytomas and gangliogliomas will have a good outcome.[25,30,33] Patients with tectal plate tumours may be subjected to a shunting procedure followed by direct radiotherapy or radiosurgery.[5,40] Recently, we have performed endoscopic third ventriculostomy and stenting in 12 cases of tectal plate gliomas along with simultaneous biopsy during the endoscopic procedure. This has an advantage of performing a biopsy and a shunting procedure at the same sitting.

Once the floor of the fourth ventricle is exposed (or the lateral surface of brainstem), it should be carefully inspected under high magnification for any abnormal "bulges" or any "discolouration". A mapping of the floor should be then performed as per the technique described earlier. We have found direct stimulation of cranial nerve nuclei quite useful to map out the eloquent areas. The floor of the fourth ventricle is usually screened first with a low intensity bipolar. Following this a stimulation of 0.1 mA single or continuous stimulation with 10 Hz frequencies at 50–400 mS is given. The evoked response may then be recorded with electrodes from the orbiculi oculi, oris and the tongue muscles. We have not found somatosensory evoked potentials or auditory evoked potentials very useful. This helps in localising the VI and the lower cranial nerve nuclei. If no exophytic component is seen, then one of the "safe areas"[31] should be used to make an incision after mapping. This usually includes the dorsolateral sulcus lateral to the cranial nerve nuclei. Otherwise the exophytic component should be tackled first. The incision should be as small as possible, longitudinal nearest to the tumour surface and away from the nuclei. The senior author prefers to use



Figs 3A to D: (A) Magnetic resonance imaging (MRI) shows another example of an "expanding type" of tumour located in the midbrain. The margin of the tumour is well enhancing and within the brainstem axis. (B) The patient underwent a total excision (MRI-gadolinium enhanced at 3 months). No radiotherapy was given. (C) A follow-up MRI (with contrast) 6 years after surgery still showed no recurrence. (D) The patient had right ptosis and ophthalmoparesis (left picture) immediately following surgery that resolved at 1 year. Photo at 6 years (right picture) shows complete resolution of eye movements

the tissue vapouriser, as there is minimum heat dissipation to the surrounding structures even when applied close to the cranial nerve nuclei. Cyst aspiration, if any, should be performed before removal of the solid component. Use of micro-tip ultrasonic aspirators and irrigating non-stick bipolar forceps are very useful. The tumour rim should be left behind if no distinct plane is seen.[6,13-15,19,23,30,33,35] All the patients should be started on methylprednisolone just before making an incision on the brainstem and this should be continued for 24–48 hours in doses of 30 mg/kg for the 1st hour followed by 5.4 mg/kg/hour for the next 24 hours. All patients should be electively ventilated with sedation for 24 hours (Figs 2A to D and 3A to D).

Management of Diffuse Tumours

The diffuse tumours carry the worst prognosis and the survival is usually not more than 18 months after diagnosis. Parts of the tumour may start off as a fibrillary astrocytoma but, by the time of death, usually the entire tumour is either a malignant astrocytoma or a

glioblastoma multiforme. Thus, a stereotactic biopsy is totally unreliable for diagnosis, while the imaging characteristics are almost diagnostic of this dreadful condition.[7–10] These patients may be directly subjected to radiotherapy. The type of radiotherapy is undergoing a change. The standard therapy has been 55 Gy to the tumour area with a weekly dose of 800–1000 cGy. In hyper-fractionated therapy, higher doses up to 76 Gy may be tolerated and has improved short-term survival without obvious toxicity.[1,14,16,19,23,35,39,47]

CONCLUSION

The identification of various subgroups of brainstem tumours has led to more rational treatment strategies and allows for a more accurate assessment of prognosis. The focal tumours with paucity of neurological signs are a distinct subgroup of brainstem tumours. Most of them are low-grade astrocytomas and are amenable to radical surgical resection, but this should be performed by an experienced surgeon in a set-up with adequate intra-operative and post-operative facilities. Surgical intervention in this subgroup of brainstem tumours may be associated with a good long-term prognosis. Exophytic tumours, particularly those associated with diffuse brainstem enlargement, should undergo a limited decompression. Purely diffuse tumours should preferably undergo direct radiotherapy.

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136 Hypothalamic-Optic Nerve Gliomas

Ramakrishna Easwaran

INTRODUCTION

Optic pathway gliomas (OPGs) are unique in many ways. They occur commonly in children and young adults. They may show little growth over years. Their location makes them a surgical challenge. Controversy surrounds the optimal management.

INCIDENCE

Optic pathway gliomas are rare. They account for 1% of all intracranial tumours, 3–5% of paediatric brain tumours and 6% of all orbital tumours.[18] Gliomas account for two-thirds of all tumours in the optic nerve. About 25% of OPGs are in the optic nerve [Optic nerve glioma (ONG)] and 60% involve the chiasm (Optic chiasm glioma).[8] Nearly one-third of patients with OPG have neurofibromatosis-1 (NF-1). Symptomatic OPG occurs only in 5% of patients with NF-1, but imaging series report a 15–20% incidence, as computed tomography (CT) and magnetic resonance imaging (MRI) are able to detect several asymptomatic OPGs in NF-1 patients.[31] The OPGs in NF-1 differ in many ways from the non-NF-1 OPGs and these differences are summarised in Table 1.[27,30,40] The mean age at diagnosis was 8.8 years in a review of 2297 patients reported till 1992. About 60% of OPGs are diagnosed before the age of 5 years, 75% before the age of 10 years and 90% before the age of 20 years.[18] The male:female ratio is nearly equal but pure optic nerve tumours are commoner in girls.

PATHOLOGY

Macroscopic Appearance

ONG can be purely intraorbital or purely intracranial. Often the tumour starts in one compartment and spreads to the other through the optic foramen causing a dumb-bell pattern with smooth enlargement of the bony optic canal and foramen. The nerve is expanded by the tumour and also by the extension of the tumour into the subarachnoid space. The chiasmal variety may diffusely infiltrate the hypothalamus and the floor of the third ventricle. There is difficulty in distinguishing whether the primary site of origin is in the chiasma or in the hypothalamus and so they are dubbed as hypothalamic-chiasmatic glioma.[16] The non-NF-1 OPG in the chiasma may become a large mass and show areas of cystic change. Large cysts have been reported to extend to the middle fossa or third ventricle.[21] The largest OPGs (up to 9 cm) are seen in non-NF-1 patients.[3] Involvement of the optic radiation may indicate aggressive behaviour in NF-1 patients.[32]

Microscopic Pathology

The histology of OPG is almost always a pilocytic astrocytoma. Of all pilocytic astrocytomas, 11% occur in the optic pathways.[10] The astrocytes in the tumour have hair-like long processes, which give the tumour the appellation "pilocytic". The pilocytic growth is compact in some areas and loose-textured in others (biphasic pattern). Rosenthal fibres and eosinophilic granular bodies are characteristic (see the chapter on cerebellar astrocytoma in this textbook for details of these histological features of pilocytic astrocytoma). Microcystic change is seen. The cells are positive for glial fibrillary acidic protein. The typical pilocytic astrocytoma is graded as World Health Organization (WHO) grade 1. The majority of pilocytic astrocytomas have a very low growth potential but undoubtedly a few show aggressive clinical behaviour. Why some tumours remain indolent while others progress is not clear. Age may be one factor as adults with pilocytic astrocytoma might have frequent recurrences and progress to WHO grade 3, unlike children.[43] A higher microvessel density (as assessed by immunostaining for factor VIII) is thought to indicate progression.[6] The details of the genetic abnormalities in NF-1 associated glioma are discussed in the chapter on supratentorial astrocytoma in this textbook.

Pilomyxoid astrocytoma has been recently recognised as a separate entity. It is a solid, circumscribed tumour that occurs in the chiasma-hypothalamus area of very young children. It is composed of a monomorphous population of bipolar tumour cells within a rich myxoid background, with a conspicuous angiocentric arrangement. This tumour is graded as WHO grade 2 and shows more aggressive behaviour than pilocytic astrocytoma, with 14% spreading through the cerebrospinal fluid (CSF) pathways.[26] The presumed cell of origin of pilomyxoid astrocytoma is the embryonic radial glial cell in the chiasma.[13]

Chordoid glioma is described in the chapter on supratentorial astrocytoma. It may be an asymptomatic lesion detected incidentally on imaging.[20] Fibrillary

Table 1: Differences between optic pathway gliomas in those without and with neurofibromatosis-1

Characteristic	*Non-neurofibromatosis-1 (NF-1) Optic pathway glioma (OPG)*	*OPG in NF-1*
Demographic		
Incidence	3–5% of childhood tumours	10–15% of patients with NF-1
Male : Female ratio	1:1	2:3
Mean age ± SD	6 ± 3.3 years	4.3 ± 2.1 years
Gross pathology		
Involvement		
Orbital optic nerve	32%	66%
Chiasma	91%	62%
Hypothalamus	70%	36%
Beyond optic pathway	68%	2%
Bilaterality	7%	24%
Average size	4.5 cm	2.5 cm
Shape	Globular mass	90% conform to optic pathway shape
Cystic areas	66%	9%
Growth pattern	Intraneural	Perineural
Microscopic pathology		
Infiltration of leptomeninges	Rare	Florid
Arachnoid hyperplasia	Absent	50% of cases
Non-pilocytic histology	Rarely reported	Not reported
Malignant transformation	Seen in adults	Not seen
Clinical features		
Progression	60%	12%
Asymptomatic	0%	32%
Visual symptoms	84%	21%
Proptosis	5%	21%
Hypothalamic symptoms	33%	Rare, but precocious puberty occurs
Raised pressure symptoms	66%	Rare
Hydrocephalus	75%	Not seen
Regression	Not likely	Reported
Imaging features		
Diffuse enlargement of optic nerve or chiasma	27%	91%
Vessel encasement	32%	2%
Prognosis		
5-year survival	83%	93%
10-year survival	76%	81%
Time to progression	2.3 years	8.3 years

astrocytoma is rare and is seen in the chiasma/hypothalamus only in non-NF-1 patients.[16] Adult patients may harbour anaplastic astrocytoma or glioblastoma multiforme which might mimic a cystic craniopharyngioma or pituitary adenoma on imaging.[5,17] Ganglioglioma of the optic nerve is rare.[34]

CLINICAL FEATURES

Visual Dysfunction

Visual impairment occurs in about 85% of cases of OPG.[29] It may escape being noticed, as the onset is insidious and because the tumour occurs in children too young to discern the symptom. Drop in visual acuity occurs before field cuts are detected. The differential diagnosis is with retrobulbar neuritis.[45] Primary optic atrophy takes time to set in, but is seen in about 60% of cases of OPG. Rarely the visual loss stops progressing and indeed regresses.[33] Bitemporal hemianopia progressing to bilateral visual loss occurs in adults due to chiasmal involvement. Acute visual loss might occur due to intratumoural haemorrhage.[47]

Proptosis

Painless axial proptosis is commoner in NF-1 patients with OPG, due to the frequent location of the tumour in the orbit. This may be the only symptom in young children. Painful proptosis is seen only with large tumours and may be due to compression of branches of the

ophthalmic division of the trigeminal nerve or orbital venous occlusion.

Hypothalamic Dysfunction

The symptoms of hypothalamic dysfunction in OPG are commoner in non-NF-1 patients. Emaciation despite normal caloric intake in an alert child is known as the "diencephalic syndrome of infancy". This has been found to be associated with dissemination of the hypothalamic pilocytic astrocytoma.[39] The somatic growth rate is normal in spite of the emaciation and so is the pituitary hormonal function. Ironically, some of these children become very obese in later years.[11] The diencephalic syndrome has been attributed to the dysfunction of the leptin-ghrelin system.[9] Gigantism due to OPG has been reported.[35] Spasmus nutans consists of disconjugate nystagmus, torticollis and titubation. While OPG can cause spasmus nutans, the prevalence of glioma in patients presenting with spasmus nutans is very low.[2] Precocious puberty is common in NF-1 children with OPG.[30] Adult patients may present with hypersomnolence due to involvement of the posterior hypothalamus. Diabetes insipidus is rare as a presenting symptom of OPG and must raise the suspicion of germinoma or craniopharyngioma.[46]

Symptoms of Increased Intracranial Pressure

Due to the larger size of the mass and association with hydrocephalus, symptoms of raised intracranial pressure are commoner with OPGs in non-NF-1 patients. Papilloedema is seen in about 38% of patients.[29] Foster Kennedy syndrome due to optic glioma presents with unilateral optic atrophy first followed by contralateral papilloedema.[7] Of course, the third component of this syndrome, anosmia, described with olfactory groove meningioma is never seen with OPG.

INVESTIGATIONS

The CT scan and MRI are the currently used modalities for imaging OPG. On CT the tumour is hypodense and shows variable enhancement. The MRI has the advantage of showing the extent of optic pathway involvement in all three planes without bone artifacts. Fat suppressed T1-weighted (T1W) images with contrast must be obtained. In the orbital ONG, the tubular or fusiform enlargement of the nerve is seen well in axial images. Since the small tumours may be isointense with the nerve in T1W and T2-weighted (T2W) images, the diagnosis might rest solely on detecting the smooth enlargement of the nerve that is well appreciated on comparing with the opposite nerve in coronal images. Most lesions are T1 hypointense and T2 hyperintense. The redundancy of the nerve manifested by a downwards kink of the nerve in the midorbit is a characteristic feature of the NF-1 associated OPG.[25] There is usually good but non-uniform enhancement with gadolinium. The "tram track" sign on MRI refers to a hyperintense core on T1W images, surrounded by lower signal intensity. On T2W images, the exact opposite is seen. This is due to perineural arachnoidal gliomatosis. The tram track sign is not specific for glioma and is seen with optic sheath meningioma, pseudotumour or optic neuritis. The dumb-bell extension in to the intracranial compartment is well seen in axial or oblique reformatted images. Extension in to the optic tracts, lateral geniculate bodies and to the optic radiation may be detected with T2W images. The bony optic canal enlargement is better appreciated with CT. Similarly, the calcification pattern of meningioma (which is the closest differential diagnosis of OPG) is also better appreciated on CT.

The non-NF lesions tend to be larger and have cysts (Figs 1 to 3). Calcification is rare. The non-uniform enhancement differentiates the mass from suprasellar germinoma, which is a common differential diagnosis in children. The larger tumours fill the third ventricle (Figs 1A to F), extend to the subfrontal region (Fig. 3) and may encase the vessels of the circle of Willis. Intratumoural haemorrhage is rare.[47] There are no MRI findings that can reliably predict subsequent clinically aggressive behaviour. The MRI is the modality of choice for monitoring progression or treatment response. Positron emission tomography is likely to show such changes even earlier than MRI.[38]

MANAGEMENT

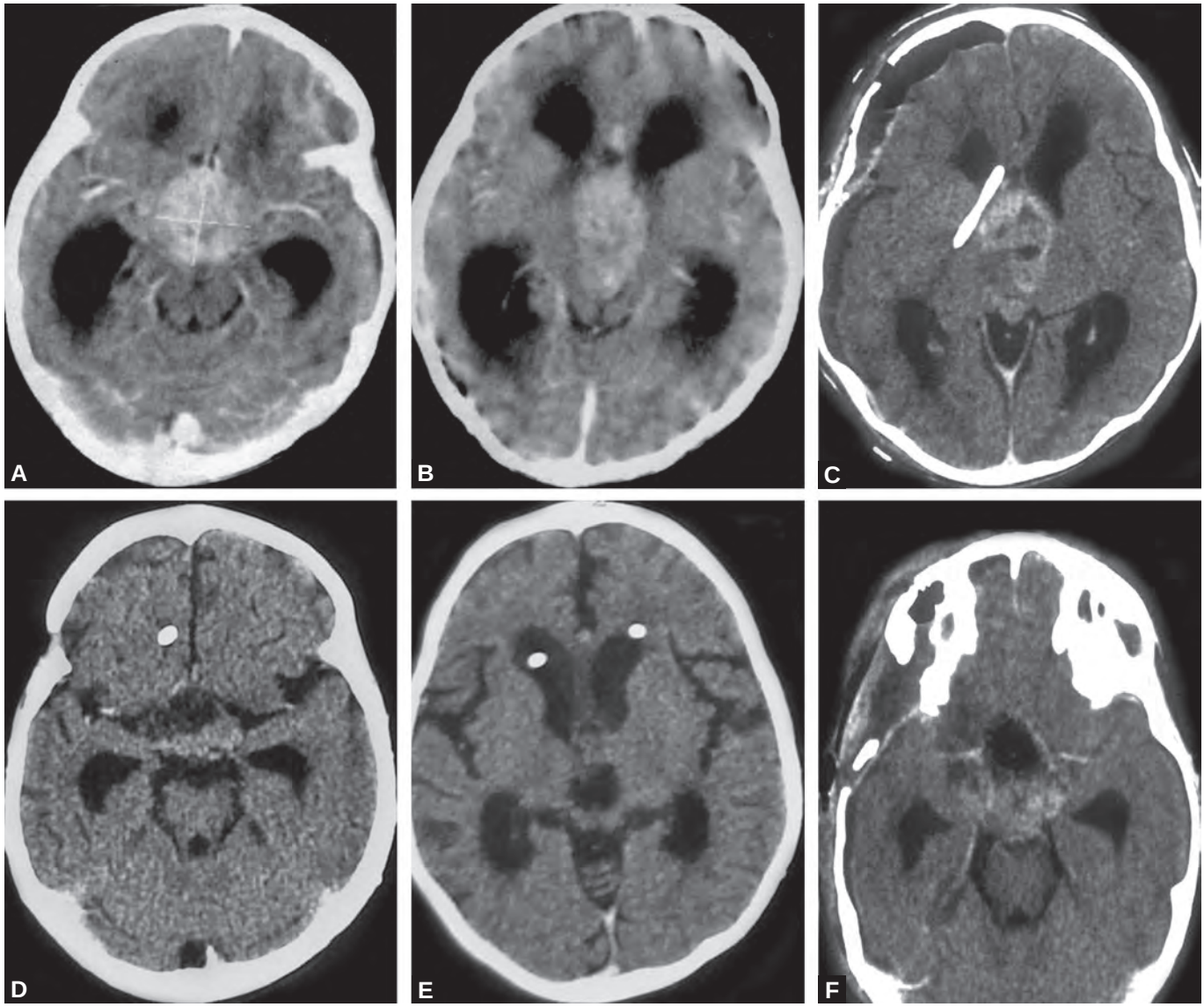
The management of OPG is influenced by several variables such as age, presence or absence of NF-1, location in optic pathway, size and symptoms (visual acuity, proptosis, raised pressure). The available methods of management are observation, surgery, chemotherapy and radiotherapy. Since OPGs are slow growing lesions, any one or more of these modalities may be needed during the course of management.

Observation

Since the growth rate of most OPGs is low, mere watchful expectancy is an acceptable choice of initial management. It has been found that on long-term follow-up (up to 11 years), the vision was good (stable or improved) in about 78% of patients.[18] The wait-and-watch approach applies to the incidentally detected asymptomatic tumours, small tumours, patients who have well-preserved vision with little proptosis and those with NF-1. The surgeon has to instruct the family about the signs of progression and maintain a meticulous clinical, neuro-ophthalmic and imaging follow-up.

Surgery

In contrast to the cerebellar juvenile pilocytic astrocytoma, surgery plays only a limited role in the tumour



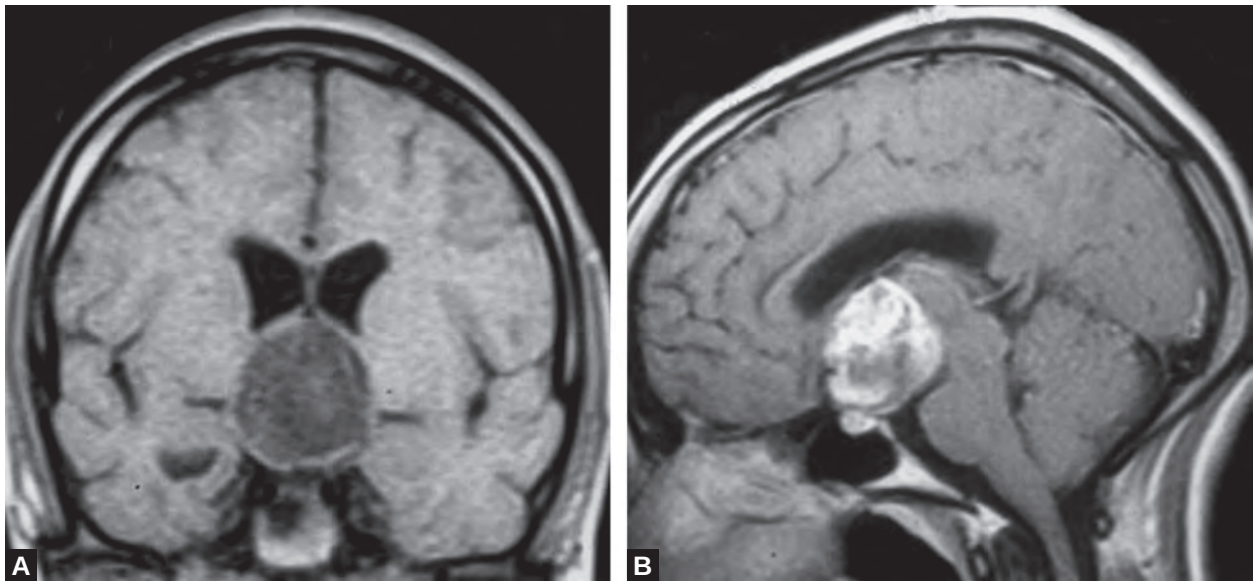
Figs 1A to F: (A and B) Contrast-enhanced computed tomography (CECT) of a 4-year-old boy without neurofibromatosis-1 presenting with loss of vision in the right eye. Note the non-uniform enhancement in the suprasellar mass, which fills the third ventricle. The boy underwent right pterional craniotomy and partial excision of chiasmal pilocytic astrocytoma followed by bilateral shunt placement. (C and D) The CECT scans after surgery—note the residual tumour. He was given chemotherapy initially. Radiation was given after he completed 7 years of age. (E and F) The CECT scans obtained 5 years after initial presentation—note the tumour shrinkage. The vision remains stable in the left eye and the growth is near normal

with the same histology occurring in the optic pathway. The indications for surgery are listed in Table 2. Radical surgery has not been proved to increase the length or quality of survival.[1]

Table 2: Indications for surgery in optic pathway glioma

- Biopsy for tumours with atypical imaging findings
- Mass reduction by cyst drainage and tumour decompression for relieving raised pressure symptoms or neighbourhood compression syndromes
- Disfiguring or painful proptosis
- Total excision for orbital optic nerve tumours with total visual loss, so as to prevent intracranial extension and to provide cure without adjuvant therapies
- Excision of exophytic masses (mainly chiasmal)
- Ventricular shunt placement for hydrocephalus

Biopsy of intraorbital tumours can be performed by lateral orbitotomy or by fine needle aspiration. Resection of ONG requires transcranial superior orbitotomy and cannot be done adequately through the lateral orbitotomy approach. Transcranial orbitotomy can be done through an eyebrow incision but the traditional method is to raise a flap from behind the hairline. Removing the superior orbital rim allows a lower trajectory and reduces frontal lobe retraction. The orbital rim may be taken with the frontal bone flap or as a separate osteotomy piece. Extradural approach is reserved for lesions that do not extend to the optic canal. Intradural approach is done for gliomas that reach into the canalicular or the



Figs 2A and B: (A) Non-contrast coronal magnetic resonance (MR). (B) Contrast sagittal MR of a 20-year-old female with non-neurofibromatosis-1 hypothalamic-chiasmal glioma. The patient underwent subfrontal approach and partial excision of grade 2 fibrillary astrocytoma followed by radiotherapy. The clinical status was normal with stable vision until 4 years later when she died of progressive infiltrative recurrence

intracranial portions of the optic nerve. The periorbita is opened medial to the superior rectus and the annulus of Zinn must be sectioned to approach the canalicular part.

The approaches to chiasmal-hypothalamic gliomas are listed in Table 3. The infiltrative chiasmal gliomas cannot be radically excised. Biopsy and sufficient decompression to open the CSF pathways can be done in big masses (Figs 1 and 3).

Chemotherapy

The risks of irradiating young children have caused a swing towards the "chemotherapy-first" approach. Carboplatin based regimes are the most studied.[29] The Packer regimen of concurrent carboplatin and vincristine in a 10-week induction phase, followed by 48 weeks of maintenance carboplatin/vincristine resulted in progression-free survival of 75% at 2 years and 50% at 5 years. Imaging evidence of tumour shrinkage was seen in 63% of patients with this regimen. Children 5 years of age or younger had a more favourable rate of response.[36] Recently, single agent temozolomide therapy has also been found to be successful.[23]

Table 3: Approaches for chiasmal hypothalamic glioma

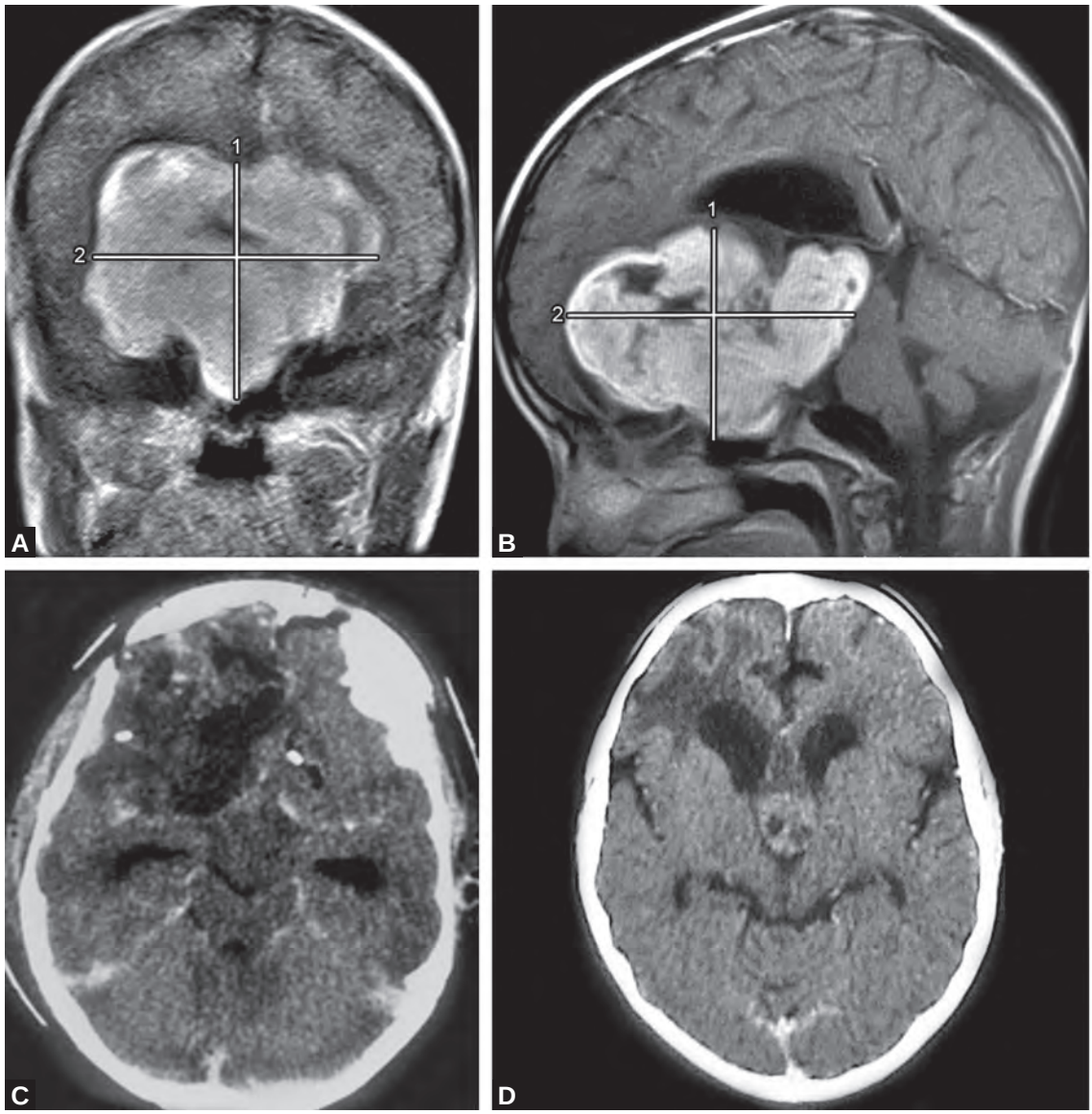
- Subfrontal
  - Lateral (pterional)
  - Anterior
- Transventricular
  - Interhemispheric transcallosal
  - Anterior interhemispheric, trans-lamina terminalis
  - Endoscopic transventricular

Radiotherapy

Radiotherapy was the initial treatment modality until a decade back. The recognition of endocrine and cognitive side effects of radiotherapy in young children has made chemotherapy the choice in this age. Sixty nine per cent of children below 10 years developed hypothalamic-pituitary endocrine deficiency after radiation in one study as compared to only 25% of those above this age.[22] Radiotherapy is the initial modality in older children and adults. The standard prescription is 45–50 Gy in 2 Gy daily fractions to the tumour and the surrounding 0.5–1 cm margin. Progression-free survival probabilities after radiotherapy were 82% at 5 years and 77% at 10 years after radiotherapy for OPG in a Turkish study.[19] The visual acuity improved in 36%, remained stable in 52% and deteriorated in 12% after radiotherapy in a German series of 25 patients.[22] The risk of developing a second (usually malignant and lethal) tumour after radiotherapy is real and is more so for NF-1 patients.[41] Fractionated stereotactic radiotherapy has been recently reported to provide 90% survival at 5 years while reducing the endocrine side effects and the possibility of a second tumour.[15] There are case reports of gamma knife radiosurgery for OPG.[28] Novalis (shaped beam) radiosurgery has been recently reported to be useful in OPG.[24]

PROGNOSIS

Optic pathway gliomas are known for their erratic behaviour.[42] Spontaneous regression (involution) of OPG has been recorded well in the literature.[37] Regression may manifest either as an overall shrinkage in tumour size, or as signal intensity change on MRI. A variable degree of improvement in visual function may accompany



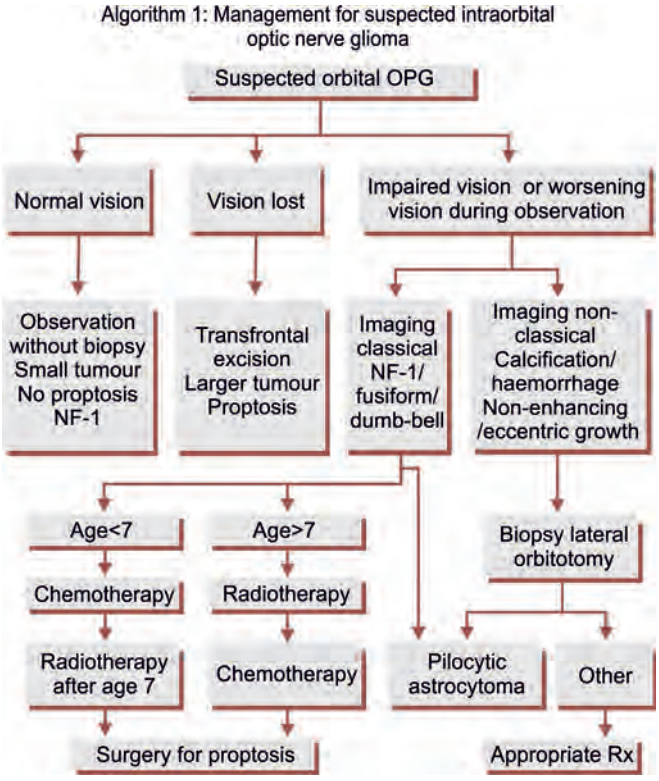
Figs 3A to D: (A and B) Pre-operative contrast magnetic resonance of a 7-year-old boy with a massive hypothalamic-chiasmal pilocytic astrocytoma. There was no light perception in the right eye and the acuity was 6/36 in the left eye. Debulking was done by the subfrontal approach. (C) Immediate post-operative contrast-enhanced computed tomography (CECT) showed good reduction in tumour size. He underwent radiotherapy. (D) The CECT at 1-year follow-up. The vision remains the same as before operation

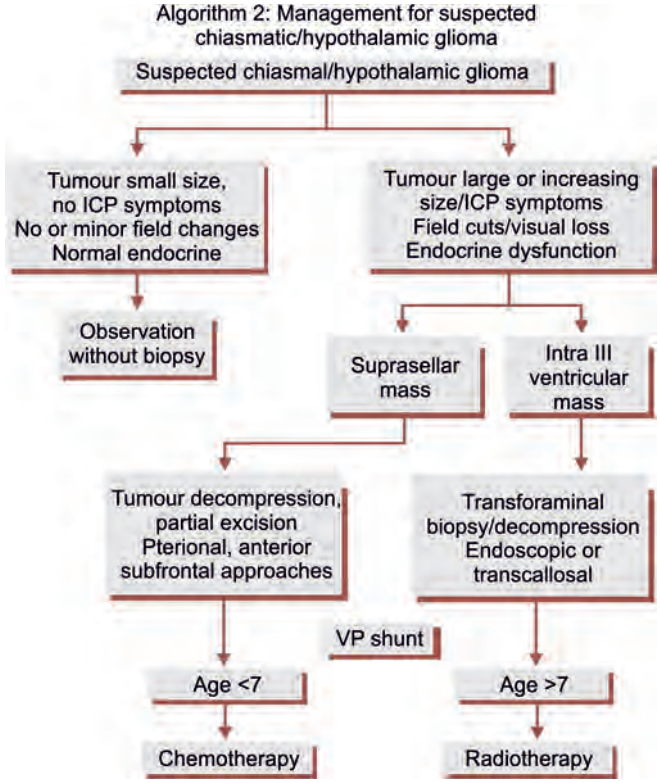
regression. While involution has been associated with childhood OPG in NF-1, adult tumours and non-NF-1 tumours have also been reported to regress.[4] The visual function has also been found to improve without treatment though the imaging does not show reduction in tumour size.[33]

In a study of patients followed up for 10 years or longer, 16 patients (mostly with NF-1) received no treatment and there was no mortality or tumour related morbidity. Thirty one patients (mostly non-NF-1) received treatment and they subsequently developed neurologic, endocrine or visual morbidity. This has led to the recommendation that OPGs should not be treated unless they demonstrate clear disease progression.[31,44] There is a two-fold difference in the visual deterioration rates of ONG (21%) and chiasmatic glioma (42%).[18] The tumour related mortality is 0–5% for optic nerve tumours, 29% for chiasmal tumours and 43% for hypothalamic tumours.[18] Visual improvement after therapy is often not seen but complete recovery has been occasionally reported.[12] Endocrine defects in survivors are mainly due to therapy and growth hormone deficiency is the commonest.[14]

CONCLUSION

Optic pathway gliomas are slow growing tumours but may behave erratically. The treatment recommendation is to observe the course and intervene only when one is forced to. Chemotherapy for younger children and radiotherapy for older patients is effective in achieving long-term tumour control. Surgery does little to alter





the natural course of the tumour. The management is summarised in Algorithms 1 and 2.

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137 Oligodendrogliomas

Ravi Ramamurthi, Nigel Peter Symss

INTRODUCTION

The oligodendrocyte, Cajal's third element of neuroglia, is reported to have been first recognised by Ford Robertson in 1900, using the platinum impregnation technique. He called it "mesoglia".[15] Hortega, in 1918, identified it by using silver carbonate impregnation techniques and designated it oligodendroglia because of its few dendritic processes. Bailey and Cushing[2] were the first to describe oligodendroglioma as a distinct pathological entity. Bailey and Bucy[1] further defined the morphological features of this tumour based on a study of 13 cases. Cushing[9] in his classical monograph, in 1932, recorded 27 oligodendrogliomas in a series of 2023 tumours of the brain, 862 of which were gliomas. The first large series (200 cases) of these tumours was reported by Earnest et al. in 1950.[15] The largest series documented so far, consisting of 323 cases, has been by Ludwig et al.[30] from the Armed Forces Institute of Pathology, USA.

Recently published series have shown that oligodendroglial tumours represent a type of tumour in which molecular alterations may become a significant prognostic factor. During the last decade, enormous progress has been made in understanding these alterations. Oligodendrogliomas show distinct genetic alterations, allowing us to distinguish them from other types of gliomas and this has increased our insight into the response of these tumours to therapy.

CLASSIFICATION

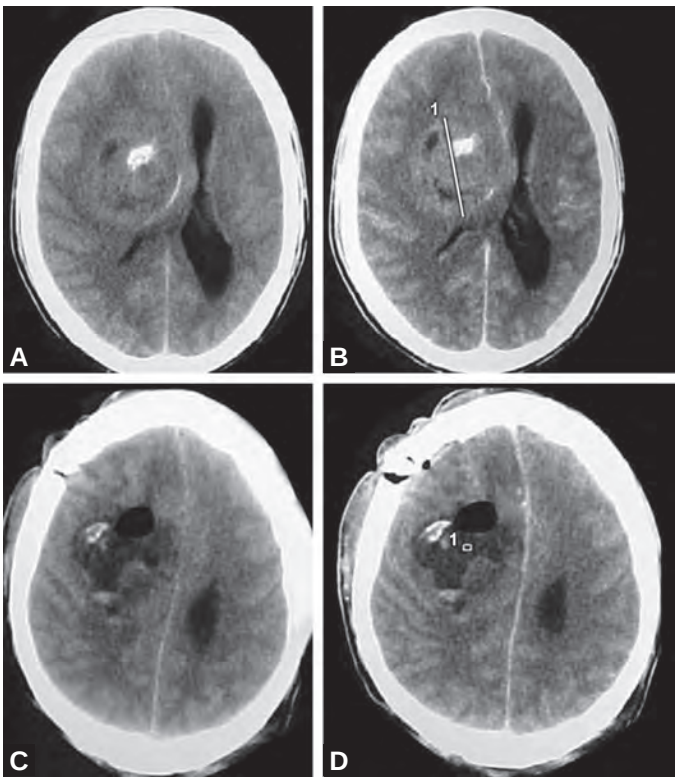
Oligodendrogliomas are now generally accepted as a distinct pathological entity with special clinical features. However, there has been some divergence of view regarding their classification and histogenesis. Elvidge et al.[16] divided these into two groups: (1) oligodendroglioma and (2) oligodendroblastoma. Kernohan[23] further elaborated the morphological characteristics of these two subgroups. Attempts were later made by the Mayo Clinic group to grade these tumours on the same lines as astrocytomas (grade 1–4).[24] It is interesting to note that Kernohan's group itself concluded that these tumours did not lend themselves well to grading with respect to the degree of malignancy.[15] Smith et al.[42] defined histological criteria that allowed an effective grading system pertinent to prognosis. Based on the presence, absence and degree (high or low) of the following criteria, viz. endothelial proliferation, necrosis, nuclear/cytoplasmic ratio, cell density and pleomorphism, they graded these tumours into four groups: A to D. While most pathologists have given up this grading system, a recent report found definite correlation between the grade of the tumour and post-operative survival.[40] The WHO classification[51] recognises three subgroups: (1) oligodendroglioma; (2) mixed oligoastrocytoma and (3) anaplastic (malignant) oligodendroglioma. Sarkar et al.[39] on the basis of a detailed immunohistochemical and electron microscopic study on 55 cases of this tumour observed that both oligodendrogliomas and oligoastrocytomas arise from a common progenitor cell capable of differentiation into both oligodendrocyte and astrocyte. Earlier studies based only on GFAP immunohistochemistry had arrived at a similar conclusion.[6,19] It was proposed that the nature and degree of differentiation depends probably on gene expression and/or some micro environmental factors.

A more recently used classification is the one proposed by the Sainte-Anne Hospital (SA). According to the WHO, the typing of diffuse gliomas is based on the predominant cell type, oligodendroglial versus astrocytic. In contrast, the SA classification is based on the distinction of two patterns of tumour growth, solid tumour tissue versus isolated tumour cells and also relies on imaging and clinical features. The SA classification includes in the category of oligodendrogliomas, the fibrillary or gemistocytic diffuse astrocytomas (WHO grade II), as well as a substantial proportion of astrocytomas WHO grade III. The WHO uses multiple histological criteria for the grading of oligodendrogliomas (grade II versus grade III), including the degree of differentiation, cellular atypia, mitotic activity and necrosis. In contrast, the SA grading of these tumours (grade A versus B) only uses two criteria: (1) the presence or absence of endothelial hyperplasia and (2) the presence or absence of contrast enhancement on imaging. This last criterion allows overcoming the problems related to the representativeness of surgical samples. Difficulties and discrepancies regarding the diagnosis of oligodendrogliomas are in part due to the lack of an immuno-marker for the identification of tumoural oligodendrocytes.[48] The grading system proposed by Daumas-Duport et al. separating oligodendrogliomas

into low and high grade (grade A and grade B), found tumour grade to be a strong prognostic indicator, but the degree of nuclear atypia and presence of mitosis did not correlate with survival.[14]

INCIDENCE AND SITE

Oligodendrogliomas constitute approximately 5–7% of all primary brain tumours. Mork et al.[32] found their incidence to be 4.2% of all primary brain tumours diagnosed in the Norwegian population in 25 years. Most of these tumours are supratentorial, predominantly affecting the frontal lobes, 50–75% in different series (Figs 1A to D). In a series of 323 cases of oligodendrogliomas, the incidence at various sites was found to be frontal 55%, parietal 20%, temporal 17% and spinal 1%.[30] Most of these are subcortical but, as the tumour grows, it mushrooms through the cortex. Lesions that are close to the ventricles or the subarachnoid spaces may spread along the CSF pathways.[5] Intraventricular oligodendrogliomas are very rare and infrequently reported.[44] Das et al. reported an oligodendroglioma of the pineal region in a 59-year-old woman. The patient presented with intermittent confusion, memory disturbance and headache associated with a cystic pineal region mass demonstrated on magnetic resonance imaging.[11] Packer et al. reported 4 oligodendrogliomas of the posterior fossa in children and found that these tumours may behave more aggressively in this location and may require post-operative craniospinal radiation.[34] Oligodendrogliomas of the spinal cord are uncommon.[17,35] Uzuka et al. reported a rare case of cerebral anaplastic oligodendroglioma developing in adolescence, with rapid haematogenous spread of the glioma cells into the systemic organs, occurring after a relatively long clinical course.[46] Gliomatosis cerebri of oligodendroglial origin is very unusual.[13]



Figs 1A to D: (A) CT scan of the brain plain study. (B) CT scan of the brain contrast study. (C) CT scan of the brain post-operative–plain study. (D) CT scan of the brain post-operative—contrast study

PATHOLOGY

Details are described in the "Neuropathology Section".

Gross Morphological Features

Briefly, the tumour is a pinkish red, vascular and friable mass with a rather deceptive pseudoplane of demarcation. These tumours have been reported to have a tendency for haemorrhage; an incidence of 22% was reported by Ludwig et al.[30] Central foci of necrosis and cystic degeneration occur in the larger lesions. There is a propensity for calcification and a marked tendency to infiltrate the cortex.

Microscopic Features

It consists of a monotonous pattern of small round nuclei, with perinuclear halos, scanty cytoplasm and a prominent cell wall. Like any other glioma, these neoplasms form a spectrum from the cytologically well differentiated to the anaplastic.

Ultrastructural Features

Oligodendroglial tumour cells may have either scanty or abundant cytoplasm, rich in organelles, including microtubules, free ribosomes, mitochondria and prominent Golgi apparatus. Polygonal intracytoplasmic crystalline inclusions have been described, but are not specific. Laminated cell processes overlying the cell body are commonly present and are typical of oligodendroglioma.

Immunohistochemistry

Angiogenesis has been proposed as essential for the growth of solid tumours. The determinants of this process, the growth factors and the vascular endothelial receptors have a role in determination of tumour prognosis, as well as perspectives of "targets" for antiangiogenic therapy. In oligodendrogliomas (OL), angiogenesis is little known. In order to clarify angiogenesis in OL, Corteze Netto et al. have evaluated the immunohistochemical expression of vascular endothelial growth factor (VEGF) and the microvascular density (MVD) through the expression of TGF-beta (CD105/endoglin) (MVD-CD105) and CD34 (MVD-CD34) receptors, using the Chalkley point method in 30 OL. No significant immune reaction was found for the VEGF. If present, the expression was restricted to tumour and endothelial cells. Their findings suggest that VEGF has little

influence on OL angiogenesis. All specimens showed CD105 and CD34 expression in the intratumour vascular endothelium, suggesting involvement of CD105 in OL angiogenesis. The absence of correlation between DMV-CD105, DMV-CD34 and tumour grades suggests that anti-CD105 and anti-CD34 antibodies have different vascular specificities. MVD-CD105 was greater in OL grade III than in OL grade II ($p = 0.0032$), indicating an increase in the vascular neo-formation, something which must be evaluated as a possible prognostic factor in OL. Both TGF-beta and CD105 bring perspectives as "targets" for antiangiogenic treatments in OL.[8] OLIG2 is a basic helix-loop-helix transcription factor regulating the generation of oligodendrocytes from neural progenitor cells and the function of OLIG2 is inhibited post-translationally through the interaction with ID2. Mikami et al., in their study, found that OLIG2 expression was predominant over ID2 expression in oligodendroglial tumours, while ID2 expression was predominant over OLIG2 expression in astrocytic tumours. Comparative genomic hybridisation revealed that gliomas with loss on chromosome 1p, which is closely associated with chemosensitivity, also showed the predominant expression of OLIG2 over ID2. Their results indicate that the immunohistochemical study on the relative expression level of OLIG2 to ID2 can be a useful screening for oligodendroglial tumours.[31] Carbonic anhydrase IX is a hypoxia-induced enzyme that has many biologically important functions, including its role in cell adhesion and invasion. Jarvela et al. studied the role of CA IX expression in a series of 86 oligodendroglial brain tumours (71 primary and 15 recurrent; 48 pure oligodendrogliomas and 40 mixed oligoastrocytomas). 80% of the tumours showed CA IX expression by immunohistochemistry. Tumours with moderate or strong CA IX expression had decreased level of cell proliferation compared to weak or no CA IX expression (median 2.9 vs. 5.8, $p=0.015$). CA IX correlated with two antioxidative enzymes, manganese superoxide dismutase (MnSOD) and regulatory gammaglutamylcysteine synthetase (GLCL-R): CA IX expression was significantly higher in MnSOD-positive tumours ($p=0.008$) and decreased in GLCL-R-positive tumours ($p=0.044$). In Cox multivariate analysis CA IX expression, patient age and histological component (pure oligodendroglioma vs. mixed oligoastrocytoma) showed independent prognostic values ($p=0.009$, $p=0.003$ and $p=0.022$, respectively), CA IX positivity predicting poorer outcome. They concluded CA IX proved to be an independent prognostic indicator in oligodendroglial brain tumours and it also correlates reversely with cell proliferation. It may have a role in the biology of oligodendrogliomas and most interestingly, as it is mainly expressed in tumour tissue, CA IX could serve as a target molecule for anticancer treatments.[22]

Cytogenetic and Molecular Studies

During the last decade, enormous progress in understanding of these molecular alterations has been accomplished. Oligodendrogliomas show distinct genetic alterations, allowing us to distinguish them from other types of gliomas. The loss of heterozygosity (LOH) on chromosomes 1p and 19q were reported to be the most frequently observed alterations. While loss of heterozygosity on chromosome 1p is a statistically significant predictor of chemosensitivity, combination with deletions on chromosome 19q was reported to be associated with both chemosensitivity and longer recurrence-free survival after therapy. Conversely, allelic loss on chromosome 10q, observed in many anaplastic oligodendrogliomas, predicts rather poor outcome.[18] The favourable response of oligodendrogliomas correlates well with characteristic chromosomal losses, of which loss of the short arm of chromosome 1 is most predictive. Oligodendrogliomas are histopathologically heterogeneous tumours and, in addition to the classic honeycomb histology, fields of non-classic histology are often encountered. Information about the distribution of 1p loss in various regions of oligodendroglioma is, therefore, important to interpret findings in tumour biopsies. Kros et al. investigated the distribution of 1p loss in multiple fields in 24 biopsy specimens of oligodendroglioma, consisting of classic and non-classic histology by fluorescent in situ hybridisation and loss of heterozygosity analysis. By fluorescent in situ hybridisation analysis, loss of 1p was found in all fields examined in 37% of the tumour samples and no loss was detected in 46%. In fields of classic oligodendroglial and polar spongioblastoma-like histology, significantly more loss for 1p was found ($p < 0.001$ and $p < 0.01$, respectively). Although fluorescent in situ hybridisation analysis indicated heterogeneity for 1p loss in the other 17% of tumours, loss of heterozygosity analysis of these samples pointed to homogeneity of 1p status in all fields. The 1p status of the fields with classic histology significantly correlated with the status of the other fields in the same tumours (Spearman's rho 0.918, $p < 0.001$). These results point to genotypic homogeneity for 1p in oligodendroglial tumours.[26] Importantly, the possible effect of combined 1p/19q loss has not been studied in patients who were not treated with radiotherapy or chemotherapy. Weller et al. identified 76 patients with oligodendroglioma (n = 33), oligoastrocytoma (n = 30), anaplastic oligodendroglioma (n = 6) or anaplastic oligoastrocytoma (n = 7) who had not received radiotherapy or chemotherapy after their first operation, until the end of follow-up or until the first progression and had tissue for 1p/19q status available. 1p/19q status was assessed by multiplex ligation-dependent probe amplification. They concluded that combined 1p/19q loss is not a sensitive prognostic biomarker in patients with oligodendroglial tumours who do not receive radiotherapy or chemotherapy. The gene products lost as a consequence of this codeletion may include mediators of resistance to genotoxic therapies. Alternatively, 1p/19q loss might be an early oncogenic lesion, promoting the formation of glial neoplasms, which retain high sensitivity to genotoxic stress.[50]

The functional single-nucleotide polymorphism (SNP) in codon 72 of TP53 has been shown to be both a risk factor and a prognostic biomarker in various cancers. Such results were also reported in other brain tumours, notably in astrocytomas. This SNP has never been precisely investigated in oligodendroglial tumours. Idbaih et al. retrospectively analysed blood samples of 275 oligodendroglial tumour patients for the TP53 codon 72 polymorphism and compared them with a series of 144 healthy controls. Arg/Arg, Arg/Pro and Pro/Pro genotypes were found in 54.2 versus 60.4%, 39.3 versus 34.0% and 7.3 versus 5.6% of patients and controls, respectively. This suggests no association between oligodendroglial tumours and the SNP in codon 72 of TP53. Similarly, no correlation was found among the TP53 codon 72 polymorphism and prognosis, p53 expression and chromosomes 1p and 19q status.[20] The expression of coronin-3 varies in different brain tumour entities. However, in diffuse gliomas, the number of coronin-3 expressing tumour cells correlates with the degree of malignancy. High-grade gliomas, such as anaplastic astrocytomas, anaplastic oligodendrogliomas, anaplastic oligoastrocytomas and glioblastomas show high numbers of tumour cells positive for coronin-3, while diffuse low-grade gliomas, such as diffuse astrocytomas, oligodendrogliomas and oligoastrocytomas, exhibit low numbers of coronin-3-positive tumour cells. In order to explore and verify a contribution of coronin-3 to the malignant phenotype of diffuse gliomas, Thal et al. employed an efficient shRNA-mediated coronin-3 knockdown in U373 and A172 human glioblastoma cells. Coronin-3 knockdown glioblastoma cells exhibited reduced levels of cell proliferation, cell motility and invasion into the extracellular matrix compared to control cells. Their findings demonstrate evidence for a contribution of coronin-3 expression in the malignant progression of diffuse gliomas.[45] Abnormal expression of peroxiredoxin 6 and rho GDP dissociation inhibitor alpha may be associated with malignant transformation in oligodendroglioma and these proteins might be candidates of molecular predictive factors.[36]

AGE AND SEX

Characteristically it is a tumour of middle-aged persons, although the age range has been recorded from 3 years to 76 years, with a biphasic peak between the ages of 6 years and 12 years and a second peak between the ages of 26 years and 46 years. In several large series, the median age was around 44 years.[30,40] Only 5–6% of tumours occurred in the paediatric age group. Males are more frequently affected (60–65%). Ludwig et al.[30] reported a male to female ratio of 3:1.

CLINICAL FEATURES

These tumours tend to grow relatively slowly. The average duration of symptoms has been reported to vary from 33 months to 43 months, the range being 3 days to 29.9 years.[40] Due to the predominantly frontal location and a relatively slow growth rate, the tumour attains a large size before symptoms occur. Epileptic fits constitute the most common initial symptom. The highest incidence of epilepsy in patients with supratentorial gliomas was observed in oligodendrogliomas. The other presenting symptoms include headache, visual disturbances, papilloedema and focal neurological deficits. There are no characteristic clinical features attributable to this tumour, except a high propensity for calcification, seen in 25–30% even in plain X-rays of the skull.

RADIOLOGY

The age of the patient, the location of the tumour in the frontal lobe and the presence of calcification in plain X-rays of the skull should arouse the suspicion of an oligodendroglioma. On CT scan, the lesion appears as a heterogeneous mass, isodense to hypodense, as compared with normal brain. With contrast, the tumour may show variable enhancement, usually to a mild to moderate degree (Fig. 2A). Low-grade oligodendrogliomas usually do not enhance with contrast. More malignant lesions are characterised by more intense, irregular enhancement, associated with vasogenic oedema and mass effect. Linear or nodular calcification has been reported in 50–90% of oligodendrogliomas on CT.[28] On MR, (Figs 2B to E) oligodendrogliomas are usually heterogeneous and isointense to grey matter on long TR images. Calcification, which cannot be seen on conventional spin echo MR, can be demonstrated on gradient echo imaging. Fifty percent show contrast enhancement.

Positron emission tomography (PET) has the ability to differentiate low-grade oligodendroglioma from astrocytoma, based on the methionine uptake. Low-grade oligodendrogliomas have a high methionine uptake, while in astrocytomas it can be decreased, moderately increased or may be normal.[12] [11C]-L-methyl-methionine (MET)

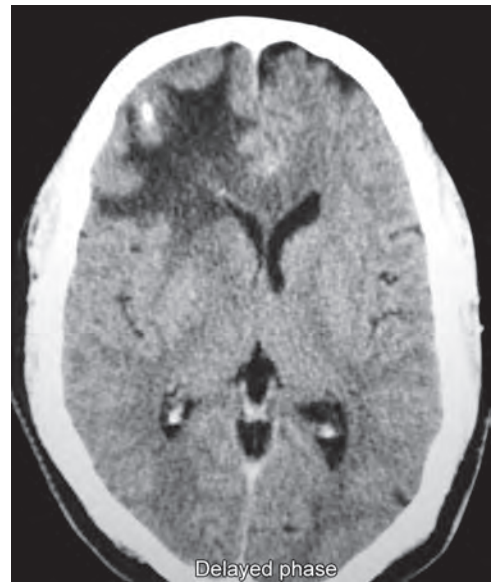
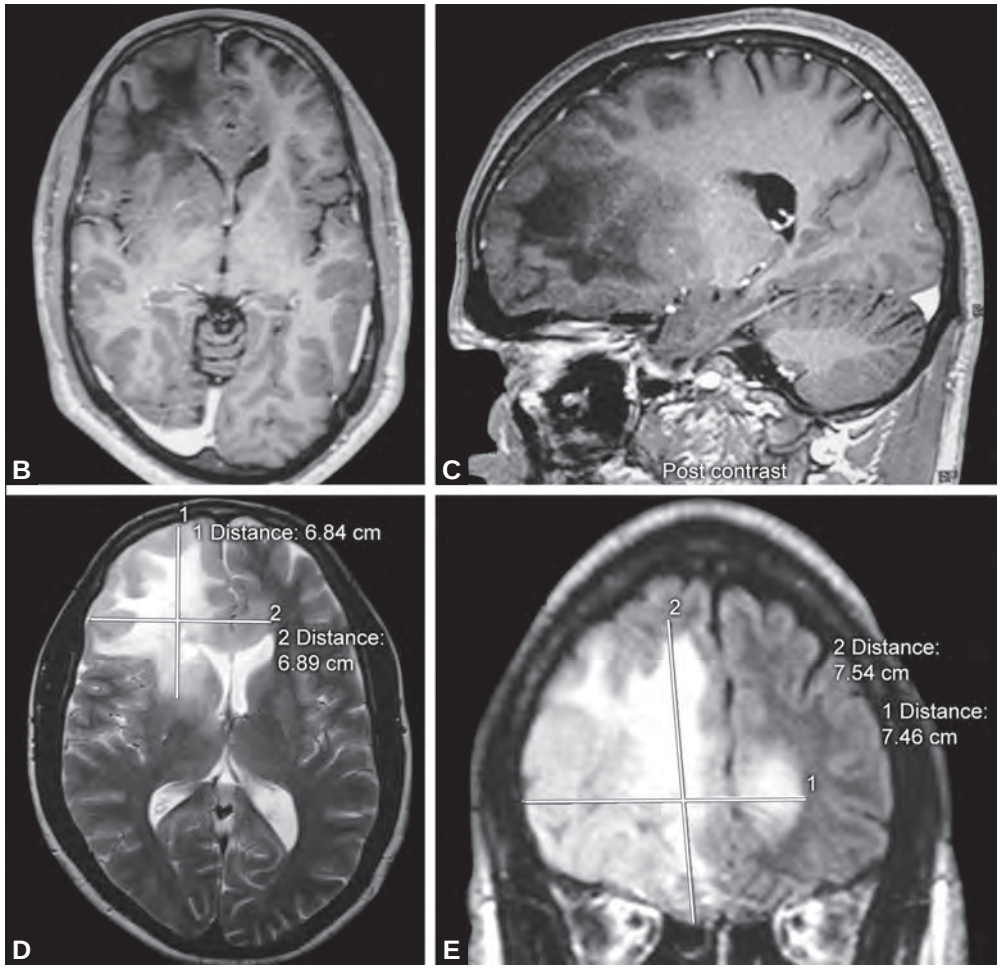


Fig. 2A: CT scan of the brain contrast study



Figs 2B to E: (B) MRI brain T1 axial. (C) MRI brain T1 sagittal. (D) MRI brain T2 axial. (E) MRI brain T2 coronal

appears more sensitive than [18F]-flurodeoxyglucose (FDG) to detect proliferation in ODG. The preferential protein metabolism, already noticeable for low-grade tumour, correlated with glucose metabolism and helped to separate, *in vivo*, high-grade and low-grade tumours. (11)-C methionine (MET) PET image fusion may facilitate the targeting of anaplastic foci in homogeneous MRI non-enhancing gliomas for biopsy, may identify oligodendroglial histology pre-operatively, as well as characterise biologically active tumour volumes within MRI T(1)/FLAIR tumour areas of candidate patients for resection.[38]

DIFFERENTIAL DIAGNOSIS

The dysembryoplastic neuroepithelial tumour (DNET) is a tumour which contains foci similar in appearance to oligodendrogliomas. Dural based oligodendrogliomas may be confused with meningiomas. Intraventricular oligodendrogliomas must be differentiated from central neurocytomas which histologically can be very similar in appearance.[25] Clear cell variant of ependymoma is a rare entity which morphologically mimics oligodendroglioma and poses a diagnostic dilemma. Jain et al. described three cases of clear cell ependymoma in male children which were supratentorial in location. On microscopic examination, these tumours were composed of sheets of clear cells and resembled oligodendroglioma. Electron microscopy confirmed the ependymal nature of these tumours.[21] High-grade oligodendrogliomas should be differentiated from other anaplastic gliomas and metastatic carcinoma.

TREATMENT

General Management Plan

The optimal treatment for patients with oligodendrogliomas is unknown and current management strategies remain controversial. It is becoming increasingly apparent that oligodendrogliomas are a distinct disease on a molecular level and that key genetic derangements can signify a response to treatment and favourable outcome. The combination of improved imaging techniques, molecular profiling and new therapies should result in improved outcome with reduced treatment-related toxicity for patients with newly diagnosed, progressive and recurrent oligodendrogliomas. Most patients harbouring oligodendrogliomas present with a long-standing history of epilepsy. However, the seizures due to these lesions are commonly refractory to medication.[41] The efficacy of surgical resection in decreasing seizure frequency has been reported.[27] It is necessary to obtain a histological

diagnosis in all cases of suspected oligodendroglioma. This can be achieved by a stereotactic biopsy or excisional biopsy. Subsequent treatment options available are surgical resection of the lesion, followed by post-operative radiotherapy and/or chemotherapy.

Surgical Management

Oligodendrogliomas are managed (Figs 1C and D) like any other glioma, with as radical a removal as possible. However, the role of resection on prognosis, the most appropriate time for surgery along the natural history of these tumours and the best operative strategy remain debatable. Surgical or stereotactic biopsy is the first surgical procedure which enables confirmation of the diagnosis suggested on imaging, assessment of extension of tumour cell infiltration beyond the abnormalities limit described on imaging and currently available molecular biology studies. Biopsies may be the only surgical procedure in patients having a deep-seated tumour with minimal mass effect or prior to a surgical resection or a "wait and watch" strategy. Surgical resection may be indicated for the other patients. However, it has not been demonstrated that time for resection has an influence on survival, except in patients with rapidly growing tumours with mass effect causing increased intracranial pressure. The present trend is for maximal safe resection, preserving 'eloquent' cerebral areas, since truly large or complete resection of the tumour based on imaging is not associated with significantly longer survival. Neuronavigation guidance, intra-operative imaging and cortical stimulation techniques are helpful neurosurgical techniques enabling maximal safe resection with preservation of functional areas. In a series of 170 non-randomised patients treated for cerebral oligodendrogliomas, Lindegaard et al.[29] observed a significant prolongation of post-operative survival, if irradiation was given in addition to surgery.

Radiation Therapy

The 5-year survival for the group who had surgery plus irradiation was 36%, as compared to 26.5 for surgery alone. However, 8 years post-operatively, there was no significant difference between the two groups. Radiation doses between 40 Gy and 50 Gy were as effective as doses between 50 Gy and 60 Gy. Wallner et al.[49] reported 10-year survival of 56% for those treated with surgery and irradiation, as compared to 18% with surgery alone. It has been suggested that selected patients who undergo gross total resection, particularly younger patients with low-grade tumours, may not require post-operative radiation therapy.[40]

Chemotherapy

Cairncross et al.[7] have identified a sub-group of aggressive oligodendrogliomas which proved to be highly chemosensitive. Fifty to seventy percent of patients with recurrent oligodendroglial tumours may respond to chemotherapy. Genetically, 60–70% of oligodendroglial tumours are characterised by the loss of the short arm of chromosome 1 (1p) and the loss of the long arm of chromosome 19 (19q). Virtually all tumours with the combined loss of 1p/19q respond to chemotherapy, which has been the first demonstration of the clinical usefulness of the genotyping of brain tumours. These tumours have a classical oligodendroglial histology and more often have a much better prognosis than oligodendrogliomas without 1p/19q loss.[47]

Two independent large Phase III trials on adjuvant procarbazine, lomustine and vincristine chemotherapy in anaplastic oligodendroglial tumours have shown improvement in progression-free survival, but not overall survival, regardless of 1p/19q status. If given sequentially, the timing of procarbazine, lomustine and vincristine chemotherapy has no clear effect on the survival of anaplastic oligodendroglioma. Virtually, none of the many new targeted agents directed against pathways that are up-regulated in high-grade gliomas has shown significant clinical activity as a single agent in phase II studies. The exceptions are trials with the vascular endothelial growth factor signalling system inhibiting agents bevacizumab and AZD2171 (cediranib), that showed high response rates (which might be due to vessel normalisation similar to the effects of steroid treatment) and promising 6-month progression-free survival rates in glioblastoma. Further research to define the role of vascular endothelial growth factor inhibition in the management is indicated.[4]

Temozolomide is a methylating agent that is typically administered once daily. Because preclinical studies suggested that a twice daily dosing schedule might be more effective, Balmaceda et al. studied the safety and efficacy of twice-daily dosing of temozolomide in patients with recurrent gliomas at their first, second or third recurrence. They concluded twice-daily dosing may enhance the efficacy of temozolomide in the treatment of recurrent gliomas, without increasing toxicity.[3]

Sunyach et al. found front-line exclusive chemotherapy results in prolonged overall survival in patients with confirmed pure oligodendroglioma. Whether this strategy improves quality of life remains debatable.[43]

Chemoresistance is a widespread therapeutic challenge in glial tumours. The molecular basis of chemoresistance is poorly understood, precluding advances in glioma treatment and leaving gliomas among the most lethal tumours. Oligodendrogliomas provide a unique model to study the molecular basis of chemoresistance, as there are two distinct genetic subtypes with significant differences in chemosensitivity. Despite a high morphological similarity, tumours with allelic loss on the short arm of chromosome 1 (1pLOH) are more chemosensitive than those without 1pLOH. Okamoto et al. identified seven candidate proteins that are overexpressed in oligodendrogliomas without 1pLOH. Two of these proteins (glyoxalase I and Rho GDP dissociation inhibitor)

have previously been shown to enhance chemoresistance in other tumours. In turn, they identified twelve overexpressed proteins in tumours with 1pLOH that have previously been reported to induce chemosensitivity in other forms of human neoplasia. They concluded that these identified proteins are potential targets for pharmacological therapy and may also be useful as biomarkers for differentiation of chemoresistant and chemosensitive oligodendroglioma.[33]

What is the safety and efficacy of interstitial chemotherapy with carmustine-loaded polymers (Gliadel® wafers) in the treatment of newly diagnosed or recurrent malignant gliomas? Perry et al. from their study found Gliadel® to be an option for selected patients with newly diagnosed malignant glioma, where a near gross total resection is possible. No evidence is available comparing Gliadel® with systemic therapy and a decision to combine Gliadel® with systemic therapy should be made for patients individually. The most frequently reported adverse events were convulsions, confusion, brain oedema, infection, hemiparesis, aphasia and visual field defects.[37] Da Fonseca et al. reported a case of a patient with anaplastic oligodendroglioma managed with intranasal delivery of 0.3% concentration of perillyl alcohol (POH), following a radical surgical excision of the lesion.[10]

PROGNOSIS

The median duration of disease from the onset of symptoms to death was 14 months in nine untreated cases. The median post-operative survival period was 14 months longer in those patients who were considered to have gross total removal of the tumour.[32] Histopathologically, using univariate analysis, Burger et al.[6] observed five prognostically significant factors, in order of decreasing importance: mitoses, necrosis, nuclear cytologic atypia, vascular hypertrophy and vascular proliferation. When studied by stepwise regression, the presence of necrosis and the number of mitoses contained all of the prognostically useful information. Post-operative radiotherapy improved the 5-year survival rate of patients who had subtotal tumour removal. The presence of calcification and the absence of CT enhancement were associated with longer survival.[40]

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138 Ependymomas

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DEFINITION

Ependymoma is a slow-growing tumour arising from the wall of the cerebral ventricles or from the ependymal lining of the central canal of the spinal cord and filum terminale and is composed of neoplastic ependymal cells. The tumour is of neuroectodermal origin and corresponds histologically to WHO grade II (Table 1).

INCIDENCE

Of all neuroepithelial tumours, 3–9% are ependymomas. Ependymoma is a tumour of childhood and accounts for 6–12% of all paediatric intracranial tumours. Nearly 30% of intracranial tumours in children less than 3 years of age are ependymomas.[11] Ependymoma is the most common spinal cord tumour, comprising 50–60% of glial tumours of the spinal cord.[40]

ORIGIN

Ependymomas arise probably from a differentiated ependymal cell, although there is another view of their origin, being from a less differentiated ependymoglial precursor cell.[24] Rare, familial cases have been reported. Adult tumour cells show allelic losses of chromosome 22, suggesting the presence of a tumour suppressor gene.[29]

LOCATION

Although these tumours can occur at any site where there is an ependymal lining, nearly two-thirds of the ependymomas are infratentorial, while one-third are above the tentorium.[39] Most infratentorial ependymomas occur in the midline, often involving the floor of the fourth ventricle, particularly in the region of the obex, and hypoglossal and vagal triangles (Fig. 1). These infratentorial tumours are solid and can grow laterally into the lateral recesses and foramina of Luschka. A tongue of tumour may extend below the foramen magnum[22] and the tumour can infiltrate into the pons and medullary tegmentum. Rarely, extraventricular ependymomas may be seen in the supratentorial region, especially in children. These probably originate from embryonic remnants in the brain parenchyma. Anecdotal case reports of extraneural ependymomas originating in the ovaries, mediastinum and sacrococcygeal region have been described.[26] In adults, infratentorial and spinal ependymomas occur with equal frequency, while infratentorial ependymomas are predominant in children.[21]

In the spinal cord, the cervical and cervicothoracic segments are most frequently affected. The conus and cauda equina regions are the preferred sites for occurrence of myxopapillary ependymoma.

Table 1: Classification of ependymal tumours[18]

1.	*Ependymoma*
	Cellular
	Epithelial
	Papillary
	Clear cell
	Mixed
2.	*Anaplastic ependymoma*
3.	*Myxopapillary ependymoma*
4.	*Subependymoma*
5.	*Ectopic ependymoma*
	Parasacral
	Intra-abdominal

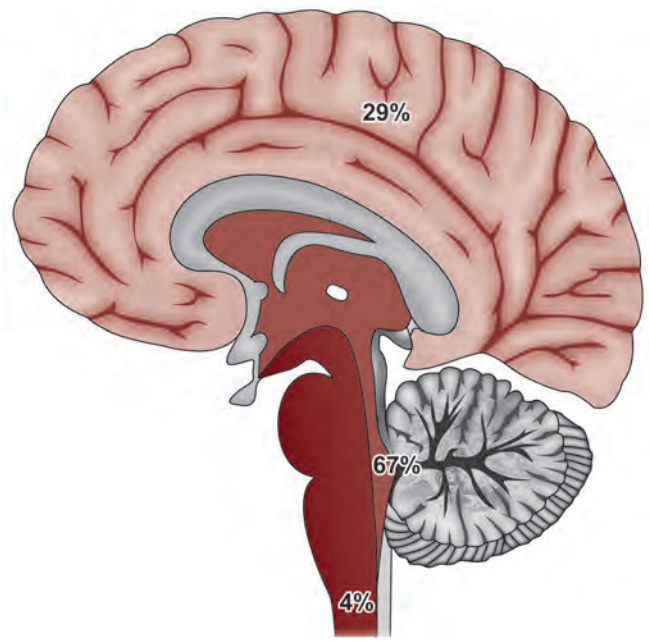


Fig. 1: Distribution of ependymomas in the paediatric neuraxis

CLINICAL PROFILE

Ependymomas, as with other posterior fossa tumours of childhood, often present with features of raised intracranial pressure due to obstructive hydrocephalus. Generally, this manifests as headache and repeated vomiting. Infants can present with lethargy and macrocephaly.[1] Symptoms are worse in the morning, as recumbency and raised carbon dioxide blood levels during sleep cause an increase in cerebral blood flow and a consequent rise in intracranial pressure. Vomiting may precede other symptoms in case the tumour originates in the caudal part of the fourth ventricular floor and these children may often undergo initial evaluation by a paediatric gastroenterologist. Gait or truncal ataxia may be seen with involvement of the cerebellar vermis. Nystagmus, papilloedema and ocular cranial nerve palsy may be seen, and lower cranial involvement may be seen in tumours with lateral extension. Neck pain, head tilt and nuchal rigidity can occur if the tumour extends caudally through the foramen magnum. Seizures occur in one-third of patients with supratentorial tumours.[15]

Supratentorial ependymomas constitute about 30% of all intracranial ependymomas.[25,42] The tumours may be intra-or extraventricular. Of the intraventricular tumours, the ones in the lateral ventricles are more common.[30] Intraventricular tumours present more often with obstructive hydrocephalus, while extraventricular tumours may manifest as seizure disorder with raised intracranial pressure. Some supratentorial tumours reach the pial surface.[2,35]

Intraspinal Ependymomas

These are intramedullary, filum terminale or sacral in location and often have a long history spanning several years. The intramedullary tumour extends over several segments, is usually discrete, elongated and sausage-like with a clear plane between it and the cord tissue, causing fusiform expansion of the cord. Backache is often the only symptom for some time and sphincter dysfunction occurs late. Clinical features reveal myelopathy and there may be a suspended zone of sensory impairment. There may be syrinx above or below the tumour. Tumours involving the filum terminale arise from ectopic ependymal cell rests and may attain a large size before detection. Presentation is in the form of cauda equina syndrome, wasting of calves and talipes deformity of the feet and ankles.

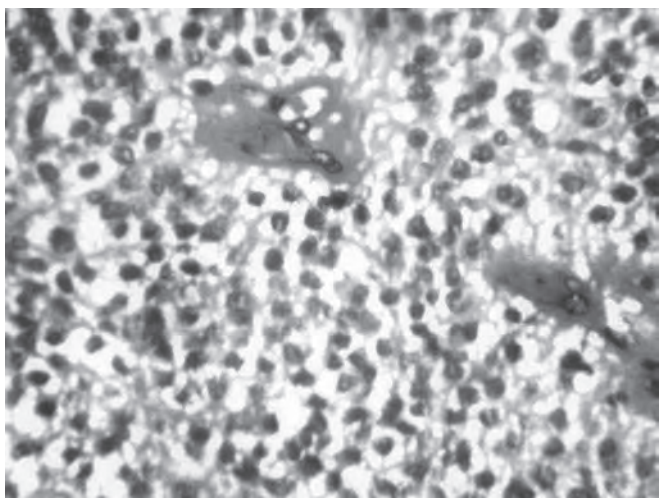
PATHOLOGY

(See Section 11)
(Figs 2 and 3)

IMAGING

Ependymomas are generally solid tumours. CT shows calcification in nearly 50% of cases and areas of haemorrhage and cyst formation may be seen (Fig. 4). On MRI, these tumours are circumscribed, and appear isointense or hypointense on T1-weighted images and intensely enhance with contrast. They appear hyperintense on T2-weighted and proton-density images. They appear heterogeneous on MRI in the presence of cyst formation, calcification, haemorrhage and necrosis. Cyst formation is often seen in supratentorial tumours.

Spinal ependymomas may appear like astrocytomas on MRI. A "tumour cap" at either pole of the intramedullary tumour is highly suggestive of an ependymoma. On administration of intravenous Gadolinium, tumoural contours are clearly defined in ependymomas, unlike that of astrocytomas (Figs 5 to 11). Nearly a fifth of ependymomas may, however, show no contrast enhancement. Besides astrocytoma, an intramedullary ependymoma should be distinguished from sarcoidosis, a rare condition which responds to corticosteroids.



Figs 2: Histopathology showing pseudorosettes typical of ependymoma (H & E, X40)

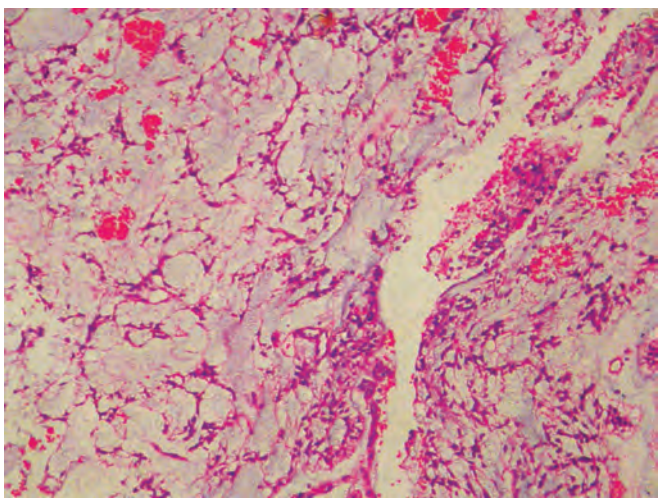


Fig. 3: Histopathology showing myxopapillary ependymoma (H & E, X40)

MANAGEMENT

Surgical excision is the mainstay in the management of these tumours – whether supratentorial, infratentorial or spinal intramedullary. In patients with supratentorial tumours, a craniotomy is performed and the tumour—intraventricular or extraventricular—is approached. Real-time ultrasound can reliably demarcate the tumour and a cystic component can be tapped to relax the brain. Gross total excision is the desired goal, so as to achieve satisfactory cytoreduction.

Infratentorial tumours often lead to hydrocephalus by the time treatment is sought. Although hydrocephalus can resolve with excision of the tumour, it is preferable to divert the CSF pre-operatively. This will reduce intracranial pressure and improve the general well-being of the patient. CSF diversion can be achieved by ventriculoperitoneal shunt (with a filter device to prevent tumour seeding) or by endoscopic third ventriculostomy. Alternatively, a ventricular catheter can be placed at the time of surgery to release CSF and reduce brain swelling and intracranial pressure. Treatment with parenteral glucocorticoids for several days helps in reducing intracranial pressure pre-operatively.

Posterior fossa lesions occurring in the fourth ventricle can be exposed by suboccipital craniectomy or craniotomy. The patient is positioned prone with the neck flexed. The arch of the atlas and the lamina of the axis are removed to facilitate exposure in cases with intraspinal extension. After dural opening, the operating microscope is brought into the operative field. CSF is released from the cisterna magna and the vermis is split to a variable extent. The tumour is excised by cutting and coagulation and the ultrasonic aspirator can be used to reduce the tumour bulk. A thin layer adherent to the fourth ventricular floor may have to be left to avoid post-operative dysfunction of the upper aerodigestive track. Complete vermis section and excessive lateral retraction should be avoided to prevent post-operative cerebellar mutism. The dura should be closed after haemostasis, if necessary, with a dural graft. Repeat surgery by the lateral approach may be required when tumour extends into the lateral recesses. Children in whom the posterior arch of atlas and lamina of the axis are removed will require post-operative assessment for instability at the craniovertebral junction.

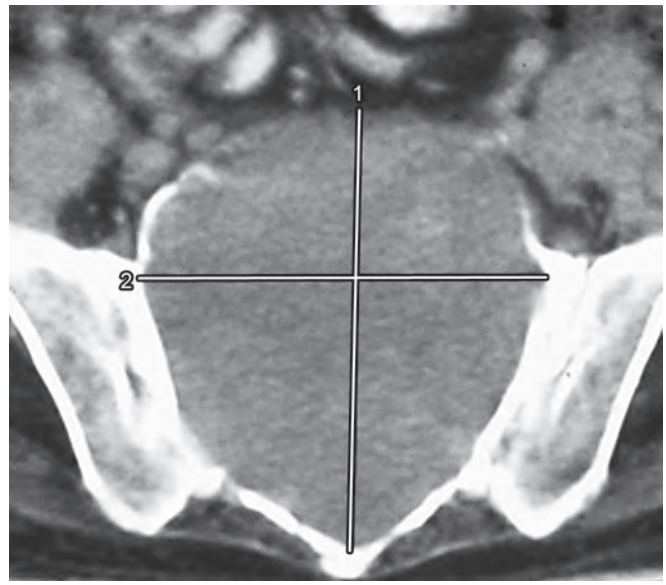
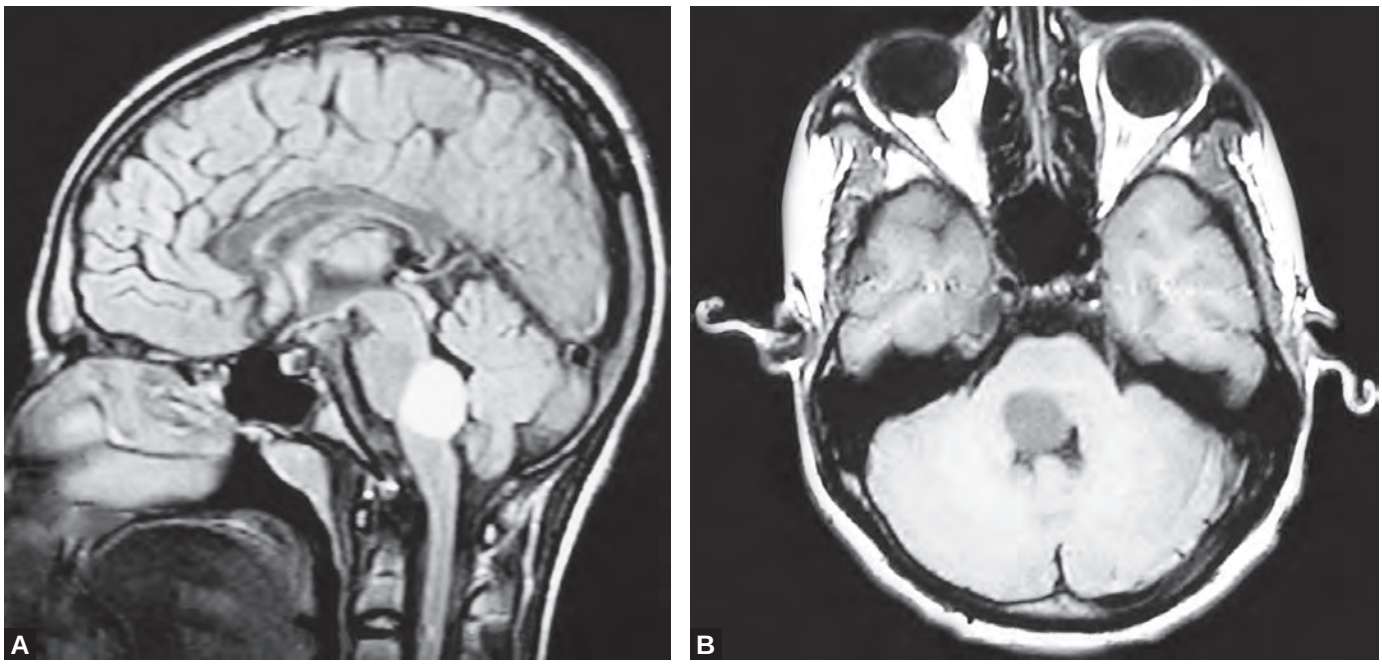


Fig. 4: CT showing large sacral ependymoma



Figs 5A and B: MRI brain (gadolinium enhanced T1-weighted) sagittal and axial sections showing ependymoma in the floor of the fourth ventricle

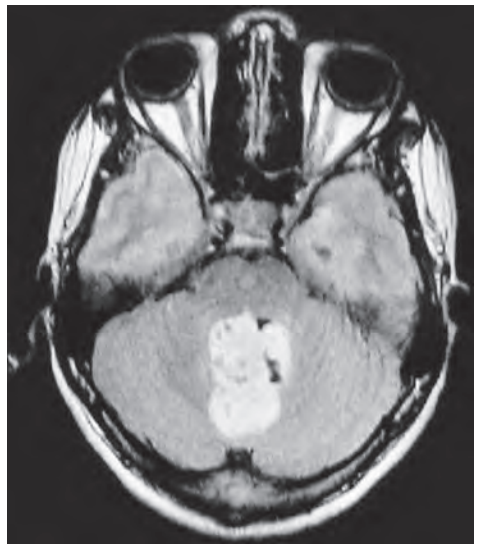
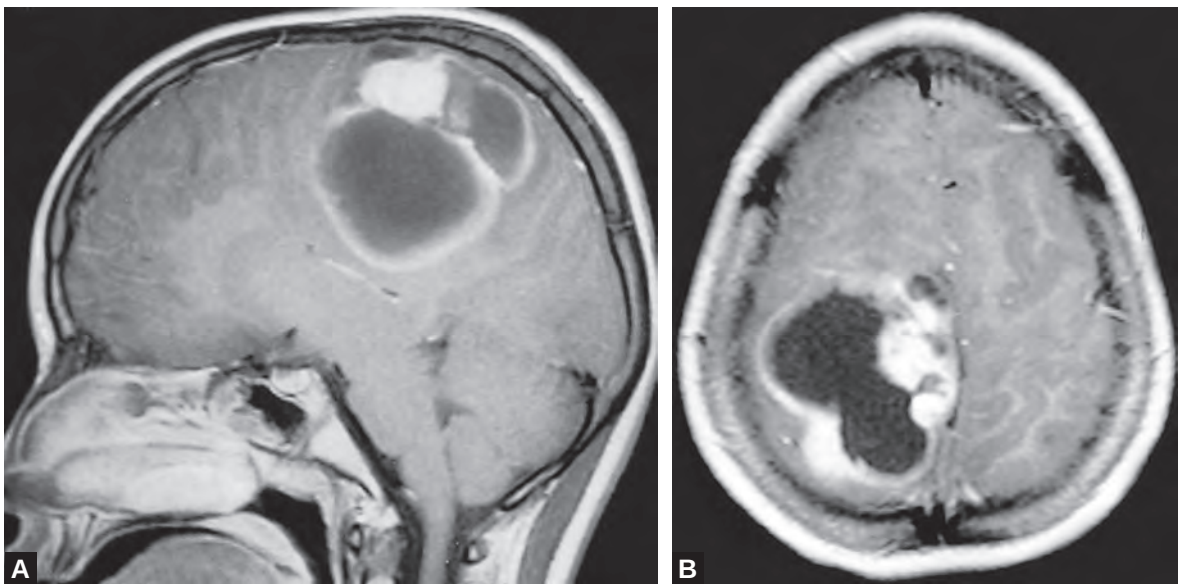


Fig. 6: MRI (FLAIR) showing ependymoma occupying the cavity of the fourth ventricle



Figs 7A and B: MRI brain (gadolinium enhanced T1-weighted) sagittal and axial sections showing cystic supratentorial ependymoma in the right parietal lobe without any ventricular attachment

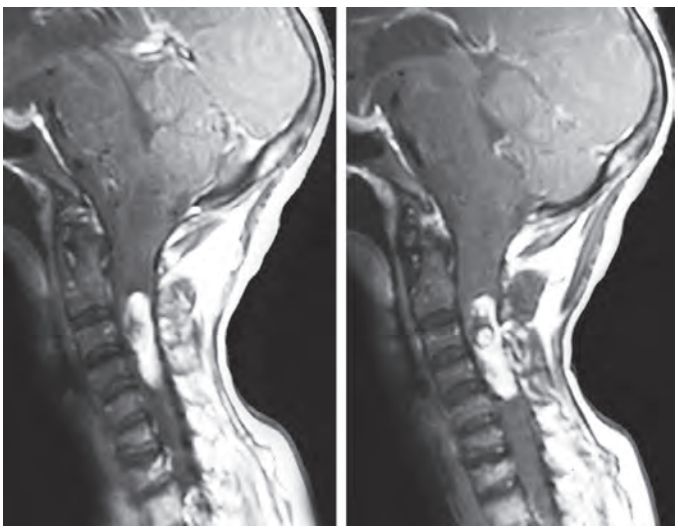


Fig. 8: MRI (gadolinium enhanced T1-weighted) cervical spine sagittal section showing intramedullary ependymoma

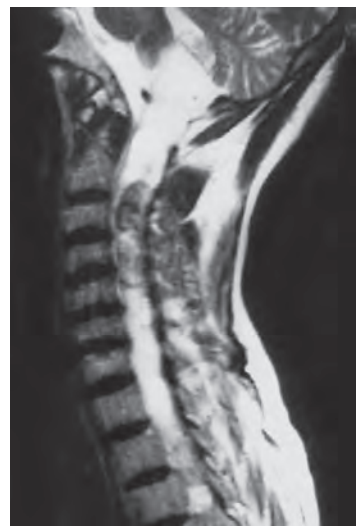


Fig. 9: MRI (T2-weighted) cervicodorsal spine showing syrinx rostral and caudal to the solid intramedullary ependymoma

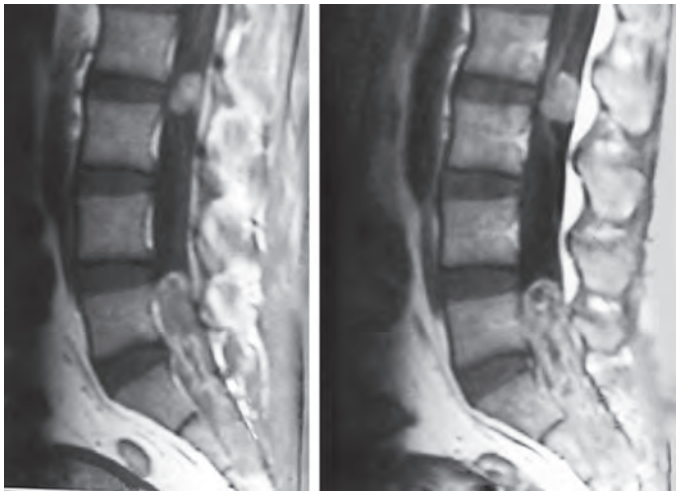


Fig. 10: MRI lumbar spine (gadolinium-enhanced T1-weighted) showing intradural ependymomas at L2 and sacral regions

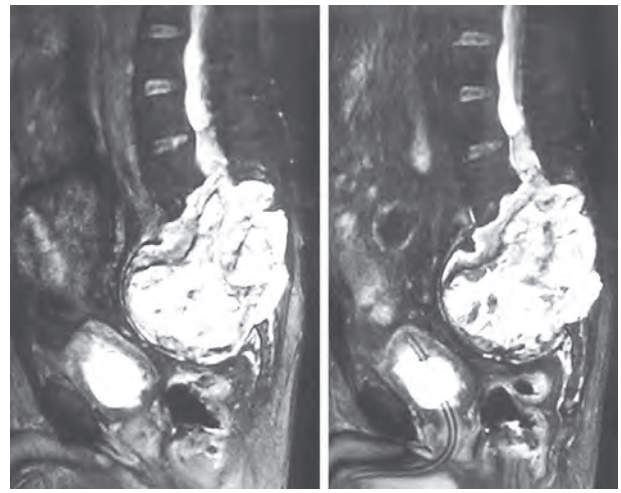


Fig. 11: MRI (T2-weighted) lumbosacral spine showing giant ependymoma

Intramedullary spinal cord ependymomas are best treated by surgical excision (Figs 12 to 14). The MRI data in three planes should be analysed and it is essential to define the length and depth of the tumour. Most ependymomas are centromedullary, although uncommonly, they may be exophytic. Limits of the tumour's solid portion will determine the extent of laminectomy/laminotomy. However, one must bear in mind that with rare exceptions, patients do not recover from severe pre-operative neurological deficits and patients with little or no deficits are the ones who are likely to remain free from deficits post-operatively. Post-operative quality of life depends upon the pre-operative neurological status.

Adjunctive Therapy

Radiotherapy

The role of radiotherapy in ependymomas has been difficult to validate, although these tumours are radiosensitive. Local field irradiation is the treatment recommended. The recommended dose is 4500–6000 cGy over 5–6 weeks. Prophylactic irradiation of the spinal cord is not advised, since the incidence of spinal seeding is low. However, for adults, craniospinal irradiation has been advocated in case of incomplete resection. Children below three years do not receive radiotherapy and in the presence of anaplastic tumours, have a lower progression-free-survival. Stereotactic implantation of iodine-125 seeds has been reported in a case of large benign intraventricular ependymoma and the tumour shrank within a few weeks and the patient had a long progression-free survival.[46] Efficacy of chemotherapy is still not established in ependymomas.

ANAPLASTIC EPENDYMOMA

As with other glial cell tumours, ependymomas can show aggressive behaviour in their malignant forms. Anaplastic ependymoma is a high grade malignant tumour (WHO III) with an aggressive course and unfavourable outcome. Histologically, they exhibit high mitotic activity, microvascular proliferation, perivascular

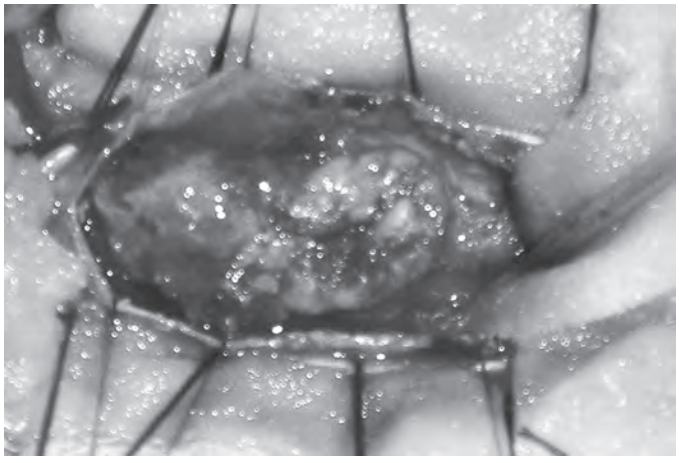


Fig. 12: Operative photograph showing discrete intramedullary tumor in the cervical cord

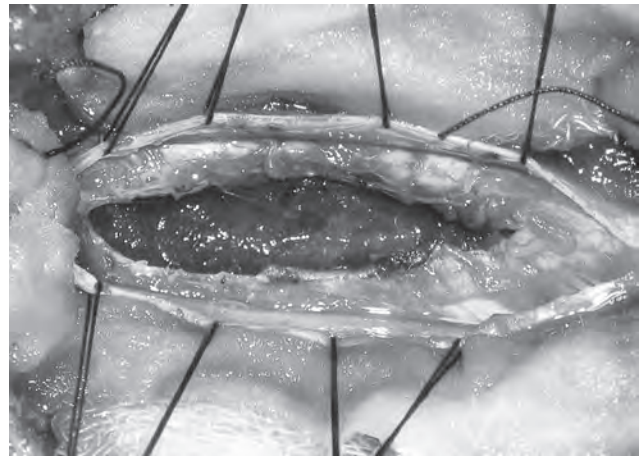


Fig. 13: Post-operative appearance after complete excision of the intramedullary ependymoma

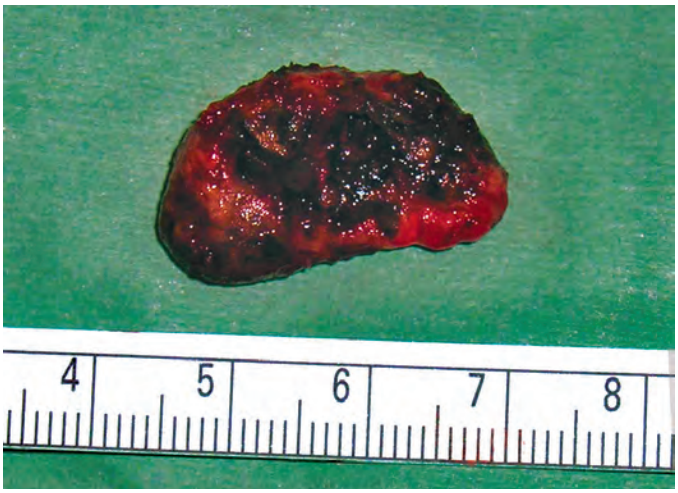


Fig. 14: Intramedullary ependymoma of the cervical cord—excised specimen

rosettes of narrow width and pseudopalisading necrosis. GFAP expression is reduced but other immunohistochemical markers of ependymomas are positive. Anaplastic tumours in children less than three years of age with evidence of CSF metastases have an adverse outcome.[16]

PROGNOSIS

Recurrence rate is high in incompletely resected ependymomas.[45] Deterioration after initial treatment occurs due to local recurrence and subarachnoid seeding. Seeding of ependymal tumours through the cerebrospinal fluid pathways is reported with varied frequency and often follows recurrence at the site of previous excision, suggesting the surgical procedure as the initiating factor.[31] Autopsy studies have revealed 30% incidence of seeding of the spinal subarachnoid space in infratentorial tumours, while no such seeding was observed in supratentorial tumours.[44] Other studies too have documented frequent CSF seeding with infratentorial tumours, while the overall incidence of seeding through the cerebrospinal fluid is less than 3–5%,[28] an incidence of 75% too has been reported.[13] Seeding is seen more often in infratentorial tumours and anaplastic histology.[33]

Extraneural metastases, usually to the cervical lymph nodes and lungs, are seen in high grade tumours.[12,23,41] Such metastases have been seen even in low grade neoplasms and ependymomas occurring in the spinal cord.[12,36] As with subarachnoid seeding, most of the cases of extraneural metastases occur after surgical excision of the primary tumour.

Overall 5-year-survival with surgery and post-operative radiation therapy is about 50–60%, and long-term survival drops to 40% or less.[9] Prognosis is poor in children with high grade anaplastic lesions in the posterior fossa. Supratentorial lesions, unless they are high-grade extraventricular tumours, carry a better prognosis. Spinal ependymomas have a better prognosis with a 5-year-survival of 83%.[14] Thus, the overall prognosis in ependymomas is determined by a matrix of variables comprising age, location, completeness of surgical resection and histological type and grade.[32]

MYXOPAPILLARY EPENDYMOMA

This tumour is listed as an independent subgroup of ependymal tumours in the WHO classification. The tumour preferentially involves the filum terminale and is known for its striking histological appearance. The overall incidence is about 5% of all ependymal tumours[7] and in the region of the cauda equina, they account for nearly 50% of ependymomas, most of them arising from the filum terminale.[4,34] They arise from ependymal glia of the filum terminale and can grow to a large size. Rarely, they involve the nerve roots or the sacrum, where they may be extradural.[37] Rare occurrences have been reported in the cervicothoracic cord,[43] lateral ventricle[38] or brain parenchyma.[47] Subcutaneous sacrococcygeal and presacral myxopapillary ependymomas represent a distinct subgroup. They probably arise from ectopic ependymal remnants.[17]

Presentation

Myxopapillary ependymomas typically present with back pain, often of long duration. Large tumours cause pressure and stretching of nerve roots causing wasted legs, foot drop and sphincter dysfunction with saddle anaesthesia and absent tendon jerks in the lower limbs. Small tumours can be suspected by virtue of their intradural location on MRI, while large, sacral and subcutaneous tumours can be mistaken for chordoma. In contrast to other ependymomas, myxopapillary tumours are hyperintense on T1-weighted images.[19]

Management

Intradural tumours need excision through a laminectomy. Total excision with preservation of neural function is the goal of surgery. Large tumours involving the sacrum may need spinopelvic stabilisation, if involvement of the sacroiliac joints causes instability.

Histopathology

These tumours are characterised by radially arranged cuboidal cells in a papillary manner around a vascular stroma, with a background of mucoid matrix that forms microcysts. The mucoid matrix can be deposited by tumour cells and vascular extravasation via endothelial fenestrations.[5] There is low mitotic activity. The tumour cells are positive for GFAP, S-100 and vimentin with lack of reactivity for cytokeratin.[6,20]

Prognosis

Myxopapillary ependymomas show good outcome with more than 10-year-survival after total or even partial excision.[43] Sacrococcygeal ependymoma, however, can recur early and distant metastases may appear.[17]

EXTRANEURAL EPENDYMOMAS

Ependymomas can rarely occur ectopically in the parasacral region and in the abdomen, although there are only case reports of such tumours.

PARASACRAL EPENDYMOMAS

These can occur in an anterior or posterior (subcutaneous) location. They originate from ependymal cell nests and present from infancy to the fifth decade of life. Posterior lesions generally present as a subcutaneous mass, while anterior lesions present as an abdomino-pelvic mass with sphincter disturbances. Imaging studies show a sacral mass and the diagnosis of an ependymoma is often made only after surgery. These tumours are well circumscribed and histologically are typical of myxopapillary ependymomas. These tumours have to be distinguished from other mucinous or myxoid lesions, such as chordomas, chondroid tumours and mucinous metastatic adenocarcinomas. However, there have been reports of non-myxoid or anaplastic ependymomas or even ependymoblastomas in the sacrum.[27] The possibility of a teratoma should also be kept in mind in children.

INTRA-ABDOMINAL EPENDYMOMAS

These tumours can occur in the ovary and adnexae.[3,10] Tumour occurring in the omentum too has been reported.[8] The aetiology is obscure and presentation is in the form of an abdominopelvic mass. Histology is like that of a typical ependymoma, with ependymal rosettes and perivascular pseudorosettes. The tumour should be distinguished from serous carcinoma of the ovary, the differentiating feature being expression of GFAP in ependymoma.

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139 Medulloblastomas

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Medulloblastomas account for approximately 20% of all childhood brain tumours and 40% of all paediatric posterior fossa tumours. In a series of 419 cases of intracranial neoplasms in childhood, Misra et al. (1984) reported an incidence of 14.4%. The term medulloblastoma was first used by Bailey and Cushing in 1925. Medulloblastomas occur more frequently in children with 70% of all cases occurring below 10 years of age. Twenty per cent of medulloblastomas are seen below 2 years of age. The peak age of incidence is 5 years. Cases have been reported in neonates and infants. Twenty per cent of all medulloblastomas may occur in adults, of which 80% are paramedian (i.e. cerebellar hemisphere) and 40% desmoplastic.[25]

PATHOLOGY

In 1934, Stevenson and Echlin postulated that a medulloblastoma arises from the foetal external granular layer of Obersteiner—a sub-pial layer of small, primitive cells present throughout the cerebellar cortex at birth, which gradually disappears during the 1st year of life.[26] This external granular cell layer provides cells which ultimately give rise to the definitive, internal granular layer as well as basket cells and stellate cells. Alternative cells of origin include the sub-ependymal cells of the medullary velum and possibly the internal granular cell layer.[16]

GROSS APPEARANCE

The tumour is soft, greyish-purple, granular and deceptively circumscribed, with areas of necrosis. Cyst formation and calcification are rare. The desmoplastic form of the tumour seen more commonly in adults is darker in colour, firmer and often occupies a lateral cerebellar location. Medulloblastomas have also been reported in the cerebellopontine angle and rarely in the supratentorial region.

HISTOLOGY

The tumour is composed of small blue cells. It is highly cellular with frequent mitoses, occasional necrosis and clustering in Homer-Wright rosettes (Fig. 1). The cells have a high nuclear-cytoplasmic ratio, coarse chromatin and angular/carrot-shaped nuclei. Angiogenesis and endothelial cell proliferation is less striking. Five histological variants are recognised. Neuronal, as well as rhabdomyomatous or melanocytic differentiation, may point to a multipotential, undifferentiated precursor cell, which suggests that medulloblastomas may have a PNET origin. The WHO classification of brain tumours (1979) prefers to designate it as a primitive neuroectodermal tumour (PNET). Neuronal differentiation is indicated by immunohistochemical positivity for beta 3 tubulin, MAP 2, TAO, synaptophysin, somatostatin, substance P and bombasin. Astrocytic differentiation may reveal areas of GFAP positivity. Neuronal differentiation may reduce the malignant potential and show a decrease in cellular proliferation, as indicated by a low Ki-67 labelling index.[23] The relationship of desmoplasia to prognosis is controversial.[7,23,29]

MOLECULAR GENETICS

Medulloblastomas may also arise in association with the naevoid basal cell carcinoma syndrome (Gorlin's syndrome), the Li Fraumani syndrome associated with a germline p53 mutation on chromosome 17p, familial Wilms' tumour and the APC form of Turcot's syndrome.[23]

Molecular markers, such as amplification of MYCC, ERB B2 and a low apoptotic index, have been shown to have a poor prognosis. Tumours with high TRKC (neurotrophin-3 receptor) have a better outcome.[19]

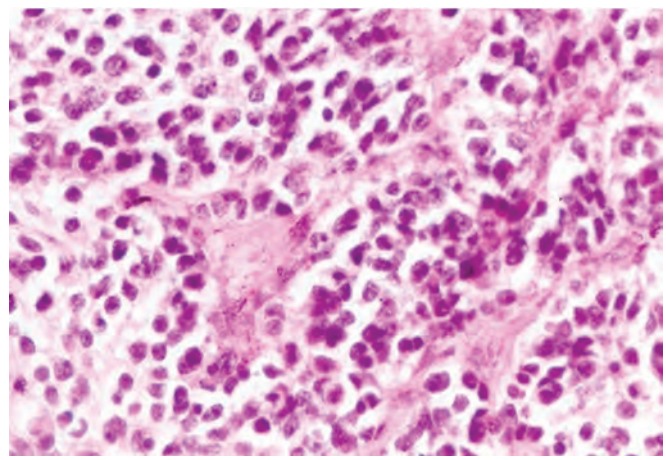


Fig. 1: Photomicrograph (H&E) revealing classical small round blue cells arranged in sheets, as well as around pale pinkish areas of fibrillarity (Homer Wright rosettes)

Aberrant signal transduction in medulloblastomas has been implicated in its tumourigenesis and has opened exciting avenues for development of newer chemotherapeutic regimens and risk stratification. These are:

a. Wingless (WNT) signalling. The WNT pathway, when activated, inactivates the adenomatous polyposis coli (APC) complex, resulting in the transcription of genes such as Cyclin D1 and MYCC.
b. The Sonic Hedgehog (SHH) pathway is implicated in Gorlin's syndrome, which is a familial predisposition to basal cell carcinomas, medulloblastomas and rhabdomyosarcomas. Medulloblastomas that carry mutations in the SHH pathway preferentially show a nodular, desmoplastic morphology.
c. ERB B2 pathway—Up-regulation of the tyrosine kinase 1 ERB B2 receptor signalling results in cell transformation and may be seen in 80% of paediatric medulloblastomas. These may amplify the metastatic and angiogenetic cascade, resulting in a poor prognosis.[9]

CLINICAL FEATURES

Medulloblastomas characteristically arise from the cerebellar vermis and grow into the fourth ventricle obstructing the flow of CSF.[21] They frequently infiltrate the brainstem and hence, produce clinical features attributable to it.

INVESTIGATIONS

Medulloblastomas on CT scans appear as hyperdense, intensely enhancing, well-defined vermian masses, usually accompanied by hydrocephalus (Fig. 2). Twenty per cent of tumours may show calcification.

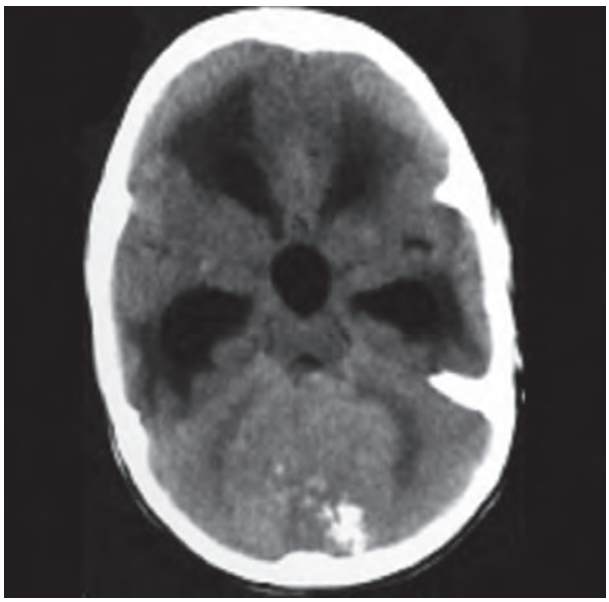
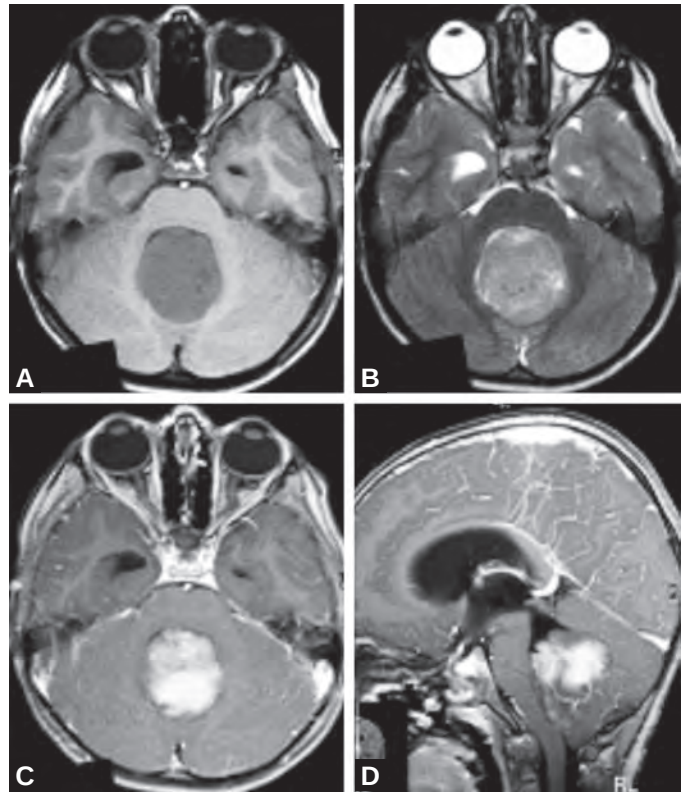


Fig. 2: Axial section of an unenhanced CT head, revealing a hyperdense vermian mass and obstructive hydrocephalus



Figs 3A to D: (A) Weighted axial MR image revealing a hypointense midline cerebellar mass separated by a CSF cleft from the floor of the fourth ventricle. (B) T2-weighted axial MR image revealing a hypointense signal from the mass with a hyperintense CSF cleft indicating a good plain of cleavage from the brainstem. (C) Gd-enhanced sequences of the same mass indicating bright enhancement. (D) Gd-enhanced sagittal sequences revealing inhomogeneous enhancement and a dilated aqueduct

MRI reveals a vermian mass usually separate from the floor of the fourth ventricle on axial and sagittal (sign of the superior medullary velum) sequences, which is homogeneously hypointense on T1-images. On T2-weighted images, the signal is intermediate between grey matter and white matter, while it is isointense to grey matter on FLAIR sequences (Figs 3A to D). These findings are in contrast to other CNS tumours which are mostly hyperintense to grey matter on T2 and FLAIR sequences.

Magnetic Resonance Spectroscopy (MRS) is non-specific indicating high choline and lactic acid with low N-acetyl aspartate levels.[24]

STAGING

Medulloblastoma is the most common CNS tumour with a propensity for extra-neural spread to the bone, bone marrow, liver and lymph nodes. These may occur in approximately 1–2% of all cases at the initial presentation itself. Tumour staging, based on surgical findings was proposed by Chang et al. in 1969.[1] Langston proposed an MRI-based modification of Chang's system with the main difference being that the T stage did not account for hydrocephalus or the number of structures

involved. The T stage has not been as powerful a prognostic factor for disease free survival, as has the M stage.

Currently, children are divided into two risk groups:[14]

a. Standard risk—includes patients with non-disseminated (MO) disease with less than 1.5 cm^2 of residual tumour and > 3 years of age.
b. High risk—includes all cases with disseminated disease and with residual tumour greater than 1.5 cm^2 and children < 3 years.

PROGNOSTIC FACTORS

Age

Very young children less than 3 years of age represent 25–30% of the case load and their 5-year survival rate is 12%. Poor prognosis may be linked to larger tumours at presentation, as this age group tends to be relatively clinically silent. More aggressive tumours, a low rate of complete surgical resection, higher proportion of CNS dissemination and the inability of the immature brain to tolerate radiotherapy may also account for the poor outcome in this age group. Adults with medulloblastomas have a better prognosis than the less than 3 population, but have a shorter median survival than children.[21]

Histology

The prognostic significance of a desmoplastic component amongst tumours remains uncertain with variable results emanating from a search of the literature.[2,3,10,12,13,25]

Glial Differentiation

In a study of 86 patients with PNETs, tumours expressing GFAP but not neuronal intermediate filament had a 5.9 fold greater risk of relapse than those tumours which did not express either. The risk for relapse was also directly proportional to the amount of GFAP expressed.[15]

ERB-B2 Expression

Multicentre analysis of molecular defects in paediatric medulloblastomas reveals that children with standard risk ERB-B2 negative disease had a median survival of 100% at 5 years, compared to 54% of children with average risk ERB-B2 tumours ($p = 0.0001$).8 Pomeroy et al. using an eight-gene model divided 16 patients into low-risk and high-risk groups with an 80% and 17% 5-year overall survival, respectively.[22]

The Children's oncology group (COG), International Society for Paediatric Oncology (SIOP) and the St. Jude Children's Research Hospital (SJMB) all plan to redefine a molecular disease risk stratification system for medulloblastomas.

In summary, children less than 3 years old, amplification of MYCC, ERB-B2, a low apoptotic index, distant metastases, partial resection, brainstem infiltration and glial differentiation are poor prognostic indicators, whereas adults and patients whose tumours are desmoplastic or have neuronal differentiation fare better.

MANAGEMENT

SURGERY

Microsurgical Anatomy

The fourth ventricle is roughly a pyramid with its floor formed by the pons and the medulla; the superior and inferior medullary vella are the roves; the superior, middle and inferior cerebellar peduncles form the lateral boundaries; the inferior apex opens into the cisterna magna through the foramen of Magendie; the superior apex opens anteriorly into the cerebral aqueduct; and the lateral apices open into the cerebellopontine angle. The floor is divided by the transverse medullary stria and the vertical median sulcus. Cranially, the median sulcus is flanked by the facial colliculi and inferiorly by the hypoglossal trigone, the vagal trigone and the area postrema. They derive their blood supply from the tonsillo-hemispheric branch of the posterior inferior cerebellar artery. Medulloblastomas arise commonly from the superior medullary vellum and may invade the cerebellar peduncles and the dorsal brainstem in about one-third of cases.

Surgical Strategies

Management of Hydrocephalus

The basic principles for surgery were described by Cushing and have changed little. However, advances in anaesthesia, introduction of the operating microscope and intra-operative use of electrophysiology have made surgery far safer. Most patients present with hydrocephalus and therein lies the first controversy in the surgical management of this illness. Some centres believe that ventriculoperitoneal shunting may decrease operative mortality, by affording time to perform diagnostic tests, prepare the patient and schedule a major neurosurgical procedure electively. Reduction in intracranial pressure also permits safer resection.

The other stratagem is a course of pre-operative steroids, external ventricular drain placement and emergent surgery. If the patient is stabilised with steroids alone, surgery may be scheduled at the next elective operating date. This latter approach prevents the need for shunting and, therefore, all the possible shunt related complications, such as infection, migration, intracranial haematomas, shunt block, dissemination of malignant cells into the peritoneal cavity, delaying definitive treatment, reverse herniation and tumour haemorrhage.

Either strategy is acceptable. Intermediate stratagems involve the use of Millipore filters to prevent tumour dissemination and endoscopic ventriculostomy.[28]

Definitive Surgery

Positioning: In the prone position, the risks of air embolism, pneumocephalus and hypotension, which are often associated with the sitting position, are reduced. It is also less tiring for the operating surgeon. The advantages of

the sitting position, however, are, a more anatomical orientation, gravity assisted drainage of CSF and blood, lesser retraction and the ability to look directly up into the superior recess of the fourth ventricle.

Three-point pin fixation with short paediatric pins at a pressure of 40 pounds/sq. inch is recommended in children above the age of 3 years, whereas, a horse-shoe shaped padded head rest is preferred in children less than 3 years. Surgery is begun with an occipital burr hole to permit ventricular puncture, if required. A midline vertical skin incision is placed from the inion to the mid-cervical region and a wide craniectomy is performed from the transverse sinuses up to the arch of C1, where the tonsils may be impacted. It is advisable not to remove the arch of atlas. The alternative procedure involves raising a free bone flap with a craniotome. The dura is opened with a Y-shaped incision, taking great care to control bleeding from the occipital and other dural sinuses. Desmoplastic tumours generally presenting on the surface may be adherent to the dura. Care is necessary in dissecting these adhesions, when reflecting the dural flap. If the dura is bulging and tense, it is advisable to drain the ventricle prior to opening the dura.

To relax the cerebellum, CSF can either be drained by a ventricular puncture or by opening the cisterna magna via a small, vertical midline cervical durotomy. The tumour may be visible in the vallecula itself or after retracting the cerebellar tonsils. Before incising the vermis, it is important to identify the obex and the floor of the fourth ventricle. After delivering the herniated tonsils and draining the CSF, the cisterna magna should be packed to prevent seeding of tumour cells. The vermis may either be retracted or split. The dorsal surface of the tumour is cauterised, incised and then penetrated with a suction-cannula or a CUSA for internal decompression. The tumour is soft, suckable and highly vascular with the blood supply derived from the branches of the PICA. In very young children, even a small amount of blood loss during tumour decompression could cause serious hypotension. All efforts must be made to reduce blood loss and promptly replace the amount lost. As the tumour collapses, a plane is usually evident along the cerebellar vermis, the hemispheres, the cerebellar peduncles and most importantly the ivory white floor of the fourth ventricle, which must be guarded with a cottonoid. The ventral plane of the tumour is breached first at that portion where the tumour is free from the brainstem. The rest of the tumour is subsequently removed. Medulloblastomas are not truly encapsulated and are highly vascular. One has to work fast as haemostasis is generally spontaneous, but achieved only when the major part of the tumour is gutted. The aqueductal section of the tumour is the last to be removed, to prevent blood from entering the third ventricle and producing obstructive hydrocephalus or shunt dysfunction.

Medulloblastomas may infiltrate the brainstem and cerebellar peduncles. Attempts at removal can permanently harm the child. Small bits of tumour adherent to the brainstem or vessels should be left behind and have not been shown to diminish survival or increase relapse.[28] CO_2 laser can help in removing the tumour adherent to the brainstem and in achieving haemostasis. At the end of surgery, bleeding points from the floor of the fourth ventricle should be controlled either by saline irrigation or small strips of oxidised cellulose. Using haemostatic agents extravagantly is to be strictly avoided, as the CSF pathways will obstruct if they float away. Patients should be extubated on the table, but in the event of elective ventilation, an external ventricular drain may be used for monitoring intracranial pressure and draining CSF. Forty per cent of patients may require eventual VP shunts. Surgical mortality is less than 1% in experienced hands due to improvement in anaesthesia, surgical techniques and diagnostic and monitoring equipment.

Peri-operative Complications and their Management

Air Embolism

Early detection and prevention is the key. It usually occurs in patients operated upon in the sitting position during the bone-nibbling phase but has been reported at any time during the operation from pin fixation itself. The anaesthetist needs to be continuously informed about the operative steps and in turn should place a precordial Doppler, trans-oesophageal echo, $ETCO_2$ monitor and an atrial catheter. In the absence of these, a stethoscope may be taped on to the chest to detect the characteristic 'millwheel' murmur of venous air embolism. The earliest indication is a drop in $ETCO_2$ followed by a rise in CVP, a drop in cardiac output, hypotension and arrhythmias. Management involves the application of bone wax to the bleeding calvarial edge, copious saline irrigation and smothering the wound with a soaked sponge. The head end is immediately lowered and bilateral jugular vein compression attempted. The anaesthetist should institute cardiac support, increase the fraction of inspired oxygen to 100% and aspirate the atrial central venous catheter. In the event of a cardiac arrest, towel clips are applied to the skin edges and the patient is immediately turned supine to enable cardiopulmonary resuscitation.

Pressure Sores

When a horse shoe support is used in children less than 3 years of age, pressure necrosis of the forehead is often encountered and catastrophic blindness secondary to orbital compression may also occur. The use of fixation pins may result in scalp laceration, air embolism, depressed skull fracture, epidural haematomas or even osteomyelitis later on.

Delayed Anaesthetic Arousal

Unless the patient wakes up fully at the end of the operation and anaesthesia, it is best not to extubate the patient and if necessary institute artificial ventilation. An

emergent CT scan will detect treatable possibilities, such as hydrocephalus, extradural or subdural haemorrhage, operative site haematoma, cerebellar infarction or tension pneumocephalus. In the absence of these, brainstem dysfunction secondary to either operative trauma or retraction may be a possibility. Infarction secondary to vascular injury is a dreaded complication with little chance of recovery. Brainstem injury can be minimised by newer operating aids, such as CUSA and evoked potential monitoring. The treatment is supportive and includes feeding gastrostomy, tracheostomy and long-term ventilation.

Pseudobulbar Palsy

Patients may develop irritability, emotional lability, dysarthria, nystagmus and bilateral facial palsy, 1–3 days after surgery, secondary to retraction-induced oedema of the cerebellar peduncles and brainstem. It tends to resolve over time.

Cerebellar Mutism

This is seen particularly in young children with large, vermian medulloblastomas, when for a day or two after surgery, the patient may speak normally but then becomes mute. This may be accompanied by personality changes, dysphagia and akinesia. It recovers spontaneously within weeks to 4 months but may be accompanied by dysarthria. The aetiology remains unknown but dentate nucleus manipulation and the bilateral interruption of the dentato-thalamo-cortical pathways have been implicated. It may affect between 8% and 25% of children and is not thought to be influenced by the degree of surgical resection.[21]

Aseptic Meningitis

This syndrome appears 5–7 days after surgery, as steroids are being tapered. Signs classically suggest pyogenic meningitis with fever, neck rigidity, photophobia, irritability and CSF pleocytosis. Bacterial cultures are essential after a spinal tap to rule out the same. If cultures are sterile and CSF sugar level is not significantly low increasing the dose of steroids and tapering them over two weeks may prove to be beneficial.

Stress Ulcers

There appears to be a predilection for GI haemorrhage in patients with posterior fossa tumours, which is unrelated to steroids. Neutralising gastric acidity has to be balanced against the increased incidence of nosocomial pneumonia.

Post-Operative Pseudomeningocoele

Whenever possible, a dural patch should be used to achieve anatomical closure. A truly water-tight closure may be more a myth than a reality. Lumbar punctures and compression bandages can be tried initially; else ventriculoperitoneal shunting may be resorted to, especially if serial brain scans show a progressive ventricular dilatation. Some pseudomeningocoeles may resolve in due course of time, as the bone reforms. Replacing bone flaps after craniotomies is thought to reduce this risk.

Cervical Spine Instability

This is a rare complication, which may be seen at the end of a year after surgery. It is associated with a C2 laminectomy and local infection.

RADIATION THERAPY

Historical Perspective

The initial attempts at irradiation with a 3,600 cGy craniospinal dose coupled with a posterior fossa boost of 5,000 cGy yielded survival rates of 50% at 5 years. This, however, resulted in tremendous cognitive decline and hence, a combined Children's cancer group/Paediatric oncology group randomised trial (CCG 9014/POG9331) was undertaken to compare standard dose neuraxis radiation (3600 centigrade/20 fractions) with reduced neuraxis radiation(2340 centigrade/30 fractions) in patients with standard risk medulloblastoma, with the use of adjuvant chemotherapy. Chemotherapy consisted of weekly vincristine during radiotherapy followed by seven cycles of cisplatin, vincristine and cyclophosphamide.

In Europe, the neuraxis dose remains 3,500 cGy, whereas, in the US, the standard radiation dose has been decreased to 2,340 cGy from 3,600 cGy. However, even this dose has been associated with neurological toxicity. Thus, a Children's Oncology Group Phase-3 study is planned for further reduction of the neuraxis dose to 1,800 cGy for patients with standard risk medulloblastomas, aged between 3 years and 8 years. This will evaluate the benefits of decreasing morbidity at the expense of disease control.

Intensity modulated radiation therapy, which involves conformal radiation delivery, using multileaf collimators, multiple beam angles, varied exposure times and fused digital imaging helps deliver stereotactic radiation, while reducing normal brain exposure. Its main benefit would appear to be reduced cochlear radiation and hearing loss.[11]

CHEMOTHERAPY

Adjuvant chemotherapy was first used in high-risk medulloblastomas by the Children's Cancer Group (CCG) and the International Society of Paediatric Oncology (SIOP). These trials employed 3,600 cGy craniospinal irradiation and a posterior fossa boost to 5,600 cGy, as well as a randomisation between adjuvant chemotherapy versus none. The CCG group used vincristine with radiotherapy followed by post-radiation vincristine, prednisone and CCNU.[5] The SOIP study did not use prednisone.

Both trials demonstrated significant success. Other regimens include methotrexate, carboplatin, iproplatin,

etoposide, cyclophosphamide,[18] cisplatin,[20] in addition to CCNU and vincristine.[18,20,27]

At present, chemotherapy allows greater survival in high-risk medulloblastomas and helps reduce the craniospinal radiation dose for paediatric patients with standard risk. Chemotherapy has not been proven to better outcomes in adult medulloblastoma patients, as tolerance is poor.

Management Strategies

High-Risk Disease

Clinical trials employ radiation therapy along with radiosensitising chemotherapy and high-dose chemotherapy with peripheral blood stem cell rescue in patients greater than 3 years of age.

Average Risk Disease

The Children's Cancer Group managed to maintain a progression-free survival of 79% at 5 years, by reducing the craniospinal dose from the standard 3,600 cGy to 2,340 cGy, while maintaining the posterior fossa boost at 5,580 cGy total dose and adding adjuvant chemotherapy consisting of vincristine, cisplatin and CCNU.

Infant Medulloblastoma

In children less than 3 years of age, chemotherapy is used to delay or eliminate the need for irradiation. Protocols include chemotherapy with cyclophosphamide/vincristine and cisplatin/etoposide till the patient is 3 years of age following which radiation therapy is instituted. Other protocols deal with high dose chemotherapy to overcome the blood-brain barrier, followed by bone marrow rescue with autologous stem cells.[4,17] A third alternative is the direct intrathecal infusion of chemotherapy, using Maphosphamide along with vincristine, cisplatin, etoposide and cyclophosphamide, followed by stereotactic radiotherapy and further chemotherapy.[24]

Relapsed Medulloblastoma

Medulloblastoma remains relatively haemosensitive, despite relapse. Conventional chemotherapy has disappointing results. High dose chemotherapy supported by PBSC rescue dose demonstrate a response in 1/3rd of patients but carries a toxic death rate of 16%.[6]

Chemoradiotherapy Sequelae

Radiation therapy to the developing, immature brain can result in most of the side effects mentioned below:

Neurocognitive Decline

This is delayed in onset and then progresses over 3–5 years, depending on the age at onset, dose of radiation and volume irradiated. Children may experience a drop in IQ of about 25 points and suffer from lapses of memory and fine motor, visual motor skills, visuospatial skills and poor organisation, attention, learning and processing speed. This underlines the rationale for reducing the dose of radiotherapy with adjuvant chemotherapy.

Neuroendocrinologic Dysfunction

- *Growth failure:* Decreased growth velocities remain the most common form for neuroendocrinologic dysfunction. Growth hormone replacement therapy can be employed safely, but 2 years should elapse after completion of therapy.
- *Hypothyroidism:* It may be due to either irradiational damage to the hypothalamus or thyroid gland. Routine screening and hormone replacement is essential.
- *Secondary malignancies:* As survival improves, secondary malignancies occurring in the fringes of the radiational fields have assumed greater importance. Meningiomas and high-grade gliomas may occur in survivors of medulloblastomas. Secondary acute myeloid leukaemias may occur in patients who have undergone chemotherapy, as can cancers of the salivary glands, cervix, central nervous system, thyroid and acute lymphoblastic leukaemia.
- *Hearing loss:* Ototoxicity may be secondary to either whole brain irradiation with cochlear exposure or may be cisplatin induced. Consequently, oxaloplatin, a cisplatin derivative may be preferred, since there is no ototoxicity and nephrotoxicity.

Newer Chemotherapeutic Agents

Molecular genetics studies may provide some of the best chemotherapeutic agents in the years to come, by targeting abnormal signalling sequences within the cancerous MB cells. These include erlotinib, an ERBB2 receptor inhibitor. SCH66336 is an oral farnesyl transferase inhibitor that blocks the ras pathway. Gefitinib, a PDGF inhibitor is also undergoing trials.

CONCLUSION

Surgery, along with craniospinal irradiation and chemotherapy has led to 5-year survivals in excess of 75% with feasible cure. Reported 10 year survival rates approach 50% in average risk disease. Future directions will involve better and safer drugs, targeted drug delivery systems focused on abnormal signalling sequences, lower dose craniospinal irradiation and stereotactic radiation in an effort to reduce long-term morbidity, without increasing mortality and relapse.

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140 Metastatic Brain Tumours

Ravi Ramamurthi, Harinivas

Metastatic deposits in the brain were first reported by Bucholz in 1898.[14]

DEFINITION

Metastasis is defined as the spread of malignant tumour cells from a primary neoplasm to distant tissue to form a new growth.[93] Single brain metastasis (BM) is defined as a single cerebral lesion arising outside the central nervous system (CNS) without any reference to systemic status. A solitary metastasis is a single brain lesion without evidence of metastatic spread elsewhere in the body. When there is more than one brain lesion it is called multiple metastases. A metastasis is called synchronous when it is detected at the time of diagnosis of the primary tumour and metachronous when diagnosed later, sometimes several years later.

INCIDENCE OF BRAIN METASTASIS

Metastatic brain tumours are the most common intracranial neoplasms in adults.[134]

The incidence of metastases is much higher if it is based on autopsy series as compared to clinical series. Approximately 10% of patients with cancer develop BMs.[50]

The incidence of metastases is thought to be rising due to better detection and treatment of systemic malignancy.[90,95] It is more common in adults compared to children. Among adults the highest incidence is seen in the fifth to seventh decades.[116] Approximately 75–85% of lesions are supratentorial and 15–25% are infratentorial.[130] The reported incidence in India by Ramamurthi[94] and by Dastur and Lalitha[24] were lower, but these were in the pre-computerised tomography (CT) era.

FACTORS GOVERNING THE METASTATIC PROCESS

The first phase of pathogenesis is invasion of cancer cells into blood, lymph or cerebrospinal fluid (CSF). In the second phase, there is dissemination with transport of cancer cells. Most of the cells are killed and only viable cells which reach the target organs develop into micrometastasis.[99] The final phase involves the growth of these viable cells into either single or multiple metastases.[3] The factors which determine the detachment of tumour cells from the primary tumour are growth rate of the tumour, tumour necrosis, enzymes and stress.[125]

CLASSIFICATION DEPENDING ON SITE OF ORIGIN[89]

Skull and Dura

The deposits are mainly located in the vertex or low occiput. They are seen commonly with prostate carcinoma, lymphoma, breast carcinoma, melanoma, neuroblastoma and osteosarcoma.

Leptomeninges

The spread is usually via the CSF pathways. Obliteration of the subarachnoid space with development of hydrocephalus is more common.

Parenchyma

Most common
- Cerebrum—80%
- Cerebellum—16%
- Brainstem—3%.

PATHOPHYSIOLOGY

Pagets Seed and Soil Theory

The first process in the formation of metastasis is tumour cell adhesion to the local extracellular matrix, cell locomotion and proteolysis, which is followed by invasion into lymphatics, venules and capillaries. This is followed by haematogenous embolism to distant sites and the tumour cells interact with various blood components to survive the hostile environment of circulation. Once again adhesion and extravasation should take place at the new host site. If the new host (soil) is conducive to proliferation of the cells (seed) then metastasis is established.[130]

MOLECULAR BIOLOGY OF BRAIN METASTASIS

Following any type of brain insult such as a lesion, stroke and tumour/cancer invasion, microglia are rapidly activated and recruited to the site of insult. Microglia is the main immune effector cell population of the CNS and control immune cell recruitment. However, the

molecular mechanism of BM and interaction between neuron-glia-tumour cells is poorly understood.[77]

The Hedgehog (Hh)/glioma-associated oncogene signalling network is among the most important and fascinating signal transduction systems that have critical functions in the regulation of many developmental and physiological processes involved in tumour progression. The target gene products induced through persistent Hh activation can contribute to the self-renewal, survival, migration and metastasis of cancer stem/progenitor cells and their progenies.[70]

The transcriptional regulator SnoN has a fundamental role as a modulator of signalling and responses by the transforming growth beta family (TGFb) of cytokines, though how SnoN regulates TGFb responses remains incompletely understood. Due to the critical and complex roles of TGFb in tumour genesis and metastasis, identification of novel SnoN regulatory and effector mechanisms holds the promise of advances being made at the interface of cancer biology and neurobiology.[92]

MOLECULAR GENETICS OF NON-SMALL CELL LUNG CANCER

Patients with non-small cell lung cancer (NSCLC) harbour mutations in the epidermal growth factor receptor (EGFR) that predict the unique sensitivity to EGFR tyrosine kinase inhibitors (TKIs). In NSCLC patients with BM, EGFR mutation status is associated with improved survival, independent of age, functional status, extracranial disease status and number of BMs.[37,104]

MOLECULAR GENETICS OF BREAST CARCINOMA

Aneuploidy is commonly observed in breast cancer and is associated with poor prognosis.[2] The frequently found type of aneuploidy is hypertetraploidy. The hypertetraploid progenies show increased metastatic potential to lung and brain, but not to bone, which may be partially explained by the distinct capillary structures in these organs that confer differential lodging advantages to tumour cells with enlarged size.[66] Hexokinase 2 (HK2) is important in glucose metabolism and apoptosis. The HK2 levels (both mRNA and protein) are elevated in brain metastatic derivatives.[82]

MOLECULAR GENETICS USING REAL TIME IMAGING

Using multiphoton laser scanning microscopy the single steps of metastasis formation in real time can be found out. The essential steps are arrest at vascular branch points, early extravasation, persistent close contact to microvessels and perivascular growth by vessel co-option (melanoma), or early angiogenesis (lung cancer). The inefficient steps differ between tumour types. Vascular endothelial growth factor-A inhibition induces long-term dormancy of lung cancer micrometastases by preventing angiogenic growth to macrometastases.[52]

The common neoplasms metastasing to the brain are carcinoma of the bronchus, breast, kidney, stomach, colon, prostate, thyroid, lymphomas and melanomas. In the fifth to seventh decades, the most common primary sites are lung, breast and skin.[60] In children, leukaemia is the most common followed by lymphoma.[118] Osteogenic sarcoma and rhabdomyosarcoma are the most common solid metastasis to the brain among children younger than 15 years.[30] Germ cell tumours are the most frequent cause between 15–21 years.[41] A review of some of the publications on BMs[8,17,28,29,42,61] shows the following trend in the frequency of primary sites: Bronchial adenocarcinoma (19–23%), squamous cell carcinoma of the lung (11%), breast cancer (5–19%), and melanoma (12%), followed by renal tumours, carcinomas of thyroid,[36] parotid, pancreas, testis and bladder. In about 18–37% of metastatic carcinomas, the primary is not traceable in spite of extensive investigation. Neoplasms of the reticuloendothelial system like lymphoma, Hodgkin's disease and leukaemia are also known to spread to the brain. In leukaemias and lymphomas meningeal deposits are well known.[89] Various types of sarcomas can cause cerebral metastases. Rarely, a glioblastoma of the spinal cord can spread to the brain through CSF pathways. Bronchogenic tumours and cancers of the breast that spread to the lung more commonly also exhibit a high incidence of BMs. Multiple metastases are common in melanoma, choriocarcinoma and small cell lung cancer. Single metastasis is common in breast, thyroid, renal cell, colon, as well as adenocarcinoma lung.[130]

Metastatic melanomas have the highest tendency for spontaneous haemorrhage. Secondary deposits may occur anywhere in the brain, but are more common in the supratentorial compartment. They may be single or multiple, small or large. Meningeal carcinomatosis results from metastatic deposits along the arachnoid.[112] This leads to vague neurological signs, symptoms and signs of raised intracranial pressure. Extensive meningeal enhancement in the absence of infection gives the clue on CT scan in a patient with known malignancy elsewhere in the body. This picture may also be seen in patients with leukaemia.

A patient with cerebral metastasis may present like a stroke due to tumour emboli in the blood vessels leading to cerebral infarction without any obvious deposit,[80] the aetiology becoming apparent only at autopsy. A metastasis in the pituitary may be missed at autopsy. It has been reported in 6% of all patients with cancer and in 20% of patients dying from carcinoma of the breast.

In an anatomical sense most of the secondaries in the brain are extracerebral as they are outside the blood-brain barrier. The majority of these lesions can be easily shelled out from the brain. A small lesion with extensive oedema and mass effect disproportionate to the lesion is generally indicative of metastasis though intracranial tuberculomas may produce an identical picture. The profound oedema is the result of breach of the blood-brain barrier and immunological barrier which incites a reaction in the surrounding brain tissue.

PATHOLOGY

On gross examination a secondary deposit is usually well circumscribed and spheroidal in shape.[98] The cut surface is pinkish-grey, granular and soft. Cystic degeneration and necrosis may be seen on CT scan.[135] Choriocarcinomas are haemorrhagic. Calcification has been noted in some metastases usually from the gastrointestinal tract and these have a relatively benign course.[47]

Histopathology

Histopathology of the lesion usually reflects the tissue of origin, i.e. the primary site. Occasionally, in anaplastic and undifferentiated metastases, the differential diagnosis will be highly anaplastic glioma, lymphoma, amelanotic melanoma[58] and a small round-cell tumour like a medulloblastoma. Immunohistochemistry will usually settle the issue.

Immunohistochemistry

The chemokine/receptor system CXCL12/CXCR4 plays a key role in multiple biological functions including homing of neoplastic cells from the primary site to the target and metastasis progression.[62] CXCL12 is expressed in tumour cells and in tumour vessels. CXCR7 is expressed by tumour and endothelial cells (both within the tumour and in the adjacent brain tissue).[20] CXCR4 showed positivity in all samples with a nuclear pattern. Among the investigated immunohistochemical parameters, only CXCL12 expression in tumour endothelial cells showed a statistically significant correlation with shorter survival, identifying more aggressive tumours.[102]

CLINICAL FEATURES

In a solitary cerebral metastasis, symptoms and signs of the cerebral lesion may precede those of the primary malignancy. In such cases, only after the tumour is removed at surgery, its true nature becomes apparent. Symptoms and signs depend on the site and size of the metastasic deposit. Metastases in the brain become symptomatic more often and earlier than in other organs such as liver and lungs, though the incidence is much higher in these organs. Increased intracranial pressure or focal signs may be the presenting feature.

The usual symptoms are headache, decrease in cognitive function, nausea and vomiting. Seizures occur less commonly in BM than in primary neoplasms.[115] Papilloedema is also common. Features of raised intracranial pressure are usually caused by cerebral oedema, but it can be present due to ventricular obstruction secondary to cerebellar and brainstem metastasis, and also obstruction of venous sinuses by the neoplasm.[116] Neuropsychological disturbances are common as the frontal lobe is a common site for secondary deposits (33%).[29] Metastasis from the highly vascular choriocarcinoma may present as a cerebrovascular accident due to tumour emboli dislodging from the pulmonary secondary, where the pulmonary lesion may be misdiagnosed as a primary lesion.[1]

Stroke like picture may also result from haemorrhage in the metastasis.[67] The duration of symptoms is often short with rapid progression.[117] This can be explained on the basis of extensive oedema associated even with small subcortical lesions.

Whenever a secondary deposit is detected in the brain, either pre-operatively or post-operatively on the basis of histopathology, a thorough search for the primary lesion is mandatory. In a patient with carcinoma of the breast, the suspected cerebral lesion may turn out as a meningioma.[54] Occasionally, because of high blood flow, meningiomas themselves may harbour metastases.[136]

INVESTIGATIONS

Computerised Tomography

On CT metastasis are isodense with abundant hypodense perilesional oedema disproportionate to their size.

Magnetic Resonance Imaging

On the non-enhanced T1-weighted magnetic resonance (MR) image metastases are hypointense to isointense compared to grey matter and are surrounded by vasogenic oedema.[53] They are hyperintense in T2 images.[25] Usually metastasis are located at the grey-white junction, often in watershed territories such as in the parieto-occipital regions.[130]

Magnetic Resonance Spectroscopy

Proton MR spectroscopic imaging is a non-invasive diagnostic tool for the investigation of cancer metabolism.[7] As an adjunct to morphologic and dynamic magnetic resonance imaging (MRI), it is used for the staging, assessment of treatment response, and therapy monitoring in brain, breast and prostate cancer. Recently, its application was extended to other cancerous diseases, such as malignant soft-tissue tumours, gastrointestinal and gynaecological cancers, as well as nodal metastasis.[88]

Positron Emission Tomography

High-grade and low-grade tumours, recurrence and radionecrosis can be distinguished by using positron emission tomography (PET) with fluorine–18. The PET does not distinguish secondary from primary neoplasms.[26] Several clinical reports have suggested that 18F-flouorodeoxyglucose PET is useful for detecting unknown primary tumours in patients with BM. The PET has incomparable abilities to determine the metabolic activity of tissues, but it needs the assistance of higher-resolution anatomic information. The CT is the easiest and highest-resolution tomographic modality to be integrated into PET imaging. Because of this, the market for PET devices has shifted so dramatically towards PET-CT.[48]

Whole-Body Magnetic Resonance Imaging

The advent of whole-body MRI (WB-MRI) has introduced tumour imaging with a systemic approach compared to established sequential, multi-modal diagnostic algorithms. Assessment of individual organs with various soft-tissue contrast, spatial resolution and contrast media dynamics can be combined with whole-body anatomic coverage in a multi-planar imaging approach. For initial tumour staging PET-CT as a competing whole-body modality in oncologic imaging has proved more accurate for the definition of T-stage and lymph node assessment, using the additional metabolic information of PET for the assessment of tumour viability and therapy response.

The WB-MRI has shown advantages for the detection of distant metastatic disease, especially from tumours frequently spreading to the liver or brain, and it is especially useful as a radiation-free alternative for the surveillance of tumour patients with multiple follow-up exams. Furthermore, it has been introduced as a whole-body bone marrow screening application. The WB-MRI is highly accurate for the detection of skeletal metastases and staging of haematologic diseases such as multiple myeloma or lymphoma.[105]

Using diffusion tensor imaging, metastasis can be differentiated from glioblastoma using metrics from the tumour volume and surrounding peritumoural oedema,[15] unlike the gradient-echo-planar perfusion-weighted imaging technique. Spin-echo (SE) planar perfusion weighted imaging enables cerebral blood volume maps select for blood volume in microvessels less than 8 micron in diameter. This helps to differentiate metastasis from glioma.[131]

DIFFERENTIAL DIAGNOSIS

- Primary brain tumour:[55] Meningioma, the most common primary intracranial tumour to be associated with breast carcinoma
- Brain abscess[59]
- Infarction and haemorrhage[40]
- Encephalitis
- Demyelinating lesion
- Resolving haematoma
- Radiation necrosis.[114,130]

TREATMENT

To select the appropriate therapy, one must consider the extent of the systemic disease, primary histology, and patient age and performance status, as well as the number, size and location of the BMs.[95] A tissue diagnosis is necessary when the primary tumour is unknown or the findings on CT/MRI are atypical.[111]

Ideal management of BMs requires simultaneous control of the existing BM (local brain control), prevention of future BM and control of the systemic cancer (systemic control).[119] The available tools include whole brain radiation therapy (WBRT), surgery, stereotactic radiosurgery (SRS), and systemic therapies, such as chemotherapies, biologic agents and radiosensitising agents.[119]

Medical Management

Dexamethasone is the corticosteroid of choice for cerebral oedema associated with metastasis as it has high glucocorticoid potency and minimal mineralocorticoid potency. Anticonvulsants should not be prescribed prophylactically.[111]

Treatment must be directed not only at the BM (definitive care), but also at a multitude of other symptoms that plague patients with BMs (supportive care). Judicious selection of pharmacologic agents and non-pharmacologic techniques can effectively treat many serious symptoms in patients with BMs, but injudicious selection of pharmacologic agents may have side effects and make the patient's quality of life worse.[32] A solitary cerebral metastasis in malignant disease poses a particular therapeutic challenge. The options consist of surgical resection, stereotactic radiation and total brain irradiation.[18,91] No significant therapeutic advantage for any of these methods has as yet been demonstrated in the literature.[127]

Surgery

Surgical excision of solitary metastases offers a good chance for reducing intracranial pressure and improving neurological deficits.[79] The incidence of solitary metastasis varies from 50 to 89%.[8,17,29,35] Renal cell carcinoma (RCC) is well known for manifesting with a single deposit, and in one series was seen in 10 out of 11 patients.[89] A notable feature was the long interval between the removal of the primary growth and occurrence of the deposit in the brain.[96,123] Surgical excision of a solitary lesion also helps in diagnosis, especially in cases where the primary has not been detected.[33] Surgical mortality is defined as death within 30 days of surgery and varies from 0 to 10% after resection of a single metastasis.[39]

The ideal candidates for surgical excision are:

- Patients with good performance status [Karnofsky performance scale (KPS)]
- Minimal or no evidence of extracranial disease
- Surgically accessible single BM amenable to complete excision.

To reduce the risk of tumour recurrence for patients who have undergone resection of a single BM, postoperative WBRT should be considered. The optimal dose and fractionation schedule for WBRT is 3,000 cGy in 10 fractions or 2,000 cGy in 5 fractions.[95] Surgical adjuncts such as bischloroethylnitrosourea (carmustine) wafers and the glia site radiation system may be useful in the future in achieving optimal local tumour control.[86]

Alternatives to surgical excision in solitary metastasis: WBRT followed by SRS should be considered.[11] The

evidence is insufficient to recommend SRS alone as a single-modality therapy.[71]

Factors influencing the risk of local recurrence after resection of a single BM are:

- Biological factors (such as tumour volume)
- Treatment (such as the resection method).

Early administration of post-operative WBRT may be particularly useful when negative tumour-related prognostic factors are noted.[83] Surgery should be considered in patients with up to three BMs, being effective in prolonging survival when the systemic disease is absent/controlled and the performance status is high.[111] Surgical resection followed by WBRT represents a superior treatment modality in terms of improving tumour control at the original site of the metastasis and in the brain overall, when compared to surgical resection alone.[49] Surgical resection plus WBRT and SRS plus WBRT, both represent effective treatment strategies, resulting in relatively equal survival rates.[49]

Further investigation and treatment of the primary may follow excision of the secondary.

Stereotactic biopsy of a solitary deep lesion in an eloquent area may be helpful in achieving the diagnosis. Debevec[28] reported complete removal in 22 out of 35 patients, partial removal in seven patients and biopsy in six patients. All their patients received post-operative irradiation. Delarine and de Tribolet[29] found solitary metastasis in 89% of their patients and reported total removal in 70%, sub-total removal in 19% and partial removal in 11% of patients. They gave post-operative WBRT.

The prognosis for long-term survival of patients operated for solitary cerebral metastasis depends on the site of the metastasis, the extent of removal, the age of the patient and the tissue of origin, the kidney being the most favourable.[126]

The effect of the concomitant therapy of gefitinib and WBRT[45] in patients with BMs is better than WBRT alone, and the concomitant therapy is well tolerated.[84] The dose of gefitinib is 150 mg/d and the radiotherapy dose is (3,000–3,600) cGy/(10–12) F.[133] Gefitinib is one of the small molecule inhibitors of the EGFR tyrosine kinase (EGFR TKIs). Gefitinib has been generally considered to be a relatively safe agent. Besides a small proportion of fatal interstitial pneumonia, the common adverse drug reactions of gefitinib include diarrhoea and skin rash, and occasionally haemorrhage.[129]

WBRT alone is the treatment of choice for patients with single or multiple BMs not amenable to surgery or radiosurgery. Chemotherapy may be the initial treatment for patients with BMs from chemosensitive tumours.[111]

Chemotherapeutic Regimen

In the TP regimen paclitaxol 175 mg/m^2 on day 1 and cisplatin 20 mg/m^2 on days 1–5 are given. The NP regimen consists of navelbine 25 mg/m^2 on days 1 and 8 and cisplatin 20 mg/m^2 on days 1–5. Gemcitabine 1 g/m^2 on days 1 and 8 and cisplatin 20 mg/m^2 on days 1–5 are given in the GP regimen. All regimens were repeated every 3 weeks. Each regimen must be given for at least two cycles and but not more than four cycles.[19] The third generation regimen-based sequential chemotherapy combined with WBRT was effective for NSCLC patients with BM with an encouraging survival and acceptable tolerability.[19]

Stereotactic Radiosurgery

SRS using the gamma knife or cyberknife has been employed for solitary cerebral metastasis. Lesions less than 3 cm in size can be targeted using 1,600–3,500 cGy in a single session and may be a safe alternative to surgical excision in old frail patients with associated medical conditions like diabetes and hypertension. Loeffler and Alexander have reported a survival rate of 88% as compared to 45% with WBRT alone.[22] Short hospital stay and lower steroid requirement is an added advantage. SRS provides good tumour control for small BMs from various primary cancers, with minimal untoward effects on surrounding normal brain. This excellent tumour control prevents neurological death and maintains good activity of daily life.[106]

The cyberknife can greatly raise the fractional dose of SRS, thus improving its clinical efficacy.[46] Cyberknife has produced perfect clinical outcomes by using a higher dosage per fraction. It is an appropriate and valid treatment shortcut for BM.[123]

Radiosurgery is an effective and safe minimally invasive option for patients with BMs from an unknown primary site.[76] Image-guided radiosurgical treatment of BMs resulted in high rates of tumour control comparable to control rates reported for frame-based methods. High control rates were seen for small lesions in which spatial precision in dose delivery is critical.[18] The combined treatment of SRS and WBRT is effective in the control of brainstem metastasis, improving the neurological symptoms and, therefore, early diagnosis and treatment is important.[103] Gamma knife SRS is a safe and feasible strategy for treatment of patients with a single radioresistant BM. Radiosurgery alone is a reasonable treatment option, but may carry a greater likelihood of distant brain recurrence.[21]

Surgery is indicated in patients with a single lesion located in an accessible zone and SRS is indicated for lesions up to 3 cm in diameter, and in patients with up to three or four metastasis, no matter their location.[101]

In those patients with symptomatic mass effect after radiosurgery, resection may be warranted. Patients who have delayed local progression after SRS (greater than 3 months) have the best outcomes after resection.[51]

PROGNOSIS

In the short-term, extent of resection of the metastasis (complete or incomplete), location (supratentorial or infratentorial) and size of the metastasis were found to be statistically significant factors in predicting prognosis.[128]

Prognostic Factors Associated with Better Survival

- KPS higher than 70
- Solitary BM[100]
- Age less than 65 years
- Controlled primary tumour and no extracranial metastasis.[19]

Lung Metastasis to Brain

Aggressive treatment, including resection of both metastasis and primary tumour, has been found useful in patients with NSCLC with synchronous solitary BM.[31] Involvement of mediastinal lymph nodes is considered a poor prognostic factor and a contraindication to surgical resection of the primary lung tumour after treatment for BM.[107] A high carcinoembryonic antigen serum level is a risk factor for BM development and is associated with a poor prognosis in patients with advanced NSCLC.[4]

Factors leading to a good prognosis:

- Absence of mediastinal lymph node involvement
- Surgical resection of NSCLC with complete resection of the BM
- Low CEA levels at presentation[57]
- Response to pre-operative chemotherapy before focal treatment
- A high KPS.[73]

Breast Metastasis to the Brain

The prognosis of BMs from breast cancer is poor, especially in patients with HER-2 and TN subtypes.[121] Usually WBRT in combination with chemotherapy is the standard treatment modality.[6] In HER2+ breast cancer, trastuzumab has been shown to be very effective, although it cannot cross the blood-brain barrier.[13]

Novel biologic agents like lapatinib, which is the most promising, are currently being investigated in the treatment of BMs of breast cancer with promising results.[5]

Germ Cell Tumour Metastasis to the Brain

Although most patients with BM have a poor clinical outcome, aggressive local treatment and employment of novel anticancerous agents may contribute to improve the clinical course in selected patients with germ cell tumours and BM. Testicular germ cell tumours with BMs can be managed with the combination of WBRT, stereotactic radiotherapy, and/or surgical resection in combination with chemotherapy.[78]

Chemotherapy consisting of irinotecan and nedaplatin resulted in normalisation of the tumour markers and complete remission was proved by the subsequent surgical resection.[68]

Renal Metastasis to the Brain

Surgical resection and/or radiosurgery contribute to prolonged survival. Systemic treatment might play a role in the management of these patients. Recent advances like immunotherapy, angiogenesis inhibition and other signal transduction inhibitor approaches might be helpful.[75]

Patients with metastatic RCC should undergo CNS screening to allow the identification of smaller lesions that are more amenable to treatment.[122] Those patients with solitary metastasis are less likely to develop CNS recurrence after local therapy. Selected patients with good performance status may exhibit prolonged survival and should be offered aggressive therapy.[108]

Melanoma Metastasis to the Brain

WBRT, microsurgery and radiosurgery alone or in combination is the treatment of choice for patients with BM from a melanoma.[69] Chemotherapy has been ineffective.[109]

RECENT ADVANCES

The molecular targeting of distinct deregulated gene products, including Hh and EGFR signalling components and other signalling elements that are frequently deregulated in highly tumourigenic cancer-initiating cells and their progenies, might constitute a potential therapeutic strategy to eradicate the total cancer cell mass.[70]

MULTIPLE METASTASES

The decision to treat or not, and how to treat metastases when multiple is difficult. One of the large life-threatening symptomatic metastasis in a young patient may be removed, followed by WBRT if the primary neoplasm is known to be radiosensitive.

Steroids and diuretics are helpful in alleviating symptoms by reducing the oedema surrounding the lesions. In terminal cases, steroids can be used with good effect; of course the side effects may dictate the cessation of therapy. This may be followed by remission for a few months. The radiation therapy oncology group[6] has demonstrated that high dose fractionated therapy 2,000 cGy in 1 week or 3,000 cGy in 2 weeks is quite effective in palliation. This is based on the assumption that even if primary investigations have revealed a single lesion and the operative removal of a solitary lesion has been complete, there always exist multiple microscopic undetected metastases.[27,110]

However in a small series of patients, no difference in survival has been found in patients who did and did not receive radiation after resection of a solitary lesion.[34] When the primary is unknown in a patient with multiple cerebral metastases, stereotactic biopsy will be required to confirm the diagnosis.

RECURRENCE OF BRAIN METASTASIS

The probabiltity of local or distant recurrence in the brain after local excision and radiotherapy for single metastasis is 10–20%. The rate of distant metastasis in the absence of radiotherapy is 30–40%. The median time to recurrence is 5–7 months.[9]

MENINGEAL CARCINOMATOSIS

Meningeal carcinomatosis refers to diffuse metastasis in the leptomeninges by systemic cancer. Saenger (1900) and Lilienfeld and Benda (1901) described it.[63] The most frequent primary sites are the breast and lung.[64] Malignant melanoma is the third most common primary tumour.[72] This condition is distinct from both metastatic deposits that occur in the substance of the brain and spinal cord and nodular deposits in the dura. Meningeal carcinomatosis is characterised by a diffuse widespread involvement of the meninges by carcinomatous infiltration.[65] The dura appears thickened over a wide area both at the base of the brain as well as the vault. This may occasionally cause occlusion of the CSF circulation leading to hydrocephalus. The patients are also known to present with pseudotumour cerebri as is seen in leukaemic deposits of the meninges.[56]

Aetiopathogenesis

The aetiopathogenesis of this condition is not clear; the CSF may be involved via the choroid plexus which may be affected by the malignancy.[74,81] A deposit in the nerve root or the surface of the brain may spread along the leptomeninges. Lymphomas may metastasise exclusively to the leptomeninges. Meningeal carcinomatosis is a better term than neoplastic meningitis. Lymphocytic leukaemia, non-Hodgkin's lymphoma, carcinoma breast, carcinoma lung and melanoma are reported to spread in this manner.[124] Spread may occur via the venous route from the Batson's plexus.[81]

Clinical Features

Because the symptoms resemble a meningeal infection, it has also been referred to as carcinomatous meningitis. There may be cranial nerve palsies and if the spinal dura is involved, the patient may present with paraparesis.[44] Olson et al.[81] have classified the symptoms as cerebral, cranial and spinal. They may antedate any symptoms of malignancy and, therefore, may be confused with tuberculous meningitis, cysticercosis, cryptococcal meningitis or sarcoidosis.

Investigations

Cerebrospinal Fluid Analysis

The diagnosis is confirmed by CSF examination, sometimes with the help of multiple filters to filter the CSF, or examining a centrifugate revealing carcinomatous cells will clinch the diagnosis.

Computerised Tomography/Magnetic Resonance Imaging

The MRI shows nodular contrast enhancement lining the CSF. There may be hydrocephalus as well.[113] Gadolinium-enhanced MRI will show neoplastic spread involving the spinal cord and spinal nerves.[132]

Unenhanced fluid-attenuated inversion recovery (FLAIR) images are of more value than SE T2-weighted images for the diagnosis of intracranial meningeal carcinomatosis. Contrast-enhanced FLAIR images are more useful than contrast-enhanced T1-weighted images in their quality.[120]

Meningeal Biopsy

It is helpful when the diagnosis is strongly suspected and clinical and other investigations fail to demonstrate it.

Staging of leptomeningeal metastasis requires contrast-enhanced brain and spine MRI and radionuclide CSF flow study.[16]

Treatment

- Irradiation of part or of entire neuraxis[87]
- Chemotherapy (methotrexate, cytosine arabinoside and thiotepa).[10]

Intra-CSF drug therapy primarily utilises one of three chemotherapeutic agents (e.g. methotrexate, cytosine arabinoside and thiotepa) administered by a variety of schedules either by intralumbar or intraventricular drug delivery.[16]

A good prognosis is possible in the following:

- Lymphomatous or leukaemic meningitis
- Chemosensitive tumours such as breast cancer
- Low tumour burden
- Minimal neurological deficits
- Good performance status
- Controllable systemic disease.

Recent Advances

Novel intra-CSF agents, such as targeted monoclonal antibodies rituximab (anti-CD20 for B-cell lymphoma-related leptomeningeal metastasis) and trastuzumab (anti-Her-2/neu for breast cancer-related leptomeningeal metastasis) are being utilised now.[16]

Treatment is largely palliative (median survival 2–4 months). The prognosis for meningeal carcinomatosis is gloomy. However, Olson et al.[81] have reported that with early diagnosis it is possible to eradicate the disease with radiotherapy and intrathecal methotrexate as done in leukaemia.

CARCINOMATOUS ENCEPHALOPATHY

Neurological signs of encephalopathy or myelopathy may appear when there is an occult malignancy elsewhere in the body.[12] Sensory neuropathy[23] and proximal myelopathy in the elderly may be seen. This is known as carcinomatosis neuromyeloencephalopathy.[43]

This may be the first manifestation of an occult malignancy in the body and is described as a non-metastatic manifestation with an immunological basis for its pathogenesis. Central pontine myelinolysis may occur as a reaction to a systemic tumour.[97] Histological examination of the brain in these cases reveals neuronal

loss, gliosis and tract degeneration without any evidence of infiltration by malignant cells. The immunological mechanisms involved in carcinomatous neuromyopathy have been described by Paty et al.[85]

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141 Radiation Therapy for Malignant Brain Tumours

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INTRODUCTION

According to the Globocan 2002, cancers of the brain and nervous system account for some 189,000 new cases and 142,000 deaths annually (1.7% of new cancers; 2.1% of cancer deaths). The corresponding figures for India are 19,680 and 16,086, respectively. The highest rates are observed in developed areas (Australia/New Zealand, Europe and North America) and are lowest in Africa and the Pacific Islands.[49] Surgery is the primary modality of treatment for the majority of primary brain tumours. Radiotherapy is an essential component in the management in most of them after a maximal safe surgical resection. Radiotherapy can be delivered by fractionated external beam irradiation, small field stereotactic irradiation or by interstitial implantation. Current regimens generally use 50–60 Gy delivered in 25–30 fractions over 5–6 weeks. Regimens with either higher dose or more than 2 Gy per fraction are associated with late neurotoxicity.

Radiation treatment volumes for these tumours generally include the enhancing volume (which contains solid tumour tissue), surrounding oedema (which is comprised of normal brain infiltrated by microscopic tumour) and a margin of normal brain. Thus, even with the use of very conformal techniques, a substantial amount of "normal" brain is included in the full dose volume. One should remember that the volume of normal brain irradiated should be kept to a minimum, in order to decrease the late side effects. The tolerance of normal brain (and spinal cord in the case of cord tumours) is the major limiting factor in achieving local control and cure. Tolerance dose is usually expressed as TD5/5 and TD 50/5. "TD 5/5" is the dose that leads to 5% risk at 5 years. "TD 50/5" is the dose that leads to 50% risk at 5 years. TD 5/5 and TD 50/5 values for whole-brain fractionated radiotherapy at 2 Gy per fraction are 60 Gy and 70 Gy, respectively. With partial brain irradiation, the corresponding values are 70 Gy and 80 Gy, respectively. For tumours with high-risk to spread to the CSF space, elective irradiation of the whole craniospinal axis with localised boost to the area of gross tumour is necessary.

Adverse reactions associated with cranial irradiation include: (1) acute reactions; and (2) late reactions.

Acute reactions: A transient worsening of pre-treatment symptoms can occur due to peritumoral oedema. This is very well managed by corticosteroids. Other acute side effects include nausea, vomiting, skin discolouration, alopecia, otitis externa, serous otitis media, fatigue, mucositis, oesophagitis (last two only in craniospinal irradiation) and haematologic toxicity.

The late sequelae include:

- Radiation necrosis, which can mimic a recurrent tumour both symptomatically and on radiology.
- Auditory apparatus damage can occur due to the inclusion of the middle or inner ear in the field.
- Visual disturbance can occur due to damage to the eye, optic nerve or chiasm.
- Endocrine dysfunction due to damage to the hypothalamo-pituitary axis
- Neuropsychological changes.

RADIOTHERAPY TECHNIQUES

Proper immobilisation is necessary for better planning. One can restrict the clinical target volume (CTV) to planning target volume (PTV) margins, only if proper and reproducible immobilisation is done. The most important aspect in stereotactic radiotherapy and stereotactic radiosurgery is the superb immobilisation that is used in these situations. Depending on the condition, the radiotherapy may be partial brain, whole brain or craniospinal. Initially, people used simple two-dimensional planning with point dose calculation. Patients were treated by parallel opposed portals, ipsilateral wedge fields, a combination of vertex and wedge fields, etc. With the advancement in computer technology and treatment planning systems, we moved to three-dimensional conformal radiation (3DCRT) and now to intensity modulated radiotherapy (IMRT). In 3DCRT, we limit the dose to much of the normal structures, focusing the beams to the target. IMRT is a further refined conformal radiation where we can modulate the intensity of the beam by further restricting the dose to normal brain and adequately treating the involved region. Non-coplanar beams are also used in the treatment of brain tumours, especially in stereotactic radiotherapy (SRT) and stereotactic radiosurgery (SRS). Craniospinal irradiation needs considerable expertise as it involves different techniques of field matching.

Stereotactic Radiosurgery

It involves the combined work of the neurosurgeon, radiation oncologist and physicist. SRS can be delivered using a Gamma Knife or a linear accelerator. Gamma Knife contains 201 cobalt-60 (^{60}Co) sources and it is collimated using a helmet with circular apertures ranging from 4mm to 18 mm focusing a single point. Linac based radiosurgery can be either cone-based or multileaf collimator-based. The treatment is delivered using multiple non-coplanar arcs that intersect at a single point to treat a tumour of less than 4 cm in diameter.

Stereotactic Radiotherapy

It is delivered using a linear accelerator. A fractionated schedule is followed maintaining the precision targeting techniques of SRS. Either cone or MLC with non-coplanar beams are used as in the case of SRS.

TREATMENT OF INDIVIDUAL TUMOURS

Gliomas

High-Grade Gliomas (Anaplastic Astrocytoma, Glioblastoma Multiforme)

They are highly aggressive tumours that have a characteristic ring like enhancing appearance on CT/MRI with central necrosis, infiltrative margins and surrounding low density changes. They account for 35–45% of adult brain tumours. They can occur in any age group but the peak incidence is in the fifth and sixth decade of life. Of the high-grade gliomas, glioblastoma multiforme (GBM) constitute 85% and anaplastic astrocytoma (AA) constitute 10–15%. These tumours typically infiltrate the adjacent normal structures. Halperin compared antemortem CT scan findings with postmortem topographic distribution of tumour cells and found that radiotherapy with fields designed to treat the contrast enhancing region alone or this region plus "oedema" with a tight margin will frequently miss tumour, whereas a 3 cm margin around the "oedema" would have covered histologically identified tumour in all cases.[26,28]

Surgery is never complete in high-grade gliomas. Even macroscopic complete removal is possible in 10–20% of cases only. One needs to add post-operative radiotherapy in these cases. The less the residual tumour after surgery, the better is the prognosis. Radiotherapy has been used in malignant gliomas for the last six decades. The first randomised trial to demonstrate the benefit of RT is the BTSG 69-01. Walker et al. in the randomised control trial, evaluated the role of radiotherapy in the treatment of anaplastic gliomas. Median survival of patients in this study is as follows:

- Best conventional care: 14 weeks;
- BCNU: 18.5 weeks;
- Radiotherapy: 35 weeks; and
- BCNU plus radiotherapy: 34.5 weeks.[72]

The second one is the SGSG, Scandinavian Glioblastoma Study Group trial, where the median survival rates of patients were 10.8 months in the radiotherapy group versus 5.2 months in the supportive care group.[36,43]

RT can only delay the disease progression or recurrence. Almost all GBMs and 65–80% of AA recur within 2–5 years and lead to death. Garden studied the patterns of recurrence in these tumours and found that recurrence almost always occurs in the central or enhancing portion of the tumour.[20] Perhaps the central tumour is radioresistant because of hypoxia. Several trials tried to overcome this by using hypoxic cell sensitisers[9,42] and by different techniques like interstitial brachytherapy, SRT, etc. Altered fractionation schedules were also tried by many authors to improve survival. Hyperfractionation,[18,27,42] acceleration[7,23,39,40] and hypofractionation all did not prove to be of benefit. Boost with radioactive implants also did not reveal any added advantage.[37,57]

Dose of Radiotherapy

Results from BTSG 69-01 and two successive BTSG studies were pooled together to evaluate the median survival for 60 Gy versus 50 Gy. It was 10.5 months versus 7 months (p=0.004).[73] The MRC trial compared 45 Gy with 60 Gy and suggested a statistically significant prolongation of median survival from 9 months in the 45 Gy group to 12 months in the 60 Gy group (hazard ratio = 0.75).[4] RTOG 7401/ECOG 1374 study showed that there is no added survival advantage by escalating the dose to 70 Gy.[9] So the present standard dose is 60 Gy in conventional fractionation.

Volume of Irradiation

It was assumed that it was impossible to accurately localise these tumours because of inadequate imaging modalities available and the tendency of these tumours to infiltrate the surrounding brain. So, initial studies treated patients with parallel opposed lateral portals and treated whole brain. Hochberg et al. evaluated CT scans, performed on glioblastoma patients within 2 months of postmortem examination and showed that CT defined both gross and microscopic tumour extent within a 2 cm margin in the majority of patients evaluated. Serial CT scans revealed that glioblastoma recurred within a 2 cm margin of the primary site in 90%.[29] Wallner et al. showed that 78% of unifocal tumours recurred within 2.0 cm of the pre-surgical, initial tumour margin, defined as the enhancing edge of the tumour on CT scan.[74] The present standard is to take the tumour (enhancing T1 contrast volume on MRI) and oedema (Flair or T2 abnormality) with an added margin of 2–3 cm around.

Role of Chemoradiation

Chemotherapy is mainly added as a radiosensitiser. The main concern in brain tumours is that to be active, the chemotherapeutic agents must reach the brain crossing

the blood-brain barrier. The chemotherapeutic agents that are used include the nitrosoureas-CCNU, BCNU, Procarbazine, etc. We have published the results of concurrent chemoradiation with Paclitaxel in 18 cases of glioblastoma. The overall 1-year survival rate was 70%, with 12 patients alive at 13 months.[32,38]

The newer drug is temozolomide, which is a lipophilic second-generation alkylating agent. At physiological pH, it is converted into MTIC. Stupp et al. conducted an open-label, phase II trial in GBM in which Temozolomide (75 mg/m^2/d x 7 d/wk for 6 weeks) was administered orally concomitant with fractionated radiotherapy (60 Gy total dose: 2 Gy x 5 d/wk for 6 weeks), followed by temozolomide monotherapy (200 mg/m^2/d x 5 days, every 28 days for six cycles).[64] They observed that concomitant radiation plus temozolomide therapy was safe and well tolerated. Median survival was 16 months and the 1-year and 2-year survival rates were 58% and 31%, respectively. This regimen of concomitant chemoradiotherapy followed by adjuvant chemotherapy prolonged the survival of patients with glioblastoma. Jalali et al. studied 42 patients of glioblastoma treated with a similar approach. At a median follow-up of 12.5 months, they observed 1-year and 2-year survival of 67% and 29%, respectively. The median overall and progression-free survival was 16.4 and 14.9 months, respectively.[31]

Based on randomised data available, chemotherapy has consistently failed to improve the outcome of patients with anaplastic astrocytoma, while a meta-analysis showed a small, but significant improvement in survival favouring the use of chemotherapy. Outside a clinical trial, post-operative radiotherapy (30 x 2Gy) remains the standard adjuvant therapy for most patients.[65]

Brachytherapy

Permanent or temporary I-125 or temporary Ir-192 sources can be after loaded into catheters placed in the tumour bed. The catheters can be placed either during craniotomy or stereotactically. This can be used as a boost dose after external beam radiation in glioblastoma. Most trials are limited to supratentorial tumours less than 6 cm and that do not involve the corpus callosum. Only some authorities showed a slight advantage.[24]

Low-Grade Gliomas

Low-grade gliomas account for approximately 20% of gliomas and approximately 10% of all primary intracranial tumours in adults. This is constituted by low-grade astrocytomas 67%, mixed oligoastrocytomas 19% and oligodendrogliomas 13%. Astrocytomas are well differentiated tumours. They show increased cellularity and mild to moderate pleomorphism. The presence of microcysts differentiates it from reactive gliosis. The different subtypes of astrocytomas include the fibrillary, protoplasmic, gemistocytic and pilocytic ones. They are differentiated by the intracytoplasmic fibrillary processes, which stain with GFAP. With time, 50% of the fibrillary and protoplasmic types transform to more anaplastic ones. Since the majority of the gemistocytes transform to highly anaplastic ones and behave in an aggressive fashion, they should be treated like anaplastic astrocytomas. Pilocytic astrocytomas have a long natural history and rarely dedifferentiate into more malignant ones. The biologic behaviour of the different astrocytomas varies considerably. This can be predicted to an extent by the DNA labelling index,[29] which shows the proliferative potential of a cell.

The majority of low-grade gliomas are present with seizures without any neurologic symptoms. Other presentations include headache, vomiting, motor deficit, visual or sensory loss, language deficit or personality changes.[2] Pilocytic astrocytomas grow by expansion, while non-pilocytic ones diffusely infiltrate the surrounding structures like malignant gliomas.

Complete resection is the treatment of choice for pilocytic astrocytomas. Post-operative radiotherapy is indicated only in incompletely resected tumours. Complete resection is associated with excellent survival with more than 90% cured of the disease, whereas incomplete resection is associated with 10-year cure rates of 70–80%.[58]

In non-pilocytic astrocytomas (Grade 2 gliomas), the initial treatment is surgery. Since these tumours are diffusely infiltrative, complete resection is rarely possible. The dose and timing (immediate versus delayed) of post-operative radiotherapy in grade 2 gliomas is debated. In EORTC 22844,[33] 379 adult patients with cerebral LGGs were randomised centrally at the EORTC Data Centre to receive irradiation post-operatively (or post-biopsy) with either 45 Gy in 5 weeks or 59.4 Gy in 6.6 weeks. With 343 (91%) eligible and evaluable patients followed-up for at least 50 months with a median of 74 months, there is no significant difference in terms of survival (58% for the low-dose arm and 59% for the high-dose arm) or the progression free survival (47% and 50%) between the two arms of the trial. In EORTC 22845,[68] after surgery, LGG patients from 24 centres across Europe were randomly assigned to either early radiotherapy of 54 Gy in fractions of 1.8 Gy or deferred radiotherapy, until the time of progression (control group). One hundred and fifty-seven patients were assigned early radiotherapy and 157 controls. Median progression-free survival was 5.3 years in the early radiotherapy group and 3.4 years in the control group (hazard ratio 0.59, 95% CI 0.45–0.77; p<0.0001). However, overall survival was similar between the groups: median survival in the radiotherapy group was 7.4 years compared with 7.2 years in the control group (hazard ratio 0.97, 95% CI 0.71–1.34; p=0.872). In the control group, 65% of patients received radiotherapy at progression. At 1 year, seizures were better controlled in the early radiotherapy group. An intergroup study conducted by the North Central Cancer Treatment Group (NCCTG), Radiation Therapy Oncology Group (RTOG) and Eastern Co-operative Group (ECOG) randomised 211 adults to low versus high-dose RT. There was no difference in the 5-year OS or PFS rates between

the two dose groups in either study.[60] The Southwest Oncology Group (SWOG) study randomised 60 adults with incompletely resected LGG to RT alone or RT plus lomustine (CCNU) chemotherapy. There was no difference in outcome between the two treatment arms. Five-year overall survival (OS) and progression-free survival (PFS) rates in low-grade gliomas ranged from 58 to 72% and from 37 to 55%, respectively.[60] Our institutional policy presently is to deliver immediate post-operative radiotherapy for Grade 2 gliomas with a dose of 50 Gy in 25 fractions over 5 weeks delivered to the Flair or T2 abnormality on MRI with a margin of 1–1.5 cm, followed by a boost of 6 Gy in three fractions to the gross tumour without margin.

Brainstem Gliomas

Brainstem gliomas (Table 1) occur in the pons, the midbrain or the medulla. The tumour may contiguously involve the cerebellar peduncles, cerebellum and/or thalamus. About two thirds of brainstem gliomas occur in children. The survival and prognostic factors are entirely different for adults compared with children. The majority of childhood brainstem gliomas are diffuse pontine gliomas, which have a very poor prognosis. Focal pilocytic astrocytomas have a better prognosis. They most frequently arise in the tectum of the midbrain, focally, within the pons or at the cervicomedullary junction. Generally, the diagnosis is made radiologically and biopsy is not mandatory. The tumours of the midbrain, especially in the tectal plate region, are usually low-grade and have a greater likelihood of long-term survival (approximately 80% 5-year progression-free survival vs less than 20% for tumours of the pons and medulla).

The standard treatment for children with diffuse intrinsic pontine glioma is radiation therapy to involved areas, but 90% of patients will die within 18 months of diagnosis. The conventional dose of radiation therapy ranges between 5,400 cGy and 6,000 cGy given locally to the primary tumour site in daily fractions of 1.8 Gy. The utility of chemotherapy in the treatment of patients with newly diagnosed diffuse pontine gliomas is unproven.[1,8,15,76] To date, neither adjuvant or neoadjuvant chemotherapy nor immunotherapy when added to radiation therapy, has been demonstrated to improve survival for children with diffuse intrinsic pontine glioma. High-dose therapy with stem cell rescue also failed to extend the survival.[6]

In focal or low-grade brainstem gliomas, maximal surgical resection should be attempted, followed by adjuvant radiotherapy.[69] Mehta et al. have recently published a series of focal intrinsic brainstem gliomas treated initially with surgery. They have also proposed a surgical strategy oriented classification. The intrinsic brainstem tumours were classified into three types: Expanding, diffuse infiltrative and pure ventral varieties. Surgical intervention in the expanding variety was associated with excellent long-term prognosis. The other two varieties were associated with poor outcome and the authors recommend that they should be subjected to radiotherapy only.[39] Patients with small tectal lesions and hydrocephalus but no other neurological deficits may be treated with cerebrospinal fluid diversion alone and have follow-up with sequential neuroradiographic studies, unless there is evidence of progressive disease.[69]

Ependymomas

Ependymomas (Table 2) occur in both adults and children. The peak incidence is at 5 years and 34 years. In adults, approximately 33% of ependymomas arise infratentorially and 66% arise supratentorially; the opposite is true in children. It is classified into ependymomas (low-grade) and anaplastic ependymomas (high-grade) according to WHO classification. The 5-year survival ranges from 60 to 80% in low-grade versus 10 and 47% in high-grade tumours. They usually originate in the ependymal linings of the ventricles in the posterior fossa or supratentorial region and have access to the cerebral spinal fluid (CSF) and, therefore, may spread throughout the entire neuraxis. These tumours can cause hydrocephalus and increased intracranial pressure, mimic brainstem lesions, cause multiple cranial nerve palsies, produce localising cerebellar deficits and cause neck stiffness and head tilt if they infiltrate the upper portion of the cervical cord. Every patient with ependymoma should be evaluated with diagnostic imaging (CT/MRI) of the spinal cord and whole brain. In addition, CSF cytological evaluation should be conducted.

Patients with totally resected tumours tend to have the best prognosis. Surgery should be performed in an attempt at maximal tumour reduction. Supratentorial ependymomas generally have a poorer prognosis than their infratentorial counterparts. Radiotherapy significantly improves tumour control and survival. The volume of CNS to be irradiated is controversial. Many authors recommend the inclusion of the entire craniospinal axis

Table 1: Selected studies of brainstem gliomas in adults

Author	*Year*	*Pt no*	*RT Dose (Gy)*	*Med survival (mo)*	*2 YSR*	*5 YSR*
Kim[34]	1980	30	50–60	15	40	30
Grigsby[22]	1989	19	49.8	33	68	47
Shibamoto[61]	1989	79	57–65	-	-	17
Shrieve[62]	1992	19	66–78	44	53	-
Prados[51]	1995	42	72–78	16	-	-

Table 2: Selected studies of ependymomas

Author	*Year*	*No*	*RT Dose (Gy)*	*5 YSR (%)*	*10 YSR (%)*
Chin[10]	1982	16	34.5–60	37	-
Salazar[55]	1983	51	55	-	69
Garrett[21]	1983	102	-	60	54
Read[53]	1984	79	42.5–50	50	-
Shaw[59]	1987	33	48	62	-
Vanuytsel[71]	1992	93	24–59.2	51	42

or whole brain in the treatment of anaplastic ependymomas.[75] In a review by Vanuytsel et al. the spinal seeding was 9.5% (15/157) in the event of failure at the primary site compared to 3.3% (4/122), when local control was achieved and the development of spinal metastases was not influenced by the extent of irradiation. Spinal metastases are not prevented by prophylactic spinal irradiation, regardless of tumour grade and site.[70] With the availability of MRI to detect involvement of the spine, it is generally agreed that one can go ahead with local RT even in anaplastic ependymomas, unless the spine or CSF are involved.

The treatment algorithm for adult ependymomas revolves around histology, extent of surgical resection and extent of disease in the craniospinal axis. Patients with a well differentiated ependymoma who have undergone a gross total resection and have a negative screening spinal MRI scan, may be treated by limited-field radiation. However, if a contrast enhanced spinal MRI scan reveals disease, craniospinal irradiation should be administered. In patients with anaplastic ependymoma, if the spinal MRI scan is negative, limited-field RT is normally given. However, if the spinal MRI scan is positive, craniospinal irradiation is indicated.

Based on dose-response analyses for ependymomas, the typical radiation dose is between 50 Gy and 55 Gy locally using 1.8–2.0 Gy per fraction.[71] For a low-grade ependymoma, the usual dose is 54 Gy to tumour plus 2 cm margin. For a high-grade ependymoma, it is 60 Gy to tumour plus 2–3 cm margin. If CSI is used, then the entire craniospinal axis receives 36 Gy and the tumour with margin is boosted for the rest of the dose.

Ependymomas do not appear particularly responsive to chemotherapy. However, chemotherapy is sometimes considered as a salvage option to best supportive care in cases of recurrence.

Medulloblastoma

Medulloblastoma is the most common type of malignant brain tumour in childhood (peak 5–10 years). About 15–20% of cases occur in adults. It belongs to the group of tumours known as primitive neuroectodermal tumour, which is a highly malignant, small round blue cell tumour of the central nervous system. This tumor usually originates in the cerebellum. It may spread contiguously to the cerebellar peduncle, floor of the fourth ventricle, into the cervical spine or above the tentorium. In addition, it may spread via the cerebrospinal fluid intracranially and/or to the spinal cord. The incidence of CSF spread at diagnosis is 10–15%.

The work up investigations include contrast enhanced MRI of the brain and whole spine and CSF cytology. A bone scan as well as a bone marrow aspiration and biopsy may be useful in symptomatic patients or in those with abnormal blood cell counts at diagnosis. Two major risk categories are now being used:

1. Average risk: Children older than 3 years with posterior fossa tumours; tumour is totally or near-totally (<1.5 cc's of residual disease) resected; no dissemination.
2. Poor risk: Children 3 years old or younger or those with metastatic disease and/or subtotal resection (>1.5 cc's of residual disease) and/or non-posterior fossa location.

The patients should undergo maximal resection. The traditional post-surgical treatment for these patients has been radiation therapy consisting of 5,400–5,580 cGy to the posterior fossa and approximately 3,600 cGy to the entire neuraxis (i.e. the whole brain and spine). The standard boost in medulloblastoma is the entire posterior fossa. Some studies suggest that a tumour-bed boost would be equally effective.[17] Thomas et al. reduced the dose to the neuraxis without adding chemotherapy and found that reduced-dose neuraxis irradiation (23.4 Gy) is associated with increased risk of early relapse, early isolated neuraxis relapse and lower 5-year EFS and overall survival than standard irradiation (36 Gy).[66] But the lower radiation dose to the neuraxis (2,340 cGy), when coupled with chemotherapy, has been shown to result in disease control in up to 80% of patients and may decrease the severity of neurocognitive sequelae.[19,46,47,54]

In poor-risk patients, the addition of chemotherapy has improved the duration of disease-free survival. Some studies show that approximately 50–60% of such patients will experience long-term disease control.[13,48] Children younger than 3 years are particularly susceptible to the adverse effect of radiation on brain development. Debilitating effects on growth and neurologic development have frequently been observed, especially in younger children. For this reason, chemotherapy is administered to delay the administration of radiation

Table 3: Selected studies of medulloblastoma in adults

Author	*Year*	*N*	*Median age(YR)*	*5YSR (%)*	*10YSR (%)*
Kopelson[35]	1982	17	24	46	46
Hughes[30]	1984	15	23.5	63	38
Haie[25]	1985	20	26.5	78	55
Skolyszewski[63]	1989	13	22.4	62	-
Bloom[5]	1990	47	24	54	40
Frost[16]	1995	48	25	62	41
Prados[52]	1995	47	28	60	-

therapy. Different chemotherapeutic regimens have been employed and most have utilised an alkylator (cyclophosphamide or ifosfamide), cisplatin and/or carboplatin, oral or intravenous etoposide and vincristine. Outcome of such treatment has been relatively disappointing, resulting in disease control in only 20–30% of patients.[12] High-dose chemotherapy and autologous stem cell rescue is also tried in children less than 3 years.[67]

The treatment of medulloblastoma in adults is similar to that of children. The management is by surgery followed by radiotherapy to the neuraxis. Chemotherapy is added for poor-risk patients. The 5-year survival ranges from 46 to 78% and the 10-year rates from 38 to 55%, as shown in the Table 3.

Primary Central Nervous System Lymphoma

Primary central nervous system lymphoma (PCNSL) is a rare form of non-Hodgkin's lymphoma (NHL) that is restricted entirely to the brain, leptomeninges, eyes and rarely the spinal cord, without systemic disease. It accounts for 0.5–2% of all primary brain tumours. This disease is seen more commonly among patients with acquired immunodeficiency syndrome (AIDS) and other immunocompromised states. Primary central nervous system lymphoma is probably a substantially different disease in persons with and without AIDS with regard to patient characteristics, clinical and radiographic presentation and prognosis.[14]

More than 50% of the lesions on computed tomographic (CT) scans in patients with AIDS are ring-enhancing and multifocal, a pattern rarely described in immunocompetent patients. Patients without AIDS almost always show only homogeneous enhancement.[14] A periventricular, diffusely enhancing lesion on magnetic resonance imaging (MRI) is suggestive of primary CNS lymphoma.[41] Tumours are often periventricular and may involve ependymal lining cells or, if more peripherally located, may extend to the leptomeninges. Leptomeningeal involvement may remain localised to adjacent parenchymal sites or can be more diffuse with positive CSF cytology. Ocular involvement may develop independently in 10–20% of primary CNS lymphoma patients with primary brain disease. Less often, the tumour arises within the eye as the initial manifestation of primary CNS lymphoma. In rare cases, the spinal cord parenchyma may be an initial or secondary site of primary CNS lymphoma.

The work up investigations include haemogram, liver and kidney function tests, HIV, chest X-ray, MRI of brain and spine, and a biopsy from the lesion (preferably a stereotactic biopsy). If there is no risk of herniation, a lumbar puncture with evaluation of CSF is recommended. An ophthalmologic evaluation including a slit-lamp examination should be done to exclude an obvious malignant uveitis. If there is a reasonably high suspicion of primary CNS lymphoma, it is preferable not to start therapy empirically with steroids, unless medically indicated.

Because of the diffuse nature of central nervous system (CNS) lymphomas, aggressive surgical decompression with partial or gross total removal of the tumour is of no benefit to the patient. Systemic treatment is compromised by the blood-brain barrier, which is impermeable to several cytostatic agents. The role of RT for patients with primary CNS lymphoma continues to evolve. Early studies demonstrated that these tumours were radiosensitive and that complete and partial responses could be obtained using doses ranging from 3,000 cGy to 5,000 cGy. However, the responses were brief and patients often developed recurrent disease within a matter of months. Between 1983 and 1987, the Radiation Therapy Oncology Group conducted a prospective phase II study on 41 patients to evaluate survival in primary non-Hodgkin's lymphoma of the brain treated with whole brain irradiation to 40 Gy and a 20 Gy boost to tumour plus a 2 cm margin. Overall median survival was 12.2 months, with 48% surviving 1 year and 28% surviving 2 years. Patients with a Karnofsky Performance Status of 70–100 had a median survival of 21.1 months compared to 5.6 months for patients with a status of 40–60 ($p < 0.001$). Fourteen patients less than 60 years of age had a median survival of 23.1 months, while 27 patients older than or equal to 60 years of age had a median survival of 7.6 months (log-rank $p = 0.001$).[44]

The currently recommended dose of RT for cerebral primary CNS lymphoma is between 4,000 cGy and 5,000 cGy (whole brain), without a boost. However, RT should be avoided in patients older than 60 years. For patients

with ocular lymphoma, irradiation is the treatment of choice; 3,600 cGy should be administered to both eyes.

Median survival times for studies with pre-irradiation CHOP (cyclophosphamide, doxorubicin, vincristine and dexamethasone) were no better than for radiation therapy alone.[45,56] In a retrospective series of 226 patients, it was shown that patients with PCL treated with regimens that included HDMTX followed by radiotherapy, have an improved survival, but not a higher risk of late neurotoxicity, as compared with other treatment modalities.[3] RTOG 9310 study, published in 2002, showed that high-dose methotrexate combined with cranial irradiation is an effective therapeutic approach to PCNSL.[11] A multicentric study evaluated two cycles of MBVP (MTX 3 g/m^2 days 1 and 15, teniposide 100 mg/m^2 days 2 and 3, carmustine 100 mg/m^2 day 4, methylprednisolone 60 mg/m^2 days 1–5 and two intrathecal injections of MTX 15 mg, cytarabine 40 mg and hydrocortisone 25 mg) followed by 40 Gy of RT. The overall response rate of all 52 patients was 81% and the median estimated overall survival was 46 months with 10% toxic death rate during treatment.[50] Several different chemotherapy regimens and agents have been used with no current consensus on the optimal regimen. However, high-dose methotrexate (≥ 3 g/m^2) is the single most active agent against primary CNS lymphoma and should be a part of any chemotherapy regimen chosen to treat this disease. For healthier patients (i.e those 60 years or younger with a KPS ≥ 40 and a creatinine clearance ≥ 50; those older than 60 years with a KPS > 50), some type of pre-radiation chemotherapy is generally recommended; a high-dose methotrexate based regimen is most commonly used. In patients older than 60 years, RT may be omitted to avoid neurotoxicity. For patients with extremely poor KPS (< 40) or creatinine clearance less than 50, it is recommended that treatment consist of whole brain irradiation (45 Gy), in order to rapidly induce a response, diminish neurologic morbidity and optimise quality of life.

The survival is very poor without therapy (1–3 month mean survival). The overall survival for treated patients without AIDS is 18.9 months compared with 2.6 months for patients with AIDS.[14]

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142 Adjuvant Therapies for Malignant Brain Tumours

Raj Kumar R, Ashok Kumar Mahapatra

Over the years, extensive research has been done to improve management strategy for central nervous system tumours. Advances have been made in both surgical and adjuvant therapy.[2,14] It has been progressively realised that adjuvant therapy plays a very significant role in the management of CNS tumours. Adjuvant therapy has helped in increasing both the duration of survival and the quality of life.[14] Adjuvant therapy, for long, has meant radiotherapy and chemotherapy. However, over the past decade, new fields such as immunotherapy and gene therapy have come a long way in providing us with a wider repertoire of treatment options to choose from. The fields of radiotherapy and chemotherapy have also been evolving with regards to technological advancements. Now radiotherapy can be provided with far more accuracy with minimal damage to surrounding structures. Similarly, new chemotherapeutic agents are finding acceptance. In this chapter, we discuss the present available options for adjuvant therapy for central nervous system tumours.

CHEMOTHERAPY

Major strides have been made in the management of brain tumours within both the surgical and radiotherapy fields. However, advances in chemotherapy have been restricted. This has been attributed to certain distinctive properties of brain tumours which are discussed below.

Blood-Brain Barrier

The highly effective blood-brain barrier (BBB) is one of the main reasons for the relative inaccessibility of the brain.[7] The continuity of this barrier is maintained by the tight junctions of the capillary endothelial cells, lack of fenestrations with the endothelial cells, limited pinocytosis, normal astrocytes and the presence of 'P' glycoprotein. The capillary permeability, the molecular weight of the drug and its lipophilicity regulate drug penetrance in the CNS. Drugs with a molecular weight greater than 450 kDa cannot cross the BBB, despite being lipophilic.[7] The BBB may get partially disrupted by malignant gliomas. Similarly, higher doses of chemotherapeutic agents increase BBB penetration. The intrathecal route of drug administration is an effective route for bypassing the BBB.

Tumour Heterogeneity

Following BBB penetration, the availability of the drug at the tumour site is dependent upon the transcapillary flow of the drug to the tumour. This is restricted due to the heterogeneity of the tumour seen more commonly in brain tumours. The tumour cells are in various stages of the cell cycle which is another factor in limiting drug efficacy, since the sensitivity varies in different portions of the tumour, hence resulting in the variable response.

Drug-Drug Interaction[7]

Drugs which induce hepatic cytochrome 450 enzymes reduce the efficacy of the chemotherapeutic aspects, by altering and increasing drug metabolism and clearance of the drugs. This in turn allows suboptimal dosage at the tumour site, resulting in treatment failure (Fig. 1).

Tumour Resistance[7]

Over the years, inherent tumour resistance to chemotherapy has been noticed, resulting in a low response rate. Glioblastoma has been shown to have the least response rate. Some anaplastic oligodendrogliomas,

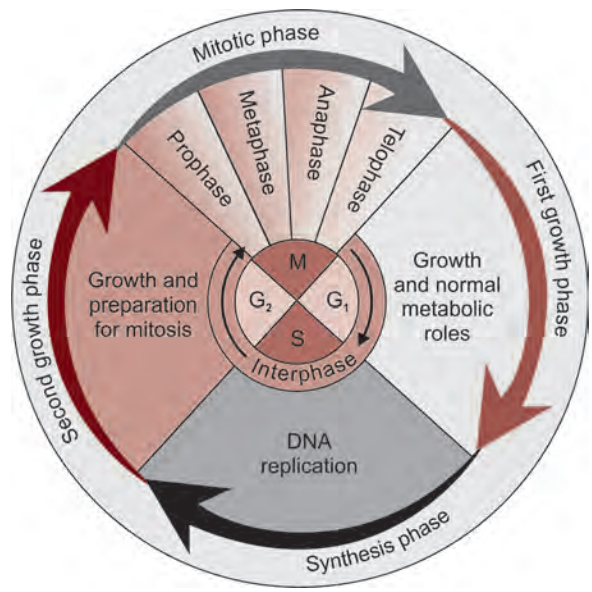
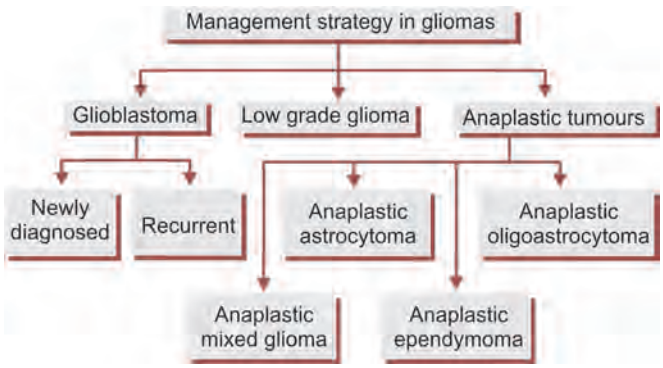


Fig. 1: Cell cycle

especially those with LOH at 1p/19q, have been shown to have a higher response rate. Sometimes it has been noticed that tumours which were initially responsive demonstrate progressively decreasing levels of response. This indicates that the tumour had certain resistant cells, the population of which has grown rapidly.

Chemotherapeutic Agents

Group	*Agent*		*Mechanism*
Nitrosourea	Carmustine Lomustine Nimustine	BCNU CCNU ACNU	DNA cross links, carbamoylation of amino groups
Alkylating (methylating) agents	Procarbazine Temozolamide Carboplatin Cisplatin	P TMZ	DNA alkylation, interferes with protein synthesis Chelation via intrastrand crosslinks
Nitrogen mustard	Cyclophosphamide Isofamide Cytoxan		DNA alkylation, carbonium ion formation
Vinca alkaloids	Vincristine Vinblastine Pacilataxel		Microtubule formation inhibitor
Epidophy-llotoxins	Etoposide Teniposide	ETOP VM26	Topoisomerase II inhibitor
Miscellaneous	Topoteca Irinotecan Tamoxifen Hydroxyurea Bleomycin Methotrexate	CPT11	Topoisomerase I inhibitor Protein kinase inhibitor



Newly Diagnosed Glioblastoma

Neo-adjuvant chemotherapy: Neo-adjuvant refers to administration of chemotherapy prior to radiotherapy. Repeated trials have failed to demonstrate any benefit of neo-adjuvant therapy, despite using different combination regimes.

Concurrent radiotherapy and chemotherapy: This is the widely accepted treatment of choice following surgical cytoreduction. Trials using temozolamide at 75 mg/m^2 orally for 42 days, concurrently with external beam radiotherapy have shown promising results with survival up to 16 months.[13] Presently, radiotherapy followed by TMZ (100 mg/m^2) for 5 days every 28 days for 6 cycles is the standard treatment.

Carmustine (BCNU) is the other agent for which a standard protocol has been described. This involves surgical cytoreduction followed by radiotherapy and then BCNU at 6 weeks intervals at 110 mg/m^2.

Local delivery of chemotherapeutic agent: Agents used for local delivery of chemotherapeutic drugs to the tumour cavity are in the form of biodegradable polymer wafers. These are loaded with BCNU (Gliadel® wafers) and are designed to release the drug over 2–3 weeks after their placement within the surgical cavity. Trials have shown them to be more effective than placebos.[3] Gliadel® wafers are, however, not appropriate for use in deep, multifocal bilateral disease, tumour in eloquent areas and in a juxtaventricular location.[7]

Treatment of Recurrent Gliomas

Treatment of recurrent GBM presents a challenge to the treating unit. Despite the use of different combination regimes no data supports the supremacy of any one over the other.[7]

The treatment involves the use of first line drugs and if they fail to have an adequate response can be followed-up with the second line drugs. The first line drugs are temozolamide, BCNU and CCNU. Patients who have already received TMZ should undergo treatment with a nitrosourea, such as BCNU or CCNU.[15] Sometimes they may also be used in combination.

The second line drugs are carboplatin, etoposide and irinotecan. Carboplatin alone or in combination with tyrosine kinase inhibitors have been used. Hydroxyurea is used for its radiosensitising properties, along with cell specific cytotoxic activity.[7]

Anaplastic Astrocytomas

Neo-adjuvant therapy has not shown any beneficial result. Trials have been conducted using PCV and BCNU, following surgery and radiotherapy. Patients undergoing treatment with the PCV regime have shown higher response rates.[9]

The outcome of patients with recurrent anaplastic astrocytoma is dismal with a maximum survival period of 47 weeks, despite adoption of aggressive measures. Although nitrosoureas are the most frequently used, development of resistance with myelosuppression limits their use in recurrent cases.[7] Irinotecan has recently been shown to give encouraging results in recurrent malignant gliomas.[8]

Anaplastic Oligodendroglioma

Ongoing trials have reported high response rates to chemotherapy, most commonly using PCV regimes. Hence, keen interest is being shown in order to further

improve the survival. It has been demonstrated that patients with LOH (1p/19q) have much better response rates.[4]

In a trial, patients with anaplastic oligodendrogliomas were divided into two groups. One group received radiotherapy alone followed by surgery. In the other group, radiotherapy was followed by six cycles of PCV. Although survival rates in both the groups were identical, the progression rate was significantly less in the latter group.[4]

Presently the use of PCV as adjuvant therapy has become the treatment of choice. Temozolamide has been increasingly used due to a better toxicity profile. PCV is effective as salvage therapy in patients having recurrence following temozolamide administration.[7]

Low Grade Gliomas

Low grade gliomas include WHO grade II tumours mainly oligodendrogliomas, astrocytomas and oligoastrocytomas. The role of chemotherapy in these tumours is still under scrutiny and many ongoing trials are evaluating their usefulness. So far, trials using PCV/TMZ for recurrent/previously untreated oligodendrogliomas and astrocytomas have reported higher response rates.

Although definitive results of the trials have yet to come in, available data suggests that chemotherapy for low grade gliomas can be used for oligodendrogliomas with LOH at 1p/19q in patients older than 40 years, patients with incompletely resected tumours, residual tumours after surgical resection/radiotherapy or oligodendroglioma with or without LOH 1p/19q with extensive tumour infiltration. Observation alone is recommended in patients younger than 40 years and patients having low grade gliomas.[7]

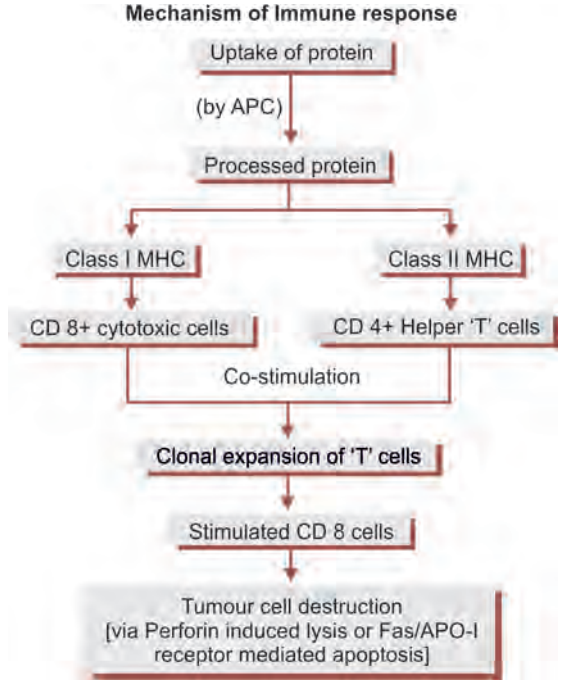
IMMUNOTHERAPY

Immunotherapy has been recognised to be a potent weapon against gliomas for many years, but research in this field has only gained momentum during the past decade. Various modalities of treatment which result in enhancement of the immune response have been developed to enhance the armoury against gliomas.

Over the years, it has been noted that patients with gliomas are immunosuppressed. Many factors have been studied in this regard: TGB-β, IL-10 and PGE2[7] have been found to be responsible for the immunosuppression. The immunosuppressive state results in defects which have been enumerated in the Table 1.

Table 1: Causes for immunosuppressive state

- Decreased CD4 'T' cell activity
- Increased CD4 suppressor T cells
- Low reticulocyte count
- Decreased delayed type hypersensitivity
- Diminished immunoglobulin synthesis by B cells



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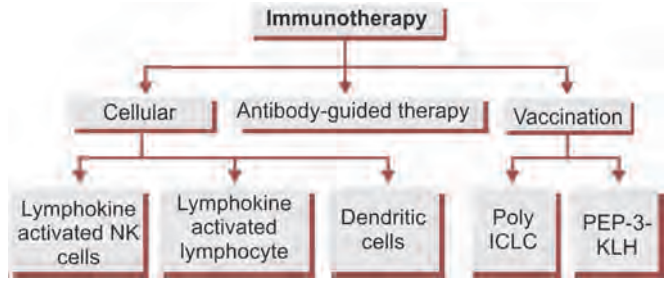
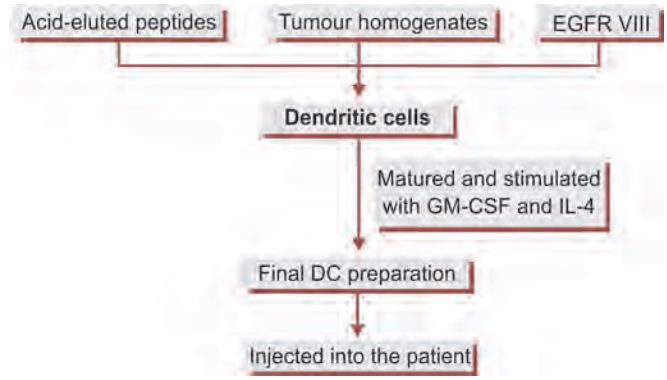


Cellular

This involves the isolation of immune effector cells from a patient, following which they are multiplied using stimulating factors and are then activated. Finally they are injected back into the patient to cause tumour lysis.

The immune effector cells are lymphokine activated natural killer cells, lymphokine activated lymphocytes, tumour infiltrating lymphocytes and dendritic cells.

Dendritic cells have been studied with great interest recently to evaluate their efficacy and have been giving promising results. Dendritic cells are loaded with acid-eluted peptides, tumour homogenates or tumour specific antigen EGFR VIII and are then stimulated and matured.



Yu et al. 2001[16] had reported median survival time of 15.1 months [vs 8.6 months in a control population] in a phase I clinical trial using dendritic cell preparations in malignant astrocytoma. Another trial[1] using dendritic cells against EGFR VIII showed median survival of 20 months in patients with GBM [vs 7 months for control population]. Plauz et al.[10] have utilised the 'T' cells generated in the patients in response to tumour cells. The tumour cells obtained during surgery are cultured and injected back subcutaneously into the patient. Following this, draining lymph nodes are resected to obtain tumour activated lymphocytes. These in turn are stimulated to produce clonal expansion. The 'T' cells hence produced are infused back into the patient. Out of the 10 patients, two showed tumour regression in the study. The extensive set-up and costs required for the *ex vivo* techniques of cellular immunotherapy are a major drawback for widespread usage of this technique.

Antibody-Guided Therapy

Antibodies can be used either as delivery vehicles for chemotherapeutic agents or as apoptosis inducers themselves. Tenascin, the extracellular matrix glycoprotein expressed in malignant gliomas has often been targeted. 81C6 monoclonal antibody binds to the epitope within the spliced fibronectin type III region of Tenascin. In a trial,[11] Iodine^{137} labelled murine 81C6 was injected into the surgical cavity. The survival of newly diagnosed GBMs was 19.9 months and for recurrent GBMs was 12 months. MD Anderson is planning to undertake a phase III clinical trial of 81C6 antibody.

Vaccination

This method of therapy involves utilising the patient's own immune system to counter high grade gliomas. Theoretically speaking, this is the ideal method of treatment. Poly ICLC, a double stranded RNA has been investigated for these purposes. The trials[12] have reported significant improvement in survival rate of patients with anaplastic astrocytomas (96 months vs 22 months with conventional chemotherapy). This has, however, not been demonstrated in patients with GBM.

GENE THERAPY

Better understanding of the molecular genetics of brain tumours has opened new options. Attempts have been made to manipulate the molecular biology of tumours by making alterations in the genome of tumour cells. This, in turn, either inhibits the growth of the tumour or makes the tumour cells more susceptible to the other modes of adjuvant therapy.

It is important to ensure that these alterations in the genome are restricted to the tumour cells and do not affect the normal neural tissue. These alterations in the genome are carried out by the use of genetically engineered viruses which are inserted into the tumour cells. The retrovirus and the herpes virus have been the most popular agents to be used. The genome of the retrovirus has been mapped in detail[5] and has the advantage that it tends to integrate only in the dividing cells, thereby not affecting the normal neural tissue which is in the post-mitotic state. Retrovirus that carries the thymidine kinase gene[6] tends to render the cell sensitive to ganciclovir, resulting in the death of the cells containing this gene. Herpes virus has the advantage of having a large genome and retains replication competence. However, it does not differentiate between dividing and non-dividing cells.

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143 Colloid Cyst

Nigel Peter Symss, Ravi Ramamurthi

INTRODUCTION

In 1858, Wallmann published the first description of a colloid cyst. It was found on autopsy in a 50-year-old man who presented with "staggering gait and involuntary micturition and defecation".[58] The term "Colloid cyst" has been used since the late nineteenth century to describe these cysts because of their glue-like contents.

These constitute less than 1% of all intracranial tumours.[10] Ante-mortem diagnosis of this entity was possible only after the introduction of ventriculography and pneumoencephalography by Dandy, who incidentally was also the first one to excise this tumour completely. Dandy performed this surgery through a posterior transcallosal approach to the third ventricle. He stated that no treatment short of total removal could have any possible value in the treatment of tumours in this region and that there could be no relief of hydrocephalus, except by removal of the obstructing lesion. In 1933, he reported removing five colloid cysts with only one death.[14] The anterior transcallosal approach was suggested by George Ehni who used this approach for different pathological entities over a period of 38 years.[17]

REGIONAL EMBRYOLOGY OF THIRD VENTRICLE

The third ventricle develops from the diencephalic vesicle at the rostral end of the neural tube during the third week of gestation. Soon it is surrounded by the rapidly developing cerebral vesicles except at its roof. The roof of the third ventricle then begins to invaginate and forms the pia mater that eventually covers the floor of the third ventricle. Rathke's cleft pouch forms an invagination of the distal end of the stomodeum into the overlying mesoderm. This eventually gives rise to the anterior pituitary. The posterior pituitary and pituitary stalk are derived from the cerebral vesicle posterior to Rathke's cleft pouch. This invagination of mesodermal tissues into the neuroepithelium may give rise to a number of developmental anomalies and tumours that characterise the third ventricle.[12]

INCIDENCE

Although colloid cysts have been reported in all age groups, they more commonly present between the age of 20 and 40 years. The incidence is equal in both sexes. Isolated case-reports suggest a genetic predisposition in certain cases. Akins et al. also pointed out that a number of congenital conditions (including agenesis of the corpus callosum and frontal encephalocoeles) and tumours (astrocytoma, craniopharyngioma, neurofibromatosis and capillary hemangiomas of the choroid plexus) may be associated with colloid cysts.[3] Familial cases have also been reported. Ahmed et al. have reported colloid cysts of the third ventricle in identical twins.[2]

Incidental Colloid Cyst

Colloid cysts have been found incidentally. The rapidly increasing availability of CT and MRI scanning for the investigation of patients with unrelated symptoms and minor trauma has resulted in an increase in the frequency of diagnosis of a colloid cyst. The management of incidental colloid cysts is a topic of debate. The rate of growth of the cyst is uncertain and whether these cysts eventually become symptomatic is unclear. Sudden deterioration followed by death has not been reported in patients with a colloid cyst of less than 1 cm in size.[8,11,53] Patients with colloid cysts larger than 1.5 cm should be considered for surgical excision, as these cysts are more likely to become symptomatic.[48] MacDonald et al. stressed that younger patients are more likely to become symptomatic during their life time and thus require surgery.[40] Desai et al.[15] reported 5 patients with colloid cysts detected incidentally. Out of these, three had small colloid cysts, which were asymptomatic and managed conservatively.

We are reluctant to recommend conservative management for asymptomatic and incidentally discovered patients with colloid cysts. We have found the transcallosal approach with limited anterior callosotomy a good and safe approach, and have been able to remove anterior third ventricular colloid cysts with an accepted surgical morbidity and mortality less than the one arising from the natural progressive history of the disease.[50]

PATHOLOGY

The wall of a colloid cyst usually consists of a single layer of columnar epithelial lining and a collagenous connective tissue stroma. Although electron microscopy suggests a secretory function for these cells, there is some

controversy regarding their development.[52] A neuroepithelial origin is suggested by most authors, although some believe that it originates from the ependymal epithelium.[52] Others believe that it derives its origin from the epithelium of the choroids plexus.[23,55] A recent immunohistochemical study of colloid cyst suggests that it is not a derivative of the ependyma or the choroid plexus[33] but that it is derived from the primitive neuroectoderm, involved in the formation of the tela choroidea. A non-epithelial origin has also been proposed.[35] Stochdorph, on the basis of light microscopy, suggested its origin from ectopic epithelium of the upper respiratory tract.[52] Ho and Garcia[25] and Lach et al.[37] confirm this view by ultrastructural studies which show that colloid cysts are endodermal in origin. The cyst contents may consist of soft suckable pultaceous material or could be firm, non-suckable and hyaline. This PAS positive material is presumably derived from the secretory activity and desquamation of the lining epithelium.[52]

LOCATION

Except in rare instances, colloid cysts are located in the anterior third ventricle and the wall of the cyst is often firmly adherent to the walls of the foramen of Monro, the fornix or the lateral wall of the third ventricle. They are located in the roof of the third ventricle, usually attached to the tela choroidea or rarely to the choroid plexus by a narrow pedicle and are located just behind the fornices and between the foramina of Monro. Occasionally, they are found more posteriorly and obstruct the posterior segment of the third ventricle. Intrasellar occurrence of a colloid cyst has also been reported.[54] Rarely, a colloid cyst may grow to a large size, compressing the surrounding structures and simulating a glioma clinically and on CT.[6] A colloid cyst occurring in the fourth ventricle has been reported.[28] Campbell and Varma found a right frontoparietal extracerebral colloid cyst.[9] A rare occurrence of intracerebellar colloid cyst has been reported by Muller et al.[45] Jaskolski et al. reported a case of a 44-year-old man showing an oval lesion located at the anterior surface of the pons on CT and MRI scans. The tumour was excised through a right pterional-transsylvian approach.[30]

CLINICAL FEATURES

Colloid cysts display a typical constellation of symptoms because of their strategic location in the anterior third ventricle. They act as pure mass lesions, possessing no intrinsic pathologic properties and they cause symptoms by acting as inert masses. Most of the symptoms are related to hydrocephalus secondary to obstruction of cerebrospinal fluid (CSF) flow within the middle or posterior third ventricle, as evidenced by the symmetrical widening of both the lateral ventricles as seen in Figure 1.

More than 75% of patients report with headache due to raised intracranial pressure, as the presenting complaint.

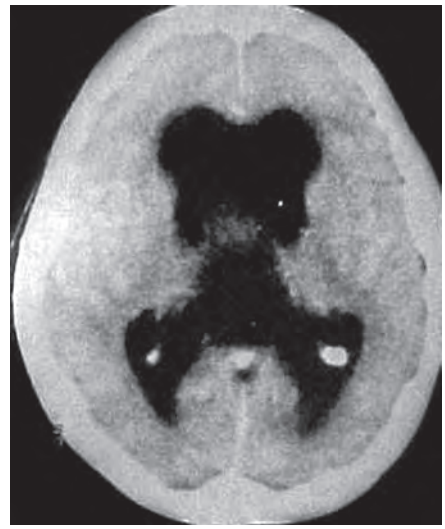


Fig. 1: CT scan of the brain showing symmetrical dilatation of both the lateral ventricles secondary to the obstruction of foramen of Monro

It may be insidious in onset and progressive in nature or it may be intermittent or of sudden onset. The second common pattern of presentation has been named by Kelly as "the classical story"[32] which is characterised by the intermittent and postural nature of the attacks with remissions. The postural component of the classic headache invokes the "ball valve" theory, implying a movable mass that dislodges from the foramina when the patient is recumbent. These paroxysmal attacks are generally considered to be due to intermittent obstruction and disimpaction of the cysts in the third ventricle.

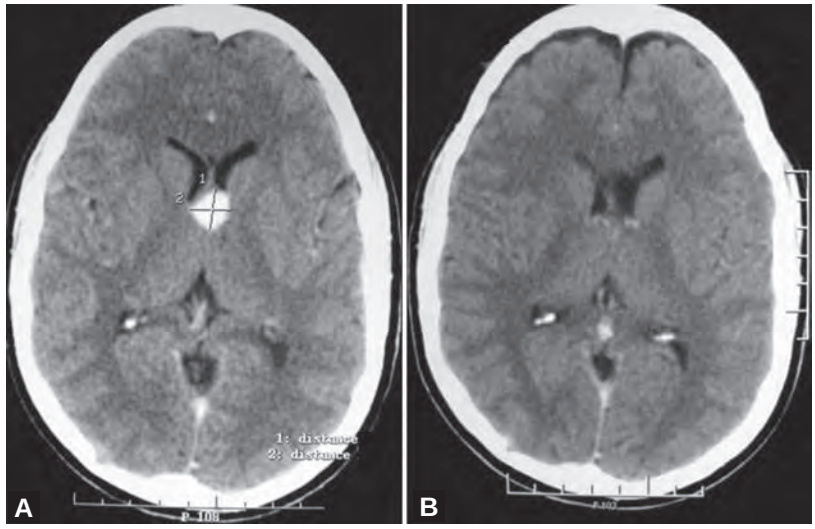
A drop attack due to sudden weakness of the lower limbs accompanied with features of raised intracranial pressure may be the presenting feature.[33] Progressive or fluctuating dementia may be seen or there may be a normal pressure hydrocephalus syndrome.[7] Seizures may occur in about 20% of cases. The dangers of asymptomatic colloid cysts have been underestimated.[36] There have been several reported instances of sudden death in patients with colloid cyst,[4] but the reasons are not clear. The sudden elevation of intracranial pressure, with the subsequent decreased cerebral perfusion pressure induces a vigorous cerebroprotective neuroendocrine system activation that can lead to the neurogenic stunned myocardium. Sudden death in patients with colloid cysts may be related to acute neurogenic cardiac dysfunction and not necessarily cerebral herniations, as previously thought.[29] Another explanation for the acute deterioration of patients is haemorrhagic changes in the cysts. This complication has been published only four times before, all diagnosed at post-mortem examination.[5] Neither the size of the cyst, the degree of dilatation of the ventricles, nor the duration of symptoms seem to provide reliable prognostic indications for this fatal complication. Patients have been discovered to be harbouring a colloid cyst after diagnostic work-up for

spontaneous CSF rhinorrhoea.[31] This rhinorrhoea most likely results from chronically elevated intracranial pressure causing erosion of the cribriform plate and meninges, with a resultant CSF fistula. The coexistence of colloid cyst of the third ventricle with pituitary dwarfism has been reported.[44] As the dangers cannot be underestimated, surgical excision may be advisable even for asymptomatic colloid cysts.

INVESTIGATIONS

When the cyst is situated at its usual location, the venous phase of the cerebral angiogram shows elevation of the anterior part of the internal cerebral vein, resulting in a curve which is concave downwards. The posterior part of the internal cerebral vein is flattened and depressed due to the dilated lateral ventricles. The CT appearance is of a lesion located at the foramen of Monro, varying from hypodensity or isodensity to moderate or marked hyperdensity on the plain scan. This hyperdensity is secondary to a combination of desquamated material within the cyst, haemosiderin and calcium.[18] However, the colloid cyst is frequently isodense or only slightly hyperdense. It enhances with contrast to a mild degree in some cases. Enhancement may be secondary to blood vessels in the wall of the cyst or leakage of contrast into the cyst cavity.[18] Figure 2A shows CT scan of the brain highlighting an anterior third ventricular colloid cyst. Figure 2B shows the CT scan of the same case, post-operatively, following cyst removal.

MR findings are very variable, ranging from hypo-to-iso to hyperintense in all sequences (Figs 3A and B). The signals may be homogeneous or heterogeneous.[38,59] High signals on short TR/TE sequences are correlated with high cholesterol content.[41] Wilms et al. reported a group of colloid cysts that show an isointense peripheral thick rim and extremely hypointense centre on T2-weighted images. These cysts are usually large.[59] MR venography gives a better visualisation of the adjacent venous structures, including the internal cerebral vein.



Figs 2A and B: (A) CT scan of the brain showing anterior third ventricular colloid cyst. (B) Post-operative CT scan showing total removal

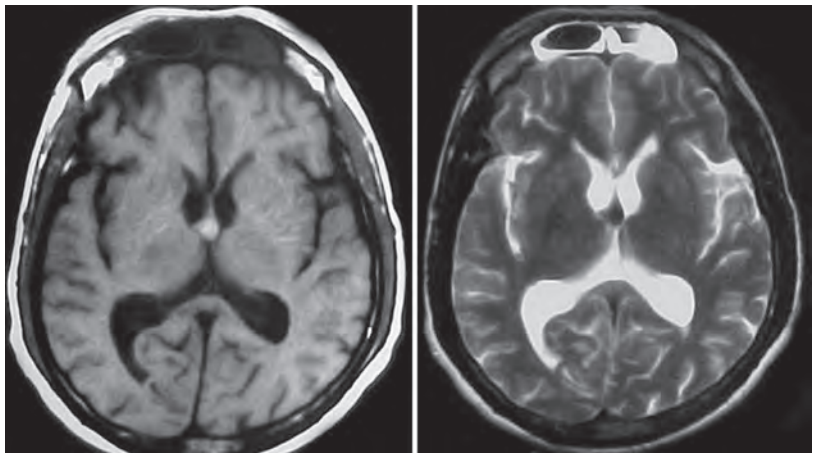


Fig. 3A: MRI of the brain (T1, T2) showing anterior third ventricular colloid cyst

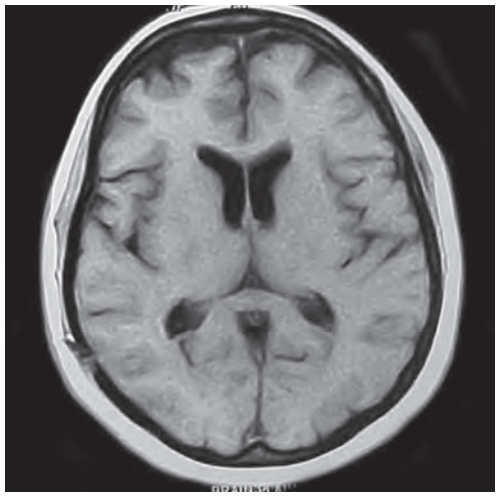


Fig. 3B: Post-operative MRI of the same patient as in Figure 3A showing total removal

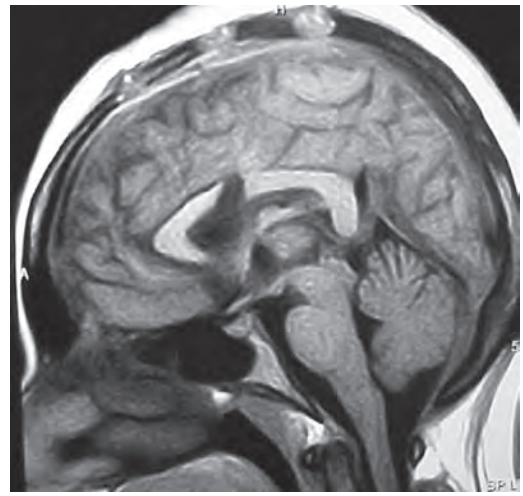


Fig. 4: Post-operative MRI-mid sagittal plane of the same patient as in Figure 3A showing anterior callosotomy

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of third ventricular lesions may be divided into intraventricular extra-axial lesions (colloid cyst, cysticercal cysts, meningiomas, haemangioblastomas, xanthogranulomas and cavernous angiomas); intraventricular intra-axial lesions (gliomas, choroid plexus tumours, teratomas, ependymomas and subependymal giant cell astrocytomas) and lesions with basal origin but third ventricular extension (meningiomas, craniopharyngiomas, giant basilar aneurysms and pituitary adenomas).

TREATMENT

For a lesion that is relatively rare, substantial literature on various methods has accumulated since Dandy's first report of a surgical extirpation. Each technique has its advantages and disadvantages. The surgeon must select the approach best tailored to his patient's unique presentation, his own experience and training and a clear understanding of the strengths and limitations of each approach.

The various microsurgical approaches to colloid cysts are:

1. Transfrontal/transventricular
   a. Transforaminal
   b. Subchoroidal
2. Transcallosal/transventricular
   a. Transforaminal
   b. Interforniceal
   c. Subchoroidal
3. Subfrontal Translamina terminalis.

Opening the CSF pathway obstruction is the goal of treatment. There are various options available.[8,57] Total surgical excision would be the ideal therapy, provided that the complications are kept to a minimum. A transcallosal transventricular approach, when the lateral ventricle is small and an anterior transcortical (middle frontal gyrus) transventricular approach, when the ventricle is dilated, are the options available to reach the foramen of Monro (Fig. 4).[51] The tumour in the third ventricle could then be dissected, either through the dilated foramen of Monro or by widening the opening anteriorly by cutting one fornix, widening the opening posteriorly by coagulating the thalamostriate vein, or by the subchoroidal approach. A direct approach to the third ventricle following the transcallosal approach may be made between the fornices, following the midline strictly and incising the tela choroidea and entering the third ventricle between the internal cerebral veins. The transcallosal approach allows safer access if the ventricles are normal sized or small and has greater flexibility in exploring the entire extent of the third ventricle. There is no cortical incision, the ventricular size is irrelevant and an excellent unobstructed view of the third ventricle may be obtained. The disadvantages of the transcallosal approach include less familiarity with the anatomy for some neurosurgeons, thereby increasing possible injury to frontal draining veins and the sagittal sinus, injury to the pericallosal arteries, problems related to corpus callosal section and forniceal damage (Fig. 5). Good results from the transcallosal approach have been reported by many authors.[27,50]

Dandy first used the transcortical approach in lateral ventricular and third ventricular lesions. It is useful, if the ventricles are enlarged and access to the foramen of Monro and third ventricle is readily obtained. The transcortical approach avoids injury to the frontal draining veins of the sagittal sinus and decreases the chance of injury to the pericallosal arteries. However, in the presence of small or normal sized ventricles, it may be difficult to enter the lateral ventricles without undue trauma and retraction, thereby increasing the incidence of post-operative morbidity. Moreover, in the presence of large lesions, the angle of vision of the foramina and of the third ventricle is limited.

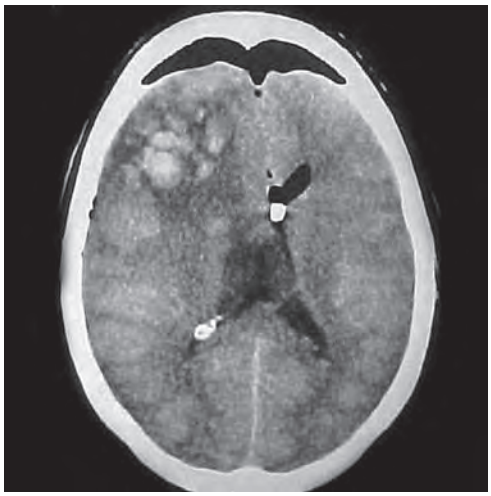


Fig. 5: Post-operative CT scan showing bifrontal pneumocephalus and frontal venous infarct

The transcortical-transventricular approach has been associated with the following complications: Seizure in 8.6–27% of cases,[4,7,39] hemiparesis in 4.3–20%,[4,39] memory loss, usually transient in 4.2–27%,[4,7] subdural fluid collection, meningitis in 9%,[7] ventriculitis in 4.3%,[4] confusion and mutism. In two of the reported series, the mortality rate has been about 17%.[4,39]

The reported complications in the transcallosal approach have been hemiparesis in 2.5–16%,[21,56] transient memory loss in 33%,[26] transient akinetic mutism in 8.3%,[56] impairment of interhemispheric transfer of sensory information, bacterial meningitis and aseptic meningitis in up to 12%,[21,56] confabulation, aphasia and obtundation. There are also complications pertaining to the approaches used to enter the third ventricle, once the foramen of Monro has been reached. In the transforaminal approach, haemorrhage and memory loss has been reported.[4,39] Transient memory loss up to 33% and transient paresis may occur with the interforniceal approach. Transient hemiplegia, drowsiness, mutism and haemorrhagic infarction of the basal ganglia have been found with the subchoroidal and the trans-velum interpositum approach.[47]

Palliative ventricular shunting, although a simple way of avoiding surgical complications, is not advisable because there is no tissue confirmation, the signs due to the tumour mass *per se* are not alleviated and it exposes the patient to the risks of infection, epilepsy and shunt blocks.[13,19] Although advocated by some neurosurgeons,[22] unilateral shunting of the ventricles may lead to sudden enlargement of the opposite ventricles resulting in coma or even sudden death.

Some authors believe that, except for cases where surgical intervention is urgent (acutely raised intracranial pressure), CT-guided stereotactic aspiration should be routinely used for the management of colloid cysts.[16,46,49] The advantage of this procedure is the low morbidity and mortality rates. The disadvantages are the occasional inability to aspirate the cyst contents and recurrence 6–15 years after successful aspiration.[42] The aspirability of the cyst may be predicted by its CT appearance. When the pre-operative CT showed a hypodense or isodense lesion, it was possible to aspirate the cyst successfully.[34] In view of the risks of open surgery and failure to aspirate the colloid cyst with CT-guided stereotactic techniques,[21] stereotactic microsurgical approach and total removal of the colloid cyst by laser has been advocated.[1,43] Stereotactic-guided endoscopic laser therapy has also been employed. The advantages claimed for this technique are:

- Limited cortical dissection.
- Avoidance of callosal or forniceal injury.
- Ease of localisation of the lesion, regardless of ventricular size.
- Good haemostasis achieved by bipolar or LASER.
- Possibility of total resection.

Neuroendoscopic treatment of colloid cysts has gained increasing acceptance and is being used more widely.[24] Continued improvement in endoscopic techniques and instruments, together with good long-term results in endoscopically treated patients, have established this method as an alternative to microsurgical techniques and might even set a new standard for treatment.[24] Endoscopes have also been used with interactive image-guided methodology.[20]

For the practising neurosurgeons, without other special facilities, direct excision of the cyst using microsurgical techniques preferably via the trancallosal route or the transcortical transventricular route is the best course of action. It is against these two approaches that new surgical methods should be measured. Direct surgical approach and complete removal of the colloid cysts are possible through both of these open procedures. The goal of both the transcallosal and the transcortical approach is to gain access to the lateral ventricle, with secondary access to the foramen and fornix.

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144 Choroid Plexus Tumours

Vasudevan MC

Tumours of the choroid plexus are rare neoplasms of neuroectodermal origin, accounting for less than 1% of all intracranial tumours. These tumours primarily occur in children but they are also observed in adults and infants.[20,25,27-29,41] Prenatal occurrence has also been reported.[1,39]

HISTORY

Choroid plexus papilloma was first described in an autopsy specimen of a 3-year-old girl by Guerard in 1832. In Cushing's series, papilloma of the choroid plexus was present in 0.06% cases. Papers between 1833 and 1925 emphasised the rarity of this tumour and its association with hydrocephalus.[10,11,48] The first surgical resection of a choroid plexus tumour in an adult was reported by Bielschowsky and Unger in 1906. The first long-term survival of an adult with choroid plexus tumour was reported by Perthes in the year 1919. Van Wagenen in 1930 reported excision of the tumour from the lateral ventricle of a 3-month-old child and Dandy in 1934 described the removal from a 14-year-old girl.[49] It was Dandy who described the transcallosal route to the third ventricular region and was the first to describe it for removal of a choroid plexus tumour in 1922. The first transfrontal removal of third ventricular choroid plexus papilloma was published by Masson in 1934.

Choroid plexus tumours are among the more frequent tumours in children under the age of 3 years.[23] Among 245 patients of all ages, the distribution was as follows: lateral ventricle, 43%; third ventricle, 9%; fourth ventricle, 39%; CP angle, 9% and multiple sites, 3.7%.[40] In children, tumours of the choroid plexus are located most often in the lateral ventricle but they can also be found in the third ventricle and in the posterior fossa.[21,22,41] Choroid plexus tumours of the posterior fossa in adults are likely to be benign, whereas, in children, tumours occurring in the lateral ventricle tend to be anaplastic.[40] Third ventricular tumours are usually prevalent in adults and children and most such tumours are benign.[16] Lateral ventricle tumours equally occur on either side,[26] though some reports indicate a preference for the left lateral ventricle.[43] A predominance of males has also been reported.[24] Malignant changes occur in less than 20%[26] and a majority of such tumours are found in infants and children less than 4 years of age, mostly in the lateral ventricle. Choroid plexus carcinomas are rare and according to Russell and Rubinstein,[43] they are likely to be secondary from an undiagnosed primary bronchial carcinoma (Table 1).

The papilloma appears as a pink or reddish grey globular mass with a rough irregular surface resembling a cauliflower and is usually attached to the plexus at the trigone. The consistency is firm and occasionally, significant calcification may be present. These tumours are very vascular. Although evidence of leptomeningeal spread has been reported on post-mortem examination, there are no symptoms to indicate this during life.[43] The microscopic appearance of choroids plexus papilloma resembles the normal architecture of the choroid plexus and shows papillae composed of a single layer of columnar or cuboidal epithelium lining a stroma of vascularised connective tissue. It is important to differentiate it from an ependymoma where the stroma contains neuroglial tissue, epithelial cells with cilia and blepharoplasts.[43] Features of microscopic invasion, especially mitotic activity and pleomorphism should raise the possibility of malignancy, even when the general architecture indicates a well differentiated papilloma.[26] The two characteristics that are suggestive of malignancy in choroid plexus tumours are: (i) invasion of the brain by malignant-looking cells and (ii) loss of the regular papillary architecture of the tumour in the region where the normal brain has been invaded. In young patients, in whom metastatic adenocarcinoma is highly unlikely, it may be difficult to distinguish these tumours from medulloepithelioma, an embryonal carcinoma or an endodermal sinus tumour. Immunohistochemistry may be useful. Leptomeningeal spread is common in choroid plexus carcinoma and extraneural metastasis has also been reported.[43]

Hydrocephalus in choroid plexus tumours is due to several following factors: (i) overproduction of CSF; (ii) obstruction of the CSF pathways due to tumour and (iii) recurrent occult bleeding from the tumour resulting in subarachnoid fibrosis and adhesions.[13,17,33,34,42,43]

Table 1: WHO classification of choroid plexus tumours

Tumours of the choroid plexus	*Grade*
Choroid plexus papilloma	I
Atypical choroid plexus papilloma	II
Choroid plexus carcinoma	III

From their attachment to the choroids plexus, the tumours frequently extend from one ventricular compartment to another and to the subarachnoid space.[19] Lateral ventricular tumours may extend through the foramen of Monro into the third ventricle and to the quadrigeminal cistern or to the contralateral ventricle through the choroidal fissure. Third ventricular tumours are usually situated posterosuperiorly.[7,40] Tumours in the fourth ventricle may, occasionally, burrow into the cerebellum or the floor of the fourth ventricle or may extend to the CP angle.

CLINICAL COURSE

The symptoms are insidious in onset. Acute symptoms appear when brain herniation occurs secondary to hydrocephalus or when the tumour bleeds into the ventricle. Headache is the most common symptom and is later associated with vomiting and visual disturbances. The headache is the result of raised intracranial pressure secondary to the tumour mass or due to obstructive hydrocephalus. In supratentorial tumours, headache could be positional and intermittent. Seizure, hemisyndromes and mental changes also occur.[4,7,16,36] Progressive enlargement of the head is present in the majority of infants and young children.[31]

Choroid plexus tumours of the anterior third ventricle present with obstructive hydrocephalus and posterior third ventricular tumours have tectal syndromes in addition. In fourth ventricular tumours, headache, gait ataxia, nystagmus, cerebellar signs, loss of vision, vomiting and diplopia are seen.[7] Exophytic fourth ventricular lesions with extension into the foramen magnum presenting as CSF rhinorrhoea have been reported.[47] Tumours extending into the CP angle can give rise to cranial nerve deficits, apart from hydrocephalus.[9,50]

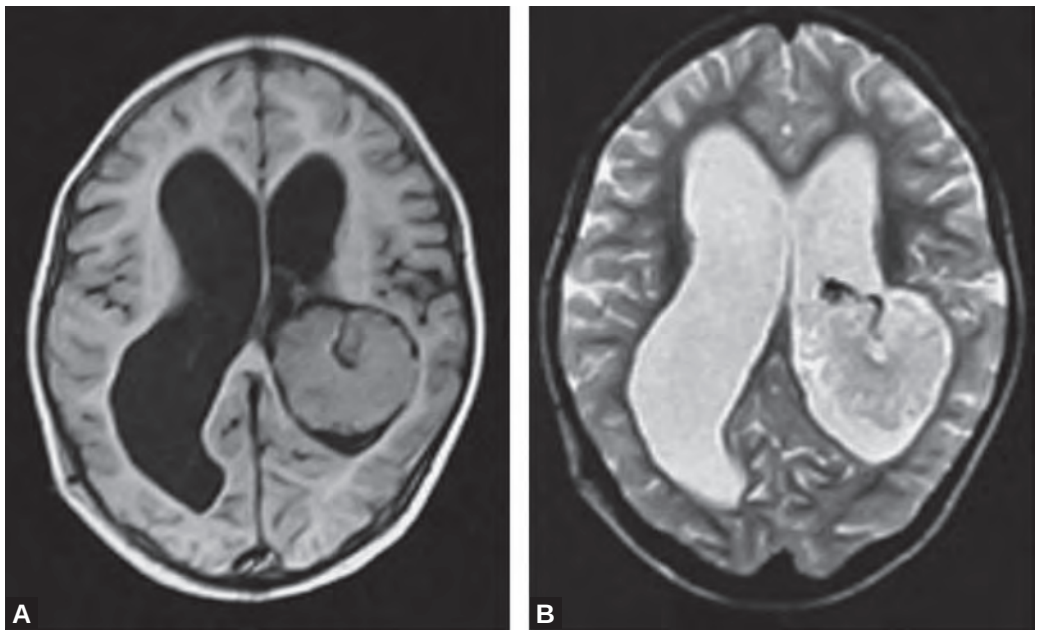
INVESTIGATIONS

Plain X-ray shows only non-specific signs of raised intracranial pressure and tumour calcifications are generally not apparent.[38,42] Angiograms may show an enlargement of the corresponding arteries, depending on the location and a tumour blush is often seen. The CT scan shows a lobulated hyperdense intraventricular mass which enhances brightly with contrast. Finely speckled calcification is often present within the tumour. The MR shows a hypointense or isointense lesion which is hyperintense relative to CSF in T1-weighted images and a hyperintense mass in T2-weighted images. Following gadolinium injection the tumour becomes hyperintense in T1-weighted images (Figs 1A and B).

Magnetic resonance spectroscopy (MRS) is a novel *in vivo* technique to identify biochemical features of choroid plexus tumours that facilitate diagnosis and treatment. Both, the choroid plexus papilloma and carcinoma characteristically contain high levels of choline compounds (CHO), and a complete absence of creatine and the neuronal/axonal marker N-acetyl aspartate (NAA). However, a choroid plexus carcinoma demonstrates higher levels of choline compared to the papilloma and in addition, it also has elevated lactate.[2] The myo-inositol (mI) level is significantly higher in choroid plexus papillomas (10 mmol/kg), uniquely distinguishing these tumours. The absolute 'mI' levels and the 'mI/Cr' ratio can be used to differentiate these tumours from choroid plexus carcinomas and all other tumours. Choroid plexus carcinomas, on the other hand, have significantly elevated levels of choline, when compared to choroid plexus papillomas.[30]

TREATMENT

The majority of patients are younger than 3 years of age at the time of presentation. This makes management of



Figs 1A and B: (A) T1W axial MRI of the brain showing choroids plexus papilloma in the atrium of the left lateral ventricle which is slightly hypointense. (B) T2W axial MRI of the brain showing choroids plexus papilloma in the atrium of the left lateral ventricle which is hyperintense

their disease challenging. Total excision of the tumour is the surgical goal and the treatment of choice. Choroid plexus tumours tend to be large, fragile and very vascular. This presents a particular challenge in a baby with a small total circulating blood volume, risking intra-operative death from uncontrollable haemorrhage.[21,39] This complication occurs more commonly in carcinomas than in papillomas.

The critical aspect of the surgical approach is to expose the vascular pedicle during the initial stage of the procedure, to avoid avulsion of the feeding arteries, which can occur when manipulating these large lesions. This does not always prove successful because of the large size of the tumour that prevents access to the vascular pedicle, which usually is deeply situated, away from a direct approach.[39]

Attempts to debulk the tumour without control of the vascular pedicle can result in significant blood loss and subsequent high morbidity and/or mortality.[39,45] For these reasons, microsurgical rather than endoscopic approaches are favoured, although small CPPs have successfully been resected using endoscopic techniques.[38] Endoscopy can be used as an adjunct to microsurgery to get at the vascular pedicle in the early stages of surgery. Pre-operative angiographic evaluation and embolisation can be extremely useful in cases of highly vascular lesions.[46] Hypertrophy of one of the choroidal arteries is a usual angiographic feature and tumour blush is commonly seen, occasionally with several minor feeding vessels contributing. Although pre-operative embolisation would appear to be easy, in clinical practice it is very difficult to cannulate these feeding vessels.[3,39]

Gross total resection of tumour is possible in 60–90% of cases.[7,18] The mortality rate in a relatively recent series has been reported to be 20%.[18] Hydrocephalus is generally relieved following removal of the tumour but in certain cases it may persist and is attributed to subarachnoid fibrosis. A ventriculoperitoneal shunt may then be necessary.

Not uncommonly, the predominant symptoms of intracranial hypertension, in relation to acute hydrocephalus, demand controlled CSF diversion for a short duration (few days) prior to performing surgery for excision of the tumour. The objective of such a staged treatment would be to improve the condition of the brain by relieving raised intracranial pressure, in preparation for a major intervention, while at the same time the advantage of ventriculomegaly is maintained. In the presence of dilated ventricles, excision of a choroid plexus papilloma is easier because the tumour is floating inside the ventricular cavity. If this advantage is lost and the ventricles are dramatically reduced in size, the operation is significantly complicated.[39]

Previously, attention was focussed on the relationship between cerebral mantle thickness and the risk for chronic subdural fluid collection. Pre-operative controlled CSF diversion allows the cerebral mantle to expand. An important detail of surgical technique is the closure of the corticotomy with biological glue at the end of the procedure. This is better achieved when the cerebral mantle has expanded. Closure of the corticotomy will isolate the ventricular system from the subdural space, thus significantly decreasing the chances of post-operative subdural hygroma that requires subduroperitoneal diversion. In the presence of such a communication, any diversion of the subdural space is likely to be insufficient.[39]

Alternatively, an intersulcal splitting approach to the lateral ventricular trigone, combined with a peri-operative external ventricular drainage, may be of value in the avoidance of symptomatic subdural effusions.[35]

Pre-operative radiation to reduce the vascularity is not advisable, as it may produce adhesions that hinder resection.[8] Post-operative radiation therapy has been recommended for patients with incomplete excision, although its validity is doubtful.[9]

In choroid plexus papilloma, it is accepted that complete excision is curative.[37] Choroid plexus carcinomas have a high propensity for recurrence and despite some reports adjuvant treatment has not been found to be very effective in these tumours. In older children, radiotherapy can be effective against recurrence. Unfortunately, radiotherapy is not an option in the majority of cases because of the young age of the patients and the size of the field to be irradiated.[3,6]

Total excision is the major predictor of long-term survival in patients with CPC,[12] the 5-year-survival rates range from 26% to 50%. Because of their invasive nature and propensity to metastasise, most CPCs are not amenable to gross-total resection.[6,46] Although it contributes to long-term survival,[12] chemotherapy cannot prevent recurrence. At present, total surgical excision is the main predictor of long-term survival and achieving total excision should be the goal of any treatment strategy.[3,5,6,32,41,44]

Diffuse enlargement of the choroid plexus, termed as 'villous hypertrophy of the choroid plexus' by Davis,[15] can pose considerable confusion in its differentiation from a papilloma, as both of them present with hydrocephalus as a consequence of excessive production of CSF. Bilateral choroid plexus papilloma is extremely rare and distinct from diffuse villous hypertrophy and, if suspected, total surgical resection should be performed.[14]

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145 Pineal Region Tumours: Clinical Features and Management

Ramakrishna Easwaran

INTRODUCTION

The epiphysis cerebri (pineal gland) has fascinated scientists and philosophers for centuries. Historically, in Galenic times, it was thought to be a sphincter between the third and the fourth ventricle, controlling the flow of 'spirits'. Descartes, in the 17th century, described it as the "seat of the soul". Evolution has transformed this organ from a superficially located third eye in amphibians and reptiles to a structure buried in the depths of the human brain. The human pineal retains this phylogenetic link to the visual system by connections with the retina by a circuitous route (optic chiasma → suprachiasmatic nucleus → medial forebrain bundle → intermediolateral column of the upper thoracic spinal cord → superior cervical sympathetic ganglion → pericarotid sympathetic fibres → nervi conarii on the tentorium → pineal gland). The pineal output is mediated through the release of melatonin into the vascular system. Serotonin and several neuropeptides are also produced by the pineal. Through these afferent and efferent mechanisms, the pineal has now been proved to play a central role in the modulation of circadian rhythms, sleep-wake cycles, growth and puberty, reproduction, ageing, immune responses, cancer inhibition, epilepsy inhibition, mood, behaviour and even motor activity.[4] We are perhaps fortunate that pineal tumours leave these myriad functions intact and instead only cause symptoms due to mechanical compression.

PATHOLOGY

It is indeed surprising that a gland that is just 8 mm × 4 mm × 4 mm in size is home to more than 40 different types of tumours. Pineal tumours account for 1% of all brain tumours and about 3% of childhood brain tumours.[16] Table 1 summarises the classification of the tumours in the pineal region. This table also indicates the typical frequency of some of the major tumour types across nations. Of course, the data from neuroradiological, surgical-histopathological, autopsy based and population-based studies cannot be compared directly. Nevertheless, the difference in the geographical incidence of the various tumour types is striking, but the reasons for this difference are unknown. The details of the histopathology of pineal tumours are dealt with in another chapter. Certain special features are highlighted in this chapter.

Pineoblastomas may be associated with bilateral retinoblastoma in children and is known as 'trilateral retinoblastoma'.[81] Trilateral retinoblastoma is genetically determined and is associated with inactivation of the tumour suppressor gene (rb1) in the chromosome 13q14.[60] Apart from histology, the presence of neurofilament protein (NF) and low MIB-1 labelling index demonstrable by immunohistochemistry seem to confer a survival advantage in primary pineal tumour according to a recent study from NIMHANS, Bangalore.[5]

Germinoma may appear synchronously or metachronously in the pineal and suprasellar regions.[42] Note that the term 'pinealoma' is an archaic description for pineal germinoma and the term 'ectopic pinealoma' was used to refer to a germinoma in a non-pineal location. Germ cell tumours (GCTs) of the pineal have a strong male preponderance.[121] Klinefelter's syndrome and Down's syndrome may predispose to intracranial GCTs.[91,110] Distinguishing a pineocytoma with lymphocytic infiltration and a true germinoma might be a close call, especially on small endoscopic or stereotactic biopsies, as both these tumours display a 'two-cell pattern'. Immunohistochemical demonstration of placental alkaline phosphatase in the cells helps to identify a germinoma.[38] To add to the confusion, there is a prominent granulomatous component in certain germinomas and this might lead to an erroneous diagnosis of an inflammatory disease on small samples.[75] The original theory that the germinomas and the non-germinomatous germ cell tumours (NGGCTs) arose from the midline rests of the primordial germ cells is contested by Keiji Sano. He has advanced the theory that the only true GCT is germinoma. The so-called NGGCTs are, according to his theory, only enfolded cell-derived dysembryogenetic tumours.[100]

Gliomas are known to arise in the pineal gland but the majority of the glial tumours in this region arise in the neighbourhood structures such as the posterior third ventricle or dorsal midbrain.[6] Synchronous pilocytic astrocytoma in the optic pathway and pineal region occur in neurofibromatosis (NF-1).[84]

The histological type of tumour in the pineal region depends on the age of the patient. This information,

Table 1: Classification of pineal tumours and their incidence

Type of tumour	*Indian series*[55]	*Japanese series*[103]	*Western series*[15]
	Surgical series N = 54	*Tumour registry*	*Surgical series N = 191*
Pineal parenchymal tumours	39%	14%	25%
Pineoblastoma		5%	6%
Pineocytoma	19%	9%	14%
Pineal parenchymal tumour of intermediate	7%		5%
differentiation (PPTID)[101]	13%		
Germ cell tumours (GCT)	8%	61%	32%
Germinoma[70]			16%
Non-germinomatous germ cell tumours (NGGCT)		50%	2%
Embryonal carcinoma			
Endodermal sinus tumour (yolk sac tumour)			6%
Choriocarcinoma			
Teratoma		11%	
Mature			
Immature			8%
Teratoma with malignant transformation			
Mixed germ cell tumour[111]			
Glial cell tumours	37%	6%	27%
Astrocytoma[6]			14%
Giant cell astrocytoma (in tuberous sclerosis)[27]			1%
Oligodendroglioma[26]			7%
Ependymoma[86]	1.8%		1%
Choroid plexus papilloma[108]			4%
Anaplastic astrocytoma and glioblastoma multiforme[3]			
Mesenchymal cell tumours			
Meningioma[52]	3.7%		
Cavernous angioma[77]			5%
Hemangioblastoma[45]			
Other tumours			
Epidermoid tumour[28]	3.7%		
Craniopharyngioma[117]	3.7%		5%
Ganglioglioma[113]			
Lipoma[107]			
Chemodectoma			
Myxoid chondrosarcoma[106]			1%
Metastatic tumours[58]			
Lymphoma[88]			
Fibrosarcoma[61]			
Primary melanoma[64]			
Primary osteosarcoma[98]			
Non-neoplastic masses			
Pineal cyst[112]			
Arachnoid cyst[34]			5%
Cysticercosis[55]	1.8%		
Tuberculoma[9]	1.8%		
Sarcoidosis[126]			
Aneurysm of vein of Galen[96]			
Recently described tumours			
Atypical teratoid rhabdoid tumour (ATRT)[21]			
Papillary tumour of pineal region (PTPR)[49]			

Table 2: Frequency of pineal mass lesions at different ages

Age group	*Most common*	*Next so common*
Infants	Pineoblastoma	Arachnoid cyst, aneurysm of vein of Galen
Childhood	Germinoma, NGGCT	Pineoblastoma, glioma, tuberculoma
Young adults	NGGCT, glioma	Pineocytoma, pineal cyst
Older adults	Pineocytoma, glioma	Meningioma, epidermoid, metastasis

important in making clinical decisions, is presented in Table 2.

SYMPTOMS AND SIGNS

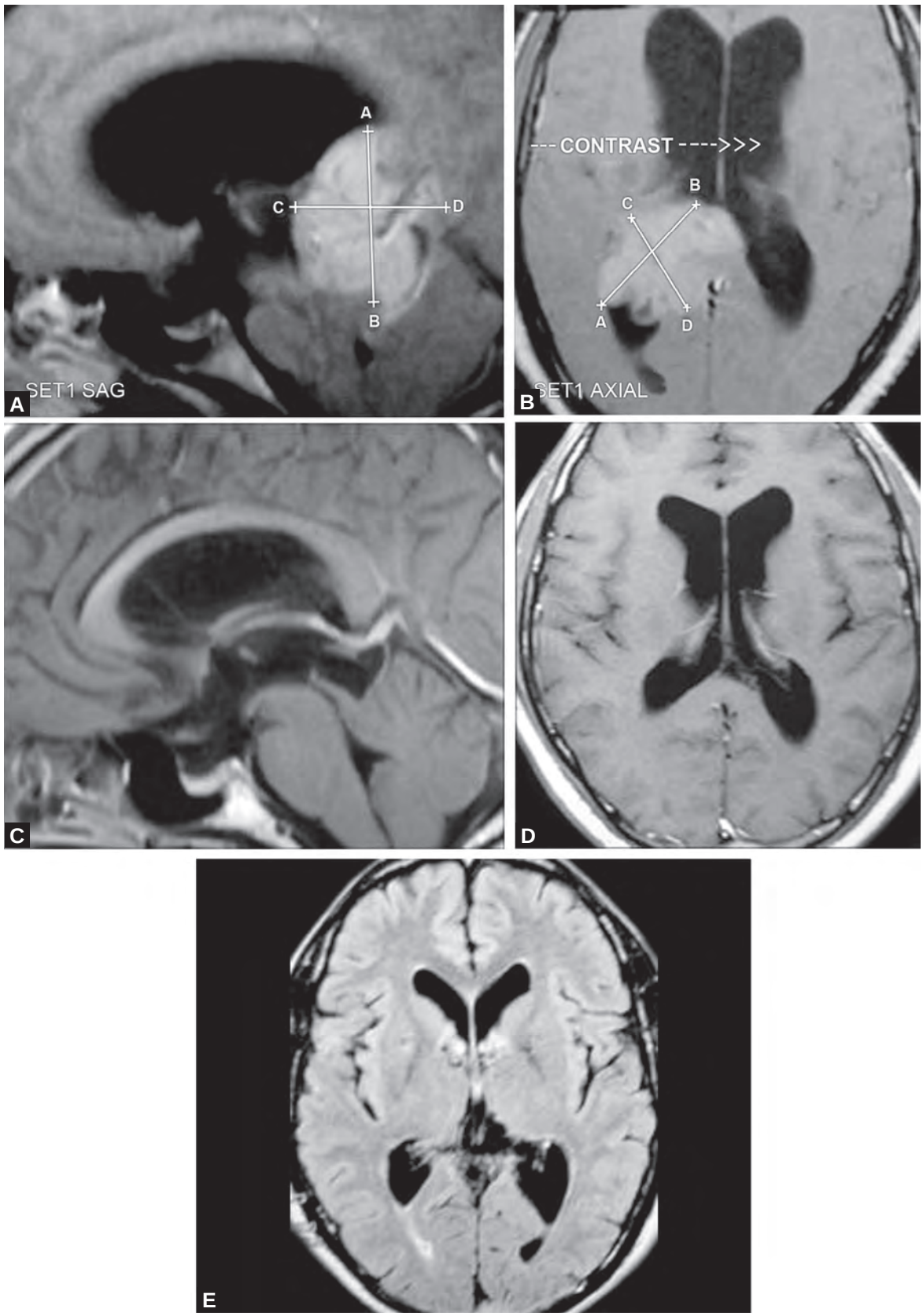
Pineal masses present in a variety of ways. The mechanisms of production of symptoms are: (1) Raised intracranial pressure due to obstruction of the posterior third ventricle or aqueduct or both; (2) Direct compression or infiltration of the neighbourhood neurological structures such as the tectum and the midbrain nuclei or white matter tracts; and (3) Endocrine dysfunction.

Raised intracranial pressure syndrome is the most common presentation of pineal masses across the ages. Older children or adults with raised pressure syndrome present mainly with headache. Vomiting or rapidly increasing head size is the symptom in younger children. Lethargy and obtunded mentation are seen in the later stages. Three fourths of the patients have papilloedema at presentation. Spells of loss of consciousness with limb rigidity might occur and is known as hydrocephalic attack. Sudden neurological deterioration may also be due to intratumoral haemorrhage (pineal apoplexy), which seems to be common in pineoblastoma and choriocarcinomas of children.[43] The intratumoural haemorrhage can also be precipitated by shunt or endoscopic procedures.[65,76]

Ocular signs are seen in about 50% of patients with pineal tumour. The differentiation of the ocular syndrome into Parinaud's syndrome, dorsal midbrain syndrome, pretectal syndrome and syndrome of the aqueduct of Sylvius (Koerber-Salus-Elschnig syndrome) appears to be a mere hair-splitting academic exercise. Paralysis of vertical gaze (up gaze alone or up and down gaze), deficiency of convergence, convergence-retraction nystagmus, disjunctive horizontal eye position, pupillary light-near dissociation, lid retraction (Collier's sign) and ptosis are seen in descending frequency.[50] Parinaud's syndrome is not pathognomonic of a pineal mass, as stroke, demyelination and hydrocephalus account for about 75% of the causes of the syndrome. The other eye signs reported with pineal tumours are reverse Parinaud's syndrome (paralysis of downgaze alone instead of upgaze),[67] unilateral supranuclear abducent paresis (lack of abduction during saccadic or pursuit volitional movements but preserved reflex abduction while performing oculocephalic manoeuvre or caloric testing),[127] bilateral superior oblique palsy,[7] contralateral relative afferent pupillary defect,[20] isolated vertical diplopia,[72] and paroxysmal tonic upgaze of childhood.[87]

Neurological signs are less common than signs of raised pressure or ocular signs. Involvement of the superior cerebellar peduncles can cause the ataxia-dysmetria syndrome even when hydrocephalus is absent. Gait ataxia is mostly due to hydrocephalus. Inferior colliculular involvement may present with tinnitus or hearing impairment. Hearing disturbance could be a symptom of a pineal mass and has been found in 18% in one series.[68] The hearing impairment has been noted to recover on treating the tumour.[40] Parkinson syndrome has been reported as a presenting manifestation of childhood pineal immature teratoma. This syndrome is known to remit with treatment of the tumour and might relapse when the tumour recurs.[30] Alexia, agnosia and amnesia have been rarely reported.[120] Vivid, coloured, formed visual or multi-sensory, long-lasting, non-epileptic hallucinations known as "peduncular hallucinosis" have also been reported with pineal tumour.[69] An example of such a presentation is given in Figures 1A to E from the author's case material.

Endocrine dysfunction is a childhood phenomenon restricted to pineal GCTs. Diabetes insipidus has been shown by neuroendoscopy to be due to involvement of the floor of the third ventricle, even when the MR imaging does not show such an involvement.[122] Precocious puberty is seen in 10% of boys with pineal GCTs. The most obvious explanation for the precocious puberty is the secretion of human chorionic gonadotrophin (β-HCG) from the syncytiotrophoblastic (choriocarcinomatous) elements in the tumour, but this is not the most common. It is believed that compression of the posterior hypothalamus by the mass results in loss of its inhibition of the median eminence resulting in excess of gonadotrophin releasing hormone (GnRH). There might also be a deficiency of antigonadotrophic substances (melatonin and others) that should normally be released by the pineal. Pineal tumour is only a rare cause of isosexual male precocious puberty as proved by a study from India.[29] Most of the cases were due to an adrenal or testicular cause; among the central causes the idiopathic variety and hypothalamic hamartoma were commonly seen. There was only one patient with a pineal tumour in this series of 22 boys. Anorexia nervosa may rarely be due to a pineal germinoma that involves the hypothalamic feeding centre.[123] Insomnia due to melatonin deficiency



Figs 1A to E: A 32-year-old male presented with three episodes of vivid, formed, coloured visual hallucinations lasting 30–60 minutes ('peduncular hallucinosis'), on a background of headache and gait ataxia. (A and B) Contrast MRI showed a pineal-posterior third ventricular mass extending into the right lateral ventricle. Endoscopic third ventriculostomy and biopsy of the mass in the lateral ventricle was done through a single coronal burr hole. Histopathology showed a primitive neuroectodermal tumour. He was given external beam radiotherapy (36 Gy for the neurospinal axis and a booster of 18 Gy to the tumour area). (C and D) The follow-up contrast MRI after 4 months. (E) After 18 months, showed total resolution of the tumour and normal ventricular size

caused by pineal germinoma has been reported and oral melatonin can be used to treat it.[35]

Rarer presentations include myelopathy or radiculopathy with spinal drop metastasis, which might predate the detection of the primary pineal tumour. They might also appear years after the pineal tumour has been eradicated by therapy. Similarly, delayed extraneural growth into bone or the chest is rare.[118] A clinical presentation similar to tuberculous basal arachnoiditis can occur due to extensive subarachnoid seeding of germinoma.[109] Haematogenous spread to bone has been reported with pineoblastoma.[24] Spread to the peritoneal cavity via shunt tubes[116] and spread along the endoscopy tract have also been observed.[23] Recurrent subarachnoid haemorrhage from a pineocytoma has been reported.[83] Progressive enlargement of an immature teratoma or NGGCT, following chemotherapy or radiotherapy, despite the normalisation of tumour markers, has been dubbed as the "growing teratoma syndrome". The enlarging mass is histologically a mature teratoma and is generally amenable to surgical excision.[11,71] An example of this syndrome is given in Figures 2A to C. In a neonate, presentation of a pineal cystic mature teratoma mimicking an encephalocoele has been reported.[8]

Asymptomatic patients with pineal masses are being increasingly detected with widespread use of neuroimaging. Asymptomatic small glial cysts are found in routine autopsies in about 25–40% but, until recently, they were seen only in less than 10% of cases on neuroimaging. The newer high-resolution MRI scanners can detect pineal cysts in about 23% of healthy adults.[90]

NEUROIMAGING

Calcification of the pineal is a physiological phenomenon. It is readily seen in plain radiographs and CT. Calcification increases with age; below the age of 6 years calcification is seen in only 1% of glands and by 14 years, 40% of glands are calcified as seen on CT.[32] In the days of plain radiographs, calcification larger than 1 cm in any one diameter, or any calcification before the age of 4 years were considered pathological.

MRI, with or without gadolinium, is the investigation of choice for diagnosing pineal masses. MRI gives information on the size, content, intratumoural haemorrhage or necrosis, degree of invasion and vascularity of the tumour and also shows the degree of ventriculomegaly. The sagittal and coronal images help to depict the slope of the tent and the relation of the tumour to the neighbourhood brain structures/deep venous system. This information is invaluable in planning the operative approach. MR imaging of the entire spinal cord is recommended to detect spinal seeding in children with malignant pineal tumours. Computed tomography demonstrates abnormal calcification in the tumour more obviously than MR and is useful for planning stereotactic approaches.[94]

Purely cystic lesions in the pineal region include pineal cysts, pineocytomas, arachnoid cyst, cysticercal cyst, low-grade astrocytoma and, rarely, teratoma.[34] Magnetic resonance imaging can generally distinguish pineal cyst from pineocytoma.[36] A recent report suggests that intrinsic T1 hyperintensity may be a characteristic imaging appearance of a papillary tumour of the pineal region provided the presence of fat and haemorrhage are ruled out.[18] Highly cellular tumours such as germinomas and childhood pineoblastomas may appear isointense or hypointense in T2-weighted images. In spite of the advances in neuroimaging, an exact histopathological diagnosis for most tumours can be made only by obtaining tissue. Table 3 gives some characteristic neuroimaging findings of pineal tumours. Figures 1(A to E) to 8(A to D) give examples of neuroimaging in various pineal lesions.

TUMOUR MARKERS

Pineal GCTs declare their presence by characteristic cell products that are found in the ventricular or lumbar CSF and in the serum. Alpha-fetoprotein (AFP), an oncofetal glycoprotein, is a marker for tumours with yolk sac elements, while β-human chorionic gonadotrophin (β-HCG) indicates a tumour with trophoblastic elements. Placental alkaline phosphatase (PLAP) is a marker for germinoma, but this is less widely used.[104] The normal levels and the extent of elevation of these markers in various tumours are given in Table 4. The CSF levels are more sensitive than serum levels.[92] Of course, lumbar puncture cannot be done unless the raised intracranial pressure is dealt with first. In a small subset of patients with characteristic imaging and elevated tumour markers, surgical biopsy may be avoidable. Figures 8A to D show an example of a patient in whom the diagnosis was based initially on detection of tumour markers. The analysis of tumour markers helps in follow-up and in detecting recurrence or spinal seeding. The diagnosis of growing teratoma syndrome rests on finding an enlarging mass on imaging even though the tumour markers have normalised[11] (see Figs 2A to C).

MANAGEMENT

The goals of management of pineal tumour are: (1) Management of hydrocephalus; (2) Establishing a firm diagnosis, preferably from tumour tissue; (3) Excision or mass reduction; (4) Avoidance of surgical morbidity and complications; and (5) Effective adjuvant therapy.

Direct surgical attacks on pineal tumours in the first half of the 20th century carried an unacceptable mortality. Hence, shunt placement and direct radiotherapy became the choice of treatment in the 1960s. In the 1970s, using the operating microscope, it was possible to approach pineal tumours with acceptable morbidity. In the 1980s, CT guided stereotaxy was introduced and it provided tissue diagnosis for the non-excisable lesions.

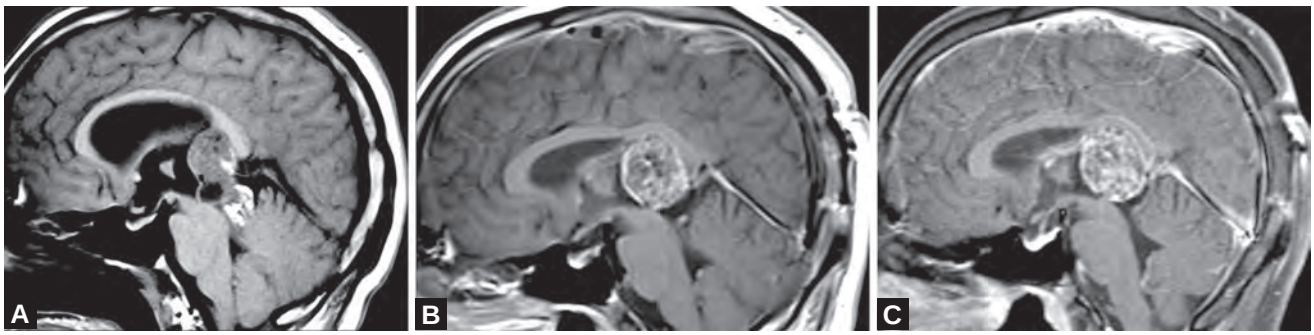
Table 3: Neuroimaging of pineal masses

Tumour type	*CT*	*T1 MR*	*T2 MR*	*Contrast CT/MR*	*Special features*
Pineoblastoma	Homogeneous, iso-hypodense, fine calcifications	Iso- or hypointense	Iso- or hypointense	Intense, slightly non-uniform enhancement	Occurrence in infancy or childhood, intratumoural haemorrhage, surrounding oedema, invasion, association with retinoblastoma
Pineocytoma	Non-homogeneous, iso-hypodense, peripheral calcifications	Iso- or hypointense	Hyperintense	Non-uniform enhancement, some nodular enhancement and > 2 mm rim enhancement	Occurrence in adults, intratumoural haemorrhage, expansive rather than invasive
Germinoma	Homogeneous iso- or hypodense, non-calcific	Well circumscribed iso- or hypointense	Iso- or hypointense	Intense uniform enhancement	Occurrence in young boys, spread to suprasellar region or basal ganglia surrounding oedema, intratumoural haemorrhage, subarachnoid seeding
Mature teratoma	Strikingly heterogeneous with areas of iso, hypo and hyperdensity, dense calcification	Well circumscribed mixed intensities	Mixed intensities	Heterogeneous enhancement	Occurrence in young adults
Malignant NGGCT	Heterogeneous, variable calcification	Mixed intensities	Mixed intensities	Non-uniform enhancement	Occurrence in young males, haemorrhages in choriocarcinoma
Glioma	Homogeneous hypodense, rare calcification	Iso- or hypointense	Hyperintense	Variable, inhomogeneous enhancement	Occurrence in adults, extension from or to midbrain, thalamus, splenium
Meningioma	Homogeneous hyperdense	Isointense	Hyperintense	Marked homogeneous	Attachment to falx, tent, velum interpositum
Pineal cyst	Hypodense centre and isodense rim	Hypointense centre, isointense to CSF with wall less than 2 mm thick	Hyperintense centre and isointense rim	Peripheral enhancement, no nodularity	Non-evolution over time, no hydrocephalus

Table 4: Tumour markers in pineal tumours

	AFP	*β-HCG*	*PLAP*
Normal serum level	0-8.5 ng/ml	0-7 mIU/ml	0.2 IU/L
Normal lumbar CSF level	< 5 ng/ml	< 2 mIU/ml	0.11 IU/L
Test	CLIA	CLIA	ELISA
Germinoma	Normal	Mild elevation < 770 mIU/ml	Highly elevated 1-9 IU/L
Endodermal sinus tumour	Highly elevated > 1000 ng/ml	Normal	Normal
Embryonal carcinoma	Moderately elevated < 1000 ng/ml	Mild elevation < 770 mIU/ml	Slight elevation
Choriocarcinoma	Normal	Highly elevated > 2000 mIU/ml, CSF level > serum level	Normal
Immature teratoma	Rarely and mildly elevated	Normal	Normal
All other pineal tumours	Normal	Normal	Normal
Systemic choriocarcinoma	Normal	Highly elevated > 2000 mIU/ml CSF level < serum level	Normal

(AFP = Alpha fetoprotein, β-HCG = β-human chorionic gonadotrophin, PLAP = placental alkaline phosphatase, CLIA = chemiluminescence immunoassay, ELISA = enzyme linked immunosorbent assay)



Figs 2A to C: A 19-year-old male presented with headache and diplopia. (A) MRI showed a markedly heterogeneous (calcific, cystic and lipomatous) pineal region mass with variable enhancement suggestive of teratoma. Through a right parieto-occipital interhemispheric approach, the tumour was partially excised. Histopathology showed immature teratoma. The serum AFP was 65 ng/ml in CSF after surgery but it came down to 0.6 ng/ml in CSF after three cycles of PEB (cisplatin, etoposide and bleomycin) chemotherapy by the 4th month. However, the tumour size progressively enlarged in the MRI done. (B) 2 months. (C) 4 months later. This is classical example of growing teratoma syndrome (Case courtesy: Dr KN Krishna, Neurosurgeon, Bangalore)

The late 1990s saw the emergence of endoscopy, which provided not only a solution to hydrocephalus but also made direct tissue biopsy and some tumour debulking possible. Thus, we now have a variety of methods to deal with a pineal tumour.

Decision-Making in Pineal Tumours

The main factors that impact the decision-making are: (1) Age of the patient; (2) Neurological status; (3) Imaging characteristics; (4) Presence of hydrocephalus; (5) Available technology; and (6) Experience of the surgeon.

Young children with pineal masses are likely to have a pineoblastoma or germinoma and these tumours do not lend themselves to aggressive excision. These tumours which are hypointense in T2-weighted images are homogeneous except for areas of haemorrhage and only rarely show calcification. Both these tumours are not associated with elevation of AFP or β-HCG. Ventricular diversion, preferably by endoscopic third ventriculostomy (so as to avoid seeding along the shunt tract) is often necessary. It is a common practice in the Eastern nations to subject these children to 20 Gy local field radiation without tissue diagnosis, as these countries have a high incidence of the very radiosensitive germinoma. If the tumour disappears, an additional 30 Gy radiation is given and the child followed-up. If the tumour does not disappear and the residue is more than 2 cm, microsurgical excision is recommended.[85] With the low incidence of germinoma in India, this is not the general approach in any Indian centre. Stereotactic biopsy might be difficult in young children, sampling errors may occur and some hold that stereotactic procedures in the pineal region are more prone to complications, although this is not necessarily so.[93] Endoscopic biopsy enables one, nowadays, to establish the tissue diagnosis at the same time as the third ventriculostomy, thus providing a basis for adjuvant therapy.[105] Endoscopic debulking is not a goal in these tumours.

Older children and young adults, especially males, have a higher likelihood of harbouring other GCTs. Marked heterogeneity on imaging suggests a teratoma and surgical excision is needed. A pre-operative ventricular diversion procedure may be needed only in patients presenting as an emergency with visual failure (from papilloedema) or altered sensorium. In non-emergent situations, one can directly proceed with microsurgical excision of the tumour. Only rarely is a ventricular diversion needed after total excision of the tumour. Mature teratomas do not require any further therapy. Even if there is a small post-operative residual mature teratoma, it only needs to be carefully followed up. The immature teratomas and teratomas with malignant transformation need adjuvant therapy. On the other hand, an enhancing tumour that shows only some inhomogeneity on imaging in a young male may be: (1) Embryonal carcinoma; (2) Endodermal sinus tumour; (3) Choriocarcinoma; or (4) Mixed GCT. Elevation of AFP suggests endodermal sinus tumour or mixed GCT with yolk sac elements (see an example in Fig. 4). Very high levels of β-HCG would indicate choriocarcinoma or mixed GCT with syncytiotrophoblastic element (see an example in Figs 8A to D). Moderate elevations of both the markers might mean an embryonal carcinoma. All these four tumours carry a poor prognosis. Even though they show an initial response to radiation, they tend to recur and metastasise.[100] Stereotactic biopsy might sample only one area in a mixed tumour and this might vitiate the prediction of prognosis. Surgical excision not only rids the patient of the mass effect but also produces a complete histopathological analysis of the tumour. In the situation of elevated tumour markers, it is acceptable to give radiation first and reserve microsurgery for sizeable residual tumour mass.[100] The residue might be the mature teratomatous component of the tumour and this might continue to enlarge after radiochemotherapy, in spite of the fact that the tumour marker level has become normal.

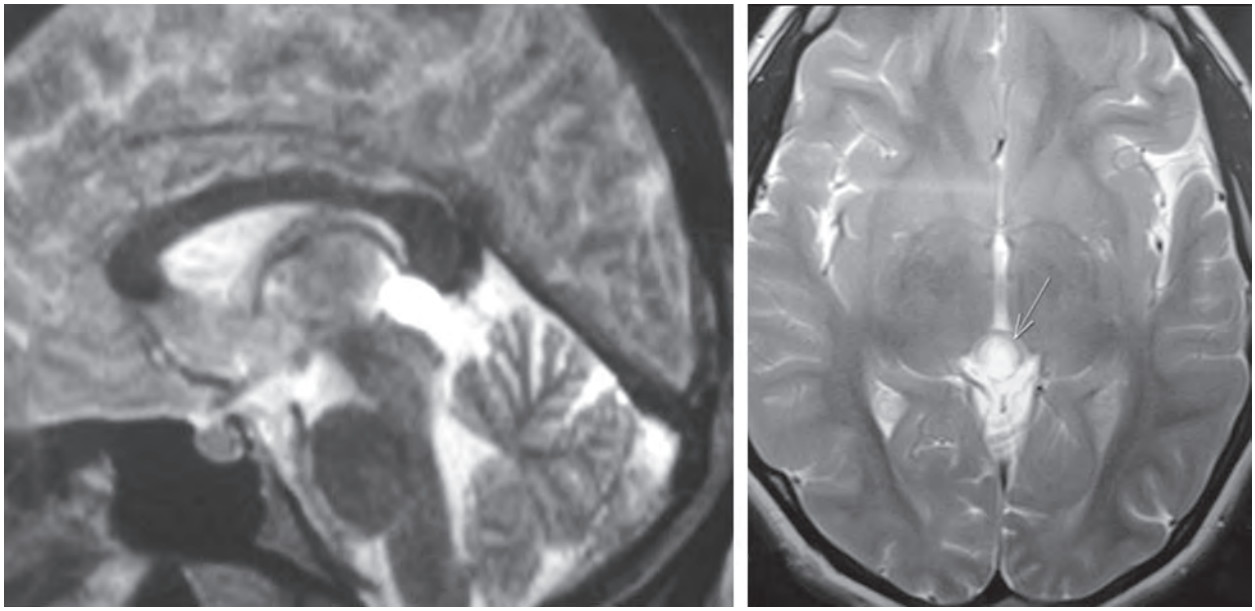


Fig. 3: MRI of an asymptomatic pineal cyst in a 17-year-old girl

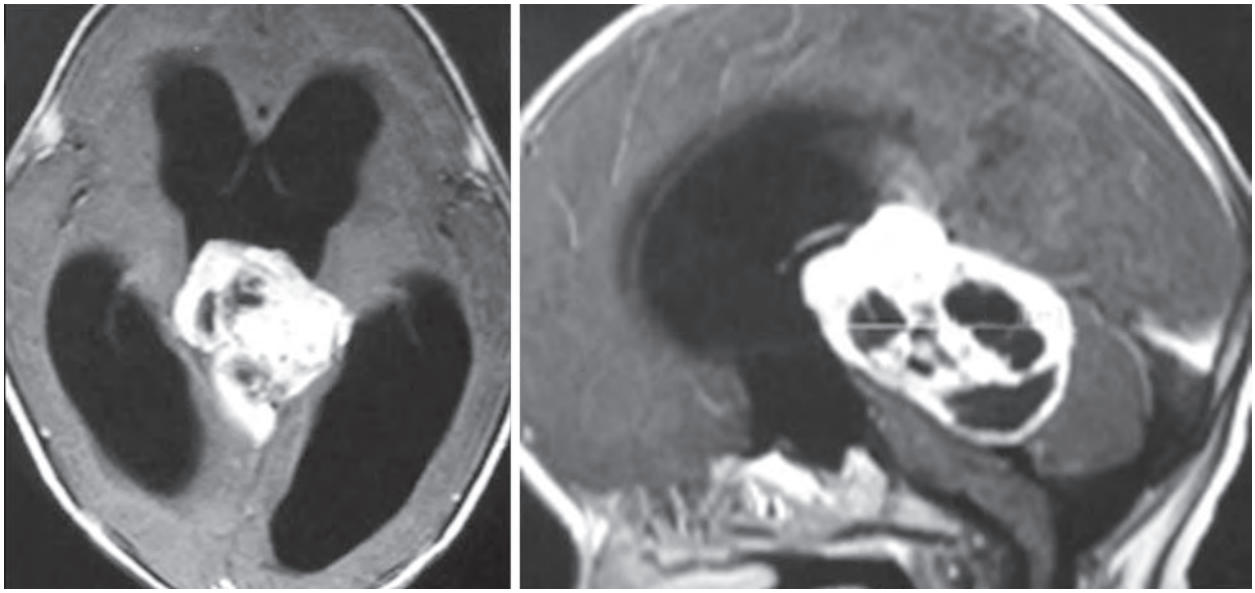


Fig. 4: A 1¼ -year-old baby presented with vomiting and loss of walking ability. MRI showed a richly enhancing large mass in the pineal region with necrotic areas. The serum AFP was 225 ng/ml. Endoscopic third ventriculostomy and biopsy through a single burr hole showed a mixed malignant germ cell tumour with components of immature teratoma and endodermal sinus (yolk sac) tumour. The family refused definitive surgery or adjuvant therapy

This 'growing teratoma syndrome' calls for microsurgical excision.[39]

Among older adults, meningiomas and epidermoids have characteristic imaging appearances and need microsurgical excision. However, pineocytomas and gliomas are the most likely lesions in this age. Masses larger than 2 cm can directly be accessed and excised using the most appropriate microsurgical route. Total excision is possible in many cases, but not all. Adjuvant therapy then is based on the histology and the post-operative residue on imaging. Smaller masses can be excised or at least biopsied by endoscopy. Stereotactic biopsy is more accurate in the smaller lesions.

SURGICAL APPROACHES

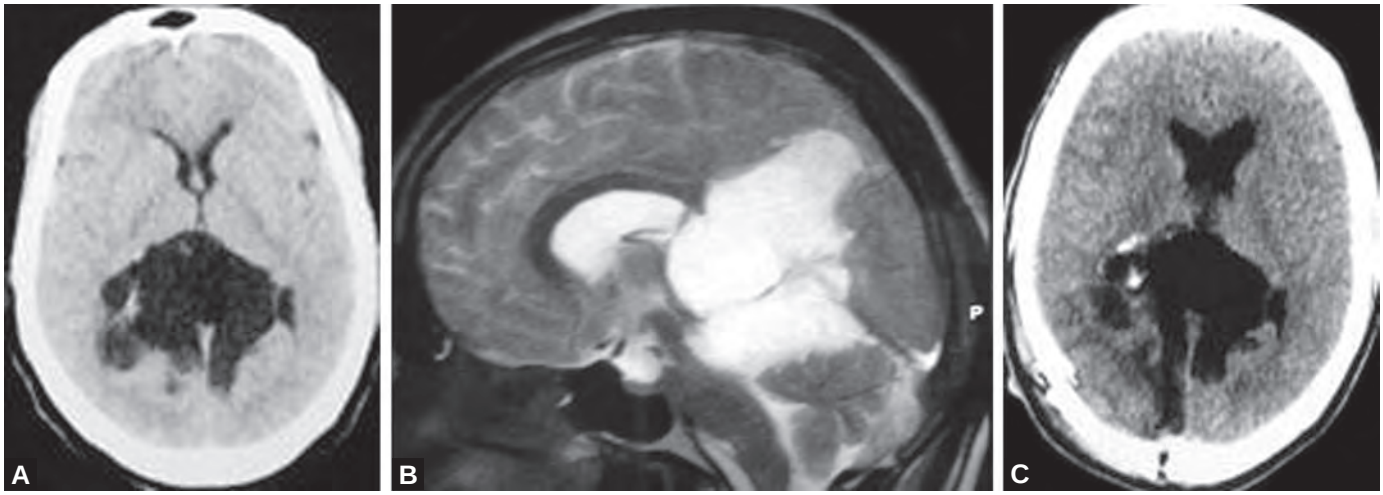
Pineal tumours are located in the geometric centre of the head and this makes them equidistant from the surface regardless of the site of surgical entry into the skull.

The depth of location, the proximity to the deep veins and the malignant nature of some of the tumours have deterred generations of surgeons from approaching pineal tumours. Even a stalwart, like Cushing, felt that he was never able to expose a pineal tumour well enough to justify its removal. Nevertheless, intrepid neurosurgeons, such as Krause (infratentorial supracerebellar approach—1926), van Wagenen (translateral ventricular approach—1931), Dandy (parafalcine trans-splenial approach—1936) and Poppen (occipital approach—1966), described operative approaches to pineal tumours with modest success. The mortality and morbidity were high in the era before steroids, safe anaesthesia and operative magnification. Shunt placement followed by radiotherapy was, therefore, perceived to be the safer choice. Availability of operating microscopes and neuroimaging rekindled interest in the direct operative approaches during the last 25 years of the 20th century. Although the mortality came down during this period, the surgical complication rate (morbidity) was still a deterrent. The trend shifted towards minimally invasive procedures such as CT guided stereotactic biopsy and neuroendoscopic intervention.

Surgical Anatomy

The pineal gland is attached to the posterior wall of the third ventricle and is between the posterior commissure below and the habenular commissure above. The suprapineal recess located above the habenular commissure is larger than the tiny pineal recess. Anteroinferior to the posterior commissure is the opening of the cerebral aqueduct and these structures are well seen through the endoscope introduced through the foramen of Monro, after passing the massa intermedia (interthalamic adhesion). The paired choroid plexus in the roof of the third ventricle and the dark internal cerebral veins shining through the ependyma of the roof are also seen.

The microsurgical anatomy of the infratentorial and supratentorial approaches has been described and compared.[125] When seen from the inferior perspective of the supracerebellar approach, on retracting the culmen of the vermis inferiorly, the thick opaque arachnoid passing up to the posterior tentorial incisura is first encountered. On opening the arachnoid, the right and left basal veins of Rosenthal coursing from below and laterally upwards towards the vein of Galen are seen lying lateral and superior to the pineal. The basal vein may also join the internal cerebral vein of the same side (35%), or the straight sinus (9%). The precentral cerebellar vein passes from the vermis to empty into the vein of Galen in the midline, in normal persons. However, in the presence of a pineal tumour, it may be found shifted to one side or the other. Sacrifice of the precentral cerebellar vein is often necessary and this only rarely results in major venous infarction in the cerebellum.[47] There may be a pair of precentral cerebellar veins in about 50% and at least one can be spared in such cases. The precentral cerebellar vein might also empty into the straight sinus. The vein of Galen above obscures the vision of the splenium and the mass itself obscures the quadrigeminal plate. After removing the tumour, the colliculi may be seen if the tumour has not infiltrated them. The posterior third ventricle often gets opened after removing the mass. The massa intermedia, the paired choroid plexus in the roof of the third ventricle, the columns of the fornix and foramina of Monro can be seen within the third ventricle. The blood vessels nourishing the tumour come from the choroidal arteries on either side and from the velum interpositum above the roof of the third ventricle. Branches of the superior cerebellar artery



Figs 5A to C: A 50-year-old man presented with headache, left haemianopia and left limb ataxia. (A) CT scan showed a hypodense, non-enhancing mass in the pineal region with finger-like extensions and peripheral calcifications. (B) T2-weighted MR images showed that the lesion surrounded the deep veins. Through a right occipital transtentorial approach, most of the epidermoid tumour could be decompressed. The lining membrane adherent to the tectum and splenium was left behind. (C) Post-operative CT showed the empty space left behind by the tumour resection to be filled with CSF. The medial occipital surgical corridor is well seen. The headache and ataxia improved but the haemianopia persists

to the inferior colliculi get exposed inferiorly and must be saved. Damage to the inferior colliculi can result in hearing impairment and word deafness.[63]

When seen from the superior perspective of the posterior transcallosal approach, the splenium of the corpus callosum covers the pineal region and posterior callosotomy is always needed. Splitting the splenium exposes the terminal portions of the internal cerebral veins and the point where they merge to form the vein of Galen. The dorsal surface of the tumour may have splayed the internal cerebral veins slightly and this corridor can be used to decompress and excise part of the tumour. The other corridor available is below and medial to the right basal vein of Rosenthal. Division of the right tentorial leaflet enhances the room available in this approach and helps to reach the infratentorial part of the tumour.

When seen from the posterior perspective of the occipital transtentorial approach, the venous anatomy is similar and the veins are often seen without the need for sectioning the splenium. The tumour might also have lifted up the splenium. The view of the colliculi is better with both the supratentorial approaches.

Endoscopic Approach

Indications

The minimally invasive nature of endoscopy is appealing to the neurosurgeon and the patient. The primary indication for endoscopy for a pineal mass is for performing third ventriculostomy to relieve hydrocephalus. If the foramen of Monro is large enough and if the mass is visible in the posterior wall of the third ventricle, a biopsy of the tumour can also be performed. Lesions less than 2 cm or larger cystic lesions can adequately be managed endoscopically, if they are not highly vascular. A second open microsurgical procedure may not be necessary in the smaller, radiosensitive malignant lesions such as germinoma, NGGCT and pineoblastoma. Endoscopic biopsy has also been used for differentiating recurrent tumour from radionecrosis.[22] It must be explained to the patient that open microsurgery might still be necessary even after a successful endoscopic approach. A new minimally invasive technique, computer-assisted cisternal endoscopy (CACE), for the biopsy of pineal tumours, has been studied in cadavers and is purported to be used even when there is no hydrocephalus.[128]

Technique

The procedure is done through the non-dominant hemisphere, generally the right. In the supine position with 20 degree head elevation, through a coronal scalp flap, a burr hole is placed just anterior to the coronal suture. Ventricular CSF sample can be collected for tumour marker analysis before introducing the endoscope. If the foramen of Monro is large enough, the rigid endoscope can be manoeuvred backwards through the same burr hole anteroinferiorly for the third ventriculostomy and posteriorly for lesion biopsy, without causing damage to the anterior column of the fornix (see examples in Figs 1A to E, 4 and 6A to D). If the foramen is small, a rigid scope can be used for the third ventriculostomy and a flexible scope for the tumour biopsy. Alternatively, a second burr hole can be placed about 2–2.5 cm more anteriorly to provide a convenient trajectory for the biopsy using the rigid endoscope (see example in Figs 7A to D). The optimal trajectory for the ventriculostomy and biopsy can be planned and executed with neuronavigation.[51]

The technique of third ventriculostomy is the same as in other cases. There may be obscuration of the floor of the third ventricle by tumour spread, especially with germinoma or tectal glioma. It is possible to work one's way through a thin layer of tumour into the subarachnoid space.[44] There is, however, a risk of the stoma shutting off over time in such cases.[62] We prefer doing the third ventriculostomy before the biopsy, as the bleeding during the biopsy might obscure the landmarks for ventriculostomy. The mass is often found covered by the ependyma and this must be opened with bipolar cautery. The outer surface of the tumour is then opened and multiple bits must be taken from the inside of the tumour for biopsy so as to minimise sampling error. It is a luxury to have a pathologist standing by for performing frozen section or smear analysis immediately.[89] If the lesion appears highly vascular, it is better to avoid endoscopic biopsy. An external ventricular drain is not used unless there has been significant bleeding during the biopsy.

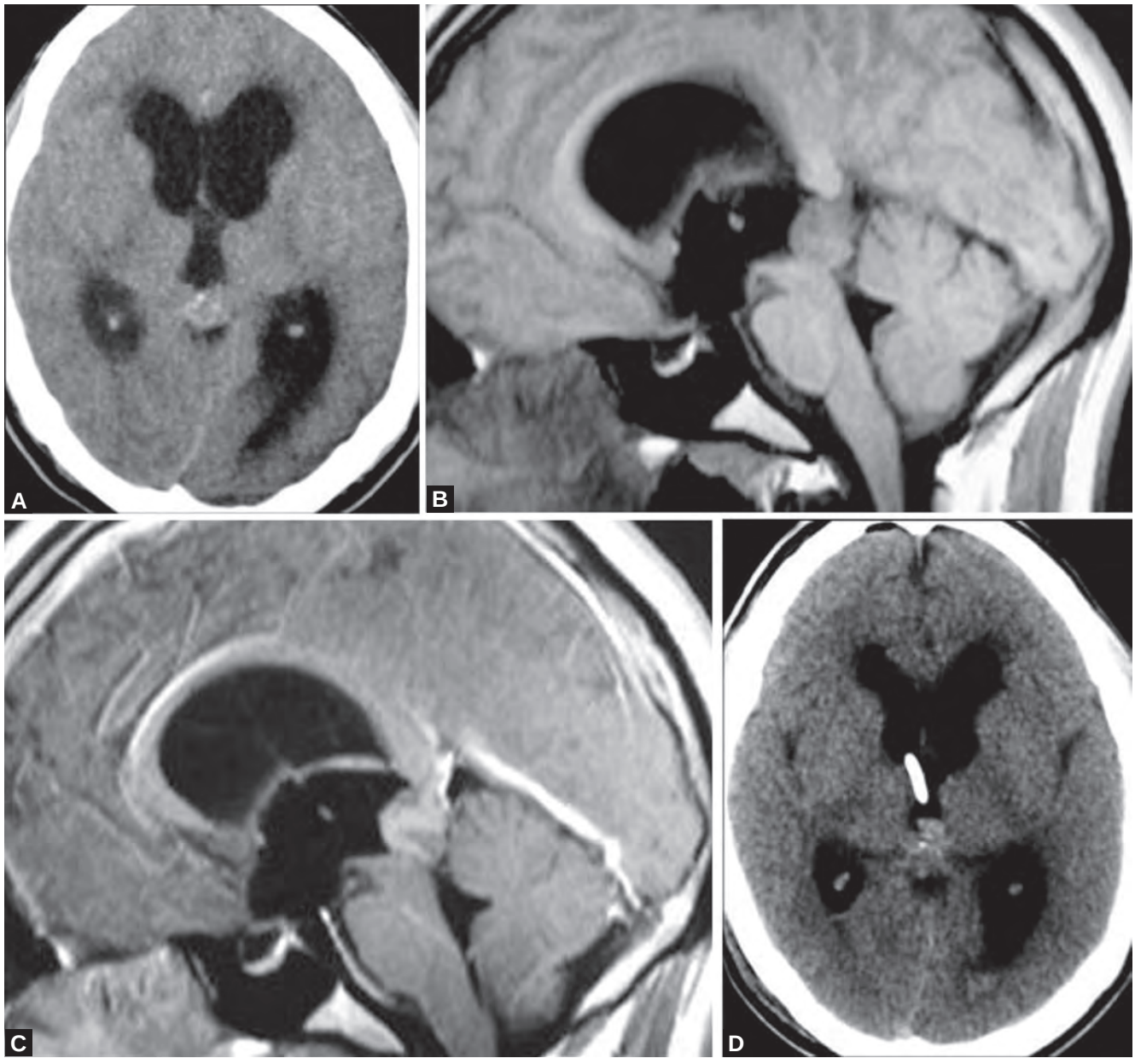
Complications

Bleeding from the tumour can be a significant problem during endoscopic biopsy or decompression. The bleeding usually comes under control with prolonged irrigation and ventricular filling. Inadequate tissue sampling by endoscopy has made some prefer the open or stereotactic approach. Damage to the fornix, resulting in memory loss, is possible after excessive manipulation of the endoscope thorough a minimally dilated foramen of Monro. Spread of tumour through the endoscopy track[23] or into the third ventriculostomy site[22,62] is known. No mortality or permanent morbidity was seen following endoscopic biopsy of pineal lesions in a recent series of 12 cases. Two cases of transient worsening of preoperative diplopia were noted. Diagnostic sensitivity for endoscopic biopsy was 75%.[2] In a long-term follow-up study, shunts were needed in nearly 25% of the patients and the biopsy yield was non-diagnostic in about 25% of cases.[82]

Stereotactic Approach

Indications

CT guided stereotactic biopsy has been viewed as being risky due to the surrounding major veins in the pineal region. This fear persists, in spite of the demonstration about a decade back by the French neurosurgeons, that

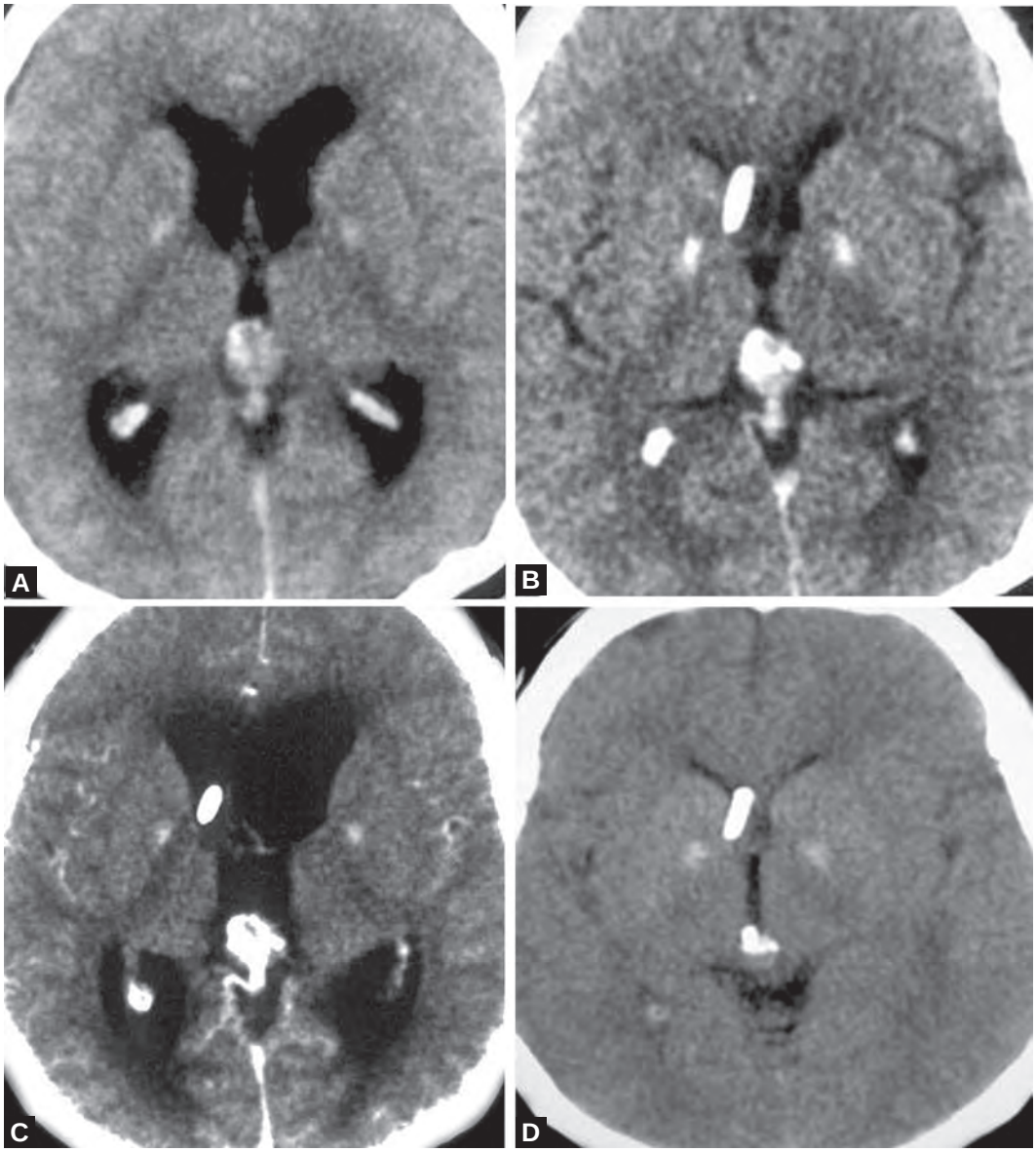


Figs 6A to D: A 20-year-old man presented with headache, papilloedema, ataxia and tremors. (A) The plain CT showed a pineal mass with punctate calcification. (B) MRI showed a T1-isointense tumour and T2-hypointense tumour. (C) There was non-uniform contrast enhancement. Endoscopic third ventriculostomy and biopsy-decompression of the tumour was done. The pathology was pineoblastoma. (D) The immediate post-operative CT, before removing the ventricle drain, showed reduction in size of tumour and no significant haemorrhage. He underwent craniospinal axis irradiation and remained asymptomatic 6 months later

stereotactic biopsy is as safe in the pineal region as elsewhere in the brain.[93] The larger tumours anyway need excision and do not need a preliminary stereotactic biopsy. If a malignant radiosensitive lesion is clinically thought to be likely, stereotactic biopsy and radiotherapy, without tumour resection, is a viable alternative. Since endoscopy is not recommended for those without hydrocephalus, stereotactic biopsy is a good choice in such patients. Aspiration of cystic lesions can be done by the stereotactic approach. Stereotaxy is also employed for implanting radioactive material (iodine-125) for brachytherapy.[53]

Technique

CT guided stereotactic biopsy is usually done through a non-dominant side pre-coronal trajectory, that is planned so as to avoid lateral ventricular entry and the internal cerebral vein. Tumours that extend laterally towards the thalamus can also be approached through a parietal trajectory. In tumours that are markedly heterogeneous on imaging multiple sites of biopsy are recommended to reduce the sampling error. Interactive image guided (frameless) surgical biopsy has also been reported to be successful.[97]



Figs 7A to D: (A) A 38-year-old woman had been diagnosed to have a pineal tumour 2 years earlier and had undergone ventriculoperitoneal shunting in another city. No definitive therapy had been given. She had improved in her headache and visual symptoms. (B) There was no ventricular dilatation and a persisting pineal tumour in the CT one year later. (C) 2 years later she returned with recurrent spells of altered sensorium. She had Parinaud's syndrome with Parkinsonian tremor and she progressed to drowsy-akinetic mute state. (C) CT showed recurrent hydrocephalus without increase in the size of the mass lesion. Endoscopic third ventriculostomy was done through a coronal burr hole. Since the foramen of Monro was small, a second frontal (precoronal) burr hole was placed and through this trajectory, the mass was biopsied and decompressed. Histologically, it was a pineocytoma. Radiotherapy was given. She made a rapid and full recovery and continues to be neurologically normal at follow-up 4 years after the procedure. (D) CT scan 18 months after the endoscopic surgery showed only a small speck of residual calcification. Note the resolution of hydrocephalus

Complications

Haematoma formation is a much feared but rare complication.[37] Implantation metastasis is distinctly rare and has been reported in a case of pineoblastoma.[95] In a series of 370 cases across several centres, the mortality of stereotactic biopsy was 1.5% and neurological complications occurred in less than 1% of cases.[93]

Microsurgical Approaches

Indications

All benign pineal lesions that can be diagnosed with reasonable certainty on imaging would certainly require open microsurgical excision. These include meningiomas, cavernomas, epidermoids and mature teratomas.

Such lesions account for about 15% of all lesions in the pineal region. A recent study showed that microsurgical removal is the only effective treatment for teratomas, even in children.[80]

Some malignant lesions are radiosensitive and they can be diagnosed by tumour marker study, endoscopic biopsy or stereotactic biopsy. Examples are germinomas and some NGGCTs (choriocarcinoma, endodermal sinus tumour, embryonal carcinoma). There is not much point in performing an open microsurgical procedure in such cases. The proportion of such tumours is variable in different races and is generally low in India.

All the remaining lesions do not have a distinctive imaging appearance and cannot be diagnosed by tumour marker study. The histological heterogeneity of the immature or mixed teratomas makes limited, minimally invasive biopsies unreliable. A more complete histological diagnosis can be expected with the entire resected tumour specimen. The poor radiosensitivity of the low-grade pineal parenchymal tumours and gliomas necessitates gross total resection. These lesions make up over a third of the pineal lesions in most countries (except in the Eastern Asian nations). In many of such low-grade lesions, further adjuvant therapy (with their potential toxicity) can be avoided or deferred when gross total resection is accomplished. Gross total resection is possible in about a third of the malignant tumours and an aggressive resection offers a survival advantage.[14] The potential benefits of open microsurgical resection must be weighed against the potential risks. The operative mortality in expert hands was 4% with 3% permanent major morbidity in a series of 160 aggressive operations on pineal tumours.[14]

Pineal tumours can be approached from either above or below the tentorium. The midline infratentorial supracerebellar approach, as described by Stein in the microsurgical era, is the most commonly employed approach.[15] The lateral paramedian infratentorial approach described by Van den Bergh is a variation.[119] The various supratentorial approaches are:

- Occipital transtentorial approach described by Poppen and modified by Jamieson[115]
- Posterior transcallosal approach, first used by Dandy[33]
- Posterior transventricular approach, first used by van Wagenen[10]
- Anterior transcallosal, transventricular, transvelum interpositum approach, described by Sano.[99]

Large tumours, especially meningiomas, may require a combined supratentorial and infratentorial trans-sinus approach, as described by Ziyal and Sekhar.[129] The advantages, disadvantages and specific indications for these various approaches are summarised in Table 5. In the following section, the two principal procedures of midline infratentorial supracerebellar and occipital transtentorial approaches are discussed in some detail.

A preliminary ventriculoperitoneal shunt or endoscopic third ventriculostomy is often necessary, before definitive surgery for the pineal tumour in patients with severe raised intracranial pressure. If the hydrocephalus is mild, a ventriculostomy catheter can be placed at surgery, left behind for 2–3 days after surgery and then either removed or converted to a shunt. Posterior third ventriculostomy that naturally occurs or is intentionally done after resecting the pineal mass may also provide relief of hydrocephalus.

Infratentorial Supracerebellar Approach

Technique

The patient is positioned sitting with the neck flexed forwards such that the tentorial slope along the straight sinus is almost parallel to the floor. Gravity assists cerebellar retraction in the sitting position. The head is fixed in a pin clamp such as Mayfield or Sugita system. The prone 'Concorde' or lateral decubitus positions are also used and they reduce the risk of air embolism. These alternative positions do not eliminate the need for air embolism monitoring (end tidal carbon dioxide or transoesophageal Doppler monitoring). There is less fatigue for the surgeon in these alternative positions as compared to the sitting position.

The incision can be a straight midline or a 'lazy S' incision that starts 5 cm above the external occipital protuberance and extends to the C2 spinous process. The pericranium above the external occipital protuberance is lifted off as a flap but left attached on one side. This can be used as dural substitute during closure. The muscles are split in the midline right down to the bone and raised on both sides, so that they can be approximated again. Burr holes are made just above the transverse sinuses and over the cerebellar convexities on either side. These burr holes are connected with a craniotome after separating the undersurface of the bone from the sinuses with a Penfield dissector. The craniotomy exposes the transverse sinuses, torcula and the lower end of the superior sagittal sinus. The posterior rim of the foramen magnum is left intact to prevent excessive sagging of the cerebellum. Performing a free bone flap craniotomy allows replacement of the bone at the end of surgery. Craniectomy is a less preferred alternative. The thick bone over the torcula must be thinned down and removed with high-speed cutting burrs so that it will not impede upwards retraction of the dural flap.

The dura is opened as a semilunar flap or three triangular flaps based on the transverse sinuses. The dural flaps are retracted upwards with sutures. If the brain is sufficiently relaxed, the undersurface of the tent should be seen at this stage. If not, further relaxation must be achieved with mannitol, hyperventilation and CSF drainage either by opening the cisterna magna or by tapping the lateral ventricle. The arachnoid adhesions between the superior surface of the cerebellum and the tentorium are sharply divided under the operating microscope. The draining veins on the superior surface of the cerebellum passing to the undersurface

Table 5: Advantages, disadvantages and specific indications of the various microsurgical approaches to pineal masses

Approach	*Advantage*	*Disadvantage*	*Indication*
Midline infratentorial supracerebellar	Midline approach Tumour is below major veins and they do not hamper resection Gravity assists in retracting cerebellum and separating tumour from the veins above, if the patient is in the sitting position No intentional neural damage	Air embolism in sitting position Narrow operative corridor, especially if the tent is steeply sloped Sacrifice of superior cerebellar draining veins and precentral cerebellar vein may cause cerebellar infarction Difficult to reach above tentorial incisura or lateral extensions of tumour	Midline pineal masses Tumour does not have lateral extension or superior extension high above the incisura Tumour not larger than 3 cm
Lateral paramedian infratentorial	No sacrifice of precentral cerebellar vein Can be done when the tent is steeply sloped in the midline No intentional neural damage Lateral decubitus position avoids risk of air embolism	Only small tumours can be approached Superior cerebellar artery and its branches may be at risk Cannot see the posterior third ventricle	Small tumour below tentorial notch with unilateral lateral extension, in patients with steep slope of the tent in the midline
Occipital transtentorial	Good view of structures and tumour above and below the tent	Retraction damage to occipital lobe and resulting haemianopia Damage to splenium, disconnection syndrome Unilateral approach, so difficult to reach across the midline to the opposite side	Tumours that extend entirely above or equally above and below the tentorial notch Tumours with unilateral (usually right) lateral extension
Posterior transcallosal (through parieto-occipital bone flap crossing the midline)	Ease of approaching lesions above the tentorial notch with extension to the third ventricle	Internal cerebral veins come in the way Callosotomy may lead to disconnection syndromes Cannot reach inferior portions of the tumour Parietal lobe retraction damage or venous damage	Posterior third ventricular mass, mass arises below the splenium, above the venous system
Posterior transventricular (through high parietal craniotomy and superior parietal lobule corticotomy)	Exposure of atrium and posterior portion of the body of lateral ventricle	Fornix sectioning needed for entering third ventricle and this may cause memory deficit Seizure risk due to corticotomy	Tumour extends laterally from the third ventricle to the posterior part of the lateral ventricle
Anterior transcallosal, transventricular, transvelum interpositum (through precoronal parasagittal craniotomy)	Wider room to deal with the anterior extent of tumour No fornix section as the approach is through the velum between the (right) internal cerebral vein and the choroid plexus of (right) lateral ventricle Supine positioning is easy and risk-free	Increased depth of approach Callosotomy deficits Fornix damage from retraction	Large tumour that extends anteriorly in the third ventricle up to the interthalamic adhesions
Combined supra and infratentorial trans-sinus (semiprone position, suboccipital and bilateral two piece occipital craniotomy, non-dominant transverse sinus and tent divided)	View of tumour above and below the tent Ample room The divided transverse sinus may be resutured	Division of transverse sinus may produce venous infarction or delayed intracranial hypertension	Large meningioma, epidermoid, teratoma

of the tent must be coagulated and divided before they snap due to the effect of gravity. Self-retaining retractors are placed on the undersurface of the straight sinus and tent and over the superior cerebellar surface. The thick arachnoid posterior to the pineal region is opened with sharp microdissection to expose the venous anatomy (mentioned above in the section on surgical anatomy). The microscope must be angled cranially towards the apex of the tentorial notch for the arachnoid dissection. The precentral cerebellar vein generally needs to be coagulated and divided. Once this is done, the posterior surface of the tumour comes into view. As the dissection proceeds, the microscope is angled inferiorly.

The surface of the tumour is devascularised and opened with long non-stick bipolar forceps. Tissue from the tumour is sent for squash/frozen section histology. Internal debulking of the tumour can be done with tumour forceps until adequate material is obtained for regular histopathological examination. The remaining portion is dealt with by suction-dissection or ultrasonic surgical aspirator using the long narrow hand piece. The wall of the tumour is then drawn away and, if it tends to separate well, the tumour can be excised in toto. This is generally possible with benign tumours and the non-infiltrating malignant tumours. The portions that infiltrate the brainstem or those that are intimately attached to the veins would have to be left behind. Venous bleeding in a narrow corridor can cause malignant brain swelling and must be avoided.[47] Through this approach, the superior portion of the tumour towards the velum interpositum is better visualised than the inferior portion towards the colliculi. Opening through-and-through the tumour into third ventricle and performing a front-to-back dissection helps to separate the lateral attachments of the tumour. Meticulous haemostasis is essential. Complete dural closure is advocated to minimise the chance of aseptic meningitis and usually needs a patch of pericranium or artificial dura. Replacing the bone flap helps to avoid pain and pseudomeningocoele.

Complications

The intra-operative complications related to the sitting position are hypotension, air embolism and cervical myelopathy.[79] Ventricular collapse might cause a supratentorial subdural haematoma. Extraocular movement disorder or ataxia that worsens after surgery is expected to recover to the baseline status over some weeks. Mental obtundation and even mutism have been observed.[102]

Occipital Transtentorial Approach

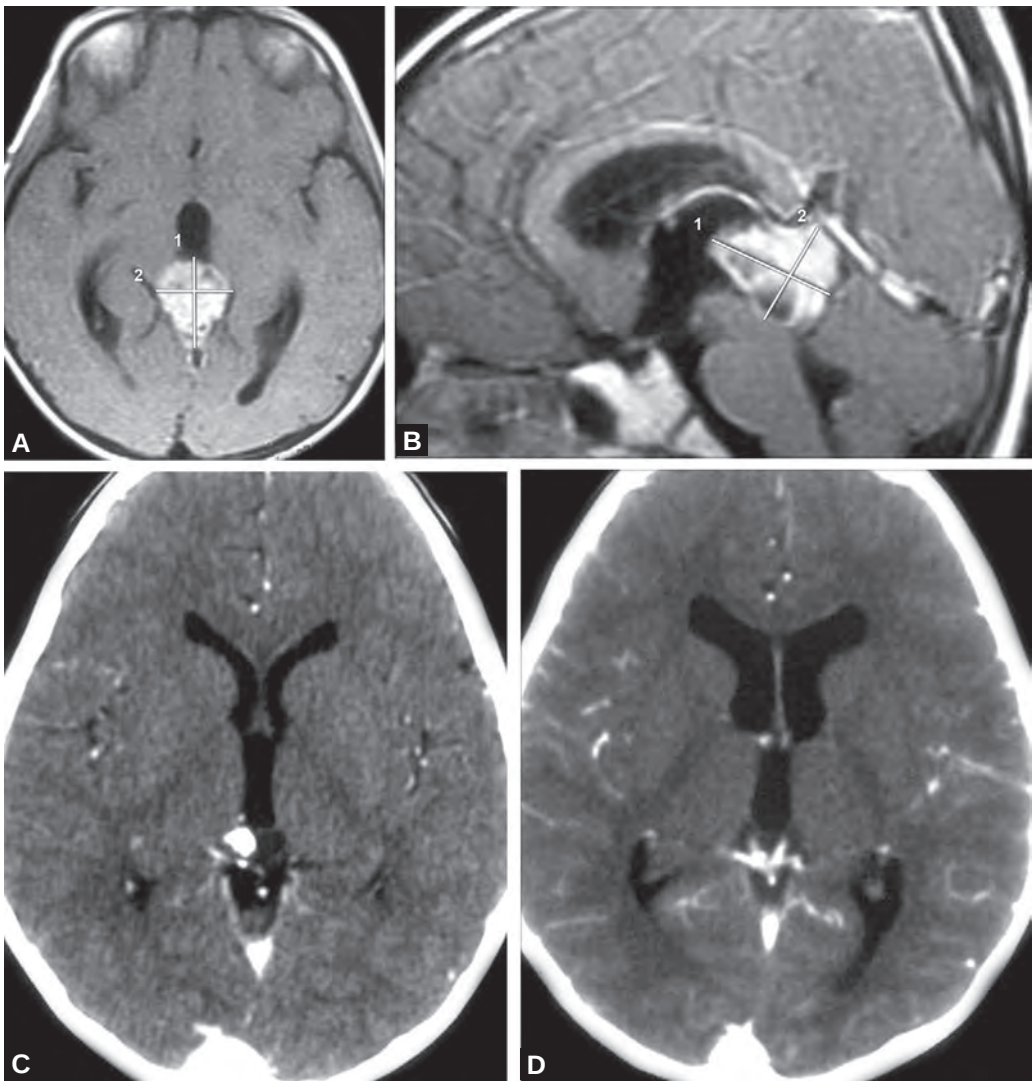
Technique

The procedure is done on the non-dominant side, usually the right. The occipital transtentorial approach can be done conveniently with the patient in the prone position and the head rotated to the left to allow some gravity retraction of the right occipital lobe. The three-quarter prone position achieves the same end.[12] The left lateral position was the originally described position. Sitting slouch position is a less preferred alternative. The incision starts below the external occipital protuberance just to the left of the midline and runs parallel to the midline before turning laterally and downwards to the lateral end of the transverse sinus. The low parieto-occipital bone flap exposes the right edge of the superior sagittal sinus but does not need to crossover to the left side. The upper edge of the sinus and the right lateral edge of the torcula are also exposed.

The dura is opened as two triangular flaps, one based on the transverse sinus and the other on the superior sagittal sinus. The right occipital horn can be cannulated if the brain is not lax. In the ideal case, the medial inferior edge of the occipital lobe drops away from the falcotentorial junction. If not, a bent self-retaining brain spatula is placed over the medial edge to retract it laterally. Lifting the inferior surface of the occipital lobe upwards is not recommended as it does not give additional room and as it damages the calcarine area. There are usually no major draining veins passing to the sinuses from the medial inferior border. Any small draining vein can be coagulated and divided. Once the tentorial edge is seen anteriorly, the tent is divided parallel to and about 1.5 cm lateral to the straight sinus from an anterior to posterior direction under the operating microscope. The division of the tent is for about 2–3 cm only and not all the way posteriorly to the transverse sinus. The arachnoid posterolateral to the venous complex is then seen and must be opened by sharp dissection. The right basal vein and the vein of Galen are first seen, the internal cerebral vein being hidden from view by the splenium. The tumour is discernible medial and inferior to the right basal vein. Small tumours without anterior extension and the larger tumours that have displaced the splenium upwards can be removed without sectioning the splenium. Only those that extend anteriorly and upwards may require splitting of the splenium. The extent of splenial section is much less than that needed for the posterior transcallosal approach. The tumour removal proceeds as described in the infratentorial approach. It is far easier to see the quadrigeminal plate after tumour removal in this approach. The anterior and left lateral extensions are difficult to approach through this corridor.

Complications

The mortality rate of supratentorial approaches has fallen from 70% in Dandy's time to about 5% in the microscopic era. In one series of 86 cases, there was only one procedure related death.[57] Mortality is related to deep venous system damage or haemorrhage. Left haemianopia is seen immediately after the surgery in nearly three quarters of the patients, but it tends to recover in most of them.[78] Ataxia, transient worsening of eye movement disorders and seizures can also



Figs 8A to D: A 6-year-old boy presented with morning headache and papilloedema. (A and B) MRI showed an enhancing pineal mass. Ventricular CSF collected during shunt placement and lumbar CSF obtained after shunting were analysed for tumour markers along with serum sample. The AFP was normal in the serum and CSF. The β-HCG level was 23.0 mIU/ml in the serum, 80.9 mIU/ml in the ventricular CSF and 127 mIU/ml in the lumbar CSF. This suggested a syncytiotrophoblastic component in the tumour. He was given radiotherapy. The shunt malfunctioned in a month and was removed at another centre. Endoscopic third ventriculostomy was done there with biopsy, which confirmed a mixed malignant non-germinomatous germ cell tumour with syncytiotrophoblastic elements. He was asymptomatic after radiotherapy. (C) The follow-up CT at 1 year showed no trace of the tumour and a small calcific speck. (D) Two years after the initial diagnosis, he became ill with diffuse encephalomyelopathy even though there was no tumour recurrence in the pineal region and the β-HCG levels were normal. MRI of the spine and lumbar CSF cytology did not show tumour. He succumbed to the encephalomyelopathy 2½ years after diagnosis

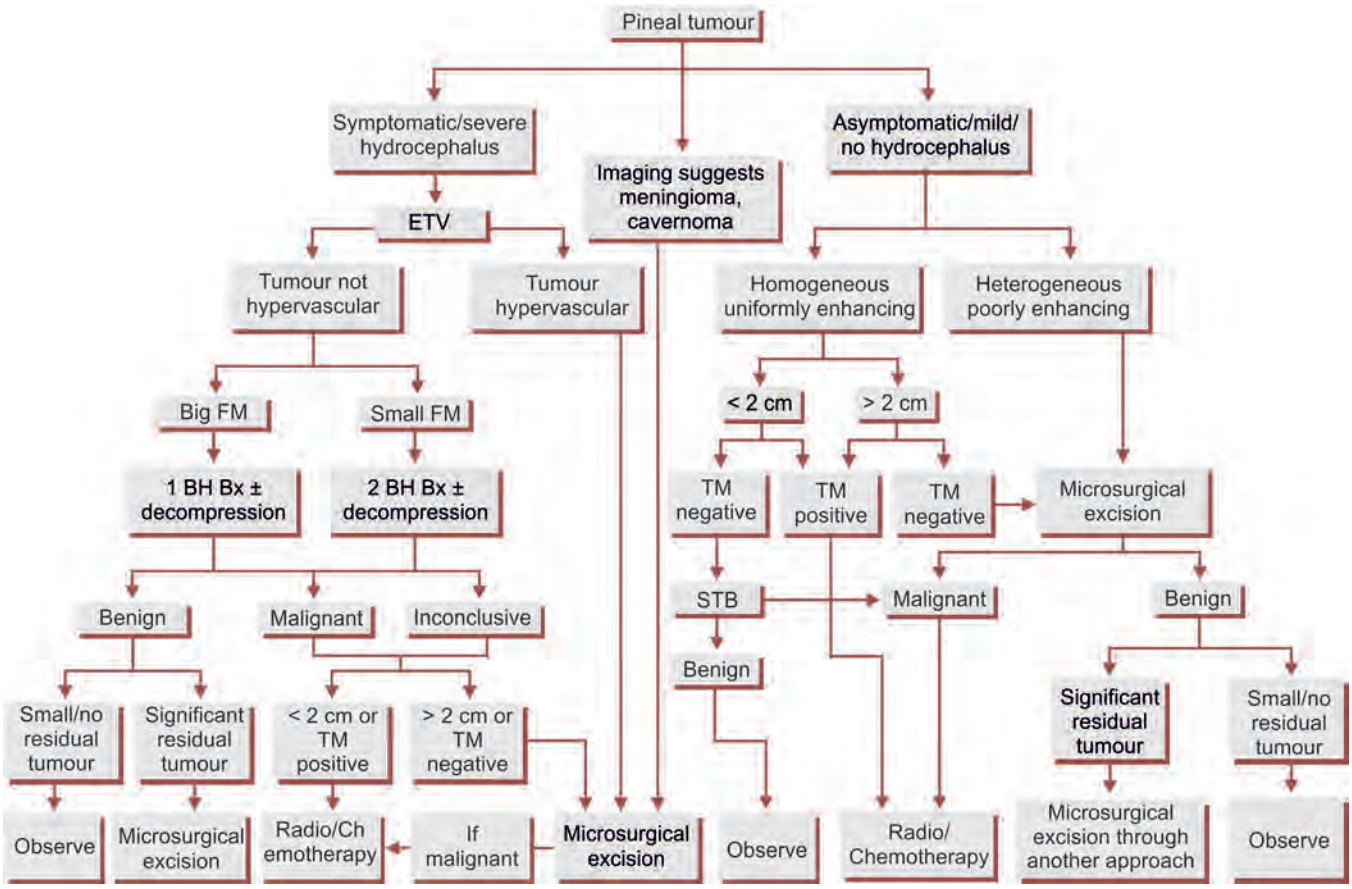
occur. Post-operative occurrence of subdural haematoma or hygroma is not peculiar to this approach and is the result of ventricular collapse.

Pineal tumours pose a challenge for the neurosurgeon due to their deep location. Microsurgical approaches have become safe in the last three decades and minimally invasive methods have become a viable alternative. Algorithm 1 summarises our present algorithm for management of pineal tumours. Algorithm 2 indicates how we choose the approach when microsurgical excision is deemed necessary.

STEREOTACTIC RADIOSURGERY

Stereotactic radiosurgery (SRS) of pineal tumours is a new therapeutic choice. The highly conformal nature of therapy makes SRS ideal for irradiating deep targets in the brain and yet allows for sparing of radiation damage to the vital structures in the neighbourhood. Performing SRS for a radiosensitive tumour, such as a germinoma, seems to be overkilled and it also does not prevent ventricular recurrence that is common with this tumour. SRS has been used: (1) As an alternative to surgical excision

Algorithm 1: Algorithm of management of pineal tumour



(ETV: endoscopic third ventriculostomy, FM: Foramen of Monro, TM: Tumour markers in serum, BH: Burr hole, Bx: Biopsy, ±: with or without, STB: Stereotactic biopsy). VP shunts are reserved for ETV failures. For the choice of microsurgical approach, see algorithm 2

for the smaller low-grade lesions; (2) For treatment of tumour residue after resection; (3) As an alternative to external beam radiotherapy so that radiotoxicity can be reduced; and (4) As an adjunct to external radiotherapy in the form of tumour boost dose for the more malignant lesions.[59] The availability of SRS does not obviate the need for histopathological diagnosis; in fact, tissue diagnosis is even more essential. In one recent report of 17 patients with varied histology, excellent local control was achieved in 16 patients and maintained for a mean follow-up of about 2½ years with gamma knife radiosurgery.[59] A group of 20 pineal parenchymal tumours treated by SRS has been shown to have 5-year survival of 68%, whereas it was 92% when only the pineocytomas were analysed. Imaging showed complete regression in 26%, partial regression in 47%, stable tumours in 11% and local in-field progression in 11%.[48] Similar success rates have been reported for SRS of GCTs from a Japanese centre.[73]

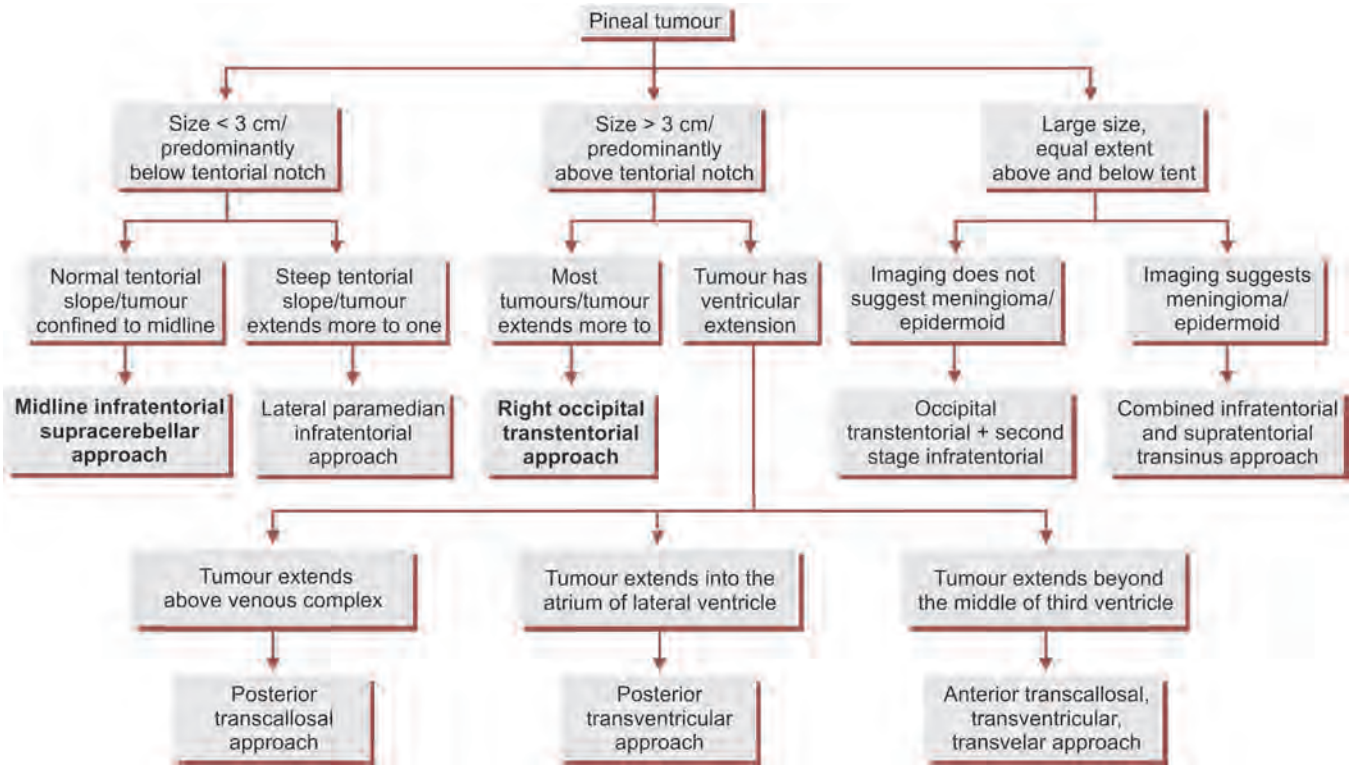
RADIOTHERAPY

Radiotherapy is the principal method of tumour control for the radiosensitive tumours such as germinoma. Limited field external beam radiation therapy (24–40 Gy) suffices for pineal germinoma, even when it involves the suprasellar region.[56] NGGCTs require 50–54 Gy and craniospinal axis radiation is recommended. Some centres favour dissemination evaluation and reserve whole neuraxis radiation for only those with documented spread.[124] Five-year disease-free survival rate is 91% for germinomas, but only 60% for NGGCTs with radiotherapy.[124] In a child younger than 3 years, radiotherapy can be deferred until that age by using chemotherapy. Pre-radiation chemotherapy has been used to reduce the dose of radiation in the responders.[54] The totally excised low-grade lesions, such as pineocytoma, do not need radiotherapy. The side effects of radiotherapy are cognitive dysfunction, growth failure, endocrine changes, radionecrosis and development of new neoplasms after decades.

CHEMOTHERAPY

The success of chemotherapy for gonadal GCTs suggests that the results might be similar with intracranial GCTs. Unfortunately, it is not so. Carboplatin-etoposide regimen or ifosphamide-cisplatin-etoposide combinations

Algorithm 2: Selection of microsurgical approaches for excision of pineal tumours. The two most commonly employed approaches are in bold letters



have been used in GCTs. When combined with radiotherapy, these regimens result in 93% remission rate in germinomas and 76% in the other malignant NGGCTs.[66] Although germinomas are exquisitely radiosensitive, cisplatin based chemotherapy is used to reduce the radiation dose and field.[31] Chemotherapy has also been used to salvage recurrences at the radiation field margin. Pineoblastoma has a poor prognosis but recent reports show a fairly good survival with gross total resection, radiotherapy and multimodality chemotherapy.[41] Pineocytoma generally does not need adjuvant therapy, but in cases where gross total resection has not been achieved or for recurrent tumours, platinum-based chemotherapy has been found useful.[46]

PROGNOSIS

Benign masses in the pineal region, such as meningiomas, epidermoids and mature teratomas, were studied in Vellore, India, over a 14-year period. Shunting followed by surgical excision resulted in most of the patients being in good or excellent condition.[17] There are a number of case series, which indicate that the extent of tumour resection positively impacts the survival for all kinds of pineal tumours and especially for the low-grade lesions.[13] However, a recent review of the Surveillance, Epidemiology and End Results (SEER) data base suggests that extent of surgical tumour resection did not affect survival in any histological subgroup and hence recommended that an aggressive surgical approach should be considered with caution in this region.[1] The 5-year overall survival was 79% for germinomas, followed by 61% for gliomas and 47% for pineal parenchymal tumours in this review.

Long-term results of multimodality therapy for GCTs are now available. The 20-year survival rate was 80% for germinoma, the 10-year survival rate was 70% for malignant teratoma and 3-year survival rate was 27% for malignant NGGCTs (embryonal carcinoma, yolk sac tumour or choriocarcinoma). The mixed tumours had a prognosis similar to a tumour of the most malignant cell type.[66] Cases of spontaneous regression of germinomas have been reported.[74]

Endoscopic management of pineal region tumours produces improved post-operative quality of life in all health domains.[114] In spite of multimodality therapy, only 50% of children with pineoblastoma are alive at 5 years.[25] In adults with pineoblastomas, the extent of spread of tumour at diagnosis has a strong bearing on the prognosis.[19]

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146 Pituitary Tumours Overview

Ravi Ramamurthi

INTRODUCTION

Tumours in the sellar and parasellar regions constitute 12–15% of all brain tumours. The most common of these are pituitary tumours, which constitute 8–12% of all intracranial neoplasms and are found in 2.7–27% of unselected routine autopsies in humans who had no symptoms of pituitary disease.[6,11,16,24,48,50,55,68] Incidentalomas or lesions of the pituitary, picked up by imaging in asymptomatic patients, have been reported in 10–37% of patients and on a follow-up, 40% of these lesions increased in size, 20% become symptomatic and 9.5% of these incidental tumours developed apoplexy. In children and adolescents, these tumours are rare and in a large series of these tumours, children accounted for 2–3.5%.[19,26,35] Pituitary tumours are more common among women. Among the elderly (65 years and above), pituitary adenomas are mostly non-functional and the incidence of gonadotrophic tumours increases with age.[23]

HISTORICAL

The pituitary gland was so named by Vesalius in 1543[1] who thought that the gland cleared noxious secretions from the brain by discharging them as nasal mucus (in Latin, Pituita means thick nasal mucus). In 1778, Hypophysis cerebri was the term used by Soemmering.[1]

Descriptions of endocrine abnormalities in humans date back to about 1365 BC. Aldred and Sandison[2] studied the monuments of the pharaoh Akhenaten and came to the conclusion that he was acromegalic and had truncal obesity. The Talmud and the Bible have descriptions of giants, probably of pituitary origin, the famous one being Goliath of Gath.[34] Rathke, in 1838,[58] described a part of the development of the pituitary gland. Lieutand, in 1742,[45] first suggested that the pituitary stalk vessels communicated with the gland. The existence of the portal circulation was confirmed by Popa, Fielding,[51] Henderson and Daniel.[29] In 1933, Riddle[58] described prolactin. Contributions to modern knowledge about the pituitary were made by Pierre Marie (1886), a French neurologist, who first described acromegaly and Sir Victor Horsley (1886), who did hypophysectomy in dogs. Harvey Cushing, Sir Victor Horsley, Caton and Paul, Herman Schloffer (who introduced the transnasal trans-sphenoidal route in 1906), Krause, Dandy, Frazier, Norman Dott, Guiot and Hardy are pioneers who developed, improved and popularised pituitary surgery. Oscar Hirsch described the endonasal approach in 1910 and later the sub-mucosal trans-septal trans-sphenoidal approach.[3,22,30,43,44]

ANATOMY OF THE PITUITARY GLAND AND ITS SURROUNDINGS

The pituitary gland or hypophysis cerebri lies in the pituitary or hypophyseal fossa of the sphenoid bone. It is basically made up of two divisions, viz. the adenohypophysis and the neurohypophysis, which have different embryological, morphological and functional characteristics. It is continuous with the infundibulum, which is a horizontal conical projection from the inferior aspect of the tuber cinereum.

Embryology

Rathke, in 1838, described the embryology of the pituitary gland. The adenohypophysis or the anterior pituitary is believed to arise from a diverticulum of the stomodeum or the primitive foregut. Prior to the rupture of the oropharyngeal membrane, a saccular recess forms in the ectodermal lining of the roof of the stomodeum. This rudiment of the anterior lobe of the pituitary (the 'pouch of Rathke') forms a closed vesicle but remains connected for some time to the ectoderm of the stomodeum by a solid cord of cells. This solid cord can be traced to the posterior end of the nasal septum. A craniopharyngeal canal from the anterior part of the pituitary fossa to the exterior of the skull can occasionally be traced and is said to mark the original position of the pouch of Rathke. Arey[5] found the craniopharyngeal canal in 0.42% of adults. However, there have been claims that the canal is formed by the growth of blood vessels and is unconnected to the formation of the anterior lobe.

A diverticulum from the floor of the diencephalon grows caudally towards the pouch of Ratkhe to form the posterior hypophysis. The walls of this hollow diverticulum increase in thickness till the contained cavity is obliterated, except at its upper end, which persists as the infundibular recess of the third ventricle.

The posterior lobe becomes invested by the anterior, which extends laterally on either side of it. The anterior lobe also gives off two processes from its ventral wall, which grows along the infundibulum and fuses with it. This forms the tuberal portion of the hypophysis. The original cavity of the stomodeum remains as a cleft and is easily identified in the fully formed gland. The dorsal wall of the stomodeal part fuses with the posterior lobe and forms the intermediate lobe of the pituitary.

Some adenohypophyseal cells have been found to be capable of amine precursor uptake and decarboxylation, thus forming part of the APUD system. These cells are believed to take origin from the neural crest. Takor and Pearse[62] suggest that the 'ventral neural ridge' gives rise to the adenohypophysis and is, therefore, of neuroectodermal origin, contrary to the classical view. The finding of occasional hypothalamic neurons capable of synthesising ACTH and MSH lends support to the theory that the posterior and anterior hypophyses shares the same embryonal origin.

Pituitary Gland

The normal adult hypophysis or pituitary gland is a horizontally positioned extra-arachnoid ovoid body measuring about 12–15 mm in transverse diameter, 8–10 mm in anteroposterior diameter and 5–7 mm in height.[38] It weighs about 0.5–0.7 gm in an adult male. The weight in a non-pregnant woman is about 100 mg more than in a man. During pregnancy, its weight increases to an average of 0.8–1.0 gm.[38,63] In Indians, the average weight of the pituitary gland in adult males is 401.26 mg +/– 105.89 mg. In females, it is (417.32 mg +/– 104.07 mg).[60] The mean weight of the gland in females is always more than in males of the corresponding age till 35 years. The maximum weight was noted in adolescent females.

The gland is continuous with the infundibulum, which arises from the inferior surface of the tuber cinereum. The infundibulum or the hypophyseal stalk contains an inner core, called infundibular stem, which contains the neural connections of the hypophysis. It is continuous with the median eminence of the tuber cinereum. The neurohypophysis is normally taken to include the median eminence, the infundibular stem and the posterior lobe of the pituitary gland. The adenohypophysis is made up of the pars tuberalis (which surrounds the neural infundibular stem) and the anterior lobe of the pituitary gland, which is divisible into pars anterior and pars intermedia. A histological pseudocapsule,[49] which develops due to the growth of the adenoma and compression of the normal gland tissue and in large adenomas a multi-layered reticulin capsule has been observed. This pseudocapsule helps in the localisation and surgical excision of an adenoma.

Blood Supply

The pituitary gland has a dual blood supply. There is a direct arterial supply[25] common to the anterior and posterior lobes and a portal supply exclusive to the anterior lobe. In 1860, Luschka described the inferior and superior hypophyseal arteries. In 1930, Popa and Fielding described the portal system of the pituitary.

The arterial supply to the anterior lobe of the pituitary gland may be divided into two groups in relation to the diaphragm sella.[25] The infradiaphragmatic supply to the gland is a capsular network which also vascularises the diaphragm.[25] This network is made up of branches of the inferior hypophyseal artery, which arises from the meningohypophyseal trunk and direct branches from the intracavernous internal carotid artery (the inferior and the anterior capsular arteries). Occasionally, direct branches from the stem of the inferior hypophyseal artery supply the posterolateral part of the anterior lobe and penetrate deeper into the gland than the capsular arteries. The inferior hypophyseal artery is the most important artery supplying the pituitary gland, its diameter being larger than any other arterial structure coursing through the region.[42] The supradiaphragmatic supply is through the middle hypophyseal artery, which is a branch of the superior hypophyseal artery. The vessel is paired and runs on the anterior surface of the stalk. The end arteries of these vessels are found mainly in the subcapsular peripheral zone and the lateral wings of the anterior lobe.

The anterior lobe of the gland receives the portal system, which originates from the capillary bed of the lower infundibular stem. There are two groups of portal vessels, the long and the short, each with their own area of supply. The blood flowing in these two groups of veins does not mix. The long portal vessels supply approximately 90% of the parenchyma of the anterior lobe, mainly the anterior and the central portions. The short portal vessels supply a small part of the anterior lobe lying adjacent to the posterior lobe. The blood derived from the portal vessels reaches the sinusoids, which form the vascular bed of the gland and lie between secretory cells. The significance of the portal system is in that it carries the hypothalamic regulating hormones to the anterior lobe, thus controlling the secretion of the anterior pituitary hormones.

The infundibulum and the posterior lobe of the pituitary are supplied by branches from the superior and the inferior hypophyseal arteries which form a confluent capillary bed, extending from the median eminence through the infundibulum to the posterior pituitary.[37] The medial and the lateral branches of the inferior hypophyseal artery form an arterial ring around the infundibular process of the neurohypophysis, while the superior hypophyseal artery supplies branches, termed the arteries of the trabeculae to the lower infundibular stem.

The venous drainage of the anterior lobe of the pituitary is via the inferior hypophyseal veins. The possibility of flow reversal in the portal system raises the possibility of the short portal system acting as a drainage system and providing the short loop feedback for endocrine

secretory control. The venous drainage of the neurohypophysis is to the inferior hypophyseal veins, the portal system and the hypothalamus via small capillaries, which pass between it and the median eminence.

Sella Turcica

The pituitary gland is housed in the hypophyseal or pituitary fossa of the body of the sphenoid bone. There are many variations in the bony surroundings of the pituitary gland due to the complex embryology of the region. The pituitary fossa is delineated in front by the tuberculum sella and chiasmatic sulcus. The dorsum sella and the posterior clinoid processes form the posterior relationship. The sellar floor, which separates the sellar contents from the underlying sphenoid sinus, extends from the tuberculum sella in front to the base of the dorsum sella posteriorly. Renn and Rhoton[57] found the thickness of the sellar floor to be equal to or less than 1 mm in 82% of specimens and more than 1 mm thick in 18%. Occasionally, the floor was very thin, only a few microns thick.

The pituitary fossa has a depth of 10–12 mm with an upper limit of 13 mm; an anteroposterior diameter of 5.16 mm with an upper limit of 17 mm and a width of 10–15 mm.[57] DiChiro and Nelson[17] have found the mean sellar volume to be 594 mm^3 using their simplified mathematical formula:

$$\text{Volume in } mm^3 = \frac{0.5 \text{ (length x width x depth in mm)}}{1000}$$

Sellar bridges are bony structures running between the anterior and the posterior clinoid processes. When present they are bilateral, although they may be incomplete. They may be found in up to 5.9% of individuals.[41] The carotico-clinoid foramen is demarcated by a bony bridge between the lateral border of the pituitary fossa and the apex of the anterior clinoid process. It transmits the internal carotid artery. The sellar spine is an osseous spine, which is a remnant of the anterior end of the notochord and protrudes from the dorsal side of the pituitary fossa into the fossa itself.

Diaphragma Sella

The diaphragma sella forms the roof of the pituitary fossa. It is a fold of dura mater, more often rectangular than circular and has a central opening, which transmits the infundibulum. Anatomical variations of the diaphragma sella are frequent. These have been classified by Busch[12] into: Type I—a funnel shaped depression of the diaphragma sella; Type II—incomplete closure of the diaphragm around the pituitary stalk; Type III—a wide defect in the diaphragm, so that there is only a peripheral rim of tissue measuring less than 2 mm in width. This may leave the pituitary gland completely exposed and covered only with arachnoid (III a) or may be associated with symmetrical or asymmetrical indentation of the pituitary gland by the herniated arachnoid pouch (III b) or there may be a complete remodelling or flattening of the pituitary gland (III c). The last defect has been found in 5.5–6.7% of autopsy series.[10,12] Bergland et al.[10] found anatomical defects in the diaphragma sella of greater than 5 mm in 37% of consecutive autopsy cases without pituitary disease. These defects in the diaphragma sella occur six times more often in females than in males. Through the defect in the diaphragm, the arachnoid invariably extends and spreads out on the upper surface of the anterior lobe of the pituitary gland. This CSF filled space, called the pituitary cistern,[40,41] usually enlarges with advancing age. The cistern can extend for a variable distance forwards and laterally and occasionally, can even cover the posterior lobe. Bergland et al.[10] could identify such a cistern in 20% of cases, studied radiologically by them. The diaphragm is usually thick at the periphery and thin at the centre. In 38% of cases, it is at least as thick as one layer of dura, while in 62%, it is extremely thin over areas of the pituitary gland.[57]

Sphenoid Sinuses

The sphenoidal sinuses are described as paired cavities lying side by side in the body of the sphenoid bone. They are separated by a bony septum, which is commonly deflected to one side or the other. The cavities vary in shape and size, are usually asymmetrical and are subdivided by minor septae.[57] The main septum separating the sinus into the two major cavities was seen in 68% of Renn and Rhoton's specimens.[57] It is usually directed anteroposteriorly and may be vertical in 25%.[28] The position of the septum can be located by tomograms and by CT scan and if located near the midline, can be used as a guide during the trans-sphenoidal approach to the pituitary fossa (Fig. 1). However, the major septum

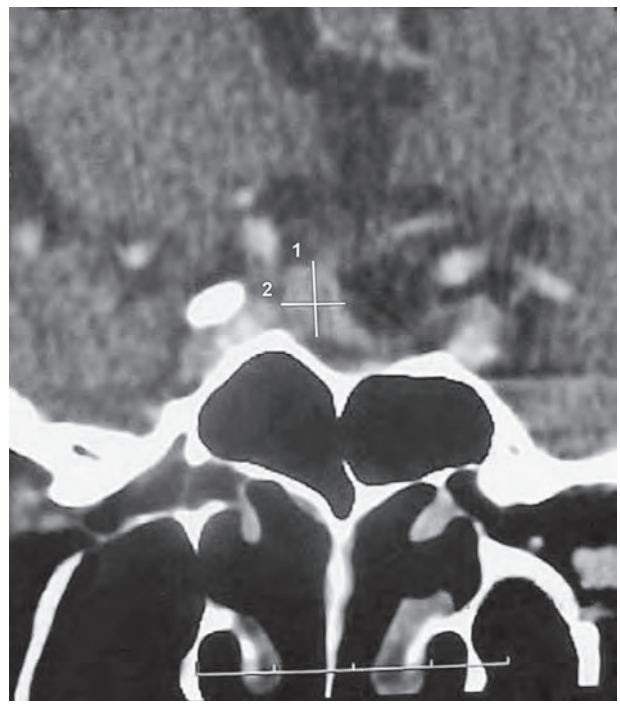

Fig. 1: CT coronal section showing the septum in the sphenoid sinus near the midline

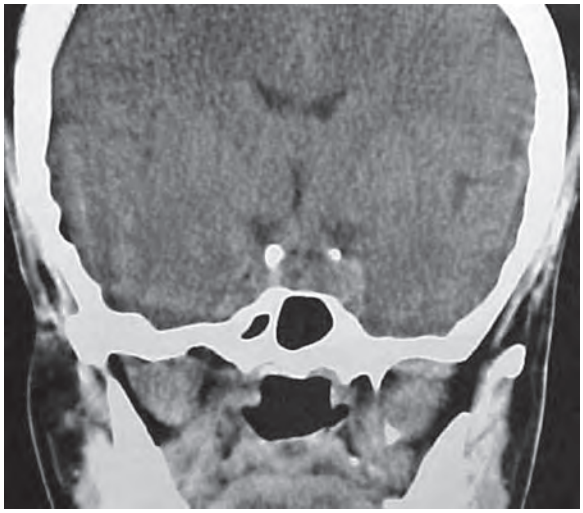

Fig. 2: CT coronal section showing the septum in the sphenoid located away from the midline

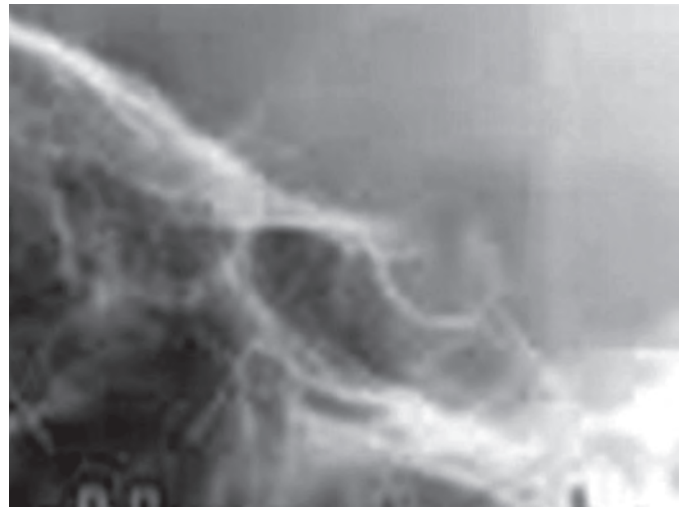

Fig. 4: Presellar type of sphenoid sinus

has been seen to be away from the midline in up to 46%.[57] (Fig. 2). In 43%, only the anterior part lies in the midline, while the rest of the septum is S, C or L shaped. The septum lies in the midline only in 27%.[39] Accessory septae arising from the synchondroses of the sphenoid are found in 76%. In 48%, they are unilateral while in 28%, they are found bilaterally.[20,57]

Hamberger et al.[27] classified the sphenoid sinus into three main anatomical types: (1) The conchal type is usually found in children but may be seen in up to 3% of adults. In this type, the sinus does not extend into the body of the sphenoid. It is small, and between it and the pituitary fossa is spongy bone, which may be as thick as 10 mm (Fig. 3); (2) The presellar type is found in 11–20% of adults. The sphenoid sinus does not penetrate the body of the sphenoid bone beyond a plane perpendicular to the planum sphenoidale. The anterior wall of the sella, therefore, does not bulge into the sphenoid sinus (Fig. 4); (3) Sellar type of sphenoid sinus occurs in 80–86% of adults. In this type, the sella has a thin floor and bulges into the sinus and occasionally, the sinus can extend from the dorsum sella to the upper clivus[38] (Fig. 5).

Carotid Arteries

The proximity of the carotid arteries to the midline is extremely important in pituitary surgery. The carotid arteries bulge into the superolateral wall of the sphenoid sinus in 71%.[57] These are usually covered by bone but in 4%, there may be no bone between the carotid arteries and the mucosa of the sinus. The average distance between the intracavernous portions of the two carotid arteries is 12–14 mm. However, the carotid siphon can be quite tortuous, sometimes narrowing the distance to 4 mm or occasionally, coursing laterally to an intercarotid distance of 23 mm (Fig. 6). The intercavernous venous connections traverse the anterior surface of the pituitary gland in 76–85% of cases or the posterior surface in 37%.

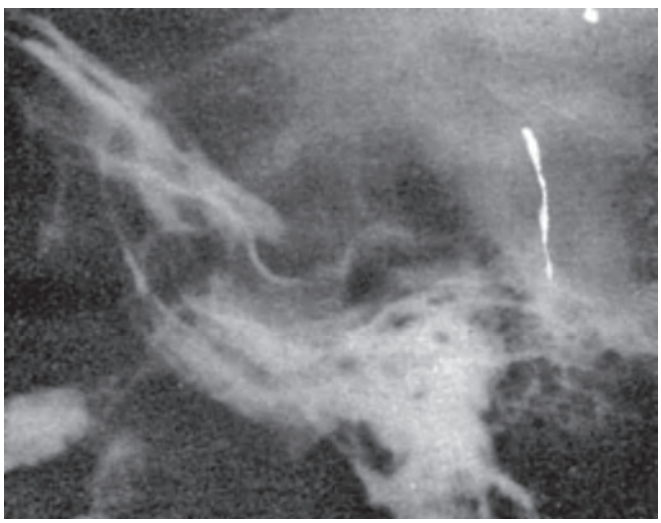

Fig 3: Conchal type of sphenoid sinus

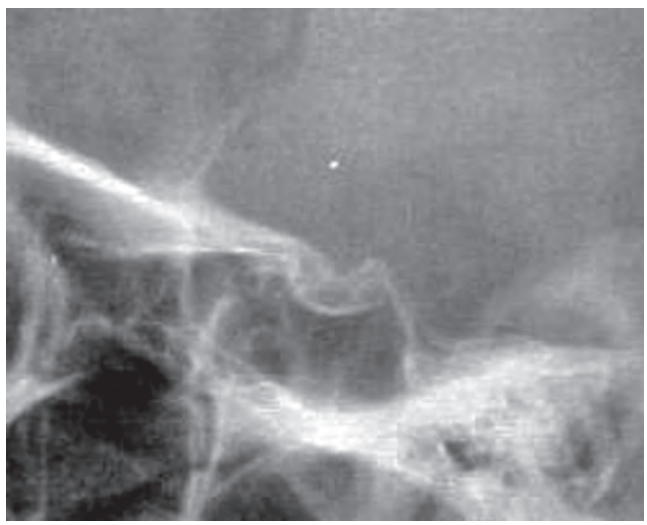

Fig. 5: Sellar type of sphenoid sinus

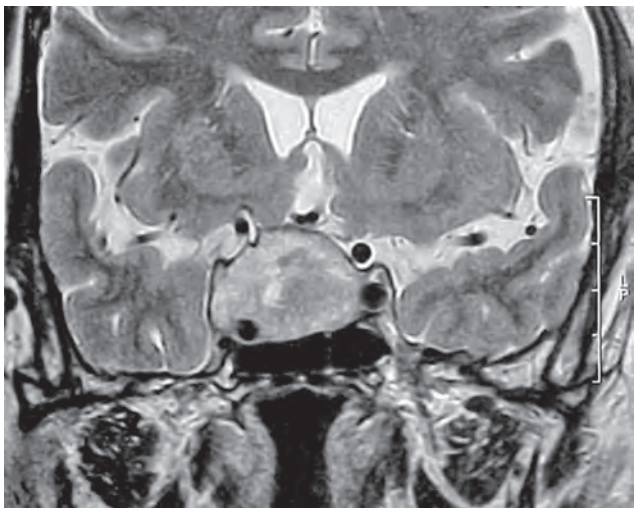

Fig. 6: MRI T2W coronal image showing pituitary adenoma extending up to the carotid artery on the left side and on the right side the adenoma is displacing the carotid inferolaterally and extending beyond it

Optic Chiasm

The position of the optic chiasma varies. Schaeffer[61] found that it lies in the sulcus chiasmaticus in 5% and over the diaphragma sella in 12%. These two positions are termed prefixed. The chiasma lies over the dorsum sella, which is its normal position in 79%. In the post-fixed position the chiasma lies over and behind the dorsum sella and is found in 4% (Fig. 7).

SYMPTOMS AND SIGNS

The symptoms and signs of pituitary tumours depend on the endocrine activity (hyper or hypo), the size of the tumour (micro, macro or invasive) and the effect on the neighbouring structures due to growth and expansion.

Visual manifestations occur when the tumour grows into the cranial cavity and compresses the optic nerve, chiasm or tract. The optic chiasm is situated 8–13 mm above the diaphragma sella and therefore, there should be considerable growth of the tumour before vision is affected.[52] Visual examination, therefore, is not of much use in following-up microadenomas. The anatomy and the pathophysiology of the field defects are described in the chapter on Visual Field Defects in intracranial lesions.

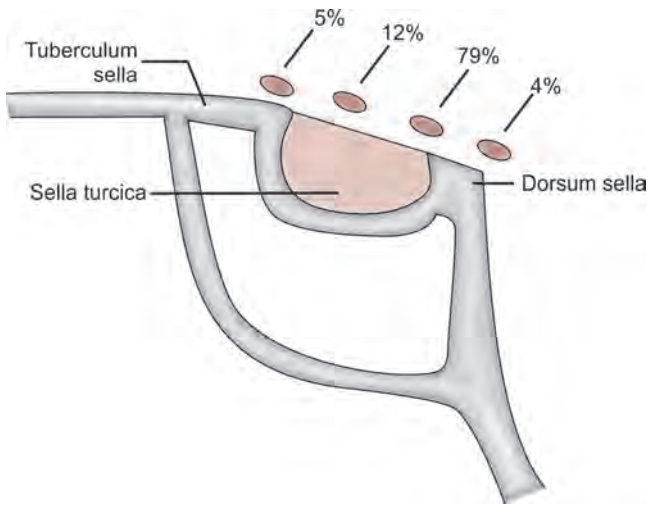

Fig. 7: Diagrammatic representation of positions of the optic chiasm in relation to the pituitary fossa

Pituitary tumours, by compressing the optic apparatus, may produce: (1) Reduction or loss of visual acuity due to compression of fibres subserving central vision; (2) Various types of field defects; (3) Positive visual phenomena in the form of hallucinations.[4]

The visual field defects that commonly occur due to pituitary tumours are: (1) Bitemporal hemianopia either incomplete or complete; (2) Temporal field defect in one eye with loss of vision in the other eye; (3) Central scotoma; (4) Junctional scotoma; (5) Homonymous hemianopia.

The percentage of patients with visual manifestations due to pituitary tumours has come down in recent years in developing countries, although not to that great an extent. In various series, from 1940 to 1974, the percentage of patients with visual involvement ranged from 69 to 96%.[13,46,47,54,56] In later years, the percentage has come down in developed countries, but is still high in developing countries.[8,33,47]

Visual hallucinations may occur in pituitary tumours. They may be formed, consisting of recognisable shapes, or unformed, and may include sparks, flashes or coloured lights.[15,53] Some may have photophobia. Amaurosis fugax, lasting 5–45 minutes, has been reported in a patient with a large pituitary tumour.[18] Foster Kennedy syndrome may be found in large tumours with compression of an optic nerve, producing optic atrophy and the mass of the tumour raising the ICP and producing papilloedema in the other eye.[54,57] This occurred in 5% of cases reported by Ramamurthi.[54]

The visual field defects may develop or worsen during pregnancy and clear after delivery.[21,54,65] This may be due to the compression of the chiasma, secondary to an increase in size of the tumour due to the pregnancy. Sudden visual loss and field defects may occur due to pituitary apoplexy,[31] which at times may be catastrophic, leading to total blindness in both eyes.

Effect on Neighbouring Structures

The tumour, once it grows outside the sella, can compress and invade the neighbouring structures, producing various symptoms and signs.

Headache

Headache is initially caused by stretching of the diaphragma sella, which is innervated by the ophthalmic division of the trigeminal nerve. When the tumour expands further, it may lead to raised ICP and headache as a result of the mass effect itself or by hydrocephalus due to third ventricular obstruction. The latter is, however, rather uncommon.

Ocular Palsies and Ptosis

Paralysis of the extraocular muscles either partial or total may occur; the III nerve being the most commonly involved there may be ptosis and the pupil may or may not be involved.[67] This is due to invasion or compression of the cavernous sinus or due to lateral extension of the tumour. The onset of III nerve palsy may be preceded by retro-ocular pain.[54] Unilateral proptosis may also occur and indicates the side of lateral extension of the tumour. The incidence of ocular palsies reported in the various series ranges from 0% to 25%.[7,8,54,59,64,66]

Fifth Nerve Involvement

The first and second divisions of the trigeminal nerve may be involved. It is essential to test the corneal reflex.[64] Facial hypoaesthesia may be present.[54] Rarely, facial pain resembling trigeminal neuralgia occur.[36]

Hypothalamic Involvement

This occurs when the tumour expands upwards and compresses the hypothalamus. This may further aggravate the existing endocrinological symptoms. There may be disturbances of consciousness.

Hydrocephalus

This can develop either unilaterally or bilaterally, as one or both the foramina of Monro may get obstructed. This may lead to headache, vomiting, papilloedema, lethargy and coma.

Psychological Changes

Dullness, apathy, loss of memory, confusion, confabulation, irrability, delusion and hallucinations may be seen. These may result from pressure effects on the frontal and temporal lobes, the third ventricle and the hypothalamus.

In 1940,[32] Jefferson made an extensive study of extrasellar extensions of pituitary tumours and described the following varieties:

- Hypothalamic extension by massive tumours growing behind a prefixed chiasma
- Extension under the frontal lobes producing personality changes
- Parasellar extension compressing the temporal lobe and producing temporal lobe epilepsy
- Extension into the sphenoid sinus and the nasopharynx. Large tumours may also extend through the tentorial hiatus and grow into the posterior fossa.[9,66]

Endocrine

The endocrine symptoms and signs may be due to hypersecretion or hyposecretion. Those due to hypersecretion[14] will be dealt within the sections on the various hypersecreting tumours. Hyposecretion can be of individual hormones or there could be panhypopituitarism. There may be diabetes insipidus, hypogonadism, hypothyroidism and abnormalities of secretion of ACTH, GH and PRL.

In panhypopituitarism, there is a pale waxy pallor, prominent fine wrinkles around the eyes and mouth, a reduction in axillary and pubic hair, diminished growth of the beard in men with a corresponding diminution in the need to shave and anaemia as a result of diminished function of the bone marrow. There may be truncal obesity.

A reduction in function of the pituitary adrenal axis (Addison's disease) may produce nausea, vomiting, postural hypotension and hyperthermia. Complete failure produces an Addisonian crisis and collapse. Reduction in thyroid function leads to myxoedema with the manifestations of sluggishness, relative inactivity, cold intolerance, dryness of the skin and in severe cases, coma. Gonadal dysfunction produces amenorrhoea, decreased libido and uterine and vaginal atrophy in women. In men, the testes become atrophic; there is reduction in libido and potency, as well as azoospermia.

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147 Prolactinomas

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INTRODUCTION

Prolactinomas are the most common pituitary tumours and account for 25–40% in different series.[29,56,57] Trisomy of chromosome 12 is a non-random chromosomal change in pituitary adenomas, particularly prolactinomas. There is a critical role of HMGA2 over expression in the generation of prolactin-secreting pituitary adenomas in humans.[21] They may be seen as micro or macro tumours. The symptoms and signs are either due to hypersecretion of prolactin or related to the size of the tumour.

SIGNS AND SYMPTOMS

The endocrinopathy produced in women is the galactorrhoea-amenorrhoea syndrome (Forbes-Albright syndrome). There may be various menstrual disorders like amenorrhoea, oligomenorrhoea and irregular periods. About 30% of women have frank galactorrhoea.[7,28] There is also associated infertility. In men, there may be loss of libido, oligospermia and, occasionally, galactorrhoea. The tumours are likely to be larger in men when they seek medical help, as the mild endocrine symptoms may be overlooked, whereas in women, generally, the endocrinopathy predominates and therefore a larger proportion of microadenomas are seen. In men, the signs and symptoms of mass effect generally predominate.[9] The predominance of large prolactinomas in men may also be due to a high frequency of rapidly growing tumours, which are often invasive and frequently bromocriptine resistant.[15] Prolactinoma has been associated with obesity. As opposed to ACTH- and GH-secreting adenomas, the mechanism by which macroprolactinoma causes obesity has not been fully understood. In a subgroup of individuals, obesity and macroprolactinoma may share a common basis, namely decreased dopamine 2 receptor-mediated actions.[16,51]

ENDOCRINOLOGY

Elevations in serum prolactin can occur due to secretion by the tumour itself or from compression of the pituitary stalk or hypothalamus. Hyperprolactinaemia can also occur in several other conditions which include pregnancy, renal failure, hypothyroidism, other sellar and parasellar tumours and ingestion of drugs such as phenothiazines, tricyclic antidepressants and centrally acting antihypertensives.

The normal range of serum of prolactin (PRL) is 10–20 ng/ml. Elevation of the fasting PRL level above 150 ng/ml is strongly suggestive of a prolactinoma, preferably, if observed in two different samples tested at different times. Values between 30–100 ng/ml may be due to other causes which have to be ruled out before a diagnosis of prolactinoma is made.[43] A PRL level higher than 1000 ng/ml is indicative of an invasive adenoma, especially invasion of the cavernous sinus. Pituitary tumour transforming gene (PTTG) abundance is a molecular marker for invasiveness in hormone-secreting pituitary tumours. The ubiquitous and prevalent expression of pituitary adenoma PTTG suggests that PTTG plays a role in pituitary tumourigenesis and invasiveness.[67] Macroprolactinaemia, defined as hyperprolactinaemia with a predominance of, or only the big big prolactin (bbPRL) isoform, is considered idiopathic and poorly symptomatic. PRL adenoma may be associated with macroprolactinaemia.[41]

There is a large body of literature showing that PRL exerts growth-promoting activities in breast cancer and possibly in prostate cancer and prostate hyperplasia. In addition, increasing evidence argues for the involvement of locally produced (autocrine) PRL, perhaps even more than pituitary-secreted (endocrine) PRL, in tumour growth. Because dopamine analogues are unable to inhibit PRL production in extra-pituitary sites, alternative strategies need investigation. To that end, several PRL receptor antagonists have been developed by introducing various mutations into its natural ligands. For all but one of these analogues, the mechanism of action involves a competition with endogenous PRL for receptor binding. Such compounds are thus candidates to counteract the undesired actions of PRL, not only in tumours but also in dopamine-resistant prolactinomas. The most recently developed antagonist, Delta1-9-G129R-hPRL, is the only one that is totally devoid of residual agonistic activity, meaning it acts as a pure antagonist.[24]

Patients with prolactinomas and patients with acromegaly often have heterogeneous adenomas. There is a common group of patients with a pituitary adenoma who secrete PRL and GH unsynchronously. Some of these patients have clinical acromegaly at diagnosis and some patients diagnosed as prolactinomas will develop acromegaly. An annual IGF-I measurement should be used as a screening test.[1]

It is necessary to have a baseline evaluation of T3, T4, TSH, cortisol, LH, FSH, oestrogen and testosterone. This helps in diagnosis, in determining the need for therapy and in the follow-up.

MANAGEMENT

There has been a lot of controversy about the management of prolactinomas, but in the past few decades a reasonable consensus has been reached regarding the indications for their medical and surgical therapy. Medical therapy is now accepted as the first line of treatment in microprolactinomas and macroprolactinomas. Medical treatment with dopaminergic compounds is effective and safe in patients with prolactinoma with onset in childhood, allowing preservation of anterior pituitary function.[11]

The drugs available are: bromocriptine, pergolide, cabergoline and quinagolide (CV 205-502).

Bromocriptine (2 bromo-ergocryptine) is an ergot alkaloid and a dopamine agonist, which was introduced into clinical trials in 1971. It acts by stimulating the dopamine receptors on the lactotroph in the pituitary gland and is considered a potent analogue of dopamine.[23]

Bromocriptine is given in a dosage of 5–20 mg/day in three divided doses. The dosage should be increased gradually, as this reduces the side effects. Indian patients do not tolerate the higher doses recommended in the Western literature.[48] A long acting depot injection of bromocriptine, which is given once in 28 days, has been developed and is in use (Parlodel LAR).[6,30] A slow release oral preparation (Parlodel SRO) is also available and helps in avoiding repeated medication and ensuring patient compliance.[38] In patients who are unable to tolerate the orally administered drug, it can be given per rectum with good effect.[22]

Bromocriptine lowers the PRL level in patients with or without pituitary tumours, significantly reduces the size of a macroprolactinoma and restores normal gonadal function.[6,7,37,58,60] Pronounced visual improvement also occurs due to reduction in the size of the tumour.[50,64] Bromocriptine is effective in restoring normal menstruation in 80% of women, abolishing galactorrhoea in 90%[58] and reversing the hypogonadal state in 80% of men.[64] Serum-prolactin levels revert to normal in 65–75% of patients with macroprolactinomas and there is significant reduction in tumour size in 50–60%.[19,36,39] In microadenomas, there is a reduction in symptoms and in serum PRL levels in over 90%.[3,40,61]

The most conspicuous pathological changes that occur in a prolactinoma after dopamine agonist therapy are a decrease in the size of tumour cells and interstitial and perivascular fibrosis.[31] In some tumours, connective tissue accumulation is pronounced. The cellular response is not uniform and large and small cells are still seen. The large cells contain immunoreactive PRL and express the PRL gene, indicating resistance to dopamine agonists. In the small cells, PRL immunoreactivity and PRL gene expression are decreased, indicating that both PRL synthesis and release are blocked.[31] In some tumours these small cells persist, but are irreversibly suppressed. This may explain why some tumours do not proliferate after dopamine agonist therapy is discontinued.

The side effects of bromocriptine include nausea and vomiting which may occur initially in 30% of patients, although it may be troublesome in only about 10%. Numbness and tingling of the toes and fingers, weakness in the legs and muscle pains may be complained of by some patients. Hypotension may occur. Visual and auditory hallucinations, inflammatory pleuropulmonary reactions or erythromelalgia in the lower extremities may be seen rarely. Orofacial and other dyskinesias may be troublesome.[36] In macroprolactinomas, CSF rhinorrhoea may occur during therapy due to shrinkage of the tumour unblocking a dural rupture in the sellar floor.

Most patients require bromocriptine indefinitely, because discontinuation of therapy may result in rapid expansion of the tumour, especially in macroprolactinomas.[55,63,66] In a small subgroup of patients, the prolactin levels may continue to remain normal after stopping the drug so it is better to discontinue bromocriptine every two years on a trial basis to decide on the need to continue therapy. Some tumours may be resistant to dopamine agonist therapy and may not respond.[2,32] In univariate and multivariate analysis there were no statistically significant differences regarding age, gender, initial dose of BRC, length of BRC use, tumour size, pregnancy during treatment, previous surgery or radiotherapy among patients who persisted with normoprolactinaemia and those who did not. BRC-induced prolactinoma cell alterations are highly controversial so whether the mechanism of PRL normalisation after BRC withdrawal is related to BRC use or whether it is attributable to natural history is a matter for debate.[45]

A special problem arises with regard to continuation of bromocriptine therapy during pregnancy. The tumour, especially a macroadenoma, may expand during pregnancy if the drug is stopped. This occurs in 1% of microadenomas and 5–20% of macroadenomas.[25] There have been no known teratogenic effects of bromocriptine in a large series of pregnancies.[59] Pregnancy is safe in patients with hyperprolactinaemia and can frequently be beneficial, inducing a decrease in prolactin levels.[4,14] It is therefore wise to continue bromocriptine during pregnancy, especially in macroprolactinomas, unless close surveillance is possible with repeated CT examination. If there is rapid growth of the tumour with visual compromise or apoplexy, trans-sphenoidal surgery has to be undertaken, with the attendant risks of major surgery during pregnancy.

Pergolide

This is a synthetic ergoline derivative with highly potent long acting PRL lowering activity. It is administered as

a once daily dose of 50–100 micrograms. In a comparative study between pergolide and bromocriptine, it was found that the effectiveness and side effects of both drugs were the same with the advantage of a once daily administration with pergolide.[8,34]

Cabergoline

This is a long acting dopamine agonist. It is administered orally at a weekly dose of 0.2–3.5 mg which may also be given in divided doses, twice or thrice a week. Good results with regard to reduction in PRL levels and tumour size were obtained. Mild adverse effects were seen in 23% and none required discontinuation of medication.[20] The successful response to cabergoline (CAB) treatment for 6 months was higher in microprolactinoma than in macroprolactinoma patients and was similar in women and men.[9] The prevalence of macroprolactinoma shrinkage after CAB treatment at standard doses for 1–3 years was higher in naive patients (92.3%) than in intolerant (42.1%), resistant (30.3%) and responsive patients (38.4%).[10]

Long-term low dose of the D2 receptor agonist CAB significantly reduced tumour volume and normalised serum PRL levels in a great majority of patients bearing macroprolactinoma. This treatment met with excellent patient compliance. CAB can be used as a first choice drug treatment in macroprolactinomas, as already shown for microprolactinomas and idiopathic hyperprolactinaemia.[12]

CAB may represent, at the moment, the only successful therapy for prolactinoma-bearing patients resistant to bromocriptine and quinagolide, as it normalised PRL levels in 22 of 27 patients, reduced tumour size in 13 of 27 patients and improved clinical symptoms in 25 of 27 patients.[13]

Quinagolide

CV 205-502 is a potent, long acting non-ergot D2-dopamine agonist. It is administered orally in a single daily dose of 75–300 micrograms. Side effects are mild and include mainly headache, nausea and dizziness. The efficacy of this drug in reducing PRL level and tumour size is similar to that of bromocriptine.[53,62,65] It has also been found useful in the treatment of non-functioning gonadotroph or alpha subunit secreting adenomas.[33]

Somatostatin receptor 5 exclusively regulates PRL secretion from prolactinoma cells. Thus, somatostatin analogues with improved selective binding affinity for these receptor subtypes may be effective in the treatment of either GH or PRL secreting adenomas.[54]

Resistance to dopamine agonists occurs in a subset of patients with prolactin-secreting pituitary tumours. The resistance is mediated by loss of pituitary D2 receptors and occurs in both microadenomas and macroadenomas. New drugs, such as antioestrogens, new DA, specific analogues for somatostatin receptor subtypes, chimeric molecules associating dopamine and somatostatin effect and PRL antagonists, are under investigation and can be future alternatives for DA resistance.[42] Invasive prolactinoma resistant to conventional therapy has been reported to have responded to the administration of the alkylating agent, temozolomide.[44]

Surgery

Surgery was the mainstay in the treatment of microprolactinomas and macroprolactinomas till the efficacy of dopamine agonists was established beyond doubt. Earlier surgical series[17,26,29] reported 65–80% endocrine normality in microadenomas and 25–35% in macroadenomas. On long-term follow-up, the endocrine cure rate dropped to 50% in microprolactinomas[49,52] and 15–20% in macroprolactinomas.

The present indications for surgery, either transsphenoidal or transcranial are limited to:

- Patients in whom the tumours are unresponsive to dopamine agonist treatment, especially cystic prolactinomas.
- Patients who are unable to tolerate dopamine agonist medication.
- Patients in whom there is rapid progression of visual loss.
- Patients in whom the tumour grows while on dopamine agonist therapy.
- Pituitary apoplexy.

In India and the developing countries, the cost factor for prolonged treatment and drug compliance should also be taken into account. These are important in patients who do not have easy access to neurosurgical and endocrinological facilities and the facility to have frequent PRL estimations and CT or MR scans. In these countries, the wisest course would be to operate on most of these patients and start dopamine agonist therapy in those in whom the PRL levels do not revert to normal and in those who have persistent symptoms.

The complications from trans-sphenoidal surgery are few and occur in 1–2% of patients. The mortality rate in microadenomas is nil and the overall morbidity is 0.4%.[18,56,57] The complications that may occur are persistent CSF rhinorrhoea which requires reoperation, meningitis, visual deterioration and non-fatal vascular injuries.

The use of a dopamine agonist, prior to surgery, has not been shown to be of much benefit in prolactinomas.[27,32] Long-term administration of a dopamine agonist may lead to tumour fibrosis and cause difficulties in surgical removal.[5,31,35] Surgery for prolactinomas, when indicated, is best performed within twelve months of starting dopamine agonist therapy.

Radiation therapy has a limited role in treatment of resistant prolactinomas and should be reserved for patients in whom medical and surgical therapy has failed.[46] Gamma knife radiosurgery should be a part of the armamentarium for treating refractory prolactinomas. Patients with tumours smaller than 3.0 cm^3 and who are not receiving dopamine agonist at the time of treatment will likely benefit the most.[47]

In summary, the current management of prolactinomas is different from what it was earlier. Surgery is done only for specific indications and the mainstay of treatment is the long-term administration of a dopamine agonist. The criteria for successful management include resolution of mass effect, normalisation of PRL values, resumption of menstruation and successful pregnancy in women, and restoration of potency and spermatogenesis in men. The overall results are much better in microadenomas and in patients who have an initial PRL level of less than 200 ng/ml.

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148 Growth Hormone Secreting Adenomas

Ravi Ramamurthi, Goutham Cugati

Disorders of growth hormone (GH) secretion can result in an excess or shortage. Reduction in GH is significant in children. Gigantism results when hypersecretion occurs before the epiphyses have fused and acromegaly after fusion of the epiphysis.

PATHOGENESIS

The excess secretion of GH can be primary or due to an excess of growth hormone releasing hormone (GHRH) from hypothalamic disease. Primary hypersecretion of GH is most commonly due to a GH secreting adenoma. Of the adenomas that secrete GH, 80% are somatotrophs and the rest are mammosomatotrophs with accompanying hyperprolactinaemia.[50] GH may also be secreted ectopically by malignant tumours of the breast, lungs, pancreas or ovaries. In rare cases, they may arise in the sphenoid sinus from ectopic tissue[65] or may be located in the lateral end of the lesser wing of the sphenoid.[27] Acromegaly due to GH secreting bronchial carcinoid has also been reported.[8]

GHRH increase may occur as a result of involvement of the hypothalamus by hamartoma, glioma, ganglioglioma or choristoma. Ectopic GHRH secretion may occur in carcinoids of the lungs, GI tract and pancreas, carcinoma lung, islet cell tumours, phaeochromocytomas and adrenal adenomas.[50] Acromegaly can occur both sporadically and in the setting of familial conditions, such as multiple endocrine neoplasia type 1 (MEN1), Carney complex (CNC) and isolated familial somatotropinomas (IFS). Each of the familial syndromes is associated with a tumour-suppressor gene, that was initially recognised by an observed loss of heterozygosity on chromosome 11q13 in MEN-1 and IFS, and on chromosome 17q in CNC.[16,24]

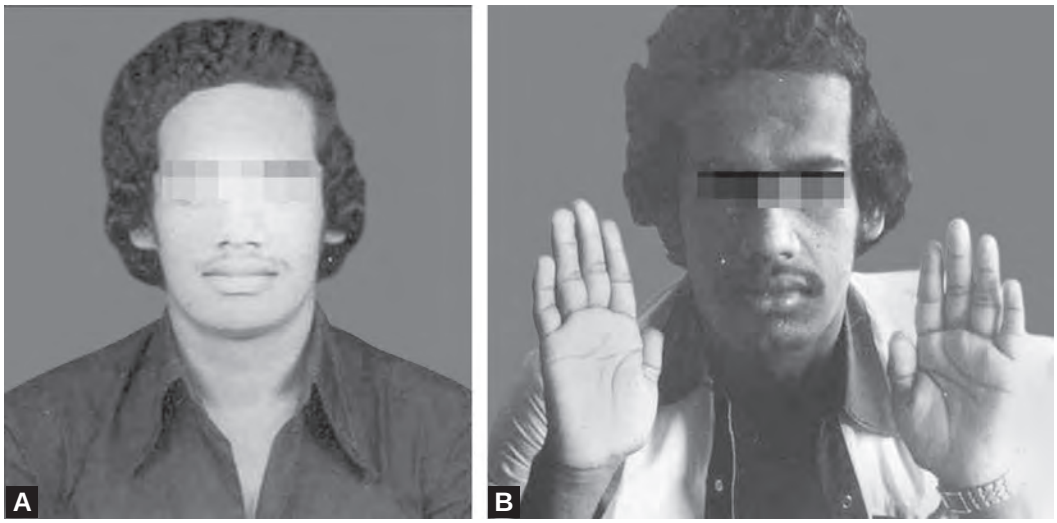
A study in Finland to find a genetic association for pituitary tumourigenesis showed a mutation of the aryl hydrocarbon receptor-interacting protein (AIP) gene located on 11q13 in 16% of patients suffering from acromegaly. The term pituitary adenoma predisposition (PAP) was proposed to describe a person with an AIP germline mutation.[1,33] It is now well documented that cytokines of the gp130 family, such as interleukin-6, that use gp130 as a common signalling protein stimulate not only the proliferation but also the hormone secretion of pituitary cells. It has recently been described that bone morphogenetic protein-4 (BMP-4), a member of the TGF-beta family, has a stimulatory role on lactosomatotropic cells promoting the development of prolactinomas and acromegaly, but it has an inhibitory action on the corticotropic lineage.[26] Familial acromegaly without features of MEN-I, has been found to have the same HLA halotypes.[73]

CLINICAL FEATURES

The mean age of diagnosis of acromegalic patients is 45 years with a slight female predominance.[51] In gigantism, the limbs and long bones uniformly enlarge and there is a proportionate enlargement of the other organs also. These results in increased height, enlargement of hands and feet, prognathism, prominent frontal sinuses and puberty may be delayed, due to the associated hypogonadism, causing a further delay in closure of the epiphyses. The usual age of onset of acromegaly is in the third to fifth decade. Distinctive changes occur in various parts of the body, making the diagnosis easy.[3,71] In the early stages, the changes in appearance may be subtle. Comparison with previous photographs of the patient helps considerably in diagnosis. Figure 1A shows an early picture of a patient with pituitary adenoma and Figure 1B shows the same patient once diagnosed with a GH secreting adenoma.

Headache occurs in 50–75% of patients with acromegaly and gigantism. The mechanism of the headaches is not clear. In large tumours, stretching of the diaphragma sella may be responsible. Intractable headache is often the presenting symptom in many patients in the developing countries, as most people do not seem to be bothered too much by the change in their facial appearance.

Changes take place in the bones and soft tissues, especially of the hands, feet, face and skull. The fingers and the hands thicken and take on a 'spade-like' appearance. Overgrowth of the mandible leads to prognathism and malocclusion of the jaws. In association with an enlarged tongue it may lead to respiratory distress. The frontal bone and sinuses, malar and nasal bones and the soft issues of the face enlarge, leading to a 'beetle brow' appearance and the characteristic facies. The cartilages in the joints, nose, ear and larynx overgrow. The sleep apnoea syndrome reportedly affects between 67% and



Figs 1A and B: (A) Earlier photograph of a patient with pituitary adenoma. (B) Photograph of the same patient after he was diagnosed with a GH secreting adenoma, showing coarsening of facial features and spade-like appearance of the hands

75% of acromegalic patients when investigated prospectively.[9] There is visceromegaly involving the kidneys, lungs, liver, heart, spleen, stomach, intestines and salivary glands.

Skin changes occur in the form of hyperhidrosis and oiliness of the skin with an abnormal odour. Multiple and excessive sebaceous cyst formation may occur. Body hair may be increased. Entrapment of peripheral nerves may occur, leading to entrapment neuropathies, the commonest being the carpal tunnel syndrome. The peripheral neuropathy may also be related to diabetes mellitus. Multiple joint pains leading to severe arthritis may occur, as a result of bony overgrowth and distortion of the articular surfaces. Fibrous thickening of the joint capsule and ligaments may occur, as in the wrist, which leads to carpal tunnel syndrome. Muscle weakness and easy fatigability may occur due to myopathy. The exact mechanism of the myopathy is not known.[49]

SYSTEMIC CHANGES

Cardiac disease is common and the exact mechanism is not known. Hypertension, coronary artery disease, valvular heart disease and compensatory hypertrophy due to generalised splanchnic hypertrophy are some of the proposed aetiological factors. The previously reported prevalence of hypertension in acromegalic patients is around 35%, but varies widely between 18% and 60%.[9] Cardiomegaly occurs and is related to the duration of acromegaly.[47] Concentric hypertrophy (biventricular) is the most common feature of cardiac involvement in acromegaly found in more than two thirds of patients at diagnosis.[81] The Tei index reflects both systolic and diastolic ventricular function. The Tei index may be superior to conventional mitral Doppler indices for identification of LV diastolic dysfunction in patients with acromegaly.[4] Hepatomegaly and renal enlargement may cause hepatic and renal insufficiency. The best characterised respiratory disease is sleep apnoea. Ventilatory dysfunction occurs as a result of bony changes of the thoracic cage, and lung overgrowth.[14]

A retrospective analysis performed on 140 patients with active acromegaly showed colonic cancer in 10, thyroid cancer in 5, breast cancer in 4 and gastric cancer in 2 patients. Hence, cancer screening is necessary in acromegalic patients.[42]

About 50% of acromegalics have impaired glucose tolerance and about 10% have diabetes mellitus. The diabetes is usually reversible after treatment of acromegaly. Menstrual disturbances and galactorrhoea in women and decreased libido and impotence in men may occur, as a result of associated hyperprolactinaemia, pituitary stalk effect or reduction in FSH and LH.

Low serum IGF-I/GH ratio was associated with abnormal glucose tolerance in acromegaly. IGF-I/GH ratio is a useful marker to understand the metabolic status in acromegaly.[25]

Acromegaly is associated with increased mortality. An average reduction in life expectancy of around 10 years and an overall 72% increase in mortality are seen. The excess deaths are due predominantly to cardiovascular, cerebrovascular and respiratory disease.[2,20]

Factors accounting for the increased mortality ratio in acromegaly are:

- Age at the time of diagnosis. Older patients had higher mortality.
- Male gender.
- Disease duration. Exposure to GH excess is associated with increased cardiovascular risk profile due to cardiac hypertrophy, diastolic dysfunction, myocardial valve insufficiency, insulin resistance, dyslipidaemia and obesity. Increased cardiovascular and cerebrovascular mortalities.
- Lowest levels of GH (less than 2–2.5 ng/ml) are associated with the lowest mortality rates.

- IGF-I concentrations were found to be related to mortality.
- Active disease.
- Hypopituitarism, present in 10–40% of patients with acromegaly is associated with increased mortality.
- Increased association of systemic cancers.
- Increased mortality seen in patients having received irradiation.

Studies conducted show that even a biochemical cure rate of 100% will not result in complete normalisation of mortality rates.[9,14,20,31,40,42,67,74]

In a nationwide survey conducted in Finland by Kauppinen-Makelin et al.[40] data did not support IGF-1 as a significant prognostic marker for survival in acromegaly. The increased mortality among patients having received irradiation was possibly linked to more aggressive disease and poorer control of acromegaly in these patients. There was no difference in the severity of disease at the time of diagnosis but men seem to have a poorer outcome. Men seemed to die more often than women from cerebrovascular disease. Malignancy was a common cause of death among women. Breast cancer was the most common cancer death. Older patients were less actively operated and achieved a poorer treatment outcome than younger patients.

The main cause of death in the large retrospective British study on 1362 patients was cardiovascular, accounting for 36.6% of the deaths followed by cancer in 22.7%. In a Spanish study cardiovascular causes resulted in death in 39.4% and cancer in 23.7%.[9,53]

AcroQoL is a disease-generated questionnaire, developed to assess quality-of-life (QoL) in patients with acromegaly. Other quality of life assessment tools include 'Psychological general well-being schedule' (PGWBS), EuroQoL (EQ-5D), HR QoL and the disease-specific signs and symptoms score (SSS). Previous radiotherapy, severe impairment, active disease, ageing, disease duration and joint symptoms have a negative effect on the quality of life.[74,83]

TREATMENT

The modalites available are surgery, medical therapy and radiotherapy.

Surgery

Surgery is the primary mode of treatment in all patients. Transcranial surgery, which was practised in the earlier days, rarely resulted in improvement of either the endocrine status or the persistent headache and, hence, is not recommended. Trans-sphenoidal microsurgery is ideal in microadenomas and macroadenomas.[28,45] Surgery offers the best chance for cure and normalisation of endocrine status. Following surgery, there is rapid clinical improvement, the beneficial changes in the hands being often apparent within a day or two and in the facies within a week. The persistent headache disappears rapidly. Surgery alone seems to be sufficient in about 50–60% of the patients.[37]

The criteria for cure and successful therapy should be: (a) GH level less than 5 ng/ml; (b) GH level less than 2 ng/ml following a glucose tolerance test; (c) normalisation of somatomedin C levels (SM-C); (d) a normal response to LTRH stimulation and (e) clinical improvement.[1] For practical purposes, (a), (b) and (c) are important.[12] The best results are obtained when the tumour is a microadenoma and the basal GH level is less than 40 ng/ml.

Complete removal of the pituitary tumour inevitably included a portion of normal tissue (microsurgical pseudocapsule). Intensive resection of the microsurgical pseudocapsule is essential to accomplish histological total resection of GH-secreting pituitary adenomas for remission of acromegaly.[32,41]

Laws[45] reported on a series of 360 patients and found normalisation of GH in 85% of microadenomas, 65% of diffuse adenomas and 48% of invasive adenomas. GH levels were normal in 82% of patients with initial GH levels below 40 ng/ml and in 35% with a level above 40 ng/ml. Ross and Wilson[61] reported that 54% had GH levels below 5 ng/ml and 74% had levels below 10 ng/ml. On longer follow-up, 79.4% had less than 5 ng/ml and 92.7% less than 10 ng/ml. They also analysed the results in 30 series comprising a total of 1360 patients. Serri et al.[66] found a 14% recurrence rate in macroadenomas on long-term follow-up.

The cure rates for microadenoma after surgery have been found to vary from 37 to 91%. Analysis of the same has shown that the number of neurosurgeons in a centre has an inverse correlation and the years of experience have a direct correlation on the cure rates.[51]

In a study conducted at Wales to evaluate the effectiveness of trans-sphenoidal surgery, 57 of 90 (63%) patients remained in remission after surgery. Seventy-nine per cent of patients with microadenomas but only 56% of patients with macroadenomas achieved remission. Meningitis occurred in 3% of patients, cerebrospinal fluid rhinorrhoea in 7% and permanent diabetes insipidus in 15%.[19]

The complications that occur with trans-sphenodial microsurgery are very low, with the mortality being 0–1%.[44,57,61] The problems that have been seen are transient and permanent DI, excessive bleeding, CSF rhinorrhoea requiring reoperation, hypopituitarism, infection, meningitis, panhypopituitarism and, occasionally, reduction in vision. Tindall et al.[72] have done a multivariate analysis of factors that may be responsible for surgical failure. The important factors are tumour stage, pre-operative GH and SM-C levels.

Medical Treatment

Octreotide and bromocriptine are the drugs that are used as adjuvants to surgery, when the GH levels remain high after surgery or when there is recurrence of tumour. GH

induced cardiomyopathy may not allow safe anaesthesia and surgery and Octreotide and Sandostatin-LAR treatment dramatically improves ejection fraction in these patients.

Somatostatin Analogues (Octreotide, Lanreotide and Pasireotide)

Octreotide is a cyclic octapeptide analogue of somatostatin, and has been used extensively for the treatment of acromegaly. The response of a GH tumour may depend on the number of somatostatin receptors in the tumour cells.[58] It is given subcutaneously in a dose of 300 micrograms per day in three divided doses. The GH levels normalise in about 25–60% of patients.[29,62,37,59] Insulin like growth factor 1 concentrations were found to return to normal in 37–81% of patients. Incremental doses up to 1500 micrograms are useful in a few patients. No additional improvement or escape from control occurred with time. A reduction in the size of the tumour ranging from 14 to 32% has also been recorded. Somatostatin analogues given pre-operatively optimise the cardiovascular, respiratory and metabolic functions and prevent peri-operative morbidity.[15] Sandostatin LAR is long-acting depot octreotide. Long-acting somatostatin analogues are given IM every 2–4 weeks and normalise serum IGF-I levels in about 65% of patients.[10,52]

Octreotide has also been used in the treatment of non-secreting,[17] subunit secreting[39] and TSH secreting[46] tumours with some benefit. It is well tolerated, but reduces gall bladder contractility and leads to the formation of gall stones.[21,29,77] It has beneficial effects in the form of improvement of acromegalic cardiomyopathy, also in patients who did not achieve biochemical control of the disease.[18] Resistance to octreotide was associated with low expression of SST2 mRNA, mutational changes of SSTR2 and SSTR5 and loss of heterozygosis at SSTR5 gene locus.[42] Lanreotide is another somatostatin analogue and a short acting preparation of lanreotide (Somatulin) is given every 7–14 days by intramuscular injection and normalises serum IGF-I levels in about 48% of patients.[22]

Dopamine subtype 2 receptor (D2DR) and Somatostatin receptor (SSTR) 1, 2, 3 and 5 are present in most pituitary adenomas. Currently available somatostatin analogues, like octreotide and lantreotide, show affinity for SSTR 2. New chimeric compounds with SSTR 2, D2DR and SSTR 5 affinity have shown an increased control of secretion and/or proliferation of different types of pituitary adenomas in cell culture.[43,63,69]

Pasireotide (SOM-230) is a small somatostatin (SST) analogue which has high binding affinity to four of the five human SST receptor subtypes and is under clinical trials.[6] It potently suppresses GH, IGF-I and ACTH secretion, indicating potential efficacy in acromegaly and Cushing's disease.[64]

Surgical debulking of the pituitary tumour causing acromegaly improves the effectiveness of somatostatin analogues. Hence, surgery should be done even when there is little chance of complete cure from surgery alone.[38]

A study conducted on 99 patients with somatostatin analogues showed 25% or greater reduction in the size of the tumour in more than 75% of the patients.[13,48]

Dopamine Agonists (Bromocriptine, Quinagolide, and Cabergoline)

Bromocriptine is less effective than octreotide. Reduction of GH levels to below 5 ng/ml has been reported in 5–40% of patients.[5,82] It is useful in mild cases. Larger doses than those used for prolactinomas are necessary and may lead to increased side effects. Cabergoline can be used in patients with adenomas cosecreting GH and prolactin, even in large tumours.[80] There have been reports of patients who continue to be in remission even after stopping cabergoline which was being given long term.[78] Dopamine agonists are generally not effective at reducing the size of pure GH-secreting pituitary tumours.[22]

Growth Hormone Receptor Antagonists

The GH receptor antagonist was first developed in the late 1980s by Chen et al. To enhance the half-life of the GHR antagonist (from 30 minutes to more than 100 hours), several polyethylene glycol (PEG) molecules were added to the molecule. A nine amino acid residue was added to it, which resulted in a molecule PEG-hGH G120K (with pegvisomant as the generic name). Pegvisomant has increased affinity to binding site 1 and inactivates binding site 2, blocking the GH receptor and eliminating the adverse effects of elevated GH levels. Studies on long-term pegvisomant therapy in the treatment of acromegaly showed decrease in serum IGF-I concentrations in all treatment groups, and 82% of patients treated with the highest dose achieved normal serum IGF-I concentrations.[76] Long-term treatment with GHRA improves acromegalic cardiomyopathy.[55]

Various studies showed deranged liver functions in 2–6% of the patients.[70] There have been case reports of tumour enlargement while on pegvisomant, especially those who have not received prior radiotherapy.[23] It has no action on tumour activity and the cost is more (AA). A newer GH receptor antagonist BVT-A is being tried on animal models.[60]

Both GHR antagonists and somatostatin analogues are useful in preventing long-term diabetic complications. Combined treatment using a somatostatin analogue with pegvisomant appears to be an effective and rational approach.[52,75] But the high cost of lifelong medical treatment is to be weighed against the cost of a single surgical procedure.[7]

Radiotherapy

First line treatment remains surgery, but remission rates vary between 50% and 90%. In case of lack of surgical remission or recurrence, somatostatin agonists can be

proposed. However, about 30% of patients are partially or totally resistant to this treatment. The indications for radiotherapy are: non-curative surgery; poor response or inaccessibility to medical treatment; growth restraining of aggressive macroadenomas; comorbidities that contraindicate surgery and surgery refusal.[34]

Conventional radiotherapy and radiosurgery are two radiation treatment modalities that can be proposed to these resistant patients. Reported rates of remission for conventional radiotherapy range between 50% and 60% in patients with acromegaly, with a time to remission delayed by several years, and adverse effects including high rates of hypopituitarism. This treatment could be proposed to patients with aggressive adenomas, in whom surgery does not lead to biochemical control. In contrast, studies on stereotactic radiosurgery reported faster GH hypersecretion decline, and a lower risk of adverse effects. Tumour shrinkage in 90% and biochemical remission in 80% have been reported. However, this latter technique requires a well defined target volume, which limits its indications.[11] In a study conducted on 22 patients treated with PSRS at an institution in USA for persistent acromegaly, who had undergone at least one trans-sphenoidal surgical procedure without biochemical cure, showed 59% of patients attaining normal insulin like growth factor-I levels, without use of any medication after a median of 6.3 years.[54]

Radiation can be delivered in a single sitting by stereotactic radiosurgery or in fractionated form of smaller doses delivered over typically 5–6 weeks in 25–30 treatments.[68] More than 95% of pituitary adenoma patients have either tumour shrinkage or stabilisation after radiosurgery. Biochemical remission is possible in approximately 80% of properly selected patients. The time to endocrine normalisation typically ranges from 1 year to 5 years. Delayed anterior pituitary deficits occur in 20–50% of patients.[56]

Gamma knife (GK) radiosurgery is being accepted as an adjuvant form of treatment. Vik-Mo EO et al. have achieved post-operative normal IGF-I levels in 86%, normal IGF-I and GH levels below 5 mIU/l were found in 38% out of the 61 patients treated with GKS.[79] Jezková J et al. achieved normal IGF-I and GH below 2.5 ng/ml in 51% of the 96 patients treated.[36] In a study conducted by Frédéric Castinetti, et al.[12] on 82 patients who underwent GK radiosurgery, with mean follow-up of more than 4 years, in 40% (17% in remission and 23% under somatostatin agonists) of the patients, the GH and IGF-I concentrations were decreased to so-called "safe" levels. In this, GK was indicated because trans-sphenoidal surgery failed to achieve remission and there was no significant difference in success rate, whether GK was used as primary treatment (16%) or after surgery (21%). The mean margin dose used was 25.8 Gy. Higher success rates were observed with higher margin doses, but with the drawback of more severe complications. Mean time of GH and IGF-I normalisation was 36 months. GK induces far fewer complications than conventional radiotherapy with 82% patients in this series having no side effects after GK versus less than 50% with conventional radiotherapy in most other studies.[30,12] In another series of 64 patients treated with GKS for acromegaly at University of Virginia, biochemical remission occurred in 36% of the patients. GK surgery offers an important treatment modality in patients with secretory adenomas refractory to surgical and medical intervention.[35]

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150 Other Secreting Adenomas of the Pituitary

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INTRODUCTION

Pituitary adenomas secreting thyroid-stimulating hormone (TSH) are rare tumours that cause hyperthyroidism by chronic stimulation of an intrinsically normal thyroid gland.[2] The first case of a TSH-oma diagnosed by measuring TSH with a bioassay was reported in 1960.[15] Hamilton et al.[13] reported the first case of a TSH secreting pituitary adenoma proven by radioimmunoassay.

Older series indicate that these tumours accounted for 0.5–1% of all pituitary adenomas.[20] The overall prevalence is around 1–2 cases per million. However, with the availability of the new generation ultrasensitive immunoradiometric assays for TSH, the prevalence rates have increased in the last decade to 1–2.8%.[22]

Early series reported these tumours to be invasive macroadenomas, but with the advent of the new TSH assays and assays for direct measurement of free thyroid hormones and improved radiological techniques, these tumours can now be identified at the microadenoma stage, permitting better therapeutic outcomes.

PHYSIOLOGY OF THE PITUITARY THYROID AXIS

The production of TSH by the pituitary is under control by TSH-releasing hormone (TRH), produced by the periventricular nucleus of the hypothalamus. TSH is a 280 kd glycoprotein composed of two subunits, the α-and β-subunits, each coded by separate genes. The α-subunit is common to other glycoprotein hormones like LH, FSH and hCG. The β-subunit is unique and confers specificity of action. The binding of TSH to its receptor on the thyroid follicular cells is influenced by the degree of glycosylation of the α and β-subunits. TSH secreting tumours secrete heterogeneous isoforms of TSH which differ in the extent of oligosaccharide residues and the degree of sialylation and fucosylation. Tumours tend to have TSH isoforms with increased fucosylation and decreased or normal sialylation. Other studies have found an increase in the ratio of biologic to immunologic activity in TSH-omas. A disproportionate release of the bioactive hormone can explain why most patients with TSH secreting tumours have a hyperthyroidism with normal TSH levels.[3,4,21]

TSH causes enlargement of the thyroid follicular cells and promotes synthesis of thyroxine (T4), which gets deiodinated in the periphery to triiodothyronine (T3). T4 and T3 have negative feedback effects on both the production and the release of hypothalamic TRH and pituitary TSH.

PATHOLOGY

The thyrotroph cells account for about 5% of the functional anterior pituitary cells and are the cells of origin of a TSH-oma. Most TSH-omas are benign, and malignant transformation is extremely uncommon.[23,24] These are invasive macroadenomas with a fibrous consistency even in the absence of prior surgery or radiotherapy.

The adenomatous cells are mostly chromophobic and monomorphous.[5] Some poorly differentiated adenomas show pleomorphic fusiform cells with sparse endoplasmic reticulum, small secretory granules with abnormal mitotic figures which do not always represent malignancy. The only hallmark of a pituitary carcinoma is the presence of distant metastasis. Immunohistochemistry is positive for TSH-B and the α-subunit in 20–75% of the cells.[25] Although most TSH secreting tumours produce only TSH, about 30% also show co-secretion of other hormones, mainly GH (16%) and prolactin (10.4%), as they are derived from a common transcription factor Pit-1.[5,14] Occasionally, FSH and LH co-secretion are seen (1.4%) and very few cases of ACTH co-secretion have been documented. Positive immunostaining, however, does not always correlate with hormone secretion *in vivo* and a tumour should be classified as a TSH secreting adenoma only if there is evidence of inappropriate excess of the pituitary-thyroid axis.

CLINICAL PRESENTATION

TSH-omas occur with equal frequency in males and females and are more common in the third to sixth decade of life, although cases have also been reported in children as young as 11 years old.[13]

Patients with TSH-omas present with symptoms and signs of either hormone hypersecretion or mass effect from an expanding sellar lesion. Goitre is the rule and is seen in more than 90% of patients, even in those who have had a partial thyroidectomy. Autonomous thyroid

nodules and multinodular goitres have been reported. This occurs because of the sustained TSH secretion over many years. Most patients have a history of long standing thyroid dysfunction with typical features of hyperthyroidism, including heat intolerance, tremors, weight loss, palpitation and diarrhoea. The severity of symptoms varies but most have mild degrees of hyperthyroidism in relation to their hormone levels, probably due to the slow development of the hyperthyroidism, leading to compensatory mechanisms like receptor down regulation. Severe features, like exophthalmos, cardiac failure and periodic paralysis, are very rare.[2,19] Often, many patients are mistakenly diagnosed as Graves' disease and have had ablative thyroid treatment in the form of thyroidectomy or radioiodine therapy. An average delay of 8–9 years has been reported before these tumours are diagnosed.[7,19] Thyroid ablative treatment eliminates the normal negative feedback by the thyroid hormone on thyrotrophs and alters the natural history of the disease. TSH-omas are usually large with 88% being macroadenomas,[7] 60% of the tumours are locally invasive. Most patients seek medical attention because of mass effects of the expanding sellar lesion. Headaches, visual field defects and cavernous sinus involvement are common. In fact, previous thyroid ablative treatment worsens the invasiveness of the tumour. Symptoms of hypopituitarism occur due to involvement of the other pituitary cells by the tumour. Signs of acromegaly, galactorrhoea, menstrual disorders and reduced libido are seen in both sexes. Rarely, TSH-omas have been described in families with MEN-1 and McCune-Albright syndrome.[12,18,26] An ectopic TSH producing tumour in the pharyngeal hypophysis has been described.[10]

EVALUATION

High levels of T3 and T4 in the presence of detectable levels of TSH are characteristically seen in patients with TSH secreting tumours or pituitary resistance to thyroid hormones. However, more common conditions which can cause similar biochemical profiles need to be ruled out first. Increase in levels of TSH transport proteins (thyroxine binding globulin or transthyretin or albumin) caused by drugs or estrogens; familial dysalbuminaemia; drugs, like amiodarone and acute psychiatric disorders, can cause elevation in total T4 levels. Heterophilic antibodies to T4 and T3 can cause spurious elevations of these hormones. These errors are obviated by measuring the free T4 and T3 levels, which are essentially normal in the above conditions but increased in central hyperthyroidism and resistance to thyroid hormones (RTH). Once increased levels of free thyroid hormones are documented in the presence of detectable TSH levels (i.e. central hyperthyroidism) by the immunoradiometric assays, the next step is to distinguish a TSH-oma from RTH. The α-subunit levels are elevated in two thirds of patients with a TSH-oma. Calculating the molar ratio of α-subunit to TSH, improves the sensitivity of detection to 80%. A ratio of more than 1 indicates a TSH-oma, although similar values have been observed in menopausal women.[16] Patients with primary hyperthyroidism and those with RTH have ratios less than 1. Measures of peripheral thyroid hormone action, like SHBG (sex-hormone binding globulin), cholesterol, angiotensin converting enzyme and carboxy terminal cross-linked telopeptide of type 1 collagen (1 CTP), can be used to distinguish a TSH-oma from RTH. Levels are elevated in TSH secreting tumours but normal in RTH states.[3]

DYNAMIC TESTING

Several stimulatory and inhibitory tests have been described to evaluate a TSH-oma. Although none of them have clear cut diagnostic values, a combination of the tests helps to improve the diagnostic yield. The stimulatory test includes the TRH induced TSH secretion, which is absent or blunted in a majority of patients with TSH-omas. This test has a good sensitivity and excellent specificity in patients with an intact thyroid but was less sensitive in patients who had a prior thyroidectomy. Patients with resistance to thyroid hormones typically have a robust response of TSH to TRH. The exact cause for the relative autonomy of TSH secreting tumours in terms of absence or functional impairment of the TRH receptor has not yet been demonstrated and remains unexplained. The inhibitory test includes the T3 suppression test, which checks for the degree of TSH suppression following T3 administration. Both basal and TRH stimulated TSH levels are not suppressed, following T3 administration in patients with TSH-omas. This test is especially useful to diagnose a TSH-oma in patients who have undergone a prior thyroid ablation and to predict long-term cure in patients with TSH secreting tumours.[7]

In summary, the combination of TRH test, α-subunit and α-subunit to TSH ratio was diagnostic in the majority of untreated patients. In patients with an intact thyroid the best combined sensitivity and specificity were seen with the TRH test (71% and 96%) and α-subunit (75% and 90%). For patients with previous thyroid treatment, the best combined sensitivity and specificity was seen in the α-subunit (90% and 82%) and the α-subunit/TSH ratio (90% and 73%). In addition, IGF-1 and prolactin levels should be measured in all patients.

RADIOLOGICAL DIAGNOSIS

The advent of MRI has made the diagnosis of pituitary tumours easier and demonstrates the extent of the tumour with more accuracy. Gadolinium contrast scans are an excellent tool to demonstrate microadenomas, which now account for 13% of all reported cases. But the presence of a microadenoma in a patient with central hyperthyroidism should always be tested by immunohistochemical analysis, before labelling it as a TSH-oma. Nuclear scintigraphy using ^{111}I labelled octreotide are more useful in ectopic tumours. Petrosal sinus sampling has also been described but reports are still preliminary.

THERAPY

Surgery is recommended as the first line of management but the cure rates are around 40% in most series.[7,20,22] Most of these tumours are hard and have a fibrous consistency and are locally invasive, making complete excision difficult. Two deaths were reported in the early post-operative period in the NIH series. These patients had macroadenomas and had a long delay in diagnosis. Complications include transient or permanent diabetes insipidus, syndrome of inappropriate secretion of antidiuretic hormone and permanent central hypothyroidism. Radiotherapy is mainly employed as an adjunctive therapy to surgery and not used as a primary modality of therapy. As most TSH-omas are macroadenomas that extend into the suprasellar cistern, they typically do not meet the criteria for safe use of stereotactic radiosurgery.

Medical Treatment

Antithyroid drugs should not be used as a treatment for patients with TSH-omas, as they increase the tumour growth and invasiveness. Their probable role is only in the preparation of the patient prior to neurosurgery. Beta blockers can be given to control the hyperthyroid symptoms. Somatostatin analogues, like octreotide or lanreotide, are the current drugs of choice in patients with TSH secreting adenomas.[1,8,9,11] Somatostatin receptors are expressed on these tumours and stimulation of these receptors by analogues reduces TSH secretion.[6] Tumour shrinkage occurs in 50% and vision improvement in 75% of patients treated with octreotide. A reduction in α-subunit, T3 and T4 confirms efficacy of the drug. It takes about 2 weeks for the full effects of the drug to occur. Normal TSH dynamics is restored and the suppression of TSH secretion with octreotide with consequent central hypothyroidism requires thyroxine supplementation. Tachyphylaxis is seen in about 25% patients necessitating dose increase. Patients need to be monitored for side effects like cholelithiasis and glucose intolerance. Lanreotide, the new long acting formulation of somatostatin is a better alternative, as it can be given once or twice a month. These new analogues may have a role in the long-term treatment of patients with TSH-oma, who have not been cured by surgery.[17] Thus no single therapy is expected to be curative for a TSH-oma. A combination of the above modalities is frequently required in a majority of patients to achieve clinical remission and cure.

Criteria of Cure

Cure is not defined by mere euthyroidism and absence of visible tumour on imaging. The most sensitive and specific test to document cure remains the complete inhibition of both basal and TRH stimulated TSH secretion, following T3 administration. Other tests include an undetectable TSH one week after surgery and a normalisation of the α-subunit/TSH ratio.[7,19,21]

Recurrence rates, although not available, seem to be low at least for a year following documenting a cure. Patients should be followed up at 3–6 monthly intervals in the first year and then every year. Pituitary imaging needs to be performed every 2–3 years.

CONCLUSION

TSH secreting adenomas, the rarest of functional pituitary tumours, are now being increasingly detected due to the advent of ultrasensitive TSH and free hormone assays. Increased awareness and early recognition of these tumours will prevent inappropriate treatment which can increase tumour invasiveness. Biochemical evaluation with measurement of thyroid hormones, TSH, α-subunit and dynamic stimulation and suppression tests are important to plan and assess therapeutic outcomes. Trans-sphenoidal surgery is the initial therapy of choice, but with cure rates of around 40%. Radiotherapy and medical management with long acting somatostatin analogues are adjunctive to control hormone hypersecretion tumour growth and cure in the long-term.

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151 Non-Functioning Pituitary Adenomas

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INTRODUCTION

Pituitary tumours are defined by the characteristic clinical syndromes that accompany tumour hormone overproduction. Approximately 25–30% of patients who present with pituitary adenomas have no clinical evidence of hormone hypersecretion; such tumours are classified as non-functioning adenomas.[18,23,36,37] The term "clinically non-functioning" appears to be preferable to "non-secreting" because many of them do secrete, but do not produce a recognisable clinical syndrome or do not elevate above normal the serum concentration of the secreted hormone. Any kind of pituitary adenoma can be clinically non-functioning, but some types are clinically non-functioning usually and other types are clinically non-functioning unusually. Gonadotroph and thyrotroph adenomas are examples of usually clinically non-functioning. At the other end of the spectrum are somatotroph and corticotroph adenomas, which usually produce recognisable clinical syndromes, acromegaly and Cushing's syndrome, respectively.[44] Several cases of each have been reported in which the adenomas were identified immunocytochemically, but the patient did not, even on re-examination, have the usual clinical syndrome or even elevated serum concentration of growth hormone or ACTH.[14,22,25,32] Silent corticotroph and somatotroph adenomas may be detected in up to 8.1% and 2.7% of tumours, respectively.[19] To say that a pituitary adenoma is clinically non-functioning, therefore, is to say that the cell of origin is not readily apparent from the clinical presentation, not that it cannot be determined. In fact, the cell of origin can usually be determined if one looks carefully.[44]

PATHOLOGY

Pituitary adenomas have long been classified according to their tinctorial affinity for acidic or basic dyes into acidophilic, basophilic or chromophobic adenomas. Acidophil adenomas were traditionally associated with acromegaly, basophil adenomas with Cushing's syndrome and chromophobe adenomas were thought to be non-functioning.[31] However, it has become obvious that this classification is inadequate to cover the diverse clinicopathologic spectrum of pituitary adenomas. Horavth and Kovacs developed a useful system of classifying pituitary adenomas that is based on the immunocytological findings and electron microscopy. It attempts to identify the cell type from which the tumour is derived and aims to correlate the morphological findings with the clinical history, immunohistochemistry, biological behaviour and endocrine activity.[47]

CLASSIFICATION OF PITUITARY ADENOMAS[12,42]

- Prolactin cell adenomas
  - Sparsely granulated
  - Densely granulated
- Growth hormone cell adenomas
  - Sparsely granulated
  - Densely granulated
- Mixed prolactin cell-growth hormone cell adenomas
- Acidophilic stem cell adenomas
- Mammosomatotroph cell adenomas
- Corticotroph cell adenomas
  - Sparsely granulated
  - Densely granulated
- Gonadotroph cell adenomas
- Thyrotroph cell adenomas
- Plurihormonal adenomas
- Null cell adenomas
- Oncocytomas.

Ultrastructural studies allowed classification of non-functioning adenomas as null cell adenomas and oncocytomas.[40] Null cell adenomas are composed of polyhedral cells, possess irregular nuclei and poorly developed cytoplasm containing short scattered rough endoplasmic reticulum profiles, a moderately developed Golgi apparatus and rod-shaped mitochondria. Secretory granules are sparse and spherical and form a single row along the plasma membrane without evidence of granule extrusion. Null cell adenomas contain a varying number of cells (< 75%) exhibiting oncocytic changes.[8] Oncocytomas appear to be a variant of null cell adenomas with the appearance and prominence of most cytoplasmic components being similar to those in null cell adenomas. The single characteristic feature is the striking abundance of mitochondria, some of them curiously shaped, filling a large part of the cytoplasm of more than 75% of adenoma cells.[8] Null cell adenomas and oncocytomas are characterized by lack of immunocytochemical markers and clinically

do not show symptoms and signs of excess hormone production.[41] These are slow growing macroadenomas occurring in older age group individuals and locally invasive.

A pituitary adenoma can be differentiated from the normal pituitary gland both in gross and microscopic appearance. Grossly a normal pituitary gland is firm in consistency and an adenoma is soft to semi-solid. Microscopically, in a pituitary adenoma, the cells are monomorphous, but they lack acinar arrangement whereas, in a normal pituitary gland, the cells are of different size, shape, types and are arranged in an acinar pattern. The loss of acinar pattern is one of the pathological hallmarks of pituitary adenoma.[46]

IMMUNOHISTOCHEMISTRY

With the advent of immunohistochemical techniques and the use of specific antisera we can identify the hormones stored within the cells. All the hormones have been found in non-functioning adenomas by immunohistochemistry. Apart from immunohistochemistry, the secretory activity of non-functioning adenomas have been established by other *in vitro* studies like tissue culture,[3,28,45,55] analysis of pituitary hormone gene expression[15] and the reverse haemolytic plaque assay.[54]

Immunocytochemical data suggest that many of these non-functioning tumours produce subunits of glycoprotein hormones, which are endocrinologically inactive. The glycoprotein hormones include follicle stimulating hormone (FSH), luteinizing hormone (LH), thyroid-stimulating hormone (TSH) and the placental hormone chorionic gonadotropin (CG). They contain two subunits: (1) The alpha-subunit, which is common to each of them, and (2) A beta-subunit (β-FSH, β-LH, β-TSH and β-CG), which confers biological and immunological specificity.[4] Several investigators have shown that many clinically non-functioning pituitary tumours are unrecognised prolactinomas or gonadotroph adenomas.[43,50] Immunoperoxidase staining using specific antibodies has shown that chromophobe adenomas less commonly show staining for ACTH despite the clinical absence of Cushing's syndrome. Horvath et al. found that 4.3% of tumours staining for ACTH were clinically silent[14] and small numbers of "silent" ACTH-secreting adenomas have been found in several other series.[13,50]

In the series by Black et al, of 160 patients referred for pituitary surgery, 37 (23%) had no evidence of excess hormone secretion on pre-operative endocrine evaluation but on immunocytochemical staining of these tumours one or more of pituitary hormones was detected in 73% of cases. The α- and β-subunits were detected most frequently, being found in 68% of cases; 27% had staining for one or more β-subunits and 37.9% had staining for both α and β-subunits. The incidence was β-FSH in 58%, β-LH in 47%, β-TSH in 33% and α-subunit in 42%. Staining for multiple glycoprotein hormones was common in 52% and mixed glycoprotein hormones and prolactin cell types were found in 16% of cases.[4] Similarly, Jameson et al. reported production of one or more pituitary hormones in 93% of non-functioning tumours on immunocytochemical studies and noted expression of one or more of the anterior pituitary hormone genes in 86% of the patients with clinically classified non-functioning adenomas.[15] Asa et al. studied 99 non-functioning adenomas (41 null cell adenomas and 58 oncocytomas) *in vitro* and found that 96/99 tumours released LH, FSH and/or alpha-subunit of glycoprotein hormones and only three tumours released no detectable hormones.[2]

Apart from immunohistochemistry, electron microscopy of cells of non-functioning tumours appears to contain secretory granules despite their apparent lack of assayable hormone product. Although secretion of intact gonadotropins or glycoprotein subunits can be demonstrated in the majority of non-functioning pituitary adenomas, clinical and serum studies in these patients typically fail to demonstrate evidence of hormone hypersecretion. The plausible explanations for this may be that: (1) The specific radioimmunoassay (RIA) for glycoprotein subunits are less available and as the sensitivity and specificity of glycoprotein subunit RIA increases, detection becomes more frequent, (2) Low levels of hormone production, (3) Abnormalities may occur in cellular processing of these hormones and despite normal biosynthesis active secretion does not take place, (4) To be endocrinologically active the β-subunit must be combined with the alpha-subunit and these tumours may therefore be producing uncombined subunits that are hormonally inactive.[4,23]

The cellular origin of non-functioning pituitary adenomas has yet not been established, but according to hypothesis by Asa et al. null cell adenomas and their oncocytic counterparts may represent neoplasms derived from uncommitted or committed precursor cells that can undergo differentiation towards several cell lines.[2] Kontogeorgoes has reported a case with multidirectional differentiation of endocrinologically inactive null cells into well differentiated somatotrophs, lactotrophs and cells of glycoprotein hormone cell line.[24]

CLINICAL PROFILE

Patients with non-functioning tumours lack a characteristic clinical syndrome or serum tumour hormone marker. They present with symptoms related to tumour mass effect such as headache, visual loss or symptoms of hypopituitarism. Visual manifestations either in the form of impairment of visual fields or loss of acuity are the most common presenting symptoms reported to be seen in as many as 72% by Ebersold et al.[10] In its most recognisable form, vision is impaired first in the upper outer quadrants of the visual fields (bilateral superior temporal quadrantanopia), which may progress to involve the entire temporal fields bilaterally (bitemporal haemianopia). The visual field impairment may be asymmetric and, when the chiasmal compression is severe, central visual acuity is also affected. The visual

deficit may be so gradual that many patients are not aware of their visual loss, until it is demonstrated on a routine eye examination. The mechanism responsible for visual field impairment may be direct mechanical compression of the optic nerve or chiasm, ischaemia or a combination of the two.[35,43]

Headache, seen in as many as 36%[10] of patients, may be due to stretching of the diaphragma sellae, elevation of intracranial pressure due to obstructive hydrocephalus or an excruciating type of headache due to pituitary apoplexy.

Paralysis/paresis of extraocular muscles may be caused by cavernous sinus extension of the adenoma, although it is a relatively rare presentation.[19] Diplopia with sudden severe headache may suggest apoplexy. Rarer presentations may include epileptic seizures and CSF rhinorrhoea.

The symptoms due to pituitary hormonal dysfunction are not the one for which the patient seeks medical attention but, according to Ebersold et al.[10] 61% of patients had pre-operative hypopituitarism. LH deficiency is the most common and results in reduced testosterone secretion, resulting in decreased energy and libido and in premenopausal women results in amenorrhoea. Symptoms of hypothyroidism and hypoadrenalism may also occur.

In our experience also, visual impairment was the most common symptom seen in 74/108 (68.5%), followed by headache in 50/108 (64.2%). Endocrinopathy was noted in a lesser number of cases 24/108 (22.2%), as compared to the results observed by Ebersold et al. and pituitary apoplexy in 6/108 (5.5%) cases.

ENDOCRINE DIAGNOSIS

The most common endocrinological abnormality observed in non-functioning pituitary macroadenomas is hypopituitarism clinically manifested as gonadal hypofunction.

Endocrine tests are divided into tests that provide assessment of pituitary hormone reserve and tests that evaluate patients who have or are suspected to have an endocrinopathy due to functioning pituitary tumours. In general, tests that provide information about the pituitary hormone reserve should be done in all patients. Baseline serum levels of prolactin, growth hormone, T3, T4, TSH, cortisol, FSH and LH should be ascertained.

The serum prolactin levels may be elevated because of stalk effect. A large sellar suprasellar tumour with prolactin levels less than 200 ng/ml is more likely to be a non-functioning adenoma than a prolactinoma.

The serum levels of TSH, FSH and LH may be elevated, as a majority of pituitary adenomas that are clinically non-functioning are gonadotroph adenomas and a significant minority are thyrotroph adenomas. Some large apparently non-functioning adenomas have solely been associated with the production of alpha-subunit.

GH and cortisol levels will usually be normal but, if on provocative testing, the levels of these hormones fail to rise, it is suggestive of hypofunctioning of the pituitary.

IMAGING

MRI is currently the best technique for imaging the pituitary gland, due to its superior resolution and ability to demonstrate the optic chiasm. In addition, MRI is able to demonstrate blood, so an aneurysm can be distinguished from other intrasellar lesions and haemorrhage into pituitary adenomas.

A pituitary microadenoma is usually hypointense compared with the normal gland on T1W images. After contrast injection, the tumour typically does not enhance to the same extent as the normal pituitary gland and thus stands out as an area of relative hypointensity. Focal hypointensity within the pituitary is the most reliable indicator of a microadenoma. Important secondary signs of microadenoma include asymmetric upwards convexity of the gland surface, deviation of the infundibulum and focal erosion of the sellar floor. The preferred imaging planes are coronal and sagittal.

A pituitary macroadenoma is generally isointense to the normal gland and brain parenchyma, unless there are cystic and haemorrhagic components. Homogeneous contrast enhancement permits clear demarcation of the tumour from normal suprasellar structures. MRI is ideal for demonstrating extension of the tumour to the cavernous sinus, optic chiasm, third ventricle and hypothalamus. Upwards extension of a pituitary adenoma through the diaphragma sella accounts for one third to one-half of all suprasella masses in adults (Figs 1A to C).

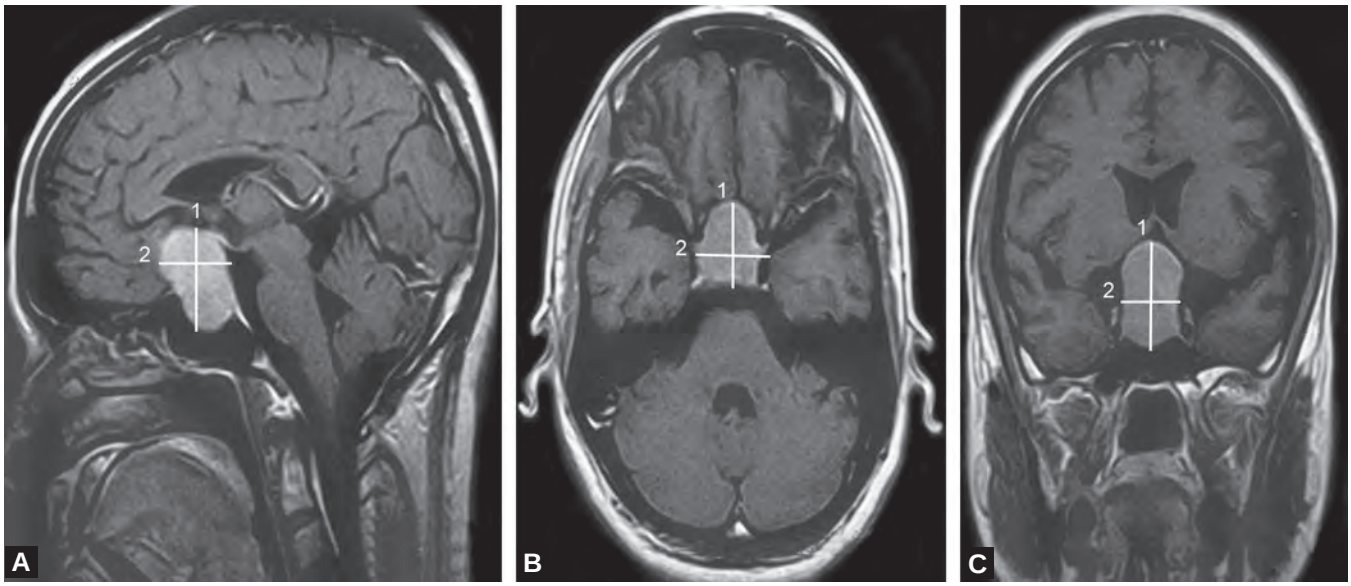
Pituitary adenomas with suprasellar extension typically have a "figure of eight" appearance and the mass is indistinguishable from the pituitary gland.[16]

CT scan with or without contrast may be done when the patient is unable to get an MRI. Typically a pituitary adenoma appears as well circumscribed, isodense to brain and with homogeneous contrast enhancement. Regions of necrosis or cyst formation in the tumour produce internal areas of low density. Microadenomas are usually less dense than the normal pituitary gland. CT scan can demonstrate adjacent bone erosion and extension of tumour beyond the confines of the sella.

Plain X-ray of the skull has limited value in the diagnostic evaluation of patients with sellar/parasellar lesions. It reveals: (1) An enlargement of the sella also known as ballooning of the sella; (2) Undercutting of the anterior clinoid process in which the processes are thinned and sharp; (3) Erosion of the sellar floor; (4) Unequal downwards displacement of the sellar floor called as double floor; (5) Thinning and erosion of the dorsum sella; (6) Degree of pneumatisation of the sphenoid sinus as presellar, sellar or conchal and (7) Supra/intra sellar calcification.

TREATMENT

The goal of therapy is directed towards reduction of tumour mass, rather than treatment of hypersecretory syndrome.[19] The extraordinary success of dopamine agonists in reducing the size as well as secretion by



Figs 1A to C: T1W image showing an enhancing pituitary macroadenoma with suprasellar extension in sagittal, axial and coronal views

lactotroph adenomas has prompted attempts to find a pharmacologic treatment for gonadotroph and thyrotroph adenomas. These attempts have so far been successful in reducing excessive secretion by the adenoma than in reducing its size. The presence of somatostatin receptors on the cell membrane of clinically non-functioning and alpha-subunit secreting pituitary macroadenomas, provides the possibility of treating these tumours with octreotide.[26,28,34] De Bruin et al. attempted to correlate the presence of somatostatin receptors in the adenomas and the outcome of octreotide treatment as measured by tumour size, improvement in visual field defects and hormonal response. High dose (1200 μg sc daily) octreotide treatment was given to four subjects, 3 of whom were somatostatin receptor (SSR) positive. Improvement of visual field defect was observed in 3 of 4 patients (including SSR negative), although no computed tomographic assessed tumour size reduction was found. Two of the four patients showed small but significant reduction in serum FSH concentrations to 83% and 93% of initial values following treatment.[9] Inhibition of gonadotrophin and/or alpha-subunit secretion by somatostatin and octreotide has also been demonstrated, both *in vitro* and *in vivo*.[9,20,39,53] Tumour shrinkage (> 20%) has been reported in 1of 3 alpha-subunit secreting pituitary adenomas[20] and in 1 of 8 non-functioning adenomas,[11] but in none out of 4[9] and none out of 17,[29] patients who were treated with 300–1200 μg of octreotide daily for periods up to 12 months. De Bruin et al. also concluded that bromocriptine was a more effective inhibitor of hormone or subunit release than octreotide in cell culture.[9] Bromocriptine has also been reported to cause reduction in tumour size.[1,21,27,52] Johnston et al. reported a case of recurrent non-functioning adenoma (14 years post-surgery and radiation) put on 20 mg bromocriptine daily for 25 months; the intrasellar tumour recurrence had diminished in size and suprasellar extension had almost disappeared.[17] Further studies with the aim to reduce tumour size in patients with clinically non-functioning adenomas could include treatment with dopamine agonists or a combination of octreotide and dopamine agonists.[27,28]

SURGERY

Trans-sphenoidal surgery is currently accepted as the procedure of choice for the initial management of most clinically non-functioning adenomas. The trans-sphenoidal approach is preferable to transcranial approaches, as it helps to preserve normal pituitary function and allows recovery of visual function.[5,7,30,33] The immediate indication for surgery is visual field loss and with decompression of the optic chiasm, improvement in visual field abnormalities is seen in the majority of patients. The principle of treatment differs between functioning and non-functioning adenomas. The primary goal of surgery for non-functioning adenomas is gross total or subtotal removal of the tumour, with preservation of normal pituitary function. Secreting adenomas must be removed completely for an endocrinological cure, although prolactinomas or growth hormone producing adenomas can be treated with bromocriptine or octreotide.[38]

The trans-sphenoidal approach is employed at our institute and is through the endonasal route, using the microscope from the beginning. After intubation, the oropharyngeal airway is packed. The patient is positioned supine with the head elevated by 30 degrees with the neck flexed and the head turned contralaterally by about 20 degrees so that the nasal septum is parallel to the visual axis (Fig. 2).

Use of C-arm fluoroscope is usually avoided. The choice of nostril used is decided on the position of the nasal septum, size of the middle turbinate and lateral extension of tumour. The nostril with more space and contralateral to the side of lateral extension of the

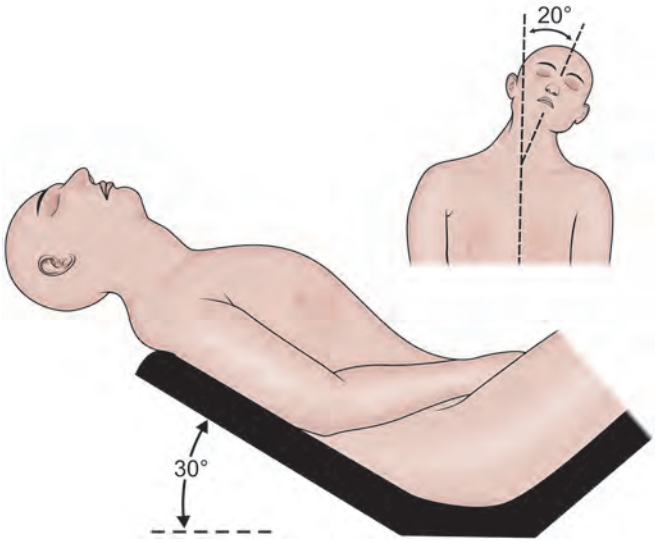


Fig. 2: Position of the patient for trans-sphenoidal approach to pituitary adenomas

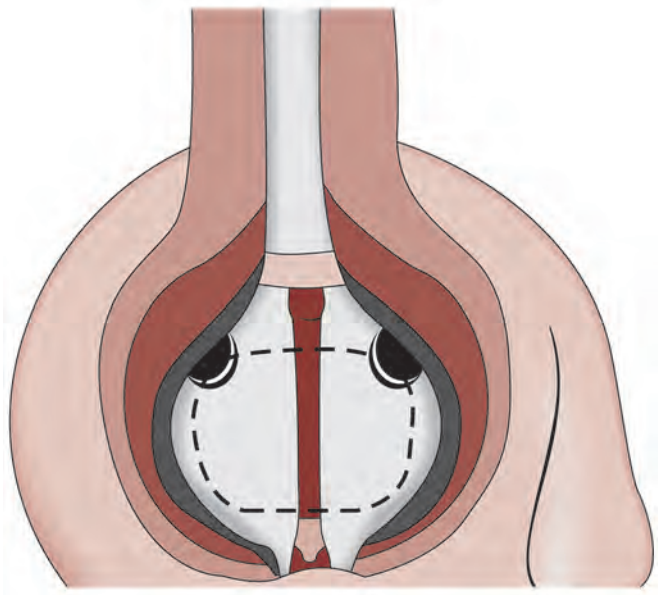


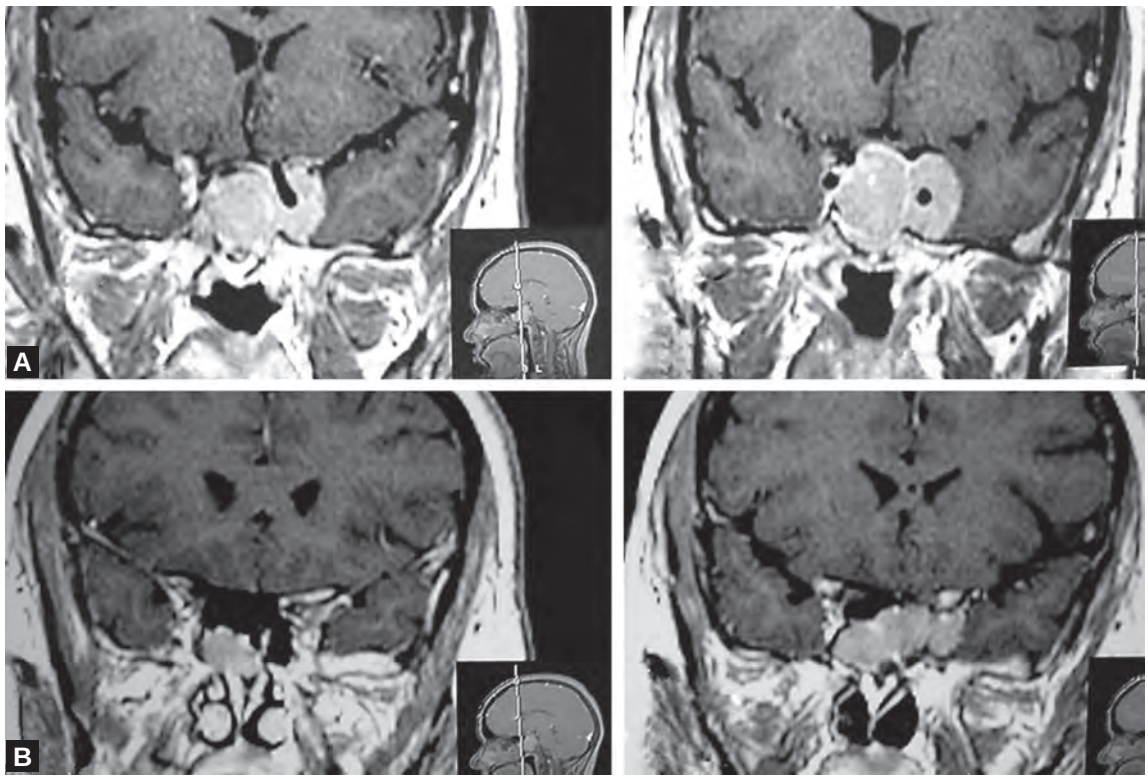
Fig. 3: Bilateral sphenoid sinus ostia and the extent of sphenoidotomy

tumour is selected. If the surgeon prefers the left nostril, then it is easier to operate standing on the left side of the patient with the head flexed and turned to the contralateral side. The first step of surgery is to identify the sphenoid ostium under the microscope. This is located usually just above the posterior end of the middle turbinate. If the ostium is covered by mucosa it is perforated. The ostium is enlarged inferiorly and medially. A branch of the sphenopalatine artery is usually located at the inferior border of the ostium, which needs to be coagulated. The septum is fractured at the level of the rostrum/keel junction to identify the ostium of the opposite side. Bone in between the ostia is removed and a larger opening is made in the sphenoid sinus (Fig. 3).

The sphenoid sinus mucosa is stripped to prevent mucocoele formation, infection and bleeding. The sellar floor is exposed and erosion of the sellar floor/maximal thinned out portion is identified and the floor is removed using rongeurs to expose the dura. The anterior wall of sella is removed from one cavernous sinus to the other and from the sellar floor to the tuberculum sellae. Durotomy is done in a cruciate fashion and the leaves of the dura are coagulated. Valsalva manoeuvre is done before starting decompression. The tumour removal is initially done from the inferior and posterior region, followed by lateral removal and finally the superior aspect of the tumour is removed. The normal pituitary gland is firmer than the tumour tissue and is yellowish orange in colour. The pituitary gland with the stalk has to be preserved as far as possible. After removal of the macroadenoma, the sinus is packed with abdominal fat and the sellar floor is reconstructed with the autogenous bone graft obtained at the time of sphenoidotomy. Abdominal fat may not be necessary, if there is no CSF leak and if it is a microadenoma. The nasal cavity is packed with lubricated betadine packs on one side for 12 hours. The removal of a pituitary tumour with suprasellar extension, in its entirety by a trans-sphenoidal approach, is sometimes difficult. If the suprasellar tumour does not descend after complete removal of the intrasellar tumour, care is taken not to induce CSF leakage and endoscope assistance is used for further removal. The remaining suprasellar tumour typically descends into the sellar space within a couple of months, at which time it can be safely removed during a second operation. We know by experience that the suprasellar tumour typically descends within 2 months and 2–3 months is the optimal interval for second surgery. The second surgery may be deferred for several months because we are not sure after how many months we could still expect descent of the remaining suprasellar mass. Trans-sphenoidal excision of pituitary adenoma can be accomplished, either by an endoscope or microscope or both. At NIMS we had operated upon 108 patients with pituitary adenomas, via the trans-sphenoidal approach over the past five years, using the endoscope in 58 cases, microscope in 45 cases and both in 5 cases. Both the groups had age-matched patient population and were analysed for extent of tumour excision and complication rates. Total/near total excision was achieved in 44/58 (74%) and 30/45 (67%) by endoscope and microscope, respectively. The incidence of CSF leak was 24% as against 13.3% by endoscope and microscope, respectively. There was no statistical difference between endoscopic and microscopic endonasal trans-sphenoidal approach to pituitary adenomas.

Transcranial Surgery

Rarely, transcranial surgery should be considered in patients with giant macroadenomas, where the bulk of tumour is suprasellar and parasellar, and symptoms are arising from tumour compression of the brain (Figs 4A and B).



Figs 4A and B: Post-gadolinium T1W coronal images showing pituitary adenoma with parasellar extension for transcranial approach

Patients with recurrent tumours with failed multi-staged trans-sphenoidal excision may require transcranial surgery.

Complications of Surgery

Trans-sphenoidal surgery has low morbidity. Surgical complications from removal of large pituitary adenomas have been reported in 5–17% of patients.[5–7,10,30] CSF rhinorrhoea is one of the most common complications occurring in 3% in most large series.[48] Injury to the cavernous sinus/carotid artery are serious complications. Cranial nerve injury may occur, especially of the III and VI nerves, if the tumour is extending into the cavernus sinus. Visual deterioration may occur after trans-sphenoidal surgery, either because of direct operative trauma, compression due to a haematoma, ischaemia or prolapse of the chiasm. Hypopituitarism, diabetes insipidus (DI) and hypothalamic damage are also known to occur. DI is one of the most frequent complications of trans-sphenoidal surgery with permanent DI occurring in less than 3% and transient DI in up to 60% of patients.[48] Meningitis and nasal/sphenoidal problems are other complications. We encountered CSF rhinorrhoea in 20/108 (18.5%) of patients with trans-sphenoidal excision of pituitary adenomas. Transient DI occurred in 12/108 (11.1%) of patients with permanent DI occurring in only one patient. One patient developed III nerve palsy.

RADIATION

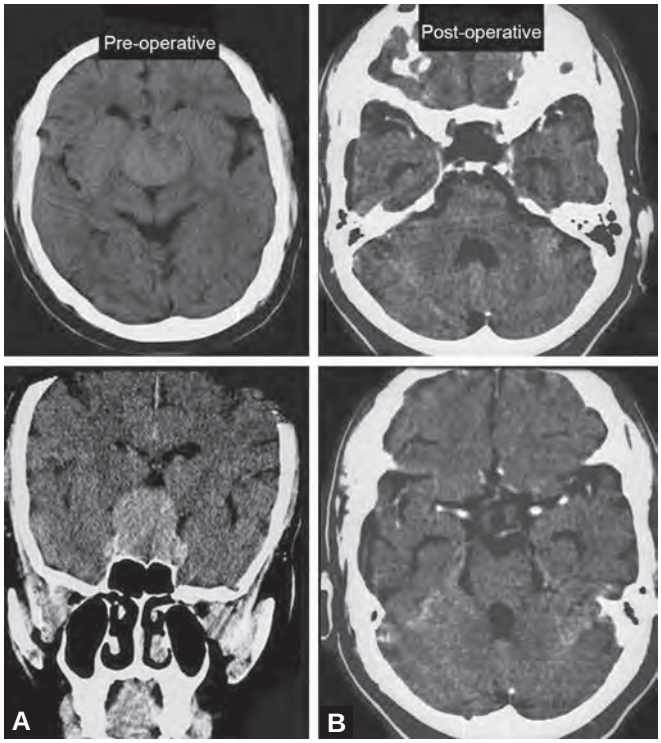
Radio-surgery/stereotactic radiotherapy is indicated, when there is inadequate tumour resection at the time of surgery and post-operative CT/MRI show evidence of residual tumour, and the patient is symptomatic. If there is no radiologic evidence of residual tumour, opinion is divided as to the role of post-operative radiation therapy, although most neurosurgeons would reserve radiation for recurrence.

FOLLOW-UP

Follow-up evaluation should include determination of the extent of residual tumour, the status of visual function and function of the non-adenomatous pituitary. All the patients with large non-functioning pituitary adenomas should be evaluated for the presence of residual tumour with a CT/MRI scan approximately 1 month following surgery, then at 6 months, 12 months and, if stable, at yearly intervals. Whatever intact pituitary hormones or subunits were abnormal before surgery should be measured again at this time, because surgery can impair previously normal function by excision of non-adenomatous pituitary tissue, but can also restore previously subnormal function. Neuro-opthalmological evaluation should include determination of visual acuity and field. These results will indicate if additional treatment is required and provide a new set of criteria by which to assess the subsequent course of the adenoma.

OUTCOME

About 70–80% of patients improve in their visual field after trans-sphenoidal surgery.[49] Saito et al. reported 72% enlargement in visual field and 76% improvement



Figs 5A and B: Pre-operative and post-operative CT scan showing complete removal of pituitary adenoma

in visual acuity.[38] Ebersold et al. observed that of 72 patients who presented with visual loss 53 improved, 15 remained stable, 3 patients had additional visual loss after the procedure and 1 died.[10] Regarding completeness of tumour removal, gross total and subtotal (≥90%) removal was achieved in 76% of tumours by Saito et al. with higher rates achieved in patients with less suprasellar extension, but completeness of tumour removal fell to 50% for tumours with a suprasellar height over 30 mm.[38] The recurrence rate reported in various series ranges from 12 to 24%.[6,7,10,51] In our experience, 54/74 (73%) patients had improvement in visual symptoms and gross total/near total resection being achieved in approximately 68% of cases (Figs 5A and B).

RECOVERY OF PITUITARY FUNCTION FOLLOWING MANAGEMENT OF NON-FUNCTIONING ADENOMAS

Partial or complete hypopituitarism is commonly found in patients with non-functioning adenoma at the time of presentation. The majority of patients with normal anterior lobe function pre-operatively have preserved function following surgery. Patients with a selected deficiency in anterior pituitary hormones often showed no change or improvement following surgery. Arafah et al. documented pituitary function studies in 26 patients with non-functioning pituitary macroadenoma before and after trans-sphenoidal surgery. Deficiency in growth hormone, gonadotropins, TSH and ACTH were found in 100%, 96%, 81% and 62% of patients respectively. Following surgery normal somatotroph and gonadotroph function was restored in 15% and 32% of patients, respectively. Normal thyroid function was restored in 57% of patients who had hypothyroidism pre-operatively and 38% of patients with adrenal insufficiency recovered normal corticotroph function post-operatively. Arafah et al. also found that normal or mildly elevated prolactin levels pre-operatively or a response in serum TSH concentrations following TRH administration was useful in predicting post-operative recovery of pituitary function.[1]

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152 Pituitary Apoplexy

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Pituitary apoplexy is a potentially disastrous condition, which occurs as a result of rapid expansion of, usually a pre-existing, often not yet known, adenoma by massive haemorrhage or infarction. Pressure, among other things, causes hypopituitarism, meningism and visual disturbances.[47,51] In 1905, Bliebtreu was the first to describe haemorrhage into a pituitary tumour.[6] In 1950, Brougham et al. described five post-mortem cases and drew attention to this clinical condition.[8] In 1954, Ramamurthi et al.[41] reported on two patients with pituitary apoplexy and this was the first report from India. The term "pituitary apoplexy" also describes acute enlargement of a non-tumourous gland, termed "Sheehan's syndrome", when seen in the context of obstetric haemorrhage.[20,37] Diagnosis is made by the typical clinical presentation, eye examination, CT/MRI and by measuring pituitary hormones.

INCIDENCE

The incidence varies in different series from 1 to 21%.[12,15,25,26,35,36,45,55] The incidence varies depending on the criteria used for diagnosis. The incidence of subclinical pituitary adenoma apoplexy was higher than acute pituitary apoplexy.[27,38,39] When subclinical presentations and patients with evidence of haemorrhage, cyst or necrosis on imaging or at surgery are also included, the incidence increases. There are also incidences of post-operative pituitary apoplexy reported following surgery for giant pituitary adenomas.[3]

PATHOGENESIS

Various mechanisms have been postulated for the occurrence of apoplexy. The growth of the tumour may outstrip the blood supply and lead to necrosis and haemorrhage.[9,26] This is more likely in tumours growing in an enclosed place like the sella turcica. The other proposed mechanism is compression of the infundibulum by an expanding mass, thus compromising the blood flow from the portal vessels, resulting in necrosis of the entire gland with haemorrhage as a secondary occurrence.[3] PRL adenomas were the most common tumour type (56.2%). Subclinical pituitary apoplexy usually occurs in patients with big or giant adenomas.[27,38] The blood supply is also limited, with the main supply to the anterior lobe being through the hypothalamo-hypophyseal portal circulation.[58] An expanding tumour may compress the infundibulum against the rigid dural opening in the diaphragma sella, leading to acute necrosis and infarction in the tumour.[44]

Pituitary apoplexy usually occurs *de novo*, but some precipitating factors may be responsible for producing the haemorrhage. Head injury,[28,52] chronic coughing and sneezing,[14] radiotherapy,[54] idiopathic thrombocytopaenic purpura,[30] lymphocytic hypophysitis,[33] spinal anaesthesia,[7] intensive thrombolytic therapy[19] and open heart surgery[46] have been reported to be associated with apoplexy. Medications, like leuprolide,[16] clomiphene,[56] goserlin,[4] GnRH and CRH administration[24,29,43] and oestrogen administration,[13] are reported to precipitate apoplexy. Bromocriptine therapy[32,55] and cabergoline administration have also been found to precipitate apoplexy.[24] Hypertension and diabetes mellitus were the possible predisposing factors. Post-operative 'pituitary apoplexy' in giant pituitary adenomas has been noticed in a series of cases with fatal outcome by Goel et al. and Mahapatra AK et al.[22,3] Mohanty et al.[34] have suggested that the incidence of apoplexy is related to the size and vascularity of the tumour, but this has not been borne out by other authors. A significant number occur in non-secreting tumours.[11]

In post-operative apoplexy, the proposed mechanisms are sudden release of tumour vessels from the internal carotid artery due to reduced tumour burden and compromise of the venous drainage of the tumour during surgery, tumour manipulation during surgery and swelling and subsequent compression of the hypophyseal arteries causing haemorrhagic necrosis.[3]

CLINICAL FEATURES

Haemorrhage into a pituitary tumour may be subclinical and not produce any symptoms or signs, or may produce signs and symptoms of varying severity, ranging from sudden onset of headache, rapid onset of visual loss, unconsciousness or death.[38] The most common features are headache (85–90%),[35,38,55] visual disturbances (70–80%)[31,53] and nausea and vomiting (50–60%).[38] Meningismus, seizures, frontal lobe syndrome,[5] ocular nerve palsies and signs resembling subarachnoid haemorrhage may occur. Altered mental status, stupor and coma have also been seen. Rarely, the presentation can be of non-ketotic hyperglycaemic coma[23] or diabetes insipidus.[50] The combination of headache, acute visual loss and ipsilateral Horner's syndrome without

ophthalmoplegia, mimicking carotid artery dissection has been reported as an unusual presentation.[47] The onset of apoplectic symptoms may be the first indication of an underlying pituitary tumour.

Endocrinologic manifestations of pre-existing hypersecretion like acromegaly, Cushing's or galactorrhoea and amenorrhoea may be present. Severe and acute hypopituitarism result either due to destruction of normal pituitary tissue or due to compression of the stalk. The hypopituitarism may be mild. In some instances, the haemorrhage may destroy the tumour tissue and amelioration of symptoms of hypersecretion may occur.[10,17]

The visual defects that may occur are diminished visual acuity, blindness in one or both eyes or field defects like central scotomata, bitemporal or binasal hemianopia or generalised constriction.[31] Ocular movement disorders occur when the tumour expands and compresses the cavernous sinus. III, IV and VI nerve palsies can occur in various combinations producing ptosis, dilated pupil and diplopia.[49] Isolated III and VI nerve palsies as the sole presenting features have been reported.[42,51] Trigeminal signs involving the first and second division may be found.

Because of its varied clinical presentation and its resemblance to other acute neurological conditions, the onset of pituitary apoplexy is often missed, unless the diagnosis of pituitary tumour has already been made. The clinical features may also be insignificant enough to escape attention. The differential diagnosis should include SAH due to aneurysmal rupture, stroke,[41] meningitis, encephalitis and uncal herniation, due to an expanding intracranial mass lesion.

INVESTIGATIONS

When the clinical presentation suggests pituitary apoplexy, plain skull films are valuable, as in the majority of patients changes consistent with an intrasellar mass are likely to be seen.[2,18]

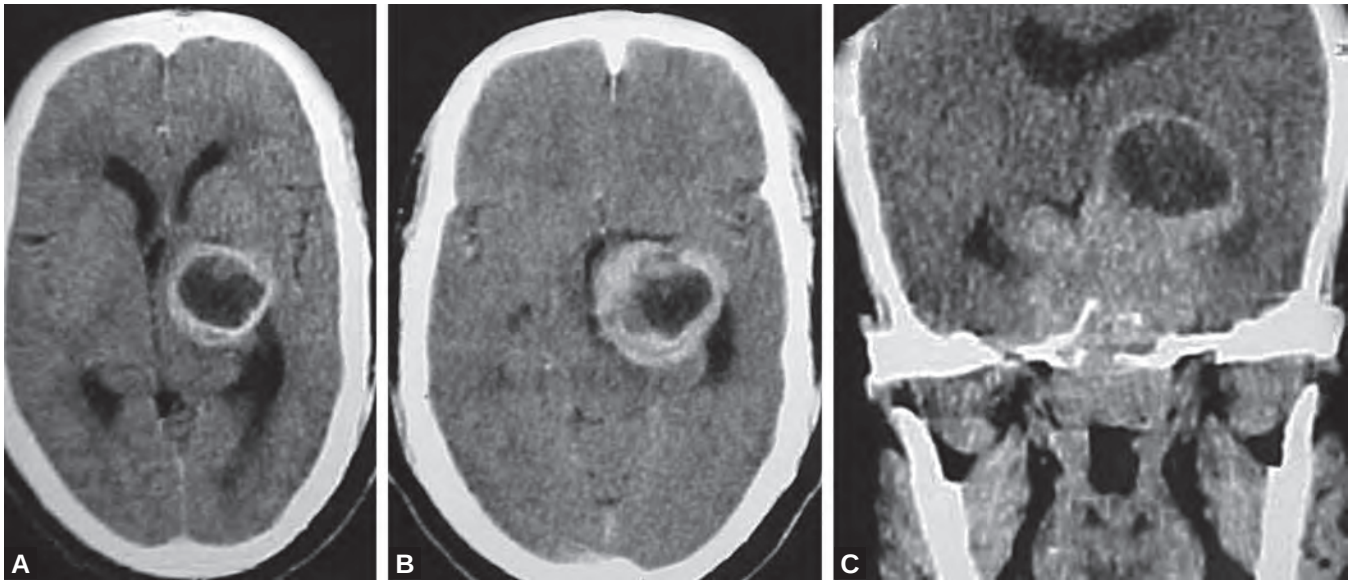
CT scan is useful, and plain and contrast enhanced scans must be done. A hyperdense non-enhancing lesion will be seen in the acute stage, representing blood. Surrounding enhancing tumour tissue may be seen. The mass usually extends into the suprasellar cistern and may displace the third ventricle producing hydrocephalus, which will be seen on the CT. When the CT is done weeks later or when there is necrosis without haemorrhage, a central isointense or hypointense lesion may be seen surrounded by a rim of contrast enhancement[39] (Figs 1A to C). CT is better than MR in the acute stages.

MR is useful, especially in the detection of silent or subclinical haemorrhage and in following up patients with apoplexy.[21,39] The MR changes due to haemorrhage will vary depending on the age of the haematoma in days and weeks (Figs 2 and 3).

Endocrine assessment is essential to decide on immediate and long-term replacement therapy. Levels of GH, PRL, cortisol and thyroid hormones should be done immediately. If necessary, provocative tests are done to evaluate the functioning of the hypothalamic-pituitary axis and to know the reserve capacity. Lumbar puncture to rule out meningitis or SAH should be done only when the plain X-rays and the CT are normal.

MANAGEMENT

The first step after diagnosis is to administer corticosteroids. When there is visual involvement, progressive decrease in the level of consciousness or involvement of the cranial nerves, emergency surgery must be undertaken to save life and vision. When there are only mild symptoms and no visual problems, the patients may be investigated further and the treatment options exercised as in any other patient with a pituitary tumour. Sibal



Figs 1A to C: CT scan axial and coronal section showing evidence of apoplexy. Hypodense core representing blood with surrounding enhancement of tumour

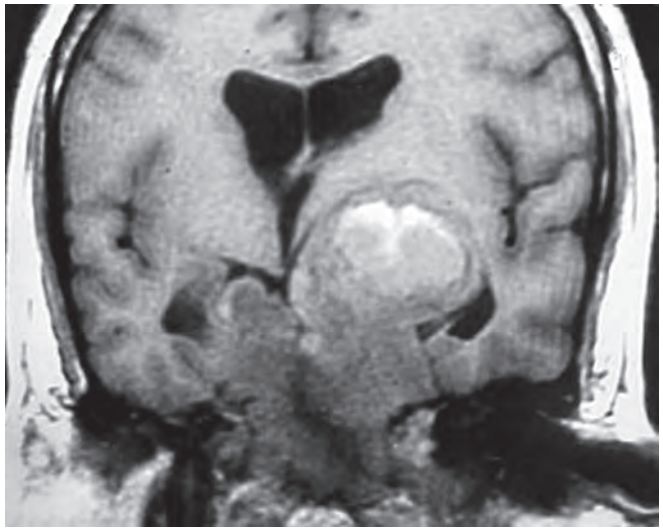


Fig. 2: MRI coronal sections of the same patient as in Figure 1 showing evidence of apoplexy

et al.[48] in their analysis of 45 patients managed conservatively found that the patients with classical pituitary apoplexy, who are without neuro-ophthalmic signs or exhibit mild and non-progressive signs, can be managed conservatively in the acute stage as their neurological symptoms improved significantly on follow-up.

Trans-sphenoidal surgery is indicated in patients with diminished levels of consciousness, hypothalamic dysfunction and visual deterioration. Trans-sphenoidal excision and decompression of the optic nerve and cavernous sinus is the ideal. Occasionally, transcranial surgery may be indicated when the sella is not enlarged or a dumb bell tumour is suggested.[55] Hydrocephalus will be relieved with tumour decompression, but occasionally a CSF diversion procedure may be required. Conservative management for patients with isolated cranial nerve palsies has been advocated but remains controversial.[51] Endocrine replacement therapy as appropriate must be instituted post-operatively, depending on the post-operative endocrine profile. Post-apoplexy long-term endocrine deficits are quite common.[53] Improvement in endocrine status may take place after surgery and this is probably due to release of stalk compression, which occurs during the apoplexy.

Since radiotherapy has been found to initiate apoplexy in some, it has been suggested that radiotherapy should not be given to patients who had apoplexy.[54,57] This contention is not supported by other data and radiotherapy may be given when indicated.[44]

Visual improvement usually occurs following decompression.[1,2,31] Visual outcome depends on the duration and severity of compression prior to the apoplexy and also on the time lag between the apoplexy and the surgery. Useful recovery of vision has been reported after total bilateral blindness[1,40] and, therefore, it is necessary to take urgent action even when the patient is blind. Recovery of cranial nerve dysfunction occurs usually and may take 8–12 weeks. Some patients are left with permanent devastating neurological deficits like blindness, hemiplegia or a chronic vegetative state.

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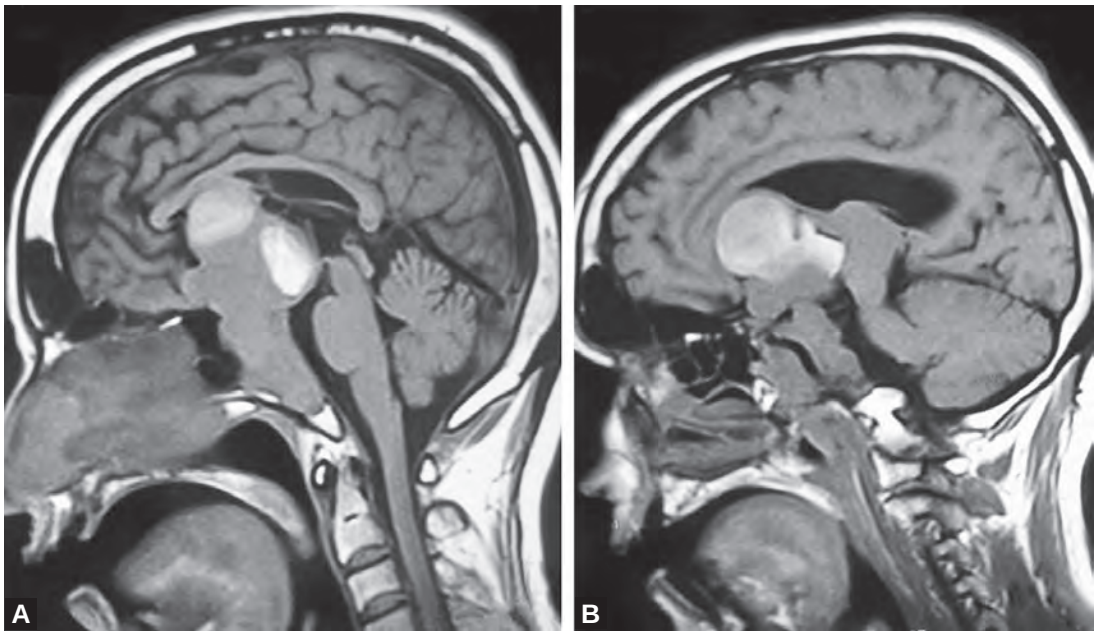

Figs 3A and B: MRI sagittal sections showing evidence of apoplexy within a pituitary macroadenoma

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153 Giant Invasive Pituitary Adenomas

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INTRODUCTION

Pituitary adenomas are the most common intrasellar tumours and account for 10% of all intracranial tumours. Of these tumours, approximately 5–6% behave aggressively and grow to gigantic sizes.[20] Those tumours measuring less than 10 mm are termed microadenoma and those measuring more than 10 mm are termed macroadenoma. Pituitary tumours with size in excess of 40 mm, or those extending less than 6 mm from the foramen of Monro are referred to as giant pituitary adenomas.[7,11,12,20,31,33] These tumours although benign, occasionally pose difficulty in management, due to technical problems in surgical resection and invasion of surrounding structures.

EXTENSION

Extension of pituitary adenoma can occur in various directions and results in various signs and symptoms, depending on the structures compressed.

Wilson[39] has classified suprasellar extension of pituitary tumours into:

Type A: Tumour occupying suprasellar cistern
Type B: Tumour obliterating the recess of the third ventricle
Type C: Tumour grossly displacing the third ventricle and having parasellar extension
Type D: Tumour having intradural extension
Type E: Tumour extending into the cavernous sinus.

Fahlbusch[6] has classified parasellar tumour extension into:

Type 1: Localised lateral
Type 2: Basal
Type 3: Massive lateral extension without invasion
Type 4a: Localised lateral invasion
Type 4b: Generalised lateral invasion
Type 5a: Supracavernous and subtemporal extension
Type 5b: Extrasellar extension with generalised invasion.

INVASION

Although pituitary adenomas grow to a very large size, they usually maintain a plane of cleavage from the surrounding tissues.[14,21,37] When the adenomas are seen infiltrating the dura, bone, blood vessel, adventitia or nerve sheath, they are termed invasive adenomas.[16] The evidence of invasion may be detected radiologically or seen peri-operatively. Simple microscopic dural involvement alone is not considered significant, as microscopic involvement of paratumoural dura was found in 69% of microadenomas, 88% of macroadenomas and 94% of macroadenomas with suprasellar extension, in the study conducted by Selman et al.[30] The frequency of gross operatively apparent invasion was found in only 40% in the same series. Endocrinologically functional tumours are more invasive than the non-functioning adenomas. Compared to non-invasive adenomas, invasive adenomas more often appear cellular, demonstrate mitotic activity and exhibit some degree of nuclear atypia.[28]

MOLECULAR BIOLOGY

It was previously thought that all the tumours have the same invasive potential but are in different stages of growth. When the ultrastructural features were studied, this proved to be wrong. A study of the genetic mutation of the retinoblastoma gene on chromosome 13, by Pei et al.,[26] showed that loss of heterozygosity is associated with aggressive behaviour of the tumour. In another study, Thaper et al.[36] found expression of the P53 gene in more than 15% of invasive tumours, as compared to non-invasive tumours which did not exhibit P53 expression in any of them. NM-23 is a metastasising suppressive gene, the activity of which, when reduced, indicates a high metastatic potential of a tumour. This was studied by Takino et al.[34] The expression NM-23 was grossly reduced in invasive pituitary adenomas. Protein kinase C alpha-isoform was over expressed in invasive pituitary adenomas,[27] as studied by Alvaro et al.[2] Excessive expression of the proliferative marker MIB-1, which is an antibody to cell cycle specific nuclear antigen Ki-67, is associated with invasive adenomas. MIB proliferation indices of more than 3% was found to be associated with invasive growth and increased incidence of recurrence by Thaper et al.[35] Similar studies by Kitz et al. and Knsop et al. showed that dural infiltration was associated with a higher Ki-67 labelling index.[17,18] Cytokine interleukin 6, heat shock protein-27,[8] type IV collagenase and matrix metalloproteinase-9[16] were also found to be increased in invasive adenomas.

CLINICAL PRESENTATION

An increased incidence of invasiveness was observed in those patients with onset of symptoms during the pubertal years, compared to patients whose symptoms first occurred during the post-pubertal years.[15] The majority of these patients present with visual symptoms, the predominant visual symptom being bitemporal haemianopia. Others like progressive or sudden visual loss in one or both the eyes are also seen. Sudden visual loss may be due to apoplexy.[11,20] Pituitary adenomas are softer than other tumours in this region and, therefore, they present with cranial nerve paresis at later stages, resulting in weakness of ocular movements. In most giant pituitary adenomas features of mass effect are more common than endocrine disturbances. Hyposecretion in the form of hypothyroidism and hypocortisolaemia is more common than hypersecretion of prolactin.[11,20] The sellar floor may be eroded resulting in CSF rhinorrhoea. A case of massive invasive pituitary adenoma with the unusual presentation of nasal obstruction has been reported.[4]

INVESTIGATION

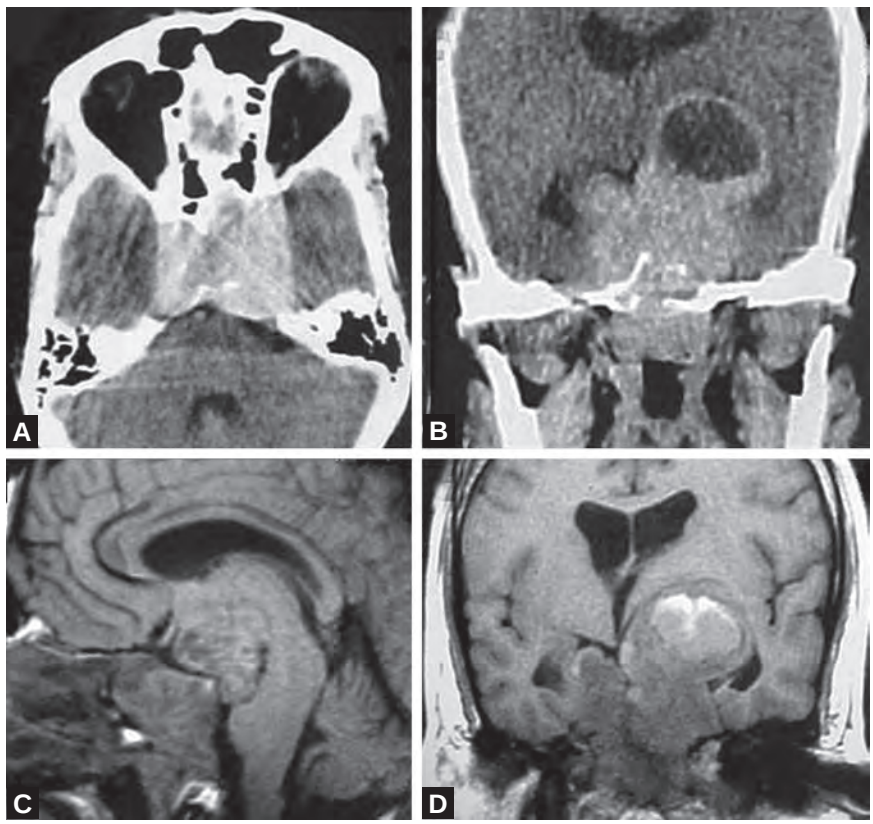
Plain skull radiographs have been proven to be insensitive and non-specific for pituitary lesions. On CT scans pituitary adenomas appear as hypodense lesions. CT scan provides better details about the bony erosion and calcification. The pituitary gland and the adjacent soft tissues, like the carotids and optic chiasma, are not well visualised. Coronal views will be required. MRI is now the imaging technique of choice. MRI shows the relation of the gland to the surrounding structures like the cavernous sinus, floor of the third ventricle and optic pathways with more clarity and has the advantage of multiplanar imaging. The internal features of the macroadenoma help in surgical planning.[5] The tumours that are soft and easily aspirated at surgery mostly appear hyperintense on T2W and those tumours that are firm appear isointense.[32]

Features suggesting aggressive behaviour in imaging:[20]

- Extensive invasion of the cavernous sinus
- Extensive suprasellar and parasellar extension
- Erosion of the skull base and invasion into the sphenoid sinus.

Figure 1 represents post-contrast CT scan axial and coronal views (A and B) and MRI T1W sagittal and coronal views (C and D).

There are many studies on parasellar extension and cavernous sinus invasion of pituitary tumours.[3,19,38] Lee et al.[24] have described that obliteration of the vein of the carotid sulcus on dynamic contrast enhanced MRI is the most reliable sign of cavernous sinus invasion. Pituitary adenomas with sinus invasion enhance less than the adjacent cavernous sinus on the side of invasion



Figs 1A to D: (A and B) Post-contrast CT scan axial and coronal views showing bony erosion with parasellar and suprasellar extension. (C and D) MRI T1W sagittal and coronal views showing retrosellar and suprasellar extension

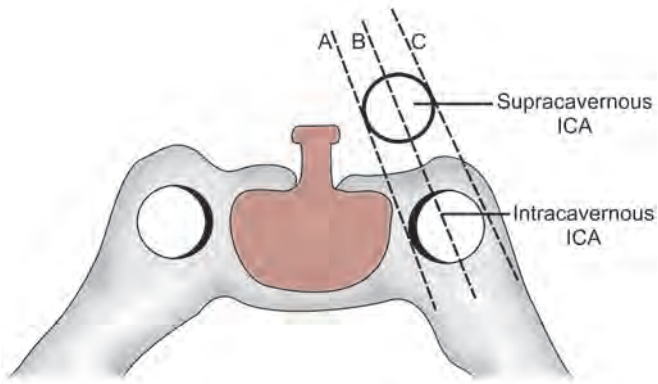


Fig. 2: Intercarotid lines which are drawn from intracavernous to supracavernous portions of the internal carotid artery. (A) Medial intercarotid line: along the medial walls. (B) Median intercarotid line: along the median walls. (C) Lateral intercarotid line: along the lateral walls

in post-gadolinium images.[23] The most sensitive sign of cavernous sinus invasion is an asymmetry in the signal intensity between the two sides. Encasement of the cavernous carotid artery is a specific but insensitive sign of cavernous sinus invasion.[5]

Knosp-Steiner classification[19] of cavernous sinus invasion based on MRI (Fig. 2):

Grade 0: When the adenoma did not cross the medial intercarotid line.

Grade 1: When the tumour passed the medial intercarotid line but did not cross the median intercarotid line.

Grade 2: When the tumour passed the median intercarotid line but did not cross the lateral intercarotid line.

Grade 3: When the adenoma passed the lateral intercarotid line.

Grade 4: When the ICA was totally encased by the tumour.

Vieira et al. have defined the following magnetic resonance criteria for cavernous sinus invasion:[38]

- Percentage of encasement of the intracavernous internal carotid artery is higher than 45%
- Occlusion of three or more cavernous sinus venous compartments
- Occlusion of the cavernous sinus lateral venous compartment.

Magnetic resonance criteria for the absence of cavernous sinus invasion in patients with pituitary adenoma were also defined by Vieira et al.:[38]

- Normal pituitary gland interposed between the tumour and the CS
- Intact CS medial venous compartment
- Tumour not crossing the medial intercarotid line
- Percentage of ICA encasement by the lesion lower than 25%.

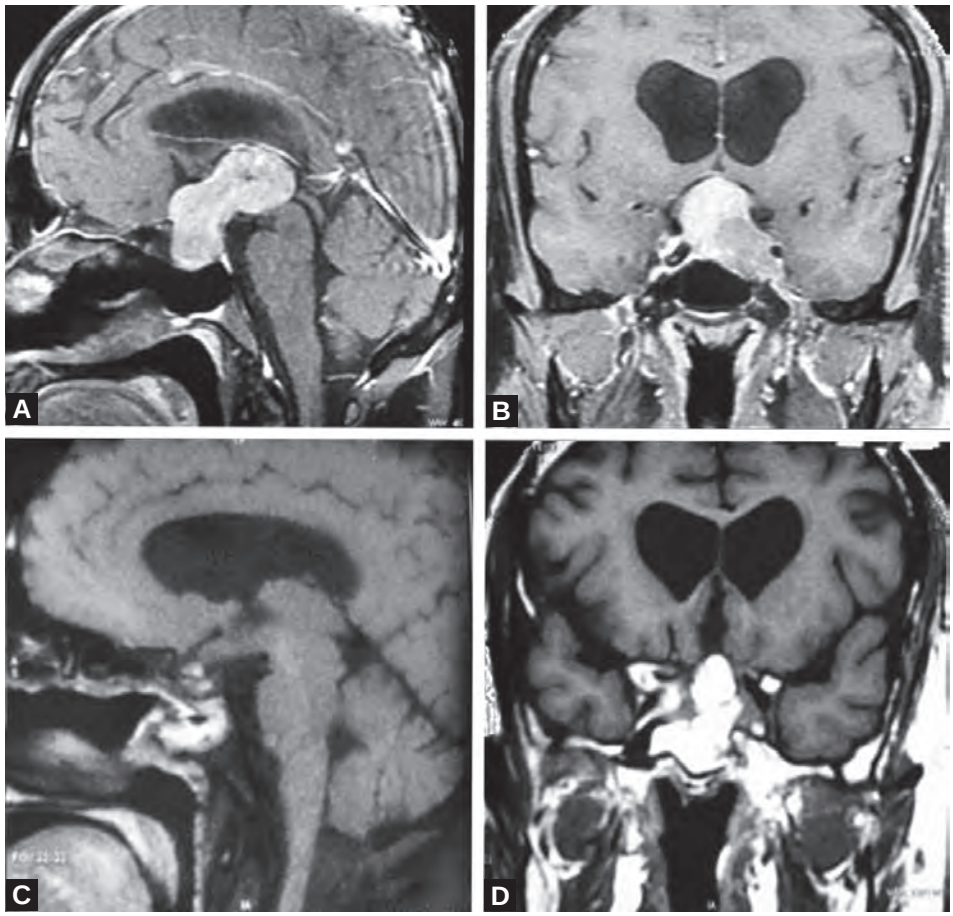
The most useful sign to predict cavernous sinus invasion is encasement of the internal carotid artery greater than 30%. This finding has the best sensitivity (92.1%), specificity (93.5%) and positive predictive value (82.5%).[38]

TREATMENT

The clinical course and surgical outcome in cases with giant pituitary adenomas have generally been reported to be poor.[11,20,28] Treatment of giant invasive adenomas by the conventional trans-sphenoid approach, followed by adjuvant therapy, leads to a relatively high recurrence rate. Although this treatment option has improved vision in a significant number, the long-term follow-up is not satisfactory, especially in young individuals.[20] Radical surgery by a trans-sphenoidal route in Grade I–III pituitary tumours and biopsy of the tumour, followed by radiotherapy in Grade IV tumours was suggested by Goel et al.[11] Except for fibrous and dumbbell-shaped adenomas, the trans-sphenoidal approach is a safe and effective way to remove large pituitary adenomas.[40,41] It allows rapid and adequate decompression of the optic nerves and chiasm, avoids major pituitary insufficiency and is associated with low morbidity-mortality rates.[22] Simultaneous trans-sphenoidal and pterional approach has been described for resection of giant pituitary tumours with dumbbell shape, where the surgeon cannot achieve complete resection by a single approach.[1] Combined treatment with initial surgical debulking followed by radiotherapy yields tumour control rates in giant pituitary adenomas similar to those of smaller pituitary adenomas without undue morbidity.[7] In patients with cavernous sinus invasion, the extended transnasal trans-sphenoidal approach and contralateral subfrontal approach have been described.[11,12,42] Oruçkaptan has reported that topical application of bromocriptine (1 mgr/mL slow-releasing gel) into the sellar cavity, immediately after tumour removal, seems to provide superior results, compared with the conventional treatment modalities.[25]

Figure 3 represents pre-operative post-contrast mid-sagittal (A) and coronal (B) T1W images. Post-operative images are shown in Figs 3C and D, respectively.

In giant prolactinomas, medical management is considered to be the first choice. Many of these tumours respond to drugs. Decrease in the serum prolactin level can be noticed within hours of starting the medication. Surgical intervention is indicated only if there is progressive visual loss or if the tumour is resistant to medical therapy. In young patients with significant parasellar extension, transcranial surgery with radical excision is to be aimed at. Patients with GH and ACTH secreting tumours have a significant morbidity. Long-term tumour control is rarely achieved by medical management. With modern skull base techniques, most of these tumours have become surgically accessible and direct radiotherapy is to be avoided. Although non-functional pituitary adenomas have a relatively benign course, radical excision is to be aimed at in younger patients with a long life expectancy.[21]



Figs 3A to D: (A) Pre-operative post-contrast midsagittal T1W images. (B) Pre-operative post-contrast coronal T1W images showing parasellar extension. (C) Post-operative midsagittal T1W images with fat suppression. (D) Post-operative coronal T1W images showing evidence of packing of sphenoid sinus with fat and fascia

A partial or a subtotal resection can lead to infarction and oedema of the residual tumour termed as post-operative pituitary apoplexy.[9] Other complications like worsened visual status, pituitary and hypothalamic dysfunction, cerebral ischaemic attacks, coma and mortality have been described. High surgical mortality has been attributed to the breach of subarachnoid spaces, and ischaemia within the hypothalamus, brainstem or cerebral hemisphere caused by small and large vessel traction.[9,13]

RADIATION

In the series of Goel et al.,[10] radiotherapy was given to all the patients with Grade IV tumour. In Grade III, with significant post-surgical residue radiotherapy was given in spite of the patients being asymptomatic, while only symptomatic patients with Grade II tumours received radiotherapy. In Grade I cases, radiotherapy was generally avoided and re-exploration of the tumour was preferred in patients with large or symptomatic residual or recurrent tumours.[11] Combined modality treatment with initial surgical debulking followed by radiotherapy in the dose range of 4500–5000 cGy over 25 fractions yields adequate tumour control rates, although normalisation of the secretory function is seen in a much less number of patients.[7] Conventional radiotherapy is not as effective as expected. The increased side effects of radiotherapy in patients with supra-parasellar extension, especially to the optic pathway and hypothalamus, limit its benefits.[25] Clinical and neuroradiological signs of radiogenic encephalopathy were encountered in 28% of patients with invasive pituitary adenoma by Rauhut et al.[29] Complications of radiotherapy, like hypopituitarism, have seriously affected the quality of life in these patients.[13] Late onset of worsening in endocrine function, seen in a significant number of patients, is attributed to delayed onset of radiation effect.[24]

Giant pituitary adenomas have a different genetic makeup which results in their more aggressive behaviour. Recent advances in medical management and adjuvant therapies, along with the use of endoscope, have helped to increase survival time, improve the quality of life and decrease the morbidity and mortality.

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154 Perioperative Endocrine Management

Murthy S

INTRODUCTION

Pituitary hormone deficiencies are of significant concern in the management of patients with pituitary tumours. Fortunately many patients undergoing trans-sphenoidal surgery have microadenomas and do not have significant pre-operative or post-operative endocrine deficiencies. However, patients with larger tumours and some of those with hypersecreting states have abnormalities that need endocrine attention before surgery, immediately after surgery, later on and sometimes lifelong.

PRE-OPERATIVE ASSESSMENT

All patients require a thorough pre-operative laboratory evaluation before surgery. Evaluation should include a complete blood count to assess the presence of anaemia or other haematologic abnormalities.

A metabolic panel to evaluate possible hyponatraemia, hypercalcaemia, hyperglycaemia and other metabolic abnormalities is also indicated.

Patients with hypercalcaemia are evaluated for the possible diagnosis of multiple endocrine neoplasia, type I. The endocrine evaluation of each patient should include a thyroid panel (T3, T4, TSH), serum levels of cortisol, adrenocorticotropic hormone, growth hormone, IGF1, insulin like growth factor-1, testosterone, lutenizing hormone, follicle-stimulating hormone and prolactin.

The frequency of deficiency among the anterior pituitary hormones at the time of diagnosis of a pituitary tumour presents a spectrum of prevalence with GH > LH > FSH > TSH > ACTH and PRL.[25]

Pituitary-Thyroid Axis

Secondary hypothyroidism is strongly suggested by low levels of free T4 in association with low, normal or minimally elevated levels of TSH. However, it should be remembered that sick patients with non-endocrine disease ('sick euthyroid') can also exhibit a similar pattern of thyroid function tests.

Pituitary-Adrenal Axis

Assessment of the hypothalamo-pituitary-adrenal (HPA) axis, and thus defining a possible need for glucocorticoid replacement therapy, is a crucial aspect of anterior pituitary function testing. Under normal circumstances, ACTH secretion shows a marked circadian rhythm with highest levels in the early morning and lowest at around midnight. Measurement of the target hormone cortisol is common to all tests of the HPA axis and cortisol has the advantage of being a more stable hormone in serum/plasma than ACTH. Exogenously administered hydrocortisone or prednisolone interferes with the measurement of endogenous cortisol secretion. Dexamethasone administration will render cortisol measurements uninterpretable, both during treatment and for several days after steroid withdrawal depending on the dose and duration of therapy. Total cortisol levels are significantly raised in patients taking oral oestrogens. Ideally, basal cortisol should be measured between 8.00 AM and 9.00 AM since HPA axis activity is maximal at this time. Random cortisol measurements, for example, during afternoon clinics are much less useful and often difficult to interpret. If the basal morning cortisol is lower than 3.5 μg/dl, it strongly suggests ACTH deficiency and glucocorticoid replacement should be commenced. If basal cortisol is higher than 15 μg/dl, adrenal insufficiency is very unlikely. An intermediate value requires interpretation based on the clinical setting. Stimulation tests, like insulin tolerance test or ACTH stimulation test, are rarely required to assess the pituitary-adrenal axis.[8,12,21]

Serum Prolactin

It is important to exclude pregnancy, PRL—elevating drugs, primary hypothyroidism and polycystic ovarian syndrome in all patients with hyperprolactinaemia. In hyperprolactinaemic patients with a pituitary mass lesion, the main challenge is to distinguish between tumoural secretion of PRL and pituitary stalk interruption. The basal PRL is of considerable diagnostic value. A value greater than 200 ng/ml is usually diagnostic of macroprolactinoma. A serum PRL level lower than 80 ng/ml in a patient with a pituitary macrolesion usually indicates pituitary stalk interruption rather than tumoural secretion. An intermediate PRL level of 80–200 ng/ml is usually diagnostic of a microprolactinoma.[6,16]

Growth Hormone—IGF-1 Axis

Basal GH levels and serum IGF-1 levels are assayed. Rarely, stimulation or suppression tests are done when there is growth hormone deficiency or excess.[23]

Pituitary-Gonadal Axis

Basal measurements of gonadotrophins (LH and FSH) and sex steroids (oestradiol and testosterone) will assess the hypothalamo-pituitary-gonadal axis.

Vasopressin

Central diabetes insipidus is rarely a presenting feature in patients with pituitary adenomas, even if the tumour is very large. However, diabetes insipidus occurs commonly in patients with craniopharyngioma or other hypothalamic pathologies. The diagnosis can usually be established by measuring serum sodium (more than 145 mEq/l) and osmolality (more than 300 mOsm/kg), together with urine output (often more than 3L/day) and urinary osmolality (less than 300 mOsm/kg). Vasopressin deficiency may be masked by adrenal insufficiency. After glucocorticoid replacement central diabetes insipidus may get unmasked.[22]

Pre-Operative Management

Glucocorticoid therapy before and during trans-sphenoidal pituitary surgery has been the conventional treatment in the past. The rationale for this practice has been the assumption that ACTH secretion is compromised by the trauma of surgery. Current data and available literature indicates that patients with normal pre-operative adrenal functions do not require glucocorticoid therapy before or during pituitary microsurgery. The argument in favour of this hypothesis is that exogenous steroid administration inhibits endogenous ADH release and precipitates diabetes insipidus.

The recommendation is that glucocorticoid therapy is not administered before or during selective pituitary surgery. Serum cortisol levels are measured twice daily during the immediate post-operative period. Those with levels above 15 μg/dl do not require therapy. If serum cortisol is below 5 μg/dl therapy is started.

For those with documented pre-operative glucocorticoid therapy, oral hydrocortisone 30 mg daily in three divided doses is started at the time of diagnosis. It is switched to injection hydrocortisone 50 mg IM twice daily the day before surgery and hydrocortisone 100 mg as an IV drip administered during surgery.

Most patients with macroadenomas do not manifest signs and symptoms of hypopituitarism until after treatment with surgery/irradiation.

Deficiency of other pituitary hormones other than TSH need not be addressed in the peri-operative period. If hypothyroidism is detected, thyroxine replacement (50–200 μg/day) is started immediately. It takes 3 weeks for the patient to become euthyroid.

Unless the hypothyroidism is severe, surgery need not be delayed in those requiring immediate surgery. In this situation, the management team should be aware of the potential impact on anaesthesia, as well as fluid and pain management. Dosages of all medications, particularly narcotics need to be decreased in hypothyroid patients because of lower metabolic rate.

Blood pressure, blood sugar levels, serum electrolytes, and fluid intake and output should closely be monitored in the post-operative period.[3,7,9,10,27,32] (Table 1).

Table 1: Pre-operative assessment

- Rule out haematological problems
- Evaluate for hyponatraemia, hypercalcaemia and hyperglycaemia
- Thyroid and cortisol deficiency should be corrected before surgery
- Other hormonal imbalances are less important

EARLY POST-OPERATIVE EVALUATION/ MANAGEMENT (1–2 WEEKS)

General Principles of Pituitary Function Assessment

Monitoring of anterior pituitary function is crucial to the peri-operative care of patients who undergo surgery for pituitary tumours. Although the development of new pituitary hormone deficiencies after trans-sphenoidal surgery is uncommon when performed by an experienced pituitary surgeon, all patients require monitoring for these possible complications in the first few days after surgery. Uniform procedures for this monitoring can be adopted and then modified, as indicated by each individual patient's history and clinical picture. Knowledge of the patient's pre-operative endocrinological function can help predict the need for post-operative hormone replacement therapy. Pre-operative hypopituitarism should always be treated in the early post-operative period as this rarely resolves immediately. In addition, the suspicion of new hypopituitarism should be heightened in patients with partial hypopituitarism pre-operatively.

The course of surgery and the operative findings provide useful information for planning post-operative monitoring. When the surgical procedure is more extensive, haemorrhage or necrosis within the tumour are seen or other complications occur at the time of surgery, concern for new hypopituitarism should be heightened. In particular, the likelihood of post-operative adrenal insufficiency is increased fourfold in patients who had post-operative diabetes insipidus, which may be a consequence of more extensive surgery. Non-pituitary lesions, such as craniopharyngiomas, are more likely to be accompanied by hypopituitarism or diabetes insipidus.

Diabetes Insipidus

The most common pattern is transient abnormality and affects most cases. It consists of the abrupt onset of polyuria within 24 hours of surgery, with resolution in 1–3 days. It may be secondary to the release of bio-inactive

arginine vasopressin (AVP) precursors, local oedema of ADH producing neurons with a temporary functional impairment or a disruption of the inferior hypophyseal artery that supplies the ADH transport and storage structures.

Proximal damage to the pituitary stalk or hypothalamus can cause a second variant of DI. After previously formed ADH is used up in 1–3 days, permanent DI ensues, with a minimal or only partial decrease in urine volume over several days. The partial improvement sometimes seen is likely caused by resolution of oedema.

The third pattern of post-operative DI is triphasic in nature. The first phase is marked by the abrupt onset of DI within 24 hours of surgery, which then lasts 1–3 days and is thought to be caused by neuronal shock and diminished or absent hormone release. An interphase then follows, during which AVP escapes from degenerating neurons. Urine output comes down and urine osmolality rises, making the patient vulnerable to hyponatraemia if intravenous fluid administration is not tapered. This interphase may last 1–14 days and is followed by a return of DI, which is often permanent owing to the loss of magnocellular neurons by retograde axonal degeneration. Polyuria in mild DI is usually 4–6 L/24 hours and in severe DI up to 18 L/day.

A urine flow of 150–200 ml/h maintained for several hours is highly likely to result from DI, although in any situation in which urine output exceeds fluid intake an abnormal cause of polyuria should be suspected. Differentiating DI from a diuresis of fluids given perioperatively, or diuresis secondary to osmotic or non-osmotic diuretics, can create a confusing clinical picture.

Polyuria of DI is associated with abnormally high serum osmolality (more than 200 mOsm/kg), an elevated serum Na level (more than 145 mEq/l) an inappropriately dilute urine (less than 300 mOsm/l). In a clinical setting measuring urine specific gravity, serum Na and blood glucose could differentiate causes of polyuria.

Patients who are not very sick and who can take oral fluids should be allowed to regulate their own intake and water balance. Patients with DI prefer ice-cold fluids as this elicits a strong oropharyngeal reflex, compared to warm fluids promptly suppressing ADH release. If not, 5% GDW could be given intravenously. As soon as possible intravenous fluids should be stopped and glucocorticoid dosage tapered. By the second or third post-operative day, the polyuria and polydipsia have usually attenuated to several litres a day and do not require any treatment. Only when adequate fluid intake cannot be maintained because of lethargy or an impaired thirst mechanism is specific drug therapy instituted in the early post-operative period.

The preferred agent is DDAVP orally 0.5 mg once or twice daily increased up to 0.4 mg every eighth hourly.

If oral medications cannot be taken, DDAVP 2–4 mg (0.5–1 ml) intravenous or subcutaneous or aqueous vasopressin (20 U/ml) in a dose of 0.1–0.3 ml every 4–6 hours could be used. In case of severe water loss and hypernatraemia, intravenous fluids in addition could be administered. Short acting preparations are preferred since DI may be transient and recovery occurs.

Permanent DI is unusual with microadenoma surgery but may occur in patients with macroadenomas. One should keep in mind that transient DI may be followed by the syndrome of inappropriate ADH secretion (SIADH). Patients with unrecognised coexistent adrenal insufficiency may not develop symptoms of DI, as glucocorticoid deficiency is a stimulus for release of ADH. The polyuria of DI may follow when steroids are replaced.[26,29]

Hyponatraemia

Post-operative hyponatraemia is a relatively common disorder. The presenting signs and symptoms are nausea, lethargy, confusion and headaches. It can be seen in patients who are hypovolaemic, euvolaemic or hypervolaemic. The causes are SIADH, hypothyroidism, hypocortisolism and hyperglycaemia. SIADH is rare and occurs in 1% of patients who have undergone pituitary surgery and usually presents 1–2 weeks after surgery.[11,20,24]

The clinical features, pathophysiology, diagnostic features and treatment modalities are listed in Table 2.

Pituitary Adrenal Insufficiency

For those on pre-operative hydrocortisone therapy, Inj. hydrocortisone 50 mg x 8 hourly is administered on the first post-operative day, followed by 25 mg x 8 hourly for 2 days, followed by 25 mg x 12 hourly for 2 days, followed by oral hydrocortisone 30 mg/day in three divided doses (physiological replacement). Since oral hydrocortisone is expensive and not easily available, the alternate would be oral prednisolone 5 mg in the morning and 2.5 mg in the evening.

In patients with macroadenomas where hypopituitarism is not permanent and there is bound to be recovery of pituitary functions, it is recommended that glucocorticoid is withdrawn abruptly after 3–4 days after surgery. Serum cortisol is measured 24 hours after withdrawal. If serum cortisol at 8.00 AM is 15 μg/dl or more, it indicates recovery of the HPA axis and further steroid therapy is not required. If serum cortisol at 8.00 AM is less than 5 μg/dl recovery of the HPA axis has not occurred and glucocorticoid therapy has to be restarted. Patients with intermediate values are monitored carefully until a determination is made, whether there has been recovery of pituitary function. An alternative approach to the protocol of rapid discontinuation of steroid therapy is to taper steroid over several weeks and then assess the patient's pituitary-adrenal axis at a later date.

In patients with ACTH secreting pituitary adenoma some advocate glucocorticoid use before, during and after surgery, others restrict their use to the post-operative period. If surgical adenomectomy is complete, signs and symptoms of glucocorticoid deficiency develop within 24–48 hours and are associated with 8.00 AM

Table 2: Differential diagnosis of hyponatraemic state in the post-operative pituitary patients

Disorder	*Clinical features*	*Hydration*	*Pathophysiology*	*Diagnostic features*	*Treatment*
SIADH	Asymptomatic to neurological symptoms	Normal	Increased ADH release	Hyponatraemia Serum Na < 130 mEq/l Urine Na > 40 mEq/l Serum Osm ↓ Urine Osm ↓	*Acute* Fluid restriction if Na^+ = 120 mEq/l or more if Na^+ < 120 mEq/l 3% NaCl + Diuretics *Chronic* Demeclocycline 600–1200 mg/day
Hypothyroidism	Bradycardia, slow mentation, coarse voice	Normal	Impaired water excretion	Low T4 Low or normal TSH	Thyroid hormone replacement
Hypocortisolism	Weight loss, malaise, nausea/emesis, hypotension	Dehydrated	Impaired water excretion	Hypoglycaemia Low serum cortisol	Steroid replacement
Hyperglycaemia Diabetes mellitus Cushing's acromegaly	Polyuria, polydipsia	Normal or dehydrated	Dilutional (Pseudohyponatraemia)	Hyperglycaemia	Lowering blood sugar

serum cortisol levels below 5 μg/dl. These patients are started on glucocorticoid therapy; Inj. hydrocortisone 50 mg × 6 hourly tapered down and later switched over to oral hydrocortisone 30–50 mg in three divided doses. It is expected that most of them will recover pituitary adrenal functions over the next 24 hours and could discontinue exogenous steroid therapy.

In our set-up, taking into consideration patient compliance, financial implications, close monitoring and assessment requirement, non-availability and cost of oral hydrocortisone, in most patients, conventional therapy of Inj. hydrocortisone 100 mg thrice daily, started pre-operatively and tapered during the post-operative period, will still be justifiable, as the risk of development of transient diabetes insipidus is much less than the risk of development of adrenal insufficiency/crisis, if not closely monitored. Instead of oral hydrocortisone 30 mg/day [physiological replacement prednisolone 7.5 mg/daily (5 mg in the morning and 2.5 mg in the evening)] could be advised.[2,4,15,28]

Functioning Tumours

Follow-up management of patients with Cushing's disease is directed towards tapering and discontinuing glucocorticoid replacement. Patients who do not have evidence of early cure are obviously not treated with steroids. Tapering protocols vary greatly and depend largely on an individual patient's symptoms. For patients taking hydrocortisone, a reasonable approach would be to decrease the dose by 5 mg/d every week and to obtain a fasting serum cortisol level 24 hours after the last dose. A serum cortisol value less than 3 μg/dl would indicate a persistent defect in corticotrophin secretion and resumption of glucocorticoid therapy would be indicated, followed by repeating the tapering and testing process again after an interval. Most patients do not require post-operative steroid replacement after approximately 3 or 4 months and, indeed, the longer the requirement for glucocorticoid therapy, the greater is the likelihood of cure. A fasting serum cortisol level of greater than 20 μg/dl after cessation of steroid therapy would raise the concern of early recurrence; in such circumstances, obtaining a 24-hour urine collection for free cortisol would be indicated.

One should be cautious about tapering of steroid dosage, as due to chronic suppression of the HPA axis, acute adrenal insufficiency or crisis could be precipitated.

In GH secreting tumours/prolactinomas or other functioning tumours, GH, prolactin, FSH, LH, oestradiol or testosterone need not be measured in the early post-operative period, as early intervention is not required.[17]

LATE POST-OPERATIVE EVALUATION/ MANAGEMENT (AFTER ONE MONTH)

Testing at this time will address the presence or absence of residual tumour, as well as to assess the function of the normal gland. It is important to document hormone deficiency before long-term replacement therapy is established. As discussed earlier, hormone deficiencies associated with pituitary adenomas are often reversible with surgical resection of the adenoma. Similarly, the surgical procedure/radiotherapy itself can, at times, result in partial or complete loss of pituitary hormone function. From a practical standpoint, pituitary function can be assessed easily through outpatient services and dynamic testing can often be avoided.

Testing of pituitary function at this time can be done in a similar way to that described earlier. A practical and clinically valuable approach commonly used in evaluating pituitary function is the determination of serum levels of pituitary hormones as well as hormones secreted by peripheral glands such as the thyroid, adrenal and gonadal steroids. This combination of hormone levels provides reasonably adequate evaluation of pituitary gland function in most patients. In some patients, especially those with mild adrenal insufficiency, dynamic testing may be necessary to accurately define pituitary function.[1]

Pituitary-Adrenal Axis

It is rare and unusual to have a patient acquire adrenal insufficiency so late after pituitary surgery, unless other treatments were given or complications occurred to explain that event. Patients with persistent or acquired glucocorticoid deficiency in the immediate post-operative period are more likely to maintain similar function months after surgery. If ACTH secretion is shown to be abnormal in the immediate post-operative period only an unusual patient will show signs of recovery of pituitary-adrenal axis weeks or months later. The only exception to this rule is patients with ACTH secreting adenomas who develop adrenal insufficiency after complete resection of the adenoma and then recover pituitary adrenal function in 6–24 months.

If there is a doubt about the integrity of the pituitary-adrenal axis and if the patient is on oral steroids (hydrocortisone or prednisolone), it is stopped for 48 hours and serum cortisol measured. If basal cortisol at 8.00 AM is below 3 μg/dl, the diagnosis of adrenal insufficiency is confirmed; if above 20 μg/dl, it indicates normal function. Intermediate values may require further evaluation. In a situation like this, dynamic testing with ACTH would be useful.

The physiological replacement dosage required for various steroids is as follows (Table 3):

During periods of stress the dose should be appropriately increased. The usual replacement dose should be doubled or tripled during fever, infection, invasive diagnostic procedures, minor surgeries (cataract, laparoscopic, dental) and radiotherapy. For those with severe infections and major surgeries, parenteral steroids and IV fluids will be required. Patients and their immediate relatives should be cautioned about this and they have to always carry a medical alert card. Once they get over the stress period, it could be changed to the physiological replacement dosage. For patients who have undergone pituitary surgery for Cushing's disease, it would take 6–18 months for recovery of the HPA axis and steroid cover over this period is required[13,14,19] (Table 4).

Table 3: Relative potencies of different steroids

Compound	*Physiological replacement dosage (mg)*	*Glucocorticoid activity*
Hydrocortisone	20–25	1.0
Cortisone	20–30	0.7
Prednisolone	7.5	4.0
Dexamethasone	0.5–0.75	30.0

Table 4: Stress dose of steroids

Minor Stress

- Febrile illness, moderate infection, trauma, invasive diagnostic procedures, minor surgical procedures (dental, cataract, laparascopic) labour delivery
- Double or triple dosage of oral steroids

Major Stress

- Severe acute illnesses, severe infection, major surgeries, inability to take oral steroids
- Inj. hydrocortisone 100 mg x 8 hourly IM or IV along with fluids
- Tapered over 1–2 days after recovery and return to previous steroid replacement

Chronic DI/SIADH

Persistence of DI beyond the immediate post-operative period presages a poor long-term outlook for recovery. It is unusual to see permanent DI in a patient following trans-sphenoidal pituitary surgery. The treatment of choice for chronic DI is DDAVP, either an intranasal preparation (100 mcg/0.1 ml/spray) starting with 0.05–0.1 ml once or twice a day or oral tablet (0.1 mg) 0.1–0.4 mg in divided doses twice or thrice daily. Chronic SIADH is managed with fluid restrictions and demeclocycline 600–1200 mg/day in divided doses[5] (Table 5).

Pituitary-Thyroid Axis

Central hypothyroidism is associated with low T4 and low or normal TSH, and requires lifelong replacement therapy (100–200 μg/day).

Pituitary-Gonadal/Prolactin Axis

Serum FSH, LH assay, prolactin and testosterone/oestradiol are useful guides to treatment. The most sensitive tests of fertility are the sperm count in the male and menstrual cycles with evidence of ovulation in the female. The concentrations of gonadotrophins (luteinizing hormone, follicle-stimulating hormone) are frequently in the normal range in pituitary hypogonadism.

It may be necessary to enquire specifically about sex drive, because many patients hesitate to complain about decreased libido, believing that this is an effect of their illness for which there is no treatment. Elevated serum prolactin levels also result in decreased libido. In males who have low testosterone and elevated prolactin levels, testosterone replacement alone will not restore normal libido; it is also necessary to lower the serum prolactin level, for example, by using a dopamine agonist like

Table 5: SIADH vs DI

	SIADH	*DI*
Presentation	Hyponatraemia	Polyuria
Plasma osmolality	Hypotonic (< 275 mOsm/l)	Hypertonic (> 310 mOsm/l)
Serum sodium	Hyponatraemia (< 135 mEq/l)	Hyponatraemia (> 145 mEq/l)
Urine volume	Low	Polyuria (4–18 L/d)
Urine osmolality	Relatively high (> 100 mOsm/l)	Relatively low (< 200 mOsm/l)
Urinary sodium	> 20 mEq/l	> 20 mEq/l
Treatment	Fluid restriction If Na < 120 mEq/l, consider 3% hypertonic saline Demeclocyline 600–1200 mg/day	DDAVP

bromocriptine/cabergoline. Hyperprolactinaemia results from disruption of the pituitary stalk.

Chronic replacement therapy consists of 200–300 mg testosterone propionate intramuscularly every 2–4 weeks in men and cyclical hormonal therapy (oestrogen + progesterone) in pre-menopausal women.

Successful treatment of infertility, using sequential combinations of human menopausal gonadotrophin (hMG) and human chronic gonadotrophin (hCG) in patients who have undergone hypophysectomy is now well established, so that hypophyseal deficiency need not preclude the possibility of parenthood. Due to its great expense and the occurrence, in some women, of ovarian hyperstimulation, this form of therapy should be administered only by physicians who are familiar with its application. After treatment, men may successfully impregnate their partners even when sperm concentrations do not exceed 10×10^6 ml.[30,31]

Pituitary-Growth Hormone Axis

Most patients with growth hormone secreting pituitary microadenoma are cured by trans-sphenoidal surgery and those with larger tumours have partial cure. They may require additional stereotactic radiosurgery. Serum GH and IGF1 should be assessed one month after surgery and repeated every 6–12 months.

Criteria for cure are normal serum IGF1 level and growth hormone levels less than 0.4 ng/ml 1 hour after oral administration of 100 gm glucose. Children with growth hormone deficiency confirmed by dynamic studies will benefit from growth hormone therapy[18] (Table 6).

CONCLUSION

Patients undergoing pituitary surgery are a heterogeneous group and management requires a multidisciplinary team approach, involving neurosurgery, anaesthesiology and endocrinology. Protocols for evaluation and monitoring have to be individualised by the centre taking into consideration practicality, financial implications and patient compliance.

Table 6: Long-term management of pituitary insufficiency

Deficiency	*Replacement regimens*
Adrenal insufficiency	Prednisolone 5 mg AM, 2.5 mg PM
	Oral hydrocortisone 10–15 mg AM; 5–10 mg PM
Hypothyroidism	100–300 µg daily morning
Hypogonadism (men)	Inj. Testosterone 100–250 mg IM once in 2–4 weeks
	Testosterone gel 5–10 gm daily
Hypogonadism (women)	Cyclical hormone therapy (estrogen + progesterone)
Fertility	hMG/hCG therapy
Hyperprolactinaemia	Bromocriptine (2.5–7.5 mg/day) or Cabergoline (0.5–3.0 mg/week)
Growth hormone deficiency	Inj. Growth hormone 0.1 U/kg body weight
	6 times a week
Diabetes insipidus	DDAVP nasal spray 0.1–0.2 ml bedtime
	DDAVP tablets 0.1–0.4 mg in divided doses

Although for most patients the post-operative period is uneventful, an individual patient developing complications may require close monitoring and the management team with the relevant knowledge could efficiently handle this. This chapter has been written keeping this goal in mind.

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155 Empty Sella Syndrome

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An empty sella is defined as a sella, which, regardless of its size, is completely or partially filled with cerebrospinal fluid (CSF). The pituitary gland is compressed and lies posteriorly and inferiorly in the sella. To describe this finding, several different terms were used in the past such as intrasellar arachnoid diverticulum, intrasellar cyst, deficient sellar diaphragm and intrasellar cistern.[2,37,39,46] In 1951,[14] Busch, in a series of autopsy studies, found that in 5.6% the diaphragma sella was deficient and the arachnoid had herniated into the sella, enlarging it and displacing the pituitary gland posteriorly and inferiorly. He coined the term empty sella for this anatomical finding. However, the term empty sella is, in fact, a misnomer as the sella is not completely empty, but the pituitary is always present both anatomically and functionally, although often it is displaced downwards and compressed by CSF pressure.[37] Bergland et al. and Kaufman et al.,[34] in 1968, elucidated the condition further with anatomical and radiological studies. Le Clercq et al.,[38] in 1974, called it intrasellar arachnoidocoele.

Empty sella syndrome can be primary or secondary. Primary empty sella (PES) syndrome is that which occurs in the absence of pituitary surgery or irradiation for pituitary disease and secondary empty sella is that which occurs following these procedures. Although the sella is empty in both these conditions, they form two distinct entities with differing aetiology, symptomatology and prognosis.

PATHOGENESIS

The diaphragma sella forms the roof of the pituitary fossa. It has a central opening which transmits the infundibulum. The diaphragm separates the cranial subarachnoid space from the pituitary fossa. Anatomical variations in the diaphragm have been seen in 22–72% of cases.[6,14,35] Defects in the diaphragm may lead to herniation of the arachnoid into the sella and accumulation of CSF.[20] These defects are more common in women than men, in a ratio of 5:1.[14] In 1926, Scaeffer was the first to observe various anatomical forms of the diaphragma sellae; these ranged from densely thick with a complete roof to that composed of a peripheral veil. Busch, in his study of 788 sellae in patients without a history of pituitary disorders, classified the diaphragma sella into the following categories, which were later referred to by Kaufman in l972.

Type 1-A: The diaphragma sellae forms a complete seal.
Type 1-B: A slight tunnel-shaped depression is present in the intact diaphragma sellae.
Type 2-A: An opening about 3 mm or smaller in the diaphragma sellae exists around the hypophyseal stalk.
Type 2-B: A slight funnel-shaped indentation towards the middle of the diaphragma sellae is present.
Type 3-A: The diaphragma sellae is composed of a 2 mm or smaller peripheral veil, leaving the pituitary gland freely exposed and covered with arachnoid.
Type 3-B: The diaphragma sellae is as described for Type 3-A but the pituitary gland is indented, often eccentrically.
Type 3-C: The deficient diaphragma sellae is as described in Type 3-A; however, indentation of the pituitary gland is marked.[1,34]

An incomplete sellar diaphragm is an essential prerequisite for the development of the empty sella.[5] All other factors are only predisposing to the development of intrasellar subarachnoid herniation, whether by causing increased pressure in the suprasellar subarachnoid space or by reduction in the size of the pituitary gland.[37]

Congenital Factors

Deficiency of the diaphragma sellae.

Suprasellar Factors

When the diaphragma sellae is incomplete, CSF pulsations act directly on the upper aspect of the pituitary gland. In addition, a posteriorly placed optic chiasma may also expose the upper surface of the pituitary gland and thereby increase the CSF pressure on it. The suprasellar cistern pressure is accentuated when the intracranial pressure is raised, secondary to hydrocephalus, brain tumours (Fig. 1), Arnold-Chiari malformation,[8] periorbital venous vasculitis,[28] superior sagittal sinus thrombosis with a dural arteriovenous malformation,[27] etc.

Impaired CSF circulation was demonstrated in more than 80% of patients by Brismar and Bergstrand, who

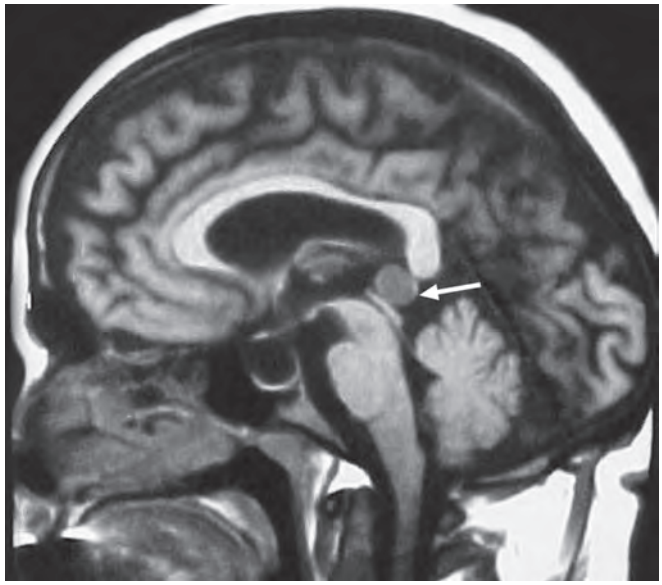

Fig. 1: MRI of a patient having a pineal tumour (white arrow) and empty sella

also pointed out the similarity between empty sella syndrome and normal pressure hydrocephalus, in their symptomatology.[10]

Intrasellar Factors

Any reduction in size of the pituitary gland favours intrasellar extension of the suprasellar subarachnoid space. Such reductions may be due to:

i. *Physiological involution:* This often occurs in women. Pregnancies bring about a large variation in the size of the pituitary gland and after delivery there is an involution. Similarly, after menopause there is a reduction in the pituitary volume. A similar situation occurs in cases of primary end-organ failure (thyroid, adrenal, gonad), wherein pituitary hyperplasia occurs due to loss of feedback control. Replacement of the deficient hormone results in feedback suppression of the pituitary tropic hormone secretion and involution of the hyperplastic pituitary gland, resulting in an 'empty sella'.[7]
ii. *Pathological involution:* Shrinkage of the pituitary gland may occur after post-partum pituitary necrosis (Sheehan's syndrome) or pituitary infarction in patients with vascular diseases, diabetes, increased intracranial pressure, head injury, meningitis or cavernous sinus thrombosis.

Pituitary apoplexy: Pituitary adenomas undergoing spontaneous necrosis (ischaemia or haemorrhage). The arachnoid descends into the sella, to occupy the space created by resolution of the tumour.

Rupture of an intrasellar or parasellar cyst: Fluid-filled cysts of the sellar region are well known and may cause visual or endocrine symptoms, as well as changes in the contour of the sella. Rupture of such a cyst allows intrasellar extension of the subarachnoid space. However, such rupture probably occurs only rarely.[37]

Systemic Factors

Hypertension

PES may be associated with systemic hypertension, which may cause an intermittent rise in intracranial pressure.[34]

Obesity

It is proposed that morbid obesity may induce hypercapnia, which can be the cause of chronic CSF pressure elevation and in turn may lead, in subjects with hypoplastic diaphragma sellae, to the intrasellar herniation of the suprasellar subarachnoid space.[4,20,42]

PRIMARY EMPTY SELLA

PES may be associated with variable clinical conditions ranging from the occasional discovery of a clinically asymptomatic arachnoid pouch within the sella turcica to severe intracranial hypertension and rhinorrhoea.[44,48]

PES may be seen anatomically and radiologically without producing any symptoms or signs. Large defects in the diaphragm without herniation of the arachnoid have also been seen.[14,35]

On routine MR screening of patients without any pituitary disease or symptoms of empty sella, a significant number had been found to have empty sella. Foresti et al.[22] found a totally empty sella in 11.3% of males and 13.5% of females. Partially empty sella was seen in 16.1% of males and 15.1% of females. The incidence of empty sella increases with age.[29] On the whole, empty sella was found in 9.6% of patients below the age of 40 and in 39.9% above 40 years.[22] It has been suggested that an empty sella found on routine MR scanning is usually of no clinical significance.[29]

Raised ICP is an important factor in the pathogenesis of PES syndrome. Empty sella is commonly symptomatic in middle aged obese women and resembles the occurrence of benign intracranial hypertension (BIH) in this respect. An empty sella has been found in 10–12% of patients with BIH.[17,18,21,56] The causal relationship between ESS and BIH can be explained by two mechanisms. Raised intracranial pressure could produce a herniation of the subarachnoid cistern into the sella turcica if the diaphragma sellae is incomplete. Alternatively, infarction in a pituitary adenoma could result in both an ESS and a CSF flow obstruction, which could lead to BIH.[17]

The diaphragm may be congenitally deficient or might have been destroyed by the tumour. In summary, the factors that lead to PES syndrome are insufficiency or absence of the diaphragma sella, increased CSF pressure due to various causes and pituitary involution.

Symptoms and Signs

These may be divided into systemic, neurological and endocrine. The majority of patients who exhibit symptoms form a fairly homogeneous group. About 80% are

females in the fourth and the fifth decades of life with predominant obesity.[32,47,57] About 30% have hypertension. These are the systemic manifestations.

The most common neurological symptom is headache, which occurs in 50–70%.[23,32,47,53] In many, the empty sella is discovered on routine skull X-rays taken during the investigation of chronic headache.[43] The pulsations of the CSF against the dura have been thought to be the cause of the headache.[45]

Visual disturbances may occur and have been reported in up to 34%,[23] although in some other series, it is not so common.[7,13,54] The visual field defects that are seen are bitemporal and binasal haemianopia. The defects are due to the descent of the optic chiasm into the sella producing traction on the optic apparatus.[12] Decreased visual acuity and papilloedema may be seen when there is raised ICP. A typical glaucomatous visual field and optic disc changes have been reported in association with empty sella.[4]

Memory disturbances, imbalance, dizziness, convulsions and CSF rhinorrhoea are the other neurological manifestations that may occur. CSF pulsations inside the sella cause bony erosions in the sellar floor and lead to dural deficiencies and CSF leak into the sphenoid sinus, leading to rhinorrhoea. It has been reported to occur in up to 11.8% of patients with empty sella.[3,23,24,48]

Endocrine symptoms are not common, being reported in 10–15%[11,19,47] of patients. Endocrine function tests have been found to be abnormal in 30–50%.[23,53] The most common is deficiency of growth hormone and reduced response of GH to insulin-induced hypoglycaemia.

Hyperprolactinaemia is not as high as in a prolactin secreting adenoma,[11] unless the partially empty sella is associated with a prolactinoma. The prolactin level is usually below 100–125 ng/ml. The pituitary stalk gets kinked against the diaphragm, as it descends into the sella, giving rise to pituitary stalk effect.[9,25] Hyperprolactinaemia, resulting in galactorrhoea and ammenorrhoea in a middle aged woman associated with a PES syndrome, has been reported.[25,49] Hypersecretion of ACTH and GH may be found, if associated with a secreting tumour.

Hypopituitarism may occur and this is most likely due to compression of the infundibulum as it descends into the sella and not due to flattening and compression of the pituitary gland. Normal morphology and secretory granules have been demonstrated in the compressed gland.[5] When the empty sella is due to necrosis or apoplexy in a pituitary tumour, hypopituitarism can occur.[28] Precocious puberty has been reported in a young girl with empty sella.[52] Hypogonadotrophic hypogonadism has been seen in association with empty sella.[16] Around 10.9% of children evaluated for disorders of the hypothalamic-pituitary axis were found to have empty sella.[15] Antipituitary hormone autoantibodies were evaluated in patients with pituitary tumours and empty sella.[43] Discrimination between the two was not possible. The presence of antipituitary hormone antibodies was neither specific for nor predictive of the endocrine deficiencies.

Radiology

Radiographs of the skull, when done for symptoms such as headache, may show an enlarged sella and this may lead to a diagnosis of empty sella. There may be uniform remodelling of the sella which assumes a globular shape. The lamina dura is intact. The globular shape occurs early and further enlargement follows that pattern. There is thinning of the dorsum sellae and slight bowing posteriorly. Displacement of the dorsum sellae does not occur. The floor of the sella is concave in the AP projection. Double contour of the floor and erosion, which are characteristic of intrasellar tumours, may be seen in PES.[33] Before the advent of CT and MR, pneumoencephalography was the procedure of choice. It was demonstrated by entry of air into the intrasellar space in the sitting or brow-up position.[41]

On the CT, low density similar to that of CSF is seen in the sella. It may be difficult to differentiate an empty sella from other conditions due to artefact. CECT and thin high resolution coronal sections make identification of the infundibulum easier. The "infundibulum sign" differentiates empty sella from other similar CSF density lesions like a cystic tumour. The infundibulum will be seen to traverse a low density space and end in the posteroinferior aspect of the sella.[30] Water soluble contrast or air cisternography may be used when MR is not available.[2,31,50] In the differential diagnosis, one should bear in mind cystic intrasellar tumours, intrasellar cyst and dilated intrasellar third ventricular recess.[41]

MR will clearly delineate the infundibulum and the flattened pituitary gland. The normally high signal seen in the posterior lobe may be absent due to compression. Herniation of the optic nerves and chiasm can be seen very clearly and the degree of descent assessed.[36] This is especially important in secondary empty sella when a differentiation has to be made between empty sella, recurrence of tumour or radiation necrosis, when there is delayed visual loss.

SECONDARY EMPTY SELLA

Secondary empty sella occurs after surgical and/or radiation therapy of a pituitary tumour (Fig. 2).

The arachnoid descends into the sella through a congenitally deficient diaphragm or due to destruction of the diaphragm by tumour. Secondary empty sella occurs when the tumour shrinks and leaves an empty space.

The predominant clinical finding in these patients is visual abnormality, occurring due to arachnoidal adhesions and traction on the optic apparatus. They may have initial improvement in visual symptoms with surgery, followed by recurrence of symptoms due to the development of empty sella. Some patients who do not have visual symptoms initially may present with a fresh onset of these symptoms.[37]

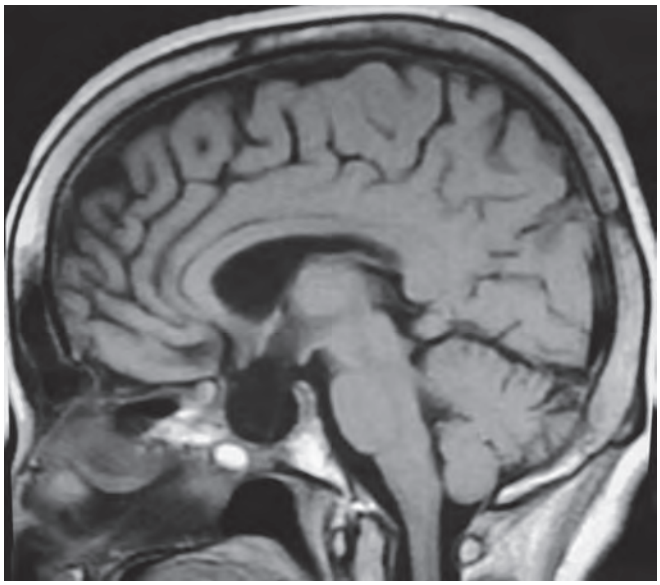

Fig. 2: MRI sagittal of a patient with secondary empty sella showing evidence of trans-sphenoidal surgery with empty sella

The presenting symptom will usually be visual deterioration, which may occur even years after the initial treatment. Bitemporal and binasal haemianopia are common, but other defects, like peripheral field constriction, central scotoma or segmental defects, can occur.[13,38,40,55] These have to be differentiated from the visual defects that arise due to recurrence of pituitary tumours, arachnoidal adhesions around the optic nerve and chiasm and radiation necrosis.

Endocrine symptoms due to hypersecretion or hyposecretion are more common in secondary empty sella than in the primary variety. This is mainly due to the tumour itself and not due to the empty sella. CSF rhinorrhoea can occur due to shrinkage of the tumour.[42]

Treatment

Empty sella syndrome is usually a benign condition. The majority of cases do not require treatment, except symptomatic, for headache. Hypertension must be treated and weight reduction advised in obese patients. Endocrine tests should be done and appropriate replacement given, if there is hyposecretion of any of the hormones including gonadotrophins. Hyperprolactinaemia is easily controlled with bromocriptine and smaller doses are required, when compared to doses used in the treatment of prolactinomas.[9]

CSF rhinorrhoea requires prompt surgical treatment, as the fistula rarely closes spontaneously. When associated with hydrocephalus or BIH, an initial CSF diversion procedure, like ventriculoperitoneal or lumboperitoneal shunt should be done and, if the leak persists, definitive surgery must be undertaken. When the fistula is from the sella into the sphenoid, the trans-sphenoidal route is ideal. The sellar dura should be opened and the sella packed with fat covered over by fascia. The sphenoid sinus is packed with fat. While operating inside the sella, care should be taken to avoid injury to the infundibulum, especially while exploring for a possible recurrence of tumour. The infundibulum descends into the sella bringing with it the median eminence and, therefore, damage to the infundibulum can occur close to the median eminence, producing permanent diabetes insipidus.

When visual symptoms are present, especially in secondary empty sella, the cause should clearly be identified. On MR, if there is a clear demonstration of descent of the optic apparatus into the sella and there is kinking of the optic nerves or chiasm, chiasmapexy is indicated.[55,58] This involves elevation of the optic apparatus and is ideally done through the trans-sphenoidal route. The dura should be elevated and the space between the dura and the bone packed with autologous tissues such as muscle, fat, fascia, bone and cartilage. Fat and muscle may get absorbed over the long term after surgery. Cartilage is more suitable due to the rigidity and resistance to absorption. Synthetic materials, such as silicone balloons and tubings, have been used with good success.[37] Opening the dura and packing intradurally may lead to troublesome CSF rhinorrhoea.[51]

Patients diagnosed to have an empty sella should be followed up regularly and any progression of symptoms should appropriately be treated. Sudden and rapid deterioration, especially in vision, may occur and the patient should be warned of this.

Patients with no abnormalities at baseline are unlikely to develop neurological/ophthalmological symptoms or endocrine abnormalities in the follow-up. Moreover, the radiological degree of PES also tends to remain constant over time. However, because of the theoretical risk of progression, a re-evaluation after 24–36 months (if there are no clinical indications before) of the endocrine, neurological/ophthalmological and radiological picture is reasonable. If progression is not observed, additional control evaluation could be even less frequent and limited to those patients requiring it clinically.[42]

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156 Diencephalic Syndrome

Anil Pande, Murali Mohan S

Russel's diencephalic syndrome was described in 1951 as a syndrome of emaciation and loss of subcutaneous fat, with normal height and muscle mass in infancy and childhood.[18,22] He observed that the symptomatology was due to a neoplasm involving the anterior thalamus, hypothalamus, optic chiasm and anterior third ventricle. This has since been elaborated by several others.[2,6,7,10]

DIENCEPHALON

The brain develops from the expanded cephalic part of the neural tube (encephalon) and the caudal part (myelon) forms the spinal cord. Two constrictions first appear in the encephalon, dividing it into three primary vesicles: (1) the forebrain (prosencephalon); (2) the midbrain (mesencephalon) and (3) the hindbrain (rhombencephalon). At approximately 2 months of gestational age, these three primary vesicles differentiate into five cerebral vesicles. The prosencephalon divides into two vesicles—the telencephalon (the end brain) and the diencephalon (the inter-brain). The mesencephalon does not divide. The rhombencephalon divides to form two vesicles—the metencephalon and the myelencephalon. The telencephalon further differentiates and separates to form two telencephalic vesicles, which eventually become the cerebral hemispheres and encircle the underlying diencephalon, making the latter, the central region of the vertebrate brain. The lateral walls of the diencephalon later differentiate to form the thalamus on either side, the ventral floor forms the hypothalamus and the dorsal wall gives origin to the pineal body (the epithalamus), but remains undifferentiated for a considerable distance to form the lamina epithelialis. The thalamus is separated from the hypothalamus by a prominent sulcus called the hypothalamic sulcus. The median telocoele and the cavity of the diencephalon transform to form the third ventricle.

The diencephalon is thus the central region of the vertebrate brain, where the thalamic nuclear complex, pretectum and anterior tegmental structures are generated. Table 1 represents the structures comprising the diencephalon. It comprises of the synencephalon, dorsal and ventral thalamus. The hypothalamus is the ventral part of the alar derived diencephalon. The median telocoele and the cavity of the diencephalon form the third ventricle. The diencephalon is derived solely from the alar plate and a hypothalamic sulcus divides the alar diencephalic area into a dorsal region of thalamus and ventral hypothalamus. The third ventricle is an important diencephalic cavity.

Table 1: Structures comprising the diencephalon

1. Derivatives of dorsal thalamus
   a. Thalamus
   b. Metathalamus—medial and lateral geniculate bodies
2. Derivatives of ventral thalamus
   a. Zona incerta
   b. Nucleus reticularis thalami
3. Derivatives of hypothalamus
   a. Dorsal nuclear group—globus pallidus, subthalamic nucleus, interstitial nuclei of the inferior thalamic peduncle and the entopeduncular nucleus
   b. Ventral nuclear group—hypothalamus
   c. Evaginations—neurohypophysis and the optic stalk derivatives
4. Derivatives of epithalamus
   a. Habenular nuclei and the commissure, stria medularis and taenia tectae
   b. Evagination—pineal body

DIENCEPHALIC SYNDROME

Russel's diencephalic cachexia (always) indicates the involvement of the hypothalamus by compression or invagination by lesions arising from the floor of third ventricle or adjacent area.[18,19] There is a uniform loss of body fat with normal linear growth, pallor, hyperkinesis, hypertension, hypoglycaemia, hyperhydrosis, increase in the size of hands and feet, precocious puberty, emesis, headache and increasing head circumference due to hydrocephalus. Ocular signs include nystagmoid rotary eye movements, optic atrophy and visual loss.[2,7]

Clinical Features

This syndrome is a disease of childhood, usually seen in children less than 2 years of age, with an age range of 14–26 months.[4,13,16] There is a slight male preponderance.[13,16] Failure to thrive and progressive emaciation with normal linear growth is the characteristic clinical presentation of this syndrome. Nystagmoid eye movements are described to be present in up to 60% of these patients, and may be the first sign of a CNS cause for

failure to thrive. Other common presentations includes lid retraction (87%), increased vigour (72%), euphoria (59%), pallor (55%), hydrocephalus with features of raised ICP (33%), optic atrophy (24%), hyperhidrosis (15%), precocious puberty (8%) and polydipsia (< 5%).[2,10,11,16] There is a reported case of this syndrome in an adult who had associated von Recklinghausen's disease.[21]

Pathophysiology

The "failure to thrive" is seen in up to 25% of children with hypothalamic lesions. This is due to failure of inhibition of GH and LHRH secreting mechanisms in the anterior hypothalamus. The growth hormone levels are elevated with no diurnal rhythm and are non-responsive to hyperglycaemic or hypoglycaemic changes.[5,6] The Somatomedin C and IGF levels are normal in these patients.[6] Lipolysis is attributed to elevated GH levels, acquired partial GH resistance, low level of leptin and impaired metabolic regulation of adiposity.[6] This lipolysis causes the look of profound emaciation with complete loss of subcutaneous fatty tissue. Leptin is an adipocyte hormone, deficiency of which causes severe obesity in children. Loss of weight in these patients is believed to be due to the effect of dysregulation of leptin secretion on transient hypothalamus-pituitary-gonadal axis activation in the 1st year of life.[5,6] Dysregulation of ghrelin, a gastric hormone found to be a secretagogue for GH and to influence appetite and adiposity, might result in loss of adipose tissues in association with elevated GH levels.[6]

Pathology

Lesions causing diencephalic syndrome are mostly astrocytic tumours (80%). Less commonly ependymomas, craniopharyngiomas, germinomas, suprasellar epidermoids, hamartomas and cysts may produce this constellation of signs and symptoms.[16]

Raimondi[17] classified paediatric supratentorial tumours as hemispheric, suprasellar, diencephalic and lateral ventricular tumours. Of the diencephalic tumours, 40% were astrocytomas, 16% glioblastoma, 6% choroid plexus papillomas, 6% PNET, 3% ependymomas, 3% colloid cysts, 3% oligodendrogliomas and 23% unknown.[17]

The astrocytomas which are associated with the diencephalic syndrome are larger, occur at a younger age and have a more aggressive behaviour.[6,7] Juvenile pilocytic astrocytomas and the recently described chondroid astrocytoma which is a glioma variant are unique to the hypothalamus and anterior third ventricle. Gross appearance of the tumour is usually soft, translucent and gelatinous; rarely it maybe large, reddish, fleshy, firm and vascular. The molecular biology of these paediatric astrocytic tumours is very different from the adults, with only 15% showing 17p mutation, and p53 mutation is very rare. Many low grade tumours often demonstrate no genetic abnormality. MIBI labelling index correlates positively with survival.[15]

Histologically, these tumours have moderate cellularity with biphasic pattern of compact pilocytic zones that stain for GFAP, which are centred round the blood vessels and loosely arranged microcystic protoplasmic cellular areas with associated open honeycomb background. There are brightly eosinophillic rounded or elongated fusiform or sausage like Rosenthal fibres, which are considered to be of degenerative origin.[15,16]

MANAGEMENT

Children with failure to thrive and associated nystagmoid movements of the eyes should have CNS screening done to rule out the possibility of lesions in the diencephalic area.[2,7,16]

Imaging Studies

X-ray of the skull can show enlarged optic foramina in cases of optic nerve gliomas, suprasellar calcification in craniopharyngiomas and features of raised ICP in the form of erosion of dorsum sella, silver beaten appearance and sutural diastases.

Cranial ultrasound, in children with an open fontanel, may reveal a third ventricular lesion with or without hydrocephalus.[6]

Juvenile pilocytic astocytoma occurs in the region of the diencephalon, including the hypothalamus, visual pathway and the basal ganglia. These are usually solid infiltrating masses but may have an associated cyst. These are usually hypodense on plain CT and seldom enhance with contrast.[16] MRI is the investigation of choice and can be supplemented by MR spectroscopy, which is extremely useful for a non-invasive probable histological diagnosis. On MRI, these are hypointense to isointense on T1 images and mildly hyperintense in T2 images with ill defined margins and irregular patchy contrast enhancement, with or without associated hydrocephalus (Figs 1 and 2).[16]

Thirty per cent of these tumours present with a large size at diagnosis, making it difficult to determine their site of origin (chiasmatic or hypothalamic). Optic nerve gliomas are seen in 15% of the patients with neurofibromatosis type I and only about 20% of the chiasmal gliomas behave aggressively.[13] Seventy per cent of these lesions occur in the first decade of life. Chiasmatic gliomas are more aggressive than optic nerve gliomas and invade the hypothalamus and the floor of the third ventricle causing obstructive hydrocephalus.[2,4]

Suprasellar germinomas are rare and only 20% of these lesions occur in this area; most of them occur in the pineal region where these are isodense to slightly hyperdense and enhance homogeneously with contrast. On MRI they are hypointense or isointense on T1 and isointense to hyperintense on T2 images, with homogeneous enhancement.

Craniopharyngiomas are seen as well circumscribed and multilobulated tumours and 90% may have an associated cystic component. Both cysts and calcification are

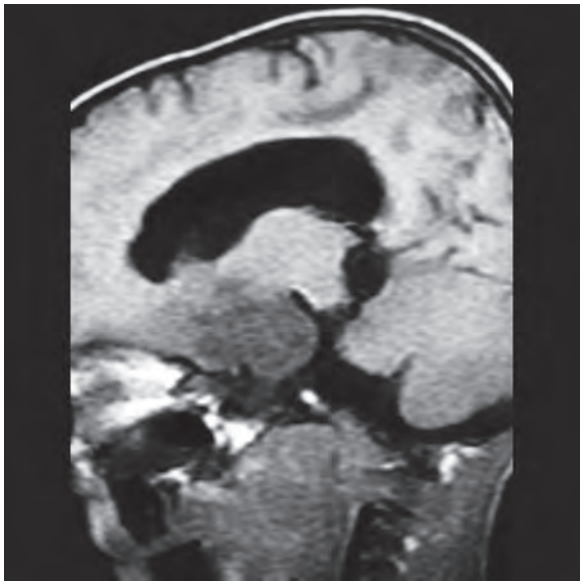

Fig. 1: MRI of the brain sagittal section showing hypointense lesion involving the hypothalamus

common in children. On MRI, the hyperintensity correlates with protein and methaemoglobin components on T1 images. T2 images will show a typically hyperintense lesion, with calcification seen as signal void areas.

Ependymomas are heterogeneous lesions and may have associated intratumoural cysts. These lesions are usually contrast enhancing. Fifty per cent of these lesions may have calcification, which can be small and flecky or less commonly large and lumpy. On MRI, they have heterogeneous intensity, with the cystic part being slightly hyperintense to CSF. The heterogeneous hyperintensity on T2 images is due to necrosis, calcification, blood degradations and intratumoural cysts.

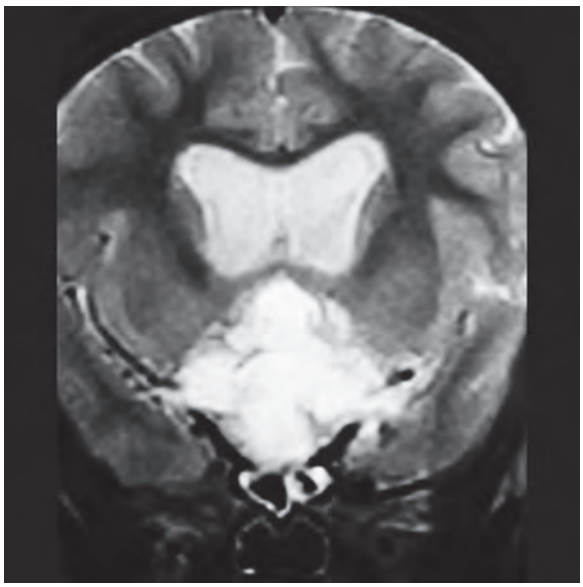

Fig. 2: MRI of the brain coronal section showing hyperintense lesion involving the hypothalamus with dilated lateral ventricles

Hamartomas of the tuber cinereum are seen as isodense masses in the suprasellar region, with no enhancement with contrast. In MRI, they are isointense on T1 images and isointense to slightly hyperintense on T2 images and are non-enhancing with contrast. Hydrocephalus has been associated with these lesions with an incidence of 55–58%.[4,6] Leptomeningeal spinal and cranial seeding has been reported in these lesions and requires clinical suspicion and may warrant a screening of the whole neuraxis.[16]

Endocrine Assessment

These children, once diagnosed, must be evaluated endocrinologically.[1,3] A complete endocrine immunoassay is performed. The T3, T4 and TSH are within normal range. ACTH stimulation and metyrapone test are abnormal and point towards an abnormal hypothalamic-hypophyseal-adrenal axis. Somatomedin levels are usually low. The growth hormone levels are usually elevated and are not influenced by change in blood glucose levels. On administration of propranolol and L-dopa there is an inappropriate fall in the levels of growth hormone.

Germinomas may present with diabetes insipidus and precocious puberty, which can occur in the male child due to elevated levels of beta-hCG. Female children do not present with precocity, as the beta-hCG requires the priming effect of oestrogen on the ovary for its action.[10]

Treatment

The treatment modalities include observation,[20] biopsy using CT or MRI based stereotaxy, surgery,[9,20] radiotherapy and chemotherapy.[12,14] The management of these lesions is difficult and although histological conformation of the lesion has been advocated as an initial step, MR spectroscopy will perhaps play a large role in the histological characterisation of these lesions non-invasively. Pre-operatively inadequate caloric and malabsorption problems have to be excluded along with proper imaging and endocrine and electrolyte evaluation.

Surgery for the lesions causing diencephalic syndrome is difficult due to a varied spectrum of pathology, younger age group, large size of the tumour at presentation, diffuse and infiltrating nature of these lesions, eloquence of the area and lastly, the problem of finding a safe corridor to these lesions. Poor prognosis has been reported by Raimondi for children under the age of 1 year, who harbour a hypothalamic optic nerve glioma and present with diencephalic syndrome.[17] Russel,[18] in his original monograph and others,[3,8,11,13] have reported survival ranging 8–12 years without treatment.

A progression-free survival period of 70–90% at 5 years has been reported for low grade astrocytic tumours. The extent of surgical resection is the only reliable prognostic factor, but this has to be taken into consideration along with a much higher morbidity, associated with

aggressive surgery in diffuse and infiltrating lesions. Surgical approaches are tailored according to the experience of the surgeon, the clinical features and imaging.[9,11]

Conventional frame based stereotactic surgery may be difficult in these small children and frameless stereotaxy has a much larger role to play. CSF diversion procedures like endoscopic third ventriculostomy or ventriculoperitoneal shunt may be required for the management of hydrocephalus.[4]

Chemotherapy has now proved to be useful in these children and can delay, if not replace, radiotherapy. In very young children, the first option of a combination of actinomycin D and vincristine can be tried out. There are reports suggesting disease stabilisation in 80% of cases, which lasted for a mean of 3 years and thereafter radiation could be given at a median age of 4.5 years, instead of 1.5 years. Carboplatin along with vincristine and vincristine with lomustine and prednisolone are other combinations, which have been tried and have demonstrated significant disease control. However, for ependymomas and germ cell tumours, chemotherapy has a limited role.[12,14,15]

Radiotherapy is beneficial in the treatment of residual and recurrent tumours and even as a primary treatment for unresectable tumours of the hypothalamus and optic pathway. Reports of chiasmatic glioma children, treated with radiotherapy alone, show that they have a 10 year progression-free survival in 89% and an overall survival of 100%.[15] The use of radiation is limited, due to its adverse effect on the developing brain. Long-term complications of radiotherapy in children include CNS necrosis, myelopathy, leucoencephalopathy, vascular injury, neuropsychological defects, hormonal imbalance, bone and teeth abnormalities, ocular toxicity, ototoxicity and secondary malignancies.[15] Recently, stereotactic radiosurgery has been advocated.

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157 Other Tumours of the Sellar Region

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INTRODUCTION

The sellar region is a small but complex area with neural, vascular, endocrine, osseous and meningeal structures. This accounts for the broad-spectrum of tumours and tumour-like conditions affecting this area. Although pituitary adenomas, craniopharyngiomas, meningiomas (tuberculum sellae, planum sphenoidale, diaphragma sellae, etc.), gliomas (optic nerve, infundibulum, posterior lobe and hypothalamus) and epidermoids/dermoids form the majority of tumours arising in the sellar and juxtasellar region, there is an impressive list of other rare tumours which may involve this area. This is of practical importance to a neurosurgeon, as these tumours may mimic the commonly occurring lesions in this area, both clinically as well as at radiology. The differential diagnosis of the many tumours and tumour-like conditions occurring in the sellar region is listed in Table 1.

Table 1: Differential diagnosis of sellar region masses

The most common tumours in this region—pituitary adenoma, craniopharyngioma, meningioma—are described in separate chapters. This chapter deals with uncommon lesions in the sellar region.

Tumours of adenohypophyseal origin
- Pituitary adenoma
- Pituitary carcinoma

Tumours of neurohypophyseal origin
- Granular cell tumours
- Neurohypophyseal gliomas
- Tumours of non-pituitary origin
- Craniopharyngiomas
- Gliomas
- Meningiomas
- Haemangiopericytomas
- Germ cell tumours
- Chordomas
- Chondromas/Chondrosarcomas
- Haemangioblastomas
- Giant cell tumours of the bone
- Lipomas
- Fibrous dysplasia
- Sarcomas
- Gangliogliomas

Contd...

Contd...
- Ganglioneuromas
- Paragangliomas
- Schwannomas
- Glomangiomas
- Esthesioneuroblastomas
- Primary lymphomas
- Melanomas

Metastatic tumours
- Carcinomas
- Lymphomas
- Leukaemia
- Plasmacytomas
- Sarcomas

Cysts, hamartomas and malformations
- Rathke's cleft cyst
- Arachnoid cyst
- Ependymal cysts
- Epidermoid cyst
- Dermoid cyst
- Gangliocytomas/Choristomas
- Hypothalamic hamartomas
- Empty sella syndrome

Tumour-like conditions

Inflammatory
- Infections/Abscesses
- Lymphocytic hypophysitis
- Mucocoeles
- Sarcoidosis
- Giant cell granuloma
- Histiocytosis X

Infiltrative
- Amyloidosis
- Haemochromatosis
- Mucopolysaccharidosis

Vascular lesions
- Internal carotid artery aneurysm
- Cavernous angiomas

PITUITARY CARCINOMA

It is a rare entity. Fewer than 140 reports exist in the English literature.[35] Pituitary carcinoma is defined as any tumour of adenohypophyseal origin with demonstrated

craniospinal and/or extracranial metastatic dissemination.[14,25,41] Diagnosis is based on tumour behaviour, rather than histology as features like nuclear atypia, mitotic activity, necrosis and haemorrhage, may also be seen in pituitary adenomas. Craniospinal metastasis occurs by dissemination via cerebrospinal fluid. Extraneural metastases to bone, liver, lymph nodes, lungs, kidney and heart have been reported.

The criteria that need to be fulfilled for classifying a lesion as pituitary carcinoma are:[26]

- The primary tumour must be identified as a pituitary tumour at histology.
- An alternative primary tumour has to be excluded.
- Discontinuous spread in the form of single or multiple, nodular subarachnoid metastatic deposits, occasionally invasive of underlying brain or overlying dura, may be seen.
- Single or multiple systemic deposits broadly similar to and grossly indistinguishable from metastases of carcinomas, arising in other organs, may be seen.
- The structural features or marker expressions of the metastases should correspond or be similar to those of the pituitary tumour.

Less than 0.5% of all pituitary tumours turn out to be malignant. They usually affect adults with a slight female preponderance. They may be hormonally active or inactive. Most common are the ACTH producing tumours. Next in frequency is prolactin producing tumours. Although GH producing pituitary carcinomas have been described, they are very rare.

Pathology

The mode of spread of these carcinomas is by means of local invasion and through the venous system, the CSF pathways and the lymphatics. It is thought that venous spread occurs through the cavernous sinus initially. From here, spread occurs to the internal jugular vein through the petrosal system. It has also been postulated that retrograde spread through the cortical draining veins may affect the superior sagittal sinus. Spread occurs through the CSF pathway once the subarachnoid space is invaded and may involve the supratentorial, infratentorial or spinal compartment. Although the pituitary gland lacks lymphatic drainage, spread through lymphatics may occur once the tumour invades the skull base, which provides access to a rich lymphatic network. Systemic spread through the bloodstream may involve the lungs, liver, bones, kidney and the heart. Pituitary carcinomas that spread to the craniospinal axis are often non-functional, while those that metastasise to extracranial sites are usually functional. Most of the tumours which spread systemically are ACTH producing tumours.

Microscopically, pituitary carcinomas originate from and are composed of adenohypophyseal cells. The histological criteria for malignancy, like hypercellularity, nuclear pleomorphism, mitotic figures, necrosis, haemorrhage and even invasion, are not reliable indicators of the malignant nature of the tumour.

Clinical Features

The age of onset of symptoms is similar to that of patients harbouring pituitary adenomas. The rate of progression of these symptoms depends upon the biological behaviour of the tumour. The initial course may be indistinguishable from that of a pituitary adenoma. However, patients may have multiple recurrences and then disseminated disease may eventually manifest. It may be that in such cases there is malignant transformation in a previously benign tumour. Alternately, the clinical course may be fulminant with rapid deterioration of vision, multiple cranial nerve palsy and evidence of metastatic disease. In these cases, the tumour is probably a carcinoma *de novo*.[33] In addition, features of endocrine hyperactivity may be present. Tic like facial pain due to involvement of the Gasserian ganglion and early onset of diabetes insipidus are poor prognostic indicators.[20,27] Features of central nervous system or systemic metastasis may be present, depending upon the site of metastasis.

Radiological Features

There are no characteristic radiological features which distinguish pituitary carcinoma from a pituitary adenoma. Scintigraphy with ^{111}I-labelled octreotide has been used to establish the diagnosis of a metastatic GH-secreting carcinoma[21] and has revealed additional lesions in an ACTH-secreting carcinoma[19] and/or tumour recurrences at follow-up.[12] More recently, PET scan using 18F-labelled deoxyglucose has revealed unsuspected pituitary macroadenomas and also identified metastases from a pituitary carcinoma.[1,17,28] Other radiotracers, such as radiolabelled 5-hydroxytryptamine, are considered to be more sensitive than 18F-labelled deoxyglucose and may lead to the recognition of additional lesions.

Treatment

The treatment of pituitary carcinoma is similar to that of large and aggressive pituitary tumours and includes surgery (usually via the trans-sphenoidal route), external beam radiotherapy and adjuvant medical treatment. The treatment of pituitary carcinomas is mainly palliative and may not prolong survival to any major extent. However, there is retrospective data suggesting that patients who received aggressive treatment may achieve a better survival rate.[25]

Medical treatment is directed against hypersecretory syndromes. Dopamine agonists have successfully been used for the treatment of prolactin-secreting tumours. Although partial biochemical or even objective tumour responses to treatment with dopamine agonists have been described, the great majority of reports have demonstrated either lack of response or tumour progression after treatment with bromocriptine or newer dopamine agonists, such as quinagolide and cabergoline. Tamoxifen has also been given to achieve a synergistic

effect. Dopamine agonists have been used in ACTH-secreting and TSH-secreting carcinomas, but with only minimal benefit. Somatostatin analogues such as octreotide, have been used to control the hypersecretory syndrome in GH- and TSH-secreting pituitary carcinomas, usually with a variable response.

Chemotherapy

5-fluorouracil and methotrexate have been used. However, there is limited experience in the use of chemotherapeutic agents in the treatment of pituitary carcinoma. Newer agents, like paclitaxel, are under investigation.

GRANULAR CELL TUMOURS

Diverse nomenclature has been used to describe this entity in the past, including choristoma, tumorette, myoblastoma and pituicytoma. The generally accepted hypothesis regarding their histogenesis suggests that they are derived from supporting glial elements of the infundibulum and posterior lobe of the pituitary. They may be incidentally detected at autopsy in as many as 17% of cases,[31] usually as barely visible aggregates of tumorettes. Symptomatic granular cell tumours occur as a result of enlargement of these tiny tumorettes. Symptomatic patients usually present in the fourth or fifth decade of life. Women are affected almost twice as often as men. They may present with diabetes mellitus, visual disturbance or other symptoms of a sellar/suprasellar expanding mass lesion. Despite the neurohypophyseal origin of these tumours, diabetes insipidus may not always be present. Histologically, these tumours consist of large polygonal or round cells with eccentric nuclei. There are abundant eosinophilic cytoplasmic granules that are PAS positive and diastase resistant. On immunohistochemistry, they may be positive for S-100, usually negative for GFAP and uniformly negative for all anterior pituitary hormones.

Radiographically, they appear as small rounded masses which are generally isointense on T1- and hyperintense on T2-weighted MR images. They may be mistaken for a meningioma on radiological evaluation, as they enhance intensely on contrast due to their high vascularity. However, they are primarily intrasellar and do not invade surrounding structures. Calcification is generally not seen in these tumours. As granular cell tumours are benign slow growing neoplasms, the prognosis of patients with these tumours is generally favourable following total or subtotal resection, although recurrences are known to occur. Recurrences may be treated with reoperation or radiotherapy.

NEUROHYPOPHYSEAL GLIOMAS

These are rare tumours, generally pilocytic astrocytomas which arise from the infundibulum or the posterior pituitary. They are also known as infundibulomas or pituicytomas. These tumours probably arise from the heterotopic glial tissue which may be present in the subarachnoid space (Fig. 1).

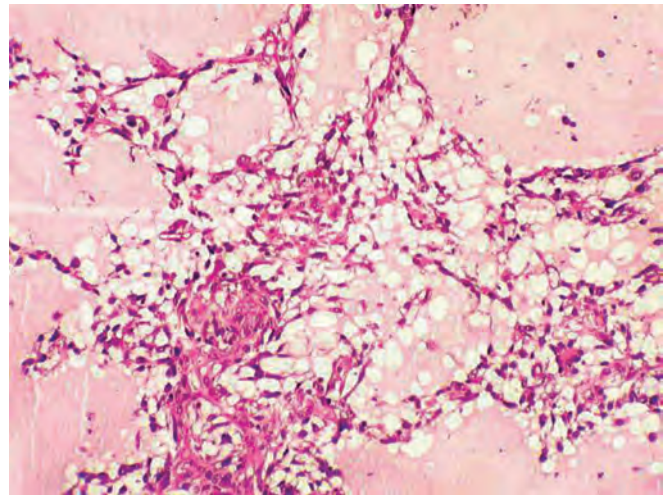


Fig. 1: Pilocytic astrocytoma: Histology reveals a biphasic tumour composed of densely packed piloid cells, displaying oval mildly anisomorphic hyperchromatic nuclei, embedded in fibrillary matrix admixed with loosely cellular areas of stellate cells with microcystic degeneration. (H and E × 100 original magnification)

GERM CELL TUMOURS

Intracranial germinomas (Fig. 2) account for 0.3–3.5% of all intracranial tumours and generally arise in the midline. They are commonly located in the pineal region, although a minority of them may be seen in the sellar/suprasellar region in isolation or in combination with pineal lesions. Therefore, they remain one of the diagnostic considerations in the evaluation of a sellar mass, especially in children.[5,22,24,29,38] Germ cell tumours are

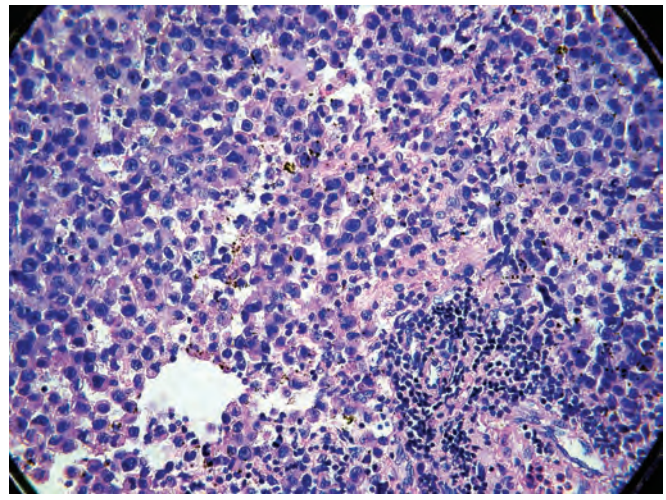


Fig. 2: Germinoma: Histology reveals structure of a tumour, composed of sheets of large uniform polygonal cells traversed by fibrous septa, infiltrated by plenty of small lymphocytes. The tumour cells display large central nuclei with vesicular chromatin, prominent nucleoli and abundant pale cytoplasm with well defined cell borders. (H and E × 100 original magnification)

broadly classified into germinomas and non-germinomatous germ cell tumours which include teratomas, embryonal cell carcinomas, endodermal sinus tumours and choriocarcinomas. Germinoma is the most commonly occurring germ cell tumour in the suprasellar region and generally affects patients in the paediatric age group.

Pathology

Suprasellar germinomas are generally infiltrative lesions, which may involve the hypothalamus, pituitary stalk, third ventricular floor, posterior pituitary and the optic chiasm, nerves or tracts. The site of origin of these tumours is generally not clearly discernable. In most cases, the tumour is located on the under surface of the hypothalamus and is intimately related to the pituitary stalk and optic chiasm. Intrasellar extension occurs in approximately 20%. Rarely, a pure intrasellar lesion may be seen.[5,22,24,29,34,38] All germ cell tumours, except benign teratomas, are known to metastasise. However, most instances of metastasis are within the neuraxis. Non-germinomatous lesions are more likely to metastasise.

Macroscopically germinomas are generally soft, greyish, homogeneous and at times, may resemble lymphomas on gross examination. The cut surface is granular and usually solid. Haemorrhage and necrosis is uncommon, the presence of which indicates a high-grade tumour like embryonal cell carcinoma, endodermal sinus tumour or a choriocarcinoma. Teratomas have solid and cystic components. Mature teratomas are grossly well defined and the cut surface has a variegated appearance. Derivatives of all three germ layers may be seen. Mucin, hair, bone, cartilage and occasionally, teeth may be recognisable.

Microscopically germinomas are composed of large round to oval cells with large nuclei and prominent nucleoli, arranged in islands or trabeculae separated by fibrovascular stroma, containing bands of lymphocytes. In 50%, syncytiotrophoblastic giant cells may be seen and in such cases, human chorionic gonadotropin levels in CSF and/or serum are elevated. Embryonal cell carcinomas are composed of cuboidal/columnar cells arranged in varied patterns. These lesions may have focal differentiation into extraembryonic or embryonic structures leading to expression of alpha fetoprotein (AFP) or human chorionic gonadotropin (HCG) in body fluids (serum/CSF/urine). Endodermal sinus tumours are generally composed of cuboidal cells with intracellular and extracellular globules, which contain AFP and alpha-1 antitrypsin, respectively, which can be demonstrated on immunohistochemistry. Elevated levels of AFP may be found in serum, CSF or urine in these cases. Choriocarcinomas are composed of large cytotrophoblastic cells surrounded by syncytiotrophoblastic cells, which are multinucleated. Human chorionic gonadotropin levels may be increased in CSF, serum or urine and may be demonstrable by immunohistochemistry in tissue sections. In teratomas, a varied combination of tissue elements from various germ cell layers may be seen.

Clinical Features

Characteristically, these tumours appear in childhood and usually present with diabetes insipidus and only later with features of hypopituitarism and visual loss. Hyperprolactinaemia is often present.

Radiological Features

Suprasellar germinomas are typically midline lesions, which are centred at or just behind the pituitary infundibulum. On MRI, they appear mildly hypointense on T1-weighted images and hyperintense on T2-weighted images. They enhance brightly on post-contrast images. Other germ cell tumours may display more heterogeneity, due to more diverse histological elements forming the tumours.

Treatment

Due to the anatomical location of these tumours and their infiltrative nature, total surgical excision is generally not possible. Germinomas are very radiosensitive. It is necessary that the subarachnoid cisterns and ventricular system are included in the radiation field to prevent recurrence from CSF spread. Radiotherapy is not very effective in the treatment of other germ cell tumours. Chemotherapy with cisplatin combined with bleomycin and vinblastin is used, in addition to radiotherapy, for disease control.[15]

CHORDOMAS

Chordomas (Figs 3A and B), derived from notocordal remnants, are uncommon tumours of the bone which may arise from any site along the axial skeleton. The preferred location is the sacrococcygeal spine. Intracranial

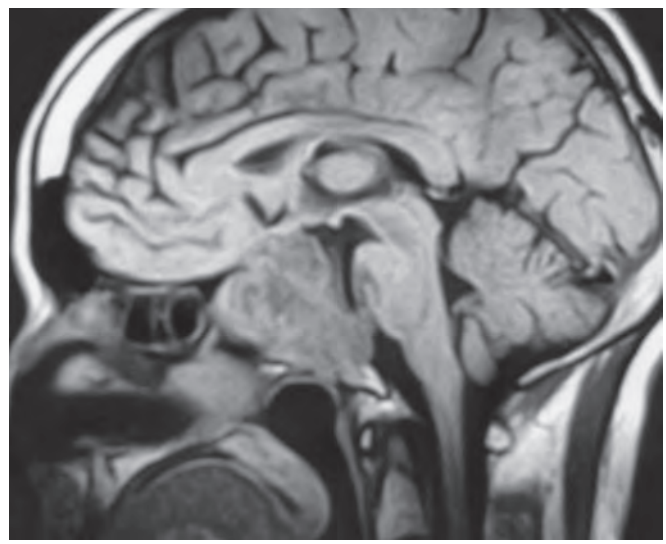


Fig. 3A: T1-weighted sagittal MR image showing a clival chordoma reaching superiorly to the sellar-suprasellar region

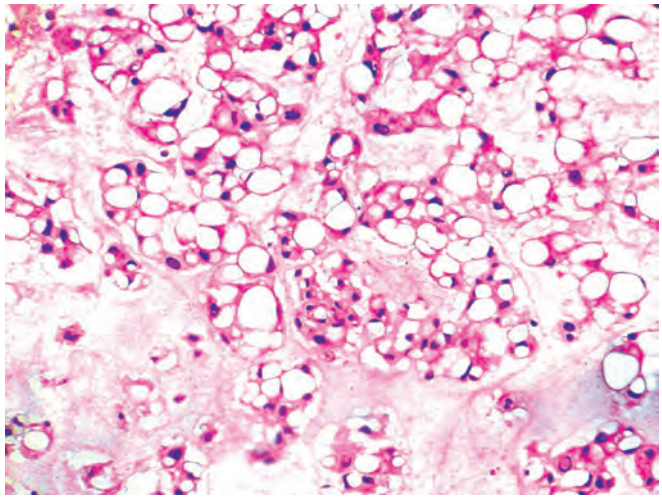


Fig. 3B: Chordoma: Histology reveals lobules of sheets, cords and islands of cells with round to polygonal appearance, abundant vacuolated and bubbly cytoplasm, with hyperchromatic mildly anisomorphic small nuclei, embedded in an abundant myxoid matrix. The physaliphorous cells are interspersed with sheets of large polygonal cells with epithelioid morphology, displaying abundant eosinophilic cytoplasm and pleomorphic hyperchromatic nuclei (H and E × 200 original magnification)

chordomas constitute about 35% of all chordomas and 0.2% of all intracranial tumours.[37] They are typically midline lesions originating in the region of the clivus. They expand the clivus and may extend intracranially to compress adjacent anatomical structures. Extension may occur laterally into the cavernous sinus, anteriorly into the sella and inferiorly into the nasopharyngeal region. Lesions which are limited exclusively to the sellar region are relatively rare.[32]

Pathology

Cranial base chordomas are slow growing, histologically benign lesions, which cause expansile bone destruction at the site of origin and later infiltrate the dura and extend intradurally to displace and compress intracranial structures. They usually arise extradurally but may rarely extend intradurally as well. Although they are histologically benign, due to their osteodestructive nature, progressive course, tendency to recur and capacity to metastasise, they are included among malignant neoplasms. Metastatic dissemination occurs in 10–20% and is generally a late occurrence. Sites most commonly involved are liver, lungs, bone, heart and lymph nodes.

Clinical Features

The clinical manifestations of these tumours depend upon the direction of growth. Lesions which are limited to the midline cause varying degrees of hypopituitarism and chiasmal syndrome due to compression of the pituitary and the optic chiasm, respectively. Lateral extension leads to involvement of the cavernous sinus with proptosis and multiple cranial nerve palsies.

Radiological Features

CT scan may reveal foci of sequestrated bone or irregular calcifications amid the destroyed clival marrow. On MRI, the lesion appears isointense to hyperintense on T1-weighted images and heterogeneously hyperintense on T2-weighted images. Variable post-contrast enhancement is seen. Foci of calcification are seen as dark foci in the soft tissue component of the tumour.

Treatment

The aim of treatment is to increase the likelihood of recurrence free survival. Options include surgery alone or surgery/biopsy, followed by radiotherapy. Radiotherapy may consist of conventional fractionated radiotherapy, proton beam radiation, brachytherapy or radiosurgery.

METASTATIC TUMOURS TO THE SELLAR REGION

A variety of systemic and haemopoietic malignancies may metastasise to the sellar region. In an autopsy series, the occurrence of carcinomatous and haemopoietic metastasis to the pituitary and parasellar region have been reported to be as high as 26.6%[36] and 23%, respectively.[10] However, regional symptom-producing pituitary metastasis is uncommon, presenting only in cases with advanced systemic disease. In many cases, pituitary involvement may be subclinical and the patients may succumb to their advanced systemic disease, before the pituitary metastasis become manifest. Rarely, symptom-producing pituitary metastasis may be the first manifestation of a systemic malignancy.[9] Most of the pituitary metastases involve the posterior pituitary. This is due to the fact that the posterior pituitary has a direct arterial blood supply, as compared to the portal circulation of the anterior pituitary. Therefore, diabetes insipidus is the most common presenting feature in these patients.

Amongst the systemic malignancies which metastasise to the sellar region, the most common are lung, breast, prostate, stomach and bladder carcinomas. The general pattern of metastasis is that of osseous involvement of the sella turcica with contiguous deposits in the pituitary, especially the posterior lobe. Hypothalamic involvement may occur by contiguous involvement from the sellar region. Rarely, isolated hypothalamic involvement may occur. Patients with metastatic systemic malignancies to the sellar region most commonly present with diabetes insipidus. Suprasellar metastasis may present with rapidly progressive visual loss due to chiasmal compression. Ophthalmoplegia may be seen due to involvement of the cavernous sinus region. Hypopituitarism occurs infrequently due to the remarkable functional reserves of the pituitary.

Among the haemopoietic malignancies, leukaemias, lymphomas and plasmacytomas may metastasise to the sellar region. Most primary CNS lymphomas involve the brain parenchyma. Sellar region lymphomas usually

originate in the hypothalamus and infiltrate the pituitary stalk and posterior pituitary. They may present with hypothalamic dysfunction, chiasmal syndrome or secondary hypopituitarism. Secondary lymphomas involving the sellar region are generally non-Hodgkin's lymphomas. The deposits of the lymphomatous lesion are generally periglandular, limited to the pituitary capsule with infrequent involvement of the pituitary substance. Lymphocytic and myeloblastic leukaemias may also metastasise to the sellar region with primarily a periglandular distribution. Patients with secondary lymphomatous deposits or leukaemic deposits in the periglandular region have diabetes insipidus as the most common presentation. Symptoms due to compression of parasellar structures and hypopituitarism are rare.

Metastatic lesions in the sellar region usually appear homogeneous on the CT scan and enhance intensely with contrast. They are isointense to brain on T1-weighted MR images, moderately hyperintense on T2-weighted images and enhance intensely.

Surgery is indicated either for diagnostic reasons or when decompression is required to relieve mass effect. Prognosis is poor in patients with metastatic disease and the average survival is approximately 8–9 months. Radiotherapy may be an option mainly for palliation.

RATHKE'S CLEFT CYST

These are epithelium-lined cysts derived from remnants of the Rathke's pouch.[44] In 1913, Goldzieher described the first case of Rathke's cleft cyst (RCC) as an incidental post-mortem finding. Rathke's pouch appears during the 4th week of gestation as a stomodeal ectodermal evagination, which extends cranially to form the craniopharyngeal duct. The proximal end of the duct obliterates by the 11th week of gestation, while the cranial part comes in contact with the infundi bulum. The anterior wall of the pouch forms the anterior lobe of the pituitary and the pars tuberalis, while the posterior wall forms the pars intermedia. The residual lumen of the pouch involutes. Cystic remnants of the pouch may persist mainly at the anterior and posterior pituitary interface. These may be seen in up to 20% of autopsy cases. Rarely, they may be large enough to cause symptoms. There are secretory cells in the walls of the cyst and the cyst enlarges due to accumulation of the secretions.

Pathology

On pathologic examination, the cysts vary in size from 2 to 40 mm. The cystic capsule frequently is described as thin and transparent. The cystic fluid commonly is thick or gelatinous but it also can be watery, serous or similar in consistency to motor oil. The cystic fluid most often is yellowish in colour. At histological examination, the cysts typically are composed of vascularised stroma of connective tissue and three types of epithelial cells: (1) ciliated; (2) non-ciliated epithelial and (3) mucous secreting. Non-ciliated cells appear as a single layer of flat cells or as stratified columnar cells. The presence of ciliated epithelial and mucous-secreting cells in a pituitary gland is pathognomonic for Rathke's cleft cyst.

Clinical Presentation

The patient's age at presentation ranges 4–73 years (mean age, 38 years). The greatest frequency is in persons aged 50–60 years. Voelker et al. reported a male-to-female ratio of 1:2.[44] RCCs often produce no symptoms and so are usually discovered incidentally, when radiographic or necropsy findings are reviewed. Symptomatic RCCs are uncommon but cysts can enlarge and cause symptoms secondary to compression of the pituitary gland, pituitary stalk, optic chiasm or hypothalamus. The most common presenting symptoms are pituitary dysfunction, visual field defects and headache. Endocrinal abnormalities include gonadotropin failure, which manifests early. Features of hyposecretion of growth hormone, hypothyroidism and hypoadrenalism occur late. Hyperprolactinaemia is common and diabetes insipidus may also occur, although late. Infrequently, hydrocephalus due to obstruction at the foramen of Monroe, aseptic meningitis due to leakage of cyst contents into the subarachnoid space and pituitary apoplexy from haemorrhage into the cyst may manifest.

Radiological Features

RCCs frequently appear as well-circumscribed, hypodense sellar masses that may have a suprasellar extension. As a result of the different cystic contents, RCCs may appear isodense or hyperdense relative to the brain parenchyma. RCCs usually have a thin wall that may enhance. Variability in CT scan contrast enhancement among individual cysts may reflect squamous metaplasia in the wall or a peripherally displaced rim of pituitary tissue. Calcification characteristically is not seen on CT scans.

MRI appearances of RCCs are highly variable (Figs 4A and B). One group of cases may be hypointense on T1-weighted images and hyperintense on T2-weighted images. The cystic contents of the group resemble those of cerebrospinal fluid (CSF). In the second group are RCCs with hyperintensity on T1-weighted images and variable signal intensity on T2-weighted images. An increase in the signal on T1-weighted images has been related to the high content of mucopolysaccharides, which is believed to result from an increase in the number of mucin-secreting cells in the cyst wall, as well as from an increase in the activity of these cells. Uncommon cases with high signal intensity on T1-weighted images and low signal intensity on T2-weighted images have been suggested to result from a combination of factors, including the presence of mucopolysaccharides, chronic haemorrhage, a high cholesterol content and cellular debris from the cyst wall. RCCs almost always are homogeneous in signal intensity, whereas other lesions, such as cystic

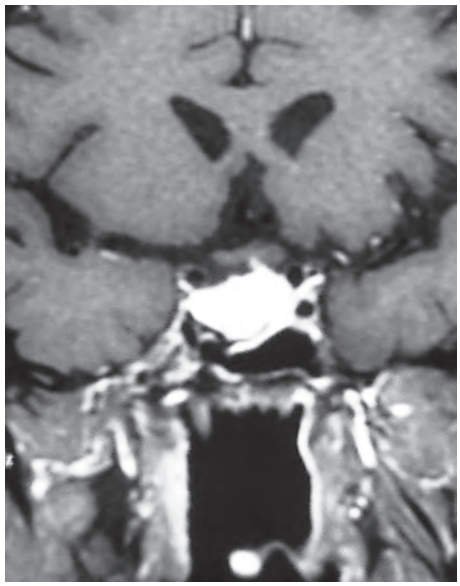


Fig. 4A: Coronal T1-weighted contrast MR image showing the sellar suprasellar Rathke's cleft cyst

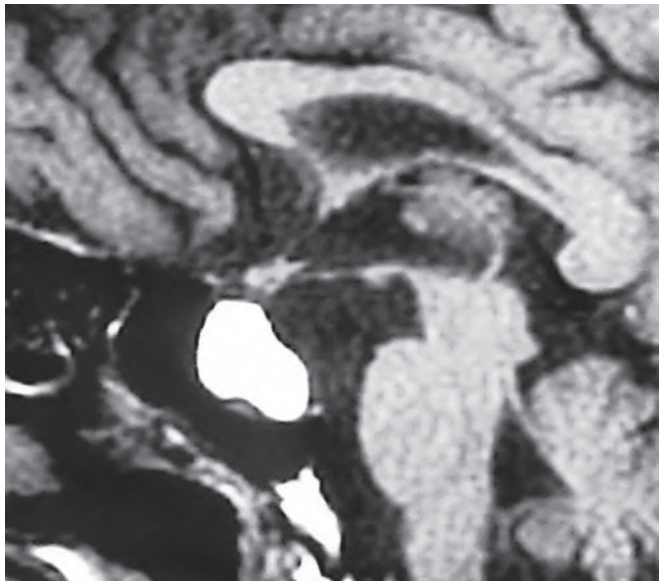


Fig. 4B: Sagittal T1-weighted contrast image showing the well defined uniformly hyperintense content of the Rathke's cleft cyst

craniopharyngiomas and haemorrhagic adenomas, more frequently have heterogeneous signal intensity. RCCs usually have a thin wall that may enhance with contrast. Variability in the gadolinium enhancement, among individual cysts, may reflect squamous metaplasia in the wall or a peripherally displaced rim of pituitary tissue.

Treatment

The most common approach in the treatment is transsphenoidal surgery, in which the cyst is partially excised and drained.[11,18] This method is effective and helps to preserve pituitary function. Radical excision can cause additional and unnecessary pituitary damage. In transsphenoidal surgery, the cyst is opened, a biopsy specimen is obtained from the wall and the cyst is drained into the sphenoid sinus. Patients in whom this approach is not appropriate because of an inaccessible cyst, craniotomy is performed.

The recurrence rate after craniotomy is twice as high as that after trans-sphenoidal surgery. In addition, leakage of the cystic contents into the subarachnoid space has been reported; this can cause aseptic meningitis. In cases with recurrence, extensive removal of the cyst wall is most appropriate and some studies recommend external beam pituitary radiation therapy, although its role in preventing further recurrence remains unclear.

HAMARTOMAS, CHORISTOMAS AND GANGLIOCYTOMAS OF THE SELLAR REGION

These are a group of histologically similar lesions, which consist of mature neurons which are clustered within a stroma of axons and astroglial elements. Various terms, like hamartomas, choristomas and gangliocytomas, have been used to describe these tumour-like lesions. These types of lesions arising in the hypothalamus are known as hypothalamic hamartomas and those arising in the sella without attachment to the hypothalamus are called choristomas.

Hypothalamic Hamartomas

Minute nodular hamartomatous foci of hypothalamic tissue are a common incidental finding on autopsy. These hamartomatous nodules are clinically insignificant. However, they may be large enough to compress surrounding structures and cause symptoms. These lesions are commonly found in the region of the suprasellar cistern or the interpeduncular cistern. In most of the cases they retain some anatomic continuity with the hypothalamus. However, they may not have a distinct attachment to the hypothalamus and may lie free in the suprasellar cistern. Others may have a wide attachment by a distinct stalk to the ventral surface of the hypothalamus or may even lie embedded in the parenchyma of the hypothalamus.

Pathology

Hamartomas usually resemble normal grey matter. Microscopically, they contain neurons which are indistinguishable from normal hypothalamic neurons and may contain secretory granules. These secretory granules may contain luteinising hormone releasing factor (LH-RF), beta-endorphin, corticotropin releasing factor or oxytocin. Immunohistochemistry reveals positivity for hypothalamic hormones in the neurons of these lesions.

Clinical Features

Hypothalamic hamartomas are rare tumours affecting young children below the age of 3 years. Characteristically, children present with precocious puberty[2], which may be as a result of either simple hypothalamic compression

or due to release of gonadotropin-releasing hormone (GnRH). Patients may present with behavioural or intellectual disturbances. There may be a variety of autonomic disturbances including abnormalities of thermoregulation, behavioural disorders, somnolence and hyperphagia. Gelastic epilepsy and complex partial seizures are also known to occur in these patients. Hemiparesis or nystagmus may occur occasionally. Occasionally, these children may present with cachexia.

Radiological Features

Plain X-ray of the skull is often unremarkable. However, it may show erosion of the dorsum sellae. On CT scan, a hypothalamic hamartoma appears as an isodense, non-enhancing suprasellar or interpeduncular cisternal mass. On MRI it appears isointense on both T1- and T2-weighted images with attachment to the tuber cinereum or posteromedial hypothalamus by a distinct stalk, giving it the so-called collar button shape. The lesion may lie entirely within the substance of the hypothalamus and may, therefore, be easily missed if small.

Treatment

Surgery is indicated in most symptomatic cases. Radiotherapy is ineffective in the treatment of these lesions. Total removal may not be possible, due to risk of hypothalamic injury in cases where there is broad-based attachment to the hypothalamus or when the tumour lies within the substance of the hypothalamus. However, subtotal removal may result in regression of precocious puberty in some cases. Surgical treatment is useful to confirm the diagnosis and to regress or abolish precocious sexual features and skeletal growth. It also results in better seizure control and improvement in behavioural and intellectual disturbances. Drugs such as medroxyprogesterone acetate and cyproterone acetate have been used to inhibit gonadotropin production in patients with precocious puberty.

Intrasellar Choristomas (Gangliocytomas)

These lesions are histologically similar to hypothalamic hamartomas. However, they differ from hypothalamic hamartomas in that they are primary intrasellar lesions with no attachment to the hypothalamus. They are generally associated with a functional pituitary adenoma. In most of the cases reported, intrasellar choristomas are seen in association with a GH producing pituitary adenoma. It has been hypothesised that the development of pituitary adenoma may be a secondary phenomenon, as these choristomas release hypothalamic hormones, which may induce adenomatous transformation of adjacent adenohypophyseal cells. This is supported by the finding of GHRH within the neurons of these choristomas. Corticotroph-releasing factor producing choristomas have also been found in association with Cushing's disease.

TUMOUR-LIKE CONDITIONS

Pituitary Abscess

Pituitary abscess, first described by Simmonds in 1914, is a rare but potentially life-threatening condition, if not adequately diagnosed and treated. It has a low incidence. Jain et al.[23] reported that pituitary abscesses constituted 0.6% of all pituitary lesions operated by them. Of 500 expansive pituitary lesions encountered by Scanarini et al.[40] during a 27-year period, only two were abscesses.

Aetiology of Pituitary Abscess

- Pituitary abscess may be the result of direct extension or haematogenous spread of infection from sphenoid sinusitis, meningitis, cavernous sinus thrombophlebitis or a contaminated cerebrospinal fluid (CSF) leakage.[8,43] When pituitary abscess does not coexist with meningitis or an adjacent sinus infection, it is difficult to determine the original site of infection.
- Pituitary abscesses may also develop, although rarely, as a result of generalised sepsis or haematogenous dissemination from a variety of distant septic foci like pneumonia, osteomyelitis, endocarditis, etc.
- They may complicate pre-existing lesions, usually adenomas, craniopharyngiomas and Rathke's cleft cyst. Tumours are possibly vulnerable to infection because of impaired circulation, areas of necrosis or local immunological impairment.

The incidence of intrasellar abscess is surprisingly low after trans-sphenoidal pituitary surgery. These abscesses may be due to intra-operative contamination or due to CSF leakage (secondary abscesses).

When culture is positive, the most commonly identified pathogens are *Staphylococcus* sp, *Streptococcus* sp, *Neisseria* sp, *E. coli, Corynebacterium* sp and *Diphtheroids*. Cases of mycotic abscesses have been reported due to aspergillus, candida, coccidiodomycosis, histoplasmosis and blastomycosis. In contrast to bacterial pituitary abscesses, most fungal infections occur when some type of immunosuppression coexists in the patients. Cases of parasitic pituitary infection have also been reported, including cysticercosis and echinococcosis.

Clinical features of pituitary abscesses resemble those of pituitary adenomas. Pituitary abscesses usually present either with endocrinologic disturbance or with symptoms related to mass effect. Headache is the most common presenting complaint. Signs of meningitis may be associated in up to 90% of cases. Fever is present in 50% of cases.

No pre-operative investigation is specific for pituitary abscess. However, several clues can suggest its presence. A past history of meningitis, sepsis and sinusitis may suggest the diagnosis. Rapid neurological deterioration in a patient with sellar tumour after a presumed bacteraemia should point to the possibility of abscess formation. CSF examination may be useful even when there are no signs of meningitis. It may reveal increased

cell count, elevated protein content or depressed glucose concentration.

Standard X-rays of the skull, centred on the sella may show widening of the sella turcica, erosion of the sellar floor and opacity of the sphenoid sinus.

CT scan findings in pituitary abscess were first reported by Enzmann and Sieling[16] as an intrasellar lesion, eventually expanding to the suprasellar region and devoid of specificity. The presence of hypodensity in the pituitary gland with enhancement of its outline by contrast injection and filling the sphenoid sinus with destruction of the sellar floor are also non-specific. The differential diagnosis of rim enhancement would include cystic lesions with or without superimposed infection.

The MRI findings in a case of pituitary abscess were first described by Dickob et al.[13] Pituitary abscess appears hypointense on T1-weighted images and hyperintense on T2-weighted images. Two important signs may lead to a correct diagnosis. The first includes disparity between the important sphenoid features (effusion within the sinus, wide sellar floor destruction) and the relatively small volume of the pituitary lesion. The second sign is the enhancement of the sellar lesion outline by both CT and MRI contrast, with simultaneous extensions to the sphenoidal sinus.

Pituitary abscess is usually treated by antibiotic and corticosteroid therapy, followed by surgery. The transsphenoidal approach is usually chosen for drainage to protect the cerebrospinal fluid from contamination and to avoid post-operative infection.

LYMPHOCYTIC HYPOPHYSITIS

It is a rare destructive inflammatory disorder affecting the anterior pituitary and is presumed to be of autoimmune origin. It occurs almost exclusively in female patients and commonly affects them, either during pregnancy or within the first year of parturition. It may coexist with other autoimmune diseases including Hashimoto's thyroiditis, idiopathic adrenalitis, pernicious anaemia and parathyroiditis.

Pathology

Lymphocytic hypophysitis is thought to be an autoimmune disease which may be precipitated following a viral infection. Prior or concurrent lymphocytic meningitis/meningoencephalitis has been considered to be an aetiological factor. In experimental studies, viral specific peptides (e.g. Rubella virus E-1 and E-2 proteins) have been shown to induce lymphocytic hypophysitis in animals.

The pathological process starts as an acute inflammation and enlargement of the gland. In chronic cases, the gland becomes atrophic and fibrotic. Microscopically, the normal glandular architecture of the anterior pituitary is replaced by infiltration of lymphocytes, plasma cells, macrophages and eosinophils. Occasionally, lymphoid follicles and germinal centres may be seen. Varying degree of diffuse interstitial fibrosis is present.

Clinical Presentation

As mentioned earlier, this disorder primarily affects females and is often related temporally to pregnancy.[3,4] Patients may present with headache, vomiting, emotional disturbances or visual field defects. The hormonal disturbances which may occur include single hormonal disturbance like hyperprolactinaemia, hypoadrenalism and hypothyroidism or panhypopituitarism. As the posterior pituitary is not involved, diabetes insipidus is rare.

Radiological Features

Plain X-ray skull is usually normal but may demonstrate an enlarged sella with occasional erosion of the dorsum sellae. On CT scan, lymphocytic hypophysitis appears as an enhancing intrasellar mass which may extend to the suprasellar region with enlargement of the sella. MRI is the investigation of choice and reveals a lesion in the sella which is either hypointense or isointense on T1-weighted images and hyperintense on T2-weighted images (Fig. 5). It enhances uniformly on contrast injection. The pattern of signal enhancement after contrast may be helpful to differentiate this lesion from a macroadenoma. A strong and homogeneous enhancement of the anterior pituitary, similar to the cavernous sinus, is more suggestive of an inflammatory process such as lymphocytic hypophysitis rather than a macroadenoma.

Treatment

Surgical intervention, in addition to providing a histological diagnosis, is very effective in achieving decompression of the sellar mass and thereby resolving

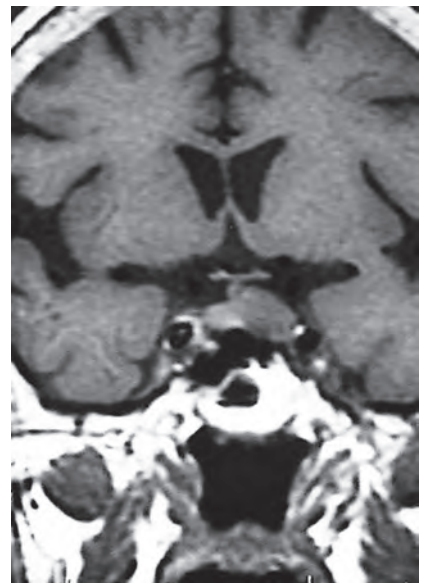


Fig. 5: Lymphocytic hypophysitis: A contrast enhanced T1-weighted coronal MR image showing an infiltrative lesion in the sella which is hypointense or isointense on T1-weighted images and hyperintense on T2-weighted images. It enhances heterogeneously on contrast with thickening of the pituitary stalk

headache and visual deficits. The aim of surgery should be to reduce the pituitary mass and associated compressive effects on surrounding structures, without introducing new endocrinal or neurological deficits. This is best achieved by the trans-sphenoidal approach. Supraphysiological doses of glucocorticoids can be effective in the treatment of lymphocytic hypophysitis. They help both by reducing the mass of the pituitary by their anti-inflammatory effects and as replacement for defective adrenal function. Other immunosuppressive drugs, such as azathioprine, methotrexate and cyclosporine, have been used with some success in patients responding poorly to corticosteroids.

MUCOCOELE

These are benign, cystic lesions arising in the paranasal sinuses. Sphenoethmoidal mucocoeles are relatively rare lesions which may erode the sellar floor to present as intrasellar, parasellar or suprasellar masses. Mucocoeles are filled with mucus and the walls consist of psuedostratified or low columnar epithelium, which contains goblet cells.

Isolated involvement of the sella is very rare. In such cases, they cause enlargement of the sella and chiasmal compression. Hypopituitarism rarely occurs. More often, involvement of the sella may just be a small component of a much wider intracranial extension involving the orbital apex and superior orbital fissure, wherein oculomotor palsies and exophthalmos may be the presenting features.

SARCOIDOSIS

Sarcoidosis is a multi-system inflammatory disorder which may involve the nervous system in approximately 5% of cases. Neurosarcoidosis is considered as a great imitator of intracranial lesions. Intracranially, it generally involves the base of the brain with infiltrative arachnoiditis, which causes entrapment of cranial nerves and may also involve hypothalamic-pituitary structures. Often it results in polyneuritis cranialis, manifesting as fluctuating or recurring paralysis of cranial nerves, specially the facial. Rarely, isolated involvement of these structures may be seen.

Histological appearance of these lesions is characterised by non-caseating granulomas consisting of lymphocytes, giant cells and macrophages. Clinical manifestations are generally due to hypothalamic or infundibular damage. MRI demonstrates enhancement of the hypothalamus, thickening of the infundibulum and meningeal enhancement, especially in the region of the suprasellar cistern.

Neurosarcoidosis has no known cure. Immunosuppression is the principal method of controlling the disease and corticosteroids are the mainstay of therapy. Alternative medications, including azathioprine, cyclophosphamide, cyclosporine, chloroquine and methotrexate have been used with variable success. Some patients demonstrate symptomatic benefits from low-dose radiation. Surgical intervention is indicated in cases of hydrocephalus or when an expanding mass lesion causes an increase in intracranial pressure.

HISTIOCYTOSIS X (LANGERHAN'S CELL HISTIOCYTOSIS)

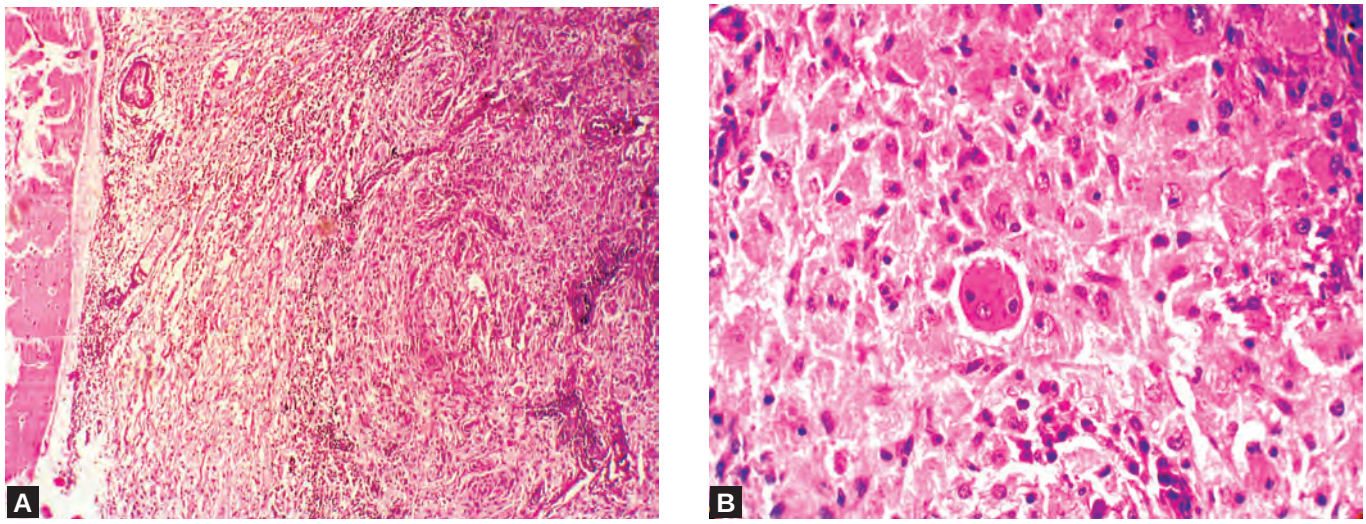
It is a systemic disease primarily affecting the reticuloendothelial system. It may involve the central nervous system with a predilection for the hypothalamus, infundibulum and posterior pituitary. Involvement of the anterior pituitary is far less common. It generally represents extension from an adjacent bony lesion. Patients generally present with diabetes insipidus. Growth hormone deficiency and hyperprolactinaemia may also be present. Histologically, the lesions consist of infiltrates of histiocytes, eosinophils and lymphocytes (Figs 6A and B). Characteristic Langerhan's giant cells are present, which express S-100 protein and HLA-DR (CD-1) antigen. Neuroimaging shows a thickened infundibulum which enhances on contrast and the presence of hypothalamic granulomas. Destructive osseous lesions may be seen in the calvarium.

CAVERNOUS ANGIOMA OF CAVERNOUS SINUS[6,28,37]

Cavernous angiomas of the cavernous sinus are rare lesions with an incidence of 1–3% of all lesions of that area. Their origin may be extracavernous with enlargement into the middle cranial fossa or primary intracavernous with enlargement into the middle cranial fossa. Growth in these lesions occurs by progressive ectasia of vascular channels, capillary outgrowth from cavernous spaces into the interstitium, internal microhaemorrhages causing thrombosis of contiguous blood vessels, followed by organisation and sclerosis and cyst formation by rupture of septae between adjacent sinusoids. Subsequent rapid expansion of the cyst may be due to imbibing water through osmosis.

These lesions occur between the second and the fifth decades of life with the male:female ratio being 1.7:2.8. The gradually expanding lesion may cause cavernous cranial nerves deficit and sellar hypothalamic involvement may result in endocrinopathies. Pregnancy, steroid administration or even physical exertion may cause exacerbation of symptoms due to engorgement of the lesion. Spontaneous haemorrhage is rarer in these extradural haemangiomas compared to their intra-cerebral counterparts.

CT scan shows an isodense to hyperdense lesion with dense homogeneous enhancement on contrast. Bony erosion in the sellar region may be seen. These lesions are angiographically occult due to the small size of the nutrient vessels, as well as extensive thrombosis within the malformation so that adequate concentration of the dye for clear definition of the lesion is not provided. Thus, angiography may be negative or



Figs 6A and B: Histiocytosis X: Histology reveals sheets of histiocytes, displaying bland vesicular nuclei and abundant foamy cytoplasm. Interspersed thin fibrous bands and focal aggregates of mature lymphocytes, plasma cells and giant cells are also seen. A rim of brain parenchyma with reactive gliosis is also seen. (H and E × 100 original magnification) (some of the histiocytes show engulfed intact lymphocytes and plasma cells within their cytoplasm Fig. 6A)

may show displacement of adjacent normal vessels, a focal capillary blush or venous pooling. This apparent avascularity is deceptive as the lesions bleed profusely during surgery. Occasionally, feeding arteries including the meningohypophyseal trunk, artery of the inferior cavernous sinus, the middle meningeal artery and the accessory meningeal artery have been identified. MRI may show an isointense to mildly hyperintense lesion on the T1-weighted image, markedly hyperintense on T2-weighted images, enhancing brilliantly with contrast administration (Fig. 7). The intensity pattern may vary. The lesion may have a reticulated core of mixed intensity with a surrounding rim of decreased intensity on T2-weighted images caused by haemosiderin-laden macrophages. The lesion may contain foci of haemorrhages with resultant intensity variations depending upon the age of haemorrhage.

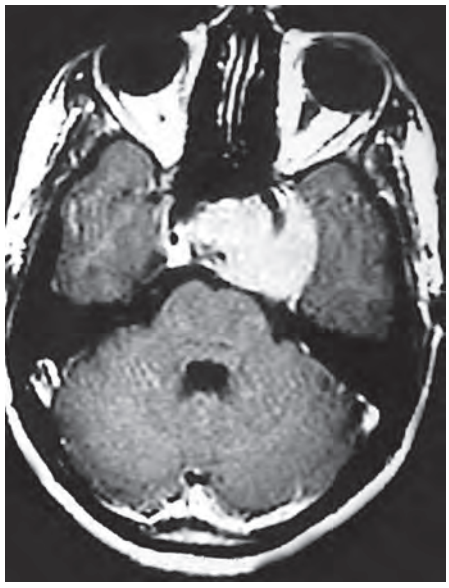


Fig. 7: Cavernous angioma of the cavernous sinus: Contrast enhanced T1-weighted MRI shows a uniformly enhancing lesion in the cavernous sinus surrounding the ipsilateral cavernous internal carotid artery

Surgical excision may cause extensive haemorrhage. The surgery is facilitated by proximal internal carotid artery control in the neck or the petrous segment, preparation for extracranial-intracranial bypass, incising the dura between the III, IV, V cranial nerves, early devascularisation of the lesion by coagulating its blood supply, developing a plane of cleavage between the pseudocapsule formed by the inner and outer layers of the dura, and avoiding piecemeal dissection. The VIth nerve and internal carotid artery, being intracavernous, have to be skeletonised from the tumour. Frontotemporal craniotomy with orbitozygomatic osteotomy with drilling of medial sphenoidal wing and anterior clinoids, facilitates the exposure.[6,30,39] A course of pre-operative radiation has been recommended to help shrink the lesion and reduce its vascularity.

MISCELLANEOUS TUMOURS

A few very rare tumours which may arise in the sellar-parasellar region include:

Schwannomas

Schwannomas may arise from the cranial nerves of the cavernous sinus, especially the trigeminal nerve and may secondarily involve the sellar region. Although a few cases of purely intrasellar schwannomas have been reported in literature, they are extremely rare. The current histopathological hypothesis for the origin of these lesions include perivascular or ectopic Schwann cells, lateral nerve plexus within the cavernous sinus, as well

Fig. 8A: T1-weighted contrast enhanced sagittal image showing the heterogeneously enhancing giant cell tumour of the sphenoid occupying the entire clivus, sphenoid and sella

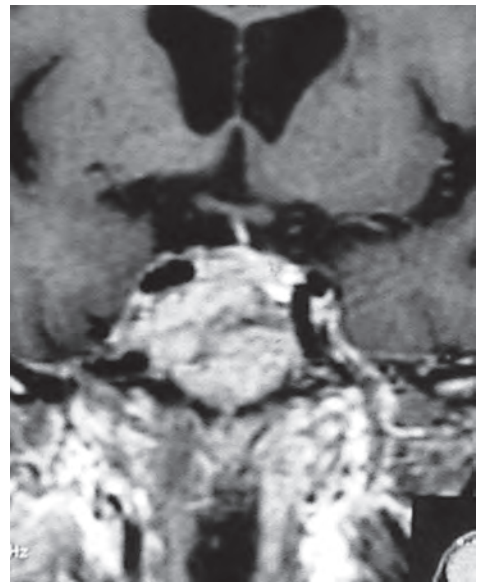


Fig. 8B: T1-weighted contrast enhanced coronal image showing the same lesion

as Schwann cells from small nerve twigs of the dura. These tumours may mimic pituitary adenoma clinically, endocrinologically and radiologically. Intrasellar schwannomas presenting with hypopituitarism, hyperprolactinaemia and visual disturbance due to chiasmal compression have been reported.

Giant Cell Tumours of the Sphenoid

These constitute 3–7% of primary bony neoplasms. Involvement of the skull is rare and occurs in less than 1% of cases of giant cell tumours and occurs in the sphenoid and temporal bones, reflecting the genesis of these bones through endochondral calcification. CT scan showing an expansile lytic lesion in the body of sphenoid or temporal bones, with marked contrast enhancement, is characteristic of this lesion. MRI reveals a low to moderate signal intensity on T1- and T2-weighted images (Figs 8A and B). Haemorrhage within the tumour may produce high signal intensities on both the sequences. A "soap bubble" image may be seen on the T2-weighted image.[7]

The histological features include oval, undifferentiated mononuclear cells with evenly dispersed, large multinucleated giant cells (Fig. 8C), with closely packed nuclei in them.

Giant cell tumours display aggressive local behaviour. Soft tissue extension may compromise vital neurovascular structures. Dural penetration, cerebral invasion and sarcomatous change may occur. The ideal treatment is wide local excision with a good margin of healthy tissue. In case of local recurrence, local resection is safer than radiotherapy. However, in many cases, radiotherapy following surgery has achieved good local control without tumour recurrence or malignant transformation.[7]

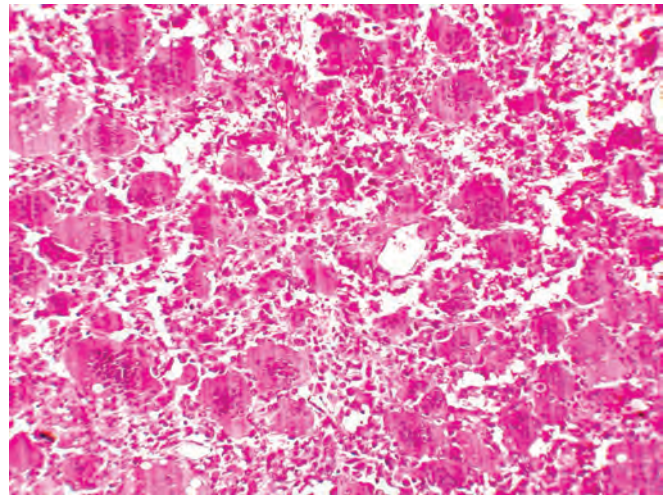


Fig. 8C: Giant cell tumour of the sphenoid: Tumour is consisting of uniformly distributed giant cells surrounded by round to oval mononuclear cells that lack cytological atypia. (H and E × 100 original magnification)

Paragangliomas

This tumour is very rare in the sellar area where there are no paraganglionic cells. The cellular origin of these tumours is thought to be from the paraganglionic tissue rests which persist from early pituitary embryogenesis.

Glomangiomas

These are tumours which arise from glomus bodies and typically affect the nail beds. Intrasellar glomangiomas are extremely rare and two cases have been reported in literature.

Lipomas

Lipomas may present as suprasellar masses. They generally arise from the hypothalamus or tuber cinereum and extend downwards. Hypothalamic dysfunction and secondary hypopituitarism may occur in these cases.

Primary Melanoma

Only a few cases of primary melanoma of the pituitary gland have been reported. They may arise from melanin containing cells of the posterior pituitary or from the meninges overlying the diaphragma sellae.

Angiofibroma

It is a benign tumour that tends to bleed and occurs in the nasopharynx of prepubertal and adolescent males. The lesion occurs commonly in the second decade with the age ranging 7–19 years. The tumour starts in the nasopharynx and pterygopalatine fossa. The rare superior growth is directed towards the sphenoid sinus, cavernous sinus and sella. Occasionally, the greater wing of the sphenoid may be eroded, exposing the middle fossa dura. Proptosis and optic nerve atrophy result if the orbital fissures are encroached upon by the tumour. Nasopharyngeal angiofibroma is usually encapsulated and composed of vascular tissue and fibrous stroma, with coarse or fine collagen fibres. Vessels are thin-walled, lack elastic fibres and have absent or incomplete smooth muscle. Stromal cells have plump nuclei and tend to radiate around the vessels. There is an abundance of mast cells in the stroma and a lack of other inflammatory cells. Localised areas of myxomatous degeneration may be observed in the stroma. Pre-operative embolisation and radiotherapy may reduce the vascularity and the size of the lesion. Surgery usually aims at complete excision but exsanguinating haemorrhage from the tumour may often be encountered during its surgical excision.[42]

Esthesioneuroblastoma

This is a neuroblastoma arising from the olfactory epithelium invading the skull base, cranial vault, orbit, sphenoid sinus and sellar area (Fig. 9). On histology, there is a lobulated structure with sheets of cells having poorly defined cytoplasm and round to oval nuclei in a densely neurofibrillary background. Sometimes, olfactory rosettes or pseudorosettes may be present. Surgery followed by radio and chemotherapy provides relief but local recurrences and metastasis are frequent.

Fibrous Dysplasia

This consists of proliferative connective tissue, causing thickening of bones (Fig. 10). There are three forms: (1) Compact form is a dense thickening of bone, especially of the skull base, resulting in ground glass appearance. It may cause stenosis of the optic foramen, superior orbital fissure, shallow orbits with proptosis, sellar and

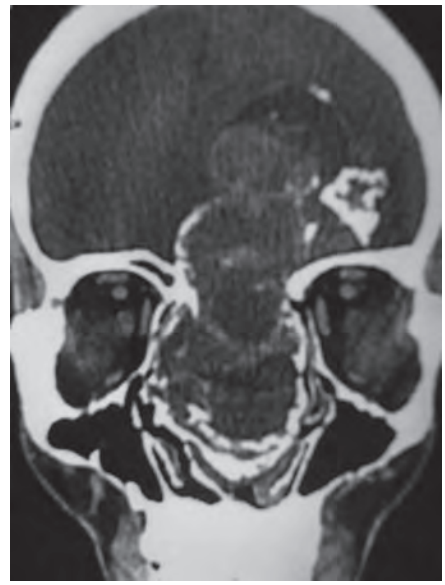


Fig. 9: Esthesioneuroblastoma: Coronal contrast MR image showing the heterodense lesion filling up the nasopharynx, sphenoid sinus and reaching the sellar-suprasellar region with extension to the frontal lobes

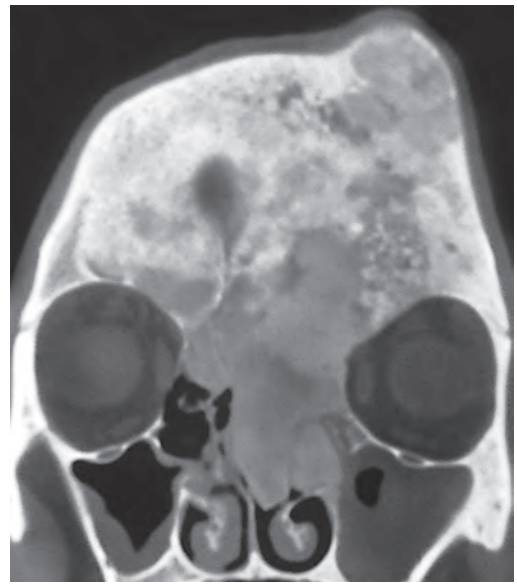


Fig. 10: Fibrous dysplasia: Coronal CT scan showing the ground glass appearance of an extensive lesion that is expanding the inner and outer skull tables and extending to the sellar-suprasellar region. These patients may present with hypopituitarism due to sellar involvement

sphenoid involvement causing hypopituitarism and expansion of the temporal bone and greater wing of the sphenoid. (2) Lytic form takes the shape of a radiolucent area limited by a thin sclerotic line. (3) Pseudo pagetoid form is characterised by both sclerotic and radiolucent forms. The lesion stabilises after the age of 25–30. There is a small risk of malignant transformation.

This chapter summarises the salient features of some rare sellar-suprasellar lesions that should always be considered in the differential diagnosis, along with

the commonly seen lesions such as pituitary adenomas, craniopharyngiomas, meningiomas, astrocytomas and epidermoids.

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158 Craniopharyngioma

SN Bhagwathi, Suresh Sankhla

INTRODUCTION

Craniopharyngiomas are the most common intracranial tumours of non-glial origin in children.[50,115,248] As a group, they have been among the most challenging and difficult tumours for neurosurgeons to treat. These neoplasms arise from cell rests from the remnants of Rathke's pouch and are histologically benign. Although a number of terms including ameloblastoma, adamantinoma, epidermoid, Rathke's pouch tumour, craniopharyngeal duct tumour, hypophyseal duct tumour, epithelioma and interpeduncular cyst have been used in the past to describe this tumour, the commonly used term "craniopharyngioma" was first coined by McLean[194] in 1930, and Frazier and Alpers[81] in 1931. Cushing[56] adopted the same nomenclature in 1932 and stated that "this admittedly cumbersome term has been employed for want of something more brief, to include the kaleidoscopic tumours, solid and cystic, which take their origin from epithelial nests ascribable to an imperfect closure of the hypophyseal or craniopharyngeal duct".

HISTORICAL PERSPECTIVE

In 1838, Rathke[234] first noted the significance of a globular, somewhat irregular depression, like a thin walled diverticulum (Rathke's pouch), lying posteriorly in the roof of the primitive mouth under the developing skull base, which was later to form the pituitary gland. Zenker[318] was the first to identify in an autopsy study in 1857, masses of squamous epithelium located along the pars distalis and pars tuberalis. In 1860, Luschka[182] performed an extensive autopsy study of the squamous epithelial cell rests in the hypophyseal area and noted that they existed as group of islets varying in number in different individuals, but were larger in elderly people, suggesting an increase in size and number with age. An increase in the frequency of squamous cell rests with age has also been observed by others.[95,183] Carmichael[43] found that the majority of these cell rests were located in the superior portion of the pars distalis and in the lower third of the pars tuberalis. Erdheim,[72] in 1904, first proposed the commonly held view that these cell rests give rise to tumours. However, these cells are usually scanty or not present during childhood and adolescence, the most common age for these tumours. Hunter[124] suggested that these cells are probably formed by metaplasia of pituitary glandular cells. Due to the different behaviour patterns of tumours in children and adults, Kahn[137] suggested that adult tumours arise in adult life and have not been present since birth or childhood.

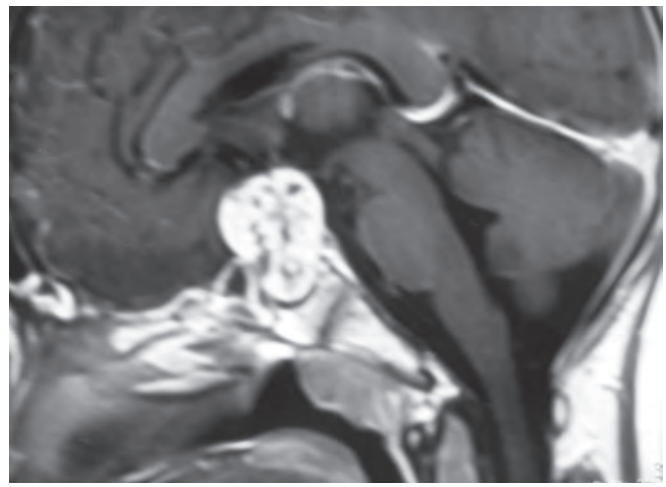


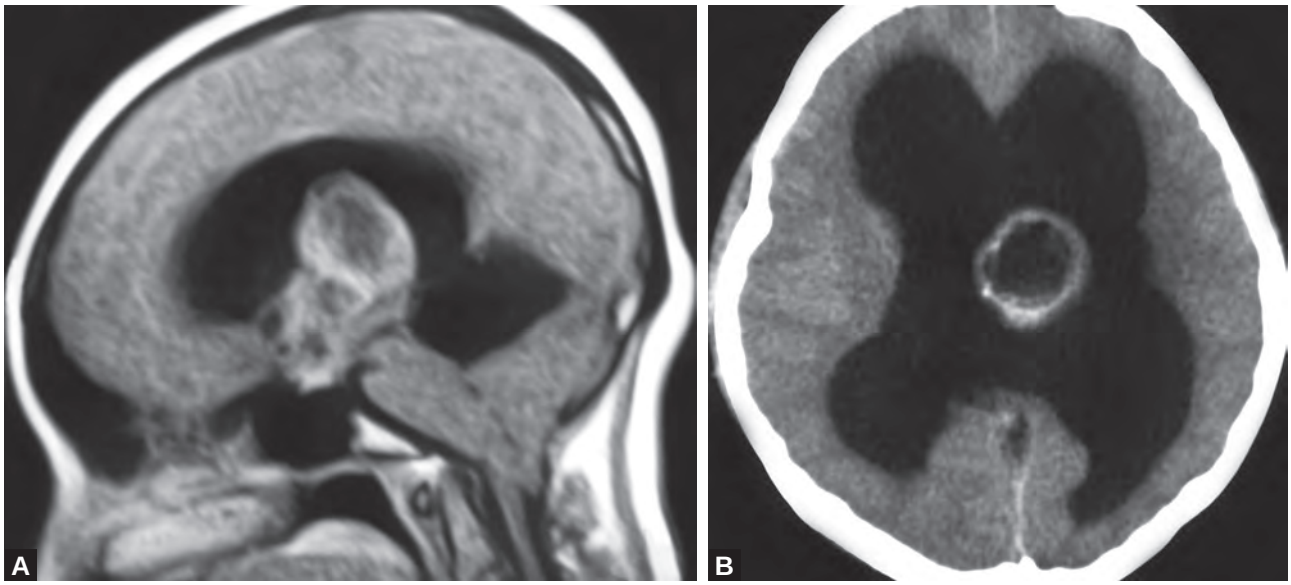
Fig. 1: Magnetic resonance imaging showing suprasellar lesion going totally into the sella

PATHOLOGY

Craniopharyngiomas are most frequently cystic tumours or have a large cystic component, although sometimes they can be entirely solid or may present as a solid rock of calcium.

These tumours are located mainly in the suprasellar region, as the site of origin is usually along the infundibulum at the floor of the third ventricle. As the tumour enlarges, it often extends into the sella inferiorly and elevates the floor of the third ventricle superiorly or it may develop preferentially in one direction (Fig. 1).

Tumours restricted to the sella or the third ventricle has been well documented. Intrasellar tumours are least common and were found in three out of 27 cases by Northfield[212] and a 10–15% incidence is reported by others,[215,275] while a predominantly sellar location is reported in 33% of the cases by Love et al.[177] An intrathird ventricular location has frequently been reported,[45,68,96,129,160,176,199,222] although Hoffman[116] feels that many of these are primarily retrochiasmal tumours, which have grown into the third ventricle (Figs 2A and B).



Figs 2A and B: (A) Sagittal view of magnetic resonance imaging showing a totally intraventricular craniopharyngioma. (B) Showing the same in axial view

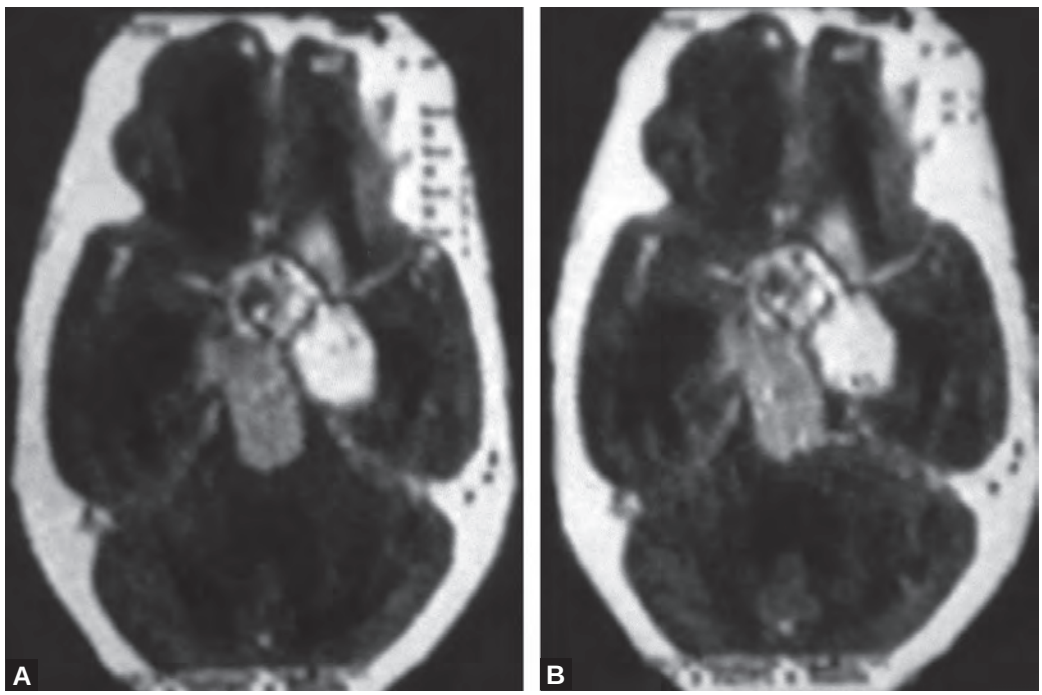
The size of the tumour varies from a centimetre in diameter to large tumours occupying the anterior and middle fossae. Involvement of the posterior fossa is also well known[94] (Figs 3A and B) and as many as 12% of the 245 craniopharyngiomas studied at the Armed Forces Pathology Institute had posterior fossa extension. Posterior extension has also been observed in the pineal region by Baskin et al.[21]

Ectopic craniopharyngiomas have been observed in the cerebellopontine angle[6,84] and even in the calvarium and the epidural space, along the tract of previous surgery.[187,229] Two unconnected craniopharyngiomas, one in the suprasellar and the other in the third ventricle, have been reported in one patient.[297]

Invasion of the skull base was seen in two of our cases (Fig. 4).

Invasion of the sphenoid bone,[54,223,297] nasopharynx,[25,77,186,204] the orbit[41] and the cavernous sinus[61] has also been reported. A rare case has been reported by Block et al.[32] where the tumour extended into both optic canals causing enlargement of the optic foramina.

Growth of the tumour superiorly into the third ventricle can cause blockage of one or both foramina of Monro, leading to hydrocephalus. A few years ago,



Figs 3A and B: CT scan showing extension of craniopharyngioma into the posterior fossa in the axial view

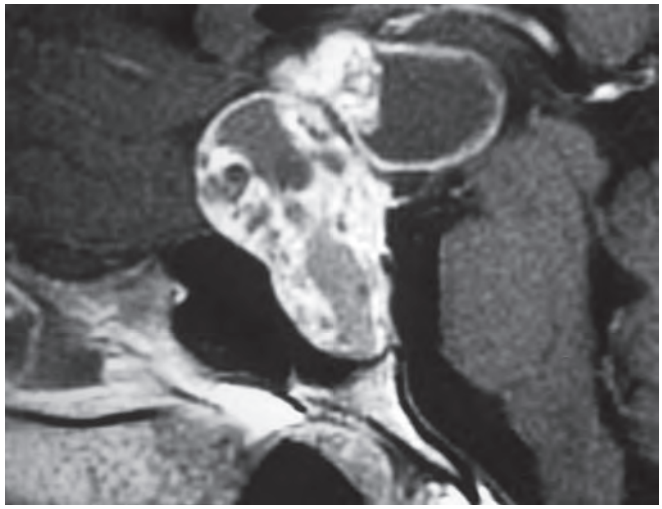


Fig. 4: Magnetic resonance imaging showing destruction of the sphenoid sinus by the tumour

an unpublished CT scan study from Mumbai showed superior extension of the tumour in 87% of patients and resultant hydrocephalus in 67%. Rarely, communicating hydrocephalus may be caused in these patients due to chemical meningitis.

The outer surface of the tumour is greyish pink in appearance. It is often irregular and adherent to the surrounding structures. A layer of arachnoid separates the tumour from almost all the structures, except in the region of the tuber cinereum. Calcification in the wall of the cyst is a common feature. The cyst contains chocolate-coloured fluid with shimmering cholesterol crystals ("machine oil" fluid). Occasionally, the cyst fluid may be lighter in colour, mildly xanthochromic or even watery. The cholesterol is derived from the epidermal layer lining the cyst. Histochemical investigations reveal such a secretion in a microcyst and electron microscopy has demonstrated zymogen granules in the epithelial cells, suggesting a secretory function to these tumours.[282] The immunohistochemical distribution of the subunits of S100 proteins for these tumours had shown them to be S100 alpha (+ve) and beta (–ve) (like pituitary adenomas and pinealomas).[100] Insulin like growth factors have been demonstrated in the cyst fluid in craniopharyngiomas.[319] Immunocytochemistry of the tumour, for pituitary hormones, has shown positivity for at least one hormone in the majority of the cases.[283] Carbohydrate moieties, such as those of blood group antigen and also those reported to be found in human skin epidermis, exist in a similar form in craniopharyngioma, epidermoid and Rathke's cleft cyst.[209]

Histologically these are epithelial tumours, the cyst being lined by simple stratified squamous epithelium over a collagenous basement membrane. The tumour enlarges by desquamation of epithelial debris, formation of cyst fluid and simple cellular proliferation. The growth of the tumour, therefore, is generally slow. However, there is experimental evidence that the craniopharyngioma cells are really neoplastic and this may explain rapid growth or recurrence in some.[210] Calcification is common on histology and is reported in over 90%.[41] Occasionally, the whole tumour may be calcified.[62] Calcification is more common in the paediatric age group than in adults.

Adamson et al.[1] correlated the clinical and pathological features in 107 craniopharyngiomas and noted two different types: either a classic adamantinous or a squamous papillary structure. The solid, uncalcified squamous papillary type of tumour was found in one third of the adult patients and not in children. It was associated with good functional outcome after surgery and showed no recurrence.

The blood supply of a craniopharyngioma is the same as that of the diencephalon, as it evolves from the embryological remnants of Rathke's pouch.[161,168] Pertuiset[221] has summarised the arterial supply of the tumour. Two branches arising on each side from the intracavernous portion of the internal carotid or the inferior hypophyseal arteries supply the intrasellar portion of the tumour. The suprasellar portion receives its supply anteriorly from branches coming off the anterior cerebral and the anterior communicating arteries and laterally on either side from branches of the posterior communicating arteries. They do not receive blood supply from the posterior circulation, except when the tumour is intraventricular or very close to the floor of the third ventricle, when the arterial supply arises from the proximal posterior cerebral arteries.

Other Epithelial Cysts in the Suprasellar Region

Other types of epithelial tumours may occur in the suprasellar region, namely, epidermoid cysts, Rathke's cleft cysts, arachnoid cysts and germinomas. Epidermoid cysts develop within the region of the infundibulum or tuber cinereum, from small nests of squamous epithelial cells which border on the pars tuberalis. They contain kerato hyaline material.

Rathke's cleft, separating the anterior (pars distalis) from the posterior (pars intermedia) part of the pituitary, is lined by cuboidal or columnar epithelium, which may be ciliated and contains mucus secreting glands. Cystic transformation of the cleft results in Rathke's cleft cyst.[23,27,53,69,75,82,93,239] They have also been described as pituitary,[8,207,235,264,312] colloid[244] or intrasellar epithelial cysts.[86,262] Gillman[92] and Shanklin[256] reported that they are found in 13.22% of normal pituitary glands. The morphological study carried out with light and electron microscopy and tissue culture by Yoshida et al.[315] suggests that they are similar to the prickle cells seen in the epidermis, and craniopharyngiomas and Rathke's cyst, therefore, have the same origin, although they may show histological differentiation. They generally contain mucoid material within, although occasionally, larger collections of xanthomatous cells like in a colloid cyst[311] and subepithelial tissue comprised of pituitary gland cells may be seen.[127] Rarely abscess formation[33,266] and haemorrhage[214] within the cyst have also been

reported. They are generally less than 3 cm in size, remain clinically asymptomatic and have a favourable prognosis.[73,241,278,307] Occasionally, however, they cause chiasmal syndrome, hypopituitarism[241] and, rarely, periodic fever due to chemical irritation and meningitis.[213,269,302] Acute adrenal insufficiency has also been reported.[286]

Arachnoid cysts may be congenital (or primary) or acquired.[267] Congenital or true cysts may be an outpouching of the membrane of Liliequist, while acquired ones are usually the result of trauma, haemorrhage or inflammation. However, arachnoid cysts occurring in the chiasmal region are still a subject of controversy, both in respect of their aetiopathology and anatomical definition.[67] Anatomically, two groups can be identified: suprasellar (developing above the diaphragma sellae) and intrasellar (within the sellar cavity). The true cyst is suprasellar, while varying degrees of outpouching may occur into the sella through the central opening in the diaphragm to form an intrasellar cyst. Pure intrasellar cysts are extremely rare and may result from a maldevelopmental splitting of the arachnoid membrane within the subdiaphragmatic cistern and it may rarely be symptomatic.[107]

Germinomas or ectopic pinealomas located in the infundibular region are identical to the atypical teratomas of the pineal gland and are morphologically similar to the germ cell tumours of gonadal origin, viz. testicular seminoma.[105,245] The suprasellar germinoma is usually situated beneath and behind the optic chiasm, which it both displaces and infiltrates as it spreads along the optic nerves and tracts to extend into the infundibulum and hypothalamus.[230] Precocious puberty, diabetes insipidus and other hypothalamic manifestations are commonly seen and, like other intracranial germinomas, they may sequestrate or spread to different sites.

INCIDENCE

Craniopharyngiomas are one of the most common intracranial tumours of childhood, forming 9% in Matson's series of paediatric tumours.[192] They formed 6% of tumours at the Hospital for Sick Children in Toronto.[118] However, they account for only 2.5–4% of intracranial tumours at all ages.[50,142,246] Indian reports show a prevalence of 3.9% of all intracranial tumours, forming 12–16% of tumours in childhood.[62,227,232,287] Dastur et al.[59] in a consecutive series of one thousand tumours, found craniopharyngiomas to account for 2.6% of all intracranial neoplasms and 16.8% of all intrasellar tumours. Selby and Pereira[251] also found craniopharyngiomas to be more common in children in Malaysia. A higher incidence is also reported from Japan, where they form 8% of intracranial tumours at all ages.[5,7]

A bimodal age distribution is seen for these tumours at presentation, with the first peak between 5 years and 10 years and the second between 55 years and 60 years.[18,39,153] Tumours may rarely develop in foetal life[87,89,130,230] and can now be diagnosed by ultrasound and MR in intrauterine life.[15]

Seventy per cent of craniopharyngiomas occur below the age of 20 years.[138,306] Eighty-five per cent of our 122 cases were under 20 years of age, the youngest patient being one and a half years old, while the oldest was 62. Males predominated 3:2. Equal sex distribution has been reported in most other large studies.[41,117] The symptoms and signs depend on the direction of the growth of the tumour: optic apparatus anterosuperiorly, hypothalamus posterosuperiorly, pituitary gland inferiorly and brainstem posteriorly.

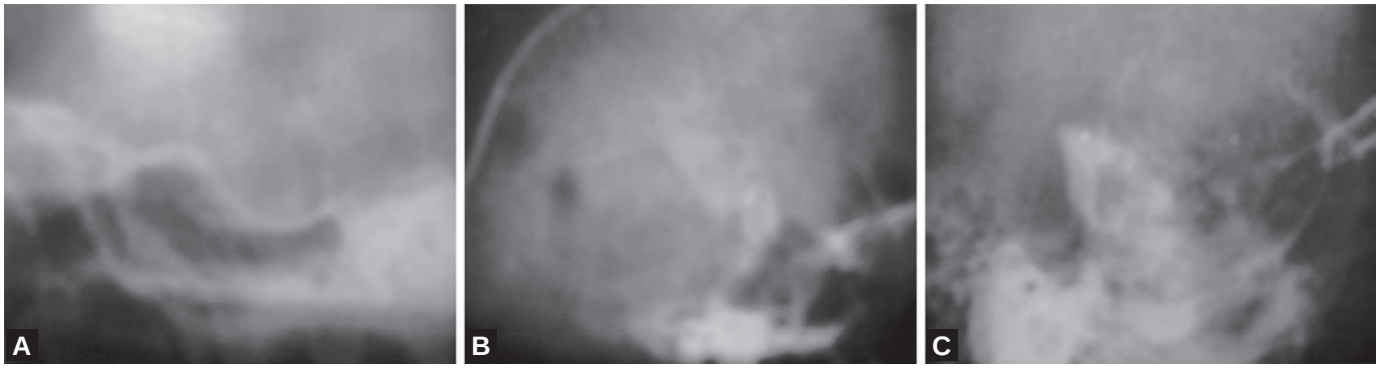
CLINICAL FEATURES

The most common triad of presenting symptoms in a child with craniopharyngioma is: (a) visual failure due to compression of the optic nerves, chiasm or tracts; (b) hormonal disturbances, most frequently growth hormone (GH) or antidiuretic hormone (ADH) deficiencies and (c) raised intracranial pressure, usually a result of large tumour mass, obstructive hydrocephalus, or both. The symptoms of hypothalamic disturbances including obesity and somnolence may be seen in large tumours.

Symptoms and signs of raised intracranial pressure predominate in children and endocrinological deficits in adolescents. Visual symptoms predominate in adults,[19,112,250] while the elderly present with mental disturbances. Although only a few children complain of visual problems, clinical examination may show visual disturbances in the majority.[52] The discrepancy between symptoms and signs in the paediatric age group is due to younger children not noticing visual impairment or a field defect. Apart from incomplete temporal field defects, diminished visual acuity, papilloedema and optic atrophy are seen in many children. Jawahar et al.[131] found some visual loss in 84% and either primary or secondary optic atrophy in 74%. Only 5% of the children had normal vision, emphasising late referrals. An aetiological profile of optic atrophy in India, in 1992, has shown craniopharyngioma to be the most frequent tumour responsible for bilateral optic atrophy before the age of 20 years.[197]

It is felt that, in India, the clinical differences between adults and children get blurred, mainly because of late presentation.[299] Fifty-three per cent of children and 76% of adults in our series had diminished vision and over 80% of children and 66% of adults had optic changes. Four children and one adult were blind in one eye. Blindness is uncommon, although still occasionally encountered. Others have reported similar experience.[63,203,243] Retrochiasmal tumours do not cause any visual signs and symptoms apart from papilloedema.[28]

Involvement of extraocular muscles has been reported infrequently. It was seen in 10 of our cases. Nystagmus and oculomotor paresis have also been reported.[296] Exophthalmos [65,202] and internal ophthalmoplegia[83] may occur rarely.



Figs 5A to C: (A) Plain X-ray skull showing enlarged sella with erosion of posterior clinoids. (B) Plain X-ray showing rim of calcification above the sella. (C) Plain X-ray showing dense suprasellar calcification of craniopharyngioma

Endocrine Manifestations

About a third of the patients are stunted, although somatotrophic function is found to be deficient in 90–100%. The second most common manifestation is delayed sexual development. Precocious puberty is extremely rare with craniopharyngiomas (4%), in contrast to other suprasellar tumours like hamartomas and germinomas. This is because craniopharyngiomas extend usually anterosuperiorly, unlike the other lesions which commonly spread posterosuperiorly into the hypothalamus. In adults, gonadal failure leads to loss of libido and secondary amenorrhoea can occur.[221] Obesity may be seen, but the emaciation syndrome common to hypothalamic tumours is extremely rare.[254,255] Diabetes insipidus was noted in only 14% pre-operatively, while it is a more common presenting feature in germinomas and histiocytosis. Hypothyroidism, hypocortisolaemia or panhypopituitarism are very rare. Disturbance of consciousness, viz. coma or hypersomnolence is due to raised intracranial pressure, rather than involvement of the hypothalamic sleep-awake mechanism. An extremely atypical presentation, like pituitary apoplexy, has also been reported.[191,225]

Neurobehavioural disorders are uncommon in children, but are a fairly common presenting feature in adults and the elderly.[19,20,39,50,221] These are due to either subfrontal extension of the tumour or to hydrocephalus and often appear before other signs of raised intracranial pressure develop.[247] They usually comprise of intermittent confusion, hypersomnia, dementia, apathy, severe depression and Korsakoff's syndrome.[138,177] A rare presentation, with intermittent explosive speech disorder, has also been reported.[294]

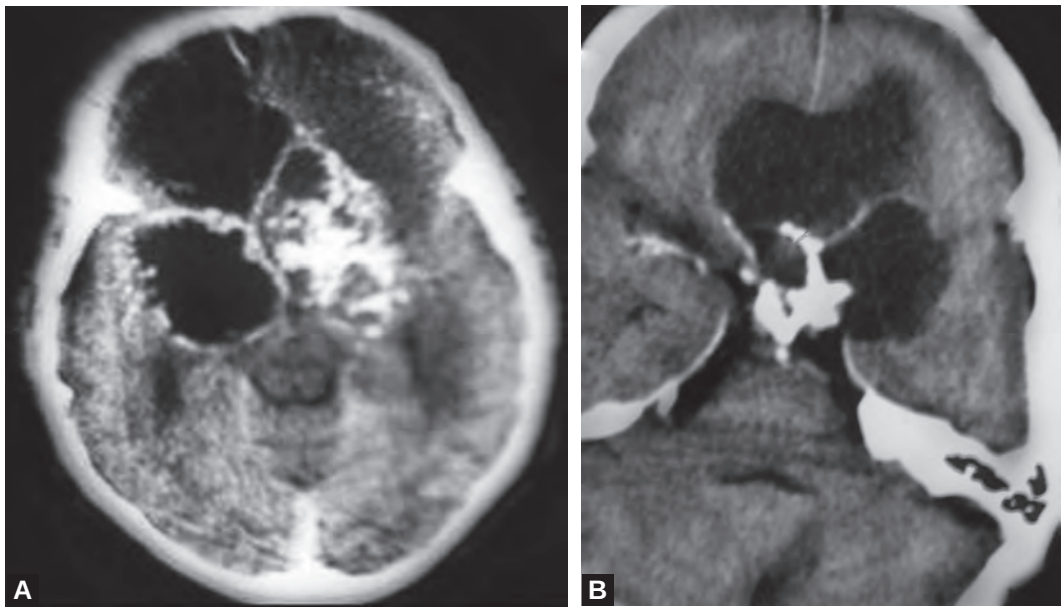
In very slow growing tumours, pressure on the cerebral peduncle may cause hemiparesis or paraparesis; pressure posteriorly on the brainstem may result in a broad based gait and ataxia, simulating a midline cerebellar tumour.[14,138,177] Aseptic meningitis has also been observed as a rare presentation of craniopharyngiomas, presumably from a leakage of keratin or cholesterol.[162,190,218,219]

Trigeminal neuralgia has also been reported as the first manifestation in a craniopharyngioma.[90] Occasionally, it may be revealed during investigations for unrelated problems, viz. head trauma.[257]

IMAGING

In spite of new modalities of imaging, plain X-rays of the skull continue to be useful in the workup of a patient suspected to harbour a craniopharyngioma (Figs 5A to C).

These are often diagnostic, especially in children. The characteristic feature is the presence of irregular, speckled calcification just above the sella turcica. Such calcification was reported in 96% of Matson's cases[193] and in 66% of cases reported by Kanaka and Ramamurthi.[138] Another type of calcification, seen less frequently, is the semicircular shell outlining the wall of a cystic lesion. Varadarajan et al.[303] reported that the density of calcification is low in Indian subjects. Calcification is much less common in adults.[19] In the authors' series, 80% of skull X-rays in children showed calcification, while it was seen in only 25% in adults. However, Sambisivan and Pillai[250] noted calcification in 60% of adults. Rarely, small specks of calcium may be seen only inside the sella. Fine flaky calcium is encountered with fast growing tumours, while slow growing tumours show dense calcification.[20,133] Other sellar changes include a ballooned sella and decalcified or eroded clinoids. In India and other developing countries, suprasellar calcification due to healed tubercular meningitis may simulate a calcified craniopharyngioma.[138] The calcification in these cases is commonly in the leptomeninges or, occasionally, in the brain parenchyma rendered ischaemic by tubercular arteritis. In elderly patients, a calcification in the wall of an aneurysm or the carotid artery may simulate tumour calcification. Sutural diastasis and even silver beaten appearance of the skull are seen in an advanced stage of the disease in children.



Figs 6A and B: CT scan images showing multicompartmental multicystic lesions with calcification in a craniopharyngioma

Computed tomography (CT) is probably the most useful investigation for evaluating these calcareous tumours.[38] A typical craniopharyngioma would show a cyst with a partially calcified contrast enhancing capsule (Figs 6A and B).

Solid portions containing calcium and isodense areas with some enhancement on contrast may be seen in solid tumours, but more commonly a mixed picture containing solid and cystic areas of varying degrees is seen. Effacement of the suprasellar cistern is seen frequently and compression of the third ventricle may be observed in larger suprasellar tumours. Distortion of the interventricular foramina may result in unilateral or bilateral lateral ventricular dilatation. This is more common in craniopharyngiomas than in pituitary adenomas.[184] Density of the cysts on the CT scan may vary from that of water to that of the brain, depending upon the content of cholesterol and other components within it. A cyst containing high protein appears isodense to hyperdense, while occasionally, keratin may have a lower density than water. Rarely, there may be layering within the cyst, cholesterol lying superiorly because of its low density. Calcification is seen more frequently in the CT scan than in plain X-rays.[279]

The cystic component in the tumour is more often seen in children than in adults, as is the enhancement of the tumour on contrast CT.[285] Coronal CT helps in defining the superolateral relationship with the optic pathways and the hypothalamus; sagittal reconstruction is useful in confirming the retrochiasmal location of the tumour.

Pituitary adenomas, meningiomas, giant aneurysms, optic and hypothalamic gliomas, arachnoid cysts, tuberculomas, and hamartomas occurring in the suprasellar region can pose problems in differential diagnosis. However, most of these lesions have distinguishing features and in difficult cases, other modalities, like dynamic CT, CT cisternography, MRI and MR angiography, are extremely helpful to clarify the diagnosis. CT scan is more reliable than MRI in detecting calcification.[66] The characteristic features of craniopharyngiomas, tumour cyst, calcification and enhancement on contrast administration are seen in over 75% of cases.[77,195] Singh and Chandy[263] have proposed a CT classification system for craniopharyngiomas, based on the extent and contents of the tumour, in order to facilitate proper planning of surgery and analysis of results.

Magnetic resonance (MR) imaging of craniopharyngiomas requires both T1- and T2-weighted images obtained in the sagittal, coronal and axial planes to determine the extent of the lesion and its relationship to the surrounding vital structures. The sagittal and coronal images are sensitive for evaluating the chiasm and its relationship with the tumour, and the signal characteristics depend upon the contents.[252] The usual cystic lesions, with a predominantly cholesterol content, are hyperintense on T1- and relatively hypointense on T2-weighted images. The cystic lesions predominantly containing keratin are hypointense on T2-weighted images, resembling water. The solid lesions are isointense to hypointense on T1- and turn isointense to hyperintense on T2-weighted images. Occasionally, the tumours are very heterogeneous, showing a solid-cystic appearance or a fluid level of cholesterol/keratin. A quantitative analysis of the cyst fluid and correlation with MR showed that the increased signal intensity of the cyst fluid on T1-weighted images is caused by a protein concentration of 9,000 or more mg per cent or the presence of methaemoglobin, while cholesterol and triglycerides do not increase the signal intensity.[2]

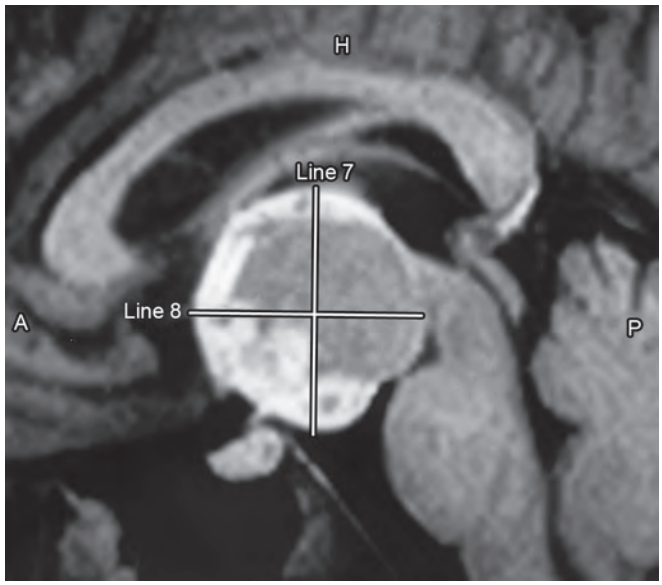


Fig. 7: Magnetic resonance imaging showing a large heterogeneous craniopharyngioma on contrast administration

Calcium in the lesion may be visualised as areas of signal dropout. Occasionally, calcium cannot be appreciated on MR, particularly if it is finely dispersed thoughout the tumour or is of a thin capsular type. Enhancement with Gd-DTPA is seen in the non-calcified solid portion of the tumour (Fig. 7).

Perifocal oedema along the optic pathways, causing a unique characteristic 'moustache' appearance, has been observed infrequently with certain craniopharyngiomas.[111]

Intraventricular craniopahryngiomas are not associated with tumoural calcification or cyst formation and are isointense on T1, hyperintense in T2 and enhance homogeneously with contrast.[125,247] Chiasmal thickening with pot belly expansion and a bilobed shape of an intraventricular tumour on the MR have been described.[85,249]

Although, generally it is possible to differentiate a pituitary adenoma with suprasellar extension because of its sellar origin and lack of calcification, it may be difficult on MR to differentiate adenomas with apoplexy from a craniopharyngioma. The signal characteristics due to haemorrhage are of a mixed intensity and may resemble a cholesterol containing craniopharyngioma.

Pituitary microadenomas, after treatment with bromocriptine may also cause difficulty in differentiation from an intrasellar craniopharyngioma, as they also contain haemorrhagic products. Rathke's cleft cyst is another lesion which may be indistinguishable from a cystic craniopharyngioma, due to its similar diverse location and signal characteristics.[241] Arachnoid cysts and an empty sella will show CSF intensity on all images and there is usually no distortion of the infundibulum. Non-neoplastic cysts and cystic craniopharyngioma and astrocytoma can further be differentiated by the administration of contrast (Gd-DTPA), where cyst wall enhancement is characteristic of the neoplastic cyst. Any confusion that may arise due to enhancement of normal pituitary tissue surrounding a non-neoplastic cyst can be cleared by dynamic studies, which show rapid enhancement in the early post-contrast period only in the neoplasm.[122] Chiasmal-hypothalamic gliomas in children can be differentiated by the demonstration of enlargement of the chiasma, spread along the optic nerves and tracts, predominantly solid tumour with microcysts, lower T1 and T2 relaxation times and homogeneous enhancement on administration of contrast.[257] Parasagittal imaging can further help in differentiation by demonstrating the lesion to be intra-axial or extra-axial. Occasionally, it may be extremely difficulty to distinguish between the two lesions.[36,316]

The presence of diabetes insipidus in conjunction with the MR findings of a well marginated round and lobular tumour, with prolonged T1 and T2 relaxation time and strong enhancement, characterise suprasellar germinomas, while teratoma can be differentiated on the basis of their internal heterogenicity with the presence of fat, calcium and various soft tissue densities.[150] Hamartomas, arising in the region of the tuber cinereum, usually project posteriorly into the interpeduncular cistern and may be difficult to differentiate from the solid non-calcified retrochiasmal craniopharyngioma.

Vascular lesions can easily be differentiated from the tumour on MR, because of their characteristic flow void on all imaging sequences. A thrombosed aneurysm may occasionally pose difficulty, because of its varied signal intensity, although the classical lamellated pattern of the thrombosis and no signal changes in T1 and T2 images should be helpful in distinguishing between the two. Further studies, with oblique imaging sequences, may demonstrate its exact relationship with the parent artery. MR angiography may be required, occasionally, for differentiation in difficult cases and is also very useful to study displacement and the relationship of the tumour to the basilar and carotid arteries and the circle of Willis.

Contrast angiography may occasionally be required, especially if facilities for MR and MRA are not available. It can also be useful for studying the circle of Willis, especially the pattern of dominance in the anterior cerebral arteries and the usefulness or otherwise of the anterior communicating artery, as it may have to be occasionally sectioned for radical removal of a retrochiasmal tumour.[155,275] Classical angiographic appearances of craniopharyngioma are of a sellar, suprasellar mass with some parasellar extension. Usually there is opening of the carotid siphon and the supraclinoid ICA is vertically oriented with lateral displacement and varying degrees of narrowing, while the A1 segments of the anterior cerebral arteries are often elevated.[47,60]

TREATMENT

Aims of Treatment

The treatment of craniopharyngioma should be aimed at reversing or halting progression of symptoms and

prevention of tumour recurrence, while leaving the child's physical, visual, hormonal and intellectual state at an acceptable functional level.[29] The modalities of treatment that may be employed are: (a) Surgery, which may include radical removal, partial removal or simple drainage of the cyst. It may be a staged procedure, especially if total excision is planned for a large tumour, to try and avoid hypothalamic damage. (b) Radiotherapy, external beam fractionated radiation or stereotaxic radiotherapy (SRT) for residual tumours or tumour recurrences.

Pre-Operative Evaluation and Management

Complete endocrinological evaluation is done to establish a baseline and to uncover hypopituitarism, especially with respect to growth hormone, cortisol and thyroid hormones. These need corrections throughout the course of management. Corticosteroid replacement is done and diabetes insipidus treated with DDAVP. Even in the absence of specific complaints, diabetes insipidus should be excluded by appropriate investigations. As thyroid replacement takes several days to two weeks with oral L-thyroxin, intravenous therapy may be given if the patient needs immediate surgery. This has to be done very carefully in elderly patients, as it may produce arrythmias and acute myocardial ischaemia.[217]

Dilemmas in Management Decisions

The treatment of a patient with craniopharyngioma calls for a wise and correct decision that will help the patient in the long run to play an appropriate social role.

Many controversies still exist in the management of patients with craniopharyngiomas. Should the tumour be totally excised? Is such excision feasible or desirable and will this cause problems in the long run? Or is subtotal excision safer and preferable from all points of view?

How much tumour removal is subtotal removal? Between these two alternatives, in which procedure are hormonal disturbances minimal? Will hormone replacement over many years become necessary and if so, can the patient or his family afford such long-term therapy?

If subtotal excision is advised, what are the chances of tumour recurrence? Does radiotherapy minimise recurrence and minimise hormonal dependence? What could be the ill effects of radiation near the base of the brain in children? In small tumours, will radiotherapy alone be effective to control further growth? These are the questions that face the surgeon and they have to be answered to suit each individual patient, bearing in mind the preservation and prolongation of a useful and active life.

Surgical Management

In 1910, Lewis[172] reported the first successful craniotomy for excision of a craniopharyngioma. Cushing[56] encountered 92 craniopharyngiomas between 1908 and 1927. Although he, as also Frazier,[81,82] used the trans-sphenoidal approach in 13 of these cases, he later pioneered the transcranial approach.

Associated Hydrocephalus

Although hydrocephalus is often associated with craniopharyngiomas, especially in children, the tumour can be tackled directly in many cases. However, if there are signs of rapidly rising intracranial pressure, the patient may require CSF diversion by a ventriculoperitoneal shunt. This is also a useful procedure in children presenting in a moribund condition or with gross metabolic disturbances, while preparing them for major surgery. It is important to drain both the ventricles separately, in view of obstruction of the foramina of Monro; this can be achieved by attaching a Y-connector to the tubing to connect both the ventricles or by inserting two separate shunts.

Hydrocephalus is more common in retrochiasmal tumours than in the prechiasmal variety.[119] Recurrent or residual tumour, aseptic meningitis or CSF rhinorrhoea may necessitate a shunt insertion post-operatively.[119,278] External ventricular drainage can be used as a temporary measure in moribund patients.

Operative Approaches

The important factors that decide the route of approach to a craniopharyngioma are the location and extent of the tumour, the configuration of the visual pathways, and the blood supply to the tumour and the optic apparatus.[238] Enlargement of the sella and the type of sphenoid sinus are also important if a trans-sphenoidal approach is being considered.[84]

Four varieties of craniopharyngiomas are recognised for surgical management: sellar, prechiasmal; retrochiasmal and intraventricular. Multicompartmental giant tumours are frequently encountered in our country and need special consideration. Atypical forms involving the sphenoid sinus, the pharynx or other basal areas need to be appropriately tackled.

The blood supply of craniopharyngiomas has already been described and the absence of blood supply from the posterior aspect is a major factor in enabling radical excision of the tumour. The blood supply to the chiasma is mainly from the inferior aspect, arising from the internal carotid, posterior cerebral and communicating arteries; and to the optic nerves from the superior aspect, from the anterior cerebral and anterior communicating arteries.[24] The lamina terminalis is completely avascular and can be entered safely to deal with retrochiasmal tumours.

The relation of the chiasma to the sella and to the tumour is an important determinant of the ease with which the tumour can be tackled. While the normal chiasma overlies the diaphragm sella in 70%, the prefixed chiasma overlies the tuberculum sella and the postfixed chiasma overlies the dorsum sella in the remaining 30% with almost equal incidence.[238] A prefixed chiasma make

the surgical task more difficult, as there is hardly any interoptic space to approach the tumour.

The operative approaches (Table 1) for tumours at different locations are summarised here:

I. Subfrontal
   a. Interoptic
   b. Opticocarotid
   c. Translamina terminalis
   d. Combined
II. Pterional
   a. Interoptic
   b. Opticocarotid
   c. Lateral carotid
   d. Translamina terminalis
   e. Combined
III. Trans-sphenoidal
   a. Transnasal
   b. Transcranial
IV. Transventricular
   a. Transcortical
   b. Transcallosal
V. Subtemporal
VI. Cyst aspiration
VII. Intracystic bleomycin
VIII. Combined approaches for giant tumours.

Radical Surgery Versus Conservative Surgery and Radiation

The optimal treatment of childhood craniopharyngioma remains controversial.[48] Most neurosurgeons advocate total excision of the tumour, both for its curative role and in order to avoid the potential side effects of radiation. Recent advances in neuroimaging and microsurgical techniques have made radical excision of craniopharyngiomas increasingly possible, and the operative results have improved remarkably, following improvement in the anaesthetic and peri-operative management in the past few years. The mortality of total excision has reduced dramatically from more than 40% in the preglucocorticoid period to less than 5% in the recent studies.[21,41,97,126,136,177,201,215,242,271,274,276,292,298,314] The risks may be higher when total removal is attempted for recurrent craniopharyngiomas.[193] Total excision in the majority of patients with craniopharyngioma has been recommended by several authors including Sweet,[227] Matson and Crigler,[193] Hoffmann,[119] Yasargil,[314] Symon,[279] Tomita and McLone[295] and Konovalov.[151,152] From a study of these series and some others, it becomes obvious that total excision, if carried out without damage to the adjacent vital neurovascular structures, would be most desirable in the management of craniopharyngiomas.

However, total excision of certain craniopharyngiomas may extremely be difficult and hazardous. A craniopharyngioma that is small or prechiasmatic in location can be easily excised completely with relative impunity (Figs 8A and B, 9A and B).

Table 1: Operative procedures used by author

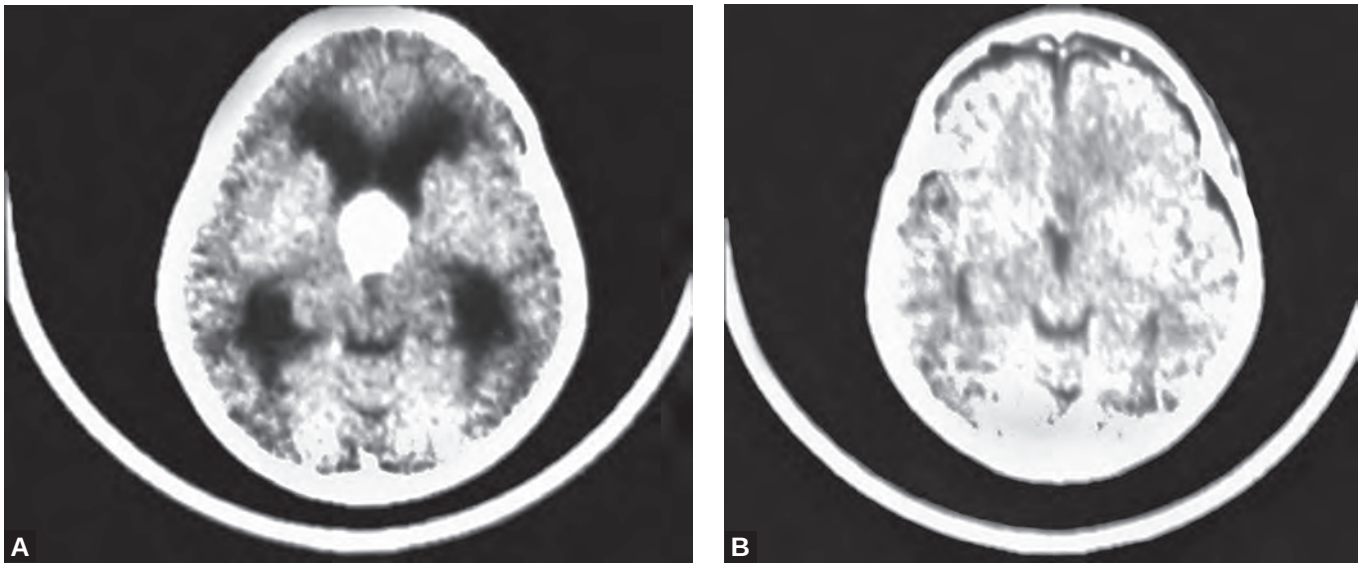
Surgical approach	*No. of cases*
1. Subfrontal: unilateral	59
2. Subfrontal: bilateral	37
3. Interhemispheric	10
4. Pterional trans-sylvian	15
Multistaged procedure	1
5. Transcallosal	3
6. Subtemporal	1
7. Trans-sphenoidal	2
8. Intracystic bleomycin	3
9. Aspiration only	2
Total	133
10. Translamina terminalis	16

When the tumour is large or multicompartmental or retrochiasmatic in location, total excision is difficult (Fig. 10).

Weiss et al.[307] found that total gross excision was felt to be accomplished in only 19 of the 31 patients on whom it was attempted and 4 of these totally removed tumours had evidence of residual tumour on post-operative imaging. Yasargil et al.[314] analysing their series of 144 patients found that in nearly 10% of their patients the tumour could not be totally excised. Even confirmed total resection can be associated with high recurrence rates.[110,119,308] Hoffman et al.[119] reported a 34% recurrence rate in patients felt to have had a complete resection. The recurrence after complete tumour removal was reported to be 10 out of 20 (Wen et al.[310]), 4 out of 16 (Cabezudo[37]), 2 out of 13 (Klun[144]) and 3 out of 38 (Symon[280]). Of our series of 133 patients treated between 1972 and 2005, 38 children and 26 adults had a total excision of their tumours (Figs 8A and B, 9A and B, 11A to C and 12A to D).

Tumour recurrence was observed in 11 children and 5 adults at a follow-up ranging from 2 to 28 years.

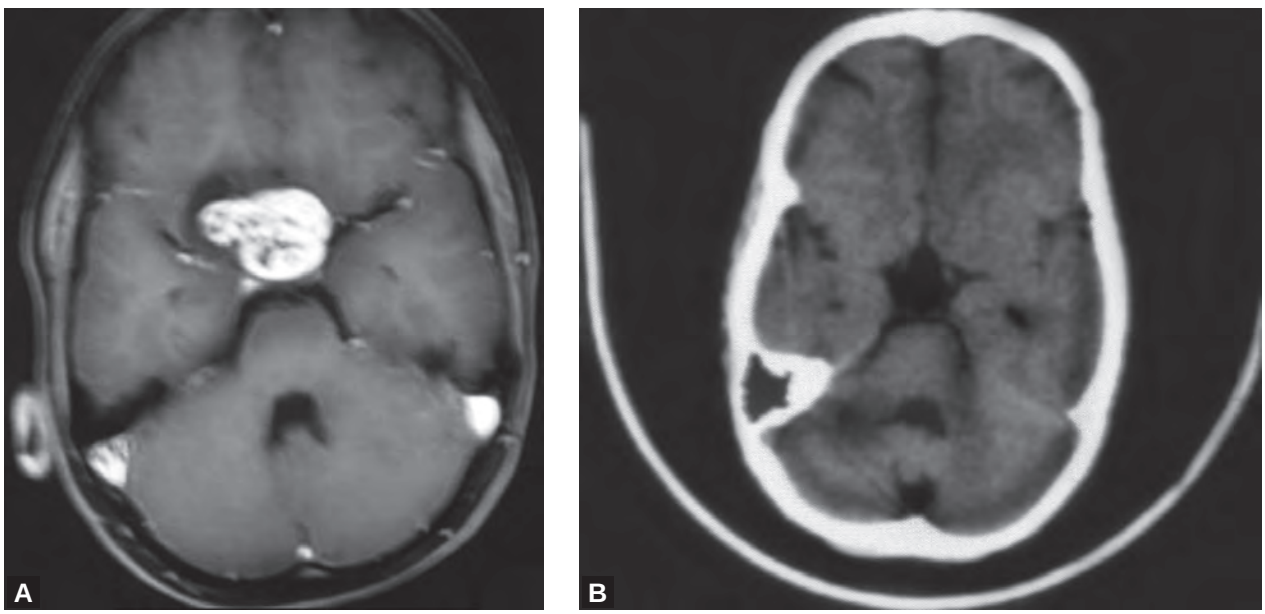
The main difficulty in removing the tumour radically is due to its adherence to the optic nerves, chiasm and tracts, pituitary stalk, hypothalamus and vessels of the circle of Willis.[40,46,62,117,137,221,278,280] The tendency of these tumours to form villous elongations or finger-like processes into the hypothalamus is well documented.[146,147,176] These tumour projections are difficult to separate from the brain and often make total excision hazardous. Although Sweet[227] and Lisczac[175] believed that there is a definite plane of cleavage between the tumour capsule and the hypothalamus that would enable one to radically excise the tumour relatively safely, Kobayashi et al.[146] have noted that these finger-like processes of tumour cells do infiltrate the hypothalamus and that reactive gliosis frequently prevents total tumour removal, without damage to the hypothalamus. Pertuiset[221] and Kempe[141] also felt that the glial or collagenous layer penetrates the hypothalamus and



Figs 8A and B: (A) CT scan showing a small prechiasmatic craniopharyngioma. (B) Post-operative MR scan showing total excision of the tumour

precludes complete resection. Shillito[259] has shown that there may not be any layer of glial tissue between the tumour and the brain and fingers of tumour tissue often invade the brain directly. Brain infiltration by tumour cells has been observed by several other authors also. A morphological study by Vichert and Korshunov[304] has revealed that in some cases the tumour does not have its own capsule and the cystic wall is formed by thickened fibrous tunica vasculosa or arachnoidea and that the tumour may penetrate the tunica vasculosa and invade the brain. The glial reaction in the infiltrated tissue, observed in our patients, was characterised by varying stages of astrocyte proliferation and fibrillary gliosis and Rosenthal fibres. Most authors who favour radical removal, including Sweet,[236] Hoffman,[114] Symon and Sprich[279] and Carmel,[40] have also indicated that one of the major obstacles to achieving total tumour removal is usually a tenacious adhesion of the tumour to an artery on the anterior part of the circle of Willis.

Aggressive surgery is usually associated with high mortality and increased incidence of hypothalamic, endocrinologic, metabolic and visual disturbances.[64,260] In the surgical series of Yasargil et al.[314] the operative mortality rate in children was 20%. Even tumours measuring less than 2 cm in size were associated with operative mortality of 6% in his hands. Fischer et al.[76] reported 12% mortality in children with craniopharyngioma who had radical excision, as compared to 7% death rate in the subtotal excision group. Ivkov et al.[128] had 33% and 20% mortality for radical and subtotal excision, respectively. The mortality rate published by Gordy et al.[97] in 1949 was 32% after radical excision and 0% in cases treated



Figs 9A and B: (A) MR scan showing a slightly larger craniopharyngioma. (B) Post-operative CT scan showing complete excision of the tumour

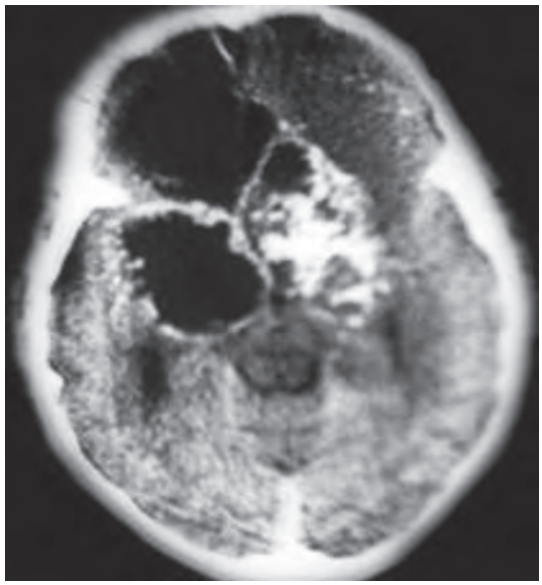
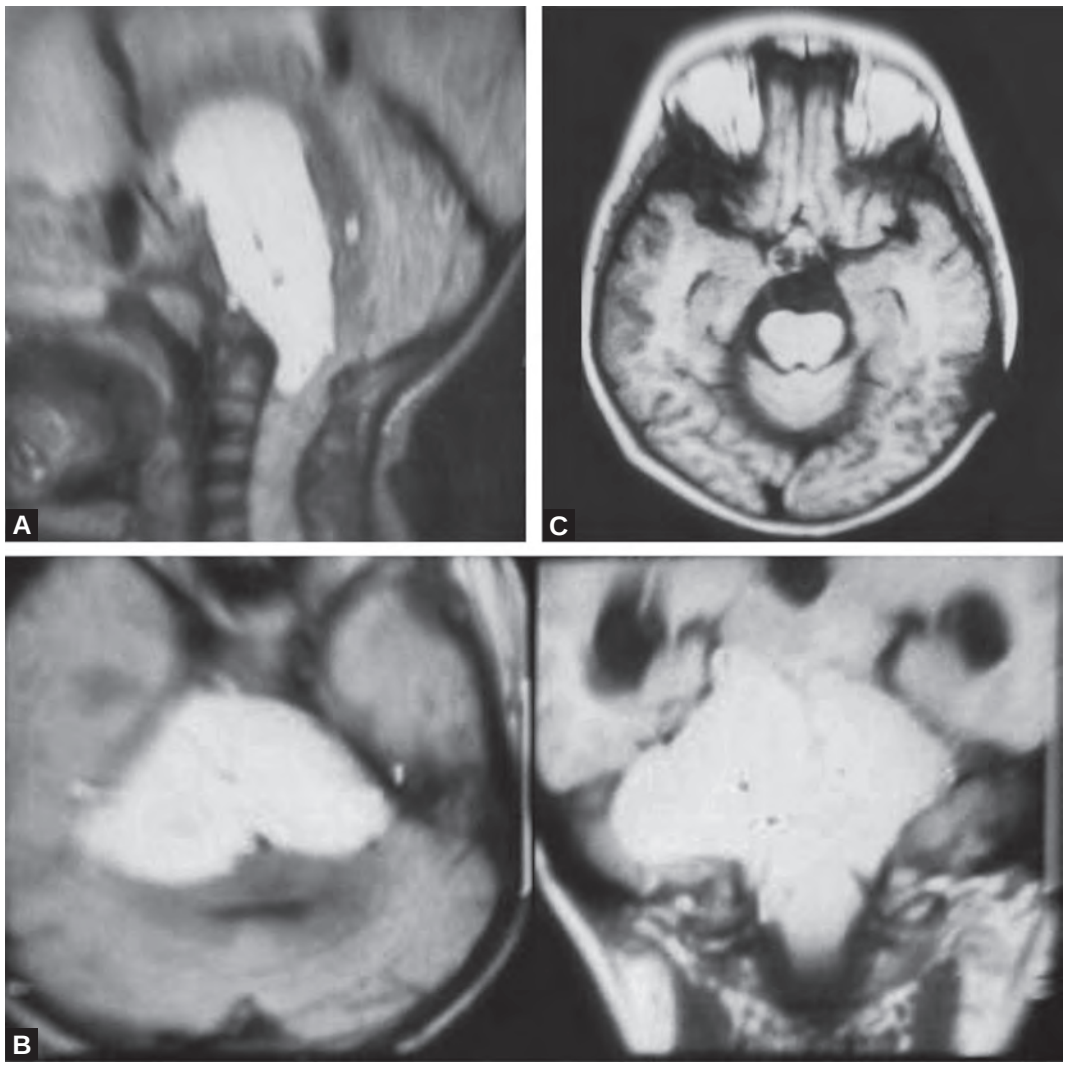


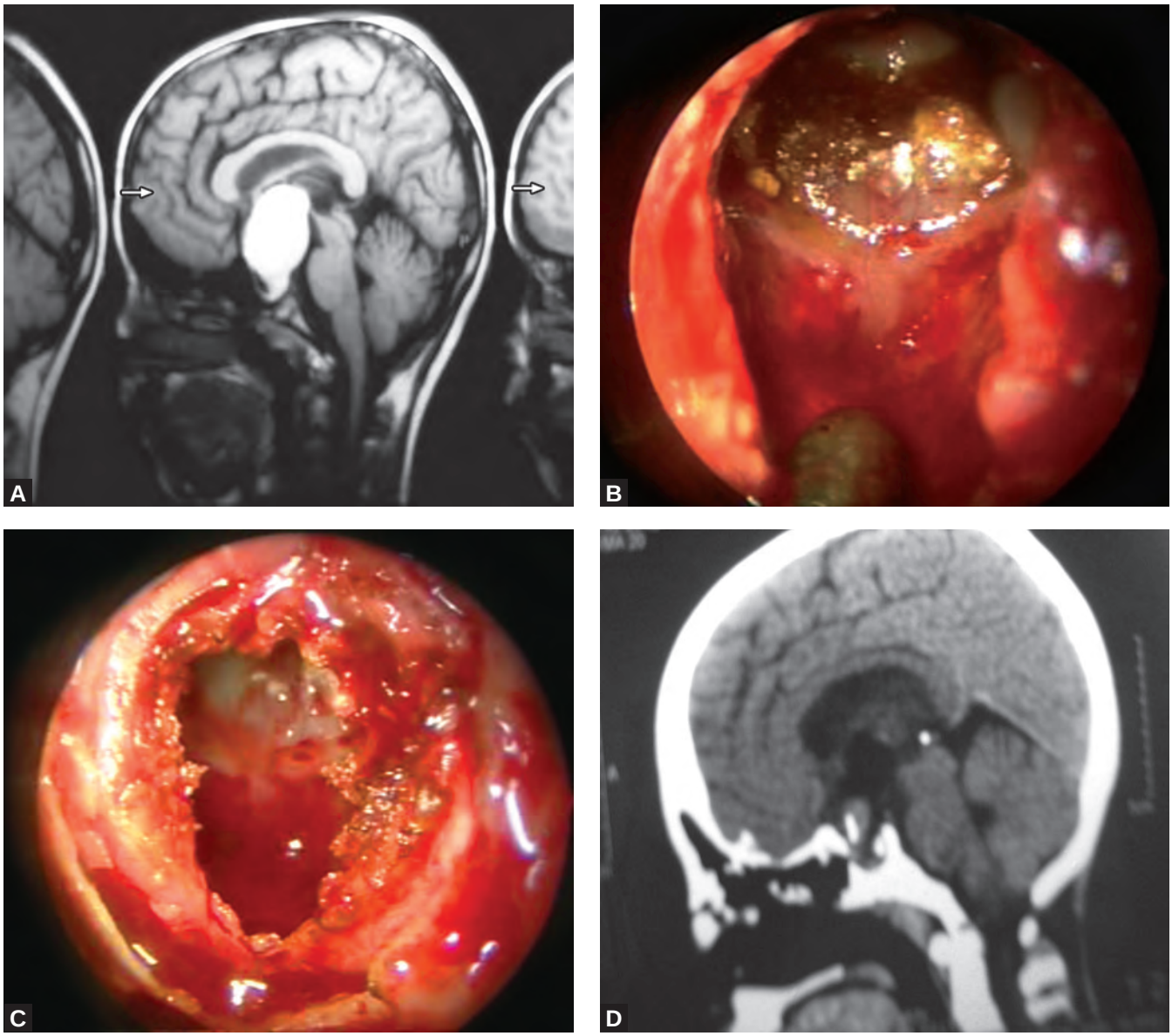
Fig. 10: CT scan showing a multicompartmental lesion not suitable for total excision

by subtotal excision. In our series of 133 cases, total excision in 64 cases was associated with 10 deaths, mainly due to hypothalamic disturbances, status epilepticus and pyogenic meningitis.

Hypothalamic damage and endocrinological disturbances are more frequently associated with extensive surgery in the suprasellar area. De Vile et al.[64] and others have reported high incidence of pathological obesity, abnormal hunger, disturbed sense of thirst, reversal of the normal circadian sleep patterns, cognitive and behavioural problems, learning difficulties and defective short-term memory as sequelae of aggressive surgery. Hoffman et al.[117] found that 43 of 46 children, undergoing attempted total excision, developed diabetes insipidus, 41 became hypocortisolemic, 38 developed hypothyroidism and 14 required six hormonal replacements. Almost 80% of the patients treated by Yasargil et al.[314] developed permanent diabetes insipidus and 79% required hormonal replacement for other endocrinological abnormalities. Matson and Crigler[193] also found a higher incidence of diabetes insipidus, persistent



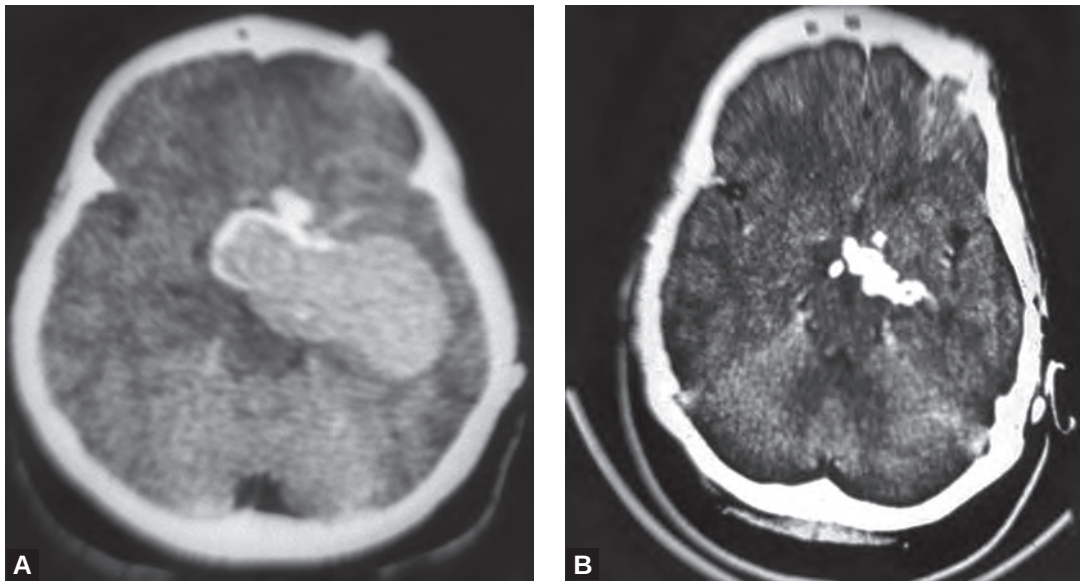
Figs 11A to C: (A) Sagittal view of MRI showing cystic craniopharyngioma extending all along the clivus in the posterior fossa. (B) Axial view showing the extent of the lesion in the posterior fossa. (C) Post-operative axial view showing complete excision of the lesion in the posterior fossa with a small residue in the cistern that was removed through a subtemporal approach



Figs 12A to D: (A) Sagittal view of magnetic resonance imaging showing cystic suprasellar lesion with extension into the sella. (B) Intra-operative photograph showing calcification of the lesion seen through the trans-sphenoidal approach. (C) Intra-operative photograph showing significant emptying of the lesion. (D) Sagittal view of MRI showing good excision of the lesion with small residual calcium in the sella

hypernatraemia, secondary hypothyroidism and hypocortisolemic with radical removal of the tumour. A recent study has reported panhypopituitarism in significantly higher number of patients after extensive surgery for craniopharyngioma.[63] Sixty-eight (56%) patients in our series developed transient diabetes insipidus, while the other 28 (23%) patients had prolonged diabetes insipidus requiring long-term DDAVP or oral carbamazepine. The incidence of hypothyroidism, hypocortisolemic and hypogonadism was significantly higher in patients with total excision. Most of these patients required endocrine support during surgery and sustained replacement therapy for many years following surgery.

Surgical resection is often advocated to alleviate visual symptoms promptly. However, surgeons must acknowledge that aggressive surgery may also be associated with new or increased visual problems.[10,22,48,224] Hoffman et al.[117] observed that while 9 children experienced improvement in their vision, 3 worsened and 16 children with no visual complaints prior to surgery were left with visual field defects following excision. In addition, 12 children with normal visual acuity prior to surgery experienced visual deterioration. Radical tumour surgery is also believed to have an adverse effect on cognitive and intellectual functions.[76] Detailed follow-up psychometric evaluation in Hoffman's series was carried out in 27 children with total tumour excision. Although only one child had an IQ score below 69, 57% had impairment of memory function. A fair number of children with radical surgery seemed to have had worsening of learning abilities, defective short-term memory and limitation of concentration span. Unfortunately, no comparable study has been carried out in patients with subtotal excision with adjunctive therapy.

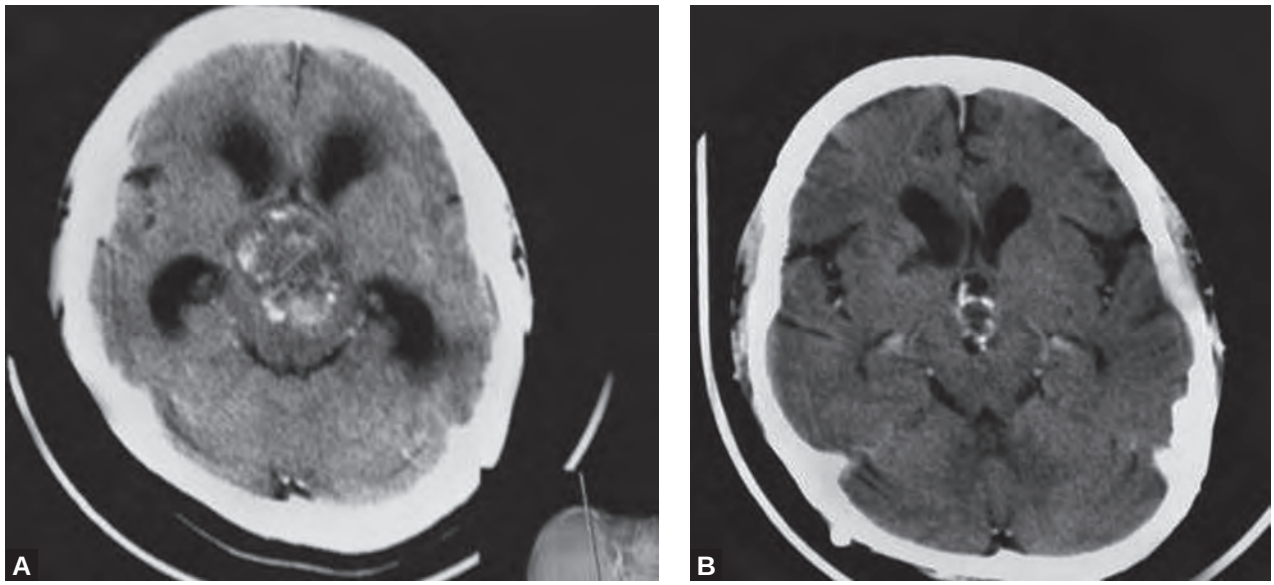


Figs 13A and B: (A) CT scan showing residual lesion in a boy of 10 years. (B) Residue on CT scan done 18 years after radiotherapy

The mortality and morbidity for planned subtotal excision is definitely less than that for total excision,[58,80,109,121,188,198,236,274,309,310] presumably due to lesser vascular and hypothalamic injury. The best results concerning tumour remission in a large series of patients with craniopharyngiomas have been reported by Baskin and Wilson.[21] In this series, a less radical surgical approach was used and recurrence of tumour was controlled with radiotherapy. Although the follow-up period in this group was short, they were able to report that 91% of these patients were in remission. However, it is clearly evident from the literature that subtotal resection alone, without radiotherapy, is not an adequate treatment for craniopharyngioma and the incidence of tumour recurrence after incomplete removal alone is high.[30,35,107,168,191,260,279] In Weiss's series,[308] all 7 patients treated with only subtotal excision experienced tumour recurrence with a median time to recurrence of 12 months. All 10 out of 144 cases reported by Yasargil et al.[314] in whom complete resection of the tumour was not possible, experienced tumour recurrence and had a high post-operative morbidity and mortality.

Radiotherapy, as an adjuvant to surgery, has been proven to offer good tumour growth control. A review of the literature shows that there is low operative mortality, 50–80% disease-free survival and good long-term functional outcome when conservative surgery is combined with adjuvant radiation therapy.[58,157,158,159,188,274] Baskin and Wilson[21] in 1986 reported that treatment with conservative surgery followed by radiotherapy was effective. The operative mortality was 3% and approximately 91% of their patients had no recurrence of the tumour. A series of patients who were treated conservatively and followed for more than 10 years was published by Fischer et al.[76] in 1990. Only 2 (7%) out of 27 patients in the conservative treatment group had tumour recurrence. The endocrinological and psychological dysfunction also seemed to be less than those treated with radical excision. The authors emphasised the good functional results of this group of patients. Regine and Kramer[236] found an overall 20 year survival of 62% of their patients who were treated with external beam radiation post-surgery.

At the Royal Marsden Hospital, 173 patients with craniopharyngioma were treated with external beam radiation between 1950 and 1986 following various modes of surgical therapy.[134,229] The 10 and 20 years survival rates were 77% and 66% respectively at a median follow-up of 12 years. The overall survival and the progression-free interval did not seem to be affected by the extent of surgical resection and there was improvement in the visual acuity and fields by 30% and 36%, respectively. The group concluded that conservative surgery with adjunctive radiotherapy achieved excellent long-term tumour control and survival with low morbidity. A similar experience has been noted by other authors (Regine et al.[237] Wen et al.[310] and Nagpal[206]) who also felt that those patients who underwent subtotal resection with radiation therapy had a significantly better recurrence free interval, compared with those who had surgery alone. In the authors' series of 23 patients who had subtotal resection and radiotherapy, 9 remained recurrence-free for a period varying from 2 to 21 years. Of 56 patients with gross total resection, 16 (28%) had recurrences. Nine of these had supplementary radiation therapy and remained recurrence-free for a mean follow-up period of 7.5 years (range 5 to 14 years). This experience confirms that radiation therapy is efficacious in delaying or preventing a recurrence in over three fourths of the cases and that it has a definite role in the management of incompletely excised or recurrent craniopharyngioma as an adjunctive therapy (Figs 13A and B, 14A and B).

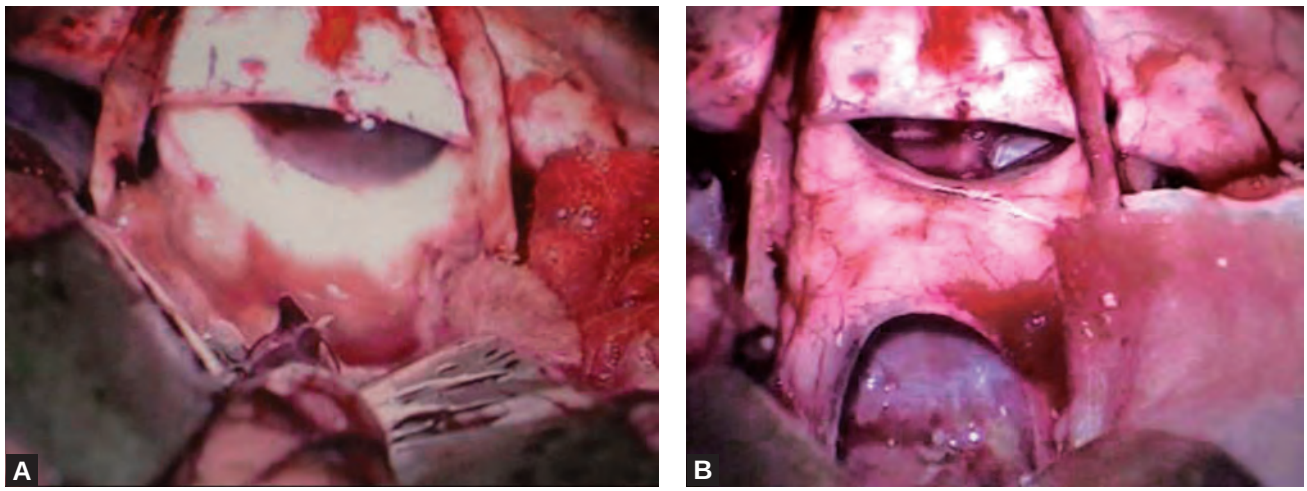


Figs 14A and B: (A) Scan showing residue after partial excision of a large craniopharyngioma. (B) Scan showing the residue 2 years after radiotherapy

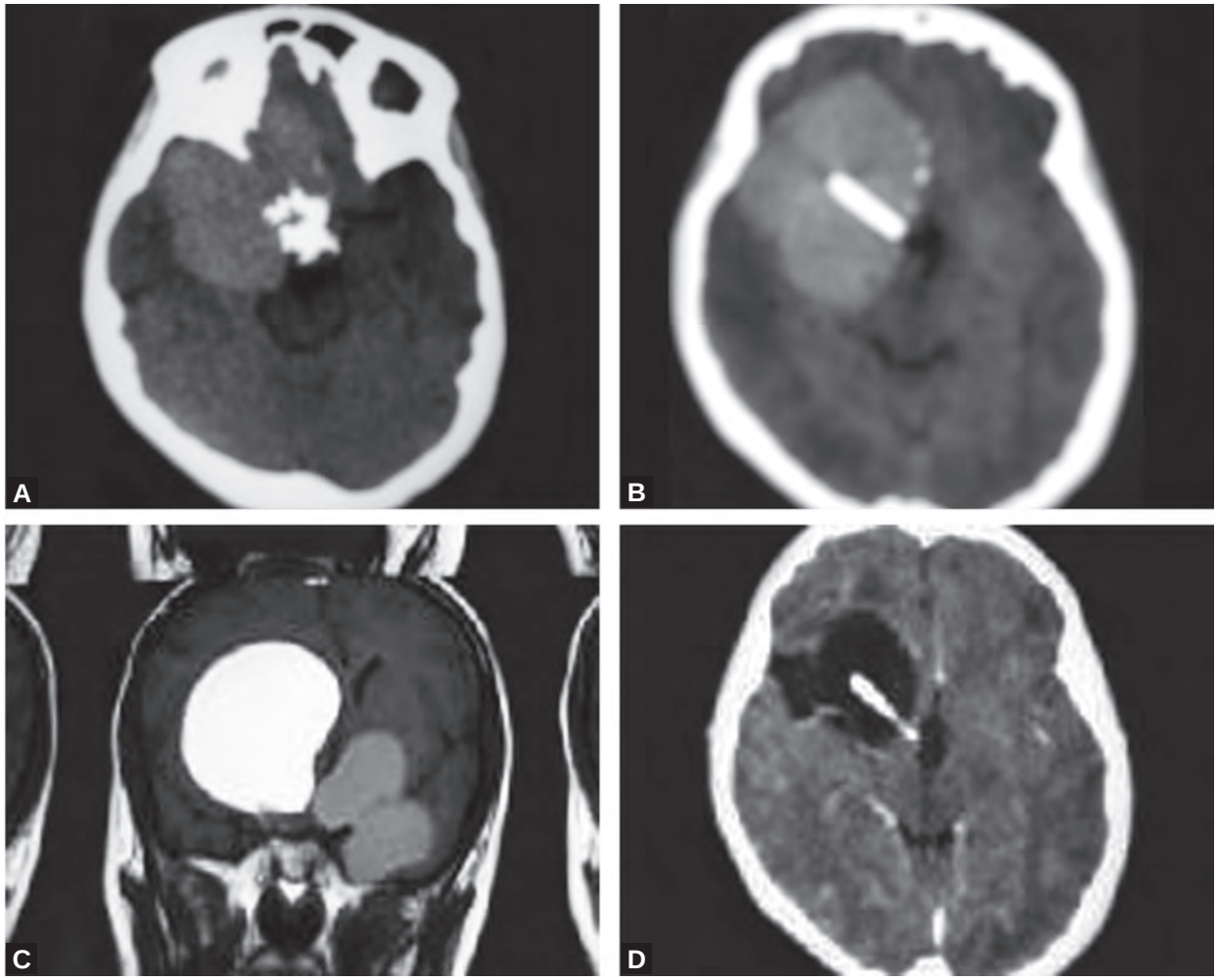
The outcome of contemporary management of craniopharyngiomas should reflect the twin goal of tumour control and enhanced quality of survival. Although with modern technology it has become possible to excise a larger number of tumours radically with acceptable mortality, the success of treatment should be measured not only by low mortality or by the length of survival but also by the residual morbidity and functional usefulness, and good quality of life should be the primary objective.[113] In the last 14 cases, keeping this goal in mind, we have totally excised 8 small and moderate sized tumours without a recurrence for 3 to 8 years in six (Figs 15A and B) and a small recurrence in one.

One was lost to follow-up. Of the six large multicompartmental tumours, three had subtotal excision with radiotherapy with recurrence free follow-up in one case, recurrence with surgery with a follow-up of 6 years, one being lost to follow-up. Two of those with a large cystic component had Omayya reservoir placement with instillation of bleomycin (Figs 16A to D).

The cysts became smaller but did not reduce sufficiently in size and required craniotomy with partial excision of cyst wall. They are receiving radiotherapy. All of them have had a better quality of life. One patient has had subtotal excision through the trans-sphenoidal route, the suprasellar extension being essentially cystic.



Figs 15A and B: (A) Bifrontal approach showing intact olfactory tract, optic chiasma and approach to lamina terminalis. (B) Shows translaminar approach with total excision of the tumour in a prefixed chiasma



Figs 16A to D: (A) CT scan showing essentially cystic craniopharyngioma with calcification. (B) Scan showing the catheter with ommaya reservoir within the cavity. (C) Cystogram to show lack of leakage from the cyst. (D) The position of the cyst after instillation of bleomycin

Hormone Therapy in Craniopharyngioma

Dosage Schedule

Pre-operative Hormone Schedule

1. Glucocorticoids — 50 mg/m^2 IM/IV
   Hydrocortisone sodium succinate — Evening prior to surgery
2. Thyroid hormone
   Sodium L-thyroxine — 100 μg/m^2/24hr PO 4–6 weeks pre-operatively
3. ADH: Diabetes insipidus — 0.1–0.3 ml IM/SC (2–6 units)
   Aqueous vasopressin (20 U/ml) — 4–6 hourly

Intra-operative Hormone Therapy

1. Glucocorticoids
   Hydrocortisone sodium succinate — 100 mg/m^2 IV
   Morning of the scheduled operative procedure
   If surgery is prolonged — Additional 50 mg/m^2 IV
   Beyond 4 hours — 4 hourly
2. Adequate fluid/blood replacement
   If surgery is prolonged and brisk, diuresis occurs:
   Aqueous vasopressin — 2–6 units IM/SC 4 hourly sos

Immediate Post-operative Replacement Therapy

1. Glucocorticoids
   Day 1: Hydrocortisone sodium succinate
   Infants: — 25 mg/IV 6 hourly
   Adolescents: — 75 mg/IV 6 hourly
   Reduce during next 24 hours, if progress is satisfactory
   Day 3: Prednisolone
   Taper rapidly to physiological replacement dosage
2. Thyroid hormone
   Sodium L-thyroxine — 100 μg/m^2/24 hour PO
3. ADH: Diabetes insipidus
   Fluid replacement
   Aqueous vasopressin (20 U/ml) — 0.1–0.3 ml IM/SC 4–6 hourly (2–6 units)
   or
   Vasopressin tannate in oil every 24 hours (5 U/ml) — 0.25–0.5 ml IM to 48 hours (1.25–2.5 units)

Long-term Hormonal Replacement Therapy: Dosage Schedule

1. Glucocorticoids	
a. Hydrocortisone acetate (cortisol)	20 mg/m^2/24 hours PO
To be given in two divided doses:	Two-thirds of the dose in the morning and one-third in the evening
Infants:	10 mg/24 hours PO 7.5 mg morning 2.5 mg evening
Adolescents:	30 mg/24 hours PO 20 mg morning 10 mg evening
or	
b. Prednisolone	One-fourth the dose of hydrocortisone
2. Antidiuretic hormone	
a. Desmovasopressin acetate (DDAVP)	2.5–15 μg, twice a day intranasal spray. Start with 2.5 μg at night—bed time dose
Increase gradually in increments of 2.5 μg until satisfactory antidiuresis obtained	
b. Chlorpropamide	4 mg/kg/24 hours PO
c. Carbamazepine	10–20 mg/kg/24 hours PO in three divided doses
3. Thyroid hormone	
Sodium L-thyroxine	100 mg/m^2 /24 hour PO
Infants:	6–8 μg/kg/24 hours PO
Adolescents:	4 μg/kg/24 hours PO
4. Growth hormone	
Human growth hormone (HGH)	UK: 5 IU thrice a week IM/SC USA: 15 IU/m^2/week divided into 6–7 Inj SC/IM
Current recommendation	0.42 IU/kg/week in divided doses daily for 6 days/week at night

Following table reproduced with the kind permission of Chandalia HB and Chopra KP (Eds). Endocrine management in childhood craniopharyngioma. Neurology India. 1991;39:64.

Radiotherapy

The first group of patients treated with radiation, following subtotal removal of suprasellar craniopharyngiomas, was reported by Carpenter et al.[44] more than 50 years ago. At that time, it was felt that only the cells that produced secretions and formed cysts could be destroyed by X-rays and the solid tumour cells essentially remained unaffected. Doubts continued for many years as to whether or not craniopharyngioma epithelium would be effectively killed by radiotherapy. A dramatic change in this attitude occurred in 1961 when Kramer and his associates[157,158,159] reported excellent results with conservative tumour surgery and supravoltage irradiation. Since then, many studies have shown the efficacy of radiation therapy in both, increasing the recurrence-free survival and improving the quality of life.

A review of the literature shows that radiation therapy added to surgery results in a 50–80% disease-free survival.[156–159,188] In 1986, Baskin and Wilson[21] reported that treatment with conservative surgery, followed by radiotherapy, was effective. Excellent recurrence-free survival rates in the patients treated with external beam radiation have been published by the Royal Marsden group in 1993.[134,231] The 10 and 20 year survival rates were 77 and 66%, respectively at a median follow-up of 12 years. The survival and progression-free survival did not seem to be affected by the extent of surgical resection and there was improvement in visual acuity in 30% and visual field defects in 36% of patients. They concluded that adjunctive radiotherapy can definitely improve the overall outcome, regardless of the degree of surgical excision. Fischer,[76] Nagpal[206] and Regine and Kramer[236] also observed better functional outcome and lesser endocrinological and psychological dysfunction in this group of patients, when the long-term results are compared with those who had radical surgery. All of their patients who underwent aggressive tumour resection developed adverse surgical sequelae, whereas vascular or neurological complications attributable to radiation were minimal when the dose did not exceed 5000 cGy.

Although radiotherapy has proven to be beneficial in the management of craniopharyngioma, complications from this form of treatment are also well known.[55,57,76,91,106,136,260,305] Increasing attention is given to the effects of high dose radiation therapy on brains of children. Duffner et al.[70] found that 40% of the children who received radiotherapy for brain tumours had IQs below 70 and only 40% had IQs in the normal range. A very detailed and careful study was published by Packer et al.[216] in 1989. In this study, children with brain tumours treated with radiation therapy had a fall in full-scale IQ from 105 at diagnosis to 91 by the end of the second year after radiation therapy. Children who did not receive radiotherapy did not demonstrate a fall in any cognitive parameter over time. The younger the child at the time of treatment, the greater was the likelihood and severity of damage. Evaluation of children, who had been given brain irradiation under the age of 3 years and who survived for a long period, showed that 55% required a special education school.

Optic neuropathy and radionecrosis of brain have been noted by Flickinger et al.[80] the risks being greater with a higher dose of radiation. Their study of 21 patients, who were subjected to megavoltage external beam irradiation with more than 5 years follow-up, showed a marked difference in the complication rate between those patients who had 51.3–60 Gy and those who had higher doses in the range of 60–70 Gy. In the high-dose group, the actuarial risk at 5 years from optic neuropathy was 30.5% and for brain necrosis was 12.5%.

However, there did not seem to be a significant difference in tumour control or recurrence rate in the high- and low-dose groups.

One of the long-term hazards of radiation therapy is the induction of a secondary tumour, following radiation therapy.[40,185,265,300,305] Tumours reported, following irradiation of craniopharyngiomas, include brainstem gliomas, supratentorial and infratentorial sarcomas and meningiomas. Occlusion of major vessels may result in ischaemic attacks or strokes.[200] Nishizawa et al.[211] reported the case of a 13-year-old girl who developed post-radiation stenosis of the internal carotid, middle cerebral and anterior cerebral arteries with development of moyamoya vessels, which had ruptured and formed an intracerebral haematoma. Endocrine deficiencies, like GH failure, hypothyroidism and hypogonadism, are not uncommon.[139,156,159] Delayed side effects of irradiation were noted by Al Mefty et al.[3] in their study which included visual deterioration, pituitary dysfunction, varying degree of parenchymal degeneration of the brain and development of a chordoma in a patient of acromegaly treated 30 years earlier with radiotherapy.

Some authors believe that although radiotherapy without doubt decreases cyst fluid, it probably does not completely destroy the craniopharyngioma epithelium. Amacher[4] has demonstrated that the mass remaining after radiotherapy can largely be necrotic with some viable tumour cells, which can lead to tumour recurrence. Numerous examples of recurrent tumours in patients who have received radiotherapy can be found in the literature.[21,76] Although it is believed that an attempt to remove a craniopharyngioma that has been treated with radiotherapy presents a difficult problem because of the development of numerous adhesions, we have been able to achieve a complete excision in a majority of our patients with recurrent tumours who had received radiotherapy earlier.

It is quite clear that radiotherapy is integral to the treatment of craniopharyngiomas. The conventional methods of radiation therapy have been associated with significant morbidity because the irradiated volume includes a significant amount of normal tissue. The degree and extent of morbidity associated with radiotherapy was related to the high dose of radiation (60–70 Gy) and lack of precise localisation of the target. Modern three dimensional conformal radiation treatment (3D CRT) using CT and MRI leads to accurate localisation. The dose of radiation also does not need to increase beyond 5400 Gy. Use of this type of irradiation has improved the therapeutic outcome; the 10 year survival was 85–96% compared to 56–78% among children treated without utilising modern imaging.[99] These complications can further be reduced with the newer modalities of treatment using more precise stereotactic methods. The stereotactic techniques permit precise delivery of highly focal ionising radiation to the tumour. Either a Linear Accelerator[163] (LINAC) is used to deliver the radiation dose to the target or intensity modulated radiation therapy (IMRT) in which conformal radiation is given to a target, using multiple small beamlets varying radiation intensity or SRT (stereotaxically) directed multifractional radiotherapy may be given.[270] This form of therapy is found to be fairly effective in either destroying small tumours or stopping their growth and is now routinely used at a number of specialised centres for the treatment of brain tumours, including craniopharyngiomas.

Surgical Technique

Various surgical approaches used to excise the tumour radically have already been described. As the tumour is located in close relationship with the optic pathways, the hypothalamus and the adjacent vascular tree, the approach should be such that these structures are well visualised and protected during removal of the tumour. The size and extent of the craniopharyngioma would often determine the optimal approach for its total excision.

The unilateral or bilateral frontal approach appears to be ideal for excision of most of the tumours, as it gives a good view of the optic nerves, chiasma and the interoptic space.[30,42] There is good scope for preservation of the olfactory tracts (Figs 15A and B). As the optic chiasm and the hypothalamus are elevated by the tumour, good debulking of the tumour can be done through the interoptic space. A gradual separation of the tumour from the floor of the third ventricle thereafter becomes easier with a gentle pull on the capsule. The perforating vessels that supply the hypothalamus need to be carefully preserved. The capsule of a cystic tumour, if it is thin, may tear and render its total removal difficult. Removal of a calcified lesion may become hazardous and result in damage to the optic pathways or adjacent vascular tree, unless it can easily be disintegrated into small bits. A large solid rock of calcium that cannot be pulverised is best left alone.

At times, a small lateral extension of the tumour can open out the optico-carotid space. The tumour can then be tackled through this space, gradually debulking it and gently pulling it into the field of exposure. This optico-carotid approach is possible with a subfrontal exposure. The pterional exposure, however, is better for such extensions.

Subfrontal exposure is ideal for the retrochiasmatic trans-lamina terminalis approach, when the chiasm is prefixed. The tumour can gradually be debulked and separated from the optic pathways, as well as the hypothalamus with good visualisation up to the membrane of Liliequist and the prepontine area. The membrane presents a plane between the tumour and the basilar artery and its branches. The anterior cerebral vessels form the posterior limit of the exposure. We have successfully utilised this approach in radically excising 13 retrochiasmatic tumours with only one mortality.

More room can be obtained in patients with a prefixed chiasm in front of the optic nerves, by the transcranial trans-sphenoidal approach.[233] Patterson and Danylevich[220] have used a combined transcranial

approach through the lamina terminalis and the sphenoid sinus in excising craniopharyngiomas with a prefixed chiasm. They excised the tuberculum sellae and gained extra space in the interoptic recess and removed the lesion by a rail-road manoeuvre. Injury to the optic nerves, while removing the tumour, was thus avoided. They feel that the pterional approach does give good access behind the tumour but the optic pathways and the carotid artery on the side of the exposure preclude good visualisation and exposure of the optic nerve and arteries on the opposite side.

Suzuki[275] advocated an interhemispheric approach through the lamina terminalis for excision of retrochiasmatic intraventricular lesions. With this approach, both the olfactory nerves can be spared; the main arteries can be exposed sufficiently with a wide operation field, to render the procedure safe; damage to the lateral wall of the third ventricle can be avoided and large tumours can be removed safely. Kanno et al.[140] have drawn attention to a pitfall in this approach. They have shown that occlusion of the bridging veins from the frontal lobe to the sagittal sinus decreased the regional blood flow and increased the chances of development of a haematoma in the retracted and infarcted portion of the frontal lobes.

A transpetrosal transtentorial approach is advocated by Hakuba et al.[101] for retrochiasmatic craniopharyngioma. They claim better visualisation of the lesion and its surrounding structures. They could totally excise the tumour in five of their eight cases. All of them had transient third nerve paresis, all developed diabetes insipidus, one became blind and developed left hemiplegia and one died in the immediate post-operative period. Being a difficult approach with possibilities of many complications, it may be used only by those familiar with it.

The subtemporal approach gives good visualisation of the tumour between the third nerve and the posterior communicating artery inferiorly and the optic tract superiorly. Symon[279,280] has used this approach for tackling most of the craniopharyngiomas and has been able to excise tumours totally. The tip of the temporal lobe may be excised to facilitate exposure. This approach can be used in combination with the pterional approach for excising small retrochiasmatic tumours or parasellar lesions with extension into the middle fossa. Banerji[17] has found this to be a good approach for radical excision of the tumour.

The transventricular approach may be used for lesions located essentially in the third ventricle.[176] We have used this approach in three of our cases.

The trans-sphenoidal approach is useful in a small proportion of cases that are intrasellar and infradiaphragmatic in location and mainly cystic with a primarily enlarged sella[49,104,164,167,258,268] (Figs 12A to D). Laws et al.[166,228] feel that these may originate in the sella and remain predominantly extra-arachnoidal, flattening the pituitary gland anteriorly. They reported a success rate of 86% in 76 cases in whom the trans-sphenoidal approach was used. Fahlbusch[74] has excised 40% of lesions trans-sphenoidally. Nagpal[205] presented a series of 11 cases of craniopharyngioma tackled through the trans-sphenoidal route and stated that predominantly calcified, firm fleshy tumours lend themselves poorly to removal by this route. Honegger et al.[120] could totally excise the tumour in 15 of 19 patients (79%) with primary trans-sphenoidal surgery and in 8 of 13 patients (62%) with the trans-sphenoidal approach following previous surgical procedures. Diabetes insipidus seemed to be a frequent complication. Transmaxillary–trans-sphenoidal as well as transpalatal approaches have been described by ENT surgeons.[103,132]

In our series of 133 cases, the subfrontal approach, unilateral or bilateral, was used most frequently. For those lesions that needed a more lateral approach, the pterional or subtemporal approach was used, whereas for essentially intraventricular lesions, either the transcortical–transventricular or the transcallosal approach was used. We had two intrasellar lesions that were tackled through the trans-sphenoidal route.

Complications

Most of the reported series have shown that radical excision results in a higher morbidity with functional impairment for life in quite a few patients.[260,261,274] The common disturbances are in visual functions and in functions of the hypothalamus and the pituitary, resulting in endocrinological deficiencies with need for hormonal replacement. Diabetes insipidus or SIADH, psychosocial impairment resulting in mental dullness, poor educability and poor intellectual performance also occur.

The morbidity is supposed to be less with conservative surgery, if it is carried out as a planned procedure in the appropriately selected cases. However, a higher percentage of mortality and morbidity have been reported with subtotal tumour resection in some studies.[88,253,292] It is likely that subtotal resection in these patients may be a result of having had to give up total excision after repeated attempts at total excision, subtotal excision not being really a planned procedure.

The incidence of immediate treatment-related complications is relatively lower with other modes of treatment including intracavitary chemotherapy, stereotactic brachytherapy, Linac therapy or radiosurgery (SRS) with gamma knife or stereotaxic radiotherapy (SRT). However, more experience and long-term results may be required to evaluate the efficacy, delayed side effects and overall outcome associated with these treatment modalities.

Other Treatment Modalities

In the management of craniopharyngioma, there are several goals: tumour control, combined with preservation of endocrine, visual, and cognitive functions. The likelihood of achieving these goals is enhanced by a multimodality approach in which staged excision of tumour,

drainage of the cyst, instillation of radioactive or chemotherapeutic agents into the cyst through a reservoir or stereotactic radiosurgery (SRS) may be employed.

Cyst Aspiration

Stereotactic aspiration of a cystic craniopharyngioma or periodic percutaneous aspiration of the cyst, using a reservoir/catheter system can be carried out easily without any significant morbidity.[98,240] This form of treatment is simple and effective in certain cases of recurrent cystic tumours. Two of our patients with recurrence of cystic craniopharyngioma were successfully managed with repeated aspirations of the cyst, using a reservoir/catheter system. However, other authors have discouraged the use of a reservoir/catheter system for multiple aspirations of the cyst.[181] In their experience, such catheters often tend to aggravate the clinical problem presented by a cystic craniopharyngioma. Cyst fluid production seems to be stimulated, leading to progressively more frequent need for aspiration. The authors also cautioned about the potential hazards of leakage of the radioactive substances outside the cyst cavity, when injected through the reservoir-catheter whose distal holes are lying outside the cyst.

Intracavitary Bleomycin Injection

A fair number of tumours are essentially cystic or have a large cystic component. These are the lesions that can respond reasonably well to intracystic instillation of bleomycin. A catheter is placed in the cavity with an Omayya reservoir either stereotactically or through an open craniotomy. If there is more than one large cyst, a catheter is placed in each cyst. A contrast cystogram is performed to make sure that there is no leakage from the cyst. Thereafter 3–5 mgm of bleomycin is instilled 2–3 times a week through the Omayya reservoir. A total of 40–50 mgm may be injected. Takahashi[284] was the first one to report the use of bleomycin in 7 patients, four of whom had excellent response with no recurrence at 5 years follow-up. Subsequently, several authors have reported their series with varying results. Significant series were those of Zanan,[317] wherein 57% of 21 patients had favourable results; Mattolesse,[202] whose 70% of 24 patients had a good response and Broggi et al.[35] whose 43% patients did well. We have used it in two cases recently. If there is a leakage from the cyst, visual impairment may occur. The worldwide experience makes one wonder whether this should be the first line of treatment, especially in young children in whom radiation may be avoided.

Intracavitary Irradiation

Stereotactic intracavitary irradiation, using beta emitting colloids is an effective alternative method to treat cystic craniopharyngiomas.[135,290] This mode of therapy is less invasive and is associated with low risks of mortality and morbidity and a high rate of endocrinological, visual and cognitive preservation.[51] Intracavitary irradiation was first advocated by Leksell et al.[170] in 1951. Wycis[313] in the United States reported his initial experience with this method of treatment in 1954. Backlund et al.[9,10,11] have been primary advocates and expostulators of the role of stereotactic modalities. He and his associates demonstrated a high tumour control rate and safety and efficacy of this procedure, in more than 100 patients in his longitudinal experience of more than 20 years at the Karolinska Hospital in Stockholm.

A variety of isotopes for intracavitary radiation have been tried and eliminated including rhenium, gold and bismuth.[34,149,174,272] Radioactive isotopes, such as ^{32}P, ^{198}Au and ^{90}Y, have been used successfully for intracavitary irradiation of large cystic craniopharyngiomas.[289,291] The isotope available in Europe and Japan is ^{90}Y, an isotope with a shorter half-life (less than 3 days) and a reduced beta-emission range. It is preferred, combining a short half-life of 64.1 hours with pure beta emission of acceptable penetration.[123,145,273,301] The only beta-emitting radioisotope approved for use in the United States is ^{32}P, which has a 0.9 mm tissue half value layer and a longer half-life (14 days).[171,178–180,226] Since ^{32}P appears to coat the cyst wall rapidly, it can be used effectively in those patients who require early and frequent aspiration of the cyst without losing a significant fraction of the therapeutic dose of the radioisotope. The lining epithelium of the cyst wall is destroyed by the isotope, resulting in gradual shrinkage of the cystic tumour.[281] Hasegawa et al.[108] treated 25 primary and 24 recurrent cysts with ^{32}P. There was a cyst control of 76% at 5 years and 70% at 10 years. There was an effective control of the tumour cysts but not of solid components. Van den Bergh et al.[301] used intracavitary brachytherapy with ^{90}Y in 31 patients harbouring cystic craniopharyngiomas. Complete resolution in size was observed in 12 patients with new cyst formation in 3 patients. Bernstein and Laperriere[26] felt that intracavitary irradiation was quite effective in controlling cystic craniopharyngiomas. Blackburn et al.[31] reported a series of 6 patients with cystic recurrence who were treated with ^{90}Y radioisotope. Five patients did not need further aspiration whereas 2 required further instillation of ^{90}Y. There was neither any visual deterioration nor hypothalamic dysfunction. Shapiro et al.[253] pointed out that intracystic instillation of radioisotope permits a far higher radiation dose than by external radiation to the cyst lining, resulting in cyst shrinkage in up to 80% of cases. Intracavitary instillation of bleomycin is also being used in the management of essentially cystic craniopharyngioma. It stimulates reactionary fibrosis with thickening of the capsule and some shrinkage of the lesion, which in turn makes its excision easier.[165]

Intracavitary irradiation should be considered as a primary management strategy in patients with a solitary cystic craniopharyngioma. Significant cyst shrinkage occurs in up to 80% of cases with more than 50% chance of endocrinological preservation and maintenance or improvement of visual functions. Patients with recurrent tumour cysts have lesser chance of improving

vision than those being treated primarily. It does not affect the solid component for which stereotaxic radiosurgery (SRS) would be needed. For those patients with multicystic lesions, intracavitary irradiation can be performed for each cyst separately if they do not communicate.

Stereotactic Radiosurgery

There is increasing enthusiasm for treatment of craniopharyngiomas by SRS and fractionated stereotactic radiotherapy (SRT).[12,13,16,148,179] SRS is a highly accurate and precise technique that utilises stereotactically directed convergent beams of ionising radiation (proton beam or gamma-knife) to treat a small and distinct volume of tissue with a single dose.[79,169] The minimum dose prescribed is 9–20 Gy. Use of stereotactic technique permits accurate localisation of the tumour, a proper planning of the treatment and exact delivery of the radiation with a proper fixation of the head in a stereotactic frame. As a result, the optic chiasm, hypothalamus and pituitary are spared. The multiple beam approach of radiosurgery results in sharp dose fall-off beyond the target, sparing adjacent normal tissue. This method, however, should be reserved for selected small lesions since it ablates normal and abnormal tissue within the treatment volume.

However, further clinical experience seems to indicate that certain parameters are associated with complications from radiosurgery.[102,189,208,293] The parameters are related to the size and location of the target volume. Certain intracranial lesions cannot safely or effectively be treated with SRS, once the target volume is relatively large or located near the brainstem, retina and optic pathways or cranial nerves. In fact there is evidence to suggest that complications from radiosurgery might be higher than those associated with conventional radiotherapy, if used in larger lesions.[71,78,143] Therefore, although precise in the administration of a large single fraction, complications associated with large volumes (more than 3 cm) and critical location (brainstem, optic pathways) limit its use to only those craniopharyngiomas which are less than 2.5 cm in size and at least 2 mm away from the optic pathways, like primary or residual/recurrent intrasellar tumours. Tumour control rates of 70–100% have been reported 1–5 years after radiosurgery.

Stereotactic Radiotherapy

Fractionation is necessary to provide highly focal and precise dose delivery to larger lesions or lesions located within the vicinity of vital neurovascular structures, without producing significant morbidity. This form of therapy is called SRT and it includes the use of SRS techniques in combination with routine fractionation (180–200 cGy/day) or some form of altered fractionation, such as hyperfractionation (a few large fractions of 400–800 cGy). SRT combines the advantages of conventional fractionation used in external beam irradiation with the accurate and focal distribution of radiation as in SRS. Relocatable stereotactic frames are preferably used or plastic masks for immobilisation so that radiotherapy is delivered at a precise location. Thus, highly focussed and precise radiotherapy can be delivered in fractioned form, enabling the treatment of selected tumours with a potentially improved therapeutic index. Dose optimisation using SRT is very important, particularly for the paediatric population. For many paediatric intracranial tumours, such as craniopharyngioma, it is likely that SRT will largely replace conventional radiotherapy in order to reduce long-term side effects.[154]

For an optimal outcome, a team comprised of a neurosurgeon, ophthalmologist, endocrinologist, physician and radiation oncologist should work together to improve the quality of life of patients diagnosed with craniopharyngioma.

Treatment Summary

The best management of craniopharyngioma in children remains a controversial topic among paediatric neurosurgeons. A review of the natural history of children, following subtotal excision without further therapy, demonstrates that approximately 71% of the tumours will show progressive growth in a relatively short period of time requiring further therapy—repeat surgery, intracyst isotope or irradiation.[112,117,173,196,268,277,288] This data effectively dispels the argument for limited surgery alone. Currently, the debate centres round the merits of radical surgical removal versus limited resection followed by irradiation. Published series document excellent and equivalent long-term survival following each treatment modality, but the most important aspect is the quality of life following each therapy.

In order to compare the two most commonly employed therapeutic strategies for childhood craniopharyngiomas, one must look at four factors: (1) recurrence rate; (2) salvageability of the recurrent tumour; (3) quality of life and (4) complications.

Recurrent Tumours

Total excision does not necessarily equate to cure. The best published results of the studies with complete excision of craniopharyngioma utilising the latest microsurgical techniques show the recurrence rate ranging from 7 to 34% with an average of 23%.[20,37,41,112,119,173,196,268,288,314] These can then be subjected to further surgery or radiotherapy which can prolong life further in nearly 75–80% of cases for several years without compromising its quality. The average recurrence rate following partial removal followed by radiotherapy, as judged from the literature, is approximately 21%.[20] The risk of recurrence, therefore, appears to be equal for both treatment regimens.

Salvageability

Studies demonstrate that approximately 80% of the 23% of children whose tumour recurred after gross total resection, can be salvaged with radiation. Surveys suggest that 50% would have a good quality of life.

Jose et al.[134] reported a 77% 10 year survival among 25 patients whose tumours recurred after radical surgery. Radical surgery remains a vital treatment option in those 21% of patients who had tumour recurrence after limited surgery and irradiation. It is a general belief that operating in a previously irradiated or operated case is more difficult and hazardous. The more vigourous the initial surgical procedure, the more extensive the post-operative scarring and the greater difficulty encountered. However, we have been able to totally excise quite a few recurrent craniopharyngiomas.

Quality of Life

Most published series list outcome based on the clinical impressions of the authors and only a few studies have reported a systematic attempt to characterise the quality of life by intelligence (IQ) testing, psychological profiles and school or job performances. Good results as reported by experienced neurosurgeons range from 60 to 87%.[119,238,314] It has been observed that such a good outcome may not be possible when an attempt at total removal is made by a relatively inexperienced surgeon. Good results following a planned subtotal excision or limited excision plus irradiation have been extensively documented in the literature. In the last 13 cases we have tackled, we had complete excision of 8 small and moderate sized tumours, without any hypothalamic disturbances. The remaining 5 large multicompartmental lesions had subtotal excisions with radiotherapy, again without any significant sequlae and a good quality of life. Two patients with intracystic instillation of bleomycin have also remained without any hypothalamic disturbances, so also the one treated through the trans-sphenoidal route. It is therefore clear that the outcome in terms of quality of life largely depends on the experience and judgement of the surgeon, regarding the mode of treatment.

Hayward et al.[109] have noted that in children below 5 years of age, in those with hydrocephalus and pre-operative hypothalamic disturbances, the morbidity following radical surgery is unacceptable due to hypothalamic damage. Even though tumour control may be achieved, the quality of life is very poor.

Complications

The surgical mortality rate has varied from 4% to nearly 20% in radical surgery, especially in children below the age of 5 years and those with large or multicompartmental tumours.[119,238,314] Death from limited surgery is 1–4%. The incidence of delayed complications due to radiation is approximately 7% including radiation vasculitis, vascular occlusion and radiation-induced neoplasms. The endocrine complications are high following both therapies, and major hormone replacement is required 95% of the time.[119,295,314] The morbidly obese and hypersomnolent child, the severe endocrine cripple who alternates between SIADH and DI only seems to occur as a complication of radical surgery.

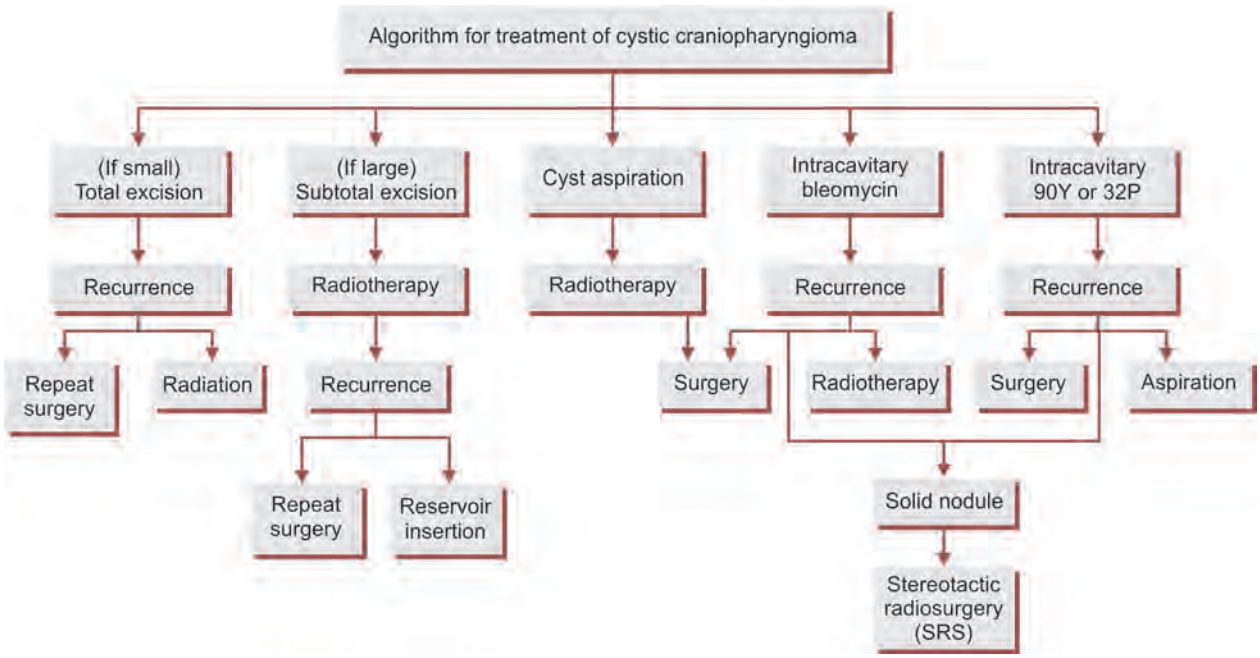
Based on this information the following recommendations can be made:

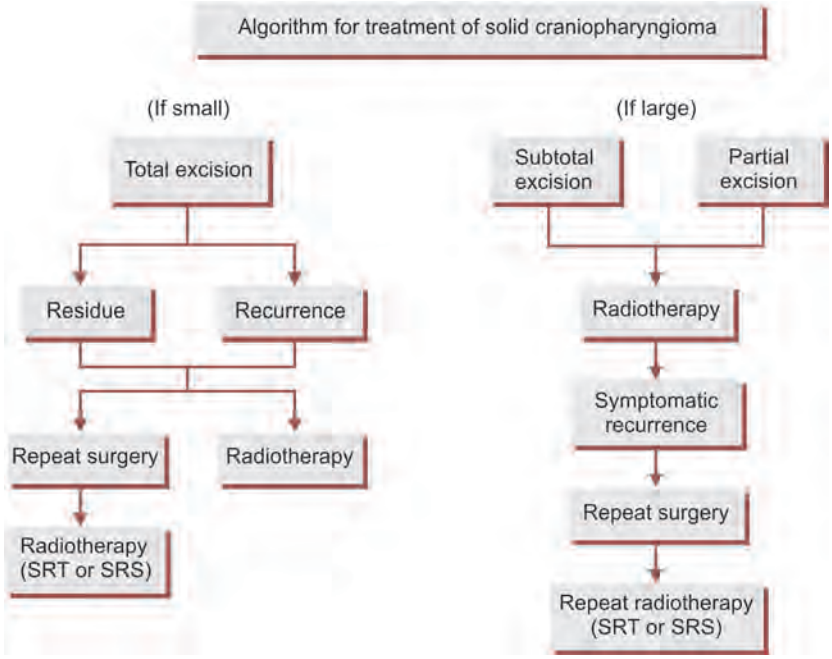
Radical surgery

1. Children older than 5 years of age
2. Tumours less than 3 cm in size
3. Favourable location—intrasellar, prechiasmatic or pure intraventricular.

Limited surgery plus irradiation

1. Large tumours greater than 3 cm in size
2. Multicompartmental tumours
3. Pre-operative hypothalamic disturbances.





Ommaya reservoir with intracystic instillation

1. Essentially cystic tumours
2. Bleomycin
3. Radioactive isotopes—^{90}Y, ^{32}P.

Stereotactic radiosurgery

1. Smaller tumours less than 3 cm in size
2. Intrasellar tumours
3. Tumours away from optic pathways.

Radiation or SRT

1. Residual tumours
2. Recurrent tumours.

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SECTION

12B

Cranial and Intracranial Tumours

CE Deopujari

159 Dermoids and Epidermoids

Ravi Ramamurthi, Amit Kapoor

Tumours of disordered embryogenesis are a heterogeneous group of neoplasms of the nervous system of congenital origin. They include dermoids, epidermoids, teratomas, chordomas and craniopharyngiomas. They are characterised by a slow rate of growth, the growth potential in some of these being so slow that they are often considered as hamartomas. Due to the slow rate of growth in some, the initial clinical manifestations may not appear till adulthood.

EPIDERMOIDS

History

In 1829, Curveilhier,[16] described the epidermoid and named it "pearly tumour". Muller, in 1938,[57] described a bony tumour of the skull containing masses of cholesterol crystals and termed it as "cholesteatoma". This resulted in some confusion later, when similar encrustations were found in chronic infection of the middle ear and the mastoid. It is best not to use the term cholesteatoma to denote cranial epidermoids, even though the desquamated epithelial cells filling the lesion are rich in cholesterol crystals.

In 1897, Bostroem[8] proposed that these lesions arise from inclusion of epithelial rests during the period of neural tube closure in the third to fifth week of gestation. Tumours from the same rests may be epidermoids or dermoids, the capsule in the former consisting mainly of squamous epithelium, whereas in the latter, dermal elements, like hair and sweat glands, are also found.

Pathogenesis

Congenital epidermoids are believed to arise as a result of cellular dysfunction during embryogenesis, which leads to an abnormal migration of ectodermal cells.[36,63] When the neural tube separates from the overlying ectoderm along the mid-dorsal aspect of the embryo, misplaced epithelial rests may be deposited between the neural canal and the skin. This epithelium lined ectopic tube may expand into a cyst, either at its inner or outer end or both and form an epidermoid or a dermoid cyst. Secondary vesicles, like otic and optic vesicles formed during development, may also have epithelial misplacement, accounting for laterally placed squamous lined cysts.[29]

This theory explains the frequency of association of intraspinal midline lesions with spinal anomalies, dermal sinus tracts and laterally situated lesions in the cerebellopontine angle and the orbit. Experimental skin implants along the neuraxis of rats have resulted in the production of dermoids and epidermoids, thus supporting the epithelial cell rest theory of histogenesis of these tumours.[96] Misplaced epithelium alone, or mesenchyme without organiser substances early in development results in a simple squamous lined cyst (epidermoid), whereas misplaced epithelium and mesenchyme in later foetal life with the organiser substances lead to the formation of a squamous lined cyst with skin appendages (dermoid).[91]

Another mode of pathogenesis is iatrogenic. Intraspinal dermoids and epidermoids may also form, as a result of inclusion of epidermis, following repeated lumbar punctures, when done using a needle without the stylet.[14] A single lumbar puncture rarely produces an epidermoid.[87,88] The Currarino triad is a unique complex of congenital caudal anomalies, including anorectal malformation, sacral bone abnormality and a presacral mass. Epidermoid cysts have been described in patients with the triad.[41]

Location

Intracranially, epidermoids are more common than dermoids. They have an affinity for the subarachnoid cisterns at the base of the brain. The suprasellar and cerebellopontine angle cisterns are the most favoured sites, whereas the lateral ventricles, optic chiasm, colliculer plate, pineal gland and paratrigeminal area, sphenoid sinus, temporal bone[36] brainstem,[73] intradiploic, and lateral orbital wall[5] are less favoured sites.[40] A rare case of a prepontine epidermoid traversing the brainstem has been reported by Bhatia et al.[3] When these are extradural, the most common location is intraosseus in the diploe of the calvarial bones. Epithelial rests may give rise to a primary congenital epidermoid in the petrous bone with gradual onset of facial palsy, hearing loss and vestibular disturbances. The roof of the petrous bone is usually eroded. Intraorbital lesions are usually located superolaterally at the site of fusion of bones and gradually push the eyeball downwards and medially. Epidermoids do not occur in the vertebrae and are uncommon in the scalp.

Over three quarters of all intracranial epidermoids occur in the basal cisterns.[44,87,92] Many involve more than one cranial fossa. A few occur entirely within the substance of the brain.[12,43,56] Intraspinally, they occur much

less frequently in the cervical region, being more frequent in the mid-dorsal area.[46] One-fifth are intramedullary in location, two-thirds are found in the leptomeninges and the remaining in the epidural space.[46] Those that occur following lumbar punctures are usually seen in the lumbar region.[51]

They may be classified as per their location as follows:

A. Extracranial
   1. Spinal
   2. Orbital
B. Cranial-extradural
   1. Intraosseous (intradiploic)
   2. Orbital
   3. Paranasal sinuses
C. Intracranial-intradural
   1. Intraventricular
   2. Suprasellar—chiasmatic
   3. Parasellar—Sylvian fissure
   4. Restrosellar—cerebellopontine angle
   5. Basilar—posterior fossa
   6. Multicompartmental

Pathology

Epidermoid is a well-delineated encapsulated lesion that has a characteristic "pearly shine" that permits diagnosis merely on inspection. It may be cystic in suprasellar[89] and intraventricular locations, but is usually solid, especially in the cerebellopontine angle, quadrigeminal cistern and over the corpus callosum.[22] The solid lesion is characteristically filled with whitish, often cheesy material rich in cholesterol crystals and a debris of desquamated keratinised epidermal cells that accumulate centrally and add to the bulk of the growth.[78] These lesions are often large, almost giant sized, insinuating between fissures and sulci, starting from one compartment and extending into adjacent ones and becoming multicompartmental. The capsule may be thin at places and nodular at others. It is often adherent to the vascular structures, cranial nerves, and brainstem, making total excision difficult without damage to these structures. Foci of calcification may be found in the cyst wall.

The diagnostic histological finding is a simple stratified squamous epithelial lining. The epithelial cells rest on an outer layer of collagenous tissue. Progressive exfoliation of keratinous material towards the centre increases the bulk of the lesion and produces a lamellar appearance of the contents. The outermost layer consists of homogeneous material, for the most part quite structureless. It is this layer that has the beautiful pearly sheen, so characteristic of these tumours. Irritation of the surrounding brain may produce fibrillary gliosis and thickening of the leptomeninges with foreign body giant cells. Daughter cysts may be found within the main mass. Their mode of production is obscure. Multiple cysts may also arise in the same location. Granulomatous meningitis may result from rupture of the lesion and contamination of the CSF by lipid and cellular debris.[47]

The tumour is entirely benign. It can recur after a long time if incompletely removed, but usually does not turn malignant. Malignant changes have been reported in the literature.[24,53,88] Squamous cell carc inomas (epidermoid carcinomas), cytologically malignant and histologically invasive, occurring essentially in the parapontine and cerebellopontine angle, have been reported. All these patients died within a year.[61]

Incidence

Epidermoids constitute 0.5–1.8% of all intracranial tumours.[97] The incidence is higher in Japan at 2.2%.[91] They become symptomatic usually in the third or fourth decades, the average age incidence being 34 years as reported by Tan.[88] In India, it is a decade earlier.[21,22,59]

Clinical Features

Epidermoid tumours typically present with symptoms related to pressure or intracranial rupture in the fourth or fifth decade of life.[83] As epidermoids are soft with a pliable capsule, they grow very slowly and tend to fill up any available space. They often reach a large size before becoming symptomatic. For the same reasons, many of these lesions attain a large size without producing signs of raised intracranial pressure. Lesions are large at presentation and the initial symptoms usually involve the cranial nerves.[36]

Papilloedema is noted in only a small percentage of cases. In the more laterally placed tumours, clinical symptoms are produced by compression and deformation of adjacent neural and vascular structures. In nearly three fourths of the patients, soft symptoms may be present for several years before they seek treatment.[62,67]

Intradiploic epidermoids present essentially as painless masses with characteristic radiological appearances.[98] These occur more commonly in the frontal and parietal bones and may occasionally be tender. They are usually small, but may be large and accompanied by signs of raised intracranial pressure and focal neurological deficit.[15,50,58,59,64,70,71] A primary epidermoid occurring in the petrous bone grows slowly, erodes the bone steadily and produces tinnitus, progressive impairment of hearing and facial nerve paresis. Orbital epidermoids are usually located in the upper outer quadrant and push the eyeball downwards and medially. They usually do not compress the optic nerve and do not produce visual impairment, although Sushil Kumar et al.[86] have reported a case of a large frontal intradiploic epidermoid that led to proptosis and visual impairment.

The clinical picture of intracranial epidermoids varies according to their location, direction and rate of growth, interference with cerebrospinal fluid pathways, compression of neural and vascular structures or chemical meningitis following rupture into the subarachnoid space or ventricle.

When the epidermoid is located in the frontal region, impairment of memory, emotional lability, depression and incontinence of urine may occur. When located in

the suprasellar-chiasmatic region, they compress the optic apparatus and produce visual impairment, optic atrophy and bitemporal haemianopia.[49] There may be associated widening of the optic foramina with a normal sella turcica and normal pituitary function. Occasionally, the patient may develop diabetes insipidus.

Epidermoids in the parasellar area extend into the Sylvian fissure laterally and spread to the temporal and frontal lobes. Depending on the direction of extension, the person may suffer from focal, complex partial or grand-mal type of seizure disorder. It may extend towards the thalamus and involve post-ganglionic fibres of the Vth nerve with occurrence of trigeminal neuralgia.[84]

Epidermoids in the parapontine and cerebellopontine angle cisterns may present initially with irritative manifestations, like trigeminal neuralgia, hemifacial spasm or tinnitus, till they grow sufficiently large to produce paresis of the trigeminal, facial and auditory nerves. Paresis of the sixth nerve will result in diplopia. Pressure on the cerebellum will result in nystagmus and ataxia and that on the brainstem in hemiparesis or quadriparesis (Fig. 1).

Symptoms like headache appear only occasionally. When located in the pineal region, these produce classical symptoms of a posterior third ventricular tumour.[50,79,89,100]

Jacksonian seizures appearing in a young patient with a slow evolution of mental symptoms without significant signs of raised intracranial pressure characterise a supracallosal epidermoid.[74] Cases have been reported of epidermoid tumours of the corpus callosum presenting with raised intracranial pressure, generalised seizure, hemiparesis and behaviour disturbances.[46,65,90] Dastur[20] reported a large bifrontal epidermoid in a middle aged patient which resulted in a bilateral lobotomy effect, making the patient unaware of severe pain due to strangulated inguinal hernia. Mental changes may also occur in basal and intraventricular epidermoids when they are associated with hydrocephalus.[2,75]

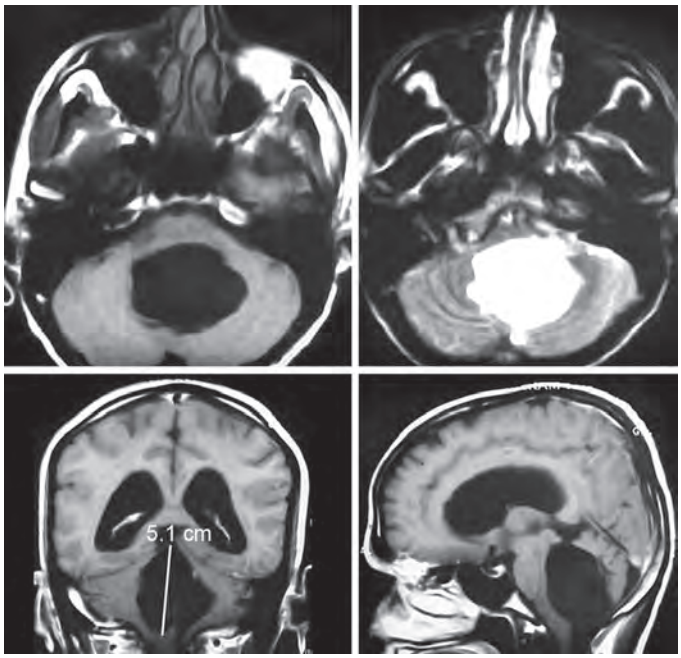

Fig. 1: MRI of the brain showing fourth ventricular epidermoid causing pressure over the brainstem

In intraventricular epidermoids, headache, dementia, psychiatric problems, ataxia, hemiparesis and cranial nerve palsies are often seen when obstruction to the CSF pathways is significant.[49] However, at times, in spite of the lesion filling up the fourth and the third ventricle and extending into the aqueduct, no manifestations of hydrocephalus may be found.[75] This is essentially due to percolation of CSF through the interstices of the tumour. At times, waxing and waning of the symptoms may occur as in demyelinating disease.[2] Remissions may occur due to the emergence of the tumour from the fourth ventricle into the cisterna magna[28,48] and it may fill up the cervical perimedullary space.[75,76]

Pineal region tumours most commonly present with headache, diplopia and vertigo. Neurological examination may demonstrate papilloedema, impaired pupillary reaction, ataxia, Parinaud's syndrome and long-pathways deficit.[41]

Leakage of cholestrin and fatty acids into the subarachnoid space may give rise to chemical meningitis, presenting with headache, irritability, and neck stiffness.[22] Repeated spinal fluid cultures are sterile. A foreign body giant cell reaction occurs around the cholesterol crystals, with the production of granulomatous ependymitis and meningitis.[93]

Spinal epidermoids have a predilection for the conus and for the low to mid dorsal region and are largely intramedullary.[51] They may be associated with other abnormalities of the spinal cord and bony vertebral column. Being slow growing lesions they may become apparent in the second decade of life. They present with backache, progressive paraparesis, sphincter impairment and sensory dysfunction or may present with recurrent aseptic meningitis.

Radiological Findings

Plain X-rays of the skull do not reveal any abnormality in intracranial epidermoids, except for occasional stippled calcification in a third ventricular epidermoid or amputation of the apex of the petrous bone in a cerebellopontine angle lesion. Rarely, one may see radiological signs of raised intracranial pressure.

Cushing[17] was the first to note that epidermoids of the skull produce a discrete area of osteolysis with a thin surrounding margin of sclerosis. The destructive area may be rounded or may appear scalloped and may cause expansion of the calvarial bones. The intracranial extension, which is always limited by the dura, can be seen only on CT and MR. In orbital lesions there is an erosion of the upper and outer margins of the orbit, whereas in the petrous bone possible thinning or destruction of the tegmen tympani is found.

Computed Tomography Scan

The lesion usually appears as a hypodense mass with an attenuation value of 22–32 Hounsfield units, although

lesions of relatively high density (80-I 20 HU) can occur[9,85,91] (Figs 2 and 3).

The varying density is due to low-density lipid and high-density keratin in the desquamated debris of the tumour. Fat and fluid may also be seen within the tumour or in the ventricle or subarachnoid space after it ruptures. Foci of calcification may occasionally be seen in the tumour capsule. Hyperdense lesions, with no enhancement on contrast injection and hypodense lesions with marginal calcification were reported by Furuhata et al.[30] in three epidermoid cysts of the callosal region.

As epidermoids grow slowly, they tend to conform to the shape of the space in which they are located. Intraventricular lesions grow slowly and distend and dilate the ventricular system, allowing cerebrospinal fluid to flow between and around the tumour, rather than obstruct it. Fissural epidermoids grow insidiously, tend to fill up and distend the subarachnoid space and present as irregular shaped masses in the CT scan. A characteristic filigree appearance may be seen on intrathecal water-soluble contrast cisternography[32] or ventriculography. Hydrocephalus is only occasionally seen. This is an important differentiating factor between an epidermoid and other tumours that act as obstructive space occupying lesions.

Epidermoids do not enhance following intravenous contrast administration.[23,26] Only one case of epidermoid with enhancement of its periphery, thought to be due to gliosis and thickening of the wall, has been reported.[53] Three cases of malignant epidermoids have been reported to show enhancement of a part of the wall after contrast administration.[24] Malignant transformation must be considered in the differential diagnosis when new contrast enhancement on imaging studies and progressive neurological deficit are seen in a patient harbouring an epidermoid cyst.[45]

Magnetic Resonance Imaging

Epidermoid tumours have variable MR features. In T1-weighted images, the signal intensity is between the brain parenchyma and the CSF and in T2-weighted images it exceeds both brain and CSF signals.[81] The signal intensity of some of the lesions is virtually the same as that of CSF in short and long T images. The presence of a cerebellopontine angle mass is usually suggested by displacement of the brainstem (Fig. 4).

Intravenous gadolinium does not show enhancement of the lesion or its capsule. In contrast, acquired cholesteatomas of the middle ear contain predominantly keratinising stratified squamous epithelium and may have moderate signal intensity in TR/TE images. Intravenous gadolinium may show enhancement in such inflammatory and neoplastic lesions.

Petrous apex epidermoids are well delineated in short TR/TE images due to the negligible signal from the adjacent bone and CSF. They may have high intensity signals from cholesterol or other fatty material in short TR/TE images.

Apparent diffusion coefficient (ADC) of epidermoid tumours is lower than that of chordomas with the accuracy reaching 100%.[102] Spontaneous (non-traumatic) seeding of multiple daughter cysts from intracranial epidermoid cysts is very rare and their multiple appearances on MR imaging should be distinguished from the simple scattering of oily contents due to cyst rupture.[55] The rarity of brainstem epidermoid cysts can make their diagnosis difficult; thus diffusion weighted MR imaging sequence of the brain is a useful diagnostic modality.[73]

Treatment

The ideal treatment consists of complete excision of the cyst and its contents. Surgery is the only effective treatment modality for these lesions and as radical a

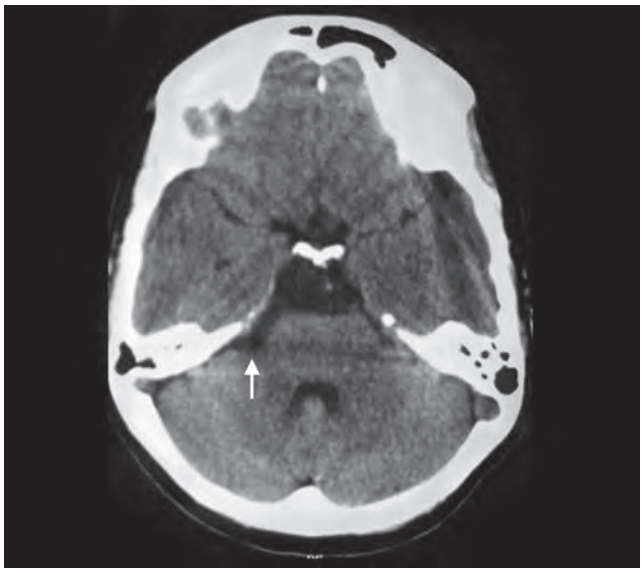

Fig. 2: CT scan of the brain showing CP angle epidermoid (white arrow) with extension into the prepontine cistern

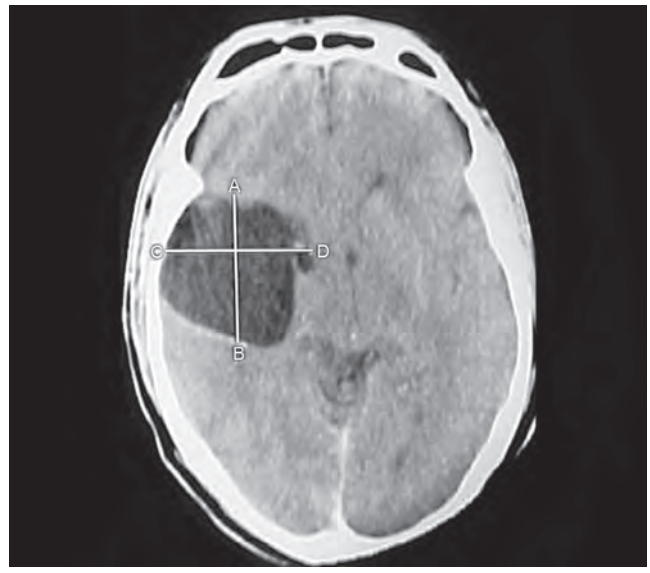

Fig. 3: CT scan of the brain showing epidermoid in the right Sylvian fissure

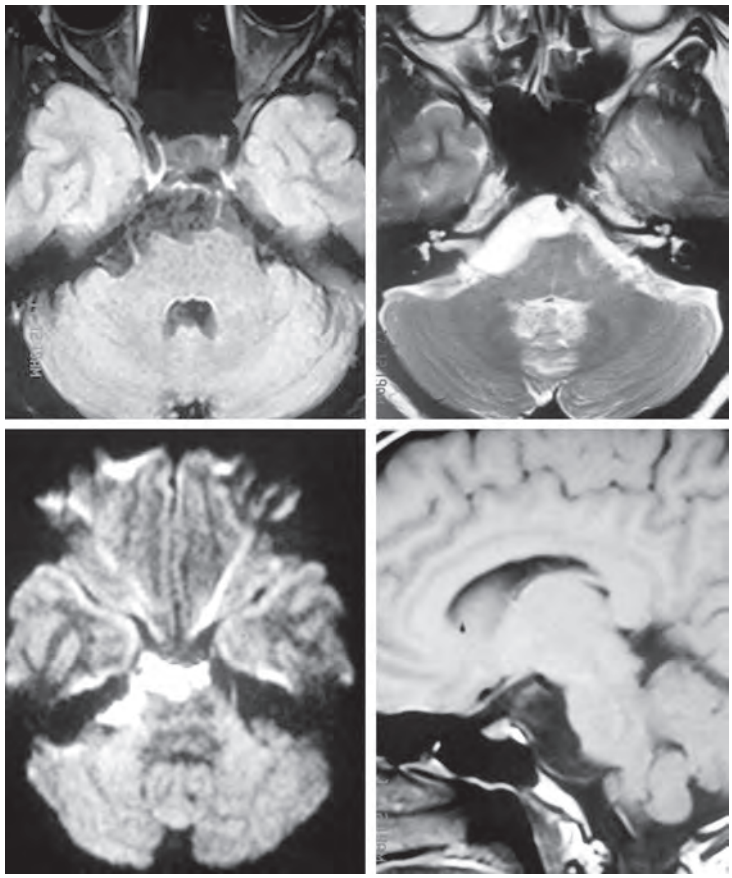

Fig. 4: MRI of the brain showing CP angle epidermoid hypointense on T1 and hyperintense on T2 and brilliant hyperintensity with diffusion restriction on diffusion weighted images

resection as possible should be performed in all cases to avoid tumour recurrence; however, because the cyst capsule can adhere firmly to vital structures and attempts at its radical removal can be dangerous, subtotal resection may be a wise option in selected cases.[11]

There is no role for radiation or chemotherapy. It is possible to excise epidermoids of the scalp and intradiploic epidermoids totally by removing them enbloc along with a margin of healthy bone or by evacuating their contents and scraping the cyst lining of the bone or the dura to which they may have become adherent. Some of these lesions may have an epidural or an intracranial extension, as indicated by the pre-operative CT or MR and this has to be tackled at the same time the calvarial lesion is excised. The extension of the lesion into a major venous sinus may necessitate surgical repair of the sinus after excision of the lesion.[70]

Many epidermoids have a clear plane of cleavage between their lining and the arachnoid membrane, enabling the surgeon to excise it totally with impunity. However, in some cases, due to a granulomatous reaction the cyst lining becomes nodular and gets densely adherent to important neurovascular structures.[96] In such circumstances it is wiser to excise the easily separable portions of the capsule and to leave the densely adherent portions behind, to prevent irreparable damage to vital structures. Tumour growth being very slow, several years may elapse before symptomatic recurrence. This is true also of intramedullary spinal lesions. The use of the operating microscope, a good knowledge of surgical anatomy and patient, gentle handling allows many tumours to be excised totally.[103] Flemming and Boterell,[39] reported only one case of recurrence in their series of 27 cases with a minimum follow-up of 7 years and maximum of 24 years.

The extended trans-sphenoidal approach, which requires a bone and dural opening through the tuberculum sellae and posterior planum sphenoidale, is increasingly used for the treatment of nonadenomatous suprasellar tumours[25] (Fig. 5).

Endoscope-assisted microsurgical techniques enable safe removal even when tumour parts are not visible in a straight line. Tumour extensions into adjacent cranial compartments can be removed with the same approach without retracting neurovascular structures or enlarging the craniotomy.[82] Endoscopic transpterygoid approach to the lateral sphenoid recess has been used to marsupialise a symptomatic epidermoid cyst.[7] The retrolabrynthine approach combined with endoscopy may be used for excision of cerebellopontine angle epidermoid cysts.[19] Pineal region epidermoids can be removed by using either the supracerebellar or occipital-transtentorial approach.[41]

Complications

While excising the tumour, spilling the contents into the subarachnoid space should be prevented, as cholesterin and desquamated keratin act as irritating agents and

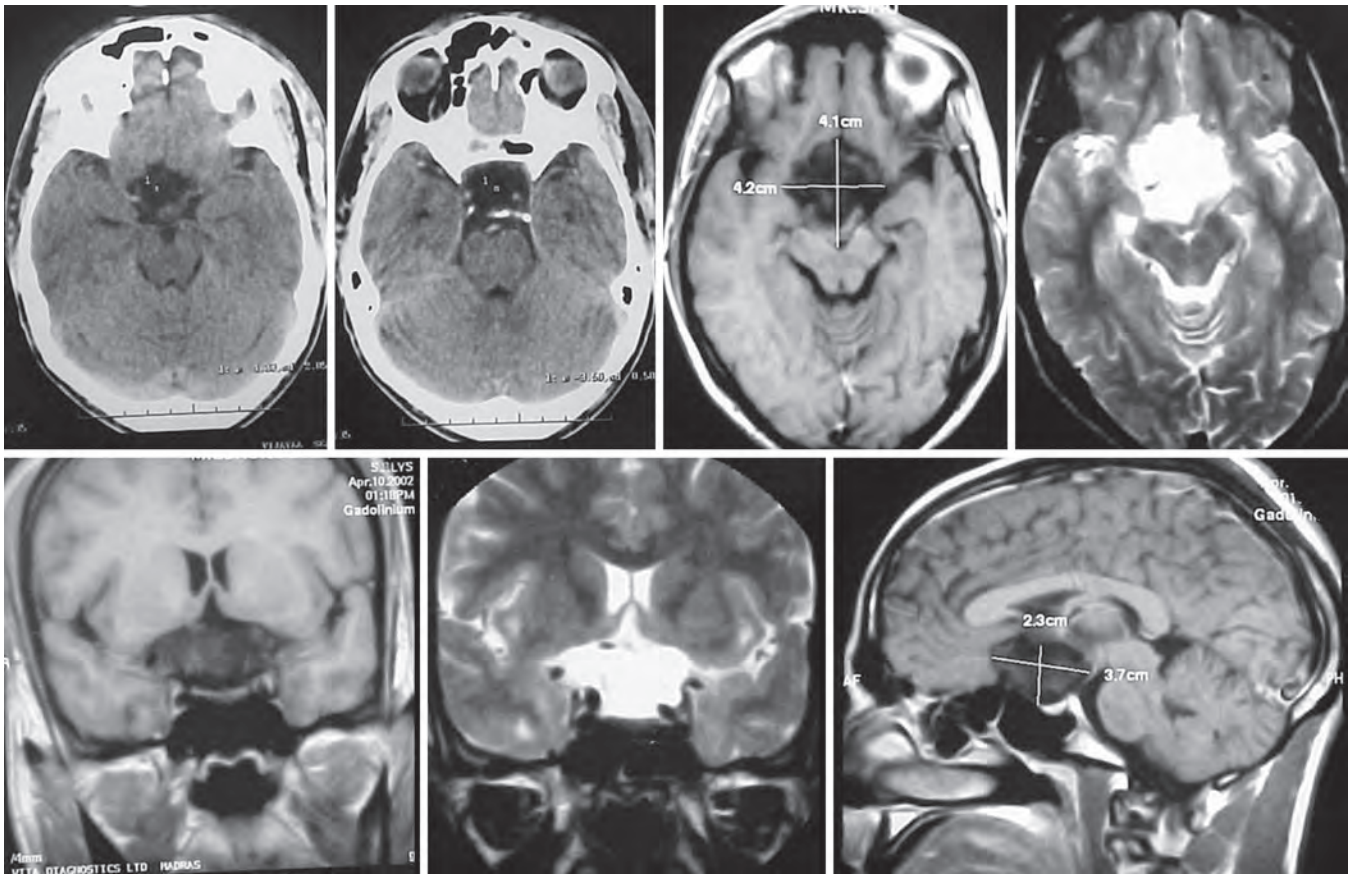

Fig. 5: CT scan of the brain showing epidermoid in the suprasellar region which is hypodense. MRI scan of the brain showing the lesion which is hypointense on T1- and hyperintense on T2-weighted images

cause aseptic chemical meningitis. Thirty-seven percent of the cases, reported by Tytus and Pennybacker,[94] experienced aseptic meningitis post-operatively. Preoperative administration of steroids and irrigation of the operative field with fluids containing steroids is said to help in alleviating the chemical irritation. Post-operative administration of steroids, similarly, helps in reducing the risk of chemical meningitis. Dastur and Deshpande[22] did not encounter a single instance of chemical meningitis in their series of 22 cases, whereas Abraham et al.[1] and Natrajan,[68] encountered it frequently. Lumbar puncture and drainage of contaminated CSF also helps in alleviating the headache and pyrexia that sometimes occur with chemical meningitis.

Chemical meningitis may end in basal arachnoiditis and communicating hydrocephalus, requiring ventriculo or theco-peritoneal shunt insertion. Transient paresis of cranial nerves may occur due to their being handled during surgery. Attempts at excising densely adherent tags of capsule from neural and vascular structures may result in permanent dysfunction and cause significant morbidity. Earlier attempts at total surgical resection were attendant with a high mortality, but the use of the operating microscope, enabling gentle handling, has significantly reduced the mortality from 20% in the 1950s to 10% in 1977 and much lower at present.[35] A review of case reports after 1970s suggests further reduction in operative mortality and morbidity. This is also partly due to early diagnosis with the availability of computed axial tomography. In spite of this, a fair number of multicompartmental giant epidermoids are still being encountered. Complete excision of these lesions poses a difficult problem.

DERMOIDS

Incidence

Dermoids develop from congenital ectodermal inclusions as a result of imperfect embryogenesis. These are usually found at the sites of epithelial fusion lines and have a tendency to occur in the midline. Their incidence varies from 0.1–0.72% of all intracranial tumours.[6] These occur more commonly in the paediatric age group. Paediatric dermoid cysts are unusual lesions with the mean age at presentation being 22 months.[68]

Dermoid cyst is by far the most common orbital cystic lesion in children, accounting for over 40% of all orbital lesions of childhood and for 89% of all orbital cystic lesions of childhood that come to biopsy or surgical removal.[84]

Location

Dermoids can occur in the scalp, the calvarium, the epidural space, intracranially at various locations and in the spinal canal.

Dermoids in the scalp usually occur in the midline over the region of the anterior fontanelle or laterally as angular dermoids over the outer aspect of the eye. These are frequently associated with midline fusion defects and in nearly a fourth of the cases these are connected with the intracranial structures or the spinal canal by a congenital dermal sinus or a stalk.

In the skull, dermoids occur more frequently in the nasal and paranasal regions and the orbits. These occupy the region of the glabella, bridge of the nose and deep part of the septum. They may extend into the anterior cranial fossa. Orbital lesions arise superolaterally at the site of embryologic fusion, erode the orbit and may enter the anterior or middle cranial fossa.[13] It is connected to the dura mater and the orbital periosteum.[31] At times, it may present as a laterally situated dermal sinus with an associated intradiploic frontotemporal dermoid. Intracranially, these occur essentially in the posterior fossa as midline dermoids associated with a dermal sinus and often present as a cerebellar lesion. Usually, these lie in the cerebellar parenchyma, but may be mainly in the meninges.

Dermoid cysts may infrequently occur "primarily" in the temporal fossa. Bone involvement and anterior temporalis muscle displacement are common. An origin from the area anterior to the confluence of the greater wing of the sphenoid, frontal, and zygomatic bones is seen.[54] Dermoids may also occur in the suprasellar region where they have to be differentiated from craniopharyngiomas. They may be intraventricular in location either in the fourth or the third ventricle.

Intraspinal dermoids are more common than epidermoids and are often associated with dermal sinuses and spinal dysraphism. They may coexist with dermoids in other organs. An intraspinal dermoid associated with another dermoid in the ovary was reported by Ramamurthi.[69]

Pathology

Dermoid cysts are developmental lesions and not true neoplasms. These occur as rounded or oval, opaque masses that may have a pearly shine externally with a wall of varying thickness. The wall is composed of dermal epithelium with external collagenous tissue and contains dermal appendages such as hair follicles, sweat glands, and adipose tissue. Dermoids contain sebaceous material and hair in addition to keratinised desquamated debris. The contents are fluid or pultaceous and resemble soft butter.

A dermoid may rarely rupture into the subarachnoid space resulting in severe reactive meningitis which may prove fatal. The most irritant element is cholesterol, which is derived from the breakdown of keratin. It excites a granulomatous form of meningitis.

Neurocutaneous melanosis (NCM), Dandy-Walker malformation and primary intracranial melanocytic and dermoid tumours have been reported to coexist, suggesting a common insult during embryogenesis.[38] The Currarino triad is a unique complex of congenital caudal anomalies including anorectal malformation, sacral bone abnormality, and presacral mass. Dermoid cysts have been described in patients with the triad.[42]

Clinical Features

Dermoids of the scalp usually occur in the midline and are mostly located over the region of the anterior fontanelle or the inion. They are globular, soft, and slightly mobile and the overlying skin may show a skin dimple. They may erode both the tables of the bone and may be adherent to the underlying sinus. When located over the inion, they may have a communication with a similar lesion in the posterior fossa.[31] When inflamed, they present as tender globular swellings.

Not infrequently, an orbital dermoid presents as a discharging dermal sinus situated superolaterally over the orbit. The underlying dermoid is responsible for the festering infection. The dermoid situated superolaterally at the site of embryological fusion tends to erode the orbit and may enter the anterior or middle cranial fossa.[13] It is connected to the dura mater and the orbital periosteum.[31]

A dermoid in the posterior fossa is usually situated in the midline. It is mostly intracerebellar, although it may be found just underneath the dura. It may present with manifestations of raised intracranial pressure and ataxia or with recurrent bacterial meningitis or as a cerebellar abscess when it is associated with a dermal sinus.[66] This brings about the need to inspect carefully the midline areas of the scalp and the skin over the spine, whenever meningitis occurs in a newborn or a young child.[34] Examination of these children with magnetic resonance imaging would be worthwhile, whenever a midline lesion is suspected.[66] Suprasellar dermoids present with visual impairment and bitemporal hemianopia and may be associated with diabetes insipidus. Intra third ventricular dermoids present with manifestations of raised intracranial pressure due to obstructive hydrocephalus. An acute picture of meningitis, often fatal, may evolve if it ruptures into the ventricle. Supratentorial dermoids are rare and may be found in connection with the cavernous sinus. The dermoid may then present with acute third nerve palsy with pupillary sparing.[60]

Nasal dermoids may be located over the glabella, the bridge of the nose or deep in the septum and are usually a consequence of an abnormality of anterior neural tube closure.[33] These may present either as a cyst or as a midline congenital fistula of the nose with an intracranial extension.[52,77] Such a presentation is less common than the sinus over the posterior fossa or the lumbar spine.[10] The sinus traverses either the cribriform plate or foramen caecum[99] and may be associated with nasal anomalies requiring rhinoplasty. Infection may result in cellulitis, abscess, osteomyelitis, and recurrent

meningitis. Uglietta et al.[95] have reported an uncommon case of a congenital dermoid cyst in a 46-year-old man that extended intracranially to form a large bifrontal intra-axial dermoid cyst.

Dermoids in the fourth ventricle may present with progressive headache, unsteady gait, balance disturbances, deglutition disorder and diplopia.[18] A large cystic tumour may displace the cerebellar lobes, push the vermis upwards and present in the cisterna magna. If it ruptures into the fourth ventricle or the subarachnoid space, it may present with acute aseptic or pyogenic meningitis. Tokkok et al.[92] have reported an unusual case of intra fourth ventricular dermoid that presented with bilateral internuclear ophthalmoplegia. Occasionally, a dermoid may mimic a haematoma or transient ischaemia in the posterior fossa, when it presents with an acute onset, waxing and waning of symptoms and a hyperdense appearance on the CT.[4] Waning of the symptoms may be due to its extension into the cisterna magna through the foramina of the fourth ventricle.

Spinal dermoids usually present with recurrent attacks of meningitis when they are associated with a communicating dermal sinus and other stigmata of spinal dysraphism. These are located mostly over the lower dorsal and dorsolumbar regions.[72] Compressing the dorsal cord, the conus or the nerve roots, they produce progressive paraparesis, sensory impairment, and sphincter disturbances. Spinal dermoids may occur at the cranio-cervical junction and may be associated with a spinal anomaly like Klippel-Feil syndrome.[28]

Radiological Findings

Dermoids of the scalp may cause erosion of the bone, often the outer table of the skull. The margins of the erosion are typically sclerotic. Plain X-ray may, at times, show the opening through which a dermal sinus traverses or erosion of the bone when a dumb-bell orbital dermoid extends into the frontal or temporal fossae. Dermoids may, occasionally, contain teeth.

CT scan often shows a cystic mass with flakes of calcium which may not be seen on plain X-ray. There is a large range of attenuation values depending on the nature of the contents, viz. desquamated debris, sebaceous secretions, hair, and fatty tissue. The dermoid may appear as a hyperdense mass if it contains oily cystic fluid.[18] Dermoid cysts are typically hypodense on computed tomography, but when hyperdense may mimic a haemorrhage.[80]

It is often associated with a dermal sinus and may show associated developmental anomalies. Associated hydrocephalus may be seen. In ruptured dermoid cysts multiple fatty globules are visualised in the ventricles or subarachnoid space.[37,100] A typical low fat density is seen in the tumour as well as in the ventricle and/or the subarachnoid space.[101]

MR scan shows the above changes more graphically, especially the tract of the dermal sinus, the relationship of the dermoid cyst to the various structures in the posterior fossa and its exact location within the spinal cord or the conus. Often, the associated tethering of the cord may be vividly seen. In case of ruptured dermoid cysts, fat appears strongly hyperintense on Tl-weighted images.[37,100,101] The imaging characteristics of dermoids and lipomas are extremely similar. Given the difference in the natural history and resectability of these lesions, lipomas should be included in the differential diagnosis of lesions with imaging characteristics similar to dermoids.[27]

Treatment

Ideal treatment consists of total excision of the dermoid cyst along with any associated dermal sinus. Radical excision of intracranial dermoids is usually possible, unless adhesions have developed following attacks of aseptic or purulent meningitis. Yasargil[103] reported a series of eight dermoid and 35 epidermoid tumours with total excision in all, except one densely adherent dermoid and one epidermoid. Excellent to good results were seen in 86% of patients.

Dermoids do not usually undergo malignant change, although a case of a 59-year-old female, who developed a squamous cell carcinoma from the epithelial component of a pre-existing intracranial frontal dermoid cyst, has been reported.[40]

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160 Teratomas

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As defined by Willis,[22] "a teratoma is a true neoplasm composed of multiple tissues of kinds foreign to the part in which it arises". It is composed of tissues of adult type and organic pattern derived from all three germinal layers.[17] When the derivatives of all the three germinal layers are not clearly defined, the lesion has been called teratoid.[6] Many of these tumours grow rapidly and may become malignant and according to Willis[22] such teratomas almost always display some tissue elements which are embryologically immature.

Teratomas most commonly arise in the ovaries and testes. In relation to the nervous system, the most common site is the sacrococcygeal region. Within the brain, most of these tumours arise in the midline anywhere from the optic chiasma to the pineal gland, mostly in the latter situation. Hosoi[6] pointed out that almost all intracranial teratomas originate somewhere near the midline, a location with great potential for misplacement of embryonal tissue. The incidence of intraspinal teratomas is approximately five times more than that of intracranial teratomas.[7]

INCIDENCE

Teratomas constitute 3.5% of all paediatric tumours.[18] The brain is considered to be one of the rare sites for teratomas. The intracranial incidence of these tumours varies in different series from 0.2 to 2%,[2,4,7,20,21,23] and is somewhat higher in children. In Japan, it is 0.4% in children. In newborn infants, the incidence is 61.9% of all intracranial space occupying lesions discovered at birth.[9,19]

Teratomas usually occur in younger age groups and males are affected more than females.[17] Nearly 50% of the teratomas are located in the pineal gland. The other preferential sites are the ventricular system and the posterior fossa. In a series of 99 cases of intracranial teratomas, 49 were pineal teratomas, 14 were in the ventricular system, 27 in the supratentorial region (of them 8 in the hypophyseal region), 4 in the posterior fossa and 5 in undefined locations.[1] Intracranial teratomas of the newborn have several characteristics different from the teratoma of the pineal region seen in older children. In the former, the sex ratio of female to male is about 2:1, while the pineal teratoma is predominantly reported in males.

PATHOGENESIS

Willis[22] felt that teratomas arise at early stages of embryonic development. For unknown reasons, many do not manifest themselves until several years after birth, occasionally not until several years into adult life. Those occurring in the newborn are a special variety, which grow to an appreciable extent at a very early period. Differences in the rate of growth seem to account for the various forms in which these tumours present themselves in infancy.

Of the various theories on the pathogenesis of these tumours (the blastomeric theory, Masson's twin theory, the parthenogenetic theory), anomalies of the primitive streak alone appear to be applicable to the nervous system. Teratomas are assumed to develop, following inclusion within the embryo of a fragment of the primitive streak in the multipotent stage. This theory lends support to the role of the neural groove, thus explaining fairly satisfactorily the appearance of sacrococcygeal spinal, midline supratentorial and infratentorial teratomas.

PATHOLOGY

Macroscopically the striking characteristic of a teratoma is its partly cystic nature, the cysts usually being multiple and containing whitish fluid from desquamation of the lining cells. The solid portion of the tumour is firm, greyish-white and discoloured yellow by previous haemorrhage. Some of the teratomas are sharply demarcated from the adjacent nervous structures and can readily be dissected away from them. Others, especially in the intraspinal group, are blended so closely with the neural tissue that no plane of cleavage can be identified. An outstanding feature is a tendency to obstruct the CSF pathways. Congenital teratomas manifesting early in life may attain massive proportions, replacing the greater part of the brain.[16,17]

Microscopically, the tumour tissue consists of elements of all the three germinal layers. Depending upon the different proportions of embryonic and mature tissues, the tumour may be classified benign or malignant. If the cells are mature and well differentiated then it is labelled benign. As a general rule, the more embryonic the tissue, the more malignant is the tumour. Typical foci of germinomas may be seen in pineal, suprasellar and other teratomas.[8,13]

CLINICAL FEATURES

The symptoms and signs are those of any space occupying lesion. There are local effects depending upon the site of tumour and pressure effects resulting from an increase in the volume of the cranial contents. There are no specific clinical signs which may suggest the pathological diagnosis pre-operatively, unless an associated congenital anomaly is present. The presence of a congenital anomaly in a patient with signs and symptoms of a space-occupying lesion does not establish the diagnosis of a teratoma or teratoid tumour but makes the chances of finding this lesion somewhat greater.

In infants, the onset is marked by rapidly progressing hydrocephalus with occasional localising signs, such as gaze palsy, pupillary change and hemiparesis and lucency on transillumination of the head. Teratomas in infants and the newborn may be classified into three groups on the basis of clinical and autopsy findings:

1. The infant may be born dead with complete replacement of the brain tissue above the brainstem by the tumour. The birth of these infants may be associated with dystocia. The lesion is inoperable because of replacement of brain tissue.
2. The infant may be born alive but show progressive cranial expansion.
3. The infant may look normal at birth but subsequently develop hydrocephalus and focal neurological deficits.

These infants may be saved if the diagnosis is made early in the course of the illness,[5,10,19] although Odeku[12] expressed a pessimistic view.

In older children and adults, localising signs are infrequent. Endocrinal disturbances, as also Parinaud's syndrome, may be found, if the teratoma develops near the pineal region. Suprasellar teratomas cause a characteristic syndrome of diabetes insipidus, visual disturbances and hypopituitarism. Occasionally, increased intracranial pressure may be present.[20]

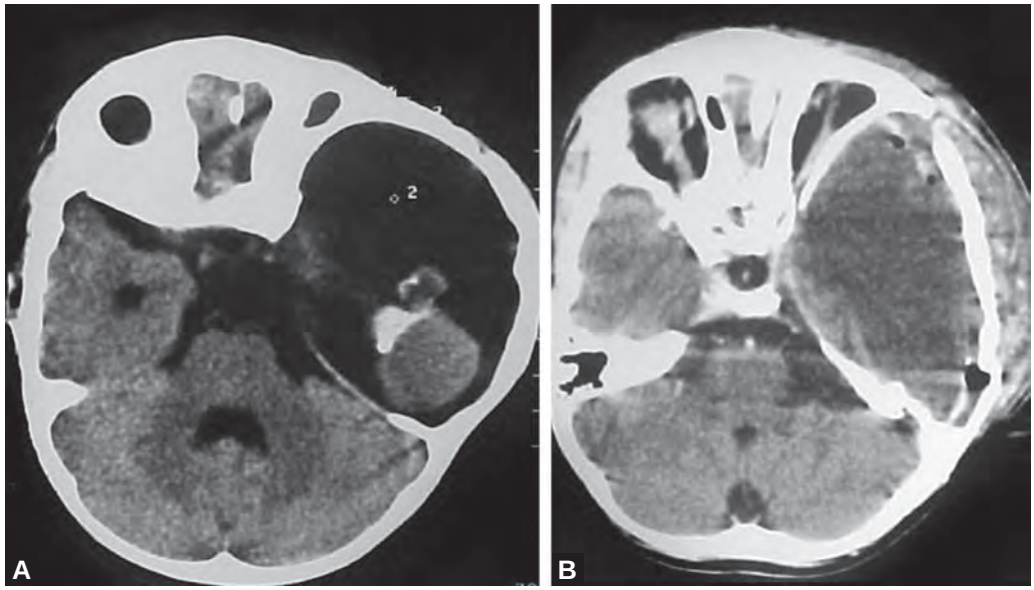
IMAGING

Roentgenograms of the skull show widened sutures, craniofacial disproportion and calcification of the tumour mass or other organoid structures like a tooth in the tumour.[15] CT is useful in demonstrating even small tumours, provided they contain fat or calcium. The CT pattern of a malformative tumour is that of a relatively well defined extra-axial mass lesion with or without calcification that fills or moderately expands the pre-existing CSF spaces.[11] While the fat components have a low attenuation value, other components may show hyperdensity (Figs 1A to H).

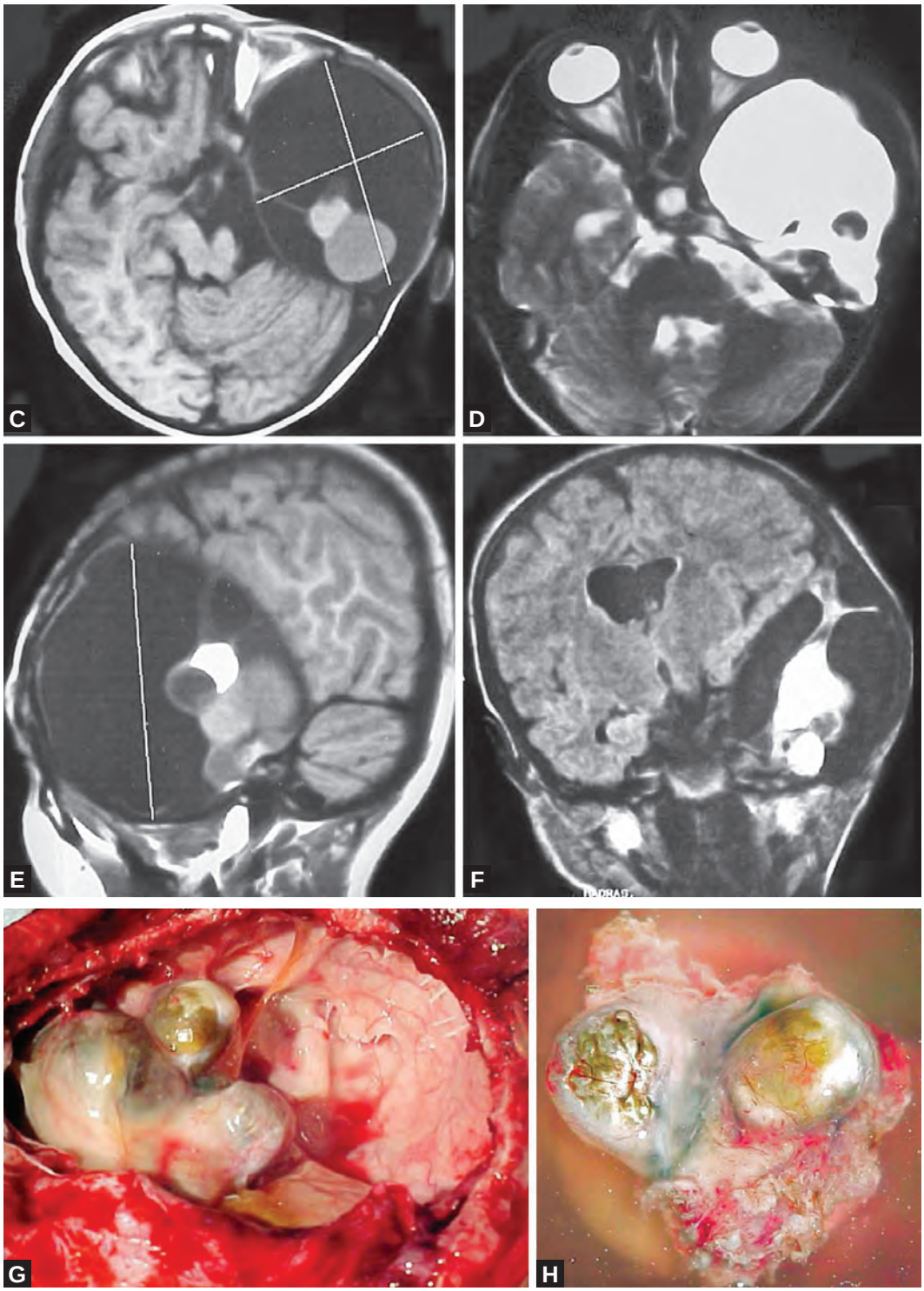
MR findings vary with the tissue component of the teratoma. The characteristic angiographic findings of intracranial teratomas are deviation of the main cerebral arteries by a large mass of tumour, a fine vascular network and early venous shunting.

TREATMENT

The ideal treatment, wherever possible, is excision. Mature teratomas have a good prognosis if completely excised.[3] This may, however, not always be possible, in which case a shunting procedure may be necessary to relieve the hydrocephalus. Aggressive resection seems to be of utmost importance in the treatment of immature teratomas of the CNS.[14] Ten-year survival for surgical excision alone varies with histological type, being more than 90% for mature teratomas, less than 70% for immature teratomas and less than 50% for teratomas with malignant components.[18] Adjuvant chemotherapy and radiotherapy can be deferred if gross total resection is achieved in low-grade, immature teratomas but



Figs 1A and B: (A) Pre-operative CT scan of the brain of a patient with left temporal teratoma. (B) Post-operative CT scan of the brain of the above patient



Figs 1C to H: (C to F) Pre-operative MRI brain axial T1, axial T2, sagittal T1 and coronal T1. (G and H) Per-operative pictures of the tumour

adjuvant therapies may be warranted in high-grade ones.[14] Diverse therapeutic protocol based on histological diagnosis is necessary to plan appropriate management. Treatment recommendations are:

- Mature teratomas completely resected and no adjuvant therapy;
- Sub-total resection: Adjuvant therapy (cisplatin) followed by second look surgery, and
- Immature teratomas: Radiotherapy and chemotherapy both are used with variable efficacy.

Chemotherapeutic agents used include carboplatin, etoposide, bleomycin, ifostamide, vincristine and dactinomycin. High recurrence rates are encountered with chemotherapy alone even if beta HCG/alpha fetoprotein levels come to normal post-operatively. Teratomas with highly malignant components including embryonic

carcinoma, yolk sac tumour, squamous cell carcinoma, adenocarcinoma and sarcoma are chemo-resistant. Chemotherapy along with craniospinal irradiation with local booster radiotherapy is indicated.

Second look surgery is indicated in cases where tumour markers are elevated and suggestive of malignancy. Non-malignant teratoma lesions or teratomas mixed with haemorrhagic necrosis or inflammatory cells may also benefit from second look surgery. Higher tumour marker levels indicate poorer treatment response and although useful for monitoring disease status, tumour markers have no impact on the patient's final outcome. Chemotherapy eliminates the malignant elements of a mixed tumour, leaving pure teratoma which paradoxically begins to grow very rapidly and this increase in the size of lesion post-chemotherapy is described in literature as growing teratoma syndrome.[18]

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161 Acoustic Schwannomas

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INTRODUCTION

Intracranial schwannomas can arise from any of the cranial nerves with a Schwann cell investing layer. However, the VIII nerve accounts for a disproportionately large number of these tumours, with the V nerve a distant second and the others being rare. Even rarer are reports of intraparenchymal schwannomas in the cerebellum and cerebrum.

A schwannoma arising from the VIII cranial nerve is called acoustic schwannoma [synonyms—acoustic neurinoma, acoustic neuroma, acoustic neurofibroma and vestibular schwannoma (VS)]. This tumour should ideally be termed as VS as they arise from the Schwann cells investing the vestibular nerve, but the term acoustic schwannomas is so firmly entrenched in the literature that its use is continued.

HISTORY

The earliest description of an acoustic schwannoma was by Sandifort in 1777 while Leveque-Lasoure in 1810 documented the first correlation of the tumour. Other notable clinicopathological observations were by Sir Charles Bell in 1830 and Cruveilhier in 1842. The history of acoustic schwannoma surgery began with the unsuccessful posterior fossa explorations performed by Von Bergmann in 1890, and by McBurney in 1891. Sir Charles Ballance is credited with the first successful removal of an acoustic schwannoma in 1894. However, Cushing felt that the tumour was a meningioma and attributed the first successful removal of a true acoustic schwannoma to Annandale in 1895. After Sir Charles Ballance and Annandale introduced the suboccipital craniectomy (SOC) approach for removal of acoustic schwannomas other neurosurgeons attempted surgery through this route without much success. Horsley, Von Eiselberg and Krause in 1913 reported a 67–84% mortality using the unilateral suboccipital approach.[158] Cushing made the first major advance in acoustic schwannoma surgery by decreasing the operative mortality to 15%.[37] Thus, he achieved by large bilateral craniectomies to relieve the raised intracranial pressure (ICP) and a palliative subtotal intracapsular decompression of the tumour. Though many patients succumbed to recurrence of the tumour, Cushing's 5-year survival rates were as high as 50%.[137] In his last 50 cases, however, Cushing's operative mortality was only 4%.[36] The classical monograph by Cushing, in 1917,[37] elaborated the clinical picture and diagnosis, and at the same time helped to dispense the pessimism regarding its surgical treatment. During the years 1890–1925, the SOC approach, the translabyrinthine and the transsigmoidal (combined translabyrinthine and suboccipital) approaches were introduced.[158]

Dandy[38] advocated total excision of the tumour and perfected the unilateral approach, which has undergone technical modifications, but has remained the prototype for the suboccipital approach. In 1925, he reported 5 patients operated upon via the bilateral SOC approach with total excision of the tumour.[38] He advocated tapping the lateral ventricle, releasing cerebrospinal fluid (CSF) from the cisterna magna, resecting the lateral third of the cerebellar hemisphere and deroofing of the internal auditory meatus (IAM) to achieve a safe and total removal. Though Dandy's operative mortality in cases where total excision was performed was 9.3%, his overall mortality in the 140 acoustics in his career was 22%.[158] Panse, in 1904, was the first to suggest a translabyrinthine approach to acoustic schwannomas. However, in view of the strong criticism by both Cushing and Dandy, it was abandoned till William House revived this approach to remove large tumours.[97]

Olivecrona was the first surgeon who attempted to save the facial nerve in a large series of patients while achieving complete tumour removal (31.8% of 217 patients),[177] though Cairns, in 1931, reported first on facial nerve preservation.[22] The first report on hearing conservation with "total removal" of the tumour was by Elliot and McKissock.[55] The first use of microsurgical techniques in acoustic schwannoma surgery was by House and Doyle who used the middle fossa approach to the tumours. In 1964, House reported a 5.4% operative mortality using microsurgical techniques.[97] He used the SOC, translabyrinthine and the middle fossa approaches and saved the facial nerve in 79% of patients. Rand and Kurze[197] used microsurgical techniques in the SOC approach and advocated its use for tumours of all sizes. Though the first report of hearing preservation was as early as in 1954, it was not until after the 1970s that emphasis was placed on hearing preservation.[158]

EPIDEMIOLOGY

Schwannomas constitute about 8% of all intracranial tumours[195,253] which present clinically. A significant number that were not symptomatic while the patients were alive have been found at autopsy.[87] The majority of acoustic schwannomas are sporadic and unilateral.[187,200]

Bilateral acoustic schwannomas are hereditary and constitute less than 5% of all schwannomas.[53]

Age and Sex Distribution

Acoustic schwannomas are commonest in the fourth to sixth decades[88] with the average age at presentation being almost a decade earlier in our country.[193,209] Acoustic schwannomas developing in patients with neurofibromatosis type-2 (NF-II) tend to present earlier, with a peak incidence around the third decade.[54,208] Acoustic schwannomas can occur in children.[124,128,149] Sambasivan et al.,[209] reported a nine-year-old patient with an acoustic nerve tumour. There is a slight female preponderance in most series,[88,187] with an aggravation of symptoms during pregnancy. This is not true of tumours in childhood, where an equal sex distribution is seen.[91]

Racial and Geographic Distribution

Acoustic schwannomas have been rarely reported in black Africans. Its incidence in Kenya was 2.6% and 0.9% in Nigeria. The incidence reported from England is 4.9% and from USA it is 4%. The incidence is greatest in Asian countries, with a rate of 10.2% from China and 9% from Egypt. Various reports from India suggest an incidence around 10%.[117]

Tumour Syndromes and Genetic Factors

Most of the acoustic schwannomas are unilateral and are sporadic in nature, accounting for 96% of cases. Hereditary acoustic schwannoma occurs in NF-II more frequently than neurofibromatosis type-1 (NF-I), though the latter is much more common. Unilateral acoustic schwannoma has been reported only in 2–4% of cases with NF-I.[117] Bilateral acoustic schwannoma is a hallmark of NF-II. Until 1980, it was considered to be a central form of Von Recklinghausen's disease. It was Kanter et al.[115] who described that these two entities were different and this was later confirmed by genetic studies.[117] Both these conditions have high penetrance and are autosomal dominant. The defective genetic locus has been localised to chromosome 17 in NF-I and chromosome 22 in NF-II.

The NF-II gene is considered to be a tumour suppressor gene. Germline transmission of the mutant gene in NF-II patients predisposes to tumour formation which results via somatic mutation of the remaining wild type allele.[117] The difference between the sporadic and hereditary forms of the disease is that the defect in bilateral acoustic schwannomas is present in the germline. The patient inherits only one copy of the tumour suppressor gene and undergoes spontaneous mutation of the other antioncogene in a somatic cell. In sporadic forms, homozygous mutation of both NF-II genes has to occur in one specific Schwann cell precursor. A subset of patients with NF-II inherits this genetic defect not only in Schwann cells, but in all cells. These patients are prone to develop multiple meningiomas in addition to bilateral acoustic schwannomas.[117]

Natural History

The growth rates of these tumours are generally slow, usually less than 2 mm per year,[6,161,287] however, there are reports of rapid growth rate of about 2.5–4 mm per year.[199] There are marked differences in the duration of symptoms at the time of presentation, and an important factor determining the future course in these cases is the initial size of the tumour at presentation. Though there are reports stating that a slow or absent growth over a period of 2–3 years makes it unlikely that there will be significant enlargement subsequently, there are other reports about significant growth after an initial period of quiescence. The growth rates in bilateral acoustic schwannomas are on an average considered to be faster than in unilateral lesions.[16,81,203]

SURGICAL ANATOMY

Modern microsurgical techniques used in cerebellopontine angle (CPA) surgery require a detailed and intimate knowledge of all structures in and around the CPA and the brainstem.

The CPA or fissure is V-shaped and is formed by the folding of the petrosal surface of the cerebellum around the lateral side of the pons and the middle cerebellar peduncle. The floor of this space is formed by the middle cerebellar peduncle. The cerebello-medullary cistern is situated between the cerebellar tonsils and the medulla, and communicates with the CPA cistern near the foramen of Luschka. The trigeminal, the abducent, the facial, the vestibulocochlear and the glossopharyngeal nerves arise between the superior and inferior limbs of the CPA. There are four nerves at the IAM; the facial (with the nervus intermedius), the cochlear and the superior and inferior vestibular nerves. The nerves are most constant in the lateral end of the meatus where a horizontal ridge (transverse or falciform crest) divides the meatus into superior and inferior portions. The facial nerve and the superior vestibular nerve are superior to the crest. Further, the facial nerve is anterior to the superior vestibular nerve and is separated from it by a vertical crest of bone. The cochlear nerve and the inferior vestibular nerve are in the inferior portion of the meatus, with the cochlear nerve anterior to the inferior vestibular. The internal acoustic pore has a width of 9–10 mm and a height of 3–6 mm. The internal auditory canal (IAC) has a length of 6–7 mm and a height of 3–7 mm.[122]

The facial nerve arises from the brainstem near the lateral end of the pontomedullary sulcus, 1–2 cm anterior to the point where the vestibulocochlear nerve enters the brainstem at the lateral end of the same sulcus. The sulcus ends just medial to the lateral recess of the fourth ventricle. The facial nerve and the vestibulocochlear nerve are furthest apart at the brainstem and converge and meet at the IAM. The facial nerve also shares a constant relationship with the IX, X and XI cranial nerves at the brainstem. The facial nerve arises 2–3 cm above the emergence of the superior most rootlets of these nerves from the brainstem. The intracisternal length of the facial nerve is 9–26 mm. As the nerve runs

medial to the vestibulocochlear nerve, it is not visible to the surgeon during the lateral approach to the posterior cranial fossa.

The vestibulocochlear nerve is usually oval and enters the brainstem 13–17 mm from the midline, slightly caudal and lateral to the exit zone of the facial nerve. The intracisternal length of the nerve averages 14.9 mm. During its course, it undergoes rotation, so that on entering the brainstem the cochlear part is lateral most, the superior vestibular the medial most, with the inferior vestibular in between. The length of the nerve with central myelin (oligodendroglia) is 8–12 mm, the transition zone normally lying near the IAM.

The average length of the trigeminal nerve in the CPA and the posterior fossa is 12.3 mm for the sensory root and 14.1 mm for the motor root. The nerve forms an angle of 10–35 degrees with the median plane as it courses from the pons to Meckel's cave. It exits from the posterior fossa through a dural opening situated at the anterior end of the medial surface of the tentorium cerebelli. Here the superior petrosal sinus is in close relationship to the nerve. The superior cerebellar artery forms a close relationship to the nerve.

The abducent nerve emerges from the brainstem approximately 3.9 mm lateral to the midline and has an intracisternal course of 15 mm in the posterior fossa. When looking into the posterior fossa through the suboccipital approach, the nerve may be seen in the depth, coursing through the CPA. When large tumours rotate the brainstem, the VI nerve may be confused for the VII, as both emerge from the brainstem at the same level and their exits are in the same horizontal plane.

The IX and X cranial nerves emerge from the brainstem from the paraolivary area caudal to the pontomedullary sulcus. They bear a constant relationship to the facial nerve at this point. The IX nerve rootlets form two delicate bundles, while the X cranial nerve emerges as multiple fine rootlets. They run approximately 15.6 mm in the CPA.

The anterior inferior cerebellar artery (AICA) is closely related to the facial and vestibulocochlear nerves. After originating from the basilar artery it passes around the pons near the pontomedullary sulcus. In most cases the AICA passes below the facial and the vestibulocochlear nerves as it encircles the brainstem. It may, however, occasionally pass between or above the nerves. The internal auditory artery (which supplies the VII and VIII cranial nerves), recurrent perforating arteries and the sub-arcuate artery are branches of the AICA which are in close relation to the facial and vestibulocochlear nerves in the CPA.

The veins on the side of the brainstem are fairly constant and have a predictable relationship to the facial and the vestibulocochlear nerves. The vein of the pontomedullary sulcus, the lateral medullary vein, the veins of the cerebellopontine fissure and the cerebellomedullary fissure and the vein of the middle cerebellar peduncle course near the lateral recess of the IV ventricle and the junction of the VII and VIII nerves with the brainstem. The superior petrosal vein (Dandy's vein) is the principal draining vein of the anterolateral posterior fossa structures. It courses anterolaterally, more or less parallel to the V nerve to enter the superior petrosal sinus between the IAM and Meckel's cave. The vein is 1–2 mm in diameter, though occasionally it may be made up of a leash of veins. The inferior petrosal vein courses along the vagus nerve.

PATHOLOGICAL ANATOMY

Acoustic schwannomas arise most commonly from the vestibular nerves (80%) with an origin from the cochlear part in only about 5–7%. Considering the nerves involved in the tumour at the fundus of the IAM, Koos et al.[122] found the inferior vestibular nerve involved in 70% of patients, the superior vestibular in 20% and the cochlear nerve in 10% of patients. The origin of the tumour is from the junctional (Obersteiner-Redlich) zone where the central and peripheral myelin meets. This zone is situated at the region of the IAM or within the IAC in most instances. The tumour grows initially within the canal and thereafter extrudes into the CPA. Inside the petrous bone, the tumour may compress the cochlear component of the nerve or the labyrinthine artery, causing sudden severe hearing loss.[226] Tumour growth into the CPA results in anterior displacement of the facial and cochlear nerves. The relationship of the tumour to the vestibulocochlear nerve varies:[122]

- In about 50% the nerve fibres are intimately involved with the tumour making separation impossible
- In 40%, though the nerve is in the form of a bundle initially, it becomes adherent to a part of the tumour capsule making functional preservation impossible
- In 10% the uninvolved portion of the nerve maintains anatomical integrity and the nerve is displaced as a separate bundle.

Clinically, this last group of cases present with preserved hearing and this should alert the surgeon to the possibility of hearing preservation. In this group of cases, the vestibulocochlear nerve is displaced inferiorly in 80%, anteriorly in 18% and posteriorly in 2% of cases.

Depending on the direction of growth of the tumour, the facial nerve may run one of four courses around acoustic schwannomas:[122]

- The nerve runs anterior to the tumour in about 70% of cases
- Superior in about 10% of cases
- Posterior in about 7% of cases
- Inferior in about 13% of cases.

The position of the facial nerve is most constant at the lateral end of the IAM and it is best to locate the nerve here, rather than more medially, where displacement may make its position more variable. The nerve may anatomically be distorted by the tumour; in about two-thirds of cases the nerve maintains the shape of a thin bundle, while in about a third of cases the nerve fibres are splayed over the tumour capsule.[122] In cases of Von Recklinghausen's disease, the proportions are reversed.

Once the tumour emerges from the canal it abuts onto softer structures and tends to grow in a symmetrical

fashion centred on the porus. Since the tumour arises from outside the CSF space, it pushes the lateral layer of the arachnoid inwards till it comes into contact with the more medial layer. The double layer thus formed contains the important vessels and nerves of the CPA and is an important aid to dissection. There is often a loculation of CSF which presents as an arachnoid cyst dorsolateral to the tumour.

The cerebellar hemisphere is displaced backwards and the brainstem is compressed and rotated along its long axis with gross displacement and stretching of the basilar artery and its branches. Nubbins of tumour may grow between the blood vessels. The tumour comes to lie in contact with the tentorium and may grow up through the tentorial hiatus into the middle cranial fossa. Some tumours may also herniate through the foramen magnum. Ramamurthi et al.[193] reported that the further direction of growth seems to be determined by the shape of the posterior fossa, the tumour tending to grow inferiorly when the posterior fossa is shallow and more superiorly if the tentorium is high and the posterior fossa deep.

As the AICA most often passes below the VII and VIII nerves, it is displaced inferiorly. In large lesions, the AICA may be seen lying in close relation to the IX and X cranial nerves. The superior cerebellar artery is displaced rostrally and the posterior inferior cerebellar artery caudally. The veins surrounding the tumour form bridging veins which empty into the superior petrosal sinus. While small tumours can be removed without sacrificing these veins, in large tumours it may be necessary to sacrifice one, if not more, or even the superior petrosal vein, to reach the superior pole of the tumour.

PATHOLOGY

Grossly the tumour is usually firm, rubbery and pale grey in colour with varying degrees of vascularity and has a well-defined capsule, which may be covered by displaced and stretched nerve fibres. The cut surface is usually pale grey and firm with a finely whorled or trabeculated appearance. In large tumours there is, frequently, evidence of cystic degeneration, haemorrhage, xanthomatous change and occasionally foci of calcification. These changes give a variegated appearance in colour and consistency to the large tumours. The blood supply of the tumour is initially derived from the internal auditory artery, which provides multiple minute ramifications over the surface of the tumour. As the tumour grows, small branches from the neighbouring cerebellar and pontine arteries may supply the tumour. Depending on the histology, the consistency of the large tumours varies. Some are firm and thus push the surrounding vascular and neural structures which lie stretched over them. These tumours are easier to excise than the softer variety, which have a tendency to grow all around the neurovascular structures and creep into the crevices.[193] Such tumours, hence, are more difficult to dissect free from important arteries and nerves.

Microscopic Features

On light microscopy, the tumour is composed of spindle cells with elongated nuclei and fibrillary cytoplasm,[21,204] arranged in two distinctive patterns termed Antoni A and Antoni B. Antoni A tissue is compact, with fairly prominent interwoven streams of elongated bipolar cells. The tendency for the nuclei to be aligned in straight or curved rows with their long axes parallel to one another gives the classical pallisading pattern. At times, the arrangement of the nuclei and fibres results in structures simulating the whorls seen in meningiomas. Antoni B is less structured and consists of random collections of cells clustered around areas of cystic change, necrosis, blood vessels and old haemorrhage. There is a variable amount of lymphocytic infiltration of this tissue. The Antoni B type of tissue, seen mostly in large tumours, is believed to be the result of ischaemia. The relative amounts of these two types determine the consistency of the tumour. Nuclear pleomorphism is common in schwannomas, but these are benign changes, as malignant transformation almost never occurs. Mitotic figures are rare. Necrosis, when seen, is also more a reflection of a poor blood supply rather than of rapid growth. The degenerative changes in the tumour tissue include oedema, formation of micro or macro cysts, xanthomatous alteration, hyalinisation and foci of calcification. Dastur et al.,[41] reported a melanotic tumour of the acoustic nerve, where the histology suggested phagocytic ingestion of melanin granules by the Schwann cells. A variety of vascular changes have been observed, especially in large tumours. These consist of acute necrosis and recanalised thrombi, aneurysmal dilatation of vessels and acute and old haemorrhages.

Electron microscopy (EM) reveals the characteristic basement membrane of the Schwann cells and the presence of wide-spaced collagen. The EM is not necessary for routine diagnosis of schwannomas, as the light microscopic picture is characteristic. Similarly, immunohistochemistry is rarely required.

A detailed pathological study of 102 cases of benign nerve sheath tumours, utilising light microscopy, EM and immunohistochemistry has been done by Sharma et al.[237] They provided evidence that all nerve sheath tumours are basically of Schwann cell origin and that the intermediate cells are fibroblast like cells which are variants of Schwann cells. The different morphological appearances and biological behaviour of schwannomas and neurofibromas may be related to some other factors like microenvironment or genetic predisposition.

CLINICAL FEATURES

The signs and symptoms of an acoustic schwannoma are those referable to the VIII nerve itself, as well as those due to involvement of the adjacent cranial nerves (VII, V, IX and X), the cerebellum and the brainstem. To these may be added the symptoms and signs of raised ICP. Small tumours may exist for a long time producing only VIII nerve symptoms. The most common symptoms of

acoustic schwannomas are unilateral sensorineural hearing loss (96%), unsteadiness (77%), tinnitus (71%), headache (29%), mastoid pain or otalgia (28%), facial numbness (7%) and diplopia (7%).[86] Usually slow growing and presenting insidiously, they can have acute presentations when there is haemorrhage within the tumour, or due to rapid expansion of a cyst.

Auditory

Though the tumour originates from the vestibular nerve, the commonest presenting symptom in acoustic schwannomas is unilateral hearing impairment, which is found in almost all cases. The hearing loss is a high frequency retrocochlear sensorineural type and is slowly progressive. Being insidious in onset, the impairment of hearing, which commonly precedes all other symptoms by several years, may pass unnoticed for a long time. An occasional patient may never complain of auditory symptoms even when the tumour has acquired a large size. Some of the patients who do not give any history of hearing defect initially accept its existence on direct questioning. They consider their hearing defect unrelated to the other distressing symptoms like those of raised ICP. The lack of importance our patients appear to give to a hearing deficit is confirmed by Sambasivan et al.[209] and Ramamurthi et al.[193] Thus, it is not surprising that small acoustic tumours are rarely diagnosed. Sudden onset of deafness has been reported in a few acoustic schwannomas.[184,226]

Even though some patients may not complain of unilateral deafness, the way they turn their normal ear towards the examiner to listen better is a characteristic sign. Deafness may be tested in the consulting room; speech discrimination by using whispered words and tone deafness by using tuning forks of varying frequency (256–1018 Hz). High tone deafness will be apparent from this. Air conduction is tested by placing the tuning fork near the external ear and bone conduction by placing it on the mastoid process and the frontal bone (Weber's test and Rinne's test). These give an approximate idea of whether the deafness is of the conduction or sensorineural type.

Tinnitus is another common symptom of acoustic schwannomas being reported as the initial symptom in about 30% of cases.[72] Tinnitus may precede or accompany the onset of hearing loss. It may be intermittent or may completely disappear after some time.

Vestibular

Subjective symptoms of vestibular dysfunction are uncommon as the presenting complaint; though on objective testing 80–96% of patients may have signs of vestibular dysfunction.[57,192] This is thought to be due to suppression of the abnormal impulses by higher centres.[57] The commonest vestibular symptom is a sensation of instability on movement of the head. A true whirling vertigo is uncommon, though a few patients may suffer from episodes not unlike those seen in Meniere's disease.

Nystagmus may be seen in a number of cases and is usually due to a vestibular disturbance in the early stages and pressure on the brainstem in the later stages. This may be spontaneous, positional (when the head is hyperextended and the head turned to the right or left) or optokinetic. The most common variety is the fine horizontal beats directed away from the side of the lesion produced due to unilateral labyrinthine dysfunction. Large tumours producing significant brainstem compression manifest as bidirectional nystagmus with a coarse gaze evoked optokinetic nystagmus on looking to the ipsilateral side and a high frequency fine small amplitude vestibular nystagmus on looking to the contralateral side. Spontaneous nystagmus, though bilateral, is usually more marked on looking to the opposite side. It is not dependent on visual fixation, but on conjugate deviation of the eyes. Dix and Halpike termed it deviation maintenance nystagmus.[46] Hyperventilation induced nystagmus beating to the side of reduced caloric response, hearing impairment or abnormal auditory brainstem responses may be a valuable sign for bedside detection of CPA tumours.[29]

Some of the above otoneurological symptoms and signs may be present in patients with raised ICP without a CPA lesion.[140,251,252]

Facial Nerve

The facial nerve has been clinically observed to be remarkably resistant to stretch, and symptoms and signs due to involvement of this nerve appear late and are minimal, except in very large tumours.[253] A slight lag in blinking of the eyelid on the affected side is an indication of early facial palsy.[193] Signs of irritation of the facial nerve, like twitching or increased lacrimation have occasionally been reported.[52,209] The increased incidence of facial paresis in Indian series compared to series from the Western countries,[194,253] reflects the large size of tumours still seen and the late referrals to the neurosurgeon. A minimal facial weakness may be detected by electromyography. Contralateral or bilateral facial weakness has been reported in isolated cases.[253]

Other Cranial Nerves

The trigeminal is the next common nerve to be involved, the nerve being stretched by the upward growth of the tumour when it reaches an extracanalicular size of about 3 cm. Symptoms and signs of trigeminal dysfunction were seen pre-operatively in 66% of 196 patients operated upon by Ramamurthi and Ravi[194] between 1980 and 1993. The common abnormality referable to the fifth nerve is impairment of the corneal reflex. Subjective numbness and/or paraesthesia in the trigeminal distribution may be complained of by many patients. Tingling of the tongue may be the first symptom of an acoustic neurinoma for many weeks. Infrequently, there may be pain which may mimic typical trigeminal neuralgia in a given case. Sambasivan et al.,[209] reported trigeminal neuralgia as the only symptom without any other neurological deficit in 3% of their cases of acoustic schwannomas. Symptoms referable to the motor root are seldom complained of even though objective evidence of such an involvement is observed in 10–15% of cases.[253]

In advanced cases, due to twisting of the brainstem, there may be impairment of corneal sensation on the opposite side.[2]

The glossopharyngeal and vagus nerves are involved usually late, and manifest as palatal paresis, hoarseness of voice and dysphagia. Though rare in most studies in developed countries, lower cranial nerve involvement has been reported in up to 20% of patients in India.[194]

Cerebellar

Symptoms related to cerebellar dysfunction are found in patients with large tumours. These have been reported in nearly 46% of patients with acoustic schwannomas.[194] The deficits are commonly gait ataxia and incoordination of the upper limb, dysarthria being rare. When nystagmus is present, it is usually due to vestibular and brainstem involvement rather than cerebellar involvement. In the presence of brainstem compression the nystagmus is slow and prolonged and there may also be a vertical nystagmus.

Brainstem

A large tumour can cause compression and later torsion of the brainstem with resultant pyramidal weakness and contralateral cranial nerve deficits.[2]

Raised Intracranial Pressure

Though the technical capacity now exists to diagnose an acoustic schwannoma when it is still intracanalicular, a significant number of patients still present for the first time only after the onset of features of raised ICP. Mental symptoms due to chronic hydrocephalus have been the presenting feature in some elderly patients with large acoustic tumours.

Headache

Headache in most of these cases results from increased ICP. Headache may also occur in the absence of raised ICP due to pressure or traction upon blood vessels. It may also be caused by pressure on the tentorium, which is innervated principally by branches of the first division of the trigeminal nerve.[188] The pain may thus be frontal or retro-orbital in the initial stages.

Papilloedema

The number of patients presenting with papilloedema is much less now than two decades ago. Ramamurthi et al.[193] reported in 1970, only three patients out of 140 without papilloedema; however, in his series of 196 cases between 1980 and 1993, it was seen in only 55% of cases.[194] Papilloedema may range in its manifestations from slight to severe. A four-tier grading scheme ranging from slight to moderate to severe and atrophic papilloedema has been used. Frisén proposed a grading scale from 0 to 5. Papilloedema that is clinically detectable can develop over 1–7 days of increased ICP.[228]

INVESTIGATIONS

Neuro-Otological Workup

Most of these tests can be performed only if the affected ear has usable hearing. A baseline workup is necessary for later comparison and to document the deterioration during follow-up or post-operatively. They also give valuable inputs in treatment planning and in decision making.[82] There are several systems for grading hearing; the modified Gardner-Robertson system is described in Table 1.

Clinical Testing of the Auditory System

The use of the tuning fork gives specific information regarding the patient's hearing. The examiner compares the patient's hearing with his or her own.

Schwabach test: In this test, a tuning fork of 256 Hz or 512 Hz is used and the patient's bone conduction is examined. The 512 Hz tuning fork is preferred. The duration of perception of the tone is noted. The stem of the tuning fork is placed on the patient's mastoid process and transferred to the examiner's, once the former can no longer hear it. The test may be repeated for the evaluation of air conduction.

Rinne test: In this test, the patient's air and bone conduction are compared. The stem of the tuning fork is first placed firmly on the mastoid process of the patient while closing the external auditory meatus (EAM). The patient is asked to indicate when he can no longer hear the sound. The tuning fork is then immediately transferred to the front of the EAM and the time up to when the sound is heard is noted. In normal individuals or a positive Rinne test, air conduction is better than bone conduction, i.e. the patient continues to hear the sound when the tuning fork is placed in front of the EAM after he has stopped hearing it from on the mastoid. In a negative Rinne test, bone conduction is better than air conduction, with the tuning fork heard better over the

Table 1: Gardner and Robertson modified hearing classification

Class	*Description*	*Pure tone audiogram# (dB)*	*Speech discrimination#*
I	Good–excellent	0–30	70–100%
II	Serviceable	31–50	50–59%
III	Non-serviceable	51–90	5–49%
IV	Poor	91–maximum	1–4%
V	None	Not testable	0

#if audiogram and speech discrimination score do not qualify in the same class, use the lower class

mastoid process. The Rinne test is negative in conductive deafness. In sensorineural hearing loss, both bone and air conduction are reduced, but maintain a normal relationship to one another.

Weber test: This test is performed by placing the stem of the tuning fork on the forehead or over the vertex of the skull. In normal individuals the sound is heard equally in both ears. In conductive deafness, the sound is heard best in the involved ear, while in sensorineural deafness the sound is best heard in the uninvolved ear.

Specialised Testing

Behavioural auditory testing in patients with suspected acoustic nerve tumours gives useful qualitative and quantitative data which enables the neuro-otologist to diagnose and workup patients with acoustic nerve lesions.

Pure tone audiometry: It differentiates between conductive and sensorineural deafness. In patients with a conductive deafness, the pure tone bone conduction has a normal threshold, while pure tone air conduction has elevated thresholds. In patients with sensorineural hearing loss, both air and bone conduction thresholds are elevated (Fig. 1).

Loudness recruitment: In patients with sensorineural deafness it is essential to further characterise the deafness, whether it is cochlear or retrocochlear in origin. A phenomenon of abnormal growth of loudness, termed as loudness recruitment serves to differentiate between cochlear and retrocochlear lesions as purely VIII nerve lesions are not characterised by this phenomenon. The alternate binaural loudness balance test (ABLB)[60] and the short increment sensitivity index (SISI)[108] are tests of recruitment.

Alternate binaural loudness balance (ABLB) test: The ABLB compares the loudness of a tone in an impaired ear with the same or a different tone in the normal ear. In the ear where recruitment is positive, tones of equal intensity will be judged equally loud in both the impaired and the normal ear, despite the fact that the threshold for hearing is elevated in the impaired ear.

Short increment sensitivity index: The SISI is measured by superimposing 1 db intensity increments on a continuous tone. The ability to perceive these small increments is associated with cochlear pathology while with lesions of the VIII nerve the scores are low.[178]

Speech discrimination: It is another phenomenon which is associated with cochlear damage. It is tested by using standardised monosyllables using a live voice or taped material. Patients with both cochlear and retrocochlear lesions have low speech discrimination scores, with patients with retrocochlear lesions having lower scores than those with cochlear lesions.

Non-behavioural auditory testing is now being used mainly in two forms: impedance audiometry and brainstem auditory evoked response audiometry.

Impedance audiometry: This is an extremely sensitive index of retrocochlear disease.[118] It consists of three separate measurements:

1. Static compliance or measurement of the "stiffness" of the conducting apparatus of the ear.
2. Tympanometry or measurement of the pressure differentials between the external auditory canal and the middle ear.
3. Acoustic or stapedial reflex.

The measurements of static compliance and tympanometry assess middle ear disease. The acoustic or stapedial reflex is a sensitive indicator of retrocochlear

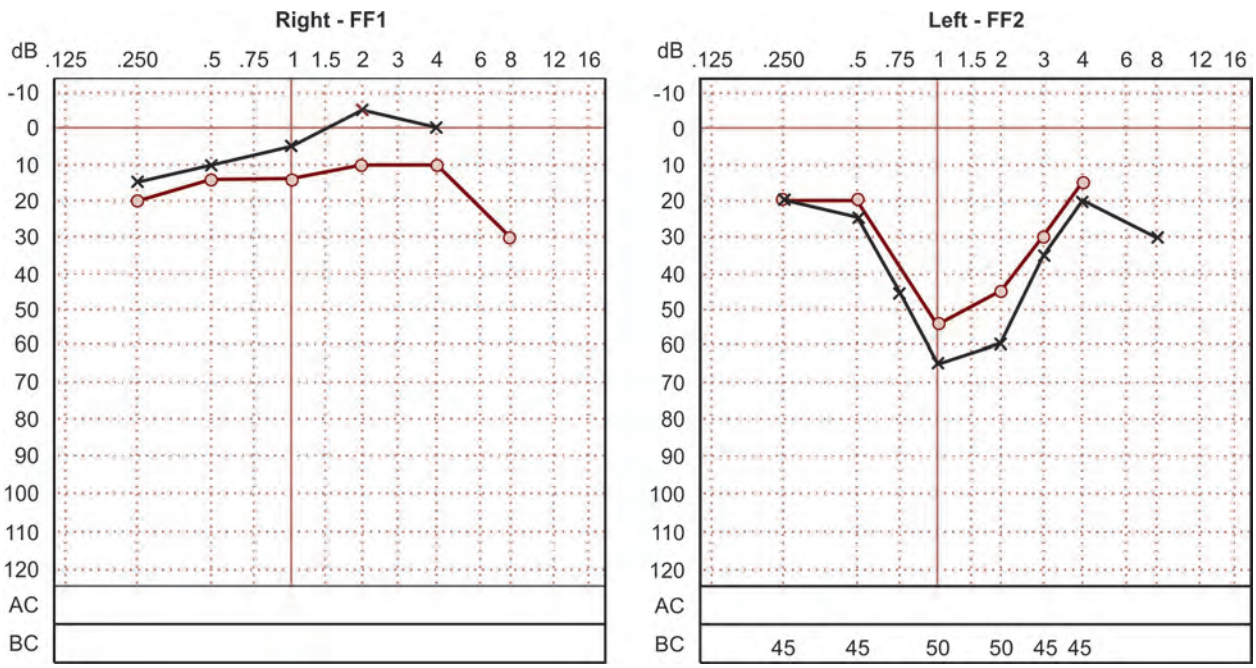


Fig. 1: Pure tone audiometry showing severe sensorineural hearing loss in the left ear

pathology. The reflex has an afferent arc in the form of an intense sound signal delivered to the VIII nerve. This produces a reflex contraction of the stapedius muscle innervated by the VII nerve. It is detected as a marked increase in the amplitude of sound reflected off the tympanic membrane when the stapedius muscle contracts and stiffens the middle ear mechanism.[238] About 95% of normal individuals demonstrate the acoustic reflex at about 85 db above their normal behavioural threshold.[107] In patients with a cochlear lesion, the gap between the behavioural threshold and the acoustic reflex threshold is small (less than 55 db). Patients with retrocochlear lesions show absent or elevated acoustic reflex thresholds.

The acoustic reflex decay measures the rate of adaptation of the reflex. To measure the decay, a sustained tone is presented at 10 db above the patient's reflex threshold for a period of 10 seconds. The testing is conducted at frequencies below 2000 Hz, because normal persons frequently show reflex decay at higher frequencies. If the reflex amplitude reduces more than 50% during the 10 second tune period, the results point towards a retrocochlear lesion.

Brainstem auditory evoked response audiometry: It has a 96% detection rate with an 8% false positive and 4% false negative rate.[236]

Imaging

Plain X-rays of the skull with special views to visualise the petrous bones are still useful as a first step. Enlargement and/or erosion of the porus acousticus and the IAC are diagnostic of an acoustic schwannoma. Different views of X-ray have been advocated to demonstrate this. Schuller, in 1911,[229] studied the petrous pyramid through the orbit. Stenver, in 1917,[245] suggested a view of the petrous temporal bone at a right angle to the long axis of the bone. Towne, in 1926, employed a 30 degrees frontal occipital projection. Schuller, Caldwell and Towne's views are employed routinely in most clinics. Of these, the transorbital projection (Caldwell view) is more useful in demonstrating the canals without interference from other natural artifacts. On the contrary, in the Towne's view, the many natural variations of the posterior surface of the petrous bone and petrous ridge may simulate canal or meatal erosion. In the Stenver view, the IAM is visualised in a shortened form, whereas the transorbital view depicts the canal and the meatus in actual form and size in one single film. Variations from the normal may be seen in these views in a small percentage of cases without any pathology and awareness of such variations help in the early diagnosis of acoustic tumours.[12]

The shape of the IAC may be bulbous in two-thirds of normal people.[132] Hence, it is important to look for suprameatal erosion, intrameatal erosion and enlargement leading to a flaring of the meatus. In a few cases, the IAC may be normal, with the tumour arising from the intracranial part of the nerve. In such cases, the canal may show no widening, though the meatus may be enlarged or eroded. The size of the IAC may vary on the two sides in the same individual. However, a measurable difference of more than 1 mm between the two sides, especially if accompanied by areas of erosion or difference in shape is of diagnostic significance. In a number of cases seen in developing countries, there are early or late signs of increased ICP.

Computerised axial tomography is now the most popular initial investigation in the diagnosis of acoustic schwannoma. A contrast-enhanced computerised tomography (CT) can easily detect a tumour with an extracanalicular extension of 1–1.5 cm. The presence of even smaller tumours may be inferred by taking the appropriate cuts with bone windows to demonstrate the classical widening of the IAM (Figs 2 and 3). However, the smaller tumours cannot be directly visualised due to artifact from contiguous bone. It is always advisable to do both unenhanced and enhanced CT as otherwise, a prominent jugular tubercle may be mistaken for a tumour in a contrast-enhanced CT.

On the non-contrast CT scan the tumours are seen as well marginated lesions centred on the IAM. A majority

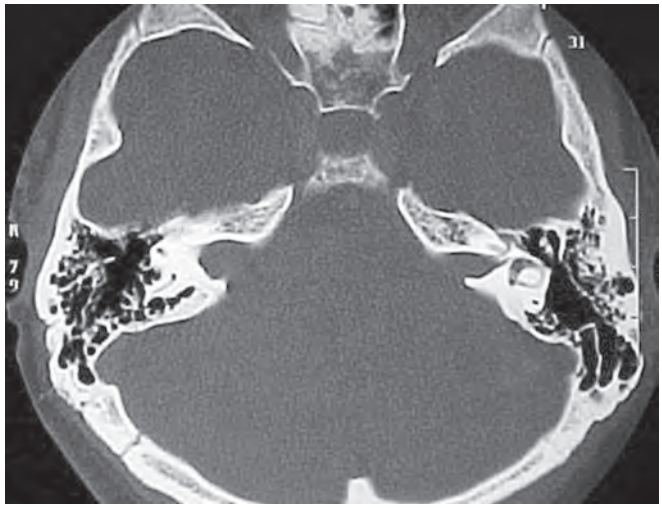


Fig. 2: Computerised tomography scan bone windows of a patient showing widening of the meatus on the right side with normal meatus on the left

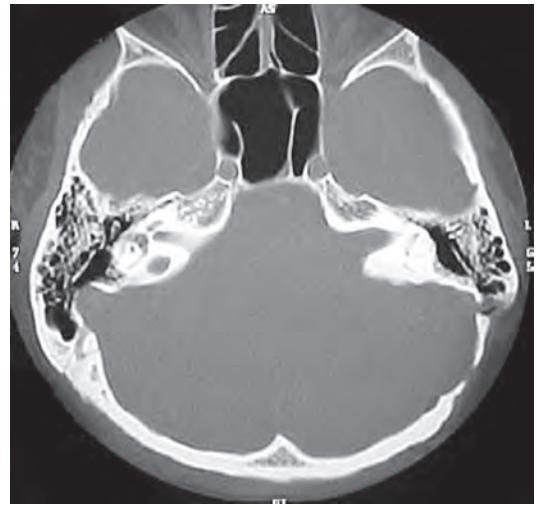


Fig. 3: Computerised tomography scan bone windows of a patient showing flaring of the meatus on the left side with normal meatus on the right

of tumours are isodense (63.3%).[261] Hypodense lesions may be seen in 17–18% and 14–15% may be hyperdense.[42,256,263] The proportion of hypodensity or mixed density lesions increases with increasing tumour size.[261] Calcification is rare and may represent a "collision tumour".[49] In NF-II patients, non-neoplastic cerebellar calcification may be seen. This is unilateral, involves the cerebellar folia and may represent "meningioangiomatosis".[266]

Following contrast injection, almost all tumours show enhancement.[49,261] Two-thirds of the tumours enhance homogeneously and have well-defined margins.[49] Approximately one-third of the tumours show ring enhancement.[160] In these cases, delayed scanning done 30–90 minutes after injection of the contrast will show diffusion of the contrast into the centre of the tumour. A good correlation exists between the cytoarchitecture of the tumour and contrast enhancement.[261] Antoni type B tumours enhance irregularly with contrast while Antoni type A tumours enhance homogeneously. Cysts are uncommon. These are usually small and often close to the arachnoidal surface of the tumour[49,181] (Figs 4 and 5).

The CT using bone window settings characteristically demonstrate the widening of the porus acousticus. 74.3% of the cases seen by Unni et al.[261] showed definite widening of the IAM, while 22.1% had equivocal erosion of the meatus. Large tumours which are purely extracanalicular may not show any erosion of the bone.

Auditory evoked response (AER) monitoring is a sensitive tool in the diagnosis of acoustic schwannomas, with a sensitivity of 98%, though a false positive rate of 7% has been reported. A combination of AER and a contrast-enhanced CT scan has been reported to detect 99% of all acoustic schwannomas[5] at a much lower cost than a MRI.

MR imaging (MRI) with its capacity to disregard surrounding bone has become the investigation of choice in the diagnosis of small acoustic schwannomas, and to study the CPA.[35,191,264] On MR, the tumour is usually hypointense in relation to the pons in T1-weighted images and isointense to mildly hyperintense on proton density and T2-weighted images.[225] Intracanalicular lesions are recognised on the basis of a differential signal between the tumour and CSF on T1-weighted images, the tumour being relatively hyperintense compared to CSF.[225] Focal swelling or obscuration of the VIII nerve may be the earliest sign of tumour growth on the MR.

The addition of gadolinium-diethylenetriamine pentaacetic acid contrast, though not routinely necessary for diagnosis, may prove helpful in certain situations[89,225] (Figs 6A and B). Small tumours may be missed because of the partial volume averaging effect, especially if they lie within the IAC (Fig. 7). The use of contrast is also helpful to exclude or demonstrate residual or recurrent tumour; the study should be done at least 6 weeks after surgery. The differentiation of an acoustic schwannoma from a meningioma is more easily done with an enhanced MR.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of a CPA mass is given in Table 2.

The pre-operative distinction between meningiomas and acoustic schwannomas is important for technical and prognostic reasons (Fig. 8). It allows the surgeon to choose the best approach and minimise the surgical risks. The facial nerve typically is located on the anterior or anterosuperior surface of an acoustic neuroma. This relationship is lost in the case of a CPA meningioma. The facial nerve may be displaced in any direction or may

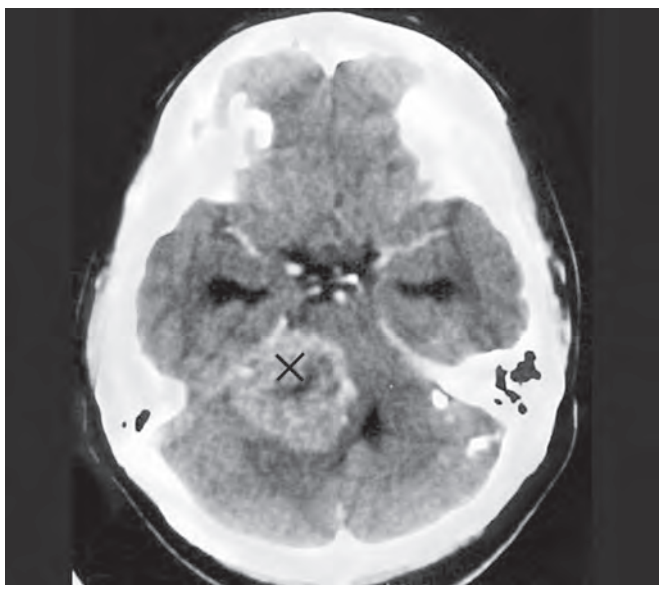


Fig. 4: Computerised tomography scan of the brain showing contrast enhancing well-defined globular lesion in the cerebellopontine angle with the pressure on brainstem and fourth ventricle with prominent temporal horns

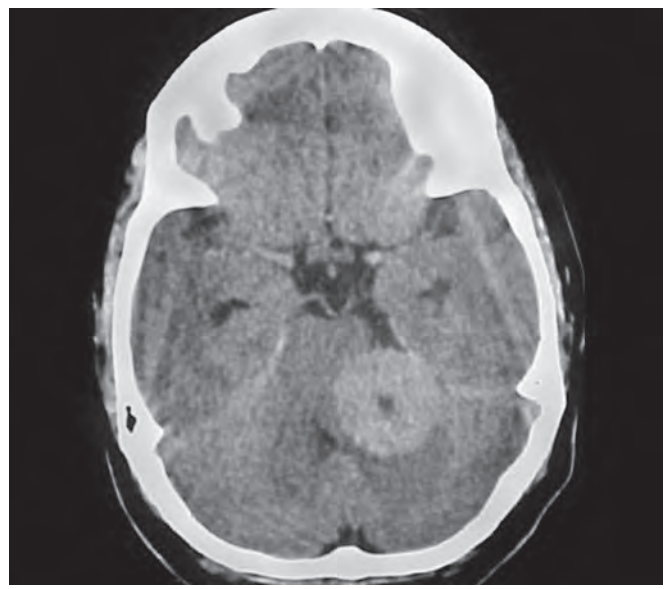


Fig. 5: Computerised tomography scan of the brain of a vestibular schwannoma showing contrast enhancing well-defined globular lesion with the pressure on brainstem and fourth ventricle

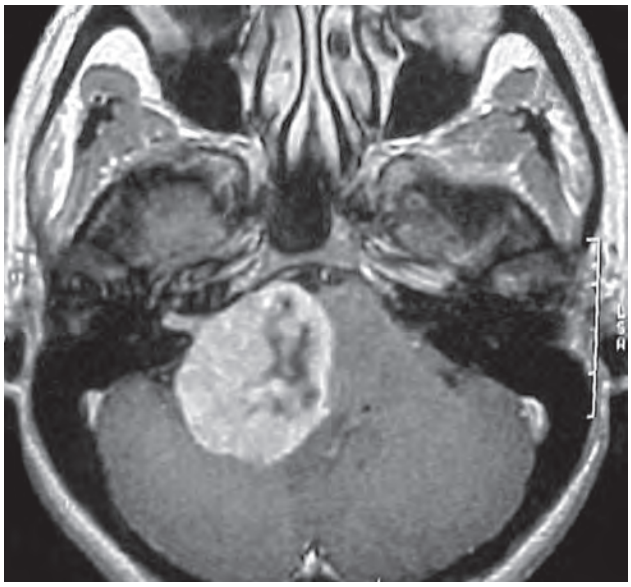


Fig. 6A: Contrast magnetic resonance imaging of the brain T1W axial view showing enhancing vestibular schwannoma

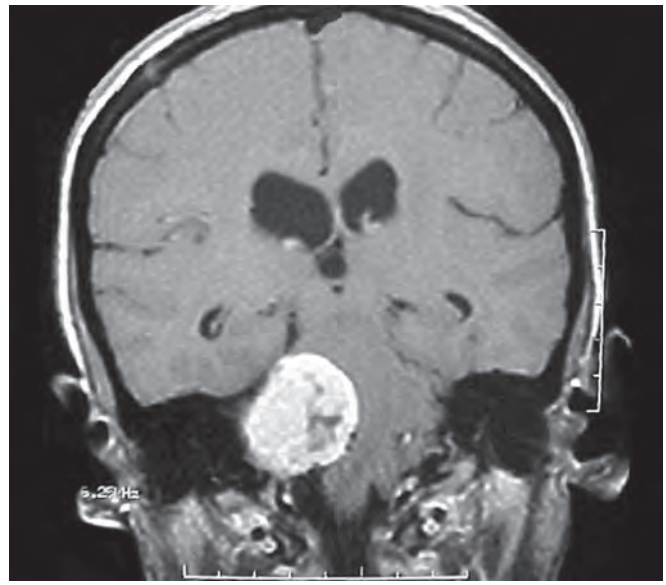


Fig. 6B: Contrast magnetic resonance imaging of the brain T1W coronal view showing enhancing vestibular schwannoma

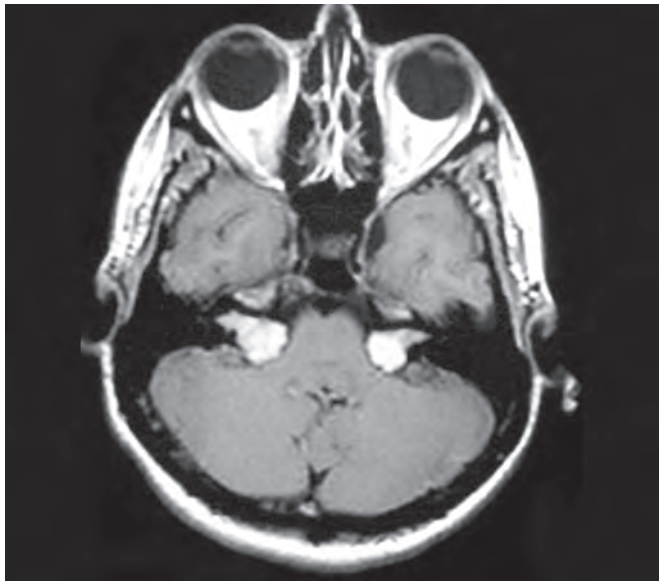


Fig. 7: Contrast magnetic resonance imaging of the brain T1W axial view showing bilateral small vestibular schwannomas enhancing with contrast

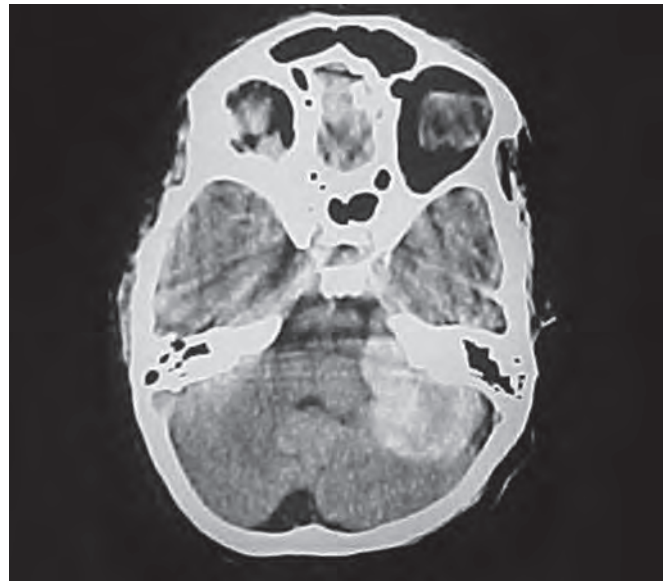


Fig. 8: Computerised tomography scan of the brain contrast axial view showing cerebellopontine angle meningioma

be engulfed by tumour, thus making its preservation more difficult. Unlike acoustic neuromas, meningiomas have a propensity to track along posterior fossa nerves and may involve Meckel's cave or the jugular foramen; the surgeon should be prepared for this eventuality. Dramatic post-operative hearing improvements have been reported in CPA meningiomas, hence if a meningioma is suspected, then one should be very cautious before resorting to an approach that results in decreased hearing (such as the translabyrinthine or the transcochlear approach).[129,268]

An important differentiating feature is that an acoustic neuroma is usually centred over the IAM, whereas CPA meningiomas are usually eccentric. The enhancement after gadolinium administration of a tail of dura adjacent to the main tumour has been termed the meningeal sign. Also known as dural tail, it was described in 1989 by Wilms et al.[279,280] It is a thickening of the dura around a meningioma. The dural tail represents enhancement of thickened dura, adjacent to and tapering away from a dura-based lesion on MRI. Goldsher et al.[77] adopted three criteria for the definition of a dural tail:

Table 2: Differential diagnosis of acoustic schwannoma

- Acoustic schwannoma [80–90% of cerebellopontine angle (CPA) lesions]
- Meningioma (5–10% of CPA lesions)
- Ectodermal inclusion tumours
  - Epidermoid (5–7% of CPA lesions)
  - Dermoid
- Metastases
- Neuroma from cranial nerves other than VIII (also see below):
  - Trigeminal neuroma: expands towards Meckel's cave
  - Facial nerve neuroma
  - Neurinoma of the lowest four cranial nerves (IX, X, XI, XII)
- Arachnoid cyst
- Neurenteric cyst
- Cholesterol granuloma (distinct from epidermoid)
- Aneurysm
- Dolichobasilar ectasia
- Extensions of:
  - Brainstem or cerebellar glioma
  - Pituitary adenoma
  - Craniopharyngioma
  - Chordoma and tumours of skull base
  - Fourth ventricle tumours (ependymoma, medulloblastoma)
  - Choroids plexus papilloma—from 4th ventricle through Foramen of Luschka
  - Glomus jugulare tumour
  - Primary tumours of temporal bone (e.g. sarcoma or carcinoma)

- Presence on at least two consecutive sections through the tumour at the same site and in more than one plane
- Greatest thickness adjacent to the tumour and tapering away from it
- Enhancement greater than that of the tumour mass itself.

Rarely, an acoustic neuroma may display a pseudomeningeal sign. This is a thin, short dural tail present on a single aspect of the tumour, which is caused by bone marrow adjacent to the porus acousticus. This pseudomeningeal sign is present on T1-weighted images before and after gadolinium enhancement, unlike the true meningeal sign that is present only after the administration of gadolinium.[79,99,126,148]

Both acoustic neuroma and CPA meningioma have a heterogeneous appearance on the T1-weighted MRI. This heterogeneity is due to cystic degeneration in acoustic neuroma, and to calcifications in CPA meningioma. On T2-weighted scans, the cystic areas will appear hyperintense, whereas the calcified areas remain hypointense. Thus, a CPA tumour that has regions of low intensity on T1 and T2-weighted MRI probably is a calcified meningioma. An angiogram or a MR angiogram may be of help in ruling out a giant calcified aneurysm.[125,288]

MANAGEMENT

The options available for the management of VSs include observation, surgery, stereotactic radiosurgery (SRS) and fractionated radiotherapy. The ideal treatment is total excision of the tumour in a single stage with preservation of neurological function.

Resection is indicated for patients harbouring larger tumours that have caused major neurological deficits due to brain compression. Surgeons perform SRS for small-sized or medium-sized tumours, their goals being to preserve neurological function and prevent tumour growth. The long-term outcomes of SRS, particularly gamma knife surgery (GKS), have proven its role in the primary or adjuvant management of this tumour. Fractionated radiotherapy has been suggested as an alternative in selected patients with larger tumours for whom microsurgery may not be feasible, as well as in some patients in whom preservation of cranial nerve function is being attempted.

The goals and acceptable clinical outcomes have evolved over time. Many years ago, the goal was simple debulking of the tumour (which was often large) and relief of regional brainstem compression and hydrocephalus; the goal was life saving. Neurological deficits such as hearing loss, facial weakness or balance disorders were tolerated as simply part of the expected result. However, with the introduction of microneurosurgery, attempts at cranial nerve preservation have been the goal. Over the last 30 years, preservation of facial nerve continuity became more common and hearing preservation became an achievable goal in selected cases. At the same time, improvements in anaesthesia-related technique and wound closure have reduced the risk of cerebellar infarction, meningitis and CSF leakage. Nevertheless, these problems still continue to exist and remain a significant problem after resection.

Before choosing any particular therapy, primary clinical issues such as avoidance of tumour-related or treatment-related mortality, prevention of further tumour-induced neurological disability, minimising treatment risks such as CSF leakage, infections, cardiopulmonary complications, maintaining regional cranial nerve function (facial, trigeminal, cochlear and glossopharyngeal/vagal), avoiding hydrocephalus, maintaining quality of life (QOL) and employment, and reducing cost should be considered and the surgeon should strive to meet all of these goals.

Surgery is indicated for the treatment of small and medium-sized VSs. The resulting QOL matches that after radiosurgery.[86,148,218] Surgery remains a necessary treatment for large VSs, however, it has a significant impact on a patient's QOL, and the patients must be well informed of the consequences of such a surgery.

Observation

There are patients for whom long-term observation may be indicated. Because surgery carries some risk and these tumours are generally slow growing, a conservative policy may be adopted especially in elderly patients without any serious neurological symptoms.[53,110]

Bederson et al.[7] reported that out of 70 patients, who were initially observed, 53% had a mean growth of 3.4 mm in the 1st year and 6% had regression of the tumour. This and another study[265] showed that there was no relationship of tumour growth to age.

A prospective cohort review of unilateral VS with mean duration of 80 months follow-up, with serial MRI for assessment of tumour growth reported the mean tumour growth rate for the entire group to be 1 mm/year (range 0.84–9.65 mm/year). The mean growth rate for CPA tumours (1.3 mm/year) was significantly greater than that of IAC tumours (0 mm/year) (P = 0.005). There was significant tumour growth in 38.9%, no or insignificant growth in 41.7%, and negative growth in 19.4%. Twenty three patients (32%) failed conservative management. Hearing deterioration with pure tone averages (0.5 kHz, 1 kHz, 2 kHz, 3 kHz) and speech discrimination scores occurred irrespective of tumour growth. This prospective study delineates the role of conservative management in selected cases of VSs.[199]

Measurement of the maximal tumour diameter on MRI is a reliable method for following acoustic neuroma growth. There is no need to perform a rigorous analysis of tumour size to determine whether the tumour is growing significantly. The vast majority of patients older than 65 years with small acoustic neuromas do not require intervention. The indications for intervention should be based on a combination of rapid tumour growth with deterioration of symptoms.[203] A substantial number of acoustic schwannomas are discovered incidentally. These incidental schwannomas have a more benign nature, and may be less likely to require intervention.[109] However, conservative management of acoustic schwannomas requires long-term clinical and radiological follow-up. The irregular behaviour of the tumour underlines the importance of monitoring with MRI at least once a year.[156]

Surgery

There are mainly three operative approaches to the IAM and the acoustic neuroma.

1. The lateral suboccipital approach (the retrosigmoid transmeatal approach).
2. The translabyrinthine approach.
3. The middle fossa approach.

Good results have been reported for all three surgical procedures. Each has specific advantages and disadvantages. Other approaches which have been utilised for the removal of acoustic neuromas include:

4. The retrolabyrinthine approach
5. The transcanal approach
6. The suboccipital–translabyrinthine approach
7. The subtemporal transtentorial approach.

The Middle Fossa Approach

This was developed by WF House.[96,97] It offers several advantages for the removal of small laterally placed acoustic neuromas:

- Dissection is mainly extradural and therefore morbidity is less
- As the lateral end of the IAM is exposed, total removal of the tumour is assured
- Early identification of the facial nerve at the lateral end of the IAC and exposure of the labyrinthine and upper tympanic segments of the nerve facilities preservation of the facial nerve
- It enables hearing preservation, especially for tumours arising from the superior vestibular nerve
- In a small group of patients with NF-II it helps decompress the IAC

The disadvantages of this approach are:

- The facial nerve is in the field and the surgeon must work beyond the nerve to remove the tumour
- Post-operative unsteadiness is encountered due to partial preservation of vestibular function
- Limited access to the posterior fossa, especially if there is bleeding at surgery

The complications seen with this approach include:

- Epidural haematoma which may occur early in the post-operative period
- Complications as in other procedures, e.g. meningitis, injury to the temporal lobe, hearing loss and facial nerve paresis. It is generally agreed that the middle fossa approach is indicated only in small laterally placed acoustic neuromas.[18,67,68,158,210]

In a cumulative series[158] serviceable hearing was reported in 32% of cases operated upon by this approach between 1975 and 1990. The facial nerve was preserved in 97% of cases. However, the patients selected for this approach had small intracanalicular tumours.

The prerequisites for hearing conservation in the middle fossa approach include:

- Speech discrimination score of greater than 50%, with a speech reception threshold of less than 50 db
- Presence of an intracanalicular tumour

The average operative mortality in this procedure is 0.8% which is significantly less than the other approaches to these tumours.

The Translabyrinthine Approach

In 1904, Panse first suggested the use of the translabyrinthine approach. In 1911, Quix removed subtotally a small tumour via this route, but the patient died 6 weeks later. House reintroduced this approach[97] when he found that he was unable to remove large tumours completely via the middle fossa approach.

The advantages of this approach are:

- Short distance between the surface and the tumour
- Absence of significant cerebellar and brainstem retraction
- Access to the anterior surface of the brainstem
- Early identification of the facial nerve
- Ability to repair the facial nerve during the primary procedure itself
- Easy access to the operative site for the management of post-operative complications

The disadvantages of the approach are:

- Total deafness on the operated side
- Reduced exposure of the tumour
- Increased incidence of post-operative CSF leaks.

Samii and Draf[210] are of the opinion that tumours that impinge on the brainstem should not be approached by this route as it does not give an adequate exposure of the vessels between the brainstem and tumour capsule. Others feel that the size of the tumour is not a limitation for use of this approach.[19,40,255] This approach would be indicated for tumours where there is no chance of post-operative serviceable hearing. For larger tumours better exposure may be obtained either by more bone removal posterior to the sigmoid sinus[19] or by dividing the tentorium and then sacrificing the superior petrosal sinus (and the sigmoid sinus, if necessary).[40]

Contraindications for this approach are:

- Middle ear infection
- A perforation of the tympanic membrane should be ruled out before surgery
- In patients with externalised mastoid cavities, obliteration with closure of the external auditory canal should be carried out before surgery.

Complications which are seen in this approach include:

- Vascular injury: The most important and potentially fatal injury is one to the AICA. The possibility of damage to the sigmoid sinus and the jugular bulb during the drilling of bone should be borne in mind
- Injury to the facial nerve with loss of continuity is not uncommon. Direct repair or use of an interposition cable graft at the same sitting is the treatment of choice
- Haematoma in the operative bed is a serious complication. Evacuation can be performed at the bedside, if necessary, when this approach is used
- CSF leak is the most common complication with this approach and may lead to meningitis.

The Retromastoid Suboccipital Approach

In 1903, Woolsey performed a unilateral suboccipital craniectomy in one stage; one year later, as Cohen reports, Fraenkel described the technique in great detail. It was, however, Krause who became most closely associated with the suboccipital procedure, after performing a successful unilateral osteoplastic operation in two stages in 1905.[33,39,111,121,145,174,282] This approach is the most commonly used by neurosurgeons and is the recommended approach.

The advantages of the suboccipital approach include:

- Good exposure of the tumour
- Direct visualisation of the major vessels in the cerebellopontine angle
- Possibility of preserving facial and cochlear nerve function
- Familiarity among neurosurgeons

The disadvantages of the approach include:

- Incomplete exposure of the contents of the IAC
- Risks associated with an intracranial procedure.

The Retrolabyrinthine Approach

This approach was first described by Hitselberger and Pulec,[93] in 1972, and was popularised by Silverstein and Norrell.[240] The concept of the procedure is to allow exposure of the CPA anterior to the sigmoid sinus, thus reducing the necessity of cerebellar retraction. Though used mainly for sectioning the sensory root of the trigeminal or the vestibular nerves, it has also been used occasionally for the removal of small acoustic neuromas in cases where it was desirable to preserve hearing. While the major advantage of the procedure is the exposure of the CPA without significant cerebellar retraction and without sacrifice of hearing, the limitation is the limited exposure available when the mastoid air space is small.[242]

The Transcanal Approach

This approach, described by Silverstein, in 1977,[242] exposes the IAC through the external auditory canal using a post-auricular incision. Silverstein felt that this approach helped the otologic surgeons to detect very small acoustic neuromas that may otherwise not be identified. The major disadvantages are the very limited operating space, risk of damage to the facial nerve and the possibility of CSF leak and meningitis.

The Suboccipital Translabyrinthine Approach

Trying to overcome the disadvantages of both the suboccipital and the translabyrinthine approaches, efforts to combine the two were finally successful through the work of Maddox[146] and of Gardner et al.[69] By being able to work on both sides of the sigmoid sinus, the surgeon gets a wider operative field and better control of the anterior and posterior extents of the exposure.

The Subtemporal Transtentorial Approach

The ease with which trigeminal neurofibromas were removed through the subtemporal transtentorial approach encouraged Banerji et al.[4] utilise the approach in large acoustic neuromas. It is an intradural subtemporal approach, and sectioning of the tentorium 1 cm behind the petrosal sinus brings the tumour into view. There is no need for cerebellar retraction. However, there is a risk of temporal lobe injury due to retraction and small tumours which are mainly intracanalicular cannot be reached via this approach. This approach is also not suitable if the tumour extends more inferiorly than superiorly. Large series with results of this approach are not available. The authors of this paper themselves abandoned this approach in favour of the retromastoid suboccipital approach.

Endoscopy

The field of endoscopy has evolved from earlier "endoscope-assisted microsurgery" to complete endoscopic tumour removal.

The adjunctive use of endoscopy offers some advantages including improved visualisation, more complete tumour removal, and a lowered risk of CSF leakage.[119,270]

However, it did not appear to increase the hearing preservation rate.[76] Kabil et al.[112] reported their experience with 112 consecutive cases with unilateral, *de novo* acoustic schwannomas with the tumour size ranging from 0.6–5.7 cm (most tumours were less than 3 cm in diameter and had a mean of 2.6 cm). Tumours were removed via 1.5 cm "keyhole" retrosigmoid craniotomies. Utilising the fully endoscopic technique, 106 out of 112 (95%) tumours were completely removed; subtotal removal was performed in 6 out of 112 (5%) patients in an attempt to preserve their hearing. Anatomic preservation of the facial nerve was achieved in all of the patients and of the cochlear nerve in 83 out of 101 (82%) hearing ears. Functionally measurable hearing (serviceable/some) was preserved in 59/101 (58%) cases who had either "serviceable" or "some" hearing pre-operatively; two patients who had "some" hearing pre-operatively had an improvement that was more than 30 db in their hearing post-operatively. There were no major neurological complications such as quadriparesis, hemiparesis, bacterial or aseptic meningitis, lower cranial nerve deficits or deaths. Endoscopic or endoscope assisted removal of acoustic schwannomas seems to be a technically feasible, effective and safe procedure; however, good equipment and special training are absolutely necessary for attainment of optimal results.[94]

Post-Operative Complications

The incidence of post-operative complications depends on numerous variables including the size of the tumour and the clinical condition of the patient, the approach used and the experience of the anaesthetic and surgical teams. The complications seen include the following:

Mortality: With the use of microsurgical techniques in acoustic neuroma surgery, peri-operative mortality varies between 0% and 3%.[10,51,173,194,216,224,243,250,255,282] Even in India where most tumours are between 2 cm and 4 cm or more in size when first seen, with microsurgical techniques the mortality is about 1% for small tumours and about 4% for large tumours. The causes of death vary and are related to the size of the tumour,[250] thrombosis of the AICA,10 post-operative haematomas[173,207,255] and respiratory and cardiac problems.[10,255]

Haematoma: Haematomas in the tumour bed, in the immediate post-operative period, are a devastating complication. It is best, therefore, to confirm haemostasis at the end of surgery by raising the systolic pressure to rule out arterial bleeding and to perform a few Valsalva manoeuvres to confirm venous haemostasis. If the patient does not recover as expected from the anaesthesia or if the patient deteriorates in conscious level a few hours into the post-operative period, a haematoma must be suspected. If the facility for an immediate CT scan exists, it should be obtained. However, if this cannot be done or if the deterioration is rapid, re-exploration may be lifesaving. Where the translabyrinthine approach is used, drainage of the haematoma may be done at the bedside, if necessary.

A similar clinical picture may be seen with subdural or epidural haematomas. These may develop either in the posterior fossa or in the supratentorial compartment, but the deterioration in neurological status is usually slower than with traumatic haematomas. Thomsen et al.,[255] found haematomas in the tumour bed requiring evacuation in five patients out of a series of 300 operations performed via the translabyrinthine approach. Ojemann[173] had four patients with post-operative haematomas out of his series of 410 patients with unilateral neuromas. Of these, two were haematomas in the cerebellum and two extradural haematomas. Ebersold et al.[51] had only two patients with a haematoma amongst their series of 256 procedures via the retrosigmoid approach.

Post-operative deterioration in sensorium can also be caused by a supratentorial subdural haematoma, due to the sudden decompression and rupture of bridging veins, especially when the ventricles are large pre-operatively. Rarely, a supratentorial extradural haematoma may be caused by penetration during pin fixation.[15]

Pneumocephalus: Tension pneumocephalus is a complication which occurs when the surgery is performed in the sitting position, though it may rarely occur even after surgery in the lateral position. During a posterior fossa procedure the air enters the intracranial space in the same way it enters an inverted bottle of water.[142,144] Symptoms arise soon after surgery, usually within a few hours, and it is specially seen after the resection of a large tumour or draining a significant amount of CSF rapidly. Nitrous oxide when used in anaesthesia diffuses out of the blood vessels into the contiguous air-filled space and potentiates the effects of the pneumocephalus.[259] If the amount of air, assessed by plain X-rays of the skull or by a CT scan is thought to be significant it can be evacuated via a frontal twist drill hole through a water seal. As this is an easily treatable complication, early recognition is important.

Hydrocephalus may become acutely symptomatic in the post-operative period, with a presentation that is difficult to differentiate from intracranial haematomas. If the CT scan confirms this, the problem may temporarily be managed with a ventriculostomy. If hydrocephalus persists a CSF diversion procedure may be performed.

Cranial neuropathies: A common sequel of total extirpation of an acoustic neuroma is injury to the facial nerve.[217] The larger the tumour, the less are the chances of saving the nerve. Facial palsy is disfiguring and disconcerts the patient to no small extent. Dryness of the cornea may be a distressing sequel of minor facial nerve trauma. In the early years it was accepted as an inevitable sequel of total removal. Rand and Kurze[197] described the transmeatal approach using microsurgical techniques and emphasised preservation of the facial nerve. The use of these refinements and the different operative approaches has achieved an overall facial nerve preservation rate of 82.5%.[158] However, anatomical preservation does not imply a good functional outcome.

Where anatomical continuity of the nerve is preserved, the patients are followed up with physiotherapy to watch for improvement in function. Ebersold et al.[51] are of the opinion that the operating team can, by comparing the amplitude of the proximal compound

muscle action potential with that obtained by stimulation of the facial nerve in the distal IAC, predict the degree of initial facial weakness and the long-term result. Electroneurography may be helpful in deciding on the possibility of post-operative recovery of function. Incomplete degeneration is a good predictor of early recovery and carries a good prognosis. Though regeneration provides good recovery, it is rarely perfect.[275] Patients with Wallerian degeneration have a worse prognosis than those with a neuropraxia.[66]

When the facial nerve is cut at surgery, either intentionally or otherwise, there are several choices for repair.[214,220] The continuity of the nerve can be restored during surgery by primary suturing or by gluing the severed ends. If necessary, a cable graft may be used to bridge the gap between the ends of the nerve. Intraoperative suturing seems to be an effective procedure. End-to-end suturing produces a satisfactory result (some facial tone and movement) in 88% of cases, while the use of an interposition graft produces up to 78% satisfactory results.[104] Patients with partial facial nerve injury may be treated using an end-to-side graft without additional risk for the remaining functional fibres from the donor and recipient nerve.[11,56,168,212] Intra-operative restoration usually results in moderate facial symmetry and movement. Typically, the facial appearance is better at rest.

Dott, in 1958, described an intracranial-extracranial graft, suturing one end of the graft to the central stump and the other end to the distal facial nerve beyond the stylomastoid foramen. Using the translabyrinthine approach, the distal anastomosis is performed by mobilising the facial nerve in the Fallopian canal. This procedure may be performed at the end of the operation when the distal stump is found to be inadequate intracranially. Some surgeons prefer this to intracranial grafting or suture.[123,221]

If the proximal stump of the facial nerve is not adequate, procedures to reanimate the facial muscles may be undertaken. These include peripheral nerve procedures (e.g. cross facial nerve grafting, nerve transfers), dynamic muscle reconstruction procedures (e.g. local and distant muscle transfers) and static procedures (e.g. canthoplasty, facial and dermal slings).[134]

The first surgical attempt to treat facial paralysis was performed by Drobnick, in 1879, by anastomosing the spinal accessory nerve to the facial nerve. The first published report of this procedure was by Sir Charles Ballance, in 1895. The first hypoglossal nerve-facial nerve anastomosis was performed by Korte, in 1901. The cross-facial nerve graft anastomosis uses the contralateral facial nerve with interposition grafts between the two nerves. Many authors found the results unsatisfactory.[31,34,260,289] Venkataswamy and Venkataramakrishnan[269] found better results than obtained from faciohypoglossal anastamoses. Nerve transfers or donor nerve techniques tend to have functional results similar to primary anastomosis or nerve grafting.[185] The nerves used for anastomosis include the hypoglossal nerve, the spinal accessory nerve, the phrenic nerve and the glossopharyngeal nerve.

The hypoglossal-facial nerve anastomosis is the most often used technique. Pitty and Tator,[185] found good and fair results following this procedure in 77.2% of cases and a failure in only one patient. The results were better in younger patients and when the anastomosis was performed early.

The trigeminal nerve is usually in contact with even medium-sized tumours, and is stretched by large masses. Post-operative dysfunction of this nerve may result in impaired sensation over the ipsilateral half of the face and masticatory problems, but the real problem is decreased corneal sensation with the risk of developing exposure keratitis and ulceration, especially with a simultaneous facial paresis. This can be conservatively managed with protection of the eye with spectacles, moisturising drops or artificial tears during the day and ointment at night, as long as improvement of facial function is expected. If no return of facial function is anticipated, a lateral tarsorrhaphy should be done, especially if the impaired sensation also persists. In most cases, trigeminal function returns within a few months, in which case the palpebral fissure should be reconstituted. Thomsen et al.,[255] found reduced trigeminal function in only 4% of patients post-operatively, though in only two patients it could be related to the surgery.

Impaired function of the glossopharyngeal and vagus nerves may be seen after excision of large tumours, with resultant difficulty in swallowing, nasal regurgitation and risk of aspiration pneumonitis. As a rule, oral feeds should not be attempted in a patient after excision of a large tumour, unless the gag reflex is checked, and even then the first feed is preferably given under supervision. The paresis is usually transient and feeding may be done through a nasogastric tube until recovery. Damage to other nerves such as the trochlear and abducens is rare.[255]

Cerebellar dysfunction: Signs of cerebellar dysfunction are seen in cases where marked retraction of the cerebellum is necessary when dealing with large tumours. The resultant cerebellar contusion or haematoma and swelling may at times result in mass effect, requiring emergency repeat surgery. Severe and prolonged cerebellar dysfunction may also result from undue traction and contusion of the cerebellar peduncles.

Brainstem: Damage to the pons is the leading cause of mortality in acoustic neuroma surgery. This can occur due to damage to the AICA, which can result in varying degrees of brainstem infarction as well as infarction and swelling of the cerebellum.[207] The brainstem may be damaged during dissection of the capsule of a large tumour off the pons. In these cases, the capsule usually has small vessels entering it from the brainstem. These must be recognised, coagulated and cut, rather than separated by blunt dissection, when they may retract into the parenchyma and form haematomas. The incidence of the complication has decreased steadily and is now rare.[10,255]

Infection: The occurrence of infection is a reflexion on the sterile precautions in the unit. It can be pyogenic meningitis or wound infection, urinary infection due to catheterisation, or chest infection in patients with lower cranial nerve paresis. The fever in post-operative

meningitis generally begins around the 4th day after surgery, earlier rise in temperature and meningism usually being due to spilled blood in the subarachnoid space. It is preferable to do a CT scan to rule out an unsuspected haematoma in the tumour bed or the cerebellum, or cerebellar swelling, before doing a lumbar puncture. If the CSF analysis is suggestive of pyogenic meningitis and the smear is non-contributory, empirical antibiotics based on the known sensitivity patterns of the institution should be started pending the culture report.

CSF leak can occur from the wound, or can be in the form of otorrhoea or paradoxical rhinorrhoea. This is the single most common complication, other than VII nerve dysfunction with the translabyrinthine or suboccipital-transmeatal approaches. Symon et al.[250] found that CSF leak was the only complication which increased in occurrence from 2.4% in the 1950s to 18.7% in the 1980s. They felt that the reason for this was the increased zeal with which the tumour was attacked in the IAM and the porus drilled. Prevention consists mainly in ensuring a water tight dural closure, either primarily or with a graft, and of thoroughly occluding any opened mastoid air cells with bone wax, free fat, muscle, fibrin glue, etc. Once the leak via the air cells occurs, a lumbar subarachnoid drain may be placed and CSF drained for 3–4 days to enable the leak to seal off. If this does not work, the wound has to be reopened and the site of the leak repacked. A wound leak rarely settles with resuturing of the skin and usually requires definitive reclosure of the entire wound. It may be precipitated or aggravated by the raised pressure of hydrocephalus or meningitis. Leak through the wound should therefore be tackled initially with lumbar drainage of CSF and the treatment of infection if any.

Results

Results of surgery via the suboccipital approach are excellent.[10,51,80,105,154,173,250,286] Cumulative data from operative series between 1975 and 1990[158] using the suboccipital approach shows an operative mortality of 2%, with total tumour removal in 95% of cases. The VII nerve was preserved in 72.8% of cases. The VIII nerve was preserved in 40.6% of cases, though hearing and serviceable hearing was preserved only in 15.7% and 14.7% of cases.

Samii et al.[211,216] in their paper on 1,000 acoustic schwannomas operated upon through the suboccipital transmeatal approach, reported complete tumour removal in 979 tumours. Anatomic preservation of the facial nerve was achieved in 93% of cases and cochlear nerve in 68% of cases. Major neurological complications included one case of tetraparesis, 10 cases of hemiparesis and caudal cranial nerve palsies in 5.5% of the cases. Surgical complications included hematomas in 2.2% of the cases, CSF fistulas in 9.2%, hydrocephalus in 2.3%, bacterial meningitis in 1.2% and wound revisions in 1.1% of cases. There were 11 deaths between the 2nd day and 69th day post-operatively (1.1%). In their recent report on 200 patients, the facial nerve was anatomically preserved in all patients, the cochlear nerve in 84% of patients, and there was no mortality. The authors concluded that the goal of acoustic schwannoma treatment should be total removal in one stage and preservation of neurological function, as they determine a patient's QOL and that this goal can be safely and successfully achieved using the retrosigmoid approach.

Jain et al.[105] in 2005 reported a series of 259 cases from India, where most patients had large tumours. About 90% had no useful hearing, 88% had disabling cerebellar ataxia and 45% presented with features of raised ICP. The tumours were large in 41.3% and in 56% they were giant sized. Complete tumour excision was carried out in 96.5% of cases and anatomical preservation of facial nerve was achieved in 79.2% of cases. Hearing preservation was achieved in eight patients. CSF leak with or without meningitis and transient lower cranial nerve paresis were common complications. The mortality was 6%.

Misra[154] has reported his results in the last 100 consecutive cases operated upon by him. About 86% were large tumours and total excision was achieved in 88% of cases. The facial nerve was preserved in 94% and was grade III or better in 88% of cases. There was no mortality.

Between the years 1975 and 1990, 1356 cases of acoustic neuroma were operated on by the translabyrinthine approach.[158] The cumulative data on these patients show an operative mortality of 1.7%, with a 96.8% rate of total tumour removal. The facial nerve was preserved in 75% of cases. Reporting on 216 patients operated upon between 1980 and 1991 by this approach, Brackmann19 had only one death (0.4%) and normal facial nerve function in 83% of the cases one year after surgery. There is a definite correlation between tumour size and the preservation of facial nerve function.[19,40]

Lanman et al. have reported on 190 consecutive cases of large acoustic schwannomas (3 cm or greater) removed via the translabyrinthine approach. Total tumour removal was accomplished in 183 cases (96.3%) and the facial nerve was preserved anatomically in 178 cases (93.7%). They concluded that use of the translabyrinthine approach for removal of large tumours, where hearing preservation is not an issue, resulted in good anatomical and functional preservation of the facial nerve with minimum morbidity and no mortality.[130]

The choice of the operative approach to acoustic neuromas is, therefore, dependent on the size and position of the tumour and the possibility of hearing preservation. For small tumours placed laterally in the IAC, the middle fossa approach is the procedure of choice. In medium or large sized tumours both the suboccipital approach and the translabyrinthine approach are equally effective. If, however, hearing preservation is to be attempted, then the suboccipital approach is to be chosen. Neurosurgeons generally prefer the suboccipital route, while otologists prefer the translabyrinthine approach.

Facial Nerve Preservation

The first report of facial nerve preservation was by Cairns, in 1931.[22] Olivecrona, McKissock and House further advocated the importance of facial nerve

preservation. Gardner and Robertson[70] saved the facial nerve anatomically in 85% of their series of 144 patients. However, 47% of patients showed a complete facial palsy at some time after surgery. Bentivoglio et al.,[10] found that only 32.1% of patients with anatomically preserved facial nerves had normal facial function at the end of 1 year. Grading of facial nerve function has been done variously[10,95] and is used to assess the function on follow-up. The results of facial nerve preservation correlate closely with tumour size.[43,45,85,173,250,283] House and Brackmann[95] devised a grading system to evaluate facial nerve function and this is now used universally (Table 3).[11] The cumulative data collected on reported operative series[158] between 1975 and 1990 shows overall 82.5% facial nerve preservation. When considering each operative approach individually, the facial nerve was preserved most (97.6%) when the middle fossa approach was used. This could be expected as these tumours were very small and mainly intracanalicular. The facial nerve was preserved in 72.8% of patients where the suboccipital approach was used and in 74.9% when the translabyrinthine approach was used. However, the prevalence of normal facial function following removal of acoustic neuromas ranges between 43% and 89%.[10,50,84,104,250,255] In medium and large sized tumours, it may not be possible to dissect the tumour capsule off the facial nerve, which is often very attenuated. Cerullo et al.,[23] however, reported normal facial function in 90% of patients with tumours between 2.5 cm and 4 cm in size and 64% of patients with tumours more than 4 cm in size. The use of facial nerve monitoring[262,281] and/or the use of microstimulators[232] may be useful to locate and delineate the nerve in these circumstances. The decision often is whether to remove the tumour completely dividing the nerve or, whether to leave a small piece of capsule with the nerve.

Anatomical continuity of the nerve, however, does not imply good functional outcome. The status of facial nerve function should be assessed periodically as what appears as reasonably good in the immediate post-operative period may worsen even to a complete paralysis within 48 hours post-operative.[194] The speed of recovery of facial nerve function is variable.[85] It is, therefore, important that patients with a paralysed face have either a tarsorrhaphy or some other procedure to protect the eye.

A retrospective analysis of 611 patients surgically treated for acoustic neuroma between 1973 and 1994 at the Johns Hopkins Hospital has been reported. Anatomical preservation of the facial nerve was achieved in 596 patients (97.5%). In the immediate post-operative period, 62.1% of patients displayed normal or near-normal facial nerve function (House-Brackmann Grade 1 or 2). This number rose to 85.3% at 6 months after surgery, and by 1 year 89.7% of patients who had undergone acoustic neuroma surgery demonstrated normal or near-normal facial nerve function. The surgical approach appeared to have no effect on the incidence of facial nerve injury. Poor facial nerve outcome (House-Brackmann Grade 5 or 6) was seen in 1.58% of patients

Table 3: Clinical grading of facial nerve function by House and Brackmann

Grade	*Description*	*Detailed description*
1	Normal	Normal facial function in all areas
2	Mild dysfunction	• Gross: slight weakness noticeable on close inspection; may have very slight synkinesis • At rest: normal symmetry and tone • Motion: – Forehead: slight to moderate movement – Eye: complete closure with effort – Mouth: slight asymmetry
3	Moderate dysfunction	• Gross: obvious but not disfiguring asymmetry; noticeable but not severe synkinesis • Motion: – Forehead: slight to moderate movement – Eye: complete closure with effort – Mouth: slightly weak with maximal effort
4	Moderate to severe dysfunction	• Gross: obvious weakness and/or asymmetry • Motion: – Forehead: note – Eye: incomplete closure – Mouth: asymmetry with maximum effort
5	Severe dysfunction	• Gross: only barely perceptible motion • At rest: asymmetry • Motion: – Forehead: none – Eye: incomplete closure
6	Total paralysis	No movement

treated via the suboccipital approach and in 2.6% of patients treated via the translabyrinthine approach.[222] When facial nerve outcome was examined with respect to tumour size, there clearly was an increased incidence of facial nerve palsy[20,111,211,244,277] seen in the immediate post-operative period in cases of larger tumours; about 60.8% of patients with tumours smaller than 2.5 cm had normal facial nerve function, whereas only 37.5% of patients with tumours larger than 4 cm had normal function.[222]

Facial nerve weakness that is evident immediately after acoustic neuroma surgery is caused by a number of possible mechanisms. A thorough understanding of these can help minimise intra-operative facial nerve injury.[116] The most common cause of post-operative facial nerve palsy is direct trauma or nerve stretching during surgery. Theoretically, both neuropraxia and axonotmesis are reversible phenomena and facial nerve function should fully return. Not surprisingly, very large tumours place the nerve under greater tension, which increases the likelihood of stretch injury and may explain the high rate of facial palsy seen in patients with tumours larger than 4 cm. Alternatively nerve dysfunction may result from devascularisation of nerve segments that are effaced by large tumours. Measures can be taken to minimise trauma to the facial nerve during surgery. First, the ability to compress and retract the tumour capsule rather than the nerve by debulking the tumour prior to nerve dissection is of major importance, particularly in cases of large tumours. Second, excessive pressure on the facial nerve should be avoided. Cotton and microsuction devices should be used at all times. Sharp dissection should be used until a clear dissection plane is established to avoid unnecessary stretch injury. Third, it is important to avoid excessive cerebellar retraction to minimise the tension placed on the facial nerve. Finally, it is essential that dissection proceed from known to unknown structures. If hearing preservation is not a consideration, early identification of the facial nerve near the lamina spiralis allows better appreciation of its relationship with the tumour.[211,222]

Another common mechanism of facial nerve injury is compromise of the vascular supply to the facial nerve. The facial nerve is supplied by three separate vascular systems:

- The labyrinthine artery of the AICA
- The greater superficial petrosal branch of the middle meningeal artery
- The stylomastoid artery of the external carotid system.

Maintaining the blood supply to the facial nerve is critical if post-operative palsy is to be avoided. The surgeon must be careful to avoid inadvertent vascular injury. Bipolar cautery should be used cautiously; when possible, blunt dissection should be used near all vascular structures. Topical administration of papaverine after tumour resection can also aid in preventing vasospasm.[222] Because most of the microvascular blood supply to the facial nerve is in the subarachnoid space, it is essential that dissection proceed in the correct plane between the tumour capsule and the underlying arachnoid. Overly aggressive dissection of the tumour capsule from the facial nerve may strip the facial nerve of its vital microvascular supply and lead to post-operative nerve dysfunction.[211,222]

Thermal injury can also cause temporary facial nerve palsy or paralysis. Overly cold irrigation may "stun" the nerve and is avoidable with use of warmed saline solutions. This phenomenon is usually transient, but occasionally it may lead to local vasoconstriction and cause secondary ischaemic injury to the nerve. Thermal injury can be more permanent if the laser is used for tumour extirpation. Both potassium-titanyl-phosphate and CO_2 lasers have become increasingly popular in recent years, especially for use in treating vascular tumours.[69,74] Laser vaporisation can be quite helpful in devascularising tumour remnants to prevent recurrence, but it should be used with great caution near the facial nerve. Cool intermittent irrigation and continuous suction of the laser plume can help minimise thermal injury.

If the facial nerve is inadvertently transected during surgery, restoration of facial nerve function becomes much more problematic. Facial nerve disruption generally leads to poor outcome even with apparently satisfactory immediate repair. Close follow-up review is necessary for these patients and facial nerve reanimation (either XII-VII or XI-VII cranial nerve anastomosis) if there is no evidence of recovery by 12 months post-operatively. After 1 year, facial nerve function with reanimation surgery is much less predictable.[211,222]

An aberrant course with distinct splitting of the facial nerve has been reported[248] and adds considerably to the surgical challenge. Use of neurophysiological monitoring allows the differentiation and identification of the aberrant facial nerve fibres, thus avoiding additional risks to facial nerve preservation.

Hearing Preservation

Elliott and McKissock reported, in 1954, the first case of hearing preservation following the surgical removal of an acoustic neuroma.[55] In 1960, House was able to preserve hearing in small intracanalicular tumours using the middle cranial fossa approach.[98] In 1988, Gardner and Robertson found 221 instances of hearing preservation in 621 operated cases.[71] In 1993, Glasscock et al.[73] reviewed 28 pertinent series since 1980, but found it impossible to correlate the results due to lack of uniformity in the series and the lack of information. There is a controversy whether preservation of hearing is a reasonable objective in acoustic neuroma surgery. While some surgeons attempt to preserve hearing in all patients who have pre-operative hearing preserved,[24,58,62,106,219] other surgeons believe that hearing loss is the sequel least important to the patient.[150,162,255,258,257] An attempt at hearing preservation may result in the compromise of gross total removal of the tumour and a subsequent increased risk of recurrence and post-operative morbidity and mortality.

There is no agreement between neurosurgeons and neuro-otologists as to what constitutes "serviceable hearing".[73] However, the most commonly used criteria are a speech reception threshold of less than 50 db and

a speech discrimination score of more than 50%.[71,241,274] Ojemann[170,173,175] uses a speech discrimination score of 35% or more, while Whittaker and Luetje[274] use a score of 70% or more.

The idea to preserve hearing in patients with a unilateral acoustic neuroma is to provide binaural hearing. This enables the individual to perceive stereophonic sound, allows him or her to localise the sound and to suppress background noise. In individuals with good hearing in one ear and a flat loss of 20 db or more in the other, these functions are lost.[73,83] These patients experience a significant range of auditory disabilities. It is important that clinicians be aware of the impact of such a profound unilateral hearing loss and its potential to affect daily life. Patient counselling prior to surgery is essential especially in patients whose loss of binaural hearing could constitute a major disability.[48,215]

Hearing preservation will, therefore, be useful only to those patients in whom the hearing can be aided with a hearing aid. An aidable ear is one that has a pure tone audiometry average of at least 70 db and a speech discrimination score of 70% with a normal dynamic range.

The suboccipital approach and the middle cranial fossa approach are used in hearing preservation surgery. Intra-operative monitoring is extremely useful when hearing preservation is attempted. Brainstem auditory evoked potential (BAEP) and electrocochleography, when used together, monitor the entire auditory system.[173] The BAEP has a slower feedback and in practice only wave V is monitored, as the other potentials are quite small and may be undetectable. Electrocochleography monitors the status of the cochlea and the auditory nerves peripheral to the tumour and provides a rapid feedback of the compound action potential of the auditory nerve and cochlear microphonic potentials generated by the hair cells. The use of monitoring is to indicate early hearing compromise, so that the dissection may be altered. The usefulness of monitoring has been documented by many surgeons,[73,173,227] though some have found it to be of little help.[30]

In intracanalicular tumours which extend for less than 0.5 cm into the posterior fossa with at least 35% speech discrimination score, there is a 60% chance of preservation of hearing at the pre-operative level. This becomes 36% if the tumour size increases to 0.6–1.5 cm. The chances of saving hearing in tumours which are 2 cm or more in size are poor,[73,173] though there are occasional reports of hearing preservation in large tumours too.[23,172] Yokoh et al.,[286] feel that a cystic tumour gives a better chance at hearing preservation than a solid one.

A syndrome of delayed post-operative hearing loss has been described,[179,246,247,284] where patients who have initial hearing preservation gradually lose hearing in the post-operative period. The cause of this deterioration is not known. It is postulated that the post-operative deterioration may be due to a combination of the effects of cerebellar retraction,[231,234,235] disturbances in the microcirculation in the vasa nervorum during mechanical manipulation of the cochlear nerve, or an increased permeability of the endoneural vessels after mechanical compression trauma.[205,206] The patients in whom this deterioration is found may be identified intra-operatively as those who show a gradual deterioration of the BAEP, especially involving the amplitude of wave V.[246] Intermediate delayed post-operative hearing loss may be seen occasionally.[75,233] The factors involved in causing this phenomenon may be similar to those causing progressive deterioration in the immediate post-operative period. Other factors may include progressive scarring in the IAC with constriction of the cochlear nerve or the microvasculature secondary to the placement of muscle bits in the canal at the end of tumour removal.[75] Sekiya et al.[233] feel that in some of these cases there may be a false positive BAEP wave I recording even with axonotmesis of the cochlear nerve. The BAEP then shows gradual deterioration over days or weeks.

The long-term results of hearing preservation are varied. Shelton et al.[239] reported a significant loss of hearing in 56% of patients operated upon by the middle fossa approach over a period of 8 years. Others[179,202] did not find a significant decline in hearing. Good rates of hearing preservation have been reported by different groups of investigators using the middle fossa approach: 52%,[101] 57%,[244] 58%,[47] 59%,[17] 60%[285] and even 100%.[20] However, with increasing tumour size, the rate of preservation lowers. In the study by Yates and his colleagues[285] the rate decreased from 72 to 34% if the tumour extended more than 1 cm into the CPA. Although some authors have stated that the rate of preservation is lower with the retrosigmoid approach, if one compares only tumours of equal size, the results of different approaches are similar.[101]

The possibility of recurrence of tumour in cases where hearing has been preserved has been discussed in the literature. Neely,[162,163] reporting on patients whose tumour was removed "totally" and hearing was conserved, found residual tumour on the cochlear nerve and suggested that "total" surgical removal of the tumour and conservation of hearing may not be compatible. However, Samii et al.[213] and Ojemann[173] have found no recurrences on follow-up in their series.

Though a detailed discussion has been given here about the possibilities of preserving facial and hearing function, it must be pointed out that in many developing countries, where large tumours are the rule, preservation of life and the functions of the lower cranial nerves are still the primary goals of treatment in many centres. Enthusiastic young neurosurgeons have still to operate against odds. While they are striving to improve their facilities and results, they should not be discouraged by the good results of facial function preservation and hearing preservation reported from many sophisticated centres, which have all the necessary facilities and whereas a rule smaller tumours are encountered. In large tumours, where facial function preservation may only be about 30% in spite of best efforts, facio-hypoglossal anastamosis offers the best chance of avoiding facial disfiguration.

In this context, it is worth looking at the evaluation of our results by patients who have undergone surgery for acoustic neurinomas. Weigand and Fickel[276] in 1989, presenting the patients' perspective reported by 541

patients, found deafness in 93% of patients, transient or permanent facial weakness in 80% and post-operative eye problems in 88.5% of patients.[194,196] If meticulous microsurgical excision, aiming at total removal, cannot preserve facial function and prevent eye problems, it is better perhaps in those cases to do subtotal excision leaving the nerves intact. The post-operative life will be more bearable and pleasant in spite of the possibility of a second surgery.

Radiosurgery

Despite major advances in skull base surgery and microsurgical techniques, surgery for acoustic schwannoma carries a risk of complications. Some are inherent to general anaesthesia and surgery of any type and include myocardial infarction, pneumonia, pulmonary embolism and infection. Some are specific to neurosurgery in this area of the brain, and include hydrocephalus, CSF leak, facial nerve paralysis, facial numbness, hearing loss, ataxia, dysphagia and major stroke. Even in the hands of very experienced acoustic surgeons, these risks cannot be eliminated. Radiosurgery provides an outpatient, non-invasive alternative for the treatment of small acoustic schwannomas. Initially radiosurgery was undertaken in "high-risk" patients including the elderly, those with severe medical comorbidities and those in whom tumour recurred after surgery. Additionally, a high rate of cranial nerve morbidity was reported. With improvements in dosimetry planning and dose selection, however, authors practicing at radiosurgical centres now report very low complication rates as well as high tumour control rates.[65]

Radiosurgery is well suited for acoustic neuromas as it is typically well demarcated from surrounding tissues on neuroimaging studies. The sharp borders of this non-invasive tumour makes it a convenient match for the characteristically steep dose gradient produced at the boundary of a radiosurgical target, allowing the radiosurgeon to minimise the radiation affecting the normal tissue.[64,127,201,271] Excellent spatial resolution on gadolinium-enhanced MR images facilitates radiosurgical dose planning. Certainly, the role of radiosurgery is limited by its inability to expeditiously relieve mass effect in patients for whom this is necessary. The radiobiological nature of SRS also requires lower, potentially less effective doses for higher target volumes to avoid complications. This limits the use of SRS to the treatment of smaller tumours.[59,186]

Reporting on their early experience, Linskey et al.,[135,136] found tumour size decreased in 58% of patients and was unchanged in 42% of patients. On the other hand, Lunsford et al.,[141] found the 4-year actuarial tumour control rate (prevention of tumour growth or reduction of tumour size) to be 89% ± 6%. The mean time until tumour shrinkage was 1 year. Post SR imaging studies show a characteristic loss of central contrast enhancement within the tumour, occurring most commonly within 18 months of therapy. This loss of central contrast enhancement has been postulated to be due to radiation induced vascular injury and obliteration. A peritumoural increased T2 signal may appear transiently as may changes in the blood brain barrier with regression in tumour size in the region of the middle cerebellar peduncle. These changes occur more commonly in tumours greater than 15 mm in diameter.

Lunsford et al.,[141] found hearing preservation to be related to tumour size, with 50% of their patients with intracanalicular tumours retaining their pre-operative hearing levels. The actuarial rate for preservation of useful hearing at two years was 34% ± 6%.

The overall risk for the development of delayed facial neuropathy is 29% ± 4% and of trigeminal neuropathy 33% ± 4%. The mean time for developing cranial neuropathy is 5 months. It shows improvement after onset in the majority of patients.

In the University of Florida series[25] of 149 patients treated with linear accelerator (LINAC) radiosurgery between 1988 to 1998, with a median follow-up of 36 months, the overall actuarial incidences of facial and trigeminal neuropathies were 11.8% and 9.5% respectively. In 41 patients treated before 1994, the incidences of facial and trigeminal neuropathies were both 29%, but in the 108 patients treated since January 1994 these rates declined to 5% and 2%, respectively. The overall radiological tumour control rate was 93% (59% of the tumours regressed, 34% remained stable and 7.5% enlarged), and the 5-year actuarial tumour control rate was 87% (95% confidence interval 76–98%). In a recent report from University of Florida,[63 390] patients treated with LINAC from 1988 to 2005 were analysed. When doses were deliberately lowered to 12.50 Gy, only two patients (0.7%) had experienced facial weakness and two (0.7%) experienced facial numbness. Based on the findings, the authors recommended administering a peripheral dose of 12.5 Gy for almost all acoustic lesions, as this dose was most likely to yield long-term tumour control without causing cranial neuropathy.

In 1993, Norén et al.[166] reported on 254 patients who underwent GKS between 1969 and 1991. The minimum tumour dose ranged from 18–20 Gy specified at the 50–90% isodose line. This dose was reduced to 10–15 Gy during the final 3 years of the study. The minimum follow-up duration was 1 year (range 1–17 years). Rates of tumour control (decreased or stable tumour volume evidenced on neuroimaging) were 94% for unilateral tumours and 84% for those associated with NF-II. Delayed facial and trigeminal neuropathies occurred in 17% and 19% of patients, respectively. These were predominantly transient deficits, but severe nerve injuries did occur in both the facial and trigeminal nerves at a rate of 4%. These complication rates had diminished significantly later in the series with the institution of MRI based dose planning and the use of lower radiation doses.[164,165] Reportedly, the rates of facial and trigeminal nerve palsy for most of the 55 patients treated later were 1.8% and 0%, respectively.[167] Of those patients with functional hearing prior to radiosurgery, only 22% had preserved hearing in the overall series. However, in a later analysis of the subset of 44 patients treated between 1991 and 1994, who had functional (Gardner-Robertson Class I or II) hearing prior to treatment, Norén reported the preservation of Class I or II

hearing in 75% of patients after 1 year and 71% after 2 years. He attributed this improvement to better quality imaging and dose-planning accuracy that has resulted in more highly conformal radiation dose delivery.[65] In 2003, Noren reported on 134 patients with unilateral acoustic schwannoma who underwent GKS between 1994 and 2000. The mean marginal dose was 12.6 Gy and the mean maximum dose delivered to the tumour centre was 25.4 Gy (range 17.4–34.3 Gy). The tumour control rate, which was defined as no change or a reduction in size at last follow-up, was 96.7%. Of the patients studied, 97.7% remained free from the need to undergo tumour resection. Overall functional hearing preservation was 61.7%; the preservation rate for intracanalicular tumours was 63.6%, for those with an intracranial diameter less than 1.5 cm it was 54.5%, for those between 1.5 and 3 cm it was 68.2%, and for those larger than 3 cm it was 33.3%. The authors concluded GKS is one of the primary treatment options for patients harbouring tumours 3 cm or smaller in intracranial diameter, regardless of their age and medical condition.[138]

Fractionated Stereotactic Radiotherapy

"Fractionated stereotactic radiotherapy" employs administration of multiple-session treatments by fractionation of radiation dose, in an attempt to reduce complications, especially hearing loss.

Varlotto and his colleagues[267] treated 12 patients with a follow-up period ranging from 16–44 months. Eight patients were treated with primary stereotactic radiotherapy, and four patients were treated after primary surgical intervention for recurrent (three patients) or persistent (one patient) disease. Median tumour volume was 10.1 cm^3. Tumours received 1.8 Gy radiation/day, normalised to the 95% isodose line. Patients received a minimum prescribed dose of 54 Gy in 27–30 fractions during a 6-week period. After a median follow-up of 26.5 months, local control was achieved in all 12 lesions. Tumour regression was noted in three patients, and tumour stabilisation occurred in the remaining nine patients. No new cranial nerve deficits developed in any patient. One patient suffered worsening of pre-existing trigeminal neuropathy, and all nine patients with useful hearing before stereotactic radiotherapy retained useful hearing at the last follow-up.

Williams[278] treated 80 consecutive patients with a prospective schedule permitting increase in fractionation according to lesion size. Seventy patients having VS smaller than 3 cm in diameter received five daily fractions of 5 Gy (total 25 Gy), and 10 patients having an acoustic schwannoma 3 cm or larger received 10 daily fractions of 3 Gy (total 30 Gy). All treatments were prescribed to the 80% isodose line and administered via the dedicated 10 MV accelerator. For both the larger and smaller VSs, the percentage decrease in volume was similar. No tumour increased in size; facial weakness occurred in no patients and hearing was preserved in all patients.

Andrews and his colleagues[1] compared the results in patients treated using GKS with those in patients treated using fractionated radiotherapy. The gamma knife technique involved a fixed-frame, multiple-shot, high-conformality single treatment, whereas the LINAC technique involved daily conventional fraction treatments involving a relocatable frame, fewer isocentres, and lower conformality. Sixty nine patients were treated using the gamma knife, and 56 patients were treated using radiotherapy. Three patients were lost to follow-up; in the remaining 122 patients, the mean follow-up was 119 weeks in those who received SRS and 115 weeks in those who received stereotactic radiotherapy. Tumour control rates were high (97%) for sporadic tumours in both groups. Cranial nerve morbidities were comparably low in both groups, with the exception of functional hearing preservation, which was 2.5-fold higher in patients who had received conventional fractionation. Most recently, Chang and his colleagues[25] reported on 61 patients treated with the cyber knife and followed up for at least 36 months. These patients received either 18 Gy or 21 Gy in three fractions. Only one treated tumour progressed. Among the patients who had serviceable hearing, 74% maintained it. No new trigeminal or facial complications developed.

Long-term outcome studies proving the efficacy of fractionated radiosurgery is awaited, and at present, only SRS administered as a single shot is accepted as one of the primary treatment options for lesions smaller than 3 cm. They are also being increasingly used for residual lesions.[63]

Subtotal Removal and Tumour Recurrence

While the goal of surgery for acoustic neuroma is total excision, it may often be necessary to limit the resection to a subtotal or near total level to prevent post-operative neurological deficit. Radical subtotal removal describes the procedure when an extensive removal is done except for a portion of the capsule left attached to the brainstem or the facial nerve.[173] The reasons for a subtotal removal include adherence of the capsule to the facial nerve or brainstem, vascularity of the tumour, age of the patient and only hearing ear.[155,173,249]

The consequences of leaving small tumour remnants depend on the size of the residual tumour, the growth rate of the tumour and the remaining viable vascularity of the tumour bed.[254] The experience with subtotal removals has been variable, with some authors reporting significant regrowth requiring operation[176,187,254] and yet others[120,173,194,273] following patients over many years without any evidence of growth. Pooling data from three series,[171,189,272] Wallner et al.,[272] found the recurrence rate following radical subtotal excision to be 9% and that following subtotal excision to be 40%. Lownie and Drake[139] reported recurrence in only 2 patients out of 11, two and three years post-operatively.

However, with recent reports clearly showing higher recurrence rates, planned subtotal removal should be reserved for a few selected cases. Near-total resection should be the aim in any patient if needed to preserve neural integrity. Adjunctive treatment with stereotactic radiotherapy may be considered in cases where near total excision is not possible.[13,61,103,182,223]

CYSTIC VESTIBULAR SCHWANNOMA

The incidence of cyst formation in acoustic schwannomas ranges from 4 to 48%.[8] Cystic acoustic schwannomas are believed to be associated with sudden expansion,[28,131] shorter symptom duration,[8,113] atypical initial symptoms (such as dysgeusia, vertigo, facial pain and unsteadiness)[113] and an increased rate of pre-operative facial palsy.[28,113,152] This type of acoustic schwannoma rarely demonstrates enlargement of the IAC in neuroimaging findings despite increased tumour size (Figs 9A to C, 10A and B).[113]

The observation that the rate of cell proliferation, expressed as the number of Ki 67–positive nuclei, was lower in cystic than in solid acoustic schwannomas indicates that the increase in volume is caused by cyst formation and not by genuine tumour growth.[26]

It is known that the cystic portion of acoustic schwannomas is located in the Antoni type B area, which is softer than the type A area.[26,159] In the studies by Charabi and his colleagues,[26] the myxomatous material in the small cysts in the Antoni type B area coalesced into larger cysts, which compressed the surrounding type A tissue, thus creating membrane like structures consisting of type A tissue with immunoreactivity to S100.

Authors of recent studies have suggested that cyst formation accompanying intra-axial tumours is due to an oedematous process caused by blood-brain barrier disruption.[157] However, the mechanism leading to cyst formation in acoustic schwannomas remains unclear. The cyst formation in acoustic schwannomas is generally regarded as resulting from degenerative changes. Other pathogeneses, such as intratumoural haemorrhage,[78] necrosis[131,157] and secretion[26] could also be involved in the mechanism of cyst formation. Fluid accumulation due to a direct osmotic effect or the extravasation of serum proteins from an impaired blood-tumour barrier augments cyst enlargement.[157]

The possibility of haemorrhage in acoustic schwannomas is well known and even massive intratumoural haemorrhage occurs.[9,102,133,153,169] Isolated or repeated microhaemorrhage as a probable mechanism for cyst formation has been commented on in various reports.[27,159,183,190] Histological features of haemosiderin-laden macrophages, haemosiderin deposits and thrombotic vessels are frequently observed in cystic tumours.[27,159,183] The factor that triggers the haemorrhagic tendency is unknown.[180]

Matrix metalloproteinases (MMPs) are zinc endopeptidases that are required for the degradation of the extracellular matrix during normal embryogenesis and in tissue remodelling. These proteolytic enzymes are also derived from tumour cells and have a fundamental effect on tumour growth, invasion, and metastasis.[100,113] They have been detected in cyst fluids and are hypothesised to be the cause for the formation and enlargement of lesions in various cystic diseases. High levels of expression of MMP-2 have been observed in the cyst fluid and wall. It may be partly involved in the pathogenesis of cyst formation and aggravate the adhesion to the facial nerve by either promoting the enlargement of the tumour or engendering the degradation of the tumour-nerve barrier proteolytically.[157]

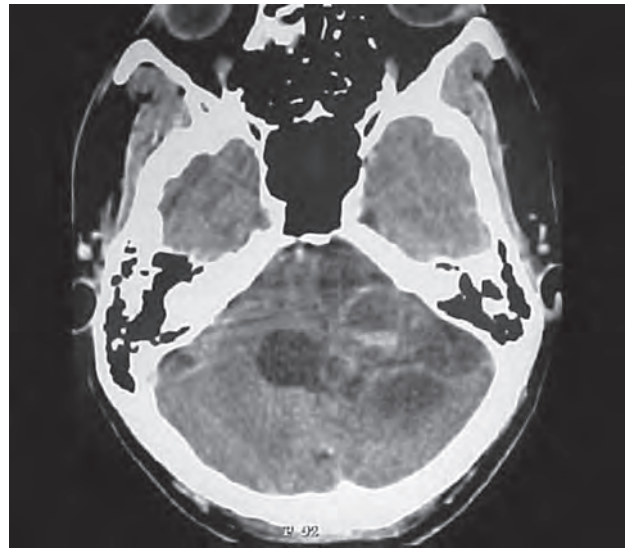
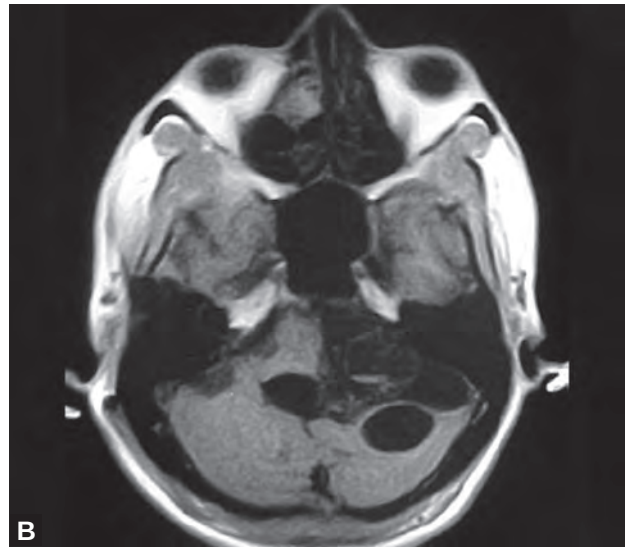
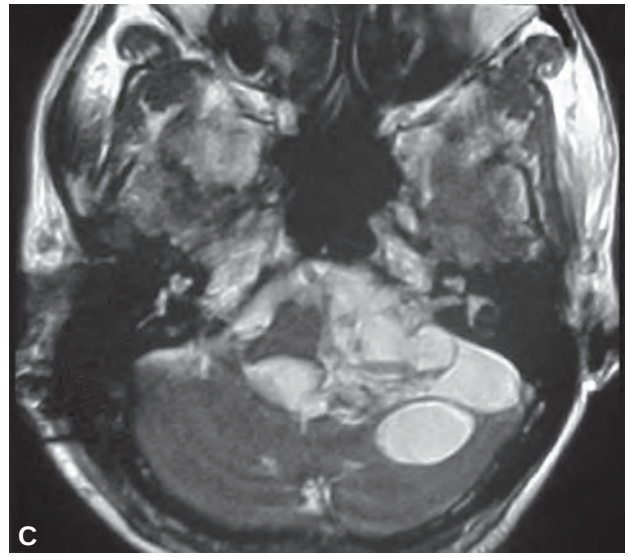
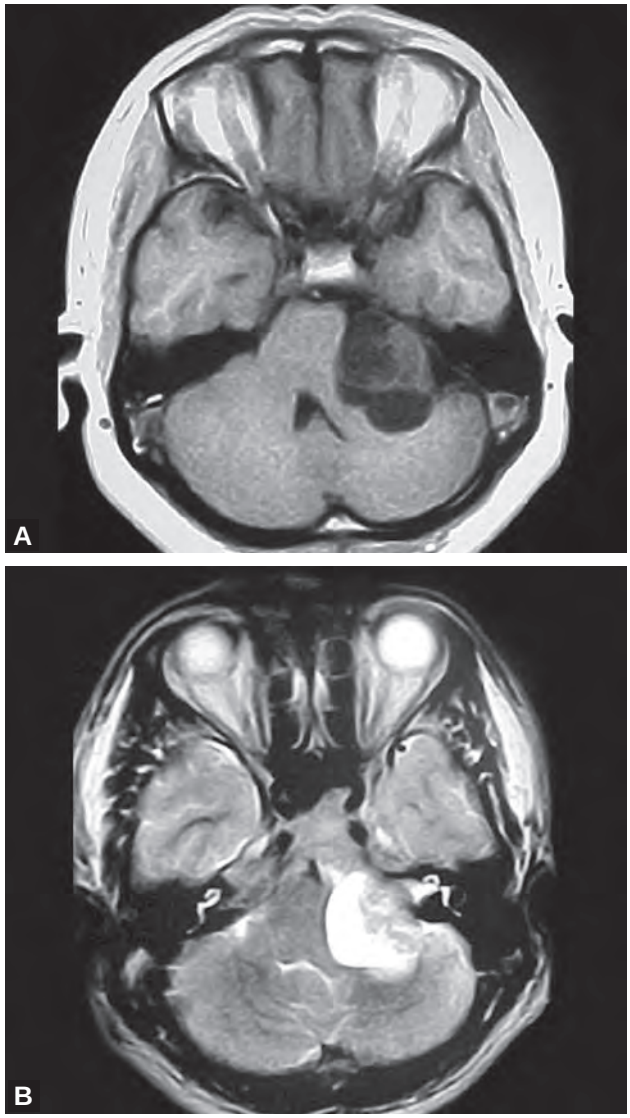


Fig. 9A: Computerised tomography scan of the brain axial view showing cystic meningioma

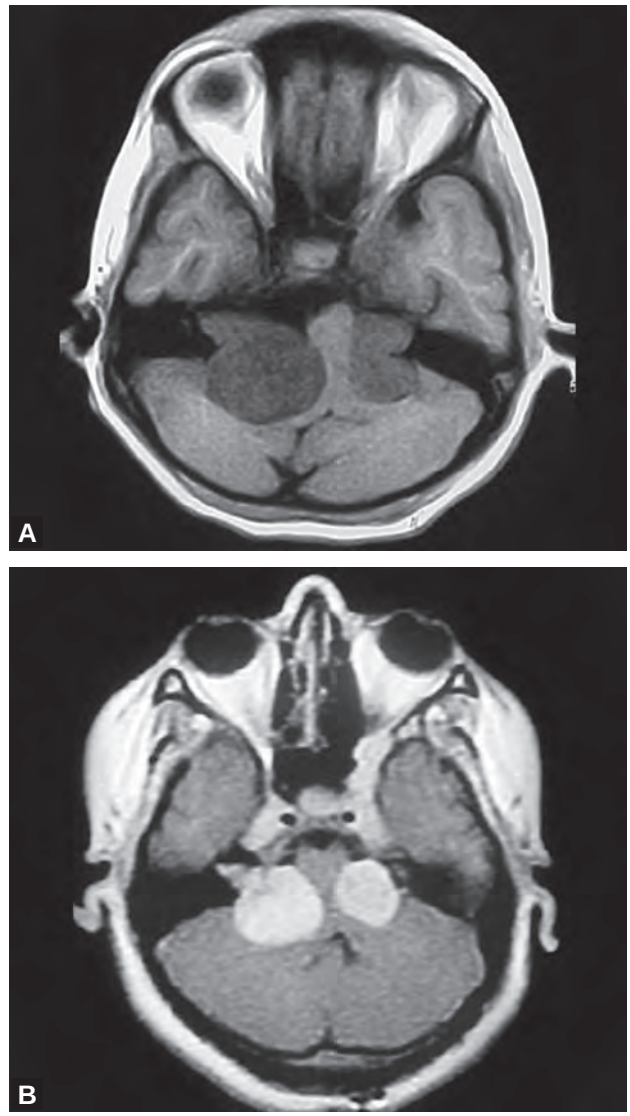




Figs 9B and C: Magnetic resonance imaging of the brain. (B) T1W axial view. (C) T2W axial view showing cystic meningioma



Figs 10A and B: Magnetic resonance imaging of the brain. (A) T1W axial view. (B) T2W axial view showing cystic meningioma



Figs 11A and B: Magnetic resonance imaging of the brain. (A) T1W axial view. (B) T2W axial view showing bilateral vestibular schwannoma

Surgical treatment of cystic tumours is favoured over radiosurgery,[183] but cyst formation is still predictive of a worse surgical outcome compared with solid tumours.[8,28,159] The "wait and scan" policy is not generally recommended, because the expanding cyst elements cause displacement of the brainstem and compression of the fourth ventricle, resulting in hydrocephalus. Even though the operation in the case of a cystic tumour may appear to be easier and faster in terms of the initial debulking than in a solid tumour[159] there is a higher risk of accidental lesions of the facial nerve, mainly because of adhesion of the cyst to the surrounding structures.[32,198] Moreover, rapid regrowth[32] and fatal haemorrhage have been reported after operation for cystic tumours.[157]

BILATERAL ACOUSTIC NEUROFIBROMAS

Bilateral acoustic neurofibromas (Figs 11A and B) are uncommon, when compared to unilateral neuromas, with the ratio varying from 1:10 to 1:50.[3,90,92,147,255] Bilateral acoustic neuroma was described by Wishart in 1822. Early reports carried a dismal picture regarding the outcome of surgery for these patients. Though with the current diagnostic and surgical facilities, the results are much better, there are still problems exclusive to these patients which have to be understood before managing them.

While bilateral acoustic neuromas are Schwann cell tumours which cannot be distinguished histologically from unilateral Schwann cell tumours, at surgery these tumours present as multilobulated masses engulfing the facial and the cochlear nerves. Studies with G-6-PD suggest a multicentric origin for these tumours.[151] Though hearing has been preserved in a few cases,[92,151,255] there is a high risk of hearing loss and facial paresis after surgery for these tumours. Large tumours showing signs of brainstem compression, hearing loss and facial paresis should be operated upon. There is a definite role for

observation and follow-up in cases where the tumours are small and the clinical condition is stable. Even intratumoural decompression can result in loss of hearing and facial function. Occasionally, decompression of the bony IAC and limited tumour decompression with use of intra-operative BAEP may help preserve hearing. Radiosurgery is a useful option in small tumours.

With large tumours requiring surgery, the side with the larger tumour should be operated on first, so that pressure on the brainstem is relieved. The tumour on the opposite side is removed at a second sitting once the patient recovers from the first surgery.

A major problem exists in the decision regarding when and whether to operate on the side of the remaining hearing ear when hearing has been lost on the other side, particularly when the remaining tumour is small and not immediately incapacitating. Though some authors advocate an early proactive strategy in order to preserve hearing,[16] classically, only symptomatic lesions are to be treated. When treatment is advisable, surgery remains the treatment of choice for tumours and an auditory brainstem implant (ABI) must be considered for hearing rehabilitation (Fig. 12).[81]

In Malis's series, patients who presented with bilateral acoustic neuromas in their thirties had a long and stable life expectancy than patients who presented in childhood. His results of hearing preservation in non-NF-II cases were 50% as opposed to 15% in cases with NF-II.

Recent reports that SRS is safe and effective in management of acoustic schwannomas in NF-II, it should be strongly considered for primary tumour management in selected patients, although results do not seem to be as good as for patients with sporadic unilateral tumours. Regarding the safety of radiosurgery when applied to conditions with abnormal tumour suppressor genes, a study with a cohort of 118 patients with NF-II demonstrated a statistically insignificant causative role for SRS in inducing malignancy.

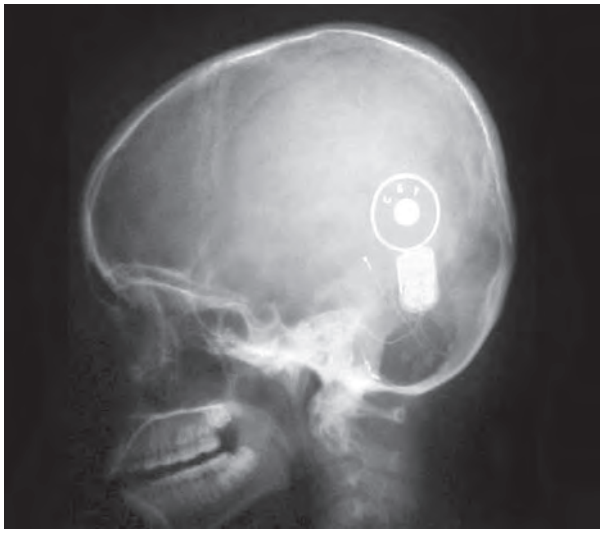


Fig. 12: Post-operative lateral skull radiograph of a patient who has undergone auditory brain implantation

Most patients in India present late in the course of illness with large tumours and disabling deafness. Sixteen patients with bilateral acoustic schwannomas treated over 10 years in a tertiary referral hospital were analysed and an attempt was made to classify the tumours into two groups by their extent in the CPA cistern (T1-T3a) and, tumours extending to or compressing the brainstem (T3b to T4b), which allows the surgical strategy to be defined.[208]

NEURAL PROSTHESIS IN RESTORING HEARING

The auditory implant provides a new mechanism for hearing when a hearing aid is not enough. The auditory implant is very different from a hearing aid. Hearing aids amplify sound. Auditory implants compensate for damaged or non-working parts of the inner ear because they can directly stimulate the acoustic nerve. There are two principal types of auditory implant: the cochlear implant and the ABI. They have common basic characteristics, but different applications. A cochlear implant attempts to replace a function lost by the cochlea, usually due to an absence of functioning hair cells; the ABI is a modification of the cochlear implant, in which the electrode array is placed directly onto the brain when the acoustic nerve is not anymore able to carry the auditory signal.[44]

The main and first indication for ABI is NF-II. Emergent indications are bilateral total ossified cochlea, VS with controlateral lesions or in a single hearing ear, cochlear nerve aplasia or inner ear malformations. In NF-II patients, best results are obtained in cases of smaller VSs and none or short-term auditory deprivation. Negative prognostic factors are duration of total hearing loss (greater than 10 years), tumour size (greater than 30 mm), difficulties in electrode array placement, complications during the post-operative course and number of active electrodes (less than 10).[14]

The implant is usually placed in the lateral recess of the fourth ventricle at the time of tumour resection to stimulate the cochlear nucleus. A report on the audiologic outcomes in 18 patients with NF-II who received ABI at the time of initial tumour resection was favourable. The authors concluded that ABIs are safe, did not increase surgical morbidity, and allowed most patients to experience improved communication as well as access to environmental sounds.[114] In selected cases of deafness in patients with NF-II where there has been anatomic preservation of the auditory nerve after acoustic neuroma resection or radiation therapy, cochlear implantation may offer some improvement in communication skills, including the possibility of open-set speech communication in some patients.[143]

Most patients with the implant have good appreciation of environmental sounds, but obtain more modest benefit with regard to speech perception. The majority of patients make use of the implant to facilitate lip reading; some can, to varying degrees, comprehend speech directly.[230] The ABI and cochlear implant continues to be an emerging field for hearing rehabilitation in patients who are deafened by NF-II.

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162 Trigeminal Schwannomas

BS Sharma, Ramdurg S, Sarat Chandra P

INTRODUCTION

Schwannomas (also known as neuromas, neurilemmomas, neurinomas and Schwann cell tumours) are benign, slow growing nerve sheath tumours composed of Schwann cells, which normally produce the insulating myelin sheath covering peripheral nerves. The tumour cells lie outside of the nerve, thereby causing compression. Intracranial schwannomas arise most commonly from the vestibular nerves but can involve any of the other cranial nerves.

Schwannomas of the trigeminal nerve are uncommon accounting for 0.07–0.36% of all intracranial tumours and 0.8–8% of intracranial schwannomas.[1,4,5,12,15–17] The first case of trigeminal nerve schwannoma was described by Smith in 1849.[21] The first successful removal was documented by Frazier in 1918.

SURGICAL ANATOMY

The trigeminal nerve emerges from the ventrolateral surface of the pons and runs anteriorly 1–2 cm through the cerebellopontine cistern to reach the petrous apex. Vascular structures, such as the petrosal vein and the superior cerebellar artery lie close to the trigeminal nerve. Over the petrous apex, 7 mm from the medial lip of the internal acoustic meatus, the Gasserian ganglion is enveloped by a dural deflection forming Meckel's cave, lateral to the cavernous sinus and the carotid artery.[6] As it leaves Meckel's cave, the trigeminal nerve divides into three branches: (1) The ophthalmic (V1), (2) Maxillary (V2), and (3) Mandibular (V3) branches. These three nerves run under the middle fossa dura mater and leave the temporal bone through the lateral wall of the cavernous sinus (for V1), foramen rotundum (for V2), and foramen ovale (for V3). The trigeminal nerve can also be surgically classified into three segments: (1) Cisternal, from the brainstem to the petrous apex; (2) Intracranial-extradural, from Meckel's cave to the foramina, and (3) Extra cranial (V1, V2, and V3). Functionally, the trigeminal nerve has two portions: (1) The "pars compacta", which constitutes the triangular portion and comprises the primary afferent fibres that are responsible for sensations of the face; and (2) The motor root, which carries the branchiomotor fibres to the muscles of mastication. The motor root runs practically separated from the "pars compacta" but together with the cranial portion of the nerve. At the level of Meckel's cave, it is oriented medially and leaves the skull together with the maxillary nerve. The intracranial-extradural portions of V2 and V3 are surgically identified, using the foramen spinosum as an anatomical landmark, which is located in the sphenoid bone and contains the middle meningeal artery. The foramina ovale and rotundum are located 2–5 mm superoanteriorly and 10–12 mm superomedially to the foramen spinosum, respectively.[23]

SURGICAL PATHOLOGY

Tumours arising from the Gasserian ganglion usually compress the ganglion, which is visualised after tumour removal. The nerve fibres usually are stretched over the tumour, although a few fibres may course through the tumour.

Microscopically they are composed of Antoni A and Antoni B regions. Antoni A regions are characterised by bipolar cells, which are arranged in compact interlacing fascicles. The nuclei line up in palisades with intervening nuclear zones called verocay bodies. A looser arrangement of cells, with poorly arranged vacuolated cells with pyknotic nuclei may be seen in Antoni B regions. These regions may represent degenerative changes. Cystic changes, hyalinised blood vessels, thrombosis and haemosiderin deposition may often be seen. Immunohistochemically, these tumours are positive for S-100 protein.[13] They occasionally are positive for Leu-7 and glial fibrillary acidic protein.

Clinical Presentation

Trigeminal schwannomas present most commonly in the third to fifth decades of life.[2,8,14] The tumours affect women slightly more than men.[17] The clinical presentation of trigeminal neurinomas depends on the site of origin of the tumour and the growth pattern.

Jefferson, in 1954,[12] divided these tumours into four groups depending on their anatomical location:

Type I. Posterior fossa (root type)
Type II. Combined posterior fossa–middle fossa (dumb-bell type)
Type III. Middle fossa (ganglion type) and
Type IV. Peripheral (division type)

Samii et al. in 1995,25 classified tumour extension into four categories based on radiological findings:

Type A. Intracranial tumour predominantly in the middle fossa
Type B. Intracranial tumour predominantly in the posterior fossa

Type C. Intracranial dumb-bell shaped tumour in the middle and posterior fossa, and
Type D. Extra cranial tumour with intracranial extensions

Cranial nerve involvement is the most common presenting symptom. Trigeminal nerve dysfunction is observed in more than 70% of cases. Facial hypoaesthesia is a much more common symptom, as compared to pain. Painless keratitis leading to corneal opacity, prior to any symptom is a rare but well recognised presenting feature of this tumour.[7] On the other hand, classical trigeminal neuralgia is also a rare initial symptom. Tumours arising from the ganglion usually produce constant pain, in contrast to tumours arising in the root, in which pain is frequently absent. The sensory disturbance may involve either one of the divisions or more frequently all the three divisions to a variable degree.

It is important to differentiate the sensory loss on the face due to root involvement, which may occur in V nerve schwannomas from that occurring due to high cervical intramedullary tumours. Usually, Vth nerve hypoaesthesia due to intramedullary pathologies lead to sensory loss starting from the periphery of the face and extending to the centre (like the French 'balaclava helmet') and is more commonly associated with dissociated sensory loss. In contrast to this, root involvement specifically involves the separate divisions (V1/V2/V3) of the face. Wasting of muscles of mastication is another important sign of V nerve involvement and is likely due to a tumour like schwannoma.[7,18,19] Sometimes, when there is a subtle motor weakness, it is of importance to ask the patient to bite a plastic or a wooden spatula and note the depth of the bites.

Abducens nerve paresis is the next common symptom, closely followed by involvement of the VIIth–VIIIth nerve complex. Less than 10% of patients have lower cranial nerve involvement. The IIIrd, IVth and VIth nerve can be involved by the tumour.[19] If the tumour extends to the middle fossa, it may cause exophthalmos. Visual loss can be either due to neuronal compression or raised intracranial pressure. Large tumours tend to present with features of raised intracranial pressure with headache, vomiting and failing vision.[26]

Very rarely, when there is a large infratemporal extracranial extension of the tumour, it may be palpable under the skin below the zygoma. They may also rarely present with pathological laughter and crying.[27]

Radiological Diagnosis

Plain X-Rays

Conventional X-rays (Fig. 1) demonstrate bony erosion of the petrous apex. The margins are smooth without sclerosis differentiating primary or secondary bony tumours of the region. Larger tumours with middle fossa extensions may demonstrate erosion of the sella turcica, clinoid process and widening of the superior orbital fissure. Tumours with a large posterior fossa component cause erosion of the inferomedial aspect of the petrous bone. Sparing of the internal acoustic meatus differentiates these tumours from acoustic neuromas.[10,20,22]

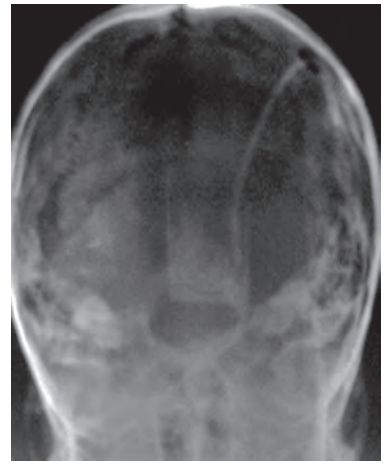


Fig. 1: X-ray skull Towne's view demonstrating bony erosion of the medial petrous bone

Computed Tomography Scans

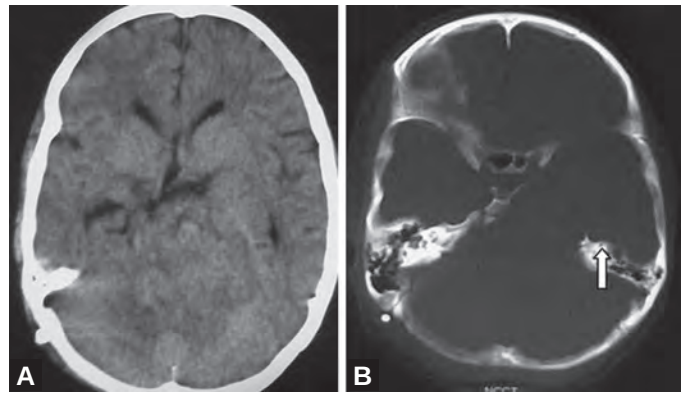
All the above described bony changes are better delineated on CT scans done with bone window settings (Figs 2A and B). The tumours are usually seen as iso- to hyperdense lesions with homogeneous contrast enhancement. However, other patterns of enhancement may be seen. Occasional cystic changes may be seen in the tumour.[9,24]

Magnetic Resonance Imaging (MRI)

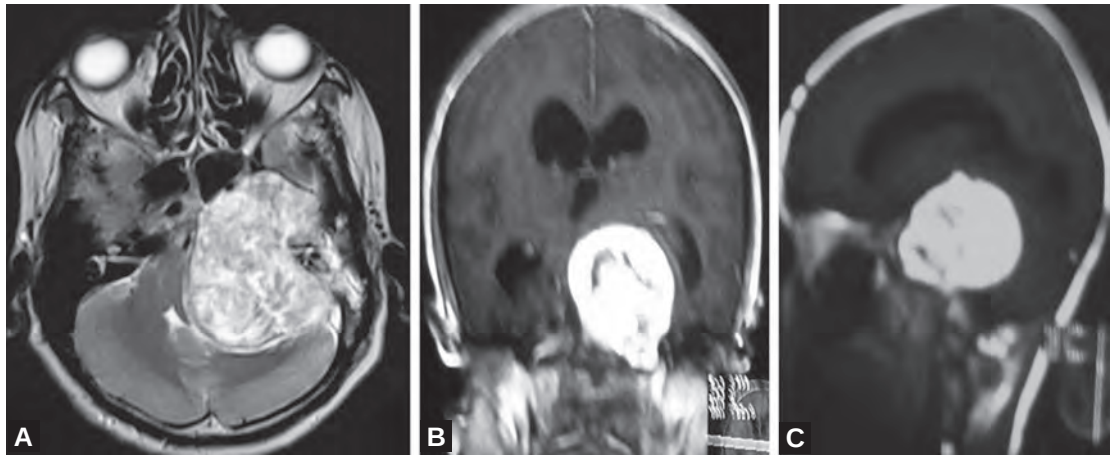
These tumours (Figs 3A to C) appear hypointense on T1W images and hyperintense on T2W images with intense contrast enhancement. These tumours may show cystic changes with occasional calcification. The extensions of the tumour can be demonstrated well with a contrast enhanced MRI scan.[11,24]

Cerebral Angiography

Small tumours do not demonstrate any change or abnormality in the vasculature. Larger tumours, however, may show enlarged feeding vessels which are usually derived from the precavernous and cavernous segments of the carotid artery. Displacement of the precavernous ICA



Figs 2A and B: Plain cranial CT scan with bone window settings showing the tumour with bony erosion of the medial petrous bone shown by solid white arrow



Figs 3A to C: MRI showing the extent of the tumour. (A) With brilliant enhancement as seen on contrast injection. (B and C) Presence of a tumour which straddles over the petrous with extensions both into the middle and posterior fossa is diagnostic of V nerve schwannoma

is the most commonly seen abnormality and it may be anterior and inferior displacement. However, superior and posterior displacement may also be seen. Tumours with a larger posterior fossa component may displace the posterior cerebral arteries medially and superiorly, while the anterior inferior cerebral arteries may be pushed downwards with stretching of the basilar artery.[3]

SURGICAL TECHNIQUES

The location and size of the tumour dictates the most appropriate approach.[19] They are usually easily separable from the cavernous sinus and the carotid artery, which facilitates their radical removal. Often, the tumour does not completely destroy the trigeminal nerve and can be separated from its fascicles, while preserving neurological function. Complete removal of the tumour should be the aim but not at the cost of neurological function. The natural history of these tumours, following sub-total excision is not known; some authors have found a high incidence of symptomatic tumour growth following sub-total excision, whereas others have found long periods of remission. In elderly or medically unfit patients and with tumours with firm adherence to the brainstem, cranial nerves or blood vessels, sub-total tumour excision may still be the optimal treatment.

Most of the tumours with a large middle fossa component may be accessed via the middle fossa approach. The medial part of the petrous may be drilled (Kawase approach) and the posterior fossa tumour may be now delivered through the enlarged opening. Rarely, a sub-temporal trans-zygomatic or an orbitozygomatic approach will be required.

The tumour should be debulked first. For this purpose, an ultrasonic aspirator may be used. It is also convenient to debulk using a sharp curette (no. 1 Penfield dissector or even a bone curette). Once this is done, the tumour should be gently dissected from the nerve fascicles, as the tumour is usually attached to 1–3 fascicles.

However, giant tumours are an exception as they may invade the entire nerve and even the brainstem. Caution must be exercised when reaching the anterior and the superior part of the tumour, where it may infiltrate the cavernous sinus densely and brisk bleeding may occur. Cavernous sinus bleeding may be easily controlled using a 'patty' made of Gelfoam® and Surgicel®, applied gently with suction and wet cotton.

The following approaches are commonly employed at our institute for trigeminal neuromas.[23]

Middle Fossa Approach

The patient is placed in the supine position with the head rotated 30 degrees to the opposite side. A pterional craniotomy is performed and enlarged to the base of the temporal fossa by removing bone with a rongeur to obtain a flat viewing angle across the floor of the middle fossa. The dura mater is then dissected and elevated from the middle fossa, exposing the superior orbital fissure. The middle meningeal artery is coagulated and transected. The second and third branches of the trigeminal nerve are identified. The foramen ovale and rotundum are exposed. The dura mater is elevated from the lateral cavernous sinus wall, revealing the tumour extradurally and the branches of the trigeminal nerve. The tumour is debulked and its capsule is dissected from the intact branches of the trigeminal nerve, which allows radical removal of the lesion. Large tumours can be approached intradurally by opening the Sylvian fissure and exposing the optic nerve, the internal carotid artery and the third cranial nerve. The lateral wall of cavernous sinus is exposed via a temporopolar approach and the tumour is removed. The trigeminal fibres are preserved as much as possible. The petrous apex is drilled and the petroclinoid ligament is cut to expose the posterior fossa portion, allowing complete excision of the remaining tumour.

Retrosigmoid Approach

This approach is used for patients with a large posterior fossa extension and smaller middle fossa component. The patient can be placed in the lateral, park bench or sitting position. A linear incision is made 4 cm behind the external auditory canal. The asterion is exposed to

determine the junction of the transverse and sigmoid sinuses. A craniotomy, 4 cm in diameter, is performed with the superior and anterior margins bordering the transverse and sigmoid sinuses, respectively. The dura mater is opened parallel to the sigmoid sinus, CSF is drained from the cerebello-medullary cistern and cranial nerves VII-XI are identified.

The tumour is thereby exposed near the tentorial margin. After intracapsular tumour debulking, microsurgical radical removal is accomplished. A watertight dural closure is completed and the bone flap is fixed in place. All opened mastoid cells are sealed with bone wax to help prevent CSF leaks.

Presigmoid Approach

The patient is placed in the lateral position with the head in a three point fixator. A 'C' shaped skin incision is made from the superior temporal line to the mastoid tip. Two burr holes are placed anteriorly and two are placed posteriorly at the intersection of the transverse and sigmoid sinuses. The temporal and retromastoid dura mater is exposed through a craniotomy. Mastoidectomy with preservation of the labyrinth and the facial nerve canal is the next surgical step. Parallel dural incisions in the middle fossa floor are made anterior to the sigmoid sinus. The superior petrosal sinus is then ligated and transected. At this point, the inferior temporal lobe and the lateral portion of the cerebellum are slightly retracted so that the vein of Labbé is preserved. The tumour is identified and the VIIth and VIIIth cranial nerves are usually displaced inferiorly. The tumour within the cavernous sinus is removed after opening its lateral wall. After complete excision of the tumour, the dura mater is closed in a watertight fashion and the skull base is reconstructed with myofascial flaps.

POST-OPERATIVE COURSE

Transient cranial nerve deficits are common in the early post-operative period. Abnormalities of trigeminal nerve, either new, or worsening of existing deficits may be seen, which may be permanent. This may be in the form of sensory loss or weakness of muscles of mastication. Prevention of corneal opacity may require an early tarsorraphy.

ROLE OF RADIOSURGERY

Smaller tumours or residual tumours may be subjected to stereotactic radiosurgery. Gamma Knife therapy is used at our institute using a Leksell Gamma Knife (Elekta Instruments, Atlanta, GA, USA), with a tumour margin dose of 12–13 Gy. The mean radiological follow-up was 15.7 months (range 6–37 months) and there was a tumour growth control rate of 85.75%. The mean volumes of tumours that decreased in size, remained stable and increased in size were 2.11, 5.33 and 8.1 cm^3, respectively.[26]

Proponents of Cyberknife radiosurgery demonstrate tumour control rates and clinical outcomes that parallel those of previous reports using Gamma Knife radiosurgery; however, long-term follow-up studies are needed.

AIIMS EXPERIENCE[26]

Sixty-eight patients were treated for TS between January 1993 and December 2005. Most patients were in the fourth decade of life, with the duration of symptoms ranging from 1 month to 13 years. Twenty-nine TSs were classified as Type A, 13 as Type B and 26 as Type C, depending upon their size. A skull base approach was used in every surgically treated case. Of the 46 patients for whom radiological follow-up data were available, complete tumour excision was achieved in 35 cases (76%). Follow-up ranged from 3 months to 12 years (mean 62 months). One patient died and nine (15%) had permanent morbidity in the form of corneal opacity (5), facial (2) or trochlear (2) nerve palsy.

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163 Jugular Foramen Lesions

Siddhartha Ghosh

INTRODUCTION

Jugular foramen (JF) lesions, once thought to be one of the most surgically unapproachable ones, are now becoming safely manageable with reasonable morbidity and mortality rates. This advance has become possible due to improvement in microsurgical techniques and instrumentation. Parallel advances in the field of neuroradiology, neuroanaesthesiology, neuroelectrophysiology and neurointensive care, have helped immensely in the successful management of these lesions, as seen today. The highly complex nature of the jugular foramen and the morphological organisation of its surrounding neurovascular structures, coupled with the plethora of pathological conditions in this region, still pose a major challenge to the neurosurgeon. From the pre-microsurgical era to the microsurgical era, various safe approaches have been established. Proper patient selection, a thorough pre-operative work-up, choosing the ideal surgical approach and interdisciplinary teamwork involving the neurosurgeon, otologist, neuroradiologist and plastic surgeon, has made the now preferred single stage procedure feasible in dealing with these lesions.[34]

In this chapter, we review the salient anatomical, pathological, radiological and clinical features of JF lesions and indications, discussing the techniques, merits, demerits and the complications of the major approaches to the JF.

ANATOMICAL CONSIDERATIONS

Since the neural, arterial, venous, muscular and osseous relationships are exhaustive, only the salient features related to the jugular foramen are mentioned here. The jugular foramen is located at the posterolateral skull base with its long axis obliquely directed in the posterolateral to anteromedial and is formed by the petrous temporal bone anterolaterally and by the jugular process of the condylar part of the occipital bone posteromedially (Fig. 1). It is configured around the sigmoid sinus and the inferior petrosal sinus. The junction where the transverse sinus continues as the sigmoid sinus is indicated externally by the asterion at which point the vein of Labbé enters the sinuses. The right foramen is larger than the left in 68%, equal in 12% and smaller than the left in 20%, possibly due to the difference in the size of the sigmoid sinus and the jugular bulb.[24] On the intracranial side, the jugular foramen is inferior to the porus acoustics and superolateral to the intracranial orifice of the hypoglossal canal. On the extracranial side it is located just behind the carotid canal separated by the carotid ridge, lateral to the anterior half of the occipital condyle, anteromedial to the stylomastoid foramen and posteromedial to the styloid process.

The jugular foramen is traditionally divided into a large posterolateral compartment (pars venosa) and a smaller anteromedial compartment (pars nervosa). This view has been challenged by Katsuta et al. who have divided the jugular foramen into three compartments: two venous compartments and one neural intrajugular compartment in between. The venous compartments include a large posterolateral sigmoid part and a small anteromedial petrosal part.[16] At the junction of these two compartments there are two bony prominences (intrajugular processes), arising from the temporal and occipital bones, joined by a fibrous or less commonly osseous bridge forming the intrajugular septum.

The dura over the intrajugular septum has two characteristic perforations: (1) The glossopharyngeal meatus for the IX nerve and (2) A larger vagal meatus for X and XI nerves.[2] Both of the meati are located on the medial side of the intrajugular processes and septum, being consistently separated by a dural septum. Over the upper and lateral margin of the intrajugular part of the jugular foramen, the dura is thickened forming a roof or lip that projects inferiorly and medially to partially cover the IX and X nerves meati. This thick dural fold is called plica occipitalis oblique or jugular dural fold.[19,24,33] The lip projects most prominently over the IX nerve meatus, whereas, the lip over the X nerve is less prominent.

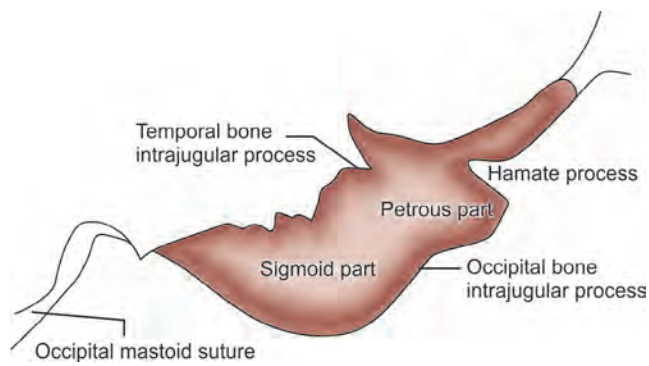


Fig. 1: Anatomy of the jugular fossa

The inferior petrosal sinus (IPS) joins the jugular bulb in 90%, passing between the IX nerve superolaterally and the X and XI nerves inferomedially. In 10% it drains directly into the internal jugular vein. The occipital condyle (OC) contains a condylar emissary vein in 70% of cases. This posterior condylar vein enters the jugular foramen at its posteromedial part and serves as a landmark to the foramen for the posterior approaches. The hypoglossal canal contains a venous plexus, called anterior condylar vein in addition to the XII nerve. The IX nerve enters the jugular foramen just below the cochlear aqueduct, piercing the dura at the pyramid fossa, expands at the site of the superior and inferior ganglia and courses forwards along the medial side of the intrajugular ridge before turning downwards. The X nerve enters the jugular foramen below the IX nerve. Its superior ganglion is located at the level of the dural roof of the JF and the inferior ganglion is located below the JF at the level of the atlanto-occipital (AO) joint. The X nerve, after piercing the dura, quickly turns downwards without having a forwards course within the JF. The XI nerve bundle blends into the lower margin of the X nerve at the level of the JF.

The relationships between the lower cranial nerves (IX–XII) and the major vessels [internal carotid artery (ICA), internal jugular vein (IJV), external carotid artery (ECA) and branches of vertebral artery (VA)], are extremely complex at the level of the JF and in the upper neck.[16,19,21] At the level of the skull base, the IJV courses just posterior to the ICA, being separated by the carotid ridge. At this level, both the artery and the vein are surrounded by a thick fibrous attachment of the carotid sheath to the periosteum of the skull base. The styloid process with the muscles attached to it separates the ECA laterally from the ICA medially. The IX, X, XI, and XII nerves at the exit from their respective foramina, first lie medial to both the ICA and the IJV with IX being most lateral and XII most medial; then IX, XI, and XII nerves pass laterally between the ICA and IJV; later the IX and XII descend forwards along the lateral surface of the ICA while XI descends backwards along the lateral surface of IJV. The posterior branches of the ECA (occipital and ascending pharyngeal) supply the meninges around the JF and are the main feeding arteries of JF lesions. The vertebral branches that are encountered near the JF region include the meningeal and posterior spinal arteries and posterior inferior cerebellar artery (PICA) having a close relationship with IJV, which lies just anterior to the transverse process of the atlas.

PATHOLOGY

Jugular foramen lesions are rare in clinical practice. Owing to the presence of osseous, muscular, neural, vascular, dural and connective tissue elements in the jugular foramen region, lesions arising from these elements are encountered in this region and some are more common than others. They are broadly classified into intrinsic and extrinsic or neoplastic and non-neoplastic.[6] Table 1 lists the lesions involving the jugular foramen region. Since the choice of the surgical approaches is dependent on the site of origin, size and extent of the lesion, attempts were made to classify these lesions into various types or classes, for example, Fisch's and Glasscock and Jacobson's classification for glomus jugular tumours and Keye's and Franklin's classification for schwannoma.[7,8,15,17] The one proposed by Bertalanffy and Ulrich is applicable to any type of lesion, which is as follows:[2]

Type I: Small lesions confined to the jugular foramen.

Type II: Intrinsic lesions of lower brainstem located in the vicinity of the jugular foramen.

Type III: Lesions of the jugular foramen with predominant intradural extension located above the level of foramen magnum.

Type IV: Lesions of the jugular foramen with intradural extension beyond the level of foramen magnum into the spinal canal.

Type V: Lesions of the jugular foramen with intradural and extradural extension into the petrous bone.

Type VI: Lesions of the jugular foramen with predominant extradural extension.

Table 1: Pathological lesions around the jugular foramen

Neoplastic	*Non-neoplastic*
Common	
Paraganglioma	Internal jugular vein thrombosis
Schwannoma	Large jugular bulb (pseudomass) (included because of radiological importance)
Meningioma	
Metastasis (haematogenous, nasopharyngeal, carcinoma)	
Uncommon	
Exophytic brainstem glioma	Aneurysm
Chondroma	Osteomyelitis
Chondroblastoma	Malignant external otitis
Chondrosarcoma	Cholesterol granuloma
Chondromyxoid fibroma	Amyloidoma
Osteoblastoma	
Plasmacytoma	
Chordoma	
Haemangiopericytoma	
Haemangioblastoma	
Choroid plexus papilloma	
Cavernoma	
Rhabdomyosarcoma	
Carcinoma of tympanic cavity	
Neurenteric cyst	

CLINICAL MANIFESTATIONS

The clinical presentation of jugular foramen lesions is dependent on the size, extent and pathology of the tumour. Typically, they produce the jugular foramen syndrome (Vernet's syndrome) and depending on their extension produce other related syndromes (Table 2).[3,26] Patients with IX, X, and XI cranial nerves dysfunction may present with dysphagia, dysarthria, hoarseness of voice, dysphonia, nasal regurgitation, ipsilateral trapezius, and sternomastoid muscle weakness and atrophy, depressed gag reflex, palatal droop on the affected side with ipsilateral vocal cord paralysis and loss of taste on the posterior 1/3rd of the tongue, paresis of the soft palate, uvula, pharynx and larynx. Some patients may present with neuralgic pain in the IX and X nerve distribution.[4] Due to the slow expansile growth of these lesions, the lower cranial nerve dysfunction is of gradual onset and, in most patients, it is well tolerated as a result of gradual compensation. As a result, although imaging studies reveal extensive involvement of these neural structures, patients may have only subtle manifestations of their dysfunction. Even though a positive correlation exists between cranial nerve palsy and tumour invasion, lack of pre-operative nerve dysfunction does not correlate with the degree of nerve invasion found at the time of surgery.[20] The anterior extension encasing the cavernous sinus and internal carotid artery may produce Horner's syndrome and III, IV, V, and VI nerve palsy. Intracranial extension can produce posterior fossa symptoms, such as nystagmus, ataxia, hemiparesis and increased intracranial pressure.[1] Extracranial extension along the internal jugular vein can produce a visible mass in the oropharynx or a palpable mass in the neck. Intraluminal growth can block venous drainage and occlude the sigmoid sinus and, if present bilaterally, increased intracranial pressure can occur. Intracranial extension superiorly can produce the cerebellopontine angle syndrome (deafness, tinnitus, VII nerve palsy) and those extending still laterally can produce bloody otorrhoea, a visible mass through the tympanic membrane and a bruit may be heard over the mastoid.

NEUROIMAGING

The cornerstone in the successful management of jugular foramen lesions is pre-operative high quality and multimodality neuroimaging. Advances in this field have led the surgeon to select the most appropriate surgical approach and technique, to anticipate the possible complications and to prevent or manage them. CT, MRI and angiography of the brain must be done in all cases to get the maximum information pre-operatively.

Plain and contrast CT scan of the brain with 1.5 mm cuts, bone window algorithm and coronal cuts help to reveal normal bony variations and the pathological bony involvement at the site of the jugular foramen and extension into the nearby osseous structures, and also the type of involvement, either expansile (compressive) or invasive (destructive) enlargement. The presence of obstructive hydrocephalus is also visualised. If spiral CT scan is available, this, with a bolus of contrast medium, will give additional information like three dimensional visualisation of the skull base and the relationship between the lesion, vessels and skull base.[18]

MRI images are extremely useful in delineating the exact location, origin, size, limits, margins, vascularity and extent of the lesion, degree of involvement of the important neurovascular structures and also to some extent the pathological diagnosis. For the latter purpose a dynamic, high dose Gd-study with creation of time intensity curves is found to be particularly useful.[37] With this technique, glomus jugulare tumours can be differentiated from schwannomas, meningiomas and metastases. MRI venography is highly predictive in differentiating pseudomas (large and high lying jugular bulb) from the

Table 2: The jugular foramen and related syndromes

Syndrome	*Cranial nerves*	*Site of involvement*
Vernet's syndrome	IX, X XI	Lesions in jugular foramen
Collet-Sicard syndrome	IX, X, XI, XII	Lesions in retroparotid space
Vallaret's syndrome	IX, X, XI, XII Sympathetic chain	Retropharyngeal extension
Schmidt's syndrome	Occasionally VII	Intradural extension
Avellis syndrome	X, XI XI (accessory to X)	Intradural extension, Occasionally inferior margin of JF
Jackson's syndrome	X, XI, XII	Intracranial extension before the nerves leave the skull base
Tapia syndrome	X, XII, occasionally	Lesions high in the neck
Cerebellopontine angle Syndrome	XI, sympathetic chain VII, VIII, V	Extension into CP angle
Garcin's hemibase syndrome	All cranial nerves on one side (often incomplete)	Infiltrative nasopharyngeal carcinoma

pathological lesions.[36] Octreotide scintigraphy, if available, is helpful in the diagnosis of multifocal paragangliomas since these tumours more than 1.5 cm in size take up the radioisotope.[12]

Finally bilateral cerebral angiography with cross-compression or balloon occlusion test will demonstrate enlarged feeding arteries, degree of vascularity, dominance and pathology of sigmoid sinus, jugular bulb and internal carotid artery. If the tumour is highly vascular, then a pre-operative super-selective endovascular embolisation can also be undertaken to assist in safe surgical removal.[35]

SURGICAL APPROACHES

Since the first reported exploration of the jugular bulb for a completely intraluminal mass by Sieffert in 1934, many surgical approaches, their modifications and combinations have been developed and utilised by neurosurgeons and otologists to deal with jugular foramen lesions. Historically, a sequence in developing these approaches with the aim to improve surgical management can be distinguished, for example, realising the need for VII nerve mobilisation, packing of sigmoid sinus, ligation of major vessels, resection of the skull base and so on. As a result, numerous approaches are now available, which vary in skin incision, soft tissue dissection and bone removal, having specific indications depending upon the site, size, extent and vascularity of the tumour, involvement of the surrounding neural (cranial nerves, brainstem and cerebellum), vascular (internal carotid artery, vertebral artery, sigmoid sinus, jugular bulb, internal jugular vein and cavernous sinuses) and osseous (petrous, clivus, condylar part of occipital bone) structures and finally upon the patient's clinical condition (hearing). The choice of the most appropriate surgical approach to a particular lesion in a particular patient has to be individualised and is dictated by the morphology of the lesion and the surgeon's experience and preference.

The surgical approaches used for JF lesions, although not always directed primarily to the jugular foramen, include the suboccipital retrosigmoid, presigmoid and trans-sigmoid, retrolabyrinthine and translabyrinthine, transcochlear and subcochlear, trans-supra and juxtacondylar, far lateral suboccipital, lateral skull base, infratemporal fossa and middle cranial fossa approaches. These approaches can broadly be grouped into posterior, lateral, anterior, superior and inferior approaches and further subdivided into limited, extended and combined approaches. In general, the limited approaches are useful for small lesions and extended and combined approaches for the larger lesions.

The latter two approaches are not suitable when used alone for JF lesions but definitely require to be combined with other approaches to deal with inferior, anterosuperior and medial extensions of the JF lesions.

Major Groups

Posterior (through posterior cranial fossa)	Suboccipital retrosigmoid transcondylar, supracondylar approaches
Lateral (through mastoid)	Lateral skull base, juxtacondylar approaches
Anterior	Preauricular subtemporal infratemporal
Superior	Middle fossa approaches
Inferior	Neck dissection

Lateral Approaches

The classification is shown in Table 3.[28] These are the most commonly used access routes for jugular foramen lesions having large extracranial extensions. These involve basically a mastoidectomy and more often, anterior re-routing of the VII nerve to drill the bone inferior to the labyrinth, to get access to the JF. The exposure can be widened anteriorly by sacrificing the external auditory canal and middle ear structures or medially by drilling away the otic capsule (translabyrinthine) or cochlea (transcochlear). When combined with upper neck dissection, it provides a satisfactory exposure of the JF, mastoid air cells, tympanic cavity and extracranial structures. The

Table 3: Classification of lateral approaches

LATERAL APPROACHES
- Juxtacondylar
- Lateral skull base
  - Approaches conserving otic capsule (extra-labyrinthine)
    1. Passing above otic capsule (supralabyrinthine):
       a. Middle cranial fossa
       b. Extended middle cranial fossa
       c. Middle fossa transpetrous
    2. Passing behind the otic capsule (retrolabyrinthine):
       a. Retrosigmoid
       b. Retrolabyrinthine
       c. Retrolabyrinthine transtentorial
    3. Passing anterior to otic capsule (prelabyrinthine):
       a. Infratemporal fossa Types B and C (Fisch's)
       b. Preauricular subtemporal—infratemporal
    4. Passing inferior to otic capsule (infralabyrinthine):
       a. Approaches to jugular foramen—infratemporal fossa Type A (Fisch's)
          - petro-occipital trans-sigmoid (POTS)
       b. Extreme lateral approach
  - Approaches sacrificing otic capsule
    1. Translabyrinthine
    2. Transcochlear
       - Original
       - Transotic
       - Modified types A–D

removal of the styloid process with transposition of VII nerve facilitates wide opening of the extracranial orifice or JF and provides access to the lower part of the petrous portion of the ICA. Still wider exposure of extracranial tumour is achieved by removing the transverse process of the atlas or dislocating or resecting the mandibular condyle. However, these approaches cannot be used for the removal of large intradural extensions, which require a combination of the posterior approaches.

These are the most suitable approaches for predominantly intradural lesions and for lesions extending down to the foramen magnum and medially to the lower and midclivus. The retrosigmoid approach provides access to the cerebellopontine angle and the intracranial orifice of the JF. Its transcondylar modification and the far lateral approach access the foramen magnum and lower clival regions by opening the posterolateral quadrant of the foramen magnum and by drilling away the posterior part of the occipital condyle.[32] The posterior and posterolateral margin of the JF is approached by removing a part of the jugular process of the occipital bone behind the JF and the portion of the mastoid just behind the mastoid segment of the VII nerve and the stylomastoid foramen. This provides an upwards view from below but to get a flatter view towards the midclivus, an additional drilling of the jugular tubercle is required.

Anterior Approaches

They use the pathway anterior to the external auditory canal and through the tympanic bone, exposed by removal or displacement of the glenoid fossa and temporomandibular joint. The subtemporal-infratemporal fossa approach alone can access the anterior part of the JF after reflecting the petrous portion of the ICA anteriorly. Further drilling exposes the midline and upper clivus anteriorly. However, more commonly, this approach has to be combined with lateral approaches to access the anterior extension of the pathology. These combined procedures are designated by Fisch as infratemporal fossa Type B and C approaches.

Posterior Approaches

- Suboccipital retrosigmoid
- Suboccipital transcondylar
- Suboccipital supracondylar.

Suboccipital Retrosigmoid Approach

This is a limited and posterior approach pioneered by Sir Charles Balance in 1894 and refined by Cushing and Dandy in 1920 and is frequently, one component of more extensive exposures. The main indications are Type A schwannomas of lower cranial nerves, epidermoid cyst and acoustic neurinoma extending down into the jugular foramen.

This is an important standard neurosurgical approach to the posterior fossa and hence does not need elaboration. The retroauricular skin incision exposes the suboccipital region including the asterion and medial portion of the mastoid process and reaches but does not extend inferiorly to the supracondylar fossa. Usually, the lateral rim of the foramen magnum is left in place. The mastoid air cells are usually opened, taking care of the emissary veins draining into the sigmoid sinus. The intracranial part of the jugular foramen is exposed by dissecting the arachnoid around the IX, X, XI nerves.

It is technically simple, familiar and associated with few complications and can be easily combined with other skull base procedures to gain further exposure. But, it has limited applicability in that, only the intradural portion of the tumour can be removed and does not allow removal of either intrajugular pathology or extracranial extensions.

Suboccipital Transcondylar Approach

Termed by Seeger (1978) and refined by Gilsbach (1987) and by Bertalanffy et al., this approach is an extended modification of the retrosigmoid approach providing more extended lateral and inferior exposure than the latter.[10,29,30] This is not synonymous with the far lateral approach for the foramen magnum (FM) lesions, which requires the resection of only the medial one-third of the occipital condyle. The indications are intrinsic lesions of the lower brainstem up to the pontomedullary junction, tumours located anterior or anterolaterally to the lower brainstem, extradural pathology from the lower clivus, occipital condyle, anterolateral rim of the foramen magnum and jugular process of the occipital bone and aneurysms of the vertebrobasilar complex.

Technique: The initial steps are like that of the standard suboccipital retrosigmoid approach. In addition to suboccipital craniotomy, the bone resection extends to include the posterior and medial portion of the occipital condyle and part of the jugular process superior to the condyle to expose the hypoglossal canal and the jugular foramen from dorsally and inferiorly. The distal extradural vertebral artery is exposed up to the point where it pierces the atlanto-occipital membrane and dura. While making the dural incision, it is desirable to leave a cuff around the vertebral artery, which aids in watertight dural closure at the end of the procedure, to prevent post-operative CSF leak. The posterior emissary vein, when present, is a useful landmark in the identification of the jugular foramen.

It provides a straight line view to the anterior rim of the foramen magnum and lower clivus, an excellent exposure of the lower brainstem, without the need to retract the brainstem or overstretching of the lower cranial nerves with an excellent control of vertebral artery in its extradural and intradural course. It can be extended laterally to expose JF lesions, either from an intradural or extradural approach. Ligation and division of the sigmoid sinus to expose the intradural portion is done according to the surgeon's preference.

There is a potential risk of injury to the vertebral artery (VA), and the lower cranial nerves and a risk of craniocervical instability, if the atlanto-occipital joint is opened. For a predominantly extradural growth with a lateral extension into the JF, Sen and Sekhar used this approach from a lateral direction by combining lateral exposure of the foramen magnum with a partial mastoidectomy.[10] Although useful for the above indication, the mastoidectomy and extensive OC resection is not necessary for the predominantly intradural growth.

Supracondylar Approach

Described by Gilsbach et al., this is a limited variation of the transcondylar approach and is indicated for small lesions confined to the hypoglossal canal and to the medial rim of jugular foramen.[11]

Technique: The initial procedure is like that of the standard suboccipital approach. Then the suboccipital craniotomy is extended down to the supracondylar fossa while preserving the foramen magnum and occipital condyles. The jugular tubercle is drilled away extradurally, exposing the medial aspect of the jugular foramen laterally and hypoglossal canal inferiorly. The advantage of this approach is the low morbidity and the disadvantage is that radical excision is not possible and is adequate only for biopsy and for small intradural lesions confined to the hypoglossal canal.

Juxtacondylar Approach

Developed by Geroge et al., it is an important limited and lateral approach and one of the primarily targeted approaches to the JF.[9] The prime indication is for extradural tumours confined to the jugular foramen like lower cranial nerve schwannoma, meningioma, etc.

Technique: The skin incision starts from the superior nuchal line behind the mastoid and extends along the medial border of the sternomastoid muscle to 6 cm below the mastoid tip. The IJV and XI nerves are exposed after resecting the muscles attached to the mastoid. The transverse process of the atlas is freed of it muscular attachments and the VA is exposed above and below the transverse foramen. The transverse process of atlas is removed and the VA can be transpositioned, if necessary. The posterolateral aspects of the atlanto-occipital and atlanto-axial joints are exposed. The posterior belly of the digastric muscle is resected and the occipital artery is ligated. The external and internal carotid arteries are exposed only if necessary. Then a partial mastoidectomy is done, which is continued medially to expose the distal SS. The remaining posteroinferior wall of the jugular bulb is drilled away which opens the jugular foramen posteriorly and inferiorly. Exposure of VII nerve at its exit from the stylomastoid foramen and at its petrosal segment, and dural opening is done only if necessary, in cases of large tumours.

It provides a wide exposure of the posterolateral aspect of the jugular foramen without extensive petrous bone drilling and hence preserves hearing and VII nerve functions. There is no risk of CSF leak because the dura is usually not opened. It can be combined with a supracondylar exposure, which is mainly indicated for intradural pathology or with infratemporal fossa approach Type A.

But this is a limited exposure of the JF with the potential risk of venous bleeding around the VA within the foramen transversarium of the atlas.

Samii and Bini advocated a combined lateral suboccipital-infralabyrinthine approach. Hirsch, Sekhar and Kamerer proposed a transtemporal and infratemporal approach for benign tumours with both extradural and intradural extensions with excellent control of the vertebral artery.[13,27]

Petro-Occipital Trans-Sigmoid (POTS) Approach

It is one of the lateral infralabyrinthine skull base approaches primarily targeting the jugular foramen, described by Mann et al. It is primarily indicated for jugular foramen lesions especially lower cranial nerve schwannomas with intracranial extensions, meningioma of the jugular bulb and some cases of glomus jugulare tumours with predominant posterior extension. It is also indicated in small petroclival meningiomas lying anterior to the internal auditory canal (IAC) with preserved hearing.

Technique: A 'C' shaped skin incision 4 cm posterior to the post-auricular sulcus with its lower limb extending inferiorly 2 cm below the mastoid tip is used. An inferiorly based 'U' shaped musculoperiosteal flap is then raised extending from 1–2 cm above the zygomatic arch superiorly to the level of the mastoid tip inferiorly. Anteriorly a strip of periosteum is left a few millimetres posterior to the EAC to allow re-suturing of this flap during closure. The sternomastoid muscle is retracted posteriorly. The lateral process of the atlas is identified and the IJV anterior to this is dissected free and ligated. Following a complete mastoidectomy, the mastoid portion of the VII nerve and JB are identified and the bone over SS and JB and posterior fossa dura in front of the SS are removed. A 4 × 4 cm suboccipital craniotomy is performed limited anteriorly by the SS and superiorly by the TS. The infralabyrinthine petrous bone is drilled away taking care not to injure the posterior semicircular canal or VII nerve. The occipital condyle is partially drilled up to the hypoglossal canal. The vertical segment of the JCA is exposed by drilling the inferior tympanic bone while preserving the EAC wall. The proximal part of the SS is compressed extraluminally and the SS is then opened and packed distally and proximally. A horizontal dural incision is made starting posterior to the SS, coursing anteriorly traversing the medial wall of the SS. Then the arachnoid is removed from neurovascular structures,

exposing IV–XI nerves and the superior cerebellar artery, AICA and PICA.

The removal of the lateral wall of the JB and, if necessary, its medial wall, fully exposes the intracranial part of IX–XI nerves. The dura over the drilled part of the OC is excised exposing the hypoglossal canal. When needed, IX–XI nerves are retracted or sacrificed if invaded by the tumour. If necessary, drilling is continued to the ipsilateral lower clivus and to the lower border of the foramen magnum. If control of the vertical portion of the ICA and of the infralabyrinthine compartment is needed, the mastoid segment of VII nerve is mobilised as far as the stylomastoid foramen. Only if the tumour extends to the hypotympanum, an extended posterior tympanotomy is performed and the facial nerve is re-routed. The retrosigmoid posterior fossa dura should be closed. The resected cavity is filled with an abdominal fat graft and the wound is closed.

The advantages of this approach are that the middle ear and VII nerve functions are preserved and it can be combined with the transtentorial approach for tumours with supratentorial extension or with the translabyrinthine approach for tumours involving the IAC in the absence of pre-operative serviceable hearing (and if hearing is preserved then the posterior and inferior wall of IAC is drilled away without sacrificing the labyrinth) or with the extreme lateral approach for tumours extending downwards to involve the CV junction ventral to the brainstem.

The disadvantages are that it only provides limited control of the ICA (dorsal and lateral aspects) and hence extensive involvement of the IAC is a contraindication for the POTS approach for which either modified transcochlear or infratemporal fossa Type A approach is indicated. Injury to the lower cranial nerves and CSF leak are the potential complications. Also this is not useful in highly vascular and invasive glomus jugulare tumours for which the infratemporal fossa Type A approach is preferable.

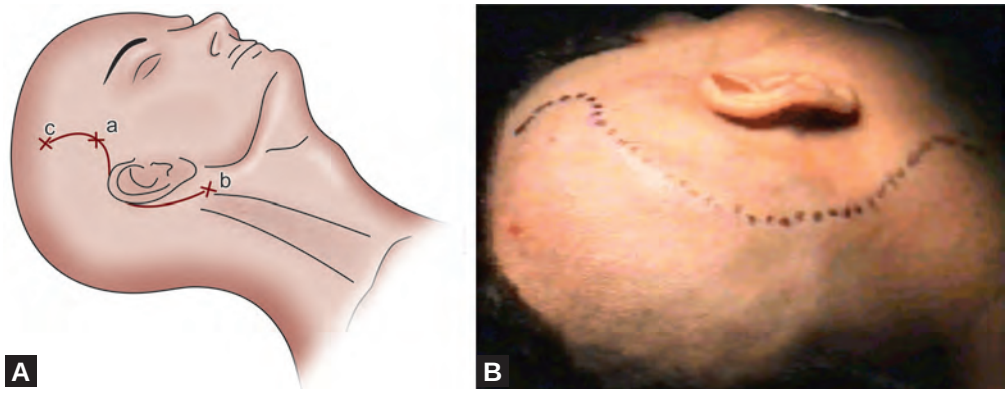
Infratemporal Fossa Approach Type A[5]

Described by Ugo Fisch, it is one of the most important combined approaches to jugular foramen lesions, belonging to the lateral group of approaches.

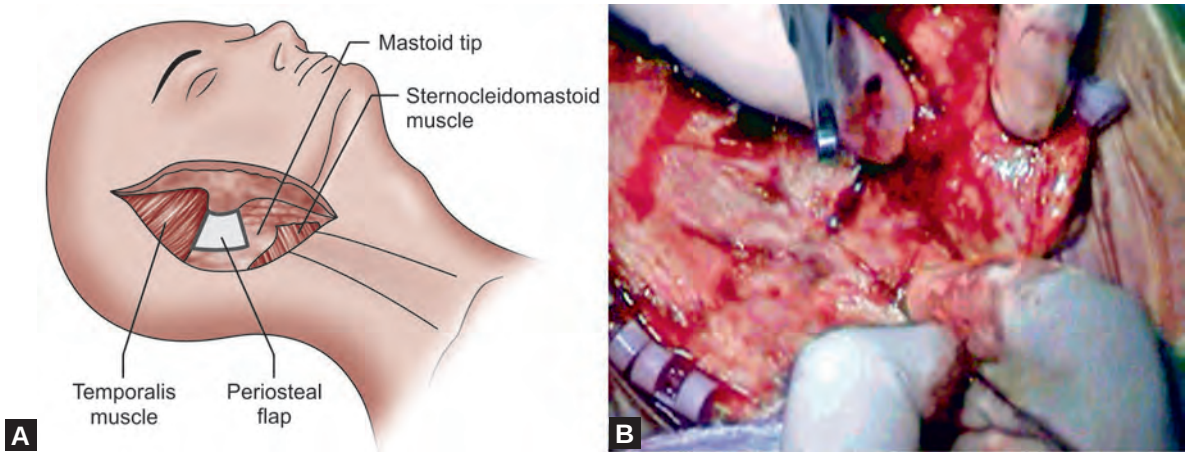
Indications: Jugular foramen lesions, especially large glomus jugulare tumours, some lower cranial nerve neurinomas and meningiomas and lesions of infralabyrinthine and apical portion of the petrous temporal bone, like cholesteatoma, chordoma of lower clivus and carcinomas invading these regions and extensive facial nerve neurinomas.

Technique: A postauricular skin incision extending superiorly to the temporal region and inferiorly along the anterior border of the sternomastoid muscle 5–6 cm below the mastoid tip with a preauricular limb is used (Figs 2A and B). A small anteriorly based musculoperiosteal flap is raised and a cul-de-sac closure of the external auditory canal is done (Figs 3A and B, 4A and B and 5). By neck dissection, the VII nerve, as it exits the stylomastoid foramen, is identified and its main trunk is traced into the parotid gland till the proximal parts of the temporal and zygomatic branches. The lower cranial nerves, the ECA, ICA and IJV are exposed in the upper neck (Fig. 6). After dividing the sternomastoid muscle and the posterior belly of the digastric muscle, the ECA is ligated distal to its lingual branch. The skin over the external auditory canal, the tympanic membrane, and the malleus and incus are removed. A radical mastoidectomy is done (Figs 7A and B). The VII nerve is freed from the fallopian canal from the geniculate ganglion to the stylomastoid foramen and transposed anteriorly and fixed to the new bony canal drilled in the root of the zygoma superior to the eustachian tube and to the tunnel created in the parotid gland to lodge the nerve. The hypotympanum is drilled completely to expose the vertical portion of ICA. The ascending mandibular ramus is displaced anteriorly and the mandibular condyle is resected in case of large tumours. The SS is either packed or doubly ligated and, if necessary, its lateral wall is removed up to the level of the jugular bulb and lateral wall of the jugular bulb is opened, taking care to pack the IPS and the entry of the condylar emissary veins into it. The IJV is doubly ligated and cut in the neck and elevated superiorly taking care not to injure the XI nerve. In case of limited intradural extension of the tumour, the dura is opened without injuring the endolymphatic sac.

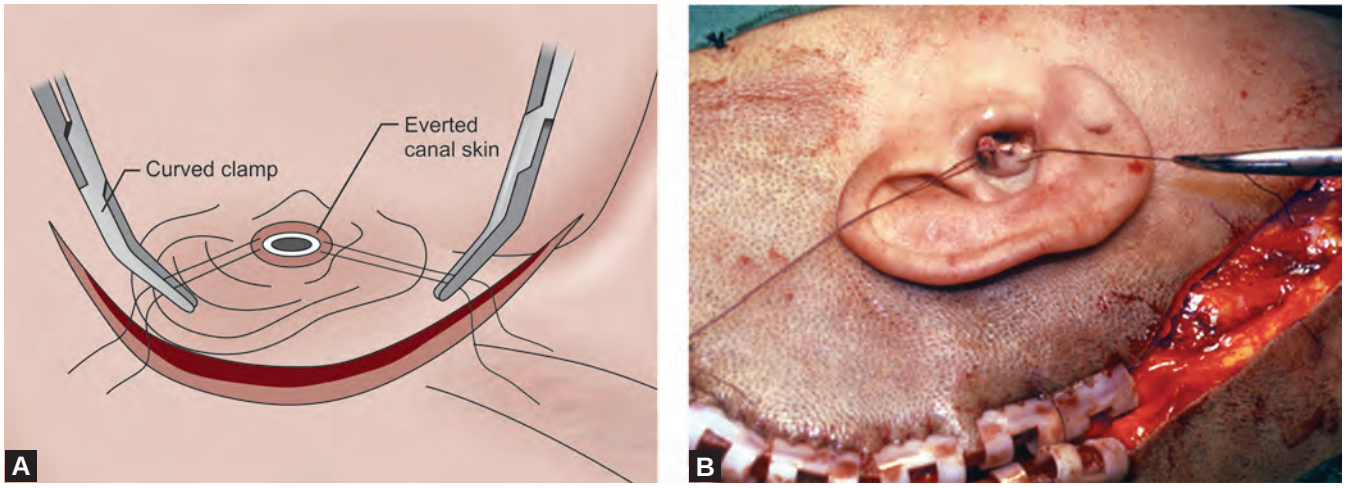
Advantage: It offers wide exposure anterior to the JF and to the infratemporal fossa up to the petrous apex.



Figs 2A and B: Incision



Figs 3A and B: Periosteal flap separation



Figs 4A and B: Cul-de-sac closure

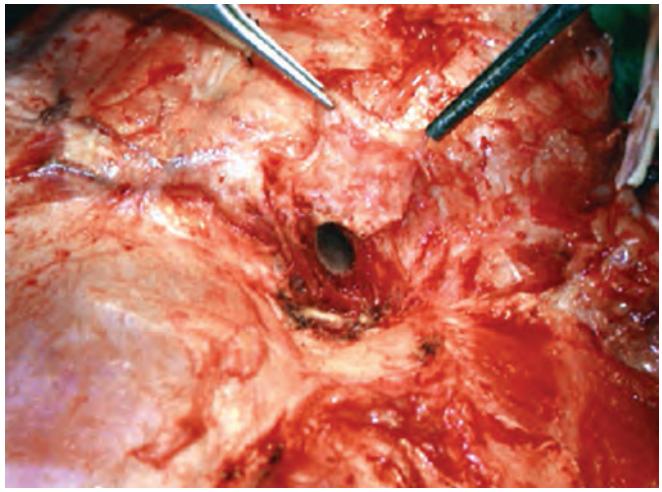


Fig. 5: Cul-de-sac closure

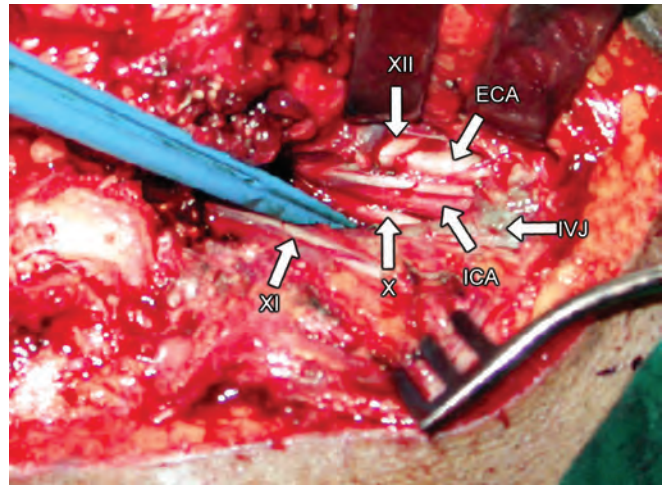
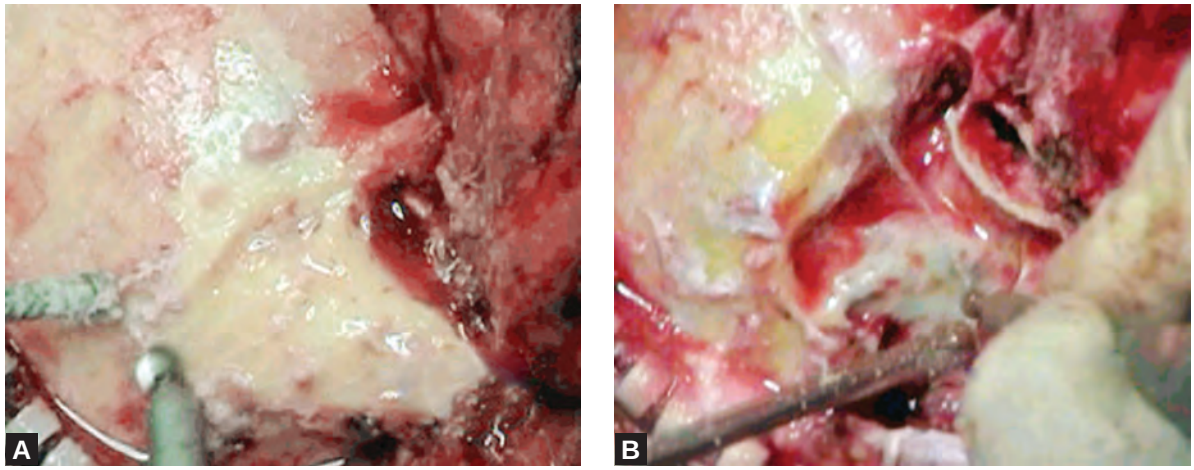
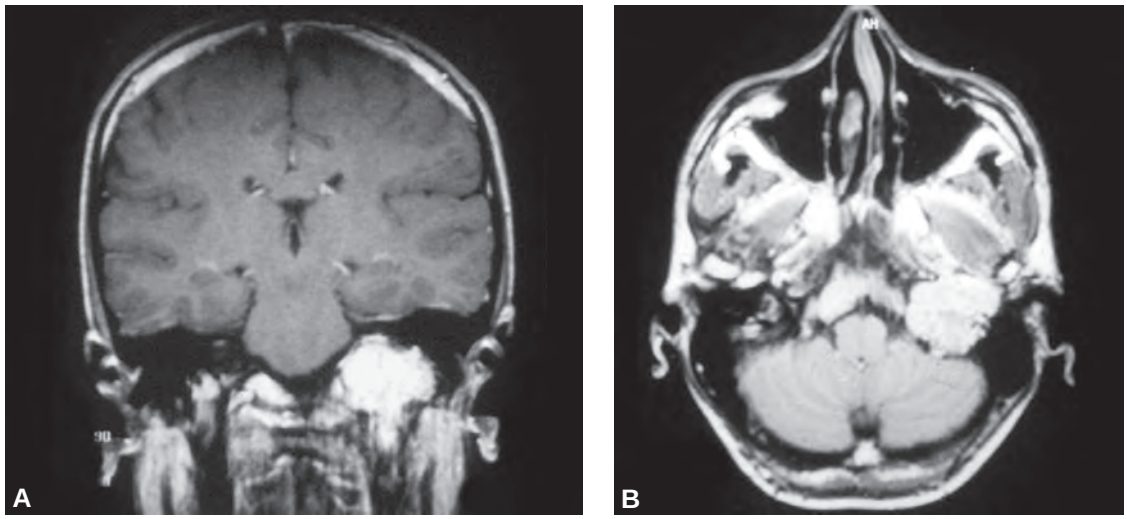


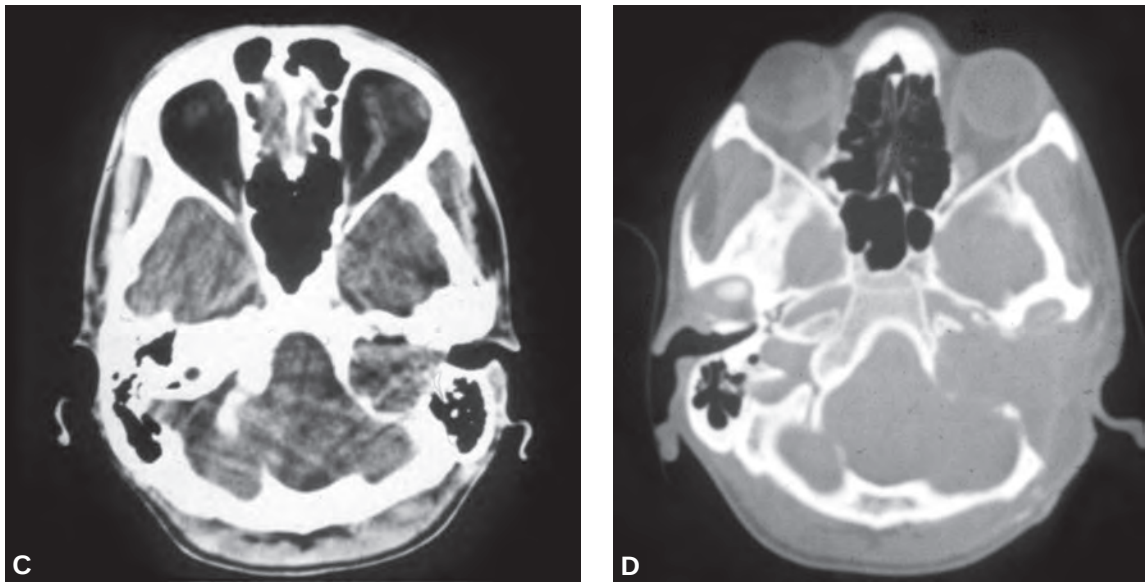
Fig. 6: Control of great vessels and lower cranial nerves



Figs 7A and B: Mastoidectomy



Figs 8A and B: Pre-operative large, highly vascular lesion in the left jugular foramen extending into the CP angle and jugular bulb



Figs 8C and D: Post-operative scans showing total removal

Disadvantage: Apart from hearing loss, facial paralysis and numbness and malocclusion, this is not suitable for large intracranial tumour extension and for the large tumours reaching the foramen lacerum or cavernous sinuses. For this infratemporal fossa, Type B or C (anterior) approaches has to be combined with this Type A (lateral) approach.

Modifications of This Approach

Since hearing cannot be preserved in Type A Fisch's infratemporal fossa approach in patients with preserved hearing, Pensak and Jackler in 1997 advocated an approach that preserves the external auditory canal and middle ear structures and allows working anterior and posterior to the descending segment of VII nerve which is not re-routed.[23] But this is possible only in tumours that do not erode the carotid genu.

Sekhar and Schramm advocated a combined lateral and posterior cranial base approach (preauricular subtemporal-infratemporal fossa) for large tumours, which differs from Fisch's approach in that the VII nerve is not displaced from the temporal bone.[31]

The Type B infratemporal fossa approach is mainly designed for extradural petrous apex and midclival tumours, with preservation of the inner ear function. It is used in association with the Type A infratemporal fossa approach for extensive glomus tumours involving the petrous and the midclivus. This involves reflection of the zygomatic arch inferiorly and division of the middle meningeal artery and mandibular branch of V nerve. This gives exposure up to the foramen lacerum, petrous apex and clivus.

The Type C approach involves an orbitozygomatic reflection, sectioning of some branches of the facial nerve in the parotid area, resection of the pterygoid process and sectioning of V3 nerve. This gives wider exposure to the carotid artery in the cavernous sinus.

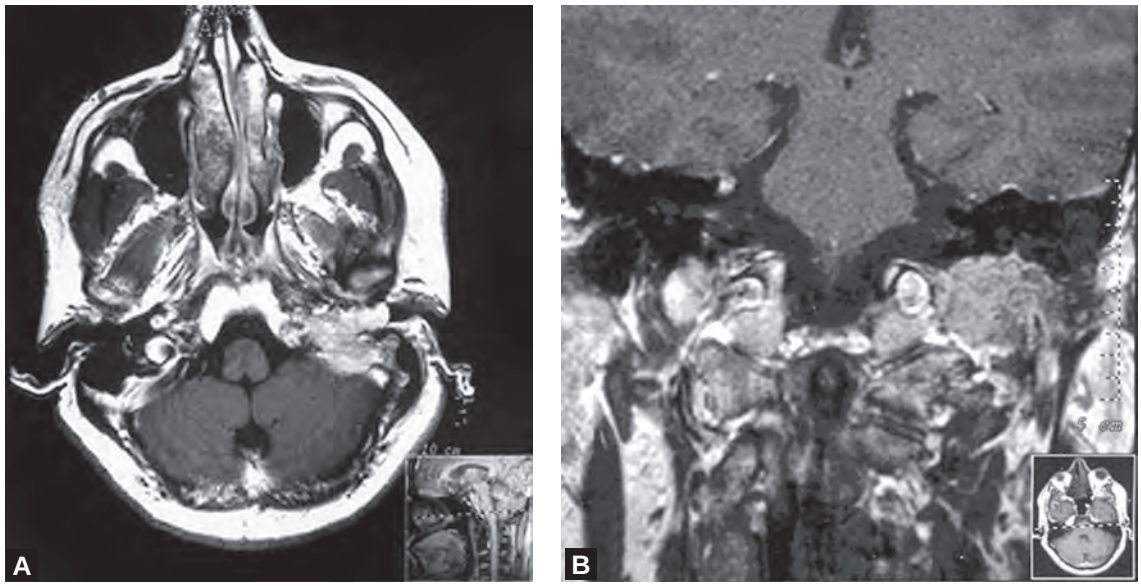
Modified Transcochlear Approach[6,22]

One of the lateral skull base approaches described by Mario Sanna provides better visualisation of the ventral brainstem and vertebrobasilar junction by removing the petrous apex and clivus and excellent control of the vertical and horizontal segments of the ICA.[6] It is classified into Types A–D. Type A is the basic approach which, but by itself, provides only limited access to tumours extending into the jugular bulb and down to the foramen magnum. It is indicated for extradural lesions involving the petrous apex with VII nerve and inner ear compromised (e.g. petrous bone cholesteatoma, extensive VII nerve neurinoma, recurrent VIII nerve neurinoma), intradural recurrent VIII neurinomas, large petroclival meningiomas and for transdural lesions invading the petrous bone like residual glomus tumour, chordoma, etc.

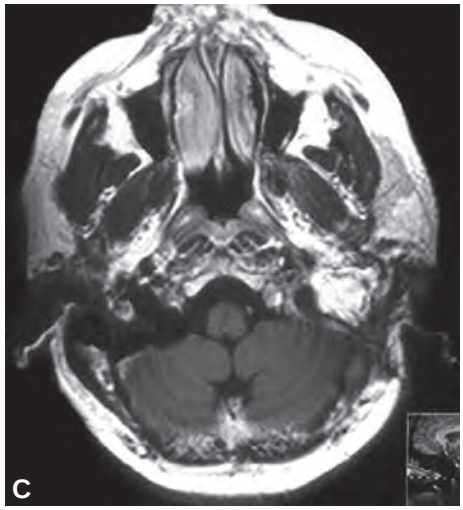
Type A Modified Transcochlear Approach

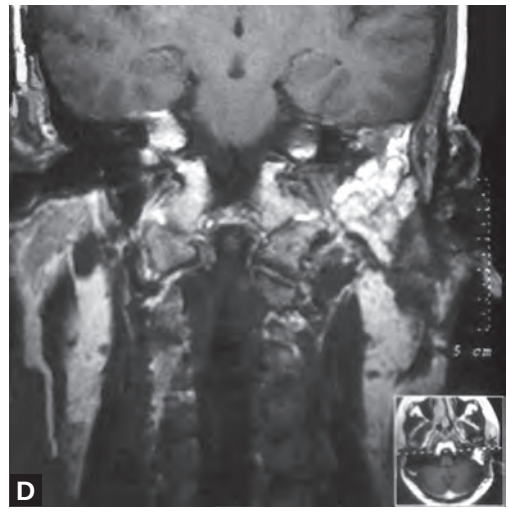
Technique: A 'C' shaped post-auricular skin incision is made. Blind sac closure of the external auditory canal, extended mastoidectomy, posterior re-routing of VII nerve after its complete mobilisation from the stylomastoid foramen up to the geniculate ganglion and labyrinthectomy are done. The greater petrosal nerve and vessels are sacrificed. The internal auditory canal is not opened. The fallopian canal and the cochlear and anterior wall of the IAC are drilled, and the vertical segment of the internal carotid artery is exposed. Then the petrous apex and anterior wall of the EAC are drilled. The mandibular condyle is displaced anteriorly. The petrous apex is drilled up to midline to get full control of the horizontal part of ICA. The dura is incised in front of the internal auditory canal taking care not to injure the VII nerve.

Its disadvantages include risk of injury to the VI nerve while incising the dura of the petrous apex and injury to the VII nerve during its mobilisation.



Figs 9A and B: Pre-operative 30-year-old male with a well defined lobulated extra axial mass in the left CP angle eroding left JF and left internal auditory canal





Figs 9C and D: Post-operative scans of the same patient

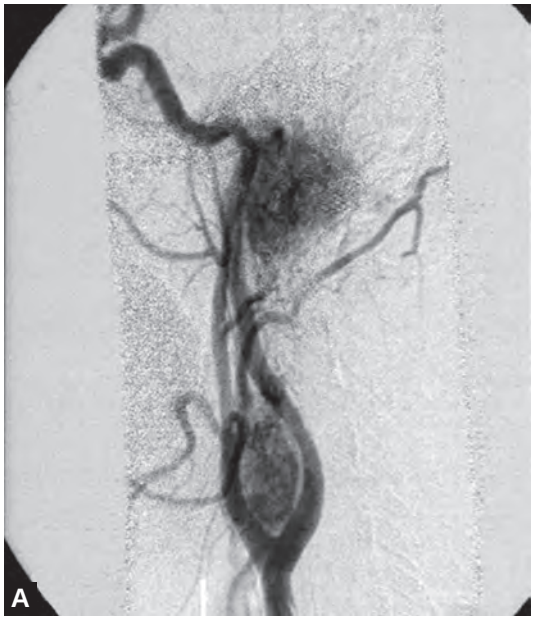


Fig. 10A: Pre-embolisation angiogram of a highly vascular glomus jugulare tumour

Type B modified transcochlear approach incorporates Fisch's Type B or C infratemporal fossa approach with Type A modified transcochlear approach and is used for lesions extending into the parapharyngeal space.

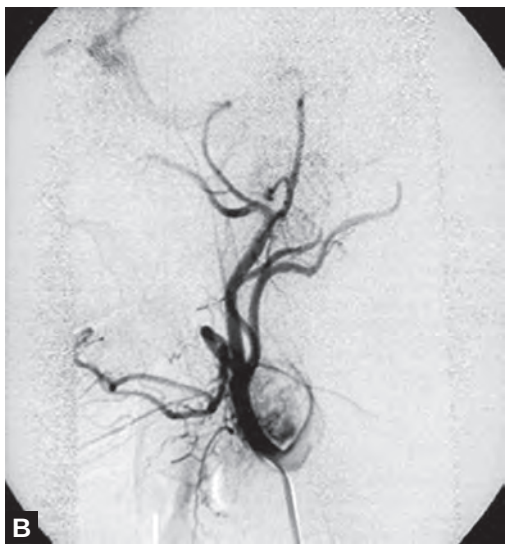
Type C modified transcochlear approach allows control of both the infratentorial and supratentorial parts of the tumour lying ventral to the pons and midbrain and is indicated for petroclival tumours with supratentorial extension.

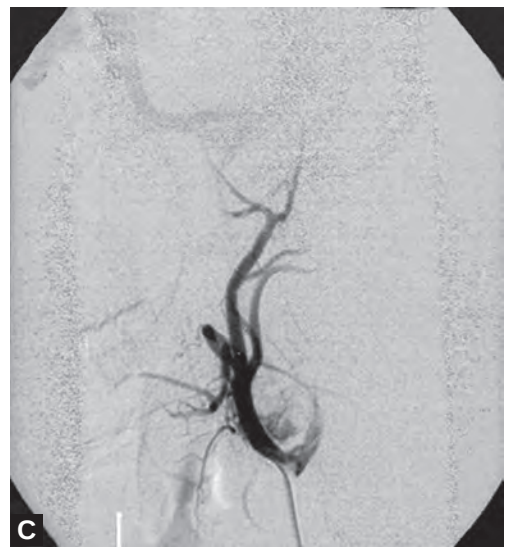
Type D modified transcochlear approach incorporates either POTS or the extreme lateral approach Type A modified transcochlear approach. This is indicated in mid and low clival lesions, petroclival meningiomas and extensive lower cranial nerve neurinomas. If it is necessary to get excellent control of the caudal part of the medulla, the VII nerve may be transposed anteriorly.

Few cases successfully managed by the author are shown in Figures 8 to 11.

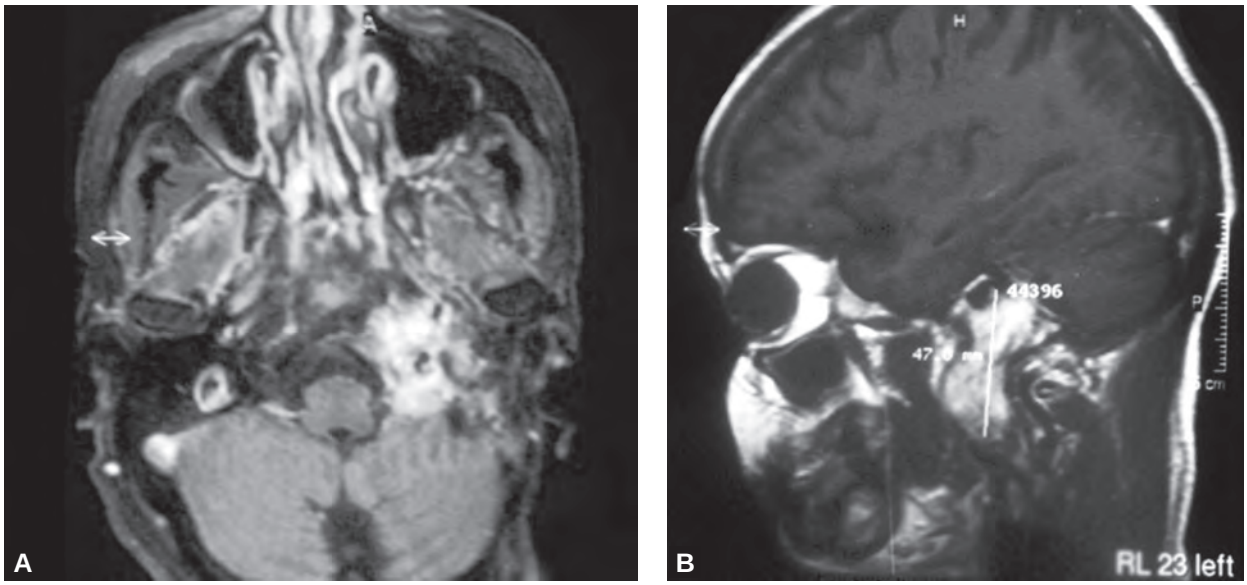
POST-OPERATIVE COMPLICATIONS

Many of the complications (Table 4) are related to the size, vascularity and extent of the tumour, choice of

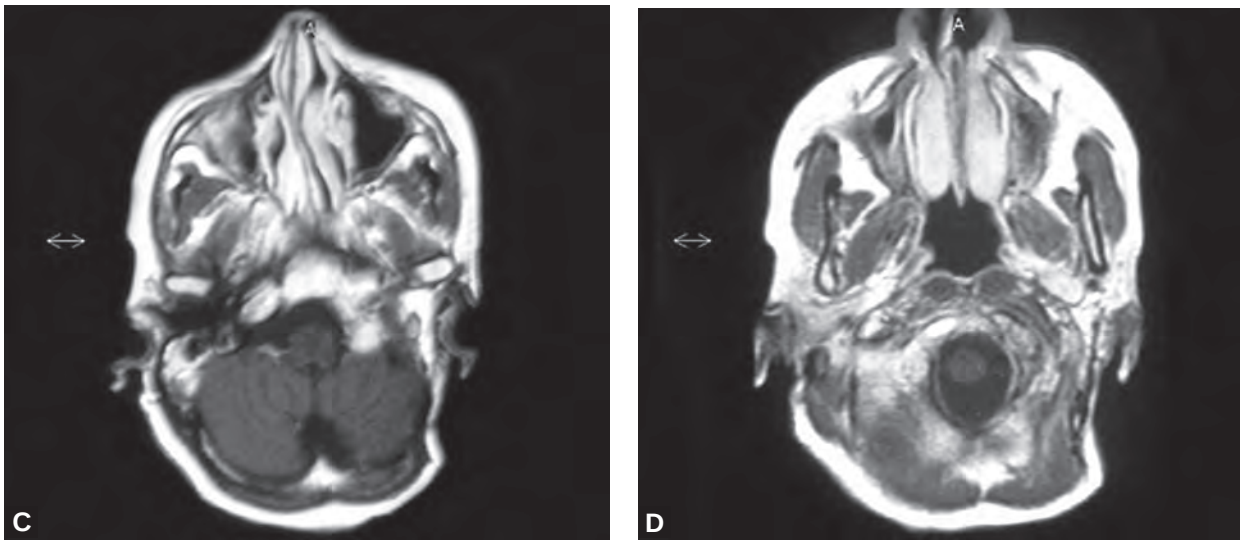




Figs 10B and C: Post-embolisation angiogram



Figs 11A and B: Pre-operative scans of a large irregular extra-axial lesion in the left jugular foramen extending medially into the CP angle with erosion of the left petrous



Figs 11C and D: Post-operative scans of the same patient

the surgical approach, skill of the surgeon and the pre-operative condition of the patient. Some complications (e.g. infarct) that are related to pre-operative endovascular embolisation can also occur in the post-operative period. In general, if there are no neurovascular deficits pre-operatively, then meticulous care is to be taken in order to preserve their functions. In preventing post-operative CSF leak, which is the most frequent complication, a lumbar drain is preferred to intraventricular drain since the latter is fraught with the risk of intraventricular haemorrhage, which may prove fatal.[6] Excessive CSF drainage is also to be avoided, to prevent low intracranial pressure and subsequent subdural haemorrhage. Special mention should be made of cranial nerve dysfunction. This is the most serious complication. The size of the lesion is generally correlated with the dysfunction and the recovery.[14] In smaller lesions the post-operative morbidity is minimal and the chance for long-term improvement is excellent. There are reports of excellent long-term recovery in patients in whom the nerves were sectioned,[14] but functional recovery is dependent on nerve continuity after surgery. Another important point is that if lower cranial nerve dysfunction is already present pre-operatively, the patients will usually be compensated for this deficit and so an aggressive surgical strategy can be undertaken without producing any increase in their pre-operative deficit.[25] In general, complications can be avoided by carefully scrutinising the pre-operative images, selecting the most appropriate approach or its modification, tailored according to the need and by giving enormous attention to the technical details.

Table 4: Post-operative complications and their prevention and treatment

Complication	*Subclassification*	*Prevention*	*Treatment*
CSF leak and impaired wound healing	Incisional Rhinorrhoea Otorrhoea Pseudomeningocoele	Watertight dural closure with graft, packing of the cavity with fat, vascularised muscle flap Pre-operative treatment of middle ear infection	Re-opening and closure of the dural defect
Infection and meningitis	Osteomyelitis Subdural Empyema Brain abscess Sepsis	Peri-operative antibiotics Attention to the technique of dural closure and use of vascularised flap Pre-operative treatment of middle ear infection	CSF culture and antibiogram and appropriate antibiotic therapy
Cranial nerve injury	III, IV, VI—diplopia V, VII—facial numbness and weakness, VIII—hearing loss IX, X—dysphagia, malformation and dysdigestion	Intra-operative neurophysiological monitoring, pre-operative radiotherapy or embolisation to reduce tumour size, choosing the appropriate surgical approach Avoid using the bipolar coagulation near the nerves Intra-operative nerve suturing XII to VII anastomosis	For VII N palsy—eye lubricants tarsorrhaphy, gold weight insertion the upperlid For IX, X, XI N Palsy—Ryles tube nutrition, PEG feeding, tracheostomy, laryngoplasty or injection of Teflon into the vocal cord Treatment of secondary chest infection due to aspiration
Vascular injury	Arterial-infarction, Pseudoaneurysm (ICA, VA, PICA) Venous—infarction, Sinus thrombosis (vein of Labbé, SS, IJV) Haematomas	Attention to pre-operative neuroimaging studies. Attention to meticulous surgical techniques Extra-intracranial or Intra-intracranial bypass procedures	Vascular repair Evacuation of clots after post-operative CT confirmation
Late events	(a) Hydrocephalus (b) Craniocervical instability (c) Catecholamine secretion (carotid sinus syndrome) (d) DVT of lower limbs (e) Trismus and incorrect dental occlusion (f) Eustachian tube dysfunction (recurrent otitis media) (g) Psychological problems (h) Neuropeptides affecting gastrointestinal function (prolonged ileus, pancreatitis, cholecystitis and biliary tract complications)	Careful haemostasis Preserve articular facets, if possible Muscle packing	EVD or rarely VP shunt OC fusion Alpha and beta blockers Fraxiparine S/C, filters in IVC Dental Tr

ACKNOWLEDGEMENTS

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164 Other Intracranial Schwannomas

Ashish Suri, Shashwat Mishra, Ajay Garg

INTRODUCTION

Schwannomas are benign, slow-growing, encapsulated tumours, which arise from the proliferation of Schwann cells. They constitute about 8% of all brain tumours.[39] Since Schwann cells myelinate all the cranial nerves with the exception of I cranial nerve and II cranial nerve, schwannomas can potentially originate from any of the remaining cranial nerves. Cranial nerve schwannomas account for 60% of all the schwannomas.[34] Along the course of the nerve root, the site of origin of these tumours is at or distal to the Obersteiner-Reidlich zone where the transition between central and peripheral myelin occurs. The zone of transition is usually within several millimetres of the origin of the nerve from the brainstem. Schwannomas have a predilection for the sensory cranial nerves. Involvement of motor cranial nerves is commonly associated with neurofibromatosis.[3,35,37] Vestibular schwannomas, with an annual incidence of 1/100,000 of the general population, comprise 80–90% of all intracranial schwannomas. The non-vestibular schwannomas most commonly involve the V nerve (40%), followed by the facial (23%) and the lower cranial nerves (LCNs) (20%).[13,31] In the absence of neurofibromatosis, schwannomas arising from the extraocular nerves are extremely rare. An intracranial schwannoma arising from the sympathetic plexus around the intracavernous carotid artery has also been reported.[40]

FACIAL NERVE SCHWANNOMAS

Facial nerve schwannomas (FNSs) make up only about 1.9% of all intracranial neuromas.[38] Although the facial nerve is predominantly motor, association of FNSs with neurofibromatosis is rare. The FNSs may arise from any segment of the nerve, from the cerebellopontine angle (CPA) to the extracranial extent of the nerve. Lipkin et al.[21] have classified FNSs according to the site of origin along the VII nerve into labyrinthine, tympanic, geniculate and vertical segment lesions. The geniculate ganglion and the adjoining labyrinthine segment of the nerve is considered to be the most common site of origin for schwannomas.[38,41] Large FNSs arising from the geniculate ganglion can present as middle cranial fossa masses with erosion of the anterior surface of the petrous bone. Extension along the course of the greater superficial petrosal nerve (GSPN) may also be seen.

Clinical Presentation

These tumours usually occur in the fourth decade and incidence in the sexes, is similar.

The presenting features of FNSs vary according to the facial nerve segment from which they arise. Slowly progressive facial paresis and hearing deficits are the most common symptoms of FNSs (Table 1). Hearing loss may either be conductive or sensorineural depending upon the location of the tumour. A proximally arising tumour may compromise the vestibulocochlear nerve while the middle ear cavity may be involved by distally originating FNS.

Occasionally, hemifacial spasms evolving into progressive facial weakness may also be seen with FNS extending within the internal auditory canal (IAC). Proximally arising intradural FNS can be virtually indistinguishable from vestibular schwannoma. Extension of tumour into the middle cranial fossa and early involvement of the facial nerve by a relatively small sized tumour often provide a clue to the facial nerve origin of a schwannoma. The diagnosis should be entertained in patients with progressive facial paresis or worsening of weakness following an incomplete Bell's palsy.

Otorrhoea and ear canal fullness is observed in tumours arising from the mastoid/vertical segment of the facial nerve. In many cases, the tumour may be incidentally detected during evaluation for other complaints.

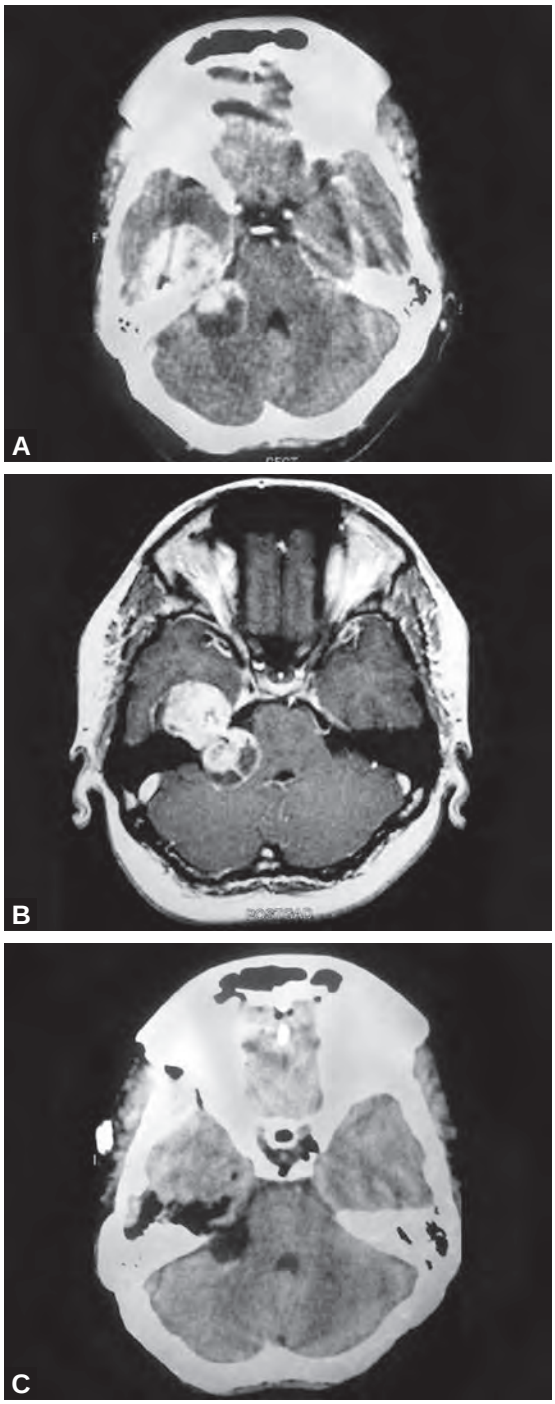
Table 1: Presenting features of facial nerve schwannomas[20]

Symptom	*Number of patients (%)*
Facial weakness	270 (63.2%)
Hearing loss	216 (50.6%)
Tinnitus	88 (20.6%)
Vestibular symptoms	61 (14.3%)
Ear canal mass	47 (11.0%)
Pain	35 (8.2%)
Otorrhoea	15 (3.5%)
Loss of taste	12 (2.8%)
Parotid mass	12 (2.8%)
Facial spasm	9 (2.1%)
Total	427

Diagnosis

FNSs appear as round, well-delineated masses in the CPA, IAC or facial nerve canal. They can extend to the middle cranial fossa, middle ear, the stylomastoid foramen or parotid gland.

The basic imaging features of schwannomas are seen in FNSs (Figs 1A to C). Computerised tomography (CT) scan shows an enhancing soft-tissue density mass. With use of bony algorithm, CT demonstrates a benign type of expansile, lytic change or remodelling of the bone. Aggressive bony destruction is not seen. On magnetic resonance imaging (MRI), FNS is mildly hypointense to isointense on T1-weighted images; is heterogeneously hyperintense on T2-weighted images and enhances following administration of gadolinium. Heterogeneity or cystic change may also be seen in large FNSs.[20]



Figs 1A to C: Facial (VII) nerve schwannoma. (A) Preoperative contrast computerised tomography (CT). (B) MRI showing enhancing dumb-bell shaped tumour in the middle and posterior fossa. (C) Post-operative contrast CT showing complete excision of the tumour using the extended middle fossa approach

Additional distinct imaging features are seen depending on the location of FNS. The FNSs in the CPA or in the IAC may be clinically and radiologically indistinguishable from acoustic schwannomas,[26] however, eccentricity of tumour mass to the axis of the IAC may be a diagnostic clue.[9] In addition, when an IAC FNS enters the labyrinthine segment of the facial nerve, it appears as a double dumb-bell shaped tumour and may be associated with benign, sharply marginated remodelling with enlargement of the labyrinthine segment of the facial nerve canal, often with enlargement of the geniculate fossa.[25] FNS in the region of the geniculate ganglion may also involve the labyrinthine and tympanic segments of the facial nerve and may extend through the facial hiatus for the GSPN to involve the middle cranial fossa. A tympanic segment FNS, often lobulates into the middle ear. Mastoid segment FNS may break into the adjacent mastoid cells. The FNS can also cause enlargement of the chorda tympani canal, situated between the mastoid segment of the facial nerve canal and the middle ear cavity.

Management

The clinical experience with these tumours is limited and no definite treatment guidelines can be proposed. In a series of 12 conservatively managed patients facial function was seen to deteriorate in 38% of the patients over a mean follow-up of 6 years.[29]

The timing of intervention in FNS is debatable. Those in favour of early intervention[34,38] argue that the risk to hearing is less and chances of preservation of facial nerve function/reconstruction of the facial nerve is better in patients with mild paresis. Proponents of the "wait and watch" policy,[17,21] emphasise the slow growing nature of these tumours with potentially prolonged preservation of facial nerve function, which has to be weighed against the risk of deterioration following surgery. Commonly, incidentally detected and small sized tumours with mild facial paresis are managed expectantly.

Microsurgical excision with repair of the facial nerve has traditionally been recommended as the treatment of choice in symptomatic patients. The main concern is facial nerve palsy following surgical excision of the schwannoma. End-to-end anastomosis with interposition cable graft and facial-hypoglossal anastomosis have been used for partial restoration of facial nerve function. However, improvement beyond House-Brackmann grade III has rarely been seen after post-operative facial palsy.

The experience with radiosurgery for FNSs is limited, in part, because of the rarity of these tumours.

Small series of radiosurgically treated patients have demonstrated good tumour control without post-treatment worsening of facial paresis.[22,24] However, longer follow-up is needed before the role of radiosurgery can be clearly established.

Surgical Approach

The approach to these tumours is determined by the location of the tumour.[20,34,36,38] Schwannomas projecting predominantly into the CPA are approached by the retrosigmoid sub-occipital route. Tumours based in the middle fossa are exposed and resected extradurally via the sub-temporal middle fossa approach. Anterior petrosectomy (Kawase's) may be added to the middle fossa approach for tumours extending into the posterior fossa. Transpetrous approaches (retrolabyrinthine, translabyrinthine, transcochlear) can be used in patients with complete loss of hearing and tumour extension into the IAC and middle ear. The transpetrous approach may facilitate anastomotic facial nerve reconstruction by identification of the proximal end of the facial nerve at the IAC and the uninvolved mastoid segment. Sural nerve interposition graft is used in these cases. Large tumours with extensive middle fossa and posterior fossa extension often require staged resection by the sub-temporal and retrosigmoid routes.

LOWER CRANIAL NERVE SCHWANNOMAS

The LCN schwannomas constitute about 2.9–4% of all intracranial neuromas.[32] They include schwannomas arising from the glossopharyngeal, vagus, and accessory and hypoglossal nerves. The IX, X and XI cranial nerves arise from the post-olivary sulcus of the anterior brainstem, traverse the jugular foramen and emerge extracranially in close relation to the internal jugular vein and the internal carotid artery. The hypoglossal nerve originates by a series of rootlets in the pre-olivary sulcus anterior to the IX, X and XI nerve rootlets and exits the posterior skull base through the hypoglossal canal. The schwannomas may arise from the intracisternal, intraforaminal or the extracranial segment of these cranial nerves.

Clinical Presentation

Intracranially, these tumours mainly present as jugular foramen masses. In most cases, the nerve of origin cannot be determined but in cases where the nerve of origin was recognisable, IX nerve origin was the most common followed by the X and XI nerve origin. The site of origin of these tumours along the pars nervosa has been postulated to manifest distinct patterns of tumour growth.[15,18,34] On the basis of this, jugular foramen schwannomas have been classified (Table 2) by Kaye et al[15] with modifications by Pellet et al.[28] and Samii et al.[30]

Overall features of raised intracranial pressure, hearing loss, tinnitus, ataxia and LCN dysfunction are the most common manifestations of jugular foramen schwannoma.[2] Other presentations include facial nerve dysfunction (facial paresis, hemifacial spasm, loss of taste sensation), ear canal masses and neck lumps.

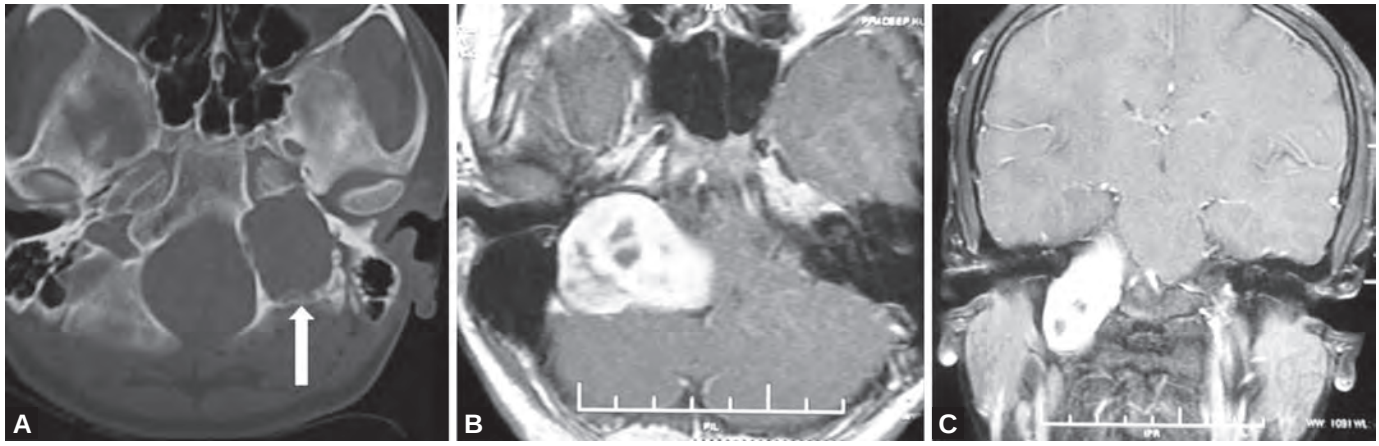
Diagnosis

The CT and MRI appearances of jugular schwannomas are similar to those of other schwannomas, varying with the proportion of cellular and cystic components of the tumour. Jugular schwannomas are isodense or hypodense on CT because of their rich lipid content (Figs 2A to C). Bone algorithm CT shows smooth and sharply-marginated jugular foramen enlargement.[7] Selective enlargement of the pars nervosa can be suggestive of glossopharyngeal schwannomas. In MRI, jugular schwannomas appear as well-circumscribed masses with low-signal intensity on T1-weighted and high-signal intensity on T2-weighted magnetic resonance images (Figs 3A to E). Following administration of gadolinium, dense enhancement with or without intratumoural cysts (in up to 25% cases) is seen.[5] No intratumoural flow-voids are seen.

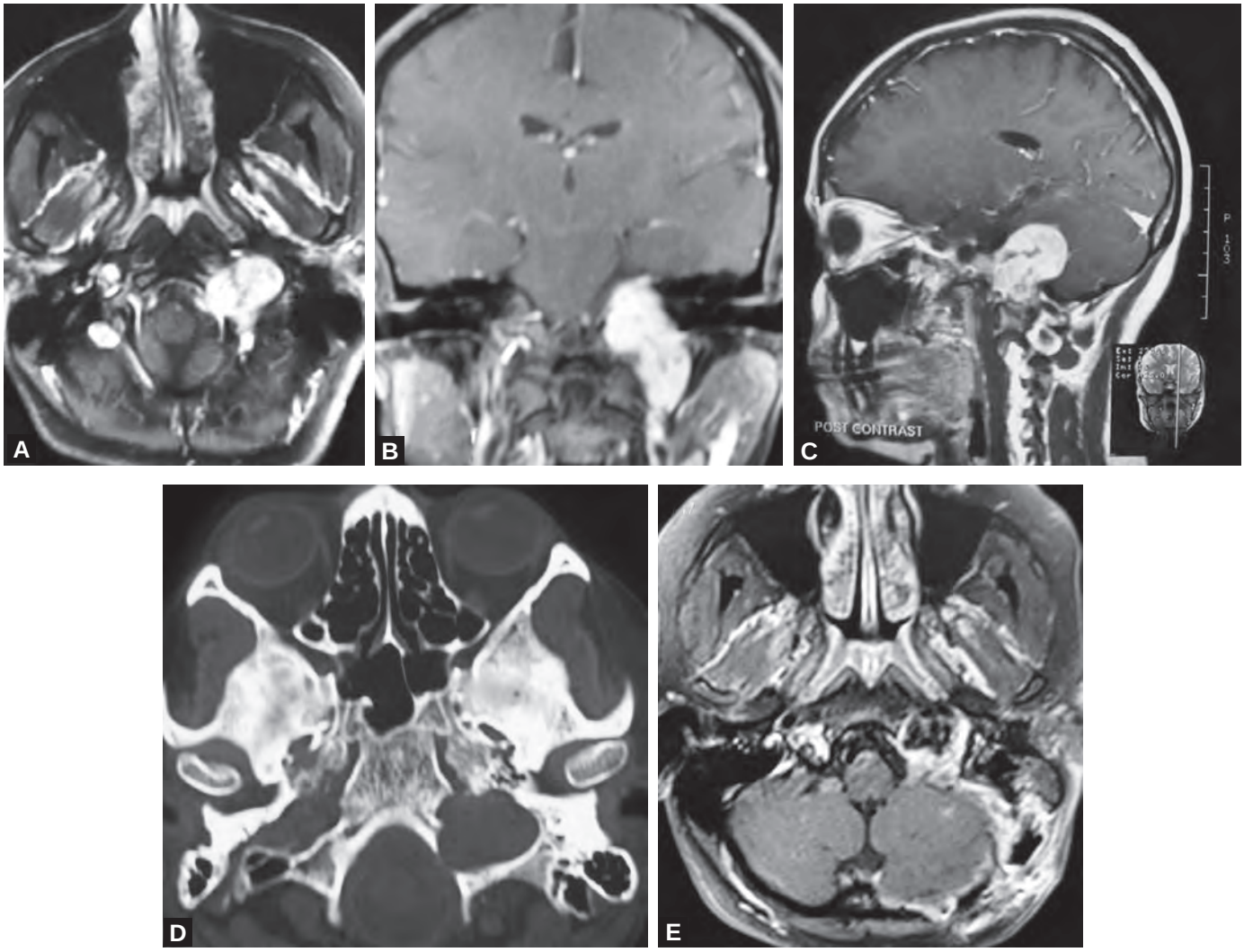
Differential diagnosis of jugular fossa masses includes glomus jugulare and jugular fossa meningioma. Glomus jugulare produces irregular erosion of the margin of the jugular foramen with decalcification or destruction of the surrounding bone. Additionally, glomus jugulare

Table 2: Classification of jugular fossa schwannomas

Class	*Growth pattern*	*Postulated site of origin*	*Clinical presentation*
A	Primary intracranial tumour with small extension into the bone	Proximal, intracisternal pars nervosa	Audiovestibular symptoms and ataxia akin to vestibular schwannoma. Lower cranial nerve involvement uncommon
B	Primary tumour in the jugular foramen with or without intracranial extension	Intraforaminal	Lower cranial nerve paresis
C	Primary extracranial tumour with extension into the jugular foramen or into the posterior fossa	Distal pars nervosa	Jugular foramen syndrome—hoarseness of voice, diminished gag and atrophic weakness of shoulder
D	Dumb-bell shaped tumour with intracranial and extracranial extension		Can have features of all the three above. Extracranial extension may be palpable as neck mass in parapharyngeal space



Figs 2A to C: Type B jugular fossa schwannoma showing. (A) Enlargement of jugular foramen (arrow) in computerised tomography head. In contrast enhanced. (B) Coronal. (C) Axial magnetic resonance imaging sections, a brilliantly enhancing tumour is seen within the jugular foramen with extension into the cerebellopontine angle cistern



Figs 3A to E: Type D jugular fossa schwannoma showing a brilliantly enhancing tumour within the jugular foramen, with extension into the cerebellopontine angle cistern and extracranial extension in contrast enhanced. (A) Axial. (B) Coronal. (C) Sagittal MRI sections. (D) Enlargement of jugular foramen (arrow) in computerised tomography head. (E) Post-operative magnetic resonance imaging showing complete removal of intracranial and foraminal portions

are angiographically highly vascular, with an intense contrast stain and readily apparent vascular pedicle(s) and have intratumoral flow-voids on T2-weighted MRI.[8] On the other hand, LCN schwannomas symmetrically expand the jugular foramen with smooth, sharply outlined and sclerotic margin of the eroded adjacent bone, do not appear very vascular at conventional angiography and have no intratumoural flow-voids.[8] Primary jugular foramen meningioma is characterised by a permeatal–sclerotic appearance of the bone margins of the jugular foramen, the presence of dural tails and an absence of flow-voids.[23]

Management

Presently, microsurgical resection and radiosurgery are the available options for the management of these patients. Observation is reserved for patients who are extremely poor surgical risks. Due to limited availability and high cost of radiosurgical apparatus, stereotactic radiotherapy has also been tried in patients with non-acoustic schwannomas.

Surgical Approach

The choice of surgical approach is determined by the size, location of the lesion and pre-operative hearing status.

Type A tumours: Since these tumours are primarily limited to the intracranial compartment with little erosion of the bone, they can safely be excised with the classical retrosigmoid approach.

Type B to D tumours: The complete extirpation of these tumours is difficult. With the evolution of microneurosurgery and refinement of surgical techniques, the optimal choice of approach for these tumours has undergone radical changes. A cervical transmastoid approach is generally recommended for these tumours. A retroauricular skin incision extending up to the level of the hyoid bone is used. The sternocleidomastoid muscle and the posterior belly of the digastric are mobilised to expose the mastoid bone. The LCNs are identified in the neck and followed-up to the skull base. The main stem of the facial nerve is identified in the stylomastoid foramen anterior to the insertion of the digastric muscle. The transverse and the sigmoid sinuses are then exposed through a sub-occipital craniectomy. The petrous temporal bone is then drilled to skeletonise the sigmoid sinus, which is then mobilised. Extent of further drilling then differs according to the growth pattern of the tumour. For type B tumours, an infralabyrinthine approach is recommended to preserve hearing function in patients with preserved hearing. The jugular bulb is skeletonised and the dura is incised in the supra jugular region below the labyrinth. A translabyrinthine-transcochlear approach is chosen in patients with complete loss of hearing. Type C tumours are best approached through an infratemporal approach (Type A) described by Fisch,[10] which enables direct access to the jugular foramen and the neck and provides good control of the adjoining vasculature.

The Type D tumours represent a special case. Though staged resections were the norm earlier, many authors have demonstrated the possibility of a single-stage resection.[14,32] For a single-stage resection, an extreme lateral transcondylar approach is combined with sub-occipital craniotomy. Alternatively, a staged sub-occipital craniotomy followed by an infratemporal approach can be undertaken.

Schwannomas do not infiltrate the cranial nerves or the jugular bulb and safe radical excision of these tumours is possible with acceptable morbidity. The post-operative morbidities generally seen are facial nerve dysfunction, transient worsening of LCN function and CSF leak. In patients with pre-operative LCN paresis, post-operative LCN deficits are generally well tolerated because the slow pre-operative evolution of deficits has allowed the other side to compensate. However, patients with intact LCNs in the pre-operative period are susceptible to life-threatening complications in the event of a lower cranial palsy following surgery and must be observed vigilantly.

Radiosurgery and stereotactic radiotherapy are the treatment options for small LCN schwannomas with intact cranial nerves though microsurgical complete excision is possible in general and is potentially curative. Tumour control rates ranging form 96 to 100% have been reported with tumour shrinkage noticeable in 47–52% patients.[27,42]

SCHWANNOMAS OF THE OCULAR MOTOR NERVES

Schwannomas of the oculomotor, trochlear and abducens nerve are rarely encountered in the absence of neurofibromatosis. Less than 100 cases of schwannomas arising from the ocular motor nerves have been reported in the literature.[16] The oculomotor and the trochlear nerves are most frequently involved. Celli et al.[6] have classified these tumours into cisternal, cisternal-cavernous and cavernous according to their location and the relationship to the course of the cranial nerves.

Clinical Presentation

Trochlear nerve schwannomas are almost always intracisternal in location and originate from the pre-cavernous segment of the nerve.[19,33] From the ambient cistern they may extend medially into the pre-pontine cistern or superiorly above the tentorium. Trochlear nerve paresis in association with these tumours is encountered in a minority with symptoms attributable chiefly to brainstem compression. Frequently, the clinical syndrome constitutes ipsilateral cerebellar ataxia, hemiparesis and sensory disturbances in association with an extra-axial tumour at the tentorial notch.

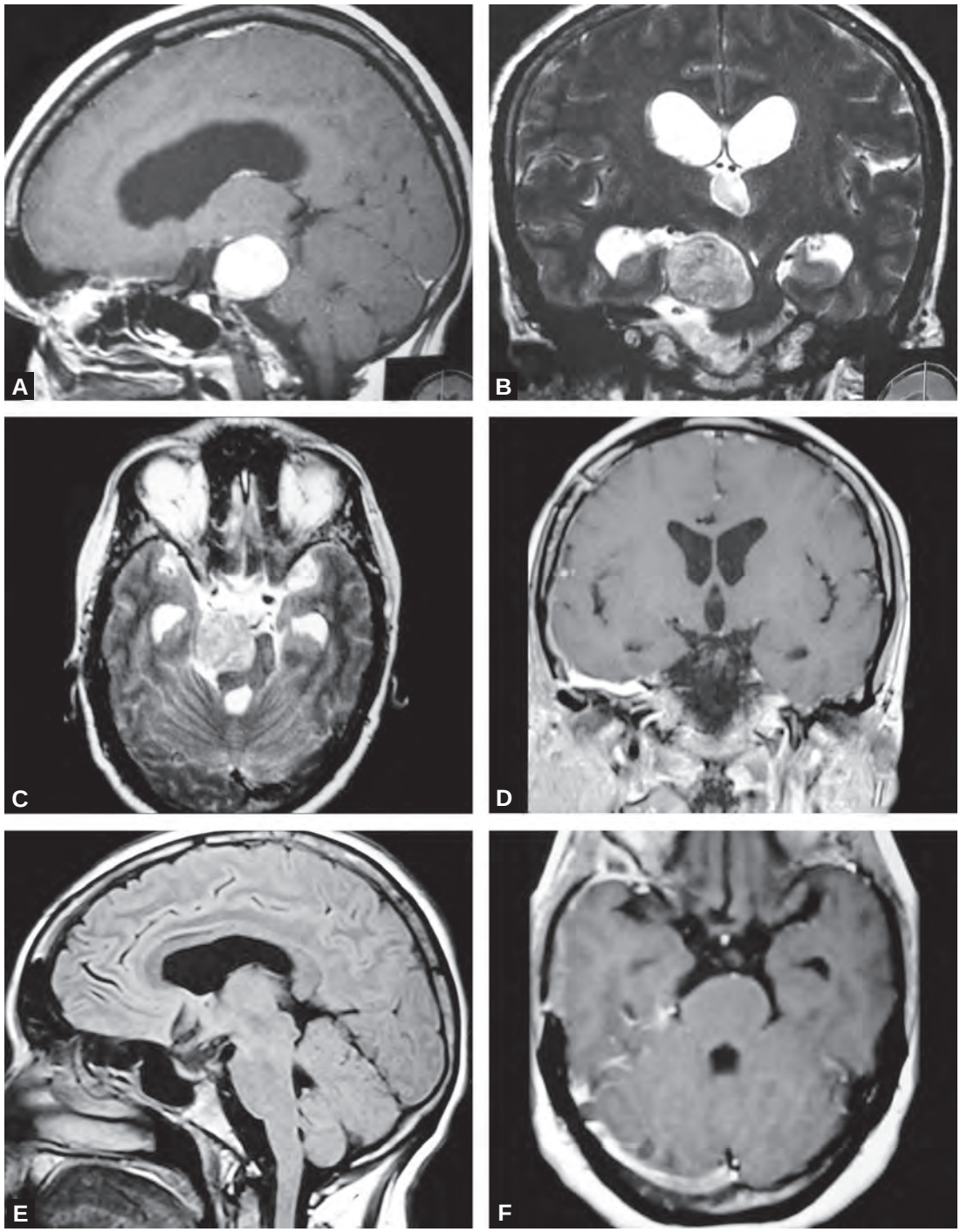
Oculomotor and abducens nerve schwannomas can arise from both the cisternal and cavernous segments of

the nerves. The most common manifestation of III nerve tumours is oculomotor paresis. The VI cranial nerve schwannomas manifest chiefly with VI nerve paresis, but tumours arising proximally within the cistern may have a more malignant course as the tumour growth causes obstructive hydrocephalus.

The nerve of origin is difficult to distinguish in intracavernous schwannomas, and the much more common trigeminal nerve tumour must be strongly considered in the differential diagnosis.

Diagnosis

On CT, schwannomas generally are of lower density than brain parenchyma and show moderate enhancement.[4] The MRI appearances of schwannomas are variable but generally of well-circumscribed lesions (Figs 4A to F), isointense or slightly hypointense to brain parenchyma on T1-weighted images and isointense or heterogeneously hyperintense on T2-weighted images.[11,12,33] The heterogeneity tends to increase with increasing tumour size and may be the result of regions of different



Figs 4A to F: Trochlear nerve schwannoma showing a brilliantly contrast enhancing tumour in the cisternal portion of the right IV nerve in (A) Sagittal. (B) Coronal. (C) Axial magnetic resonance imaging (MRI) sections. (D to F) Post-operative MRI showing complete removal of tumour

histology (hypercellular Antoni A tissue appearing isointense and hypocellular Antoni B tissue appearing hyperintense) or cystic change. Regions of hypointensity on T2-weighted image may be seen corresponding to areas of calcification, haemorrhage or hyalinised stroma. Contrast enhancement is intense but may be inhomogenous.[12]

Management

The surgical morbidity of cavernous sinus exploration for extirpation of intracavernous schwannomas is substantial. Moreover, surgical excision is associated with permanent loss of function of the affected nerve. Hence, stereotactic radiosurgery is generally recommended for intracavernous ocular motor schwannomas.

Trochlear nerve schwannomas are amenable to surgical resection owing to their cisternal location. The sub-temporal approach with division of the tentorium is suitable for the resection of the majority of these tumours. Anterior petrosectomy may be supplemented to this approach for larger tumours with significant extension below the tentorium. Post-operative loss of IV nerve function is generally well tolerated.

Cisternal oculomotor schwannomas should be considered for surgical decompression only in the presence of mass effect from large tumours. Oculomotor palsy resulting from total excision of these lesions is disabling.[1] Either a pterional or sub-temporal, transtentorial transpetrosal corridor can be used depending upon the configuration of the tumour.

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165 Phakomatoses

Ravi Ramamurthi, Nigel Peter Symss

INTRODUCTION

Phakomatoses is a term coined by Van der Hoeve, in 1920, to describe a group of hereditary neurological disorders that have cutaneous and ocular stigmata.[5] They were initially divided into:

- Neurofibromatosis (NF)
- Tuberose sclerosis (TS)
- Von Hippel-Lindau disease (VHL)
- Neurocutaneous angiomatosis.

The spectrum has now been extended to include phakomatosis pigmentovascularis, a very rare disease characterised by coexistence of a capillary malformation with melanocytic lesions.[5,16] All the phakomatoses do not manifest ocular and cutaneous findings; VHL shows no skin markers and the neurocutaneous angiomatoses show no ocular lesions. The genetic abnormality in many of these disorders has not yet been identified and the fact that stigmata of more than one of these syndromes have been seen in the same patient. This could indicate that they are all due to an abnormality in a small group of genes.

NEUROFIBROMATOSIS

This is the most common of the phakomatoses, with a reported incidence of one in 3,000 births.[23] It is an autosomal dominant disease with high penetrance but variable expression. This syndrome has been variously classified in literature but consensus is for two types designated NF-1 and NF-2, which account for over 95% of all cases.[17] Other cases of NF represent either poorly expressed or variant types.[19]

Neurofibromatosis-1

Neurofibromatosis-1 (NF-1), previously termed "von Recklinghausen neurofibromatosis" or "peripheral neurofibromatosis", was first described by von Recklinghausen in 1892. The genetic abnormality is thought to be in chromosome 17 and is of extremely variable expression, with members of the same family showing marked differences in clinical features. Individuals with NF-1 present with abnormalities of both astrocytes and neurons that result from reduced or absent expression of the NF type 1 (NF1) gene product neurofibromin. Impaired neurofibromin function in these nervous system cells contributes to the development of astrocytomas, learning disabilities and radiographic abnormalities of the brain.[11] Neurofibromin is expressed in many different tissues and it is now known that one role of neurofibromin is as a GTPase activating protein, very likely in the same pathway of signal transduction as ras. Von Deimling et al. found absence of neurofibromin in mice homozygously mutant for the NF1 gene resulted in profound developmental abnormalities. In mice, that are heterozygous for NF1 gene, an accelerated onset of tumour formation was observed. Combined with studies of tumours from NF1 patients showing homozygous deletions in the NF1 gene, their data suggest a role for NF1 gene as a "tumour suppressor", suggesting other roles played by neurofibromin in control of proliferation in some situations and differentiation in others.[28]

A diagnosis of NF-1 is made if the patient fulfils any two of the following criteria:

- Two or more neurofibromas of any type or one plexiform neurofibroma
- Six or more café-au-lait skin macules visible in room light, each 5 mm or more in size in pre-pubertal patients or 15 mm or more in post-pubertal patients
- Two or more Lisch nodules
- Optic glioma
- Axillary or inguinal freckling
- Characteristic osseous lesions such as sphenoid dysplasia or thinning of long bones' cortices, with or without pseudoarthrosis
- A first degree relative (parent, sibling or offspring) with NF-1 by the above criteria.

Not all the patients of NF-1 fulfil the criteria given above. These patients must be presumed to have the NF-1 gene but with poor gene expression.

Cutaneous neurofibromas are characteristic of NF-1. These Schwann cell tumours occur on the distal cutaneous nerve endings. They are most numerous in the thoracoabdominal region, the presence of neurofibromas on the nipple or areola of the breast suggests an association with pigmentation and/or hormones. They do not pose any serious problem to the patient except cosmetic, or rarely pain or itching. Operative removal of the lesion is done for painful or irritant lesions or for cosmetic purposes.

Plexiform neurofibromas may form along the course of any nerve. While they grow mostly from distal sensory nerves, they tend with growth to engulf major nerve trunks and motor branches, rendering operative removal

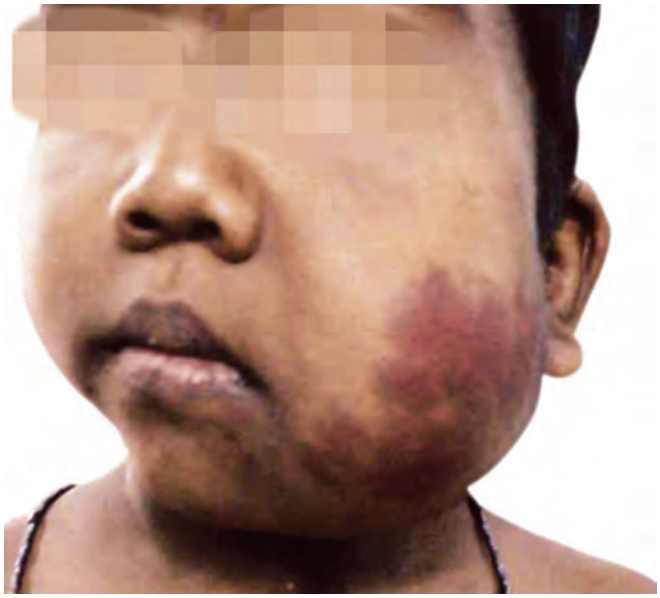


Fig. 1: Plexiform neurofibromatosis involving the left cheek and neck

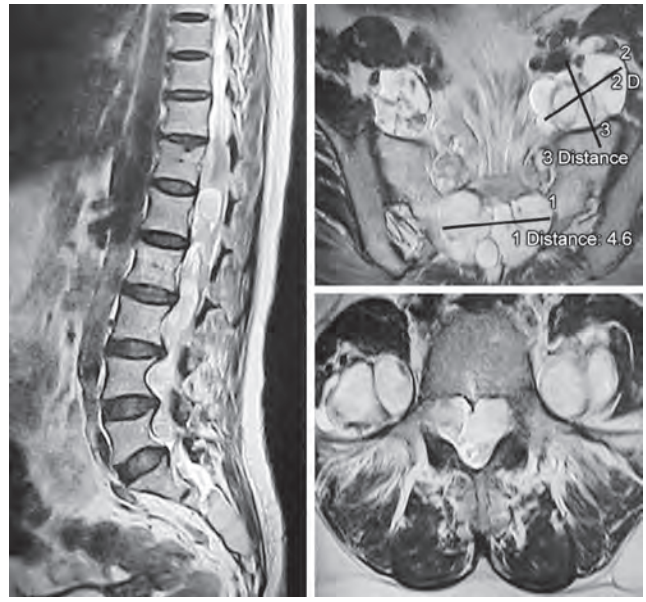


Fig. 2: Magnetic resonance imaging of lumbosacral region showing multiple neurofibromatosis

difficult with the attendant risk of a major motor deficit. There is a definite risk of malignant transformation in these patients (Fig. 1). Recent evidence indicates that the dopamine D(3) receptor [D(3)R] mediates protective roles both in neuronal and non-neuronal cell lines. Castorinal et al. in an earlier study proposed that neurofibromin, a large tumour suppressor protein encoded by the NF1 gene may increase susceptibility to apoptosis after serum deprivation in malignant peripheral nerve sheath tumour (MPNST) cells, thus acting as a proapoptotic gene. They concluded that their findings suggest that D(3)R might mediate the protective response to serum deprivation in MPNST cells through the inhibition of NF1 gene expression, further underlying a subtle role of these receptors in MPNST development.[4]

Neurofibrosarcoma occurs in about 5% of patients and is the most dreaded complication of this disease. Treatment involves amputation of the limb and major resection, followed by radiotherapy and chemotherapy. However, 5-year survival rates are only around 23%.[27]

Lisch nodules are pigmented hamartomas of the iris. Present in up to 94% of NF-1 patients, they are usually seen only after puberty.[18]

Though spinal neurofibromas occur mostly on the dorsal nerve root, the ventral roots may also be involved. These are often multiple and are most common in the cervical and lumbar regions (Fig. 2). Surgery is necessary if cord compression develops. The rare occurrence of neurofibromas within the spinal cord is seen more often in case of NF than in the general population.

Optic nerve gliomas occur in about 5–10% of patients with NF-1. The tumours behave like hamartomas and the treatment is as for these tumours occurring in the general population.

Macrocephaly, learning disorders, sphenoid wing dysplasias, pseudoarthrosis, phaeochromocytoma and kyphoscoliosis are the other lesions which may be seen in NF-1.

Neurofibromatosis-2

Neurofibromatosis-2 (NF-2) was previously called "central NF" or "bilateral acoustic NF". It is an autosomal dominant disease, with the genetic abnormality on chromosome 22, though the method of gene expression is not clear.[17] The criteria for the diagnosis of NF-2 are:

- Radiological evidence of bilateral acoustic neuromas (Fig. 3)
- A first degree relative with NF-2 and either
  - — a unilateral acoustic neuroma, or
  - — two of the following:
    - Neurofibroma
    - Schwannoma
    - Meningioma
    - Glioma
    - Juvenile posterior subcapsular cataract

Patients with NF-2 present with bilateral acoustic neuromas, which are in the majority symmetrical and present with symptoms during adolescence and early adulthood. A diagnosis of NF-2 should be suspected in any patient below 30 years of age, who has an acoustic neuroma, in a patient with multiple meningiomas and in patients with Schwann cell tumours and minimal stigmata of NF-1. All such patients and family members of NF-2 patients should be screened for bilateral acoustic tumours with brainstem auditory evoked response, contrast-enhanced high-resolution computerised tomography (CT) and/or magnetic resonance imaging (MRI).[17]

Patients with NF-2 are liable to have other tumours including multiple Schwann cell tumours on peripheral nerves, spinal roots and cranial nerves, cranial and spinal astrocytomas and meningiomas. Treatment of these patients is aimed at maintaining brainstem and spinal cord function. Surgery is offered for the larger tumours first, while small tumours without any major pressure effects are kept under observation. For the management

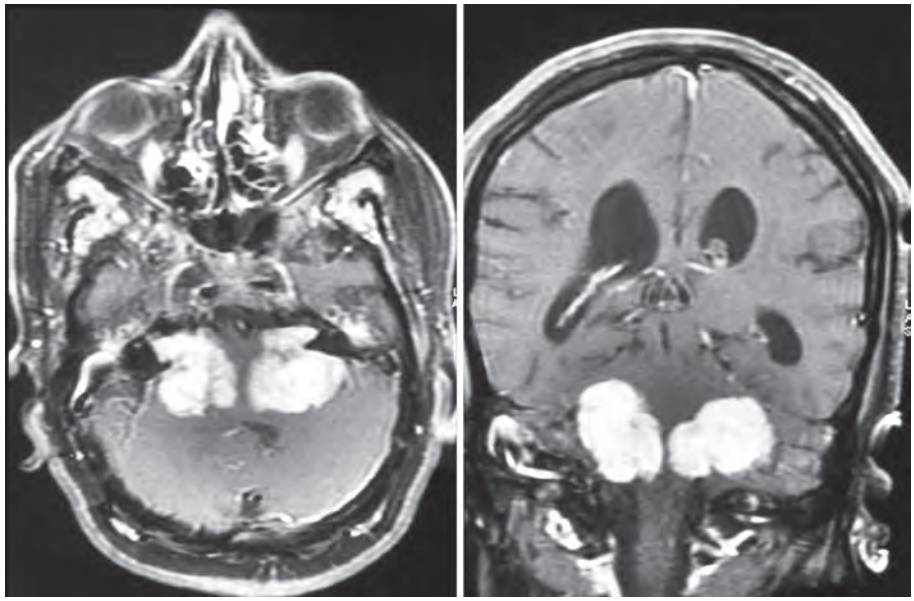


Fig. 3: Magnetic resonance imaging scan of brain showing bilateral acoustic schwannomas

of bilateral acoustic neurofibromas refer Chapter on Acoustic Schwannomas.

Ito et al. retrospectively reviewed patients with NF-2 to look for factors predicting further growth of bilateral vestibular schwannomas (VS). Their analysis included 27 patients with NF-2 with 54 VS, who were followed for a mean period of 86 months. Features distinguishing actively growing from quiescent VS were determined in 28 untreated VS and in 33 treated VS (either resection or radiosurgery). They used a general estimation equation to identify factors affecting tumour growth. Their analysis revealed, during the untreated course, 19 VS showed growth and nine VS were stable and no factors predictive of growth were found. Following the post-treatment course, which included 23 surgical resections and 10 radiosurgeries, 10 treatments were followed by growth and 23 by stability, with growth showing an association with onset at an early age ($p = 0.007$). Their multivariate analysis identified no factors predictive of growth.[14]

TUBEROSE SCLEROSIS

The first recognisable report of TS was that of von Recklinghausen, in 1862. The clinical syndrome of seizures and mental defect with pathological lesions in the brain was postulated by Bourneville (1880), who also coined the term "tuberose sclerosis", sometimes also known as adenoma sebaceum and also recognised its frequent association with renal and cardiac tumours. TS is an autosomal dominant disorder with a variable penetrance. The gene responsible is thought to be on chromosome 9.[7] The incidence is about one in 10,000 births and again the extent of expression is very variable.

Clinical Manifestations

The clinical diagnosis of TS can be made by Vogt's triad of seizures, mental deficit and adenoma sebaceum.[13] The disorder can, however, present variably.

Skin Manifestations

- Ash leaf spots and other depigmented macules are best seen under a Wood's lamp. They are seen mostly on the trunk, arms and legs
- Adenoma sebaceum is an angiofibroma. It is a progressive lesion which develops after birth and which shows rapid growth around puberty. It has a characteristic distribution, over the cheeks, nose and chin, sparing the upper lip. It is often confused for acne vulgaris (Fig. 4)
- Shagreen or sharkskin patches are dermal fibromas which usually develop after 10 years of age. They occur mostly in the lumbosacral region. They are not pathognomonic of TS and may occur in isolation
- Ungual fibromas or Koenen's tumours are angiofibromas which occur in the lateral nail groove, along the proximal nail fold or under the nail. They are more common in the toes than in the fingers.

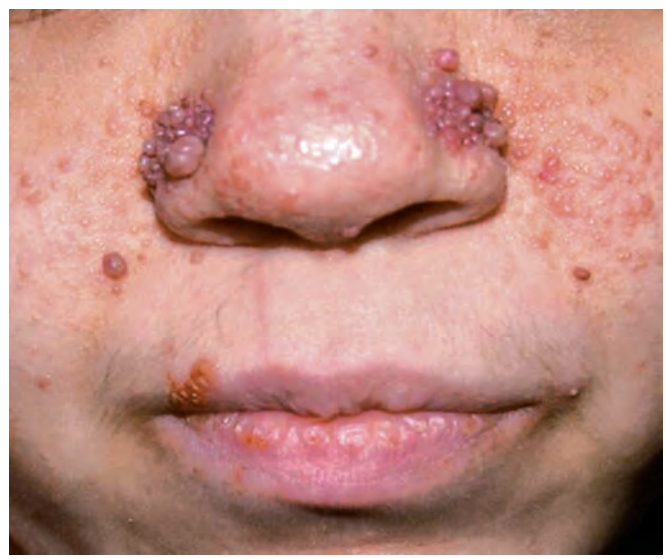


Fig. 4: Adenoma sebaceum

Sogut et al. observed the most frequent manifestations of tuberose sclerosis were those of the skin lesions (97.1%) and of the central nervous system (CNS) [seizures (94.2%), mental retardation (51.4%)], followed by renal (32.2%), cardiac (25.8%) and ocular (22.5%) manifestations. Among cutaneous manifestations, the most common was hypomelanotic macules (94.3%). They conclude the earliest and most frequent complaint is seizure and careful investigation for hypomelanotic macules and other skin manifestations typical for TS in cases presenting with convulsion makes early diagnosis possible and avoids unnecessary investigations.[24]

Nervous System Manifestations

Patients with TS present clinically with seizures and mental retardation. The seizures are mostly tonic-clonic or infantile myoclonic, though partial-motor and complex partial seizures are also seen. Petit mal attacks are not common. The degree of mental retardation in these patients varies and regression has been noticed in older patients. They may be due to either uncontrolled seizures or to the development of a brain tumour. Motor deficits per se are rare, though they may be seen as a manifestation of a brain tumour. Chou et al.[6] analysed the prognostic factors for mental retardation in patients with tuberose sclerosis complex. The most frequent CNS manifestations were seizures (91.4%) and mental abnormality (62.5%), and the most common seizure pattern was generalised tonic clonic seizures (62.9%). Poor control of seizures ($p = 0.006$) and the presence of cortical tubercles in imaging studies ($p = 0.03$) were correlated statistically with mental abnormality.

Cortical plaques (or tubers) and sub-ependymal glial nodules are developmental lesions which do not enlarge once brain growth has stopped. Cortical tubers are hamartomas containing glial and neuronal cell populations. There is no evidence of malignant transformation in these lesions. Degenerative changes take place with gliosis and umbilication of the cortex at the site of the tubers, leaving normal brain in between. Sub-ependymal nodules are scattered along the entire wall of the lateral and third ventricles. They are mainly glial hamartomas and contain prominent calcium deposits.

Sub-ependymal "giant cell astrocytomas" occur in about 10% of patients with TS. They do not develop from the sub-ependymal nodules. These tumours react negatively to GFAP and are probably neuronal in origin.[25,26] They probably arise from the germinal cell matrix which explains their vascularity.

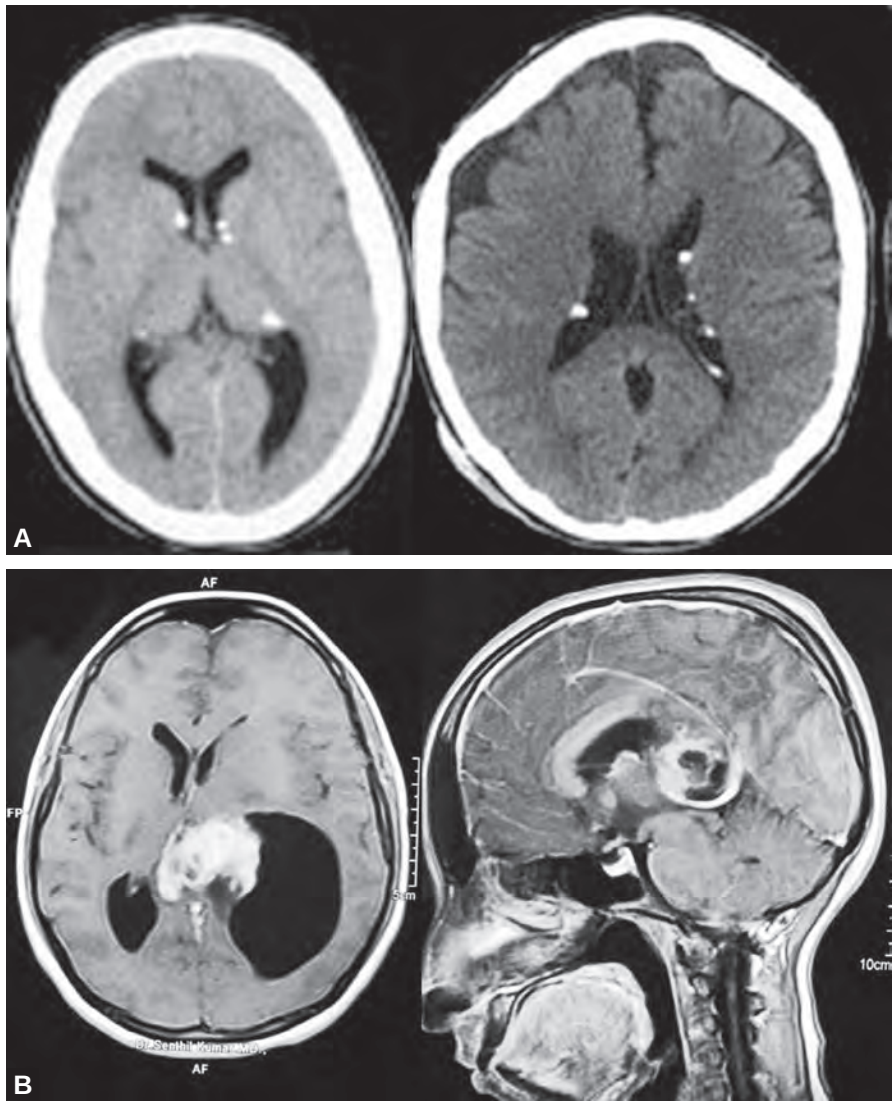
Lesions are also seen in other organs such as the retina, heart, kidney and lungs. In the eye, retinal hamartomas occur. They rarely lead to visual problems. Cardiac rhabdomyomas occur in about 39% of patients with TS. They may remain asymptomatic or may produce symptoms of heart failure early in infancy. Renal angiomyolipomas are commonly found in these patients.

Gomez[9] has listed major and minor criteria for the diagnosis of TS. The presence of any one of the primary criteria or of two or more of the secondary criteria is considered diagnostic.

The CT and magnetic resonance imaging (MRI) scan of the brain is characteristic in patients with TS (Figs 5A and B). Sub-ependymal periventricular calcification is the most frequent and characteristic finding. They are seen in 67–100% of scans done in patients with TS.[13] The tendency for these lesions to protrude into the lateral ventricle ("candle guttering" was seen on ventriculography), distinguishes them from other calcified lesions seen in cytomegalovirus infection, cysticercosis and toxoplasmosis. Other lesions which may encroach into the ventricles, e.g. heterotopic grey matter or ependymomas, either do not calcify or are not multiple. The calcifications are mostly just lateral to the foramen of Munro and in the body of the lateral ventricle, though rarely, they may occur in the wall of the third and fourth ventricles. Multiple hypodense intracerebral lesions are seen especially in the frontal, parietal and occipital lobes. These represent areas of defective myelination and heterotopic hamartomatous tissue which occur particularly at the junction of grey and white matter.[8,20] These are seen in 12–69% of cases but are not diagnostic of TS when they occur in isolation. Sub-ependymal tumours are seen as isodense lesions enhancing uniformly with contrast. They are located mainly at the foramen of Munro and produce obstructive hydrocephalus. They may, occasionally, have a cystic component. Asymmetrical ventricular dilatation may be seen in the absence of tumour. Calcified or hypodense lesions may also be seen in the posterior fossa.

With MRI scan cortical tubers were more frequently demonstrated on spin-echo images obtained with a long repetition time (TR). Because the signal abnormality is located predominantly in the subcortical portion of the tubers, the terms "gyral core" and "sulcal island" have been used to describe the patterns noted on MRI. Sub-ependymal nodules are best seen on inversion-recovery or short TR spin-echo images, although hypointensity within the nodules consistent with calcification was most evident on long TR spin-echo images.[21] Griffiths et al. evaluated which MR sequences show the pathology best and to see if "ultrafast" sequences can show the pathology robustly. Cortical tubers are shown exceptionally well on fluid-attenuated inversion recovery images, whereas sub-ependymal nodules (and calcified tubers) are best shown on gradient echo T(2) images and that single-shot fast spin-echo sequences do not sufficiently show the expected intracranial complications of tuberose sclerosis complex and should not be considered as an alternative to standard sequences in this group.[10]

Treatment involves controlling seizures with antiepileptic drugs and special education for the mentally handicapped. The brain tumours can be excised with a good prognosis. The life expectancy of these patients is decreased, the causes of death being cardiac failure, brain tumours, status epilepticus and renal failure. Koenig et al.[15] reported treating a patient with rapamycin for 5 months for bilateral sub-ependymal giant cell



Figs 5A and B: (A) Computerised tomography scan of brain showing typical candle guttering pattern of tuberous sclerosis (sub-ependymal periventricular calcification). (B) Magnetic resonance imaging scan of brain showing giant cell astrocytoma typically seen in tuberous sclerosis

astrocytomas. The MRI of the brain confirmed reduction in size of both astrocytomas after initiating rapamycin. However, they advocate further studies are needed with prolonged observation to confirm these findings, determine the length of necessary treatment and evaluate recurrence risk after discontinuation of rapamycin.[1]

VON HIPPEL-LINDAU DISEASE

The VHL disease or complex is an autosomal dominant disorder with variable expression, characterised by either more than one haemangioblastoma within the neuraxis associated with at least one visceral manifestation. No cutaneous stigmata are seen in patients with VHL complex. The association of retinal, cerebellar and visceral lesions was made, in 1926, by Arvid Lindau, who started his work by investigating cerebellar cysts. The retinal angiomas had been described earlier, by Collins, in 1894 and by von Hippel in 1904. Brandt published the autopsy results of von Hippel's patient and described tumours in the viscera in addition to those in the brain and the spinal cord.

The typical lesion in the neuraxis is a cerebellar haemangioblastoma, which at autopsy is found in at least 60% of patients with the disease.[17] Haemangioblastomas may also be found in the brainstem, spinal cord and in the supratentorial compartment. The lesions may be solid or cystic. They are commonly multiple, with the tumours appearing metachronously. Further details on the diagnosis and management of these lesions are dealt with the Chapter on "Haemangioblastoma".

Retinal angiomas are seen in over 50% of patients with the VHL complex. The lesions are seen mostly in the peripheral parts of the retina, though they have also been recorded at the macula and the optic disc. They are usually seen in both the eyes. With time, they are covered with exudates which surround the lesion, the feeding artery and the draining vein. Retinal oedema, haemorrhage, retinal detachment, gliosis and secondary

glaucoma may cause loss of vision. Photocoagulation is the treatment of choice. As new lesions may appear in course of time, the patients must be kept under regular ophthalmological follow-up.

Angiomas may also be found in other organs such as the liver, spleen, kidneys, lungs, the skeletal system, epididymis and the adrenal cortex. However, the most common and dangerous tumours are pheochromocytoma and renal cell carcinoma, which cause death in a significant proportion of the VHL patients. Renal cell carcinoma is seen in up to 25% of patients with VHL complex and differs from its sporadic counterpart in its earlier age of onset, multicentricity and synchronous or metachronous bilateral involvement. Pheochromocytomas seen in about 10% of VHL complex patients are often bilateral. Polycythaemia, when present, may be due to either renal involvement or due to the intracranial haemangioblastoma.

Thus, investigation of a patient with suspected VHL complex must include examination of the fundi with a record of the visual acuity and fields, abdominal ultrasound or CT with special focus on the kidneys, pancreas and adrenals, urinary metanephrine screening and haematocrit and blood counts, besides CT scan of the brain and upper cervical cord.

NEUROCUTANEOUS ANGIOMATOSIS

These are a group of genetic disorders which have an abnormality of blood vessels of the skin and nervous system as their only common feature and are classified together for convenience. Each syndrome has other systemic angiomata as well as haematopoietic and immunologic deficiencies.

Ataxia Telangiectasia

It is an autosomal recessive disorder with progressive ataxia, cutaneous telangiectasias and immunological abnormalities. Prognosis is poor, with death usually occurring in the second decade due to infection or neoplasia like lymphomas or leukaemias.

Sturge-Weber Syndrome

It is defined by the association of a facial capillary malformation (port-wine stain), with a vascular malformation of the eye, and/or vascular malformation of the brain (leptomeningeal angioma). Variants exist where only one of these three structures is involved with the vascular malformation. They may be caused by a somatic mutation occurring sporadically, rather than an inherited disorder. No good population-based data exist for how many people have Sturge-Weber syndrome, however, estimates range between one in 20,000–50,000 live births. The characteristic skin lesion is a unilateral facial angioma (port-wine stain) in one or two dermatomes of the trigeminal nerve. There is an ipsilateral parieto-occipital leptomeningeal venous angiomatosis with underlying cortical atrophy. Calcification of the second and third cortical layers of this region appears as the characteristic "rail-road" calcification on plain X-rays. Patients present with seizures or with hemiparesis. Subarachnoid haemorrhage is rare. Pascual et al.[22] found early onset of seizures and poor response to medical treatment, bilateral cerebral involvement and unilateral severe lesions were indicative of a poor prognosis. Uncommonly, glaucoma secondary to retinal angiomatosis may cause loss of vision. Laser therapy is the optimal approach for treating port-wine stains but whether it is effective for patients with facial dermatomal port-wine stains and Sturge-Weber syndrome is undetermined. Laser treatment produced unsatisfactory outcomes in patients with facial dermatomal port-wine stains. V3 port-wine stains responded best and V2 worst to laser.[12]

Klippel-Trenaunay-Weber Syndrome

The cutaneous angioma is unilateral on the body, involving one or more dermatomes, with a haemangioma of the spinal cord at the same level. The lesions are unilateral and may be associated with osseous and muscular hypertrophy of the involved areas. The lesion is seen as a spinal variant of the Sturge-Weber syndrome. Though an autosomal dominant pattern of inheritance is suggested, this too may be the result of a sporadic mutation.

Osler-Weber-Rendu Syndrome or Hereditary Haemorrhagic Telangiectasia

Osler-Weber-Rendu (OWR) syndrome is a rare autosomal dominant disease with angiomas of the skin, mucosal surfaces and nervous system and usually presents with haemorrhage. It is a genetic disorder caused by an abnormality in either the endoglin gene on chromosome 9, or the activin receptor-like kinase 1 gene on chromosome 12. Both of these genes are involved in blood vessel formation. A mutation in either of these genes will result in similar OWR symptoms and those who have the disorder generally only have an abnormality in one of the genes. Majority of the symptoms are the result of haemorrhage due to abnormal formation of capillaries. Arteriovenous malformations (AVMs) may occur on the surface of the skin or in the lungs, brain, liver, stomach or gastrointestinal tract. Brain AVMs may be treated by surgery, embolisation, or stereotactic radiosurgery.

Fabry's Disease

Fabry's disease results from the accumulation of ceramide trihexoside in the media and endothelium of small blood vessels due to a deficiency of alphagalactosidase. It is an X-linked recessive disorder, characterised by telangiectasias of the lower half of the body. Skin lesions apart, renal function may be impaired with resultant hypertension and myocardial infarction. More severe forms have a diffuse involvement of vessels of the

peripheral nerves and of the CNS, leading to neuropathies and strokes.

Wyburn-Mason Syndrome

It is rare, and is characterised by an AVM in the midbrain with unilateral retinal and facial vascular malformations.

Paul Bonnet[3] first described Wyburn-Mason syndrome in 1937 and Roger Wyburn-Mason[29] described it again in 1943 as a rare congenital disorder that has the autosomal dominant inheritance trait, with only one mutated gene necessary for the child to have the traits of the disease. The syndrome is present at birth and the onset of symptoms usually occurs before the age of 30 years. It tends to be more frequent in males. Patients can present with symptoms of visual loss, proptosis, pigmented facial naevi (birthmarks), pigmented retina, severe headache, vomiting, rigid neck, loss of consciousness, tinnitus, deafness, aphasia, cerebellar signs and mental retardation.

Phakomatosis Pigmentovascularis/Speckled Lentiginous Nevus Syndrome

Phakomatosis pigmentovascularis is a very rare disease characterised by coexistence of a capillary malformation with various melanocytic lesions, including dermal melanocytosis (Mongolian spots), nevus spilus and nevus of Ota. As of now about 200 cases have been reported in the literature, most are of Japanese origin and about half of reported cases are associated with various systemic involvements. Patients are prone to develop late-onset open angle glaucoma, suggesting that long-term ophthalmic follow-up is necessary in this type of patient.[2,5]

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166 Convexity Meningiomas

Vasudevan MC

INTRODUCTION

Meningiomas are classified as convexity (cranial vault) or basal based on their dural attachment. Convexity meningiomas are those tumours whose attachment is confined to the convexity of the brain and do not involve the dura of the skull base, the venous sinuses or the falx. Convexity meningiomas are the most frequently encountered meningiomas, followed by meningiomas of the sphenoid ridge and cerebellopontine angle.[24,33,36,47] The neurosurgical literature has few studies on supratentorial convexity meningiomas because their treatment does not present serious technical problems.[11] However, after saying so, these lesions can be a real challenge. The operative mortality of these lesions has declined from 15.9% (Cushing 1938), 7.4% (Olivecrona 1967)[39] and 2.4% (Logue 1975) to 0% in modern series.[34]

INCIDENCE

Intracranial meningiomas account for 20% of brain tumours[12] of which 15–25% are convexity meningiomas. These convexity lesions are the most common meningiomas. Morokoff et al.[34] in their series of 163 convexity meningiomas, found them to represent 22% of all meningiomas operated upon. They reported a female:male ratio of 2.7:1 and a median age of 57 (range 20–89 years old). Menon et al.,[29] in their review of 38 paediatric meningiomas, found convexity lesions to comprise 12% of the series. The factors that may predispose to meningioma formation are female sex, previous ionising radiation[15] and neurofibromatosis. Meningiomas may be associated with Werner's syndrome[46] and these are seen to occur two times more frequently in men and are associated with extracranial tumours like sarcomas and thyroid carcinoma.[46] These patients, after excision of the meningioma, require close follow-up to detect recurrence. The incidence of cranial vault or convexity lesions is increasing due to routine imaging, which has become a part of contemporary health care. Almost one-third of these tumours are now discovered as incidental findings on CT or MRI.

LOCATION

Cushing and Eisenhardt[11] subclassified convexity meningiomas as pre-coronal, coronal, post-coronal, paracentral, parietal, occipital and temporal types. Later, for convenience, they were classified as anterior, median, posterior and temporal convexity meningiomas. A meningioma which involves more than one location is classified according to the site of the main attachment. Anterior meningiomas are those which lie at or in front of the coronal suture and include meningiomas of the pterion. Median meningiomas are those astride the Rolandic fissure. Posterior meningiomas are those which involve the posterior parietal and occipital regions. Temporal meningiomas are those which develop in the temporal region and pterion and grow posterior and medially and project on the temporal side of the Sylvian fissure.

CLINICAL FEATURES

Like any other slow growing intracranial lesion, convexity meningiomas have a long clinical history. Zeidman et al.[50] on analysing growth rates of non-operated meningiomas, found the mean relative volumetric growth rate was 5.82% per year and 9.09% demonstrated no growth. Incidental asymptomatic meningiomas are increasingly seen on routine imaging of the neuraxis.

The clinical features are in accordance with the site of the lesion.[37,38,42,43] Patients often have a long history of headache, mental deterioration, visual disturbances, focal neurological deficit, seizures[44] and signs of raised intracranial pressure. In a series of 163 convexity meningiomas reported by Morokoff et al.,[34] headache was the most common symptom followed by seizures and hemiparesis. Thirty-two patients were asymptomatic and their tumours were found incidentally on imaging. Some of the convexity meningiomas are diagnosed solely from the presence of skull or scalp swelling, due to an often associated hyperostosis and rarely due to osteolysis and tumour involving the calvarium and scalp. The growth of meningiomas may increase during pregnancy, due to the presence of receptors for progesterone hormone in the tumour and they may become symptomatic in pregnancy and present as eclampsia. Shehu et al.[44] recommended close follow-up of patients with eclampsia and described a case where a convexity meningioma presented as postpartum eclampsia.

ANTERIOR CONVEXITY MENINGIOMAS

These tumours produce symptoms and signs of frontal lobe dysfunction, mainly mental deterioration (Fig. 1).

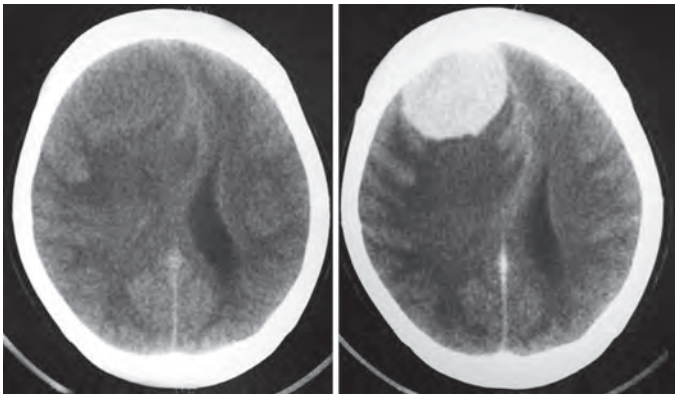


Fig. 1: CT scan showing frontal convexity meningioma isodense on plain study and uniform contrast enhancement

These are often overlooked and attributed to the ageing process as they occur mostly in elderly patients. These tumours attain a large size before showing signs of increased intracranial pressure or papilloedema. Rarely, subtle signs of pyramidal involvement are the only signs and these may be difficult to pickup.

MEDIAN CONVEXITY MENINGIOMAS

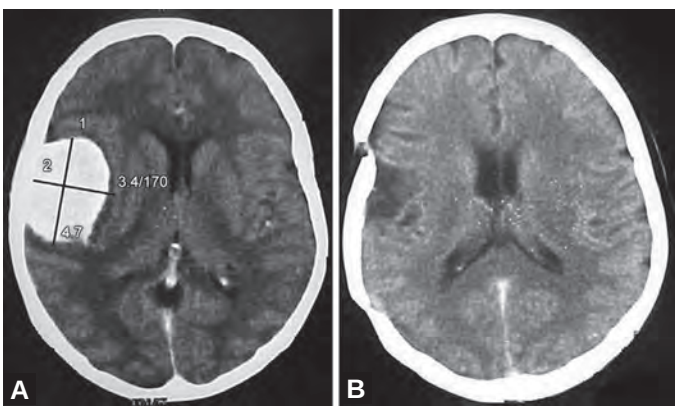
Sensory and motor signs and symptoms are characteristic of convexity meningiomas in this location (Figs 2A and B). When the dominant hemisphere is involved, speech disturbances are common. Cushing had noted that Jacksonian type of seizures starting from the face or hand, preceded by motor or sensory aura, may occur.

POSTERIOR CONVEXITY MENINGIOMAS

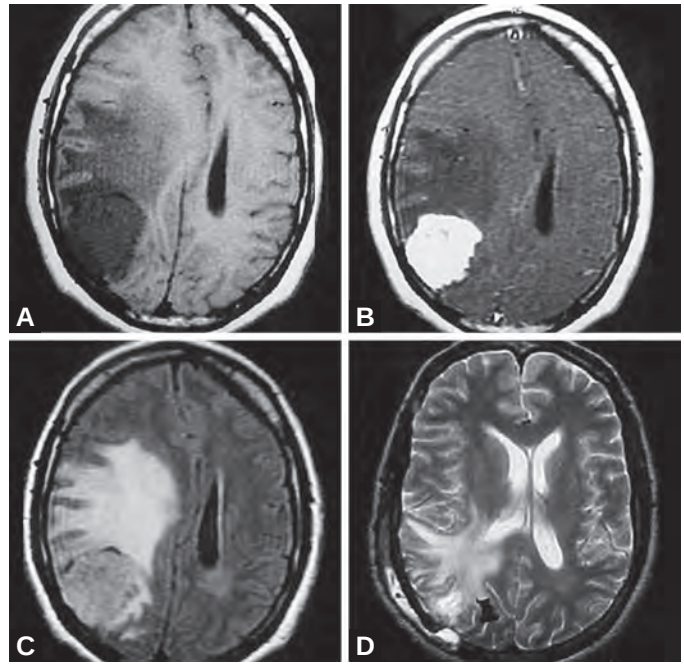
They often present with signs of increased intracranial pressure, sensory motor symptoms or, characteristically, field defects (homonymous hemianopia) (Figs 3A to D).

TEMPORAL CONVEXITY MENINGIOMAS

These often present with seizures, contralateral motor deficit and visual field defects (due to involvement of visual fibres along the temporal horn) (Figs 4A to D). Speech disturbances are common when the dominant

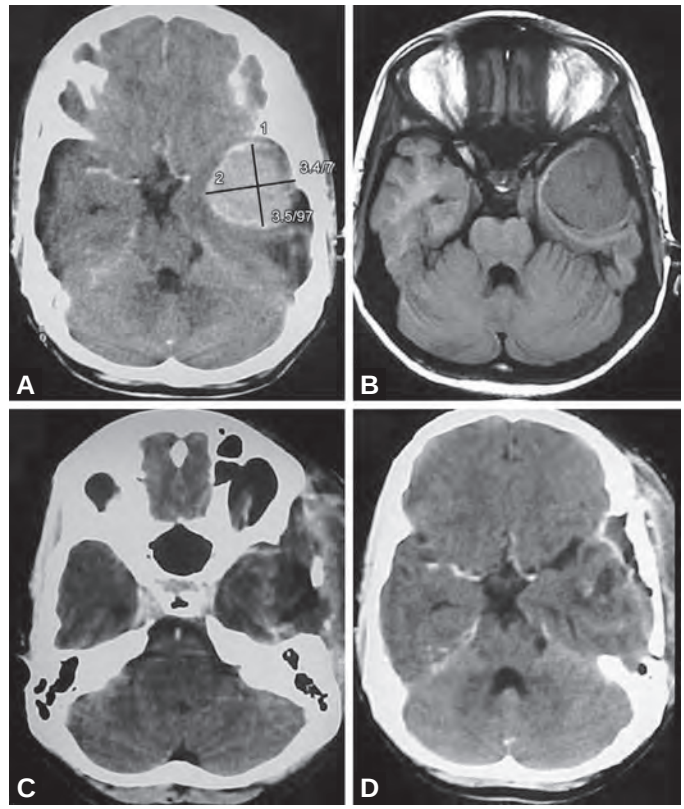


Figs 2A and B: CT scan showing posterior frontal convexity meningioma. (A) Pre-operative. (B) Post-operative



Figs 3A to D: MRI scan showing (A) T1W axial. (B) T1W post-contrast axial. (C) Flair images of parietal convexity meningioma. (D) Post-operative T2W axial scan

hemisphere is involved. Rarely, when large, they may compress the ipsilateral cerebral peduncle, leading to contralateral motor disturbances. In some cases,



Figs 4A to D: (A) CT scan brain contrast study showing temporal convexity meningioma. (B) MRI T1W plain study showing temporal convexity meningioma isointense to the brain parenchyma. (C and D) Post-operative CT scan plain and contrast study showing total removal of the temporal meningioma

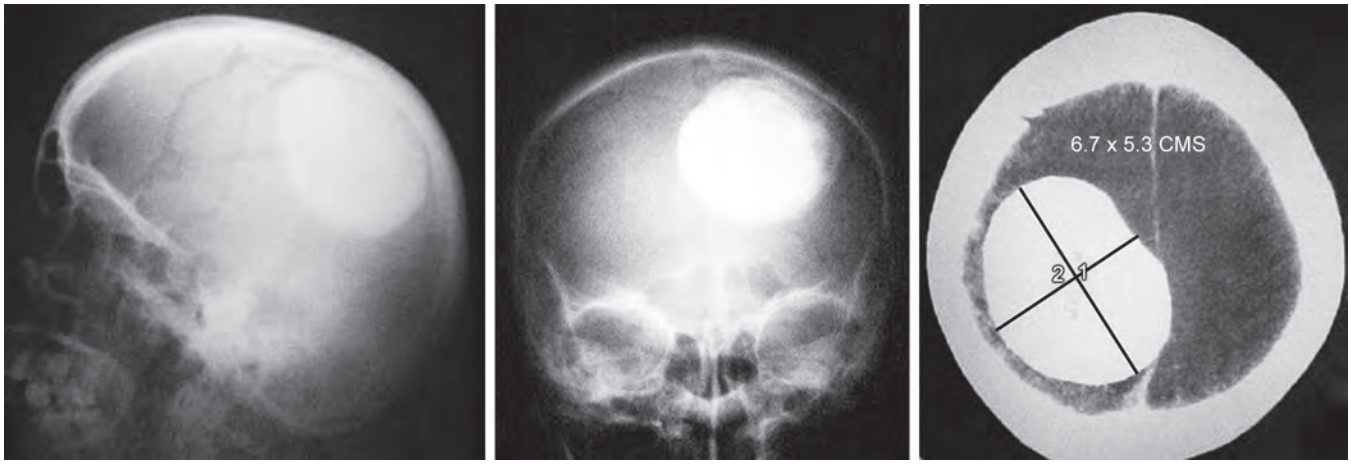


Fig. 5: Plain radiographs and plain CT scan of a parietal convexity meningioma showing extensive calcification

compression of the contralateral cerebral peduncle against the tentorial edge may result in ipsilateral hemiparesis.

IMAGING

X-rays

X-rays of the skull can show hyperostosis or osteolysis, with expansion of the calvarial bone and prominence of vascular channels, signifying the presence of a meningioma. Calcified lesions and those with specky calcification are easily made out. Plain X-ray of the skull as an initial investigation gives information regarding calcification of the lesion or erosion of the skull associated with convexity meningiomas (Fig. 5).

Computed Tomography

Computed tomography (CT) scan with contrast has a localising value of 100%. The CT scan may show hyperostosis of adjacent bone and prominent vascular channels (Fig. 6). These lesions are generally isodense with brain on non-contrast scan, have smooth contours and are in close proximity to the dura. They may be partially or, rarely, fully calcified. In 15% of cases, they can have atypical radiology with necrosis, cystic degeneration, haemorrhage, indistinct margins, severe brain oedema, multiple nubbins of the tumour which deeply invade the brain and have heterogeneous enhancement. These findings indicate a malignant transformation or an atypical meningioma.[35]

Magnetic Resonance Imaging

Magnetic resonance imaging gives much better soft tissue delineation. On T1-weighed images, they are isointense or hypointense to grey matter and on proton density and T2-weighted images, they are isointense or hyperintense.[21] These tumours compress the adjacent brain and they can extend along and infiltrate Virchow-Robin spaces and can have an infiltrating morphology.[40] Rarely, the scans will show associated pathology, like an aneurysm or subdural haematoma, which may require treatment.[17,21] Gadolinium is a paramagnetic contrast

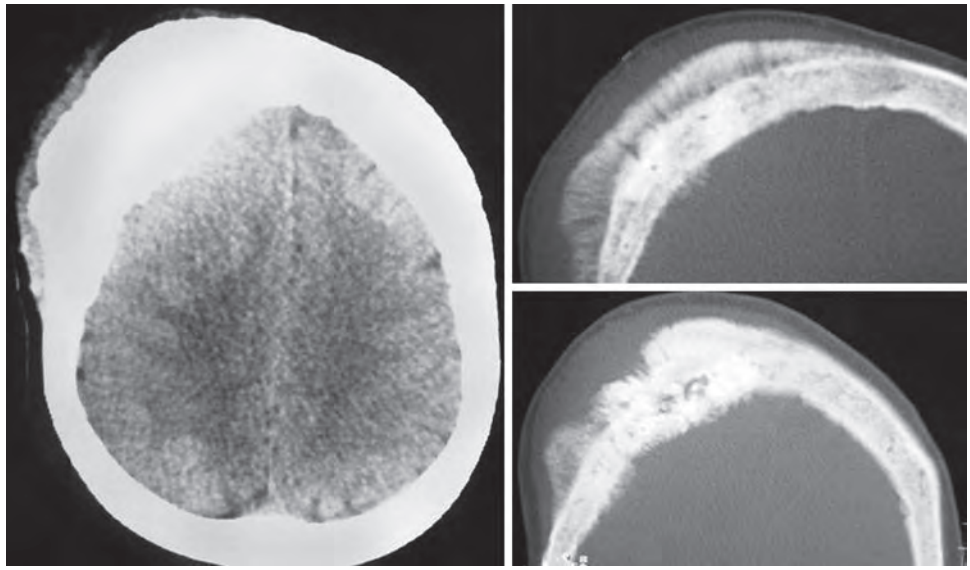


Fig. 6: Plain CT scan and bone cuts showing hyperostosis in a case of frontal convexity meningioma

agent and causes these lesions to enhance brilliantly. MRI scores over CT in demonstrating the "dural tail" and invasion of the sinuses, thereby eliminating the need for angiography. The information thus obtained outweighs the benefit of angiography in determining the vascularity and surgical approach, and avoids the minimum risk involved in angiography.

Electroencephalogram

Electroencephalogram to locate the site of a meningioma is of historical value only, but may be useful in monitoring the epileptogenicity of the affected cortical area for medical therapy.

Angiography

Angiography is done when imaging suggests a highly vascular lesion and one which may require pre-operative embolisation. The external carotid injection shows a "sunburst" pattern and internal carotid injection shows the arterial and pial blood supply.

Pre-operative embolisation is generally not necessary in cases of convexity meningiomas, as the majority of the supply is from meningeal vessels which are cut off in the early stages of surgery.

DIFFERENTIAL DIAGNOSIS

Although most meningiomas have distinct radiological features and are easily diagnosed, rare lesions that can mimic a meningioma need to be considered in the differential diagnosis. The differential diagnosis includes fibrous dysplasia, tuberculoma, sarcomas, lymphomas,[1] non-Hodgkins MALT lymphoma,[41] plasmacytomas, carcinomas, dural based secondaries,[3] Rosai Dorfman's disease,[13] melanocytoma[7] and cavernous haemangioma.[19]

SURGICAL MANAGEMENT

Generally surgery is recommended in patients diagnosed with a convexity meningioma greater than 1.5–2 cm except in the elderly and frail. The operating microscope is very helpful to preserve normal neural structures and vasculature. A good bipolar, loop electrode, CUSA, and laser also form part of the surgical armamentarium.

Pre-Operative Protocol

In the presence of raised ICP and seizures, pre-operative adequate dosage of steroids, furosemide (lasix) and anticonvulsants is essential. If needed, per-operatively, 20% mannitol (1 gm/kg body wt) may be given in the early phase of surgery.[28]

Correct positioning of the patient is essential. The surgeon and anaesthetist should be comfortable. The position of the head is fixed such that the scalp over the lesion is placed at the highest level. This allows for minimal retraction of the brain and good venous drainage. Undue rotation of the neck is to be avoided as it may lead to compression of the neck veins leading to increased venous pressure/raised ICP. If required, mild hypotension and normocapnia may be used in anaesthesia so that there is minimal blood loss.

Scalp Incision

This is of great importance, especially in surgery for convexity meningiomas. The neuroimaging, including the multiplanar MRI and the CT scan, which is better in showing the relationship of the lesion to bony landmarks, like the coronal suture, are studied before marking the appropriate scalp incision. It is also prudent to shave and visualise the patients head to look for signs of hyperostosis, osteolysis and prominent scalp vessels. The scalp incision should be large and care must be taken in cases where re-surgery is under taken. The normal blood supply and scalp anatomy should be reviewed.[2]

Normally, a U-shaped incision is sufficient. With the advent of neuronavigation, Black et al. and Morokoff[8,34] advocate linear incisions and smaller craniotomies in convexity meningiomas. Surface anatomy scanning (SAS) with the help of MRI imaging may precisely localise the tumour and also give information regarding the surrounding venous anatomy. Intra-operative image guidance is useful in precise location of the craniotomy. Navigation also helps to provide visualisation of the relationship of the tumour to the veins.[6] Current surgical strategy is to use neuronavigation, making possible a targeted linear incision and a small craniotomy, followed by resection and taking a 5 mm dural margin around the tumour.

The scalp incision and the craniotomy flap should be wider than the lesion itself. A free bone flap is preferable as it provides an early disruption of the external carotid blood supply. One needs to preserve the pericranial tissue which may be used later as a graft to replace the dural defect. The elevated bone flap needs to be inspected for any tumour invasion and, if found, this needs to be removed in toto. Hitch stitches are applied all around before opening the dura. The area of the dura where the tumour is attached is invariably vascular and one may notice large meningeal vessels coursing through the dura and feeding the tumour. Bleeding from the dural surface can be controlled with bipolar coagulation and Gelfoam®. Prior to opening the dura, any major dural vessel exposed may be ligated or secured with silver clips. This reduces the vascularity of the dura. Rapid opening of the dura helps in controlling the bleeders and minimising the blood loss and also helps to cut off the vascularity of the tumour. Excessive coagulation may lead to shrinkage of the dura, but one need not worry about this aspect, as at the end of the surgery the dura is excised adequately and grafted with pericranial tissue or a dural substitute. Adjacent to the tumour, the dura is known to be infiltrated by meningiomatous cells which are known to cause recurrence and hence resection of the dura to that extent is necessary. The dural exposure around the tumour should be adequate and generous and, at the same time, as little as possible of the

brain should be exposed. Dural substitutes are increasingly being used[25] and Balasubramanium et al.[4] have described the use of dural bridge sutures to prevent the sinking of dural substitutes. Kamitani et al.[20] have proposed that meningioma cell rests may be found in thickened arachnoid adjacent to the lesion and advocate its removal.

The major blood supply to convexity meningiomas is from the dural vessels and once these are under control the rest of the dissection will be relatively blood less. Some of the tumours may also receive blood supply from cortical vessels. The first step in the dissection of the tumour is to identify the tumour arachnoid plane. In the majority of lesions, there will be a good arachnoid plane. When the arachnoid plane is good all around and is preserved, it is fairly easy to remove the tumour without damaging the underlying cortex. Occasionally, the arachnoid layer may be deficient in some places. In such situations, it is difficult, but not impossible to separate the cortex from the surface of the tumour by fine dissection. The cortical edges at the junction of the tumour need to be protected by placing soft cotton lintines. Undue retraction of the cortex should be avoided, and great care is taken to preserve cortical veins at the tumour cortex junction. Cerebral oedema will be more pronounced post-operatively if the venous drainage has been compromised. Occasionally, an apparent feeder to the tumour may not actually feed the tumour but will skirt the tumour and these en-passage vessels need to be identified and these should be carefully dissected and preserved. Sometimes, the blood supply of the tumour comes from the contralateral middle meningeal artery and this can be hard to identify at surgery. Often it is necessary to debulk the tumour to allow the capsule to fall inwards away from the surrounding cortex. The debulking may be done with CUSA, diathermy and cutting loop. Invariably, at the end of the tumour removal, one may encounter one or two vessels supplying the tumour from the bed which need to be preserved. The contact yttrium-aluminium-garnet laser may be used, as this allows haemostasis and carving of tumour similar to the (Bovie) diathermy loop cutting.[49] After tumour removal, getting absolute haemostasis is of paramount importance as it prevents post-operative haematoma. Spontaneous intracranial meningioma bleeding can cause rapid deterioration and a one stage total removal of haemorrhagic meningioma and haematoma is the treatment of choice in these patients.[9] An increased tendency to bleed was found to be associated with two age groups (less than 30 and more than 70 years old), and in convexity, intraventricular and fibrous meningiomas.[9]

Post-Operative Care and Complications

The general principles of supervision and post-operative care as applicable to other intracranial surgery need to be followed. The patient needs constant monitoring of the level of consciousness, blood pressure, pulse rate and oxygenation and coagulation profile. The fluid balance is to be maintained. The central line is left in place, of which one line is connected to a CVP monitor. The patient is nursed in the 30 degree head-up position. Antibiotics are given. Subcutaneous LMW heparin, particularly in hefty individuals, helps to prevent deep vein thrombosis (DVT). Chest physiotherapy and spirometer exercises are helpful in preventing chest congestion, particularly in the elderly. Anticonvulsants need to be continued. Steroids are continued in high doses during the first 3 post-operative days and gradually tapered (4 mg of dexamethasone IV 8 hourly). Apart from this, furosemide 40 mg per day is given. Occasionally, intermittent mannitol is given if the patient deteriorates due to cerebral oedema. Controlled ventilation may be resorted to in this situation. During this period, electrolytes and blood gases are monitored and need to be repeated at least 8 hourly. Sometimes, the patient deteriorates on the third post-operative day due to cerebral oedema.

Post-operative anaemia due to blood loss seldom occurs with microsurgery after correction of intraoperative blood loss. Aspiration pneumonitis may occur and has to be prevented. Small frequent feeds by the "drip feeding" method help to avoid this preventable complication. Other complications include meningitis, CSF leak, chest infection and stress induced gastric bleed.

PROGNOSIS

The prognosis for convexity meningiomas is very good, as total excision is possible.[8,10,14,34] There is no doubt that the single most important prognostic factor is completeness of surgical removal of the meningioma and its surrounding involved dura. Simpsons's grading[45] can be used to prognosticate recurrence.[45]

RECURRENCE

Factors contributing to the recurrence of tumour include the type of removal and pathological patterns of the tumour.[26,31,33] The biological characteristics that are implicated in recurrence are the male sex, lack of calcification, high MIB-1 index, loss of chromosome 1p and vascular endothelial growth factor expression. Increased MIB-1 labelling index which is an immunohistochemical measure of Ki-67 antigen expression has been associated with meningioma recurrence and is useful in planning adjuvant therapy. The term recurrence should be reserved for cases for Type I or Type II excision of Simpson's grading. Some authors have suggested the necessity of an additional margin of 2 cm around the tumour (Simpson grade 0).[22] For growth of tumour after sub-total excision (Type III), the term re-growth should be used. Atypical or anaplastic tumours carry an increased risk of recurrence. Histopathological findings of increased mitosis, focal necrosis, features of atypia or frank malignancy, directly correlate with the rate of recurrence.[12]

The grading system to diagnose atypical meningiomas proposed by Mahmood et al. is the most appropriate and includes the criteria: (1) Increase in mitotic rate; (2) High cellularity; (3) Sheeting of tumour cells with loss of typical histological pattern; (4) Prominent nucleoli; (5) Focal necrosis and (6) Tumour invasion into bone or cortex.[12]

Kamitani et al.[20] emphasise that the thick arachnoid membrane which is contiguous to the meningioma, involves clusters of meningiomas cells and these may be related to recurrence. Recurrence rates have been reported as 3% at 5 years, 9% at 10 years and 21% at 25 years for benign tumours that were removed completely.[18] Morokoff et al.[34] reported a 5-year recurrence rate in convexity meningiomas of 1.8% for benign lesions, 27.2% for atypical meningiomas and 50% for anaplastic meningiomas.

Radiation is resorted to in malignant lesions, and following sub-total resection occasionally.[5,30] Modha and Gutin[32] have suggested that all grade 3 and grade 2 tumours with brain invasion or a MIB-1 index of 4.2% or greater should be treated with fractionated radiotheraphy. In small meningiomas, where primary surgical excision is not possible due to medical and anaesthetic problems, stereotactic radiosurgery may be an option.[23] The role of chemotherapy is debatable. On histopathology, expression of androgen and progesterone receptors in primary human meningiomas may allow hormonal manipulation of lesions.[27,48] The use of antiprogesterone (RU480) to control tumour recurrence has not been clearly established.[16] Vivier et al.[47] found that male patients and patients with a meningioma that has a 22q LOH are more likely to develop tumours exhibiting multiplicity, recurrence or calvarial erosion and recommend that this subset of patients be followed more closely.

Whatever factors may cause recurrence, its possibility should always be mentioned and discussed with the patient. The prognosis after surgical excision should be explained. It is better to have a regular periodic CT scan once in 2 or 3 years to detect early recurrence. About 85% of patients with recurrence can undergo one or more additional operations, usually with good and long lasting results.

LONG-TERM OUTCOME

The late outcomes of operation for convexity meningiomas are still not as good as might be expected from the ease with which they are removed.[14] The late surgical sequelae include:

- Various degrees of contralateral hemiparesis which has gradually been declining due to more general use of microsurgical methods, earlier diagnosis and recent instrumental aids including neuronavigation.
- The other serious disabling sequel is the persistence or *de novo* onset of epilepsy, a sequel that has a higher frequency in convexity meningiomas than in meningiomas at other sites.
- Recurrence is another unsatisfactory outcome which can be avoided if the first operation is truly radical.

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167 Parasagittal and Falx Meningiomas

Vasudevan MC

Parasagittal and Falx meningiomas are considered together, as they have a similar clinical presentation. Cushing,[6] in 1922, suggested the term 'Parasagittal' for meningiomas along the superior sagittal sinus (SSS). These tumours arise from the arachnoid villi of the SSS and often involve the adjacent convexity dura and falx. Nearly 50% invade the sinus, 50% get secondary attachment to the falx and 25% are bilateral.[11] Hyperostosis of the adjacent skull is associated with 25% of these tumours and is a valuable pointer to their diagnosis.[7] Falcine meningioma arises from the falx cerebri or inferior sagittal sinus and may rarely invade the SSS. It is usually completely concealed by the overlying cerebral cortex and does not cause bony changes. About 50% of the tumours grow through the falx to become bilateral.[10] Falx meningiomas are about five to seven times less common than parasagittal meningiomas (PSMs). Olivecrona was the first to distinguish these meningiomas according to the site of attachment along the SSS.[15] The distribution of parasagittal and falx meningiomas along the longitudinal axis is about 20%, 50% and 30% in the anterior, middle and posterior-third, respectively.[11]

CLINICAL FEATURES

Tumours in the middle-third, from the coronal suture to the lamboid suture, classically present with contralateral focal motor or sensory epilepsy followed by progressive weakness of the contralateral lower limb (Fig. 1). These tumours are detected at an early stage because of focal epilepsy. Bilateral tumours may, occasionally, give rise to bilateral disturbances and, rarely, paraplegia that may be wrongly attributed to spinal pathology.

Anterior-third meningiomas, located between the crista galli and the coronal suture, have a more insidious onset and often attain a large size before diagnosis (Figs 2 to 4). Headache is the predominant symptom and may be present for years followed by gradually progressive impairment of memory, intelligence and personality changes. Generalised epilepsy is a presenting symptom in 25–30% of patients.[10,14] Ataxia, tremor and ipsilateral facial pain may, occasionally, accompany a large meningioma in this location and thus may be misdiagnosed as a posterior fossa tumour.[9]

Tumours in the posterior-third between the lambdoid suture and the torcular herophili may present with features of raised intracranial pressure alone (Fig. 5). The only characteristic sign, a homonymous field defect, either quadrantanopic or hemianopic, may not be noticed by the patient.[16] Epilepsy is uncommon.

IMAGING

Either computerised tomography (CT) or magnetic resonance (MR) clinches the diagnosis. The CT scan

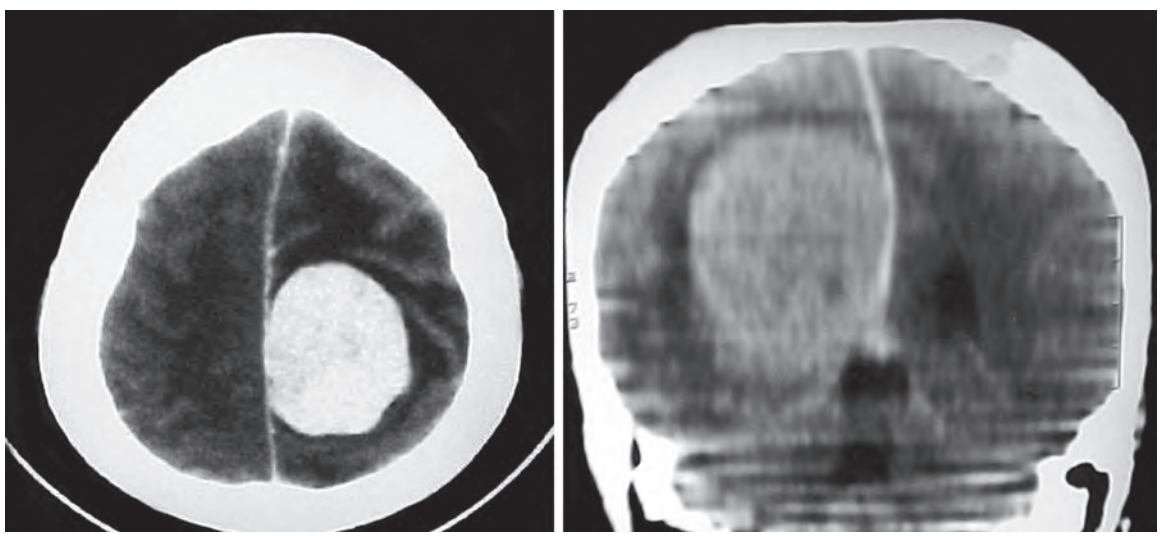

Fig. 1: CT scan showing a middle-third falx meningioma

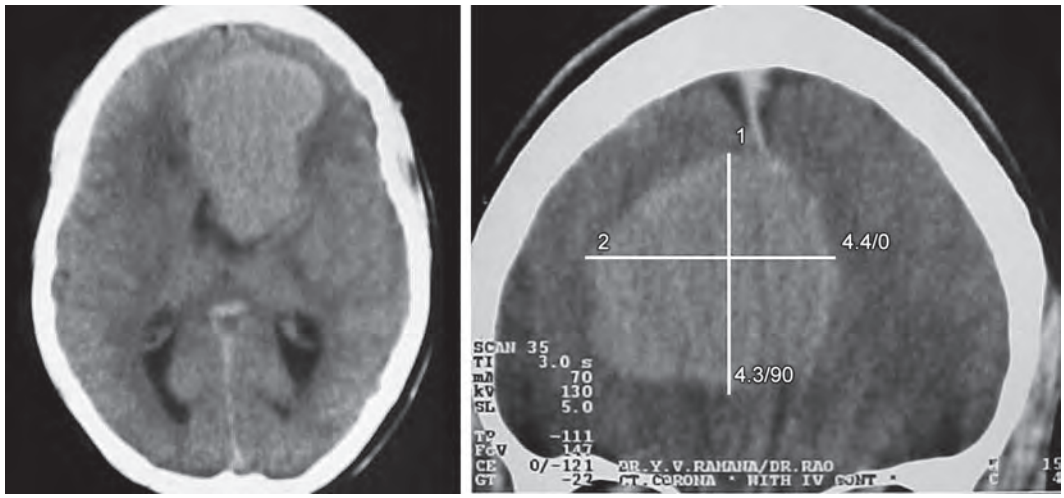

Fig. 2: CT scan showing unilateral falx meningioma with mass effect

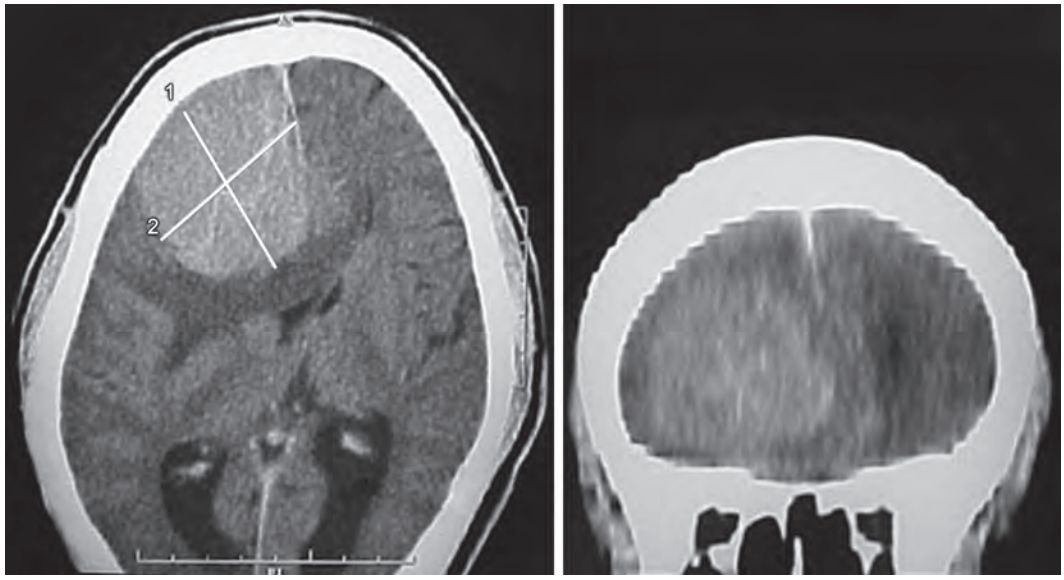

Fig. 3: CT scan showing a large anterior-third falx meningioma

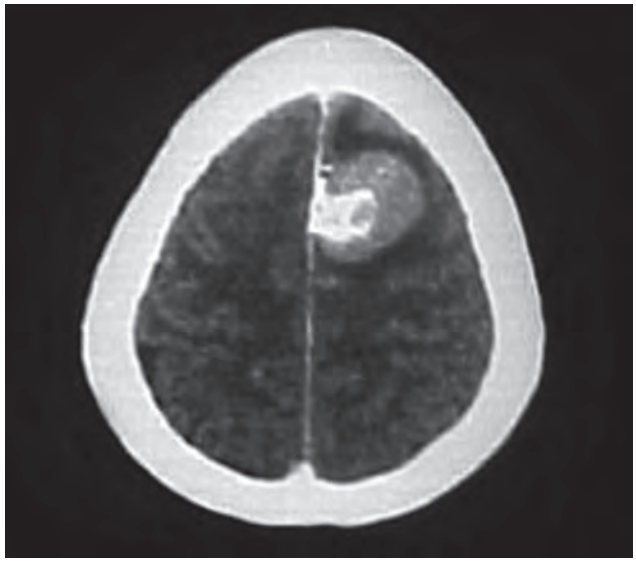

Fig. 4: CT scan showing an anterior-third falx meningioma

best reveals the chronic effects of slowly growing mass lesions on bone remodelling. Calcification in the tumour (seen in 25%) and hyperostosis of overlying skull may be seen. MR imaging reveals a number of characteristics highly suggestive of meningioma. These MR imaging findings include a tumour which is dural-based and isointense with grey matter, demonstrates prominent and homogeneous enhancement (95%), frequent cerebrospinal fluid/vascular cleft(s) and often an enhancing dural tail (60%). However, approximately 10–15% of meningiomas have an atypical appearance on MR images, mimicking metastases or malignant gliomas. In particular, these meningiomas may have a significant amount of peritumoural oedema due to venous compression.[21] Angiography, the most preferred diagnostic procedure in the pre CT era, may still be helpful in revealing the vascularity of the tumour, its blood supply and its relationship to the venous sinuses. Ramamurthi and Varadarajan in 1961 reported that the angiographic

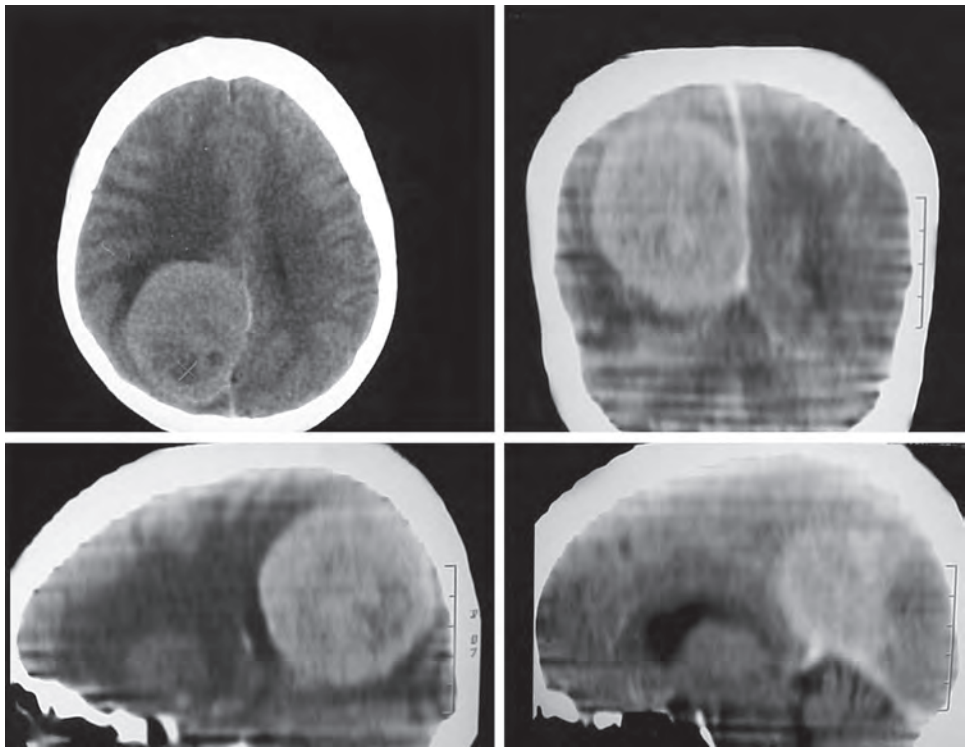

Fig. 5: CT scan of the brain showing a large posterior-third falx meningioma

appearance of a tuberculoma enplaque may mimick a meningioma.

Parasagittal meningiomas may pose a difficult surgical challenge since venous patency and collateral anastomoses have to be clearly defined for correct surgical planning. Contrast-enhanced magnetic resonance venography (CE-MRV) provides additional and more reliable information concerning venous infiltration and the presence of collateral anastomoses compared with phase contrast (PC) sequences.[3] There has also been interest in the use of MR spectroscopy to assist in the diagnosis of meningiomas. This modality may be particularly useful in patients unable to undergo surgery for whatever reason. Creatinine containing peaks in meningioma are 20% that of comparable levels in normal brain. An increase in the choline-containing peaks and the alanine peak has been reported as well. Greater than 63% of atypical meningiomas had a characteristic lactate peak on preoperative MR spectroscopy.[21]

In addition, tumours in the mid and posterior-third may be investigated by angiography, mainly to assess the status of the SSS and the distribution of the cortical veins. Middle PSMs depress the pericallosal arteries and the anterior tumours displace these vessels posteriorly and downwards. The anterior cerebral artery may be displaced to the same side and bilateral tumours often cause spreading of the pericallosal and callosomarginal arteries in opposite directions and outline the extent of the tumour.[5]

Differential diagnosis include dural metastasis, primary dural lymphoma, solitary fibrous tumours, gliosarcomas, leiomyosarcomas, hemangiopericytomas, melanocytomas, plasmacytomas, inflammatory pseudotumours, en-plaque meningiomas, neurosarcoidosis, plasma cell granulomas and Rosai–Dorfman disease.[13]

TREATMENT

Many studies confirm the tenet that many meningiomas grow very slowly and that a decision not to operate is justified in selected asymptomatic patients. As the growth rate is unpredictable in any individual, repeated brain imaging is mandatory to monitor an incidental asymptomatic meningioma. An interval of 6 months after the initial study, followed by images at increasing intervals (as stability is confirmed over the first 1–2 years) appears adequate to assess growth rate and need for intervention.[21]

The treatment of meningiomas is dependent on both patient related factors (age, performance status, medical comorbidities) and treatment-related factors (reasons for symptoms, goals of surgery and resectability which is judged by the location and bilaterality of the tumour, patency of SSS and displacement of the cortical veins). In patients who are considered surgical candidates (surgically accessible symptomatic meningiomas), the goal of therapy is total excision. As with all brain tumours, completeness of resection is determined by early (72 hours)

post-operative, contrast-enhanced brain imaging using either CT or MR imaging.[21]

Data from various studies suggests high morbidity frequently following radical surgery of tumours in central and posterior location.[4,23] Hence, whenever possible, a more conservative approach is adopted. Clearly, at least the bulk of the tumour should be removed whenever possible when the patient is progressively symptomatic. However, a small tumour, without focal deficit, especially in the elderly can be kept under serial observation or may be subjected for primary radiosurgery. Paradoxically, the relatively high morbidity associated with surgical removal of central PSMs once the sinus becomes involved, may justify the more aggressive attitude in younger patients.[1,20]

For anterior-third tumours, the patient is positioned supine and a bicoronal incision is employed.[26] In mid-third tumours, the patient is in a semilateral position and in posterior-third lesions, it is the three quarter prone position. In all these tumours, the bone flap may be carried up to 2 cm across the midline to the side opposite the tumour. For tumours near the central sulcus a generous craniotomy helps in avoiding excessive handling of the primary sensorimotor cortex.

In PSMs, as stated earlier for all meningiomas, the attachment of the tumour to the meninges is dealt with first to reduce the vascular supply. Any attachment to the sinus may be left to be dealt with later on. After internal decompression, the dissection of the capsule is started away from the midline and the tumour gradually lifted with its base towards the area of attachment to the sagittal sinus, so that if there is any brisk haemorrhage from the sinus there is enough space to deal with it under direct vision after delivering the tumour. If the sagittal sinus is completely occluded by tumour, it can be excised along with the tumour anywhere along its length. Anterior to the coronal suture, the involved sinus may be excised even if patent. An involved but patent sinus in mid and posterior-third PSMs calls for careful surgical judgement.[15] Unlike the earlier belief, it is now understood that radical resection together with removal of the sinus is not necessarily safe even when the sinus is already completely occluded before surgery, particularly with meningiomas of the middle-third of the SSS. It is hypothesized that radical resection results in removal of important cortical veins that run within the tumour or on its capsule.[19]

Tumours attached to the lateral wall, without significant infiltration into the sinus lumen can be managed by dissecting the tumour off the SSS and achieving haemostasis by a combination of coagulation and pressure over Surgicel® and Gelfoam®. If the tumour has infiltrated the sinus lumen in the lateral aspect only, it may be excised and the sinus progressively closed with a continuous running suture. Though Bonnal and Brotchi[2] have shown the feasibility of excision of the sinus followed by partial or total autogenous venous grafts to repair it, if the sinus is extensively involved but still patent it may be better left intact and some tumour left behind along the area of the sinus. In both situations, extreme care is vital for preservation of cortical veins, which may offer important collateral drainage.[8]

In falcine tumours, care is taken not to sacrifice cortical veins draining into the SSS while exposing the tumour posterior to the coronal suture. To expose the capsule of the tumour, the thinned out brain covering the tumour may be gently pushed laterally, after incising the arachnoid. Very large tumours may be operated upon in two stages, the feeders on either side of the falx being removed at each stage.[18] For details of operative procedure reference may be made to the chapter, "Surgical Therapy of Parasagittal and Falcine Meningiomas" in Volume 1 of Textbook of Operative Neurosurgery.[26]

PROGNOSIS

Rate of recurrence of parasagittal and falx meningioma significantly increases in cases of non-radical resection of tumour. Aggressive surgical treatment presents several hazards and carries an increased risk of unsatisfactory outcome; the risk of recurrence, however, is significantly decreased.[17] The extent of resection of meningiomas in this region is closely related to tumour recurrence. Recurrence rates after total resection of meningiomas involving the sagittal sinus wall range from 5 to 9%; those after sub-total resection accompanied by sinus wall excision range from 16 to 17%; after sub-total resection of the tumour is approximately 29%; and after partial resection of the tumour it is approximately 39%.[12] A classical paper on the recurrence of intracranial meningiomas was by Simpson in 1957.[22]

Hence, if total resection is aimed at, then sinus repair and reconstruction is required. However, if a conservative and less aggressive approach is adopted, then the patient has to be informed regarding the prognosis and may be given the option of adjuvant radiosurgery.[24,25]

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168 Olfactory Groove Meningioma

Ravi Ramamurthi, Nigel Peter Symss

INTRODUCTION

In 1938, Harvey Cushing[4] in his monograph entitled "Meningioma" reported that the first successful operation for removal of an olfactory groove meningioma (OGM) was by Francesco Durante in 1895. Cushing operated on 28 cases, with an operative mortality of 19%. Most of the patients had very large tumours.[4] In his publication, he emphasised the surgical management of internal decompression of the tumour, before attempting to dissect the capsule and the importance of preserving the anterior cerebral arteries which may be involved by the tumour.

ANATOMY

Olfactory groove meningiomas may arise from the anterior cranial fossa near the crista galli, from near the cribriform plate of the ethmoid bone or the planum sphenoidale[26] and account for 8–13% of all intracranial meningiomas.[21,25] The tumour may be symmetric around the midline or extend predominantly to one side. The principle blood supply of the tumour is from the ethmoidal, meningeal and ophthalmic arteries through the base of the skull along the midline. In large tumours, the anterior cerebral arteries may be involved with the tumour capsule. The frontopolar and small branches of the anterior cerebral arteries may be adherent to the superior and posterior part of the tumour capsule. In large tumours, the olfactory nerve is usually adherent and splayed out on the tumour, while the optic nerves and chiasm may be pushed downwards and posteriorly.

CLINICAL FEATURES

These are usually slow-growing tumours. Due to the ability of the brain tissue to adapt to slow compression and the absence of focal functional cortical regions in the adjacent brain tissue, these tumours can grow to large sizes before the patient becomes symptomatic. In Cushing's series of 29 patients, most of whom had large tumours, the primary symptoms were headache, visual disturbances, personality changes and loss of smell.[4]

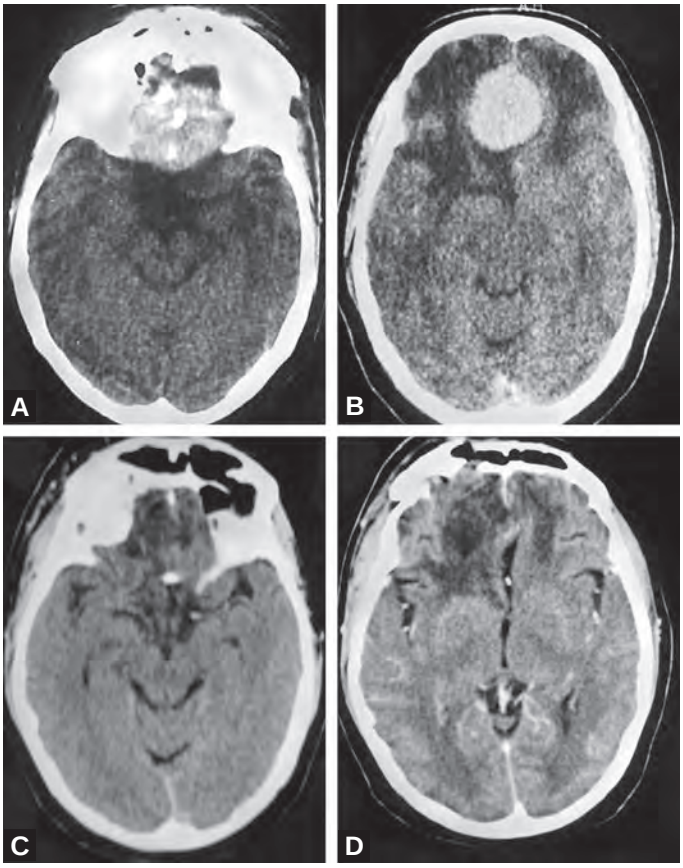
Unlike meningiomas at other locations, there was no female predominance in OGMs operated at SCTIMST.[14] These tumours can be silent for a long time. In the SCTIMST series, the most common initial symptom was long standing headache (75%); the other presenting symptoms were epilepsy (12.5%) and visual dysfunction (8.3%). Although anosmia occurs in 85–90% of cases, it is rarely the initial or presenting symptom. As these tumours grow in size, symptoms of pressure on the frontal lobe may be apparent. Mental symptoms often lead the patient to seek treatment from a psychiatrist.[3,7] While inferior tumours may cause excitement or restlessness, pressure over the convexity of the frontal lobe may lead to indifference and apathy. The more anterior tumours cause a central scotoma and papilloedema. Growing posteriorly, these tumours press on the optic nerve and chiasma, leading to unilateral blindness or bitemporal haemianopia with optic atrophy. With the rise in intracranial pressure, there may be papilloedema in the opposite eye and a Foster Kennedy syndrome may be seen. Although traditionally considered a classical sign, this syndrome is neither common nor diagnostic of this tumour. Foster Kennedy syndrome was noted in 8.3% of patients. Further extension posteriorly puts pressure on the hypothalamus and pituitary gland. By this time, the ICP rises to cause obvious features of raised ICP. It is not unusual, even today, to see large OGMs presenting with blindness and raised ICP. Rarely, by eroding through the orbital roof or the cribiform plate, the tumour may cause proptosis. In the SCTIMST series, deranged mental function and gross visual impairment were each present in nearly 30% of patients.

RADIOLOGY

The diagnosis is confirmed by computed tomography (CT) or magnetic resonance imaging (MRI) scan of the brain. On CT scan the lesion is a well circumscribed, rounded, isodense to slightly hyperdense mass, with dense uniform enhancement after intravenous contrast (Figs 1A to D and 2A to C).

The density is partly due to the cellularity and to the presence of calcified psammoma bodies. Calcification may also be seen and is easily detected by CT. There may be increased thickness of the bone due to hyperostosis at the site of dural attachment. Occasionally, bone destruction may be present due to invasion by the tumour.

With MRI, the configuration of the tumour in all directions, the anatomical extent and the relationship



Figs 1A to D: (A and B) Pre-operative CT scan of the brain contrast study showing olfactory groove meningioma. (C and D) Post-operative CT scan of the brain contrast study showing post-operative changes with total excision of the tumour

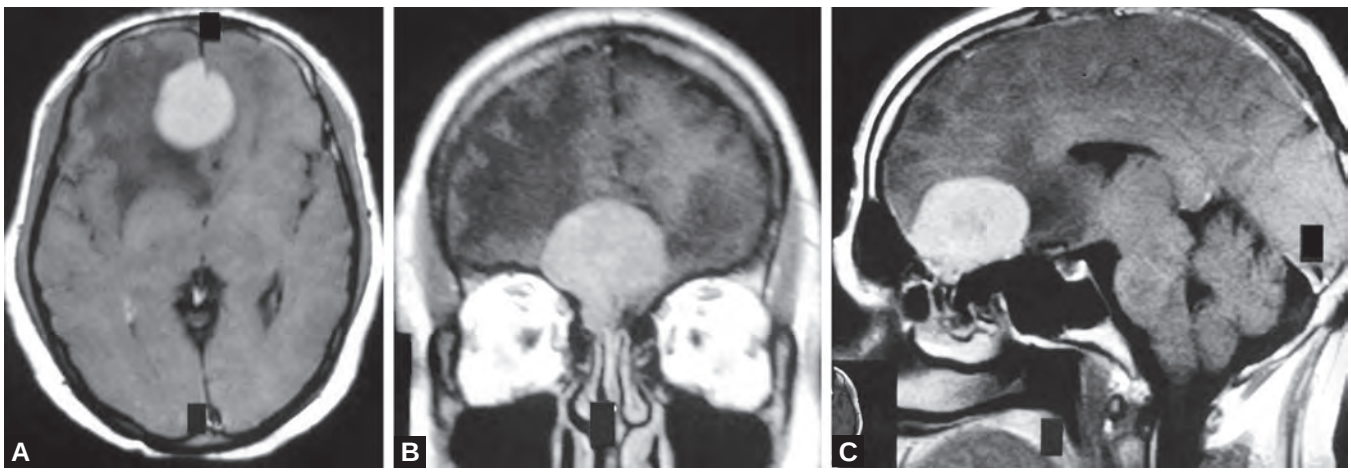
of the anterior cerebral arteries and optic nerves can be clearly defined. On T1-weighted images, the lesion is usually relatively isointense with grey matter but may have variable signal intensity. With contrast, they enhance intensely uniformly and often are seen to have a 'dural tail', probably due to dural reaction. In angioblastic meningiomas, the lesions will show flow voids within them due to rapid flow of the blood in the veins.

Although angiography is not mandatory, when performed, it provides useful information in large tumours, regarding the blood supply and location of the anterior cerebral arteries and their major branches. The anterior cerebral arteries are pushed backwards and upwards and a frontal arterial branch is generally stretched over or involved in the tumour capsule. In large tumours, the anterior cerebral artery and its branches may be involved within the tumour capsule. Care is necessary to avoid injury to these vessels during surgery.

SURGICAL MANAGEMENT

Surgical treatment should aim at total excision which is generally possible even in large tumours. In all cases, a bicoronal skin incision is preferred. Ojemann[16] prefers a bifrontal craniotomy for large tumours that extend to the crista galli and for smaller tumours that are more posteriorly located and do not extend as far anteriorly, he prefers a right lateral subfrontal approach. McCarty et al.[10] prefer a bifrontal approach. Kempe,[8] Logue[9] and Symon[25] advocate a unilateral subfrontal approach with removal of part of the frontal lobe. This will depend upon the precise extent of the tumour. In large tumours that extend equally on both sides of the midline, a bilateral bone flap is preferred. This approach is associated with minimal amount of retraction on the frontal lobes, gives adequate access to all sides of the tumour, allowing the surgeon to decompress the tumour while working along the skull base to cut off the blood supply. The anterior end of the sagittal sinus may be ligated and the falx cerebri detached from its inferior attachment when indicated.

Spektor et al.[24] used a variety of surgical approaches, such as bifrontal craniotomy, a unilateral subfrontal approach, pterional approach, a fronto-orbital craniotomy and a subcranial approach for OGM resection. They advocated an approach tailored to the tumour's size, location and extension and combined with modern microsurgical cranial base techniques, it allows full OGM removal with minimal permanent morbidity,



Figs 2A to C: Contrast MRI. (A) Axial. (B) Coronal. (C) Sagittal sections of the brain showing olfactory groove meningioma

excellent neurological outcome and very low recurrence rates.

In attempting total excision, although a frontal branch of the anterior cerebral artery involved within the tumour capsule can be coagulated and divided, no effort should be spared to preserve the main anterior cerebral artery. The dural attachment is excised and any hyperostotic bone is removed. Any extension of the tumour into the air sinuses can be removed by a frontobasal approach or a combined craniofacial approach.[5,12,23] Meticulous repair of the anterior cranial fossa is necessary to prevent CSF rhinorrhoea.[20]

The endoscopic endonasal technique represents a possible alternative approach for suitably selected cases and could be expected to minimise neuropsychiatric sequelae.[27]

Despite apparent gross total resection, OGMs have a high rate of late recurrence (average, 23%).The cranial base and paranasal sinuses are sites of predilection for recurrence of OGMs. Recurrence is the result of a direct extension, attributable to incomplete resection of involved bone and regrowth at the edge of a previous surgical field. Extensive resection of all suspicious underlying bone is a complement to radical removal of these lesions. Reconstruction of the floor with a vascularised pericranial flap to prevent cerebrospinal fluid leakage, is crucial.[15]

The mechanisms of recurrence are still unclear. Maiuri et al.[11] in their analysis of immunohistological studies, mitotic index (MI), Ki-67 LI, oestrogen and progesterone receptors (ER and PR), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF) and Bcl-2, found that tumour recurrence was not correlated with patient age, tumour location, consistency, vascularity and histology. They concluded, higher mitotic index (MI) and Ki-67 LI and progesterone receptors (PR) negativity are predictive factors of recurrence of benign (WHO I) completely resected meningiomas, particularly when Bcl-2 positivity is associated.

Complications

With the use of proper microsurgical techniques, the incidence of reported complications arising from removal of these tumours has been low. These complications can be encountered during surgical removal of olfactory groove and suprasellar meningiomas, as the surgical approaches are more or less the same. They can be divided into:

a. *Cerebrospinal fluid leak and infection:* CSF leak in the post-operative period can result from any craniotomy that breaches the frontal sinuses and infection can occur by contamination through the paranasal sinuses. Once the sinus has been breached, removal of frontal sinus mucosa, followed by a meticulous repair with muscle and a vascularised pedunculated pericranium is mandatory. The use of cranioplasty material can increase the risk of post-operative infection.
b. *Vascular injury:* The adherence of the tumour to the anterior cerebral arteries and its branches is one reason for inability to achieve total tumour removal. Injury to the anterior cerebral arteries can result in post-operative ACA territory infarct. Sacrifice of the smaller branches, such as the frontopolar arteries, is acceptable, as it is well tolerated.[18] Solero et al.[22] in their series of 98 patients with OGMs, clipped 16 anterior cerebral arteries.
c. *Post-operative seizures:* Seizures occurring in the early post-operative period are about 6% in reported series.[1,25] Ramamurthi et al.[19] reported that 7 of 12 patients (58%) with pre-operative fits and frontal tumours were relieved of their seizures post-operatively, while 6 of 38 (16%) developed new post-operative seizures.
d. *Visual loss:* Visual deterioration in the post-operative period is usually the result of surgery, due to rough manipulation of the optic nerve and chiasm or injury to the chiasmal blood supply. This can occur during removal of the midline posterior pole of the tumour. Finn and Mount reported a visual loss of 12% following excision of these meningiomas.[6] Solero et al.[22] had 20% visual deterioration in their series of large (more than 4 cm) tumours.
e. *Mortality:* Mortality following surgery has been low in most series. Mac Carty et al.[10] reported one death in 27 cases.[10] Bakay had one death in 11 patients.[2] Ojemann[17] reported one death in 17 patients, due to a pulmonary embolus.

Result

Walder[26] reported a mortality of 20% in a series of 77 cases. Use of microsurgical techniques has improved the outcome remarkably.[10,16] There was only one operative mortality in a series of 24 cases operated upon over seven years at SCTIMST.[14] The mortality in Sinha and Prakash's[21] series was 11%.

Nakamura et al.[13] operated on 82 patients with OGMs, through the bifrontal (n = 46), frontolateral (n = 34) and pterional (n = 2) approaches. Total tumour removal (Simpson Grade 1 or 2) was achieved in most cases (91.2% frontolateral, 93.5% bifrontal). The overall recurrence rate was 4.9%, with four patients requiring surgery. Even in large tumours, high rates of total tumour resection could be achieved with low recurrence rates, using the simple and minimally invasive frontolateral approach. In recent years, they preferred to use the frontolateral approach, which provides quick access to the tumour with less brain exposure while still enabling total tumour removal with a low morbidity rate and no mortality.

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Suprasellar Meningioma

INTRODUCTION

Suprasellar meningioma was first reported by Stirling[32] in 1897. These were defined as tumours arising from the presellar area around the tuberculum sellae and growing upwards between the two optic nerves and also referred to as tumours of the tuberculum sellae.[5,23,32] Cushing in 1916 was the first to remove a suprasellar meningioma totally but it was reported only in 1929.[29] They comprise 5–10% of all intracranial meningiomas.[17,31]

ANATOMY

Authors of most of the recent series include meningiomas arising from the tuberculum sellae, planum sphenoidale, diaphragma sellae and/or anterior clinoid process under suprasellar meningiomas.[16,22,33] Based on the direction of growth of the tumour, the optic nerves are elevated and laterally displayed when the lesion occupies a subchiasmal position. Lesions arising from the diaphragma sellae grow retrochiasmally and manifest with ocular paresis and endocrine dysfunction. The blood supply to these tumours is predominantly from the posterior ethmoidal arteries and, to some extent, from the smaller branches of the anterior cerebral arteries. This is the area of vital arterial perforators.

CLINICAL FEATURES

The mean age of occurrence is the fourth decade, with a female predominance in a ratio of 3:1.[10]

As these tumours arise in close proximity to the optic chiasma, displacing it posteriorly and superiorly and stretching it, visual symptoms are early and common, leading to earlier detection than olfactory groove meningiomas. Around 90–99% of the patients complain of either monocular (55%) or binocular (45%) visual loss.[16,33] In our series of 50 cases, 34 patients presented with binocular and 11 with monocular visual loss. Forty of these patients had primary optic atrophy and only three had papilloedema. The other common symptoms are headache, epilepsy and mental changes. The presence of bitemporal hemianopic field defects in the presence of a normal sized sella, should suggest the possibility of a suprasellar meningioma. The 'chiasmal syndrome'; primary optic atrophy with bitemporal field defect in adult patients with an essentially normal sella, has been the classic presentation of these tumours, since its recognition in 1927 by Holmes and Sargent,[13] which was later emphasised by Cushing.[7]

However, in the early stages, vision may be affected in only one eye. Symon and Rosenstein[33] found symmetrical visual deficits in 22 cases, whilst 79 cases in a series of 101 suprasellar meningiomas had either asymmetrical binocular involvement or only monocular defects. Pituitary hypofunction is uncommon and is found in only 4–13% of these patients. The size of these meningiomas is a major factor that determines a patient's outcome. Cushing classified these tumours into four stages according to their size: (1) initial stage; (2) pre-symptomatic; (3) favourable for surgery and (4) late, or essentially inoperable.[6]

Anosmia is rarely a presenting in these meningiomas. Poppen found that suprasellar meningiomas present with early visual deficits, while anosmia is a late finding.[26]

RADIOLOGY

Abnormalities in the plain X-rays are seen in 60% of cases.[33] Plain X-rays may show a thickening in the region of the tuberculum sellae or erosion of the dorsum sellae, planum sphenoidale or clinoids. Rarely, calcification in the region may simulate a craniopharyngioma.

The CT scan typically shows an isodense or slightly hyperdense, rounded, mildly lobulated, densely enhancing mass in the suprasellar area. There can be bony hyperostosis at the site of dural attachment to the bone. This may be associated with expansion of the underlying sphenoid sinus, a finding that can be recognised on CT scan and X-ray skull. Such erosion and extension into the subfrontal sinuses has been reported in up to 15% of cases.[9]

MRI with MRA gives additional information about encasement and displacement of vessels and also a more precise extent of the lesion (Figs 3A to F and 4).

In spite of the great advances in CT and MRI, it may not always be possible to differentiate a meningioma from a pituitary macroadenoma by imaging alone. Taylor et al.[34] have proposed a combination of three features in a meningioma that may differentiate it from a pituitary tumour in a gadolinium enhanced MR. These are: (1) bright homogeneous enhancement with gadolinium as opposed to heterogeneous relatively poor enhancement in a pituitary tumour; (2) a suprasellar rather than a sellar epicentre of the tumour and (3) tapered extension of an intracranial tumour base, described as the 'dural tail' which represents a hypervascular non-neoplastic process, not the meningioma.[19] Such a differentiation is worthwhile as the surgical approaches to these lesions are different. Angiography, in addition to showing a vascular tumour in the suprasellar area, may show displacement of the ICA inferiorly (closure of the siphon), posteriorly and laterally and elevation of the A1 segment of the ACA and proximal part of the A2. Narrowing or irregularity of the ICA suggests encasement of the artery by the tumour.

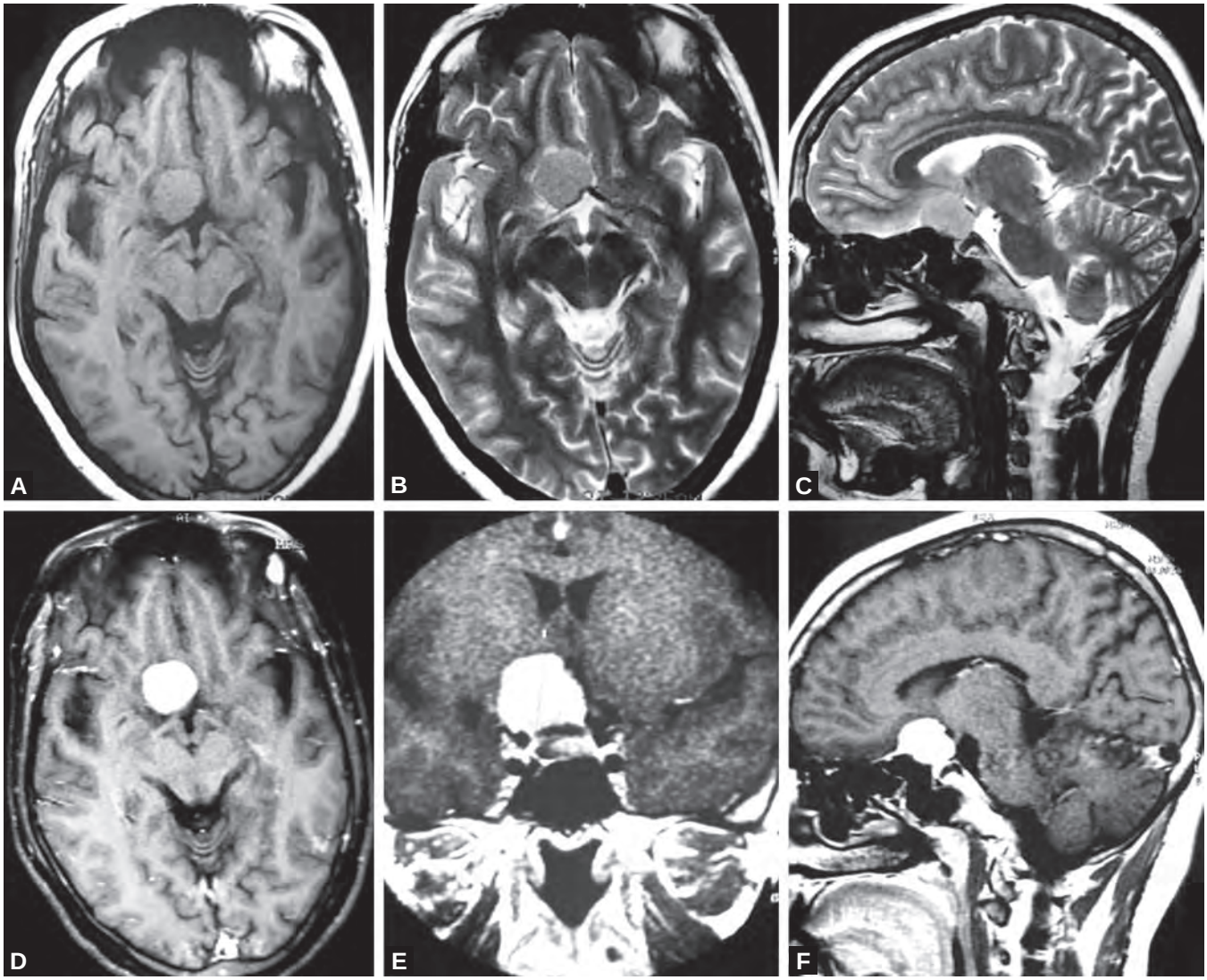
SURGICAL MANAGEMENT

Surgery for tuberculum sellae meningiomas presents a special challenge because of their proximity to arteries of the anterior circulation, anterior visual pathways and the hypothalamus.

The tumour is usually approached by a right frontotemporal craniotomy through a lateral subfrontal microsurgical exposure just in front of the lesser wing of the sphenoid. The tumour is approached from the left side, if the tumour arises from the left anterior clinoid or if the bulk is greater on that side. Occasionally, the tumour grows into the optic canal, necessitating its deroofing for complete extirpation. AI Mefty1 has advocated a basal approach, supraorbital-pterional, to minimise brain retraction and shorten the dissection distance. The best chance of total excision is at the initial operation. Elective partial excision of the tumour followed by a second-stage attempt for total extirpation is usually not successful. The author has never found this strategy helpful in basal meningiomas, as these tumours do not get separated from the vital structures in the intervening period.

Nakamura et al. removed 72 tuberculum sellae meningiomas microsurgically using three different surgical approaches: (1) the bifrontal approach; (2) pterional/frontotemporal approach and (3) the frontolateral approach. Considering the operative morbidity and mortality, the frontolateral and pterional approach provided remarkable improvement, compared with the bifrontal approach. These approaches allowed quick access to the tumour and were minimally invasive with less brain exposure, with high rates of total tumour removal. By comparison, the frontolateral approach provided the best results concerning visual outcome (77.8%) while representing the least invasive surgical approach.[20]

In our series of 50 patients, total excision was achieved in 28 patients, radical excision in 12 and subtotal in 10 patients. Three patients had total visual improvement 18 had partial improvement, in 17 the vision remained the same as pre-operative and in 10 cases the vision worsened. Our mortality was 5 cases (10%).



Figs 3A to F: Pre-operative MRI of the brain showing a suprasellar meningioma which is isointense to brain in T1 and isointense to hyperintense in T2. Post-contrast images show uniform brilliant enhancement with dural tail

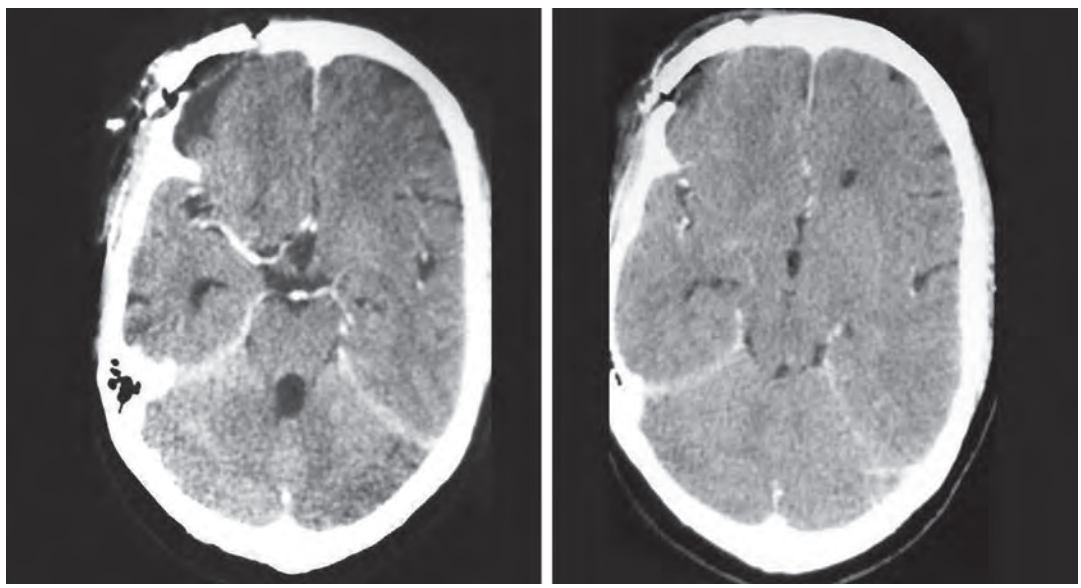


Fig. 4: Post-operative contrast CT scan of the brain showing evidence of craniotomy and total excision of the lesion with post-operative changes

In the series of 101 patients reported by Symon and Rosenstein,[33] total excision was achieved in 78.2% with a mortality of 5.9%. In their series, vision improved, remained static and deteriorated in 63.6%, 12.1% and 24.2%, respectively. In the SCTIMST series, total excision was achieved in 77% of 32 patients operated upon over a period of seven years with a mortality of 12.5%; vision improved, remained static and deteriorated in 66.6%, 20.8% and 12.5% of patients, respectively.[16] Sinha and Prakash[27] reported total excision in 42.8% of 14 patients operated upon over 10 years with one post-operative death.

Fahlbusch reviewed 47 cases of suprasellar meningiomas operated via a unilateral pterional approach. Complete tumour resection was possible in all but one patient. There were no fatalities and the rate of visual improvement was 80%. The best prognoses were found in patients younger than 50 years and in patients in whom the duration of symptoms was less than 1 year. The overall tumour recurrence rate was 2.1% (one of 47 cases). For patients in whom long-term (more than 5 years) follow-up data were available, the recurrence rate was 4.2% (one of 24 cases). In their series, complete resection of suprasellar meningiomas was possible through a unilateral pterional craniotomy and was associated with a low morbidity rate and no deaths.[11]

Pamir et al.[24] and Jallo[15] have also found that the standard pterional craniotomy using microsurgical technique provides the necessary exposure enabling total removal, while keeping the complications to a minimum.

Other Surgical Approaches

Cook et al.[4] described the benefits of the direct endonasal trans-sphenoidal approach for removal of suprasellar meningiomas. All patients underwent tumour removal via an endonasal approach with the operating microscope. Suprasellar exposure was facilitated by removal of the posterior planum sphenoidale. Ultrasound was used to help define tumour location before dural opening. The extent of tumour removal was verified with angled endoscopes in all patients and with intra-operative MRI in one patient. The surgical dural and bony defects were repaired in all patients with abdominal fat, titanium mesh and 2–3 days of cerebrospinal fluid lumbar drainage. Nasal packing was not used. The anterior skull base defect was reconstructed with a pedicled mucosa flap from nasal septum (Hadad-Bassagasteguy flap). They concluded that the endonasal approach with the operating microscope appears to be an effective minimally invasive method for removing relatively small midline tuberculum sellae meningiomas. Intra-operative ultrasound, the micro-Doppler probe and angled endoscopes are useful adjuncts for safely and completely removing such tumours.

Exclusive endoscopic endonasal approaches have also been described for the removal of tuberculum sellae meningiomas.[28] More recently, the sublabial trans-sphenoidal approach has been used to remove such tumours.

Results

Mortality and partial resection rates were lower and prognosis for visual function following craniotomy was better, if the mean duration of symptoms was less than two years and the tumour size was less than 3 cm.[33] Other factors that favourably influenced the prognosis for vision were a normal optic disc and a pre-operative visual loss of less than 50%. Tumours arising from the diaphragma sellae and anterior clinoid had a worse visual outcome.[2,16]

Puchner et al.[29] in their series with long-term follow-up (mean: 5.7 years), could achieve radiologically confirmed radical tumour removal in 84% of patients. However, 12% of patients developed late onset epilepsy. At long-term follow-up, visual function was improved in 67%, unchanged in 9% and worsened in 24%. In more than 50% of patients, the vision showed recovery over a longer time period than the first 10 days after operation. Radiographic control examinations revealed tumour recurrences in 2 patients (both asymptomatic) and progress of residual tumour in 5 patients (2 symptomatic, 3 asymptomatic). They concluded that with the introduction of modern neurosurgery, a clear improvement in the surgical treatment of suprasellar meningiomas can be observed. However, the long delay in diagnosing these tumours correctly prevents a further improvement of the ophthalmological results at long-term follow-up. Due to a relatively high rate of late onset epilepsy, anticonvulsive prophylaxis for 6 months seems to be justified.

Kim et al.[18] in their study on 27 patients, found those with symptom duration of less than 1 year had a greater likelihood of visual improvement than those with a symptom duration of more than 1 year and those with a soft tumour had a greater likelihood of visual improvement than those with a hard tumour, although this was without statistical significance. Also, patients with a high signal intensity lesion on T2-weighted images had a greater likelihood of visual improvement than those with an iso or low signal intensity with statistical significance. They concluded that an excellent correlation exists between tumour consistency and appearance on T2-weighted images ($p = 0.001$) and the results of their study indicate that MRI-T2WI can be used to estimate tumour hardness pre-operatively and that this is an important prognostic factor in visual impairment.[18]

ADJUVANT THERAPIES

Meningiomas, which invade intracranial bone structures and the adjacent areas, are frequently unresectable because of their aggressive and recalcitrant growth behaviour. Also, surgically inaccessible meningiomas may not be removed completely. They have a high recurrence rate and in approximately 10% of these tumours

there is an increased risk of malignancy. Significant morbidity and mortality rates associated with recurrent meningiomas demand non-surgical approaches. There is currently no effective chemotherapy for meningiomas and adjuvant hormonal treatment has not proven beneficial.

Gupta et al.[12] studied the effects of the topoisomerase I inhibitor irinotecan (CPT-11) on primary meningioma cultures and malignant meningioma cell line and demonstrated growth-inhibitory effects in meningiomas both *in vitro* and *in vivo*. Irinotecan was much more effective against the malignant meningioma cell line than against primary meningioma cultures. Therefore, this drug may have an important therapeutic role in the treatment of atypical or malignant meningiomas and should be evaluated further for this purpose.

The anticancer drug hydroxyurea has been tested for its potential use in the treatment of meningiomas. The addition of 5 x 10(-4) and 10(-3) M hydroxyurea over a period of 5–9 days resulted in a remarkable decrease in cell proliferation and even blocked tumour cell growth, when compared with untreated cells. A significant arrest of meningioma cell growth in the S phase of the cell cycle was revealed on DNA flow cytometry. Electron micrographs of hydroxyurea-treated tumour cells showed ultrastructural features consistent with apoptosis and light microscopy demonstrated DNA fragmentation by *in situ* DNA strand break labelling. Short-term treatment of meningioma cell cultures with hydroxyurea for 24–48 hours resulted in discrete oligonucleosomal fragments (DNA ladder), another characteristic sign of apoptosis. In addition to the *in vitro* studies, tissue from five different meningiomas was transplanted into nude mice followed by treatment with 0.5 mg/g body weight hydroxyurea over 15 days. *In situ* DNA strand break labelling demonstrated DNA fragmentation in distinct regions with different tumour cell densities in all hydroxyurea-treated meningioma transplants. These data provide evidence that hydroxyurea is a powerful inhibitor of meningioma cell growth, most likely by causing apoptosis in the tumour cells. Thus, hydroxyurea may be a suitable chemotherapeutic agent for the long-term treatment of unresectable or semi- to malignant meningiomas or for preventing recurrent growth of meningiomas after resection.[21,30]

Black et al.[3] based on their results, advocated that skull base meningiomas can be managed with aggressive surgery and conformal radiation with an acceptable functional status in 99% of cases. Fractionated stereotactic conformal radiosurgery (SCRT) is a feasible high precision irradiation technique for residual and recurrent skull base meningiomas, including both small and larger tumours with excellent early tumour control and low toxicity. Longer follow-up is necessary to demonstrate sustained tumour control and low morbidity of such a high precision localised method of fractionated irradiation.[8,14]

Intensity modulated radiotherapy (IMRT) in the treatment of central nervous system meningiomas is feasible and safe, offering highly conformal irradiation for complex-shaped skull-base tumours, while sparing adjacent critical structures. If the tumour remissions seen here are found in the ongoing treatments, IMRT may be considered the treatment of choice for inoperable or subtotally resected meningiomas and for otherwise difficult-to-treat, complex-shaped tumours of the central nervous system adjacent to critical structures, with the potential of dose escalation for malignant tumours.[25]

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169 Sphenoidal Wing Meningiomas

Trimurti D Nadkarni

INTRODUCTION

Meningiomas account for 14–18% of all intracranial neoplasms. Meningiomas arising from the sphenoid ridge constitute approximately 14–20% of all meningiomas.[4,5] The complexity of these tumours is due to the involvement of the anterior circulation, anterior visual pathways and oculomotor nerve. Higher morbidity, mortality and recurrence rates have been observed for these tumours than for meningiomas in other locations.[4,5,7] The rate of recurrence for medial sphenoid wing meningiomas is reported as one of the highest for intracranial meningiomas.[11]

Two main types of tumours have been described according to their presentation: globoid tumours with a nodular shape and en plaque tumour.[7] The nodular type is an encapsulated tumour of variable size that displaces or encases intracranial arteries or cranial nerves (CNs). This tumour has a dural site of implantation through which it receives its blood supply. In meningioma en plaque, the tumour cells fill the haversian canals spreading into the adjacent bones that include the pterion, orbital wall, malar bone, zygomatic, temporal and middle cranial fossa. The tumour produces a hyperostotic reaction of these structures causing exophthalmos and temporal bowing. In addition, an intracranial meningiomatous plaque is always present.

Cushing and Eisenhardt[7] have classified these tumours based on their site of origin along the sphenoid wing as inner third, middle third and outer third tumours. Inner third tumours have been subdivided into sphenocavernous tumours [(arising from the external wall of the cavernous sinus (CS)] and clinoidal tumours (arising from the clinoid process). Middle third tumours or alar tumours and the outer third or sphenotemporal or pterional tumours present with symptoms due to compression. Additional classifications have been put forth: Petit-Dutaillis, Bonnal et al.,[6] Al-Mefty,[2] and Sekhar and Altschuler.[18]

CLINICAL PRESENTATION

Inner Third Sphenoid Wing Meningiomas

Clinoidal meningiomas produce a progressive diminution of vision beginning with ipsilateral nasal hemianopsia. As the tumour grows, a superior temporal field defect occurs and eventually the eye becomes blind. Foster Kennedy syndrome, ipsilateral primary optic atrophy associated with contralateral papilloedema, may result.

In sphenocavernous tumours, abducens palsy is the first presentation. As symptoms evolve, total ophthalmoplegia is associated with hypoesthesia in the ophthalmic division of the trigeminal nerve. Exophthalmos may result due to venous compression at the orbital apex.

Nakamura et al.[12] have subclassified this group into Group 1 comprising tumours without CS involvement and Group 2 that includes tumours with CS involvement.

Middle Third or Alar Meningiomas

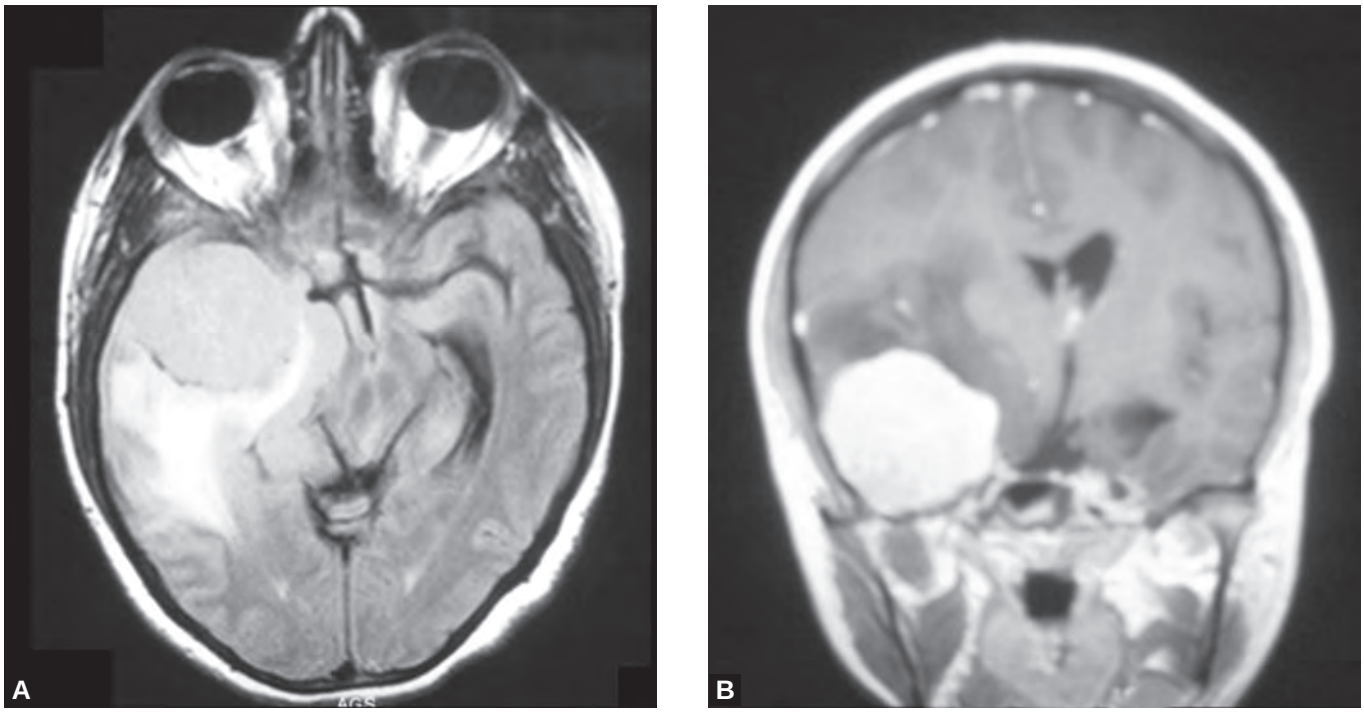
These tumours present with features of raised intracranial pressure. Headache and papilloedema are followed by anosmia, contralateral homonymous hemianopsia, personality changes, visual or olfactory hallucinations, contralateral facial palsy and hemiparesis. Seizures may occur.

External Third or Pterional Meningiomas

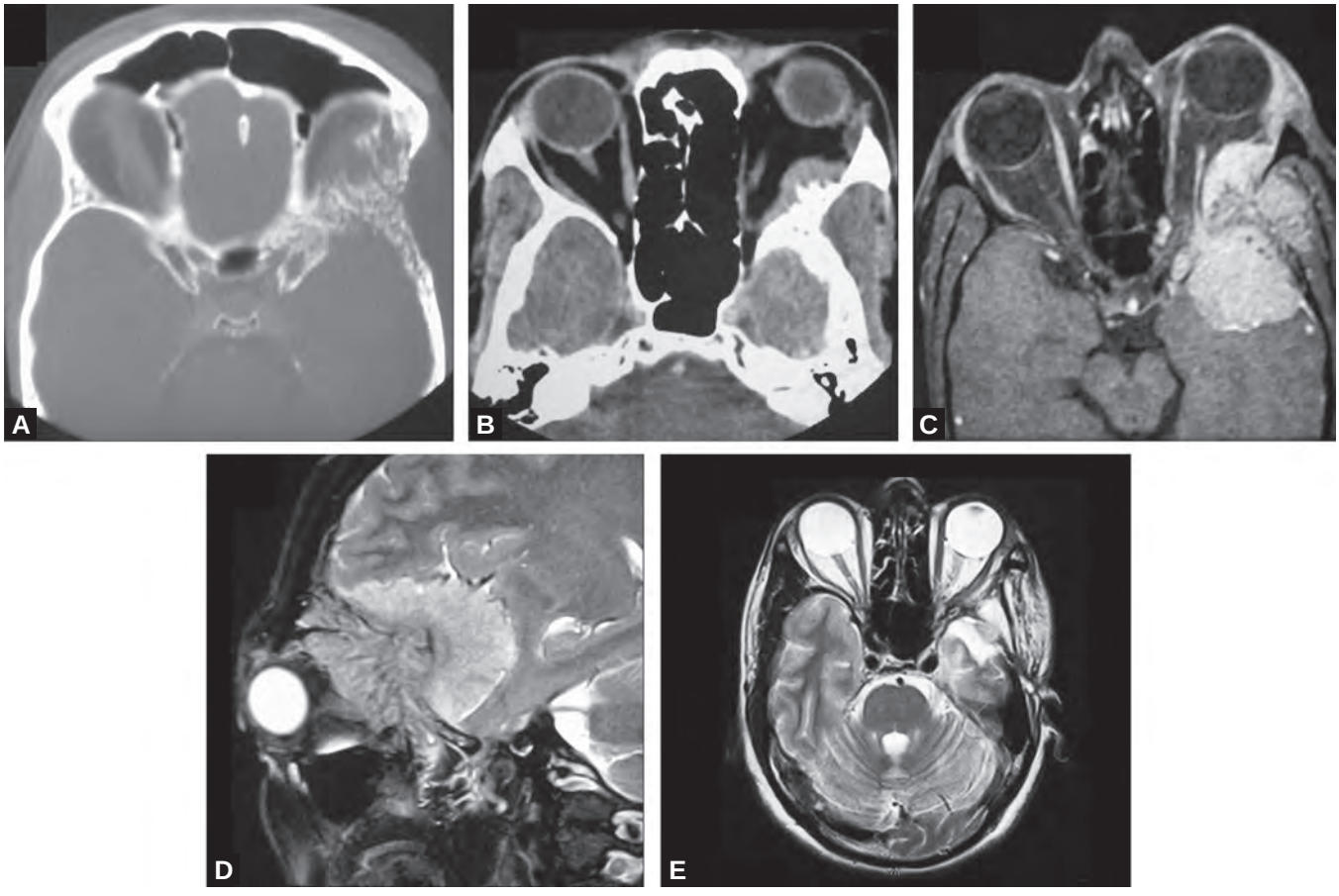
The en plaque variant presents with proptosis or chronic palpebral oedema. Skull deformities, loss of visual acuity leading to blindness, diplopia, epiphora, photophobia and seizures may occur. Globoid pterional meningiomas present with hemicranial headaches, seizures, contralateral hemiparesis and increased intracranial pressure. The tumour behaves either as a temporal or frontal mass. Signs of orbital involvement may also be present.

NEURORADIOLOGY

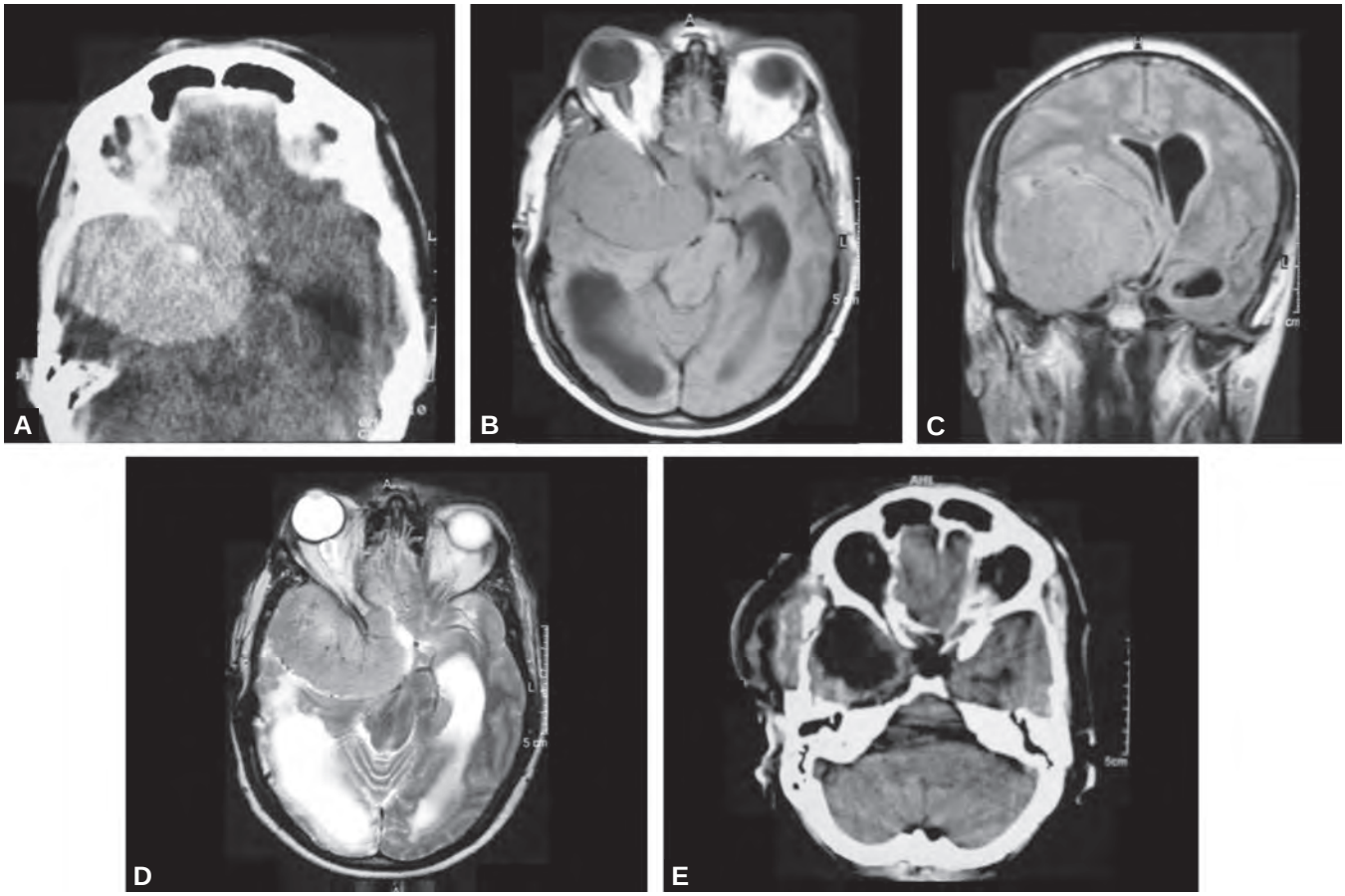
Computed tomographic (CT) and magnetic resonance imaging (MRI) have replaced the conventional radiography used earlier. Focal hyperostosis, sclerosis, erosion at the site of tumour attachment, widening of vascular grooves, superior orbital fissure and narrowing of optic canal are all demonstrated on bone algorithms and three-dimensional CT reconstruction. CT scans clearly demonstrate the bone involvement, the orbit and extension of the tumour plaque. In addition, tumour calcification and peritumoural oedema are observed (Figs 1 to 7).



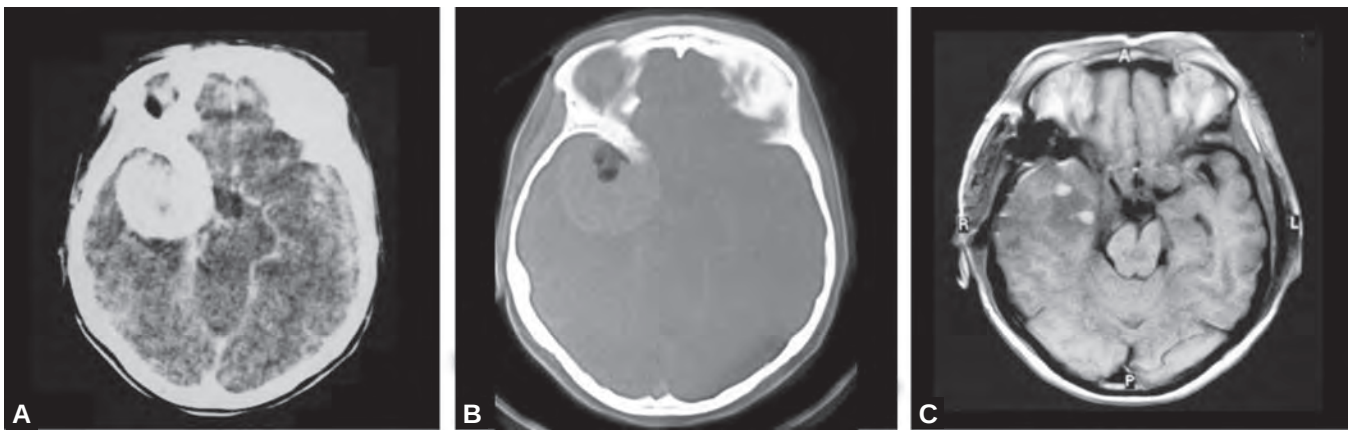
Figs 1A and B: (A) Proton-density axial MR image. (B) Post-contrast MR sagittal image shows an outer third globoid pterional meningioma



Figs 2A to E: (A) Axial CT bone algorithm shows bony hyperostosis and infiltration of anterior clinoid process, lesser sphenoid wing and pterion. (B) Axial CT scan shows the meningioma to involve the orbit, temporal muscles and middle cranial fossa. (C) Post-contrast axial MR image. (D) Post-contrast sagittal image shows the multicompartmental involvement of the en plaque tumour. (E) Post-operative T2-weighted axial image shows complete excision of the tumour



Figs 3A to E: (A) Axial CT scan. (B) Axial T1-weighted MR image. (C) T1-weighted sagittal image shows an extensive sphenoid wing tumour involving the entire ala of sphenoid bone. (D) T2-weighted MR image shows the tumour to maintain the surrounding arachnoidal plane. (E) Post-operative CT scan showing total removal

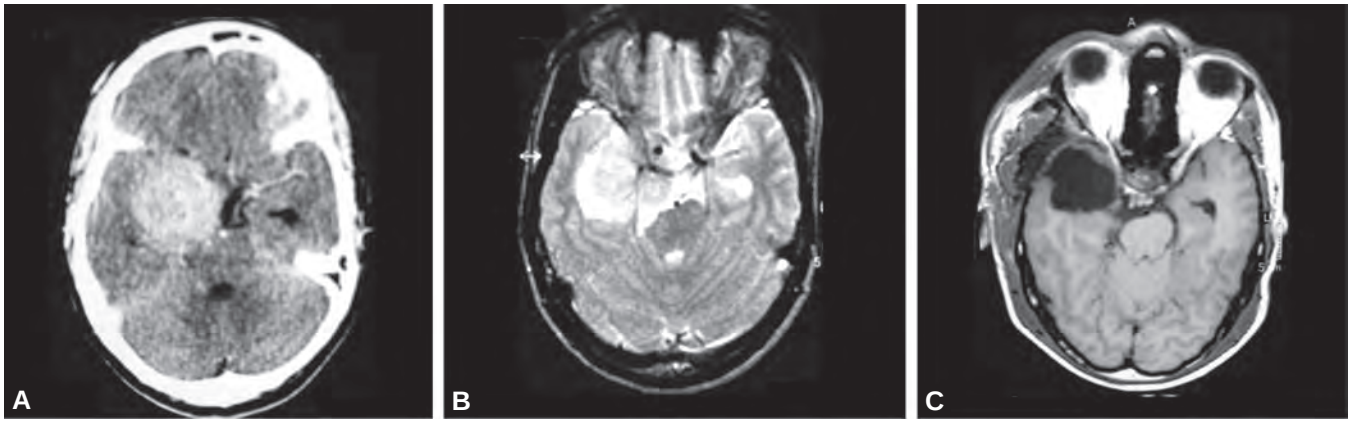


Figs 4A to C: (A) Axial post-contrast CT view shows a right clinoidal meningioma. (B) CT bone algorithm shows hypertrophy of the lesser wing and anterior clinoid. (C) Post-operative axial T1-weighted image shows complete excision of the tumour. A contused right temporal lobe is noted

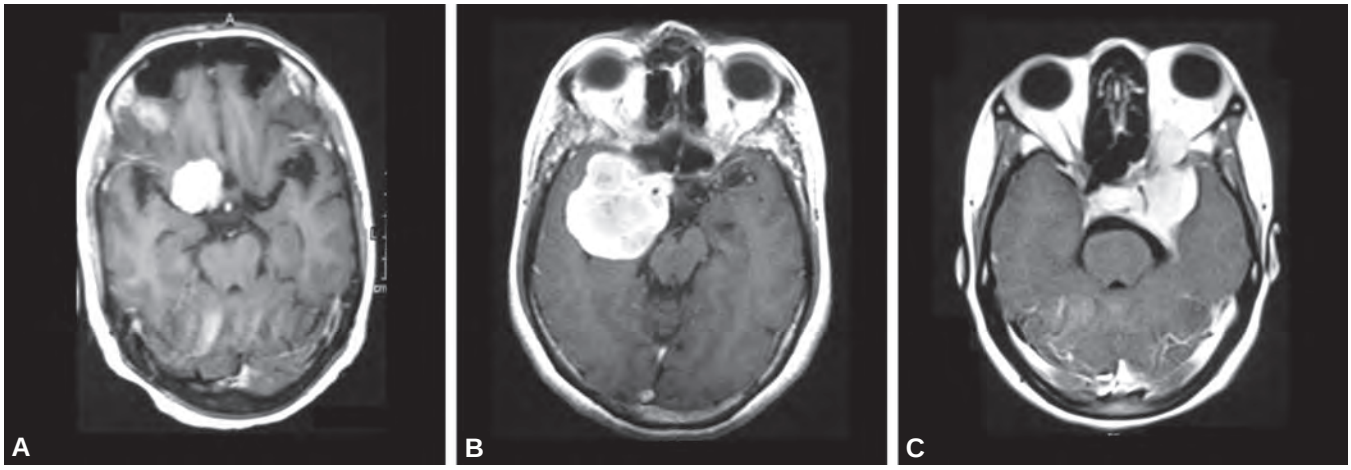
Magnetic resonance (MR) scans clearly show the intracranial extensions of the mass. Meningiomas enhance uniformly after gadolinium injection. The extent of the meningiomatous plaque and thickened adjacent dura (dural tail sign) are clearly defined. The arterial relationship of the tumour is noted as flow voids. The ICA may be encased and may be narrowed or occluded. MR angiography can be done simultaneously to demonstrate the anterior circulation in relation to the tumour. ICA encasement was more commonly seen in tumours that involved the CS.

TREATMENT

Radical excision of the tumour is the primary treatment for meningiomas and is the principle surgical goal.[2,18]



Figs 5A to C: (A) Post-contrast axial CT view demonstrates a moderate sized clinoidal meningioma. (B) T2-weighted axial MR image defines the vascular relationship along the medial border of the tumour. (C) Post-operative T1-weighted image confirms complete excision of the tumour



Figs 6A to C: Medial sphenoid wing meningiomas. Post-contrast axial MR images show: (A) A small tumour. (B) A moderate sized tumour encasing the supraclinoid carotid artery. (C) The tumour has an orbital, cavernous sinus and sellar extension

Inner third meningiomas present problems different from those of the outer third of the sphenoid ridge. Surgery is performed under general anaesthesia using an operative microscope and microsurgical instrumentation in all cases.

Sphenocavernous meningiomas arising from the outer wall of the CS, involving the oculomotor or trigeminal nerve, involve the CS and encase the ICA. In such cases total resection of the tumour is impossible. Similarly, an en plaque pterional meningiomas presenting with proptosis, frontotemporal involvement and palpebral oedema, tumour infiltrating into the dura, periorbital tissues, CS and zygomatic fossa, are difficult to operate upon. It is debatable if radical resection of tumour in the above cases should be achieved including the intracavernous component together with the encased ICA, with or without saphenous vein reconstruction.[8,19,20]

Cerebral angiography earlier used for diagnosis is now used to embolise tumour feeders to permit tumour resection without excessive blood loss.

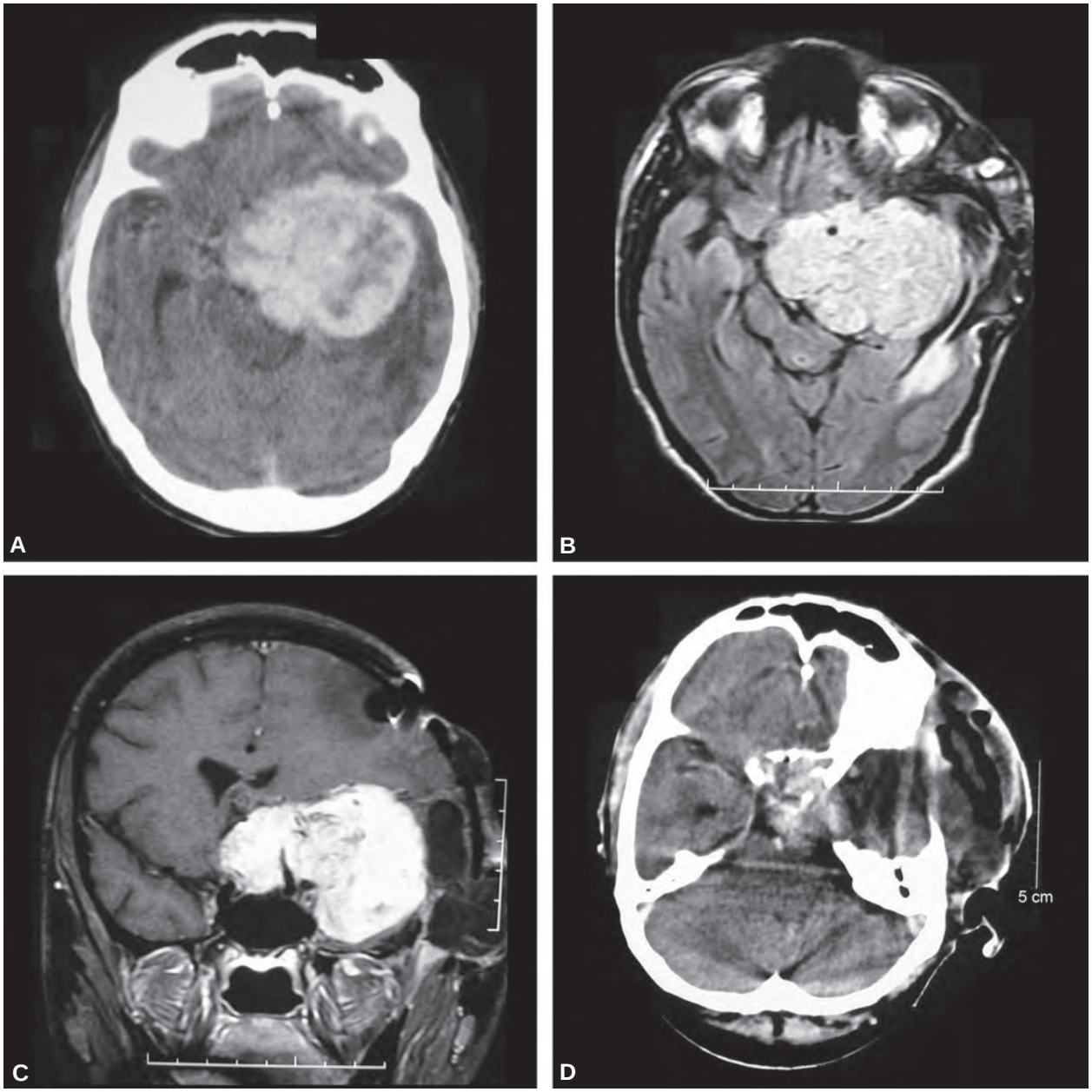
Surgical Treatment

Pterional Meningiomas

The surgery is performed in the supine position with head elevated to aid venous return and turned to the contralateral side. A frontotemporal craniotomy is performed through an incision within the hairline. This permits a wide orbital exposure and provides for a pericranial graft, if necessary. The hyperostotic thickened bone is excised, decompressing the superior orbital fissure and optic canal, along with a wide frontal craniotomy. The thickened dura, intracranial tumour and orbital extension are excised. The middle cerebral artery, carotid artery and optic nerve are preserved. The pericranial graft is used to close the resected dura. Bone reconstruction is done with methyl methacrylate, split calvarial or rib graft if required.

Inner and Middle Third Meningiomas

Clinoidal tumours have a dural attachment on the upper part of the anterior clinoid process, whereas



Figs 7A to D: (A) Post-contrast CT axial image shows a massive left medial sphenoid wing meningioma. (B) Post-contrast axial MR image. (C) Sagittal MR image shows the left carotid is encased. There is evidence of craniotomy and herniation of the brain through the craniotomy defect. (D) Post-operative post-contrast axial CT image shows a small residue in relation to the encased carotid. A large subgaleal CSF collection is noted

sphenocavernous tumours are attached to the sphenocavernous angle. The patient is in the supine position, with the head raised and turned to the opposite side. A frontotemporal craniotomy is performed. The lesser wing of the sphenoid is nibbled to the superior orbital fissure, to allow exposure of the tumour with minimal brain retraction. The tumour is debulked within its capsule. The tumour blood supply is coagulated at the dural attachment. The Sylvian fissure is widely opened and the MCA and its branches are identified in relation to the capsule of the tumour. The supraclinoid ICA, MCA and its branches need meticulous dissection to avoid vascular injury. Grade I Simpson excision of a clinoidal meningioma is possible. For sphenocavernous tumours, extracavernous extirpation with coagulation of dural attachment is advised (Simpson Grade II). In tumours with CS invasion, the CS is opened through its superior wall, the optic canal is opened and tumour is excised. The intracavernous portion of the tumour was not radically removed in 85.5% of cases to prevent any new cranial neuropathies.[12] In 14.5% of cases where only the lateral or superior walls of the CS were involved, the wall was peeled off and carefully coagulated. CSF leak and infection are carefully avoided by using pericranial graft and fibrin glue.

Surgical Complications

The most common surgical complication is post-operative subcutaneous cerebrospinal fluid collection and

hydrocephalus. Post-operative infarction of the middle cerebral artery territory occurred in 3.7% of patients.[12] The other complications seen were haemorrhage, brain oedema and meningitis.

Results

Basso et al.[4] reported that 81.37% had good results (no sequelae) and an operative mortality of 4.13%. Of the six deaths, four resulted from cerebral infarction and the other two from severe cerebral oedema. The use of microsurgical techniques has improved mortality and morbidity rates. The main causes of fair (minor sequelae) and poor (severe sequelae) results were extraocular muscle dysfunction, persistent exophthalmos, hemiparesis and visual impairment. Patients presenting with CN deficits and previous surgery did not show recovery of CN function after removal of recurrent tumour. Patients with new post-operative CN deficits showed much better recovery.[12]

Meningiomas of the skull base are associated with the highest rate of tumour recurrence, related to their wide dural attachment, invasion of the CS, invasion of the underlying bone and extension of the tumour through the foramina and fissures of the skull base into the orbit and zygomatic fossa. Basso et al.[4] have reported a 20.54% recurrence rate at 10 years. All of these received radiotherapy and 14 of 15 were re-operated. The mean time of recurrence was 6.7 years after surgery. Radiotherapy appears to halt the growth of the tumour.[3]

The extent of tumour resection can be classified according to Simpson's classification.[21] Grade I: total resection with excision of infiltrated dura; Grade II: total tumour resection and coagulation of dural attachments; Grade III: gross total resection without excising dural attachment or extradural extension (e.g. infiltrated sinus or bone) and Grade IV, subtotal tumour resection.

GAMMA KNIFE SURGERY FOR MENINGIOMAS OF THE SPHENOIDAL WING

Radiotherapy for meningiomas has been used in recurrent or partially resected tumours, especially when performed to avoid neurological morbidity. As the sphenoid bone forms the lateral and posterior walls of the orbit, these tumours involve the periorbital structures. The tumour displaces rather than invades the orbital contents. Tumour growth has been effectively controlled with a dose of 9 Gy, tolerable to the optic pathway and nerves within the CS. The dose limit for the optic nerve is 8 Gy, 15 Gy for the third, fourth and sixth CNs and 13 Gy for the fifth CN. The tumour responds within 4–20 months. Growth arrest and reduction in tumour volume is achieved in 90% of cases.[16] Actual tumour growth control rates after gamma knife radiosurgery of CS meningiomas ranged from 86.4% at 3 years to 96.5% at 5 years.[16] Neurological status improved after gamma knife surgery in 28.6%, remained stable in 62% and deteriorated in 9%.[10]

MEDIAL SPHENOID WING OR CLINOIDAL MENINGIOMAS

Clinoidal meningiomas are formidable tumours to resect when their size is large and when they involve the optic nerve, ICA and their branches and the oculomotor nerve. During 1938–1982, the rates of total resection ranged between 23% and 50%, and associated mortality rates ranged from 15 to 43%.[7,14] Since 1990, resection rates have been 59–83% with mortality rates between 6% and 14.5%.[1,2,15,17] Goel et al.[9] have classified tumours based upon the extent of visual impairment, size of tumour and the tumour relationship with the internal carotid artery. The grading system is used to plan the operative strategy, anticipating the extent of resectability and possible difficulties in dissecting the carotid artery and optic nerve during the operation. Many neurosurgeons, recognising the relatively high incidence of poor post-operative outcome, prefer to perform a conservative subtotal resection with or without post-operative radiotherapy and some surgeons have recommended radiotherapy as the sole treatment.[13]

Al-Mefty[1,2] has identified three distinct groups of clinoidal meningiomas on the basis of the site of tumour origin and the presence/absence of the arachnoidal plane between the tumour and the ICA.

Group 1 tumours are those encasing and directly attaching to the ICA adventitia, without a definable arachnoidal plane between the tumour and ICA. Total resection is not possible in these cases. Tobias et al.[22] did not encounter a single Group 1 tumour.

Group 2 consists of tumours with a separate arachnoidal plane between the tumour and the ICA that facilitates total removal.

Group 3 tumours are actually optic nerve sheath or optic foramen meningiomas and not truly clinoidal tumours.

Unilateral visual loss is the most common clinical presentation of these tumours. The visual impairment occasionally involves the contralateral eye. The deterioration is in both visual acuity as well as fields. The other presentations include headaches, diplopia, seizures, facial pain, proptosis and ptosis.

The skull base surgical technique involves the following steps:[22] (1) frontotemporal craniotomy; (2) sphenoid ridge drilling; (3) limited posterior orbitotomy; (4) posterolateral orbital wall removal (or osseous decompression of the superior orbital fissure); (5) optic canal unroofing; (6) extradural complete anterior clinoidectomy and (7) optic nerve sheath opening.

The intracranial tumour is excised as described previously. If the CS involvement is extensive and the tumour is fibrous, surgery is stopped after confirmation of the following:

1. Gross-total resection of the intradural extracavernous portion of the tumour and removal of any accessible tumour-involved dura.
2. Decompression of the optic nerve.
3. Decompression of the oculomotor nerve.

Using the above techniques Tobias et al.[22] have reported a total resection rate of 77% and improved visual outcome rate of 71%. By performing the skull base technique, the exact location of the ICA and optic nerve are known early in the surgery. Improved surgical access allows for aggressive removal of tumour, involved bone and surrounding dura (Simpson Grade 2 or even Grade 1 in some cases). Visual improvement was observed in 56% and was preserved at the pre-operative level in 44% of patients in those without CS involvement. However, in those with CS involvement, vision improved in 30% and was stable in 60%.[12]

In conclusion, total resection of clinoidal meningiomas is feasible with an excellent visual outcome, keeping the surgery related morbidity low, by the use of skull base technique. Tumours without involvement of the CS have better resection, less recurrence and neurological improvement. The CS tumours are best managed with adjuvant radiosurgery.

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170 Tentorial Meningiomas

Vijendra Kumar Jain, Sanjay Behari, Pramod Giri

INTRODUCTION

Tentorial meningiomas (TM) are relatively uncommon lesions accounting for 2–9% of all intracranial meningiomas and 30% of posterior fossa meningiomas.[6,14,39] In 1833, Antral first reported the presence of a tentorial meningioma as an incidental finding.[50] These tumours remain a formidable challenge for a surgeon since critical neural and vascular structures are often intimately involved by these lesions. Recent advances in skull base surgical techniques have facilitated more aggressive approaches for removing these tumours while maintaining acceptable rates of morbidity and mortality. High definition computed tomography, magnetic resonance imaging and digital subtraction angiography have also facilitated meticulous pre-operative surgical planning in recent times.

RELEVANT MICROSURGICAL ANATOMY

Tentorium

The tentorium separates the cerebellum from the temporal and occipital lobes and contains an opening in the centre, known as the incisura, connecting the supratentorial and infratentorial compartments. The apex of the tent shaped tentorium is formed by the posterior edge of the incisura. From the apex, the tentorium slopes downwards up to its bony attachments to the temporal, occipital and sphenoidal bones. It has three borders, namely, anterior (attached to the petrous ridge and enclosing the superior petrosal sinus) and lateral and posterior (attached to the temporal and occipital bones at the groove of the transverse sinus and internal occipital protuberance) enclosing the transverse sinus and torcula.

The free edge of the tentorium is attached anteriorly to the petrous apex and anterior and posterior clinoid processes. Between these three structures lies the oculomotor trigone through which the IIIrd and IVth cranial nerves enter the cavernous sinus. From the anterior part of the free edge of the tentorium, the dura mater slopes steeply downwards to form the lateral wall of the cavernous sinus and the base of the middle cranial fossa. In the posterior part of the tentorium, the falx cerebri fuses with the dorsal surface of the tentorium in the midline behind the apex and encloses the straight sinus in the falcotentorial junction.

The tentorial incisura is triangular, its anterior edge is based on the dorsum sellae and its apex is dorsal to the midbrain, just posterior to the pineal gland. Its width varies from 26 mm to 35 mm and the anteroposterior diameter from 46 mm to 75 mm. For further details reference may be made to Textbook of Operative Neurosurgery [Ravi Ramamurthi, K Sridhar, MC Vasudevan (Eds) 2005]. Bisaria (1983) described the developmental defects of the tentorium cerebelli with which one should be familiar.

Dural Venous Sinuses

From the torcula, at the level of the internal occipital protuberance, the transverse sinus extends laterally and continues as the sigmoid sinus. The occipital sinus extends inferiorly in the midline of the posterior fossa dura and the superior sagittal sinus joins the torcula from the superior aspect. The straight sinus continues within the leaves of the tentorium in the midline and joins the confluence of the transverse sinuses. The superior petrosal sinus runs along the superior petrosal ridge from the cavernous sinus to the transverse-sigmoid junction. Often, the transverse sinuses are asymmetrical with the right side being dominant.[24] The temporal anastomotic vein of Labbe courses back on the surface of the temporal lobe from the superficial middle cerebral vein to join the transverse-sigmoid sinus junction (Bisaria 1983).

Blood Supply of the Tentorium

The anterior and medial portions of the tentorium are supplied by branches of the meningohypophyseal trunk namely: the artery of Bernasconi and Cassinari (the basal tentorial artery) and the artery of the inferior cavernous sinus (the marginal tentorial artery). These are branches of the cavernous carotid artery. The posterior tentorial margin and apex are supplied by branches from the posterior cerebral and superior cerebellar arteries, as well as from the meningeal branches of the external carotid and vertebral arteries. The relative tumour blood supply from the meningohypophyseal trunk is approximately 48%, from the posterior middle meningeal vessels 14%, the occipital artery 45%, the vertebral artery 3.4%, the ascending pharyngeal artery 3.4% and the vertebrobasilar artery 8%.[5,14,30,39]

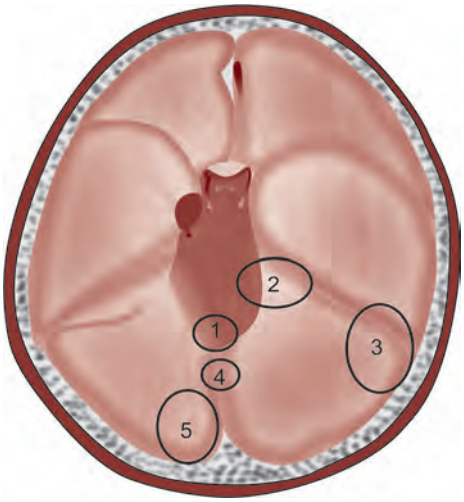


Fig. 1: Schematic diagram showing various locations of TM. 1: Medial tentorial edge; 2: Lateral tentorial edge; 3: Attached margin of tentorial leaf; 4: Falcotentorial; 5: Torcular

CLASSIFICATION (FIG. 1)

TM may have supratentorial, infratentorial or combined supra and infratentorial growth (perforating meningiomas).[14] The true dural attachment is often not reliably defined, because the tumour may extend to the tentorium after originating from the dura of the petrous bone, clivus, anterior clinoid, falx, and transverse and sigmoid sinuses. Cushing and Eisenhardt included TMs in the peritorcular, subtentorial and recess tumours group.[11,12] Castellano et al. analysed Olivecrona's series of posterior fossa meningiomas and described a subgroup of TMs.[9] Mallis has divided TMs into: (a) parasellar; (b) petroclival tentorial angle; (c) tentorial apex; (d) tentorial leaf and (e) torcular.[23] Sugita and Suzuki divided these TMs into medial, lateral and falcotentorial and further sub-grouped the medial and lateral ones into anterior, middle and posterior tumours.[43] Guidetti et al. divided TMs into free edge, petrous ridge, posterolateral, posteromedial and central tentorial.[14] Bassiouni et al. have modified Yasargil's classification of TM as: T1-2: medial; T3-8: falcotentorial; T4: paramedian; T5: peritorcular; T6-7: lateral and falx cerebelli.[49] Bret et al. distinguish the various subtypes of TM according to their relationships to the free edge (inner ring) and to the peripheral tentorium (outer ring). Thus, group I includes anteromedial meningiomas arising from the apex of the tentorial margin; group II includes anterolateral TM arising from the lateral aspect of the tentorial margin; group III includes TM arising from the intermediate aspect of the tentorium remote from the incisura and also from the dural venous sinuses; group IV includes TM arising from the posteromedial aspect of the tentorium close to the venous confluence and group V includes TM arising from the posterolateral aspect of the tentorium close to the sigmoid sinus. All these categories may have a supratentorial and infratentorial extension.[6] Rostomily et al.[32] have classified TM into two categories—those lesions with primary or exclusive involvement of the tentorium are considered as primary TM and may further be sub-divided into medial (incisural or free edge), lateral (tentorial leaf/transverse sinus), falcotentorial or torcular and complex tentorial meningiomas, including parasellar, cerebellopontine angle and petroclival meningiomas.[32]

SIGNS AND SYMPTOMS

The majority of patients are women (approximately 60%) who present in the fourth and fifth decades. The most common presentations of TM include headache, seizures, raised intracranial pressure, papilloedema, bilateral sixth nerve palsy and cognitive disturbances.[13,14] Tumours with extension into the occipital lobe may produce homonymous hemianopia, while those with posterior fossa involvement may present with cerebellar and long tract signs, multiple cranial nerve palsies and hydrocephalus. TMs involving the tentorial incisura may present as fourth nerve palsy and brainstem compression syndrome, while tumours extending up to the posterior third ventricular region may present rarely as Parinaud's syndrome; those with cerebellopontine angle extension may also present with Vth, VIIth, VIIIth, IXth and Xth cranial nerve involvement with cerebellar signs and those extending into the anterior clinoid, cavernous sinus and suprasellar region may produce IIIrd, IVth, Vth and VIth nerve palsies and visual disturbances. Other reported presentations may include impaired mentation, trigeminal neuralgia, hemifacial spasm, gelastic seizures, pituitary and hypothalamic disturbances and predominant contralateral signs due to brainstem distortion.[27,45] Syringomyelia may be associated with TMs, perhaps due to tumour induced tonsillar herniation.[34,44,48] In one patient, resolution of cluster headaches following resection of a TM has been reported. Bret et al.[6] have reported hearing impairment in nearly 30% of their TMs. They have proposed the mechanism of tumour interference with the central auditory pathways, since hearing impairment occurred even when the tumour was remote from the cerebellopontine angle.[6]

INVESTIGATIONS

Computed Tomography and Magnetic Resonance Imaging

Multiplanar CT and MR imaging with contrast (with CT or MR angiography) give an accurate localisation, supra and infratentorial extension, site of dural attachment, involvement and patency of dural venous sinuses and deep venous system, infiltration along the skull base, involvement of adjacent vasculature and relation of the tumour to the brainstem and cranial nerves. Up to 48% of patients with TM may present with cerebrospinal fluid pathway obstruction and hydrocephalus. MR imaging with contrast may often show an extensive dural tail

sign. However, the dural invasion in these benign lesions rarely extends for more than 1 mm from the tumour-dura junction and, therefore, extensive resection of the enhancing dura is not indicated in these meningiomas.[32]

Angiography with Tumour Embolisation

The blood supply to TM as well as the involvement of the dural venous sinuses and their dominance may be defined on the basis of arterial and venous phase angiography, respectively. The displacement of vessels indicating attachment of the tumour to the tentorium may be seen. In case of encasement of major blood vessels by the TM, a balloon occlusion test may be performed to evaluate the capacity of the contralateral circulation to support the circulation on the side of the TM, in the event that the latter circulation is compromised during surgery. Superselective catheterisation of the meningeal supply to the TM and pre-operative embolisation permits surgical resection with minimal blood loss. Embolisation is especially helpful when the major arterial supply is from the external carotid artery by the meningohypophyseal trunk or by the posterior middle meningeal or ascending pharyngeal arteries. It is recommended that surgical resection be performed within 1–10 days of the pre-operative embolisation to allow for maximum vessel thrombosis without recanalisation.[14,32,39] Intraoperative evaluation may be performed by brainstem evoked potential, somatosensory evoked potential and facial nerve electromyographic evaluations.

SURGICAL APPROACHES

The primary goal of surgery is to remove the TM along with its dural attachment and also the involved bone in the case of bony invasion.[41] The selection of the approach (Table 1) and decision of radical excision entirely depend on the location of the lesion. Although the ideal goal is total tumour resection, it should not be achieved at any cost and all attempts should be made to preserve the brainstem, cranial nerves and vascular structures. The tumour, medial or lateral is usually approached through a combined supratentorial-infratentorial exposure, unless the tumour is on one side of the tentorium with only a minimal extension into the other compartment.

A cerebrospinal fluid shunt or an endoscopic third ventriculostomy may be required in some patients, where a rapid normalisation of the raised intracranial pressure is needed. However, contemporary anaesthetic methods provide sufficient brain relaxation to eliminate the need for cerebrospinal fluid drainage and to facilitate retraction during surgery in most patients.

PRIMARY TENTORIAL MENINGIOMAS

Tentorial Free Edge

Anterior supratentorial lesions in this location may be approached by the subtemporal or trans-sylvian frontotemporal route or a combination of both the approaches.[1,3,40,43]

In the subtemporal approach, after a temporal craniotomy, the temporal lobe is gently elevated to expose the tumour in the inner middle fossa. In the trans-sylvian frontotemporal route, after a frontotemporal craniotomy and drilling of the lesser wing of the sphenoid to make the frontal and temporal fossa flush with each other, the Sylvian fissure is opened widely using arachnoidal dissection and the tentorial base and the anterior portion of the incisura reached. With these approaches, one can visualise the superior surface of the tentorium, the anterolateral surfaces of the midbrain and pons, the posterior cerebral, posterior communicating and superior cerebellar arteries and the IIIrd and IVth nerves. Sectioning the tentorium anterior to the tumour interrupts the tumour blood supply. The IVth nerve penetrates the tentorial edge dura 4 mm behind the posterior clinoid process. In

Table 1: Location of tumours and their surgical approaches

Tumour location		*Surgical approach*
T1–T2 (medial)	Infratentorial	Supracerebellar infratentorial
T3–T8 (falcotentorial)	Supratentorial	Suboccipital retrosigmoid
T4 (paramedian)	Supra-infratentorial	Subtemporal
	Supratentorial	Infra-supratentorial presigmoid
T5 (peritorcular)	Supra-infratentorial	Bioccipital interhemispheric
	Infratentorial	Occipital transtentorial
	Supra-infratentorial	Bioccipital/suboccipital
T6–T7 (lateral)	Infratentorial	Supracerebellar infratentorial
	Supratentorial	Bioccipital/suboccipital
Falx cerebelli	Infratentorial	Suboccipital retrosigmoid
		Supracerebellar infratentorial
		Subtemporal
		Supracerebellar infratentorial

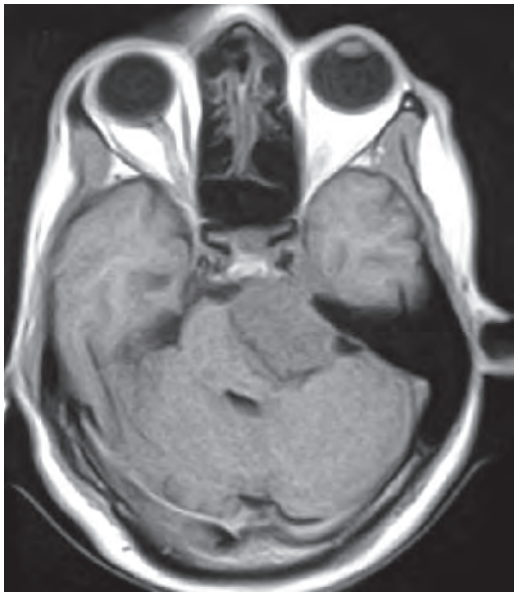


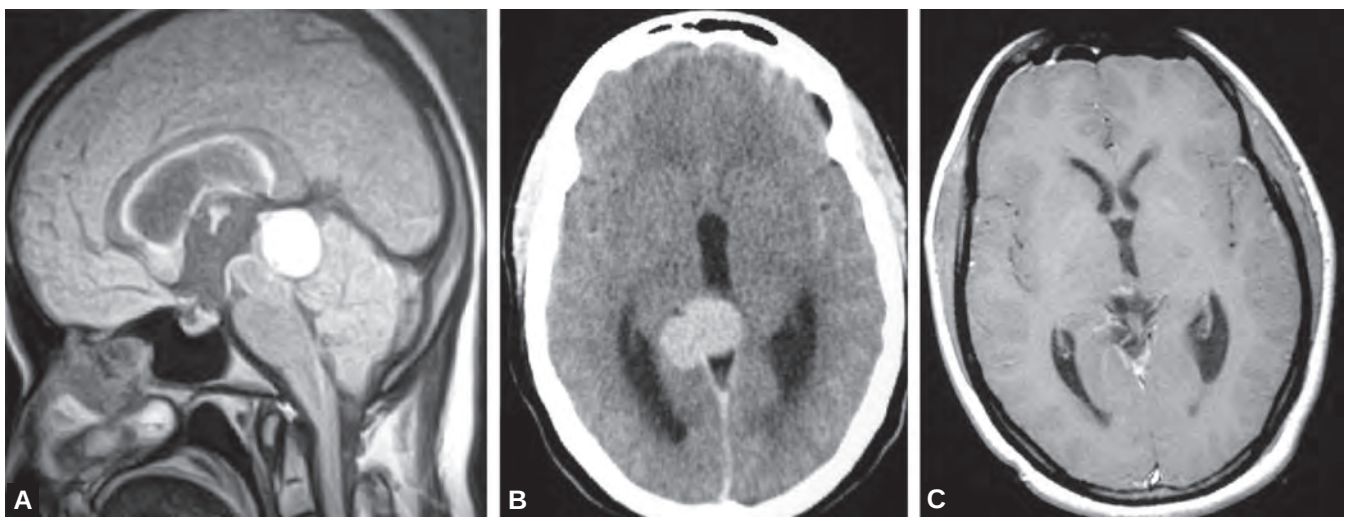
Fig. 2: Axial T1-weighted MR image showing a lateral tentorial edge TM with a predominantly infratentorial component. This was approached using a retrosigmoid suboccipital craniectomy

order to prevent injury to the IVth nerve during tentorial edge cutting, the tentorial edge should be divided posterior to the entry of the IVth nerve. There may be retraction injury to the temporal lobe during the subtemporal approach, which may be minimised by giving mannitol, furosemide, hyperventilation, cerebrospinal fluid drainage, preservation of bridging veins and by the intermittent use and frequent repositioning of retractors. The vein of Labbé requires meticulous preservation during the subtemporal approach, to prevent venous infarction of the temporal lobe. The vein may be skeletonised from the temporal lobe by arachnoidal dissection to facilitate temporal lobe retraction. Adding zygomatic osteotomy provides a flatter angle of view and lesser degree of temporal retraction. Supratentorial tumours of the anterior, outer and inner tentorial rim can be approached via the subtemporal route. Sugita et al.[43] emphasised that preservation of subtemporal veins may be facilitated by wide temporal craniotomy, particularly in horizontal length. Large supratentorial as well as infratentorial incisural meningiomas may also be excised using a combined supratentorial and infratentorial presigmoid approach.[35]

When the tumour extends along the cerebellopontine angle in the posterior fossa, compressing the brainstem and cranial nerves and reaching up to the free edge of the tentorium from the inferior aspect, the retromastiod approach should be considered (Fig. 2). This approach involves a combination of the supracerebellar and of the retrosgimoid approaches to the posterior fossa, simultaneously providing access to the inferior part of the tentorium and to the cerebellopontine angle.[13,14,38,39] The trigeminal, facial, vestibulocochlear and lower cranial nerves are visualised and dissected off the tumour. A combination of the subtemporal and retromastoid approach may also be used in case the tumour extends in both the supratentorial and infratentorial regions, as well as anteromedially to involve the cranial nerves and brainstem.[42] With the combined approach, the transverse/sigmoid sinus junction distal to the vein of Labbé may be divided to facilitate tumour excision from both the compartments.

The supracerebellar (paramedian) transtentorial approach has also been used by Uchiyama for medial temporal meningiomas with a supratentorial extension, but without involvement of the superior surface of the petrous bone.[46]

TM situated at the tentorial edge carry a much higher risk of neural and vascular compromise than at other sites. Resection of a medially situated TM requires



Figs 3A to C: (A) Sagittal contrast enhanced T1-weighted MR image showing a medial tentorial edge meningioma in close proximity to the Galenic venous system. (B) Axial CT scan showing the medial tentorial edge meningioma. (C) Axial T1-weighted MR image at follow-up showing total excision of the lesion that was approached using a suboccipital craniectomy and infratentorial supracerebellar approach

preservation of the vein of Galen and its related veins, posteromedial choroidal and superior cerebellar arteries, IVth cranial nerve and posterior aspect of the mesencephalon including the quadrigeminal plates (Figs 3A to C). The structures usually lie anteriorly or superiorly to the tumour mass and may be preserved by using dissection along the arachnoidal plane of the quadrigeminal cistern, from the vein of Galen above to the cerebellomesencephalic fissure below. Preservation of the vein of Galen is of paramount importance, even if apparently angiographically occluded, although some authors have reported successful results after surgical occlusion.[4,29,33]

When the TM lies along the lateral incisural space, preservation of the basal vein of Rosenthal, posterior cerebral and posterolateral choroidal arteries, IIIrd and IVth nerves, lateral aspect of the mesencephalon and medial aspect of the temporal lobe is required.

Extension of the tumour to the cerebellopontine angle may require dissection from the Vth to the XIth cranial nerves.

Tentorial Leaf and Lateral and Posterior Tentorial Attached Margin

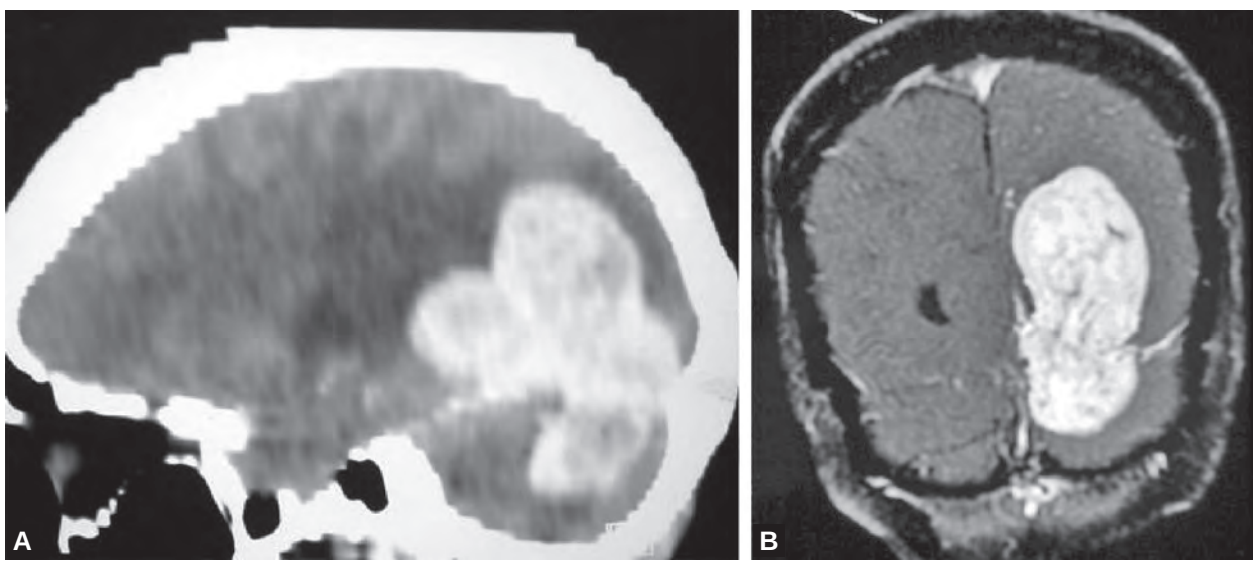
An occipital/parieto-occipital craniotomy or infratentorial supracerebellar approach or a combination of both (on either side of transverse sinus) may be adopted, depending on whether the tumour is mainly supratentorial, infratentorial or both respectively (Figs 4 to 6.[4,6,7,32] In the occipital transtentorial approach, after an occipital craniotomy is made exposing the superior sagittal and transverse sinuses, the occipital lobe is retracted from the falx and the tentorium. The tumour exposure is enhanced by coagulation and division of the tentorium up to the incisura, at least 1 cm lateral to the straight sinus. An optional procedure includes fenestration of the falx to deal with a contralateral extension of the tumour.[14,16]

In the infratentorial supracerebellar approach, after a retromastoid suboccipital craniectomy, the bridging cerebellar veins between the tentorium and the cerebellum are divided, allowing the cerebellum to drop down by gravity. Careful neck flexion brings the tentorium as close as possible to the horizontal plane. The problems include the depth of the operating field requiring long-sized instruments and the risk of cerebellar venous infarction.[38,39]

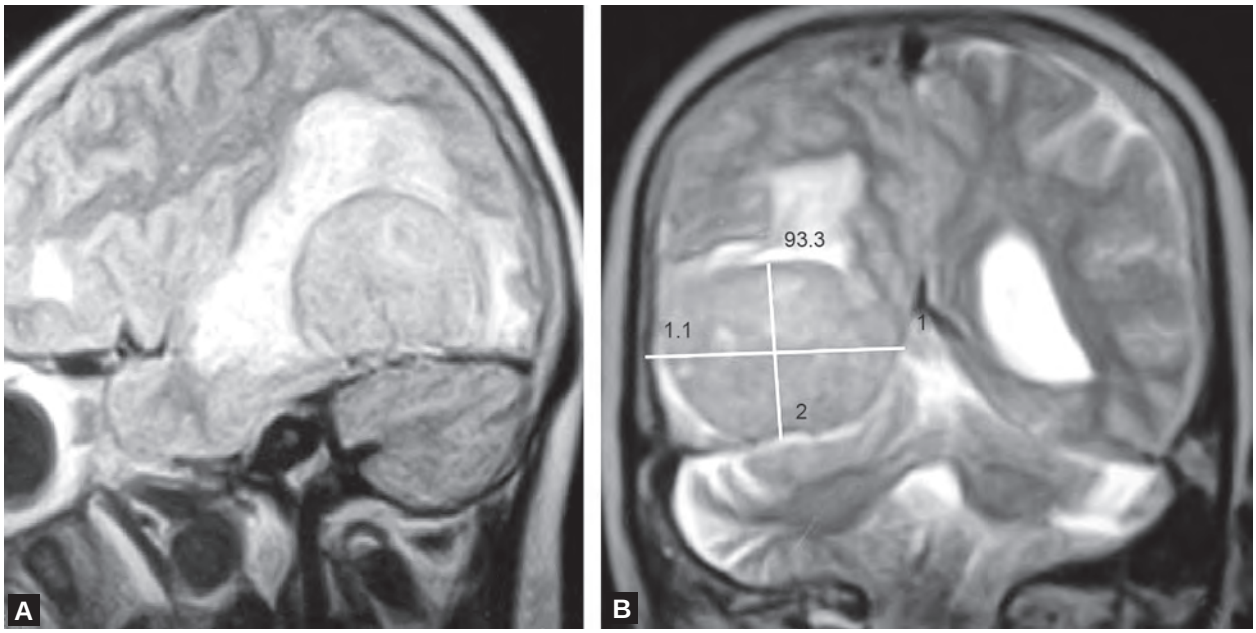
The transverse sinus may only be resected when angiogram shows the sinus on that side to be occluded by the tumour and when there is a clear demonstration of a patent contralateral one. Bleeding, air embolism from the sinus or visual field defects from occipital lobe handling are the major causes of morbidity.[10]

Falcotentorial

These may be approached by an occipital, interhemispheric, transtentorial approach utilising a bilateral or ipsilateral occipital craniotomy (Figs 7A and B).[4,13,14,16] The medial aspect of the occipital pole may be retracted laterally, as most of the draining veins of the occipital lobe drain into the transverse sinus rather than into the sagittal sinus. The falx and the tentorium around the lesion may be divided to devascularise the tumour. The tumour attached to the straight sinus is cauterised *in situ*. In case, the tumour extends anteriorly to the region of the vein of Galen and the internal cerebral vein, a small fraction of the tumour may be left behind to avoid injury to the deep venous system. The supratentorial (with) transtentorial approach may also be used for tumours which have an infratentorial extension.



Figs 4A and B: (A) Contrast enhanced sagittal reconstructed CT image showing a perforating tentorial leaf meningioma with both supratentorial and infratentorial components. (B) Contrast enhanced coronal T1-weighted image of the same patient. This lesion could be completely excised using an occipital interhemispheric transtentorial approach



Figs 5A and B: (A) T2-weighted sagittal MR image showing a tentorial leaf meningioma with a predominantly supratentorial component. (B) T2-weighted coronal MR image of the same patient. This lesion was approached using a posterior temporal craniotomy and a subtemporal approach

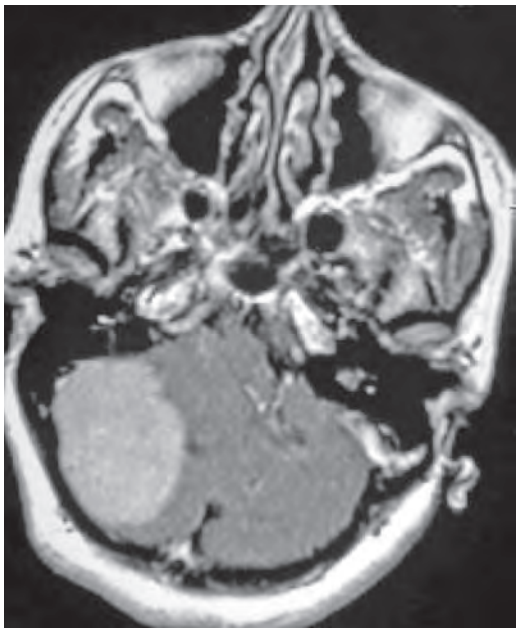


Fig. 6: Contrast enhanced axial MR image showing a lateral tentorial leaf meningioma with a predominately infratentorial component. This lesion was approached using a lateral suboccipital craniectomy and an infratentorial supracerebellar approach

With lesions that are predominantly infratentorial, the infratentorial supracerebellar approach may be used. If located at the posterior part of the tentorial incisura, an occipital interhemispheric transtentorial route may be used to access it from the superior aspect, especially when the tumour is small. In large infratentorial-falcotentorial tumours, the occipital interhemispheric route may be combined with suboccipital craniectomy and supracerebellar infratentorial approach.[28,32] A unilateral approach may cause homonymous hemianopia, while bilateral occipital lobe retraction may result in cortical blindness due to contusion and ischaemia of the calcarine gyrus.

Torcular Meningioma

The torcula consists of the confluence of five sinuses including two transverse, one straight, one superior sagittal and one occipital sinus. The surgical approach depends on tumour growth into one or more of the four quadrants—right, left, supra and infra tentorial (Fig. 8). Patients with a unilateral lesion with both supratentorial and infratentorial extensions may often be approached by a unilateral occipital or suboccipital exposure but the approach may be augmented by a craniotomy both above and below the tentorium and by cutting the tentorium and the falx. Venous infarction secondary to compromise of the venous sinus and cortical blindness due to retraction damage of the occipital lobes are the major hazards.[17,18]

Complex Tentorial Meningioma

Parasellar and Cavernous Meningioma

These may involve the cavernous sinus, the carotid, anterior cerebral, middle cerebral, posterior communicating, anterior choroidal and superior cerebellar arteries and the IIIrd, IVth, Vth and VIth nerves. They may be approached by a pterional craniotomy and trans-sylvian approach and/or subtemporal approach or a combination of both the approaches. In patients with extensive

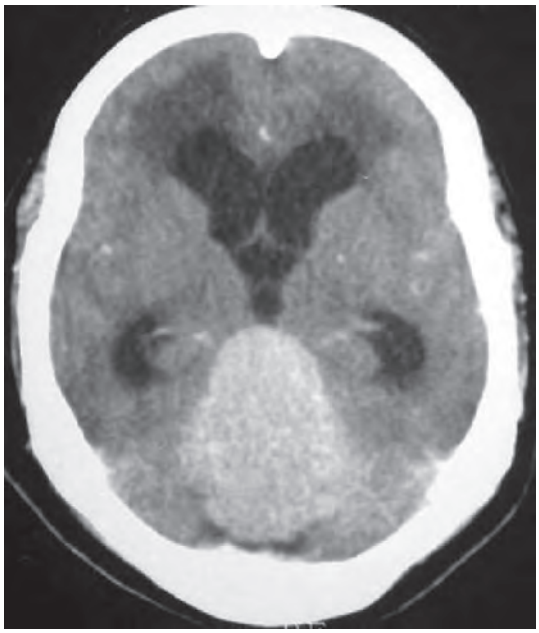


Fig. 7A: Contrast enhanced axial CT scan showing a falcotentorial meningioma with predominantly infratentorial component with associated hydrocephalus. The lesion was extending to the posterior third ventricular region obstructing CSF pathway

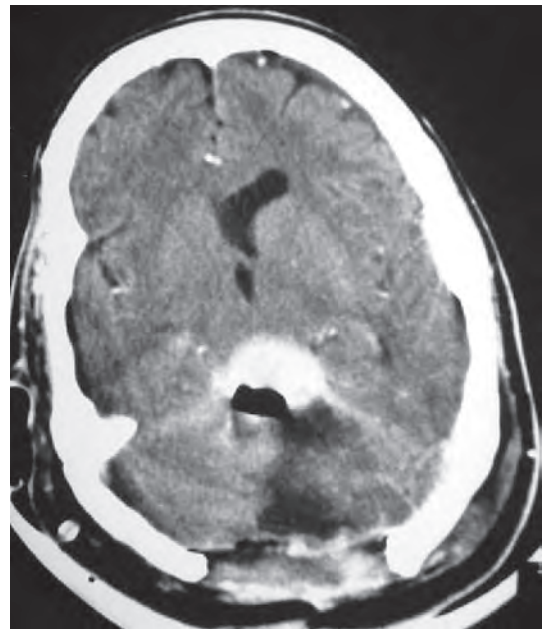


Fig. 7B: Post-operative contrast enhanced axial CT scan of the patient approached via midline suboccipital craniectomy and infratentorial supracerebellar approach. A small part of the lesion in close proximity to the Galenic venous system and the straight sinus was left *in situ*

involvement of the carotids and cavernous sinus, surgical resection may be conservative.[39,40,43]

The need for pre-operative extracranial-intracranial bypass, may be evaluated in case one expects to sacrifice the carotid artery during excision of the tumour.

Cerebellopontine Angle Meningioma

These may be approached by a retromastoid craniectomy. The cerebellopontine angle may be involved with tumours extending from the tentorium to the petrous dura/clival dura.[38]

Petroclival Meningioma

The approaches that may be used include combined subtemporal and retromastoid approach with extra exposure provided by dividing the transverse sinus and superior petrosal sinus distal to the insertion of the vein of Labbé. A large tumour in this location may also be approached by combining the presigmoid and retrosigmoid approach and dividing the tentorium parallel to the superior petrosal sinus towards the incisura.[2,3,15,31,42]

Pineal Meningioma

These arise from the velum interpositum and may be approached using either an infratentorial supracerebellar approach or via an occipital transtentorial approach.[22,25,51]

Basal Approaches to Tentorial Meningiomas

In the excision of predominantly posterior fossa TMs, those meningiomas situated posterior to the internal auditory meatus may be accessed easily using a retrosigmoid approach. However, in TMs that are premeatal, tentorial edge and petroclival, the surgeon has

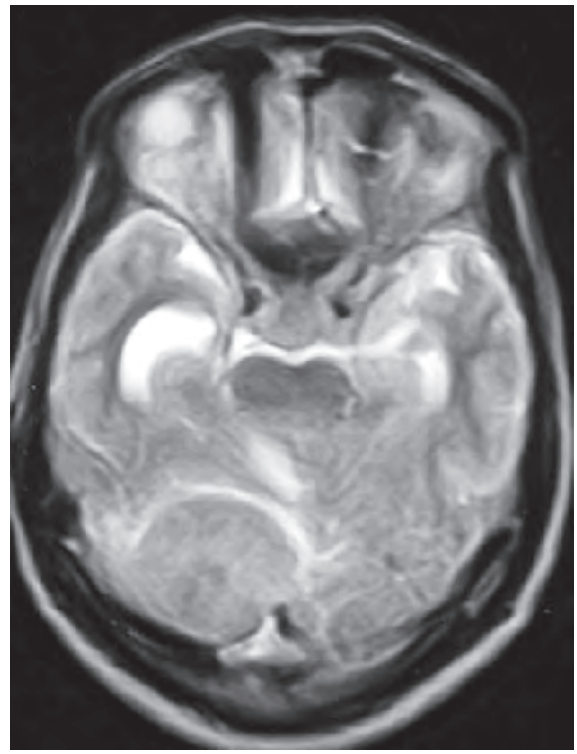


Fig. 8: Axial T2-weighted MR image showing a torcular meningioma in the supratentorial compartment. This lesion was excised using an occipital craniotomy

to traverse the cerebellopontine angle cistern and its neurovascular structures before reaching the tumour in the retrosigmoid approach. The VIIth–VIIIth nerve complex, the AICA and its branches and the perforating arterial branches to the brainstem from the vertebrobasilar complex may be at risk. Thus, these medially situated TMs may be accessed using variations of skull base approaches. These include presigmoid supra-infratentorial approach, presigmoid and retrosigmoid translabyrinthine approach, subtemporal presigmoid approach and transpetrosal approach.[3,36,37,39,42] Broadly speaking, a temporal craniotomy and lateral suboccipital craniectomy exposes the transverse sinus and the transverse sigmoid junction. The tumour exposure is then enhanced by drilling the mastoid process and petrous bone anterior to the sigmoid sinus. Careful drilling is important to avoid entering the bony labyrinth and fallopian canal. The sigmoid sinus is exposed in its full length to provide both a presigmoid and retrosigmoid exposure. The dura is opened parallel to the temporal fossa floor and the incision extended posterior to the junction of the sigmoid and lateral sinuses. Great care is taken to protect the vein of Labbé which usually drains into the lateral sinus just proximal to the junction with the sigmoid sinus. The dura of the posterior fossa is opened anteriorly and parallel to the sigmoid sinus and when required, also behind the sigmoid sinus. The skeletonised petrosal sinus is transected and the tentorium divided. Medially the tentorium is sectioned just posterior to the point where the IVth nerve joins the free edge. In premeatal meningiomas, the Vth nerve is usually splayed on top of the tumour. In tentorial edge meningiomas, the Vth nerve is usually situated inferolaterally to the tumour. In both these lesions, the IIIrd nerve is usually situated superomedial and the VIth nerve, inferomedial to these lesions.

Transection of the sigmoid sinus with the tentorium, with preservation of the vein of Labbé, may occasionally be performed if there is a patent transverse sinus on the contralateral side. These approaches minimise brain retraction and provide a more straightforward exposure of both the supratentorial and infratentorial components of the tumour. However, there is a risk of temporal lobe venous infarction due to prolonged traction on the vein of Labbé and the risk of post-operative deafness due to unintentional opening of the posterior semicircular canal.

Resection of Venous Sinuses to Achieve Complete Tumour Excision

A major issue in surgical resection of TM is resection of dural venous sinuses to achieve complete tumour removal. When a sinus is completely occluded and non-patent, it can be resected safely. However, when there is partial obliteration demonstrated on pre-operative radiology as well as infiltration of the sinus wall by the tumour that is revealed during surgery, a conservative approach should be adopted by coagulating the residual tumour on the sinus wall or resecting only the infiltrated outer dural layer of the sinus.[6,8,16,38]

Resection of the tumour with complete excision of the involved transverse sinus has been advocated in young patients when the pre-operative angiography reveals a widely patent contralateral transverse sinus and when there is evidence of venous collateral formation.[10,28,31] If brain swelling occurs after the intra-operative clamping of the sinus, reconstruction of the venous sinus from dural leaves or with a saphenous venous graft has been used. Intra-operative monitoring of sinus venous pressure along with somatosensory evoked potential monitoring prior to sinus excision has been proposed. Even when sinuses have been completely excised along with the tumour (despite the risk of post-operative venous infarct), recurrences may occur. Sekhar et al.[39] found a recurrence rate of 10% during a mean follow-up period of 5.5 years following venous sinus excision. Cudlip et al.[10] despite achieving 84% total resection, observed a recurrence rate of 21% during a follow-up of 3.5 years. Moreover, some part of the deep venous system may not be visible on angiogram, although the region may not be occluded and may be functionally important. Atresia/septations in the region of the sinus confluence may lead to misinterpretation with regard to dominance of sinuses. Thus, an infiltrated but patent venous sinus should be preserved, since even subtotal removal of a TM may be associated with a long progression free period and a high quality of life.

SURGICAL RESULTS

The rate of total tumour resection according to Simpson's grading for tumour removal has been approximately 77–83%. Rostomily et al.[32] achieved a subtotal resection in 20–40% of patients with overall recurrence rates of 7–15%. The low rates of recurrence, even when subtotal resection was performed, led Bret et al.[6] to propose that dural devascularisation resulting from extensive cauterisation or from separation of the tumour from its dural attachment, was responsible for the minimal growth capabilities of residual meningiomas. The limiting factors to total excision were breach of the pia mater of the brainstem and encasement of critical vascular structures. Series prior to 1980 reported a post-operative death rate from 14% to 44%. With the advent of modern imaging and advances in microsurgery, the mortality has decreased to below 10%; however, morbidity rates still remain high, ranging from 18.9% to 77%.[14,39] Greater surgical difficulties are often encountered with TMs located at the tentorial edge.

Considerations in Elderly Patients

Umansky et al.[47] calculating the surgical outcomes in patients aged more than 70 years with a symptomatic

meningioma, found a mortality rate of only 5.4%. The mean Karnofsky score improved from a pre-operative score of 59 to post-operative score of 80. The median annual tumour volume growth rate for meningiomas is approximately 3.6%. Thus, even elderly symptomatic patients must be given the option of surgery. However, elderly patients with incidental TM may be followed by serial imaging studies with operative treatment reserved for tumours which have a high growth rate or those tumours that become symptomatic.

STEREOTACTIC RADIOSURGERY

Total surgical resection along with the adjacent dura and involved bone may be difficult to achieve in a TM, where the tumour is adherent to the brainstem, cranial nerves and venous sinuses. Occasionally, the tumour attains such a large size that complete excision leads to unacceptable neurological deficits. Since recurrence of the tumour following incomplete resection is always a possibility, alternative management strategies may be used. These are radiotherapy, stereotactic radiosurgery, chemotherapy and steroid receptor antagonists. Radiosurgery is a viable option for TM, due to their lack of brain invasion, tendency to become symptomatic when relatively small, ability to be defined by high resolution imaging and due to their basal blood supply that can be included in the radiosurgical volume. The efficacy of radiosurgery in the treatment of meningiomas is reflected by a tumour control rate of almost 96–98%. Radiosurgery is a valuable option for patients with small tumours (less than 30 mm), those with minimal or no neurological deficits, but with a documented increase in tumour size, those with small residual tumours following microsurgical resection, elderly or medically unfit patients and those who are unwilling to undergo surgery. The maximum tumour dose varies from 24 Gy to 40 Gy; the dose received by the brainstem has to be kept at or below 16 Gy. Tumour control rate of 98% has been reported during a mean follow-up of 3 years.[19,20,21,26]

CONCLUSION

TMs currently remain challenging surgical entities. Tumours located at the tentorial edge carry a definitely worse prognosis than those attached to the peripheral tentorium. Although subtotal resection may often be required due to the critical relationship of the tumour to the brainstem or important neurovascular bundles, often the long-term outcome may remain good with relatively low recurrence rates. Skull base approaches and radiosurgery may further enhance the capability to excise and limit the growth potential of these tumours. Resection of an infiltrated but patent venous sinus is not recommended because the risk of venous infarction is high and a significant decrease in tumour recurrence has not been demonstrated even with this manoeuvre.

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171 Posterior Fossa Meningiomas

Amitabha Chanda, Abhijit Guha

INTRODUCTION

From the infancy of neurosurgery, meningiomas have posed a challenge for neurosurgeons. Harvey Cushing remarked, "There is today nothing in the whole realm of surgery more gratifying than successful removal of a meningioma with subsequent perfect functional recovery, especially should a correct pathological diagnosis have been previously made. The difficulties are admittedly great, sometimes insurmountable, and though the disappointments still are many, another generation of neurological surgeons will unquestionably see them largely overcome".[26] Following this historic remark, the science and art of neurosurgery have come a long way during the previous century. Cushing's prediction was right in that a lot of the obstacles have been overcome. For example, with the advent of advanced radiological modalities, pre-operative diagnosis is usually not a mystery. Advanced anaesthesia, microsurgical techniques, and adjuvant treatment, especially in the form of stereotactic radiosurgery, also have changed the scenario. However, there remain a few meningiomas, which are still a nightmare for the surgeons, by virtue of their location, vascularity, and biology. In this chapter, we will discuss meningiomas of the posterior fossa, including meningiomas of the posterior fossa cranial base, which still often remain a management challenge for neurosurgeons.

EPIDEMIOLOGY

Meningiomas comprise about 20% of all primary intracranial neoplasms.[25,52,174,185] The reported incidence of meningiomas per 100,000 population varies from less than 1 to just more than 6.[84,144] However, these statistics are based on a few hospital studies in the United States and in no way represent World statistics. Nevertheless, the frequency of intracranial meningiomas in European and Japanese studies are close to those in the North American studies.[41,70,84,116,124,144,166,187] Of all meningiomas, 10–15% are in the posterior fossa.[24,172] Children show an increased incidence of posterior fossa meningiomas (PFM) in comparison to adults.[29,36,58] In three major studies from North America,[84,124,166] the ratio of male to female incidences ranged from 1:1.4 to 1:2.8. These differences are less evident in Africans and African-Americans,[124] who show equal ratios or a male preponderance. Moreover, reports from Africa also indicate a significantly higher frequency of meningiomas among primary intracranial neoplasms in that population.[42,46,95,99,115,119] The incidence of meningiomas increases with age.[84,124,166] The predisposition of meningioma in Type II neurofibromatosis, multiple meningioma syndrome and post-radiation meningiomas are mentioned later.

AETIOPATHOGENESIS INCLUDING MOLECULAR BIOLOGY

Trauma, although implicated by Cushing[24] as a significant aetiological factor in development of meningiomas, has not been proven unequivocally till date as an aetiological factor. There were a number of reports, as recent as in 1999, pointing trauma as a possible aetiological agent.[80,125] However, there are several reports which have challenged trauma as the aetiological basis.[4,20,64,121]

Papovavirus antigen has been identified in human meningioma by immunocytochemical techniques.[175] Also, BK viral DNA, SV40 viral DNA and adenoviral DNA have been found in meningiomas by DNA hybridisation techniques. However, the viral DNA material was not integrated into the tumour cell DNA in any case.[39,60,61] Although the presence of viral protein, RNA or DNA in human meningiomas cells suggests a possible role in tumour induction, maintenance of transformation, or both, in which case the implicated viruses may act alone or in a permissive manner with other mutagens. The exact role of viruses in human meningiomas is not yet defined accurately.

Many reports have shown that meningiomas have occurred following low levels of radiation, such as were given in the past for *Tinea capitis* (10 Gy), following intermediate dose of radiation and following the high doses of radiation given (55–75 Gy) for the treatment of primary head and neck malignancies.[8,33,98,102,108,173] The latency of occurrence of meningioma is longer following low dose radiation than that for meningiomas following high dose radiation. The latency range is from 24 to 36 years. In these radiation-induced meningiomas there is a higher incidence of atypical meningiomas with more aggressive biological features.

It is well known that meningiomas occur with higher frequency in patients with neurofibromatosis Type II

(NF-2). With this knowledge, extensive cytogenetic examination demonstrated that monosomy of chromosome 22 (or more specifically deletion of the 22q12 locus) was the most common chromosomal abnormality seen in meningiomas.[74,130,147,182] A loss of NF-2 or other tumour suppressive genes along with activation of proto-oncogenes are thought to cause meningiomas to arise. That the prod3uct of the NF-2 tumour suppressor gene, MERLIN, is important in genesis of meningiomas was supported by the fact that over-expression of MERLIN significantly inhibited proliferation of meningioma cells.[62] However, it cannot be overemphasised that alterations of other genes on chromosome 22 and other chromosomes may be involved in the genesis of meningiomas. Chromosomes[1,6,9–11,13,14,18,19] have all been implicated.[74,89,93,94,119,123,176] In familial meningiomas and meningiomatosis, where the entire dura is transformed with meningiomas, a yet to be identified tumour suppressor gene, also on chromosome 22q and adjacent to the NF-2 gene, has been implicated.[103]

Meningiomas, which occur more frequently in females, especially those occurring in the spine, grow more rapidly during the luteal phase of the menstrual cycle and during pregnancy. This epidemiological observation has led to a search for the importance of sex hormones and their receptors in the pathogenesis of meningioma. The initial search identified the oestrogen receptors,[35] with a number of other hormone receptors subsequently found. The oestrogen receptors were found in about 30% of the tumours in a recent study and most of them were the Type II subtype,[105,161] which have lower affinity and specificity for oestrogen than Type I have. The other receptors found were progesterone receptors (50–100%), androgen receptors (almost same frequency as that of progesterone receptor), somatostatin receptors (almost 100%), growth hormone receptor mRNA and dopamine receptors.[10,15,38,59,88,87,112,128,145,161] In fact somatostatin receptor scintigraphy has been found to be a useful diagnostic modality in identifying meningiomas and differentiating residual tumour from other changes seen in the post-operative setting.[75]

Table 1: Classification of posterior fossa meningioma*

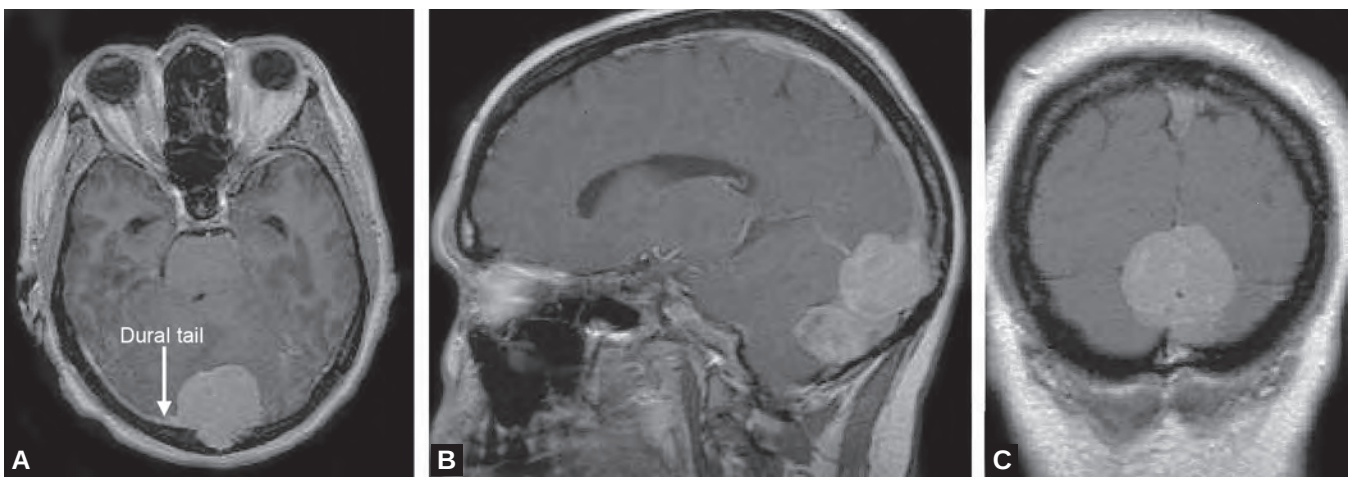
Type I	Cerebellar convexity and lateral tentorial
Type II	Pre-meatal
	Lateral petrous ridge and
	Cerebellopontine angle
	Post-meatal
Type III	Jugular foramen
Type IV	Petroclival
Type V	Foramen magnum
Type VI	Unclassified

Key:*, Modified from Sekhar et al. (1996)

From the mid 1980s, attention was paid towards growth factors and their receptors. Adams et al.[2] supported the presence of an autocrine control of meningioma proliferation. In their study, treatment with a neutralising antibody against platelet-derived growth factor (PDGF) abolished stimulation of meningioma cell culture growth by a meningioma-conditioned medium. The co-expression of PDGF-B (a potent mitogen) and PDGF receptor suggests an autocrine loop and may contribute to the growth and maintenance of these tumours.

CLASSIFICATION

Classification of PFM is a little confusing. Classification based on the site of origin of tumour[14,24,132] may be confused by the distinction between origin, dural attachment and dural adherence.[16,179] The site of profuse bleeding may indicate the site of origin of the tumour and enostosis is a good indication of the origin of lateral petrous tumours.[179] That is why it is sometimes not possible to accurately classify a meningioma before surgery, especially if it is a large one. We prefer to follow the classification by Sekhar et al.,[155] which is a modification of the classification by Castellano and Ruggiero[16] based on dural attachment (Table 1). Type I (Figs 1A to C, and 2) includes meningiomas arising from the cerebellar convexity dura, the lateral tentorium, transverse sinus, sigmoid sinus and the straight sinus.



Figs 1A to C: (A) Gadolinium enhanced T1 axial. (B) Sagittal. (C) Coronal image of torcular meningioma (Type I). Note the bony involvement in the inner surface of the occipital bone and dural tail in axial image (A)

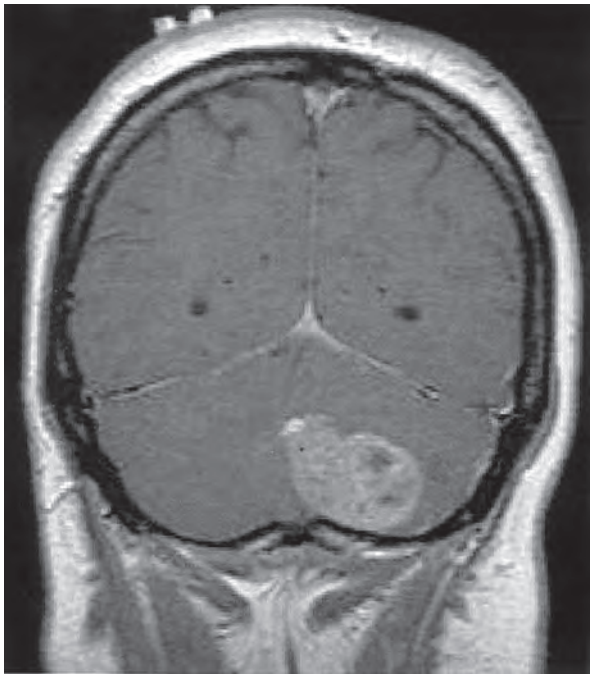


Fig. 2: A gadolinium enhanced T1 coronal image of cerebellar convexity meningioma (Type I) close to the midline

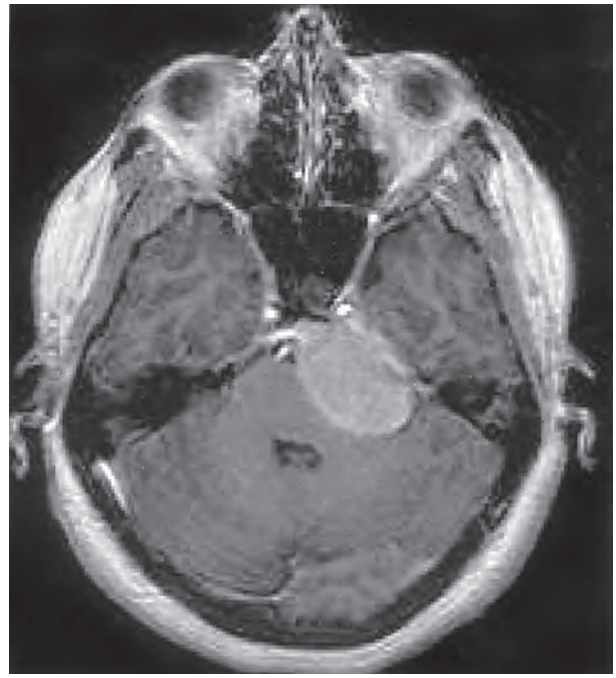


Fig. 3: Gadolinium enhanced T1 axial image of pre-meatal type of CPA meningioma (Type II). Note the relative lack of involvement of the clivus. In cases of large meningiomas, it is often difficult to assess the tumour attachment, whether it is medial or lateral to the trigeminal nerve. In this particular case it was lateral to the trigeminal nerve

These meningiomas have a propensity to invade the major venous sinuses. Torcular meningiomas are also included in this type. Meningiomas arising from the posterior face of the petrous bone dura, lateral to the trigeminal nerve are Type II meningiomas. These can also be classified as cerebellopontine angle meningiomas and can in turn be divided into pre-meatal (Fig. 3) and post-meatal types (Figs 4A to E).

We feel that these two are different entities in terms of clinical presentations and surgical results.[142] Meningiomas arising from the dura mater around the jugular foramen (Fig. 5) with or without extracranial extension,[71] are Type III meningiomas.

Type IV or petroclival meningiomas (Figs 6A to D) arise from the petrous apex, medial petrous ridge medial to the trigeminal nerve, upper two thirds of the clivus with or without extension to the cavernous sinus and/or Meckel's cave.

Meningiomas arising from the foramen magnum region, lower third of the clivus and C1, C2 regions are Type V meningiomas (Figs 7A and B).

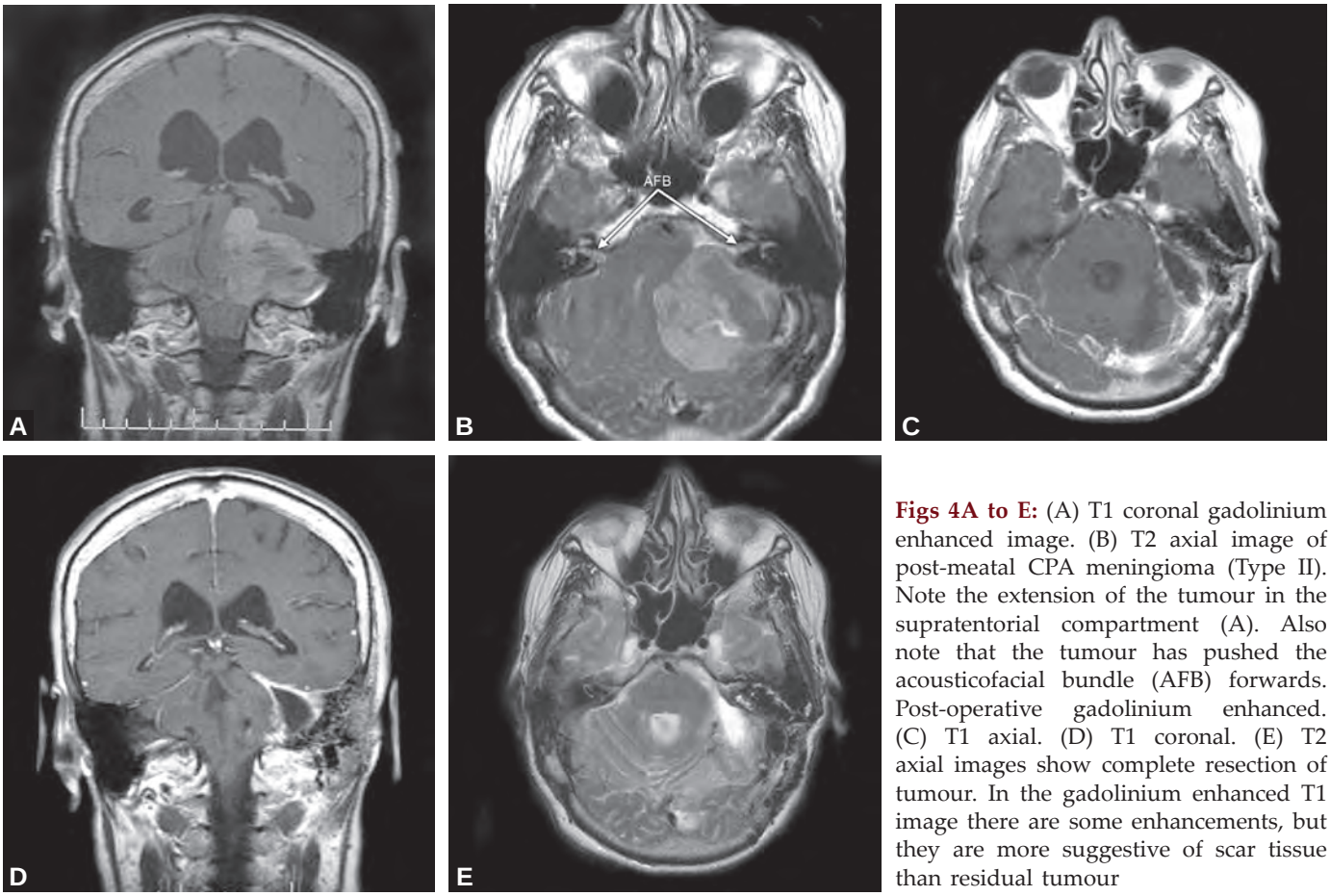
In spite of all these, there are still tumours, which cannot be accommodated in any group or may be in two or more groups. Examples of these are intracanalicular tumours (tumours in the internal auditory canal) or very large posterior fossa cranial base meningiomas, which cannot be fitted into any particular group. These are Type VI PFMs.

In this context, a special note must be made regarding meningiomas of the fourth ventricle. Five per cent of all intraventricular meningiomas arise in the fourth ventricle. PFM without dural attachment were classified by Abraham and Chandy[1] into three types: (1) Meningiomas originating from the choroid plexus of the fourth ventricle and developing solely within the fourth ventricle; (2) Meningiomas originating in the inferior tela choroidea, developing partly in the cerebellar hemisphere and vermis and (3) Meningiomas within the cisterna magna without any attachment to the dura mater.

PATHOLOGY

Meningiomas arise from the arachnoid cap cells.[73,114] This origin was supported by the fact that the arachnoid cap cells parallel in frequency the sites of meningioma formation. Macroscopically, these tumours appear smooth and lobulated with a fine leash of vessels on the surface. More vascular meningiomas are characterised by a reddish meaty appearance. Most of the tumours tend to be globular but other shapes according to the location may also be seen. For example, tentorial meningioma or jugular foramen meningioma with extracranial extension may be dumb-bell shaped. Also they may have diffuse growth (en plaque), such as those seen in diffuse meningiomatosis.

There are several histopathological classification schemes for meningiomas. However, the most popular one is the classification by Russell and Rubenstein,[131] who classified meningioma into meningotheliomatous (syncitial), fibrous, transitional and angioblastic types.



Figs 4A to E: (A) T1 coronal gadolinium enhanced image. (B) T2 axial image of post-meatal CPA meningioma (Type II). Note the extension of the tumour in the supratentorial compartment (A). Also note that the tumour has pushed the acousticofacial bundle (AFB) forwards. Post-operative gadolinium enhanced. (C) T1 axial. (D) T1 coronal. (E) T2 axial images show complete resection of tumour. In the gadolinium enhanced T1 image there are some enhancements, but they are more suggestive of scar tissue than residual tumour

Fatty degeneration, haemorrhage, calcification and cyst formation may occur. However, in this system there is always a controversy whether an angioblastic meningioma is the same as haemangiopericytoma. The World Health Organization (WHO) classification is simpler and distinguishes three grades of meningioma.[143] The meningothelial, fibrous, transitional, psammomatous, secretory, microcystic, clear cell, lymphoplasmacyte-rich and chordoid subtypes all comprise Grade I meningiomas. More aggressive meningiomas, based on histopathological characteristics, are classified as "atypical" meningiomas (Grade II) and the frankly malignant "anaplastic" meningioma (Grade III). The grading is mostly dependent on the proliferating potential of the tumour. Proliferative activity is usually determined by a labelling index (LI).[43] The LI distinguishes Grade I meningiomas (LI: 0.02–0.9%) from "atypical" meningiomas (LI: 1.5–2.0%) and "anaplastic" meningiomas (LI: 9–13%) and predicts the chance of recurrence.[66] Apart from LI and grade, several histopathological features are also associated with recurrence and aggressive behaviour. They are haemosiderin deposition, loss of architectural pattern, growth in sheets, prominent nucleoli, mitotic figures, necrosis, nuclear pleomorphism, frank invasion of brain by meningioma cells and overall atypical or malignant tumour grade.[28] A retrospective study of 160 cases done in Germany showed that grading of meningiomas should take a combined approach involving a Ki-67 proliferation index[76] and histological and cytogenetic characteristics.

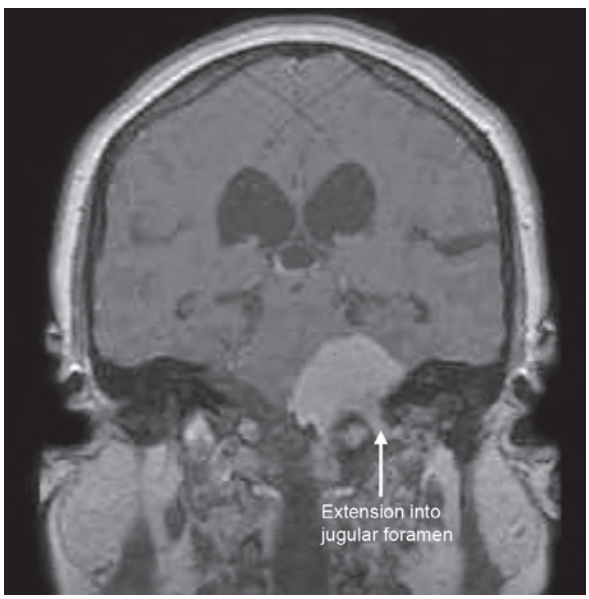
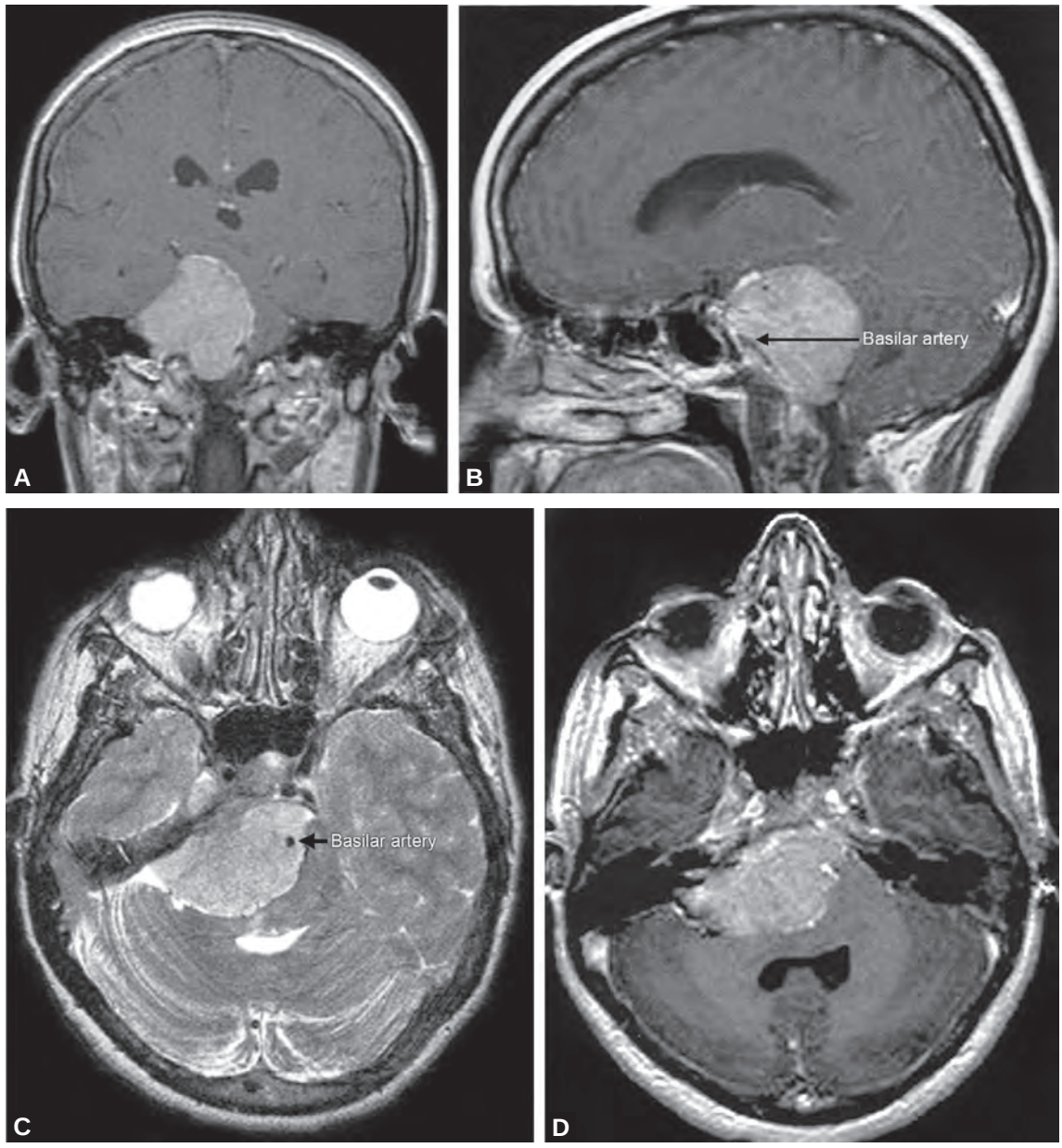


Fig. 5: T1 coronal gadolinium enhanced image of jugular foramen meningioma (Type III). Note the extension of tumour through the jugular foramen

CLINICAL FEATURES

The clinical features of PFMs vary according to the location, size and invasion of the pia mater. It must be remembered that a number of these tumours can be



Figs 6A to D: Gadolinium enhanced. (A) T1 axial. (B) Coronal. (C) Sagittal. (D) T2-axial images of petroclival meningioma (Type IV). Note the difference between the tumour here and that in Fig. 3. Here, the clivus is involved and the attachment of tumour was entirely medial to the trigeminal nerve. Also note the encasement of the basilar artery by the tumour (C and D)

asymptomatic. If the lesion is large enough, they can cause symptoms and signs of intracranial hypertension, irrespective of the site. We will discuss the clinical features according to the type of meningioma.

Type I

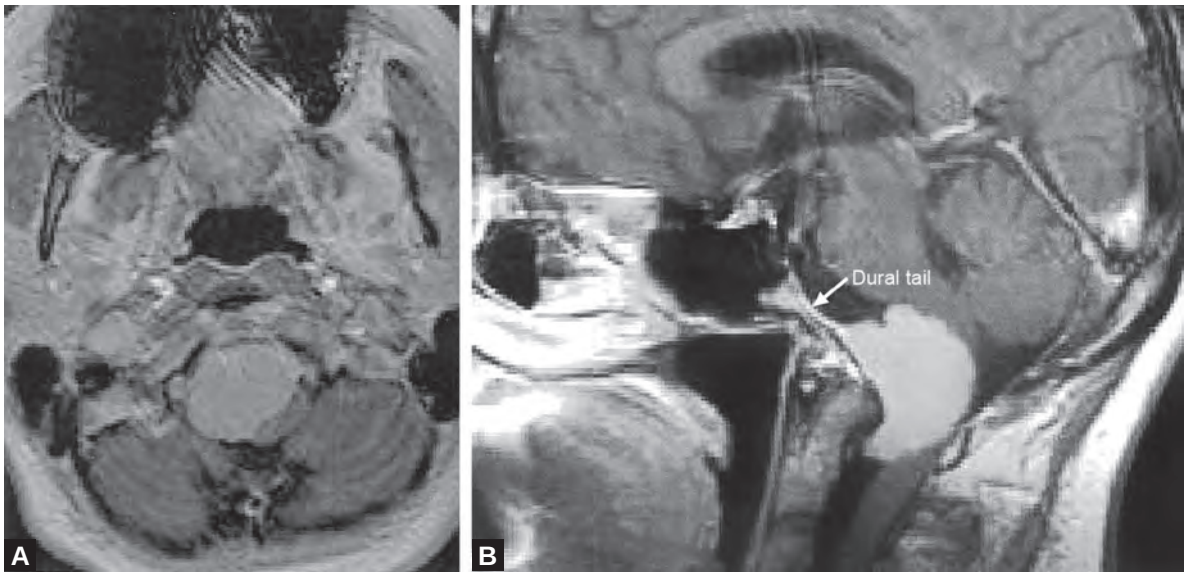
Type I PFMs usually present with raised intracranial pressure and progressive cerebellar signs (ataxia, dysmetria, nystagmus, etc.). When the supratentorial component of a tentorial meningioma is large, there may be visual field defects.

Type II

Type II PFMs commonly present with cranial nerve deficits and/or cerebellar signs and symptoms. Facial pain and/or numbness, facial weakness, hearing loss and ataxia are the usual presenting features. CPA meningiomas tend to involve the trigeminal and facial nerves with less early auditory and vestibular impairment, compared to vestibular schwannomas.[103] These Type II PFMs tend to involve the lower cranial nerves more than vestibular schwannomas. In a study,[142] it was shown that pre-meatal Type II PFMs have a propensity for facial nerve involvement and hearing loss, whereas the post-meatal/retromeatal type has a propensity for cerebellar involvement.

Type III

Type III PFMs usually present with lower cranial nerve symptoms like dysphagia, hoarseness of voice, nasal



Figs 7A and B: Gadolinium enhanced. (A) T1 axial. (B) Sagittal images of foramen magnum meningioma. Note the dural tail in the sagittal image (B)

regurgitation, etc. Additionally, they may also present with a neck mass, when there is significant extracranial extension into the neck. Several syndromes are associated with meningiomas of this group depending on the combination of cranial nerve involvement (e.g. Vernet's syndrome—Cranial nerves IXth, Xth, XIth; Collet's syndrome—Cranial nerves IXth, Xth, XIth, XIIth).

Type IV or the Petroclival Meningiomas

They most commonly present with trigeminal nerve involvement like facial numbness and/or pain. Facial nerve involvement and hearing impairment are not uncommon. The lower cranial nerves and ocular motor nerves (most commonly abducens) are involved in approximately one-third of patients.[32]

Type V

Type V meningiomas arise in the foramen magnum region and commonly present with suboccipital and neck pain (usually in C2 dermatome), ipsilateral upper limb paraesthesia, cold dysaesthesia, contralateral dissociated sensory loss, limb weakness starting in the upper limbs and wasting of small muscles of the hands. Lhermitte's phenomenon in the absence of other evidence of multiple sclerosis or cervical spondylosis may also be present. Patients may also demonstrate "piano-playing fingers", which means when they close their eyes and hold their arms outstretched, they will have slow athetosis-like movements of their arms, hands and particularly fingers.[54]

Type VI or the Unclassified Posterior Fossa Meningiomas

They can have protean manifestations. They may be asymptomatic and the symptoms depend upon the location and size of the tumour. For example, an intracanalicular meningioma will have hearing loss as the presenting feature, while very large PFMs can have multiple cranial nerve palsies, cerebellar involvement, sensory and motor dysfunctions.

The most common presenting symptom for PFM at the House Ear Clinic were otologic, with hearing loss (61%), tinnitus (58%) and imbalance (58%) as the three most common.[156]

Fourth ventricular meningiomas usually present with features of increased intracranial pressure due to hydrocephalus, truncal ataxia, nystagmus, down beat nystagmus, etc.

DIAGNOSTIC RADIOLOGY

Although MRI is the investigation of choice and has become the gold standard, computed tomographic (CT) scan can diagnose most of the meningiomas.[91] CT scans are helpful in assessing the bony changes and calcification and, moreover, is a cheap and good screening test. Plain X-rays are of academic and historic interest in some selected cases.

A typical meningioma on non-enhanced CT scan is isodense to slightly hyperdense to brain with homogeneous density. Calcification may be seen in 15–20% of cases[117] and may be punctate, rim-like, chunky or nodular. Dense calcifications may be confused with haemorrhage but can be differentiated by density numbers. Variable degree of oedema, evidenced as low density on CT scan, may be found, but is usually mild or absent in PFMs.[96] Bone changes may be hyperostotic or destructive. There is usually intense, homogeneous enhancement on contrast administration. Typically, there is sharp demarcation and a broad base against bone or free dural margins. Areas of hyperdensity, hypodensity and non-uniform enhancement may be seen, which may represent haemorrhage, cystic degeneration or necrosis. Often, aggressive meningiomas are characterised by indistinct or irregular margins.

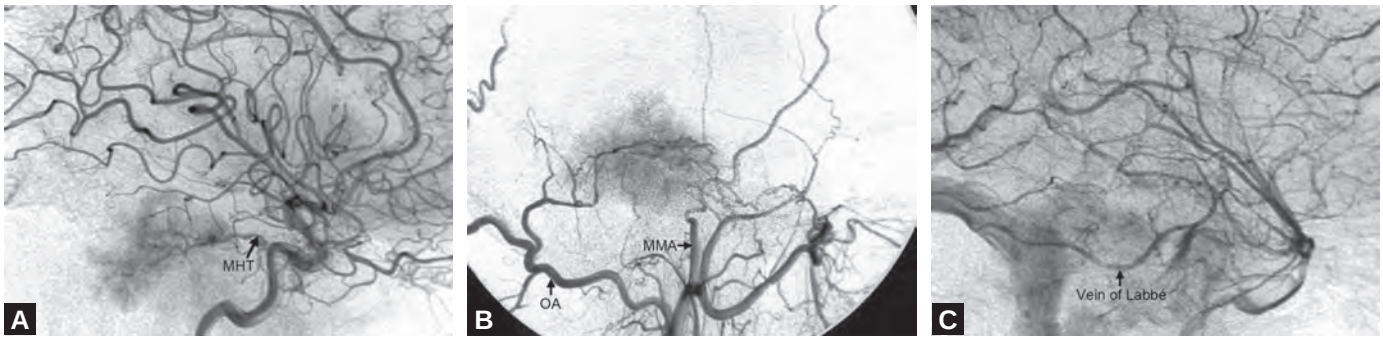
Magnetic resonance imaging (MRI) scan is usually the radiological investigation of choice. On the T1 image most of these tumours are isointense to grey matter. Up to one-third of the tumours are hypointense to grey matter. On the T2 image approximately half of the tumours appear isointense to grey matter and less than half are hyperintense to grey matter.[31,37,162,186] Features like vascular distortion and/or encasement, tumour vascularity and marginating characteristics are much better appreciated on MRI scans than on the CT scan (Figs 6C and D). Displacement of blood vessels, presence of CSF spaces between the tumour and the brain parenchyma and inward displacement of grey-white junction are the typical marginating characteristics.[45] Flow voids produced by flowing blood identify the vasculature in and around the tumour. It has been reported that T2 signal intensity may be reliable in predicting histological subtype, but until now it is at best controversial.[31,37,162] Moreover, associated T2 changes in the brain may also help in predicting the tumour subtype.[31,37] As the intensity in the T2 image depends on water content of the tumour, a hyperintense tumour on the T2 image usually means a softer tumour. It may also help to predict how easily the tumour can be dissected from the surrounding brain. The aetiology of oedema in the adjacent brain parenchyma is controversial. There are many hypotheses like venous obstruction, invasion of parenchyma, pial invasion and secretion of oedemogenic factors. The most likely aetiology is pial invasion in conjunction with release of oedema promoting factors such as vascular endothelial growth factor (VEGF).[126] It has been shown that the peritumoral "oedema" implicates difficulty in microsurgical dissection of the tumour from the brain parenchyma, worse surgical results and increased chance of recurrence.[63,100,153]

On administration of gadolinium contrast, most meningiomas enhance intensely and homogeneously. Contrast MRI is the most sensitive test and the investigation of choice to detect meningioma. Contrast enhancement of the dura mater extending away from the margin of the lesion is the "dural tail" and a characteristic sign to differentiate from other tumours (Figs 1A and 7B). Whether the dural tail represents actual tumour extension or is a juxta-tumour reaction is controversial.[50,170,177] Although once considered almost pathognomonic for meningioma, it may also be rarely seen in other tumours like acoustic neuromas, superficial intra-axial malignancies or dural-based metastasis.[85,117,177,178] Although there are situations when scar tissue (Figs 4C and D) may enhance and mimic a residual tumour, thus making the diagnosis difficult, usually thick and nodular enhancement indicates a residual or recurrent tumour.[175] Magnetic resonance sequences allowing evaluation of the arterial contribution and arterial anatomy from magnetic resonance arteriography (MRA) and more importantly the venous anatomy from magnetic resonance venography (MRV) is sometimes invaluable, especially when looking for the patency of major dural sinuses or the position of critical draining veins. In PFMs the venous anatomy is often very critical in tentorial or torcular meningiomas or the position of vein of Labbé for a subtemporal approach or looking for the position of the major venous complex at the quadrigeminal cistern in tentorial meningiomas.

The role of angiography in management of meningiomas has changed in the modern era, due to the advent of CT and MRI scans. Only in a very few cases can it really help in diagnosis, such as, to differentiate between a glomus jugulare tumour and a jugular foramen meningioma. Some indications for angiography include evaluation of the pertinent collateral circulation if a bypass or vascular sacrifice is planned, or to display the anatomy of the major veins, if MRV does not suffice (Figs 8A to C).

Visualisation of the pial blood supply, in the arterial phase of the angiogram, has been shown to predict difficulty in extrapial dissection.[160]

Magnetic resonance spectroscopy (MRS) is still evolving as a diagnostic tool for meningioma. Although both hydrogen (proton) and phosphorous-based *in vivo* MRS have been reported, proton based MRS is used clinically more often. In normal hydrogen-based MR, the spectrum for brain tissue displays well-defined peaks at 3.2 ppm for choline, 3.0 ppm for phosphocreatine/creatine (PCr/Cr), 2.0 ppm for N-acetyl aspartate (NAA) and a less well-defined peak for lactate at 1.3 ppm.[30] In meningiomas, there is a marked increase in choline



Figs 8A to C: Angiography in a petroclival meningioma. (A) Internal carotid angiography shows the supply of the tumour from the meningohypophyseal trunk (MHT). (B) External carotid angiography shows the same tumour supplied by the occipital artery (OA) and middle meningeal artery (MMA). (C) Venous phase of angiogram shows the position of vein of Labbé

signal and a marked drop in both NAA and PCr/Cr peaks.[30,82] Increase in choline signal implies an elevated concentration of mobile membrane components, which is expected in any tumour. The reduction of NAA is explained by the fact that NAA is confined to neurons. Some authors reported an additional peak at 1.47 ppm. due to alanine.[82,118] Magnetic resonance spectroscopy can be useful in differentiating many slow growing tumours from meningioma and for grading of tumour aggressiveness.[118]

DIAGNOSTIC CHALLENGES

Some CPA meningiomas may be difficult to differentiate from vestibular schwannomas, which are much more common. Certain diagnostic useful points include: (1) Relationship of the tumour to the internal auditory canal and meatus (usually vestibular schwannomas are centred over the internal auditory meatus, whereas meningiomas are eccentric); (2) Presence of dural tail in meningiomas, although dural tail has been reported with vestibular schwannomas also,[85] (3) Hearing preservation is much more likely in larger CPA meningiomas than in larger vestibular schwannomas and (4) Extension into the internal auditory canal suggests, but is in no way pathognomonic of vestibular schwannomas.[34,90]

Another diagnostic challenge is differentiation between a jugular foramen meningioma and a glomus jugulare tumour. Computed tomographic scan shows bony destruction, sclerosis or hyperostosis in meningioma, whereas in glomus jugulare tumour the smooth regular contour of the eroded bone is characteristic. Salt and pepper appearance and serpentine flow voids in MRI and angiograms with early venous drainage are characteristics of glomus tumour. Angiogram shows longer lasting tumour blush in meningiomas. A third diagnostic challenge is distinction between a fourth ventricular meningioma and other fourth ventricular tumours like ependymoma, medulloblastoma or choroid plexus papilloma.

TREATMENT

Observation, radiation treatment and surgical resection are the main treatment options. In this chapter, we will predominantly discuss the surgical management of PFMs. Several factors affect the ease of surgical removal including location, size, consistency, vascular and neural encasement or involvement, prior surgery or radiation treatment. The necessity for resection of not only the tumour but also the involved dura mater and bone are appreciated. To achieve radical resection newer surgical approaches are coming up. However, the balance between the risk and benefit of aggressive surgery must be remembered. Although a number of adjuvant therapies have come up, the only validated form of adjuvant therapy is radiation therapy, of which, gamma knife radiosurgery is a promising one. Observation in a small asymptomatic meningioma or in an elderly or medically sick patient remains a valid option.

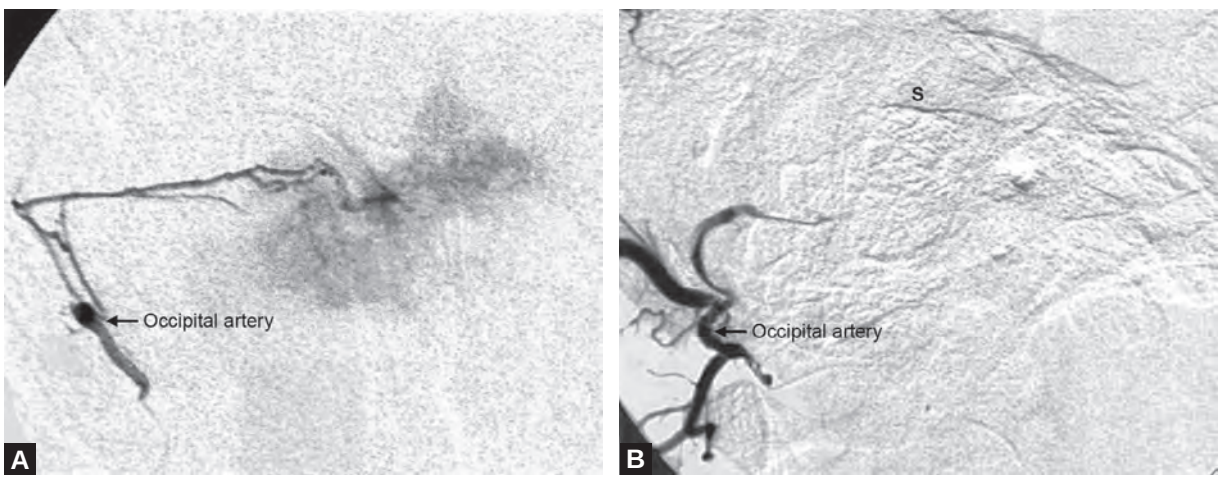
SURGICAL TREATMENT

Factors in the decision to operate include: (1) Tumour is causing symptoms; (2) Tumour is growing as evidenced by serial imaging; (3) Operation can relieve symptoms or at least stop progression of symptoms; (4) Even though asymptomatic the patient is in imminent danger of decompensation, as in a tumour with significant brainstem compression or tonsillar herniation; (5) Tissue diagnosis when diagnosis is in doubt especially when there is a confusion whether the lesion could be a dural based metastasis; and (6) Acceptable risks versus natural history of the tumour and patient characteristics.

General Principles

Pre-Operative Embolisation

Embolisation prior to surgery may reduce the tumour vascularity and decrease tumour bleeding and depends on the availability of expertise and equipment in the institution. Selective embolisation of the feeding vessels (Figs 9A and B), such as the meningohypophyseal trunk in petroclival meningioma is desired.[129]



Figs 9A and B: Process of embolisation. (A) This tumour was supplied by the occipital artery. (B) Following embolisation devascularisation is shown

The optimum time between embolisation and operation is controversial. When non-absorbable particles are used, it is prudent to wait for 7–10 days, allowing time for necrosis of the tumour. If absorbable particles are used, it is advisable to operate within 48 hours of embolisation, i.e. before recanalisation occurs. The greatest contribution of embolisation is the pre-operative occlusion of tumour vessels which, because of their location, can be reached only late in the resection of the tumour. Pre-operative angiography, in addition to arterial and venous anatomy, may also help by occlusion tests to assess whether a tumour-involved vessel can be sacrificed or not if required.

Prophylactic antibiotic should be given. We usually prefer some antistaphylococcal antibiotics like cephazolin or vancomycin. When we know that entry into the ear or mastoid is a possibility, we add metronidazole.

Positioning of the patient should account for: (1) Accessibility to the tumour; (2) Unimpeded venous drainage; (3) Maximum benefit of gravity (so that the brain falls away by gravity and not by retraction); and (4) Position is safe for the patient and comfortable for the surgeon. Most of the PFMs are operated upon either in the prone or lateral position. The sitting or semi-sitting positions can also be used, in which case prophylaxis regarding venous embolism should be addressed. Scalp flaps should be sufficiently thick, wide based, linear or gently curvilinear to allow for a rich blood supply and should be designed in such a way that re-operation, if necessary, should be easy, so far as the scalp incision is concerned. Vascular supply from the external carotid artery branches, such as the occipital artery, can be coagulated during the opening. This can take care of vascularity of the tumour as well.

Several methods are available to minimise brain retraction. The first principle is "to be gentle on the brain and aggressive on the bone", which is the guiding principle of cranial base approaches. By strategic removal of bone, like removing the petrous ridge or skeletonising the sigmoid sinus, or resection of the occipital condyle, or variable parts of the petrous bone, exposure can be made wide and shallow. The second principle is to use drainage of cerebrospinal fluid using several methods, such as ventricular drains, or releasing CSF by opening arachnoid cisterns (sufficient in most cases). The third principle is to use moderate hyperventilation, diuretics, dexamethasone and positioning to relax the brain. The fourth principle is to use gravity to make the brain fall away.

Tumour Resection

Following exposure of the tumour, an exploration to determine the morbid anatomy must be done as much as possible. For resection of cranial base meningiomas, it is necessary that the surgeon has a thorough knowledge of three-dimensional anatomy. The tumour should be devascularised as early as possible, preferably before intratumoral decompression is started. The arachnoid plane should be maintained at all costs as "arachnoid is the best friend of the neurosurgeon". In the majority of meningiomas, which have not been operated upon before, there is an arachnoid plane between the tumour and the brain parenchyma, blood vessels and cranial nerves. In these instances, it is possible to greatly increase the chance of preserving these vital structures by remaining within and respecting this plane. In some instances, it may appear that the tumour is adherent to these structures, but more often than not, this is due to the bulk of the tumour and adequate debulking can make the tumour capsule collapse away from these vital structures and facilitate dissection. The method of debulking is largely dependent on the consistency of the tumour and can include suction, bipolar cautery, sharp excision with scissors or knife (using No. 11 blade), ultrasonic aspirator, laser or even a high speed drill (for a calcified or ossified lesion).

Even after following all the principles of resection, some part may still be found to be adherent to the brainstem or critical neurovascular structures. In these cases, it is prudent to leave that part rather than to risk mortality or a major morbidity. The residual tumour may be followed closely or some form of adjuvant treatment can be given. The role of aggressive resection must be balanced with the major risks involved, with the surgeon's experience and expertise as the fulcrum. Once the tumour is resected in total, attention must be paid to removal of the involved dur amater and bone whenever possible, to achieve Simpson Grade 1 excision.[159] However, it is impossible most of the times to achieve Grade 1 excision for posterior fossa cranial base meningiomas.

Closure

Special care must be taken for the closure to avoid CSF leak.[23] The dura mater should be meticulously repaired, if possible, and following cranial base approaches most often some form of duraplasty using temporalis fascia or fascia lata or artificial dura will be required. Special attention must be paid in packing and obliterating the mastoid air cells and middle ear cavity with fat. Biological glue may be used to reinforce the closure.

Surgical Approaches Used by Tumour Location (Tables 2 to 8)

Type I Posterior Fossa Meningiomas

The status of the lateral sinus is of prime importance in these meningiomas, especially the lateral tentorial meningiomas. If the lateral sinus is completely occluded, the sinus can be transected along with the tumour. In a partially occluded sinus the status of the contralateral sinus is important before one can contemplate excision to achieve total removal. On occasion, a 20 G butterfly needle attached to a manometer can be placed into the transverse sinus just lateral to the torcula and the sinus occluded for 5 minutes. If the venous pressure does not rise more than 5 mm of Hg and if no brain swelling

Table 2: WHO classification of meningoepithelial tumours

I. Benign meningioma
   i. Meningothelial (syncitial)
   ii. Transitional
   iii. Fibrous
   iv. Psammomatous
   v. Angiomatous
   vi. Microcystic
   vii. Secretory
   viii. Clear cell
   ix. Chordoid
   x. Lymphoplasmacyte-rich
   xi. Metaplastic variants (xanthomatous, myxoid, osseous, cartilaginous, etc.)
II. Atypical meningioma
III. Anaplastic (malignant) meningioma
   i. Variants of benign meningioma
   ii. Papillary

Table 3: Surgical approaches for Type I PFMs

Type of tumour	*Surgical approach*
Cerebellar convexity meningioma	Midline or lateral suboccipital craniotomy depending on the location of the lesion
Tentorial meningioma (infratentorial)	Midline or lateral suboccipital craniotomy depending on the location or extent of the lesion
Tentorial meningioma (combined supratentorial and infratentorial)	Combined suboccipital and occipital craniotomy (midline? lateral?)

Table 4: Surgical approaches for Type II PFMs

Type of tumour	*Surgical approach*
Cerebellopontine angle meningioma (post-meatal type)	Retrosigmoid craniotomy
Cerebellopontine angle meningioma (pre-meatal type)	Retrosigmoid craniotomy with or without pre-sigmoid petrosal approach if necessary
Cerebellopontine angle meningioma with extension to supratentorial compartment	Combined retrosigmoid craniotomy with supratentorial craniotomy OR Retrosigmoid intradural suprameatal approach (RISA)

Table 5: Surgical approaches to Type III PFMs

Type of tumour	*Surgical approach*
Jugular foramen meningioma with mainly intradural component	Retrosigmoid approach
Jugular foramen meningioma with large extradural component	Posterior fossa infratemporal approach Type A or B OR

Contd...

Type of tumour	*Surgical approach*
	Infralabyrinthine approach OR Transjugular approach
Jugular foramen meningioma with extracranial extension	Posterior fossa infratemporal approach type A or B OR Infralabyrinthine approach OR Transjugular approach with extension of approach to the neck

Table 6: Surgical approaches to Type IV PFMs

Type of tumour	*Surgical approach*
Upper petroclival meningioma (small or medium sized tumour with middle fossa extension)	Pterional craniotomy with orbitozygomatic osteotomy
Upper and middle large petroclival meningioma	Petrosal approach for tumours extending no more than above dorsum sellae Petrosal approach + pterional craniotomy with orbitozygomatic osteotomy for tumours extending above dorsum sellae OR Extended middle fossa approach/ anterior transpetrosal approach
Middle petroclival meningioma	Retrosigmoid approach OR Petrosal approach OR Extended middle fossa approach/ anterior transpetrosal approach
Upper and middle petroclival meningioma with any one of the features: giant size, previous surgery, major vascular encasement, brainstem kinked to other side with good hearing	Total petrosectomy OR Transcochlear approach

Table 7: Surgical approaches to Type V PFMs

Type of tumour	*Surgical approach*
Posterior foramen magnum meningioma	Midline suboccipital approach
Posterolateral/lateral foramen magnum meningioma	Retrosigmoid far lateral approach
Anterolateral foramen magnum meningioma	Retrosigmoid far lateral approach for large tumours Extreme lateral transcondylar approach for small tumours
Anterior foramen magnum meningioma	Extreme lateral transcondylar approach

Table 8: Surgical approaches to other specific PFMs

Type of tumour	*Surgical approach*
Tumour totally confined to internal auditory canal	Extended middle fossa approach OR Retrosigmoid transmeatal approach
Fourth ventricular meningioma	Midline suboccipital craniotomy
Cisterna magna meningioma	Midline suboccipital craniotomy

is observed and there is no change in somatosensory evoked potential, the transverse sinus can be divided.[154] However, it must be seen that the sinus is non-dominant and has some collateral flow through the torcula. While making a suboccipital craniotomy for a tentorial meningioma, we usually make sure to expose the lateral sinus completely and about 1 cm of supratentorial dura mater. This helps to expose the inferior surface of the tentorium completely.

For tentorial meningiomas with both supratentorial and infratentorial components, a combined occipital-suboccipital craniotomy is helpful. For this, somatosensory evoked potential (SSEP) should be monitored. Moreover, if possible, visual evoked potential (VEP) should be monitored. For cerebellar convexity meningioma, the surgical approach is suboccipital craniotomy. Depending on the location, the approach can be midline suboccipital or lateral suboccipital. For midline suboccipital craniotomy, the patient is positioned prone and for lateral suboccipital craniotomy the patient is operated upon in the lateral position with side of the approach uppermost. For tentorial meningiomas with both the supratentorial and infratentorial components, the patient is placed in the three-quarter prone position with the side of approach lowermost. This enables the occipital lobe to fall away by effects of gravity and thus retraction is minimised. A midline incision from above the inion down to the C3 level is made for midline suboccipital craniotomy. The craniotomy is made according to the position of the tumour. The decision to resect the rim of the foramen magnum or resect the posterior arch of atlas depends on the lowermost extent and size of the tumour. A lateral suboccipital incision is made for a lateral suboccipital approach. The incision may be straight, lazy S-shaped, hockey stick or C-shaped. The exact location of the incision again depends on the location of the lesion and how much lateral it is necessary to go.

After completion of craniotomy, the dura is opened all around the tumour for convexity meningiomas. For tentorial meningiomas, the dura is opened in a horseshoe fashion with the flap based on dural sinuses. Following dural opening, the tumour is resected following the principles mentioned above. It is possible most of the time to achieve a Simpson's Grade 1 excision[159] in convexity meningiomas. However, for tentorial meningiomas, with involvement of major venous sinuses, the tumour should be resected as much as possible within the limits of safety. The dura is closed with or without duraplasty, whichever is suitable. The bone flap is usually replaced. If the size of the bone flap is significantly smaller than the craniotomy defect, which occurs when bone is drilled to expose the lateral sinus, the residual defect is covered with titanium mesh covered with hydroxyapatite (Bone source®, Leibinger Inc., New Carrolton, TX). Craniectomies for posterior fossa lesions are practically not done nowadays, to avoid post-operative headache.

Type II Posterior Fossa Meningiomas

For post-meatal type of CPA meningiomas usually a standard retrosigmoid approach allows sufficient exposure.[136,149] Brainstem auditory evoked potentials (BSAEP) and SSEP should be monitored in all cases in addition to facial nerve monitoring. Depending on the extent of lesion, trigeminal, glossopharyngeal, vagus, accessory and hypoglossal nerves should also be monitored. Several types of skin incisions, viz. straight, C-shaped, lazy S-shaped, or hockey stick shaped incisions can be used. For craniotomy, the burr holes are usually placed on the asterion, which usually represents the lower margin of the transverse sinus and sigmoid sinus junction, and at the inferomedial corner of the exposure. The decision to resect the foramen magnum or posterior arch of atlas depends on the lower extent of the tumour. Usually if the tumour extends below the jugular foramen, we resect the rim of the foramen magnum. After the craniotomy, bone is drilled to expose the transverse-sigmoid sinus junction well to achieve a good lateral exposure. Exposure of the pre-sigmoid dura is usually desirable to allow retraction of the sigmoid sinus laterally and decrease the obstruction of the surgeon's view. The dura is opened in a C-shaped manner, with the concavity of the 'C' facing medially with a few millimetres of dural cuff kept laterally to facilitate dural closure. A few release incisions are made in this cuff of dura to facilitate retraction. After adequate CSF drainage in small tumours, the petrous pyramid can be dissected to devascularise the tumour with care taken not to injure neurovascular structures. In large tumours, the principle of alternate intratumoural debulking and capsular dissection should be followed. A variety of critical structures must be dissected including cranial nerves (fourth to twelfth), superior cerebellar artery (SCA), anterior inferior cerebellar artery (AICA), posterior inferior cerebellar artery (PICA), basilar artery (BA), vertebral artery (VA) and their branches.

Most pre-meatal type of CPA meningiomas, including the larger ones, can be resected by the retrosigmoid approach. Usually, the larger tumour creates space between the brainstem and the petrous bone to facilitate removal. However, in some smaller pre-meatal tumours, with a posteriorly placed sigmoid sinus and significant anterior brainstem compression, the pre-sigmoid approach is usually done to have an unobstructed and more lateral view, without undue cerebellar retraction. A retrolabyrinthine type of pre-sigmoid petrosal approach

is sufficient in these cases and does not compromise hearing. However, the limitation of the pre-sigmoid petrosal approach is that it is difficult to reach tumours which have attachment below the level of the ninth cranial nerve. In these cases, a retrosigmoid approach can be added to reach the lower part of the tumour. In contrast, tumours reaching the supratentorial compartment, especially the Meckel's cave, may be resected by adding a supratentorial craniotomy[104] or by the retrosigmoid intradural suprameatal approach (RISA). The RISA has recently been described for posterior fossa tumours with small extension into the middle cranial fossa, especially Meckel's cave.[138] In this approach, after standard retrosigmoid craniotomy and tumoural decompression, the suprameatal tubercle is drilled to expose the distal part of the cisternal segment of the trigeminal nerve and the part in Meckel's cave to remove the part of the tumour from Meckel's cave. Although this can help the surgeon to reach Meckel's cave from the posterior fossa, eliminating the need for additional supratentorial craniotomy, the approach is technically demanding. The surgeon needs to drill in a space between the brainstem and petrous bone and through strings of vital cranial nerves and vessels. Any slippage of the drill can be catastrophic. Moreover, venous bleeding from the petrous bone may be troublesome. This approach, thus, must be used very selectively. On the other hand, the combined supratentorial and infratentorial approach is more versatile and technically easier than RISA. However, while using this approach, special care must be taken to preserve the vein of Labbé, otherwise a catastrophic venous infarct of the temporal lobe may result.

The extended middle cranial fossa approach provides excellent access and exposure to tumours in the anterior cerebellopontine angle and petroclival junction. This approach allows a more direct access to the area anterior to the internal auditory canal. The key to the approach is adequate bone removal of the petrous apex, to provide exposure down to the inferior petrosal sinus and anteriorly to Meckel's cave and the petroclival junction and combined with extradural elevation of the temporal lobe with suitable brain relaxation minimises post-operative complications.[27]

Type III Posterior Fossa Meningiomas

These lesions are best approached by a posterior fossa infratemporal,[40] transjugular or infralabyrinthine[86] approach, which are basically similar with very minor variations. The operation can be done in the lateral position or if neck dissection is necessary, in the supine position (ipsilateral shoulder elevated by bolster) with the head elevated and turned away from the side of approach. Monitoring of the lower cranial nerves, BSAEP and SSEP is necessary. A C-shaped post-auricular incision is made and extended down to the neck with neck dissection, if there is tumour extension into the neck or if vascular control is required. The external auditory canal is usually transected but can be preserved, if the anterior exposure desired is limited. The neck dissection is done to expose the major vessels and the vessel supplying the tumour and the lower four cranial nerves. A complete mastoidectomy is done to expose the semicircular canals and the facial nerve along with the chorda tympani. The jugular bulb needs to be completely exposed. After drilling the jugular process of the temporal bone, three structures will come in the way of the anterior aspect of the jugular bulb and lateral aspect of the jugular foramen. These are the facial nerve, styloid process with attached muscles and ligaments and rectus capitis lateralis muscle. The facial nerve is anteriorly mobilised by skeletonising the whole intramastoid and intratympanic part of the facial nerve and cutting the chorda tympani. The styloid process is resected along with the attached structures and reflected downward, exposing the highest portion of the cervical internal carotid artery and internal jugular vein. The rectus capitis lateralis muscle is cut and retracted. If anterior exposure is needed, this can be achieved by transecting and overseeing the cartilaginous external auditory canal and drilling the middle ear structures. If sensorineural hearing preservation is an issue, this can be done by preserving the footplate of the stapes. Significant intradural extension can be dealt with by adding a retrosigmoid craniotomy. Potential complications of this demanding approach are many, including major vascular injury to catastrophic lower cranial nerve palsy. If expertise for these difficult approaches, which benefit from collaboration with a neuro-otologist, does not exist, it may be prudent to remove the intradural portion of the tumour by the retrosigmoid approach, followed by radiation of the residual tumour.

Sanna et al. operated on 13 primary jugular foramen meningiomas, using the petro-occipital transigmoid (POTS) approach; a combined POTS-transotic approach because of massive erosion of the carotid canal; a combined POTS-translabyrinthine approach was used in patients with pre-operative unserviceable hearing and a modified transcochlear approach type D with posterior rerouting of the facial nerve and transection of the sigmoid sinus and jugular bulb was performed in patients with a huge cerebellopontine angle tumour component with extension to the prepontine cistern, together with massive involvement of the petrous bone and middle ear and encasement of the vertical and horizontal segments of the intrapetrous carotid artery. Gross total tumour removal (Simpson Grades I and II) was achieved in 11 (84.6%) cases and subtotal removal of the tumour was possible in two patients. Good facial nerve function (grades I and II) was achieved in 46.1% of cases and hearing was preserved at the pre-operative level in all four patients who underwent surgery via the POTS approach. Following surgery, no patient recovered function of the pre-operatively paralysed lower cranial nerves and a new deficit of one or more of the lower cranial nerves was recorded in 61.5% of cases. Among the various surgical techniques proposed for dealing with these lesions, they prefer the POTS approach alone or combined with the translabyrinthine or transotic approaches.[140]

Type IV Posterior Fossa Meningiomas

For this group of meningiomas, a more lateral approach is needed than in CPA meningiomas, in order to have adequate visualisation without significant cerebellar retraction. A petrosal approach is usually the ideal choice.[3] However, some exceptions are there. For lesions in the upper petroclival region or lesions lying completely above the trigeminal nerve and reaching above the dorsum sellae, a frontotemporal craniotomy with orbitozygomatic osteotomy is recommended. In this approach, the skin incision extends from below the zygomatic arch and just in front of the tragus to the opposite midpupillary line. An interfascial dissection is done to protect the frontotemporal branch of the facial nerve. The temporalis muscle is detached and reflected down, followed by a frontotemporal craniotomy and orbitozygomatic osteotomy as described in the literature.[151,179,180] The dura is opened in a C-shaped manner based anteroinferiorly, with the Sylvian fissure widely split to reach the tumour.

If the tumour is not reaching above the dorsum sellae, a petrosal or partial labyrinthectomy petrous apicoectomy (PLPA) approach[152] is preferred. For this approach the patient is placed in the lateral position with the mastoid of the affected side at the uppermost level. A C-shaped incision is made and the muscles reflected anteroinferiorly. A bone flap is carefully elevated to expose the transverse and sigmoid sinuses. A mastoidectomy is performed with exposure of the sinodural angle, Trautman's triangle, semicircular canals, facial nerve in the fallopian canal and the superior petrosal sinus. If hearing is absent, a total labyrinthectomy can be performed to increase the anterolateral exposure. The dura mater is opened along the floor of the temporal fossa and along the anterior border of the sigmoid sinus. The vein of Labbé is identified and protected with ligation and transection of the superior petrosal sinus. The division is carried medially through the tentorium to reach the tentorial edge taking care not to injure the trochlear nerve or the petrosal vein.[137] Sectioning of the tentorium allows the sigmoid sinus to fall back along with the cerebellum, thus reducing the need for retraction. By angling the microscope, it is possible to visualise the trochlear through to the lower cranial nerves, as well as the entire anterolateral brainstem with the vertebrobasilar system. The tumour resection proceeds in the usual way then. However, when hearing preservation is an issue it is advisable to use PLPA approach. This approach provides much better access to the clivus, petrous apex and posterior cavernous sinus, compared to the retrolabyrinthine approach. This approach has the advantage of preserving hearing in as much as 80% of cases.[152] This approach is different in a few ways from the traditional petrosal approach. First the mastoidectomy exposing the sigmoid sinus, middle fossa dura, retrosigmoid dura, Trautman's triangle, facial nerve in fallopian canal, superior petrosal sinus and semicircular canals is done. A temporal craniotomy is added. The whole superior semicircular canal and part of the posterior canal above the Donaldson line is drilled away. Care must be taken not to lose endolymph and the canals should be packed with bone dust or bone wax. Bone drilling is continued to resect the petrous apex medial to the internal carotid artery. This approach facilitates entry into the cavernous sinus as well. However, an intracavernous dissection is only performed in the presence of extensive cavernous sinus involvement and progressive cranial neuropathies. The dura mater is opened in the usual way and tumour is resected. If the tumour extends well below the jugular foramen, a retrosigmoid craniotomy should be added. There are surgeons, who have achieved good results using the retrosigmoid approach or combined supratentorial and infratentorial craniotomy for these lesions,[11,134,135,138,163] but we prefer to use this approach for these lesions.[18] However, there are instances when total petrosectomy should be done (Table 6). For this approach, the facial nerve is completely skeletonised from the internal auditory canal to the stylomastoid foramen. The greater superficial petrosal nerve is sectioned and the facial nerve is mobilised posteriorly. The petrous internal carotid artery is exposed completely and mobilised anteriorly. The entire petrous bone superior to the jugular foramen and part of the lateral clivus can then be drilled away. The eustachian tube must be packed to prevent CSF leak. Other approaches to this area, like anterior transpetrosal-transtentorial approach,[72] extended middle fossa approach[49] and extended lateral subtemporal approach,[48] have been described in the literature.

Goel et al. found the conventional posterior cranial fossa approach suitable for a select group of petroclival meningiomas. Gross total tumour resection was achieved in 21 cases and a partial tumour resection in the remaining 7 cases, with two patients dying in the post-operative period. The advantages are that it provides easy and quick exposure of the tumour without any petrous bone drilling. It also provides a direct and early exposure of the tumour-cranial nerve-brainstem interface facilitating the dissection. The lateral and inferior tumour extensions in relationship to the clivus can be more easily accessed and the site of attachment of the tumour to the dura overlying the posterior face of the petrous apex can be seen directly.[47]

Cho and Al Mefty advocate the combined petrosal approach, i.e. the posterior petrosal with the anterior petrosal approach for patients who have a large petroclival meningioma and serviceable hearing. This approach enhances petroclival exposure and the degree of tumour resection, especially in the area of the petroclival junction, middle clivus, apical petrous bone, posterior cavernous sinus and Meckel's cave. The approach also allows better visualisation of the contralateral side and the ventral brainstem, which facilitates safe dissection of the tumour from the brainstem, the basilar artery, the perforators and if a patient has an early draining bridging vein to the tentorial sinus or a prominent

sigmoid sinus and jugular bulb, the combined petrosal approach provides significant working space.[19]

Sanna et al. reported their surgical strategy in the management of 81 patients with posterior petrous face meningiomas. Thirty-one patients were approached by the enlarged translabyrinthine approach. The above approach combined with transapical extension Type II was performed in 29 patients. The combined retrosigmoid-retrolabyrinthine approach was used in 8 cases. The modified transcochlear approach Type A with permanent posterior transposition of the facial nerve (FN) was performed in 6 patients. Two patients underwent a retrolabyrinthine subtemporal transapical approach, one patient underwent a transpetrous middle cranial fossa approach and four patients with intracanalicular meningiomas were operated on through the enlarged middle cranial fossa approach. Total removal of the tumour (Simpson Grades I and II) was achieved in most patients (92.5%). The facial nerve was anatomically preserved in 79 of the 81 (97.5%) patients, and hearing-preserving surgery was attempted in 15 patients (18.5%) with pre-operative serviceable hearing, of which 11 had their hearing preserved at the same pre-operative level and 4 experienced post-operative deafness. They concluded total tumour removal (Simpson Grades I and II) remains the treatment of choice, taking priority over hearing preservation. Subtotal removal is preferred in the event of the absence of a plane of cleavage between the tumour and the brainstem, in the presence of encasement of vital neurovascular structures, in elderly patients with tumours adherent to pre-operatively normal facial or lower cranial nerves.[141]

The feasibility of keyhole approach in surgical treatment of petroclival meningioma has not been well evaluated. Zhu et al. treated 25 patients with petroclival meningioma via subtemporal, retrosigmoid or combined keyhole approaches. The maximum diameter of tumours ranged 2–7 cm (mean, 4.5 cm). Gross total resection (GTR) was achieved in 14 patients, giving a GTR rate of 56%. Subtotal resection (STR) was carried out in 8 patients and partial resection in 3. Thirteen patients kept normal neurological status, whereas others suffered from cranial nerve deficits (VIIth, IIIrd and lower CN), and one patient died in the post-operative period. The extent of tumour resection was evaluated by MRI 3 months after surgery. They found keyhole approach surgery, especially the combined keyhole approach is suitable for the treatment of petroclival meningioma, as it provides an easy and quick access to the supratentorial and infratentorial juxta-clival region, without drilling of the petrous bone and complications related to the approach can be minimised.[183,184]

The management of small petroclival meningiomas is still controversial, with clinical observation, radiosurgery and surgical removal being the options of treatment. The natural history of these tumours is not well known. Published series of patients treated with radiosurgery are not comparable with surgical series because the latter also includes large size tumours.

Ramina et al. treated 18 patients with small petroclival meningiomas (diameter less or equal to 2.8 cm) by radical surgical removal. Total resection (Simpson's Grade 1) was possible in all patients, with minimal morbidity and no mortality. The approaches used were retrosigmoid, fronto-orbito-zygomatic and pre-sigmoid. They concluded the effectiveness and outcome of surgery for small petroclival meningiomas should be compared with series treated by radiosurgery.[127]

Type V Posterior Fossa Meningiomas

Despite the introduction of skull base approaches, there is still controversy about the optimum surgical management for foramen magnum meningiomas. The approach depends on the precise location of the lesion. For posteriorly located lesions, it is approached by midline suboccipital craniotomy with resection of the posterior arch of atlas and laminae of axis depending on the size of the lesion. After craniotomy, the dura is opened in a Y-shaped manner with the vertical limb of the Y below the level of marginal sinus. Tumours in the lateral aspect of the foramen magnum can usually be excised by a low retrosigmoid approach. The rim of the foramen magnum is usually resected along with the arch of the atlas and hemilamina of the axis if necessary. A posterior suboccipital approach was utilised with lateral extension of the bone opening, according to the localisation of the tumour which was ventral, ventrolateral, dorsal and dorsolateral. Complete removal of the tumour was possible in 14 cases (Simpson Grade I and II). In their experience, the posterior suboccipital approach is suitable for the removal of the majority of these tumours.[68]

For tumours in the anterior or anterolateral aspect of the foramen magnum, the extreme lateral transcondylar approach[101,156,158] is recommended. However, when the tumour is large and situated anterolaterally a lateral suboccipital approach,[57] which is a modification of the traditional retrosigmoid approach, is often sufficient, as the tumour makes the space for the surgeon. Several modifications have been made of the extreme lateral approach,[133] which is undertaken in a lateral position. A C-shaped or an inverted U-shaped incision is made. The advantage of the inverted U-shaped incision is that, if the patient needs an occipito-cervical fusion, it can be performed through the same incision. The vertebral artery is exposed in the suboccipital triangle, where it is covered by a venous plexus, which can cause troublesome bleeding. The vertebral artery is mobilised by deroofing the foramen transversorium of the atlas. The occipital condyle is then drilled, dictated by the amount of exposure needed. If less than half of the condyle is drilled and the rest of the atlanto-occipital joint is stable, the patient will not need a fusion, otherwise a fusion is necessary. The tumour is resected following the above-mentioned principles. In a typical foramen magnum meningioma, which is either anterolateral or anterior to the brainstem, the vertebral artery and spinal accessory nerve are posterior to it. Care must be taken while

opening the dura, as the nerve and the vertebral artery may be very close to the dural surface. The purely anterior foramen magnum meningioma usually pushes the hypoglossal nerve posterolaterally, while the anterolateral one pushes it anteromedially. Although we prefer to use the transcondylar approach for typical foramen magnum meningiomas, there are surgeons, who have used a lateral suboccipital approach to resect these tumours.[113]

Menezes utilised the posterolateral transcondylar approach to the craniocervical junction in children for various lesions including meningiomas. Pre-operatively, the stability of the craniocervical junction was assessed so that a fusion procedure could be accomplished at the same operative setting, if necessary. Evaluation of the lower cranial nerves was vital. The occipital bone removal was carried out up to the sigmoid sinus and towards the jugular bulb and occipital condyle removal was limited to one third of the medial occipital condyle. Relocation of the vertebral artery was made at the atlas vertebra, thus providing posterolateral exposure into the posterior fossa and upper cervical spinal canal. He found this route to be a versatile avenue to approach a variety of lesions ventrolateral to the brainstem and upper cervical cord and the exposure is quite satisfactory with minimal or no retraction of important neurovascular structures in the region.[106]

Based on the relevant anatomy of the foramen magnum area, Bruneau et al. have a classification system based on the compartment of development, the dural insertion and the relation to the vertebral artery. The compartment of development is mostly intradural and less often extradural or both intra-extradural. They classified intradural foramen magnum meningiomas as posterior, lateral and anterior if their insertion is, respectively, posterior to the dentate ligament, anterior to the dentate ligament and anterior to the dentate ligament with extension over the midline. This classification system helps to define the best surgical approach and the lateral extent of drilling needed and anticipate the relation with the lower cranial nerves. In their department, three basic surgical approaches were used to foramen magnum meningiomas: the posterior midline; the posterolateral and the anterolateral approaches.[12]

Pamir et al. operated on 22 patients (23 surgical procedures) with a diagnosis of foramen magnum meningioma, using the suboccipital approach for two posteriorly located tumours and the paramedian suboccipital approach was replaced by the far-lateral modification in the treatment of ventral meningiomas. A gross-total removal was achieved in 21 patients, with an overall morbidity of 32%, with no specific and clinically significant complications attributable to the far-lateral modification being observed. They concluded that the far-lateral approach has improved the success of surgery in ventrally located lesions, while the posterior suboccipital approach is still indicated in the removal of lesions placed posterior to the dentate ligament.[120]

Borba et al. operated on 15 patients using the lateral approach in all cases. Based on the pre-operative magnetic resonance imaging, the tumours were classified as anterior or anterolateral in the axial slices and clivospinal or spinoclival in the sagittal slices. The extent of bone removal and the management of the vertebral artery were tailored to each patient. The occipital condyle was partially removed in only eight patients. Total removal of the tumour was achieved in 12 patients, subtotal in two, and partial resection in one patient. Post-operative complications occurred in two patients and there was no surgical mortality. They stated that the extent of surgical approach to foramen magnum meningiomas must be based on the main point of dural attachment and tailored individually case-by-case and the differentiation between clivospinal and spinoclival types, as well as anterior and anterolateral types, is crucial for the neurosurgical planning of foramen magnum meningiomas.[9]

Type VI Posterior Fossa Meningiomas

The surgical approach depends on the location of the tumour. Fourth ventricular meningiomas are approached via a standard midline suboccipital approach. After dural opening, the vermis is split to enter the fourth ventricular cavity. The blood supply of these tumours is usually from the branches of the posterior inferior cerebellar artery, which should be taken care of first followed by tumour removal. Utmost care must be taken not to injure the structures in the floor of the fourth ventricle. Purely intracanalicular meningiomas can be resected either by the retrosigmoid transmeatal approach or middle fossa approach.[72]

RADIATION TREATMENT

The usual forms of radiation used are fractionated external beam radiation and stereotactic radiosurgery. Although there are a few reports of brachytherapy,[55,83] it has never become popular.

Fractionated External Beam Radiation

During the 1960s and the 1970s, concerns were raised regarding the effectiveness of external beam radiation treatment for meningiomas. However, a few retrospective well-conducted studies showed its effectiveness in a higher dose of 45 to 60 Gy. This was shown to be effective both after recurrence and after subtotal resection.[6,107,169] Moreover, a longer survival was shown in patients after subtotal resection, who had external beam radiation.[21] Conceptually, external beam radiation should also be more beneficial for aggressive meningiomas, with the recommended radiation dose and target volumes greater for these malignant meningiomas.[13] However, caution must be exercised, as scattering of radiation can induce complications, especially when dealing with lesions close to the brainstem. Other complications include radionecrosis and secondary neoplasms.

Stereotactic Radiosurgery

Stereotactic radiosurgery is being used in increasing frequency and includes proton beam,[164] gamma knife radiosurgery (GKRS)[65,165,168,181] and linear accelerators (LINAC or X-knife). The recent results of gamma knife radiosurgery for meningiomas, used as a primary modality (for tumours less than 3 cm) or as an adjunctive treatment or after recurrence are excellent with a control rate of 93% over a follow-up period of 5–10 years.[77–79,97,110,111,122] However, toxicity of gamma knife or other forms of radiosurgery for meningioma exists. This includes injury to encased cranial nerves,[92,109,171] which tolerate radiation poorly. A major advantage of gamma knife is the possibility of using a larger number of isocentres. This permits greater conformality in treating irregular shaped tumours typically occurring at the cranial base.[79] The experience with LINAC in meningiomas is somewhat limited. Two studies showed a control rate of 89.3%[56] and 100%[157] over a mean follow-up period of 5 years and 23 months, respectively. Hakim et al.[56] showed an overall permanent complication rate of 4.7% and a mortality rate of 10% during the follow-up period. A potential long-term risk of either gamma knife or X-knife radiosurgery is the risk of secondary neoplasms including malignant tumours. The risk of complication is uncertain but linked to the degree of scatter radiation and length of patient survival.

Kreil et al. evaluated the effectiveness and toxicity of radiosurgical treatment for benign skull base meningiomas in 200 patients with a follow-up of 5–12 years. Of these, 99 patients were treated with a combination of microsurgical resection and GKRS, and in 101 patients, GKRS was performed as the sole treatment option. Tumour volumes ranged 0.38–89.8 cm^3 (median 6.5 cm^3) and doses of 7–25 Gy (median 12 Gy) were given to the tumour borders at covering isodose volume curves (range 20–80%, median 45%). The actuarial progression-free survival rate was 98.5% at 5 years and 97.2% at 10 years. The neurological status improved in 83 cases (41.5%), remained unaltered in 108 (54%), deteriorated in 9 (4.5%) and complications were radiation induced oedema in two patients (1%). They concluded GKRS has proved to be an effective alternative to microsurgical resection, radiotherapy and Linac based radiosurgery for adjunctive and primary treatment of selected patients with basal meningiomas. Because of the excellent long-term tumour control rate and low morbidity associated with GKRS, this treatment option should be used more frequently in the therapeutic management of benign skull base meningiomas.[81]

OTHER TREATMENTS

Apart from surgery and radiation treatment very little data is available on the efficacy of chemotherapy, although several agents have been tried. An interesting case report showed that a combination of 5-fluorouracil, folinic acid and levamisole might be effective in some forms of meningiomas,[7] but no further success was reported by those authors or other studies. Chamberlin in 1996[17] showed a modest improvement in survival (median survival 5.3 years) in patients treated with a combination of cyclophosphamide, adriamycin and vincristine for malignant meningioma. Hormonal agents, like tamoxifen and mifepristone (RU-486), have been tried without encouraging results.[51,53] Recombinant interferon α-2b has been used for a small number of patients with aggressive meningiomas[67] and it is apparently more effective than the traditional chemotherapeutic agents. Similarly, hydroxyurea has also been shown to produce some sporadic encouraging results,[146] although these initial encouraging results are not readily duplicated.

RESULTS AND PROGNOSIS

Two major issues are important in the prognosis of meningiomas. The first issue is the recurrence, which was first scientifically addressed in Donald Simpson's hallmark paper[159] based on the extent of resection. He reported a 9% recurrence rate after "complete resection" of the tumour and its neoplastic dural base, a 19% recurrence rate when the tumour was "resected" and the dural base was coagulated, a 29% recurrence rate when the tumour itself was removed but the dural base was not treated and a 40% recurrence rate when the removal was subtotal. However, this study was done in pre-CT and pre-MRI era. Excellent results have been produced by many surgeons over the years,[3,5,11,22,44,124,133–135,138,139,148–150,152,153,155,156,163,167] in terms of recurrence and complications, especially after improved microsurgical technique and advent of cranial base surgery. However, these excellent results, especially the recurrence factor, must be interpreted with caution as most studies have a follow-up period averaging 2–10 years rather than the desirable 15–20 year follow-up. The second issue in management of meningiomas is the morbidity and compromise of the quality of life associated with management options. Intervention with microsurgery, radiosurgery or combination treatment must be addressed in the context of associated morbidity. Occasionally, observation remains the optimal management choice given patient and tumour related characteristics when compared to the risk of active intervention.

Karia et al. analysed the predictive value of recurrence of protein expression in surgical samples of meningiomas, as they have been reported to be associated with prognosis of meningiomas. The study was done in a sample of 59 World Health Organization grade I tumours obtained after Simpson Grades I to III surgical resection (complete excision), that were followed for 6–16 years. The expression was investigated applying immunohistochemical and tissue microarray techniques. They found none of the correlations showed a significant association by means of logistic regression analyses. Their results indicate that the Simpson Grade significantly alters the outcome of a World Health

Organization I grade meningioma and a longer follow-up period significantly increases the risk of recurrence. They concluded that expression of none of the proteins or correlation between protein expressions previously reported to be of significance regarding recurrence can be recommended as a diagnostic tool, while assessing the risk of recurrence of World Health Organization grade I meningiomas.[69]

CONCLUSION

Despite improvements in standards of pre-operative imaging, peri-operative care, microsurgical techniques, cranial base approaches, PFMs still pose a formidable challenge to the contemporary neurosurgeons. The ideal goal of treatment is complete resection, but in some cases, this may not be possible without putting the patient in an enormous risk of severe morbidity and even mortality. In these cases, it is always prudent to back out and, if necessary, take the advantage of the recent advancement of adjuvant treatments, especially stereotactic radiosurgery.

EDITORIAL COMMENT

The variety of surgical approaches described in this chapter for PFM, especially those requiring skull-base surgical approaches require a thorough knowledge of the microanatomy, often the help of an ENT surgeon and must not be undertaken lightly by surgeons in the initial part of their career. Specialised training on cadavers in a laboratory is essential. Such facility is now available in the country, one such being at AIIMS, New Delhi. For further details of these approaches, one may consult Textbook of Operative Neurosurgery (Ravi Ramamurthi, K Sridhar, MC Vasudevan Eds 2005).

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172 Petroclival Meningiomas

Trimurti D Nadkarni

INTRODUCTION

Meningiomas account for 14–18% of all primary intracranial tumours. Approximately 10% of these occur in the posterior fossa. Amongst the infratentorial meningiomas, 3–10% are clival and petroclival. These tumours have been associated with a high risk of morbidity and mortality. Some surgeons described these tumours to be inoperable and they are considered to be one of the most difficult tumours of the skull base. Recent advances in neuroradiology, neuroanaesthesia and advanced microneurosurgical skull base approaches have led to better outcome.

Professor Gazi Yasargil laid down the treatment goal 30 years ago. "Clivus meningiomas in particular have until recent years been uniformly lethal. The outlook of such patients must be bettered by achieving earlier and more accurate diagnosis, by improving surgical technique, and better understanding of the pathological anatomy."[19]

Petroclival meningiomas are neurosurgical challenges, despite their usually benign pathology, principally because of involvement of the cavernous sinus, encasement of arteries and nerves, pial breach on the brainstem and extensions into multiple cranial compartments and foramina. The high risk of recurrence in partially resected tumours versus high risk of neurological morbidity and mortality resulting from pursuing radical gross total resection adds to the surgical challenge. Therapy must be tailored to the needs of the individual patient.

Although Simpson Grade I resection[16] is possible in many cases, in most of the patients a sub-total resection with or without radiosurgery has become the preferred treatment to reduce post-operative morbidity. Modern cranial base exposure, resection techniques and cranial base repair techniques have allowed the safe resection of many complex cranial base meningiomas. Radiosurgery has a definite role in the control of small tumour remnants, as well as small unoperated tumours. Thus, we need to incorporate changes in our management protocols with time.

In the large series published, the average reported mortality was 2% (range, 0–9%), major morbidity was 23% (range, 7–39%), permanent cranial deficits occurred in 44% (range, 29–76%), a poor functional outcome in 17% and a recurrence rate of 21% with an average follow-up of 3 years.[1,4,7,9,12–15]

NATURAL HISTORY

Authors[2,3] have described these tumours to have a relentlessly progressive growth with an ultimate fatal outcome. Partially resected tumours recur.[1,4,9,15] Van Havenbergh et al. have observed 21 untreated petroclival meningiomas over a period of 4 years. Tumour growth was observed in 76% and in 63% of these patients, there was functional deterioration.[18] These studies prove that these tumours are slowly growing but with a poor long-term outcome. In women, meningiomas may stop growing after menopause.

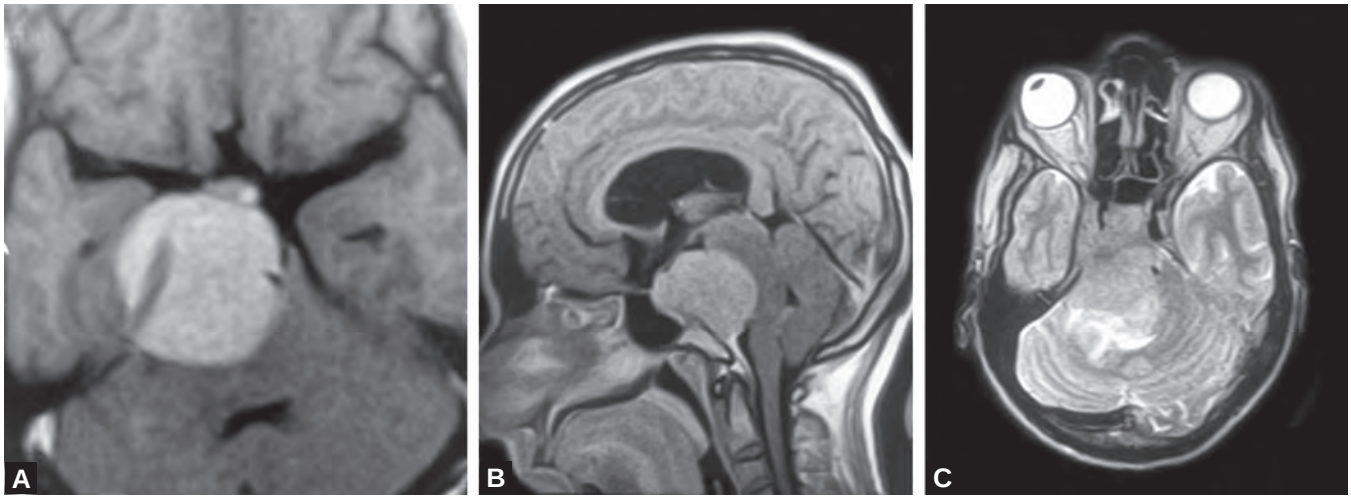
CLINICAL FEATURES

These tumours are predominantly seen in women in the fourth and fifth decades of life.[10,12] The most common neurological deficits include cranial nerve deficits, ataxia and hemiparesis or monoparesis. The clinical syndrome is of insidious onset, often mimicking other pathological processes; in elderly patients, the presenting symptoms are often attributed to vertebrobasilar insufficiency. The cranial nerve deficits include facial hypoaesthesia or anaesthesia with or without dysaesthesia, dysconjugate gaze, decreased hearing, facial paresis and decreased gag reflex.

Headache, gait ataxia, facial dysaesthesia, vertigo and deafness are the more frequent presenting symptoms with the trigeminal nerve as the single structure most often involved from onset. Later symptoms include gait ataxia, diplopia, swallowing difficulty and somatomotor deficits. The typical sign of a petroclival meningioma is a relatively fair preservation of hearing, in contrast to severe trigeminal involvement and impairment of the cranial nerves below VIII, with accompanying cerebellar signs.

NEURORADIOLOGICAL EVALUATION

A contrast computed tomographic (CT) scan with bone algorithm in axial and coronal views and a magnetic resonance imaging (MRI) scan are performed to evaluate the relationship between the meningioma and the cranial base and its bony involvement (Figs 1 to 5). Fine cuts through the temporal bone define temporal bone anatomy and the degree of pneumatisation, which facilitates the surgical exposure when a transpetrosal approach is planned.



Figs 1A to C: Post-contrast MR images. (A) Axial. (B) Sagittal. (C) T2-weighted axial images show a right petroclival meningioma that extends above the tentorium. The tumour has encased the basilar artery. The T2-weighted image clearly shows the loss of the peripheral arachnoidal plane between the tumour and brainstem. Brainstem oedema is noted

The most important information the surgeon needs to know before surgery includes the site and extension of dural attachment, tumour size, consistency, vascularity, bone involvement, tumour-brainstem interface, the position and encasement of arteries and extensions of the tumour specifically to the cavernous sinus.

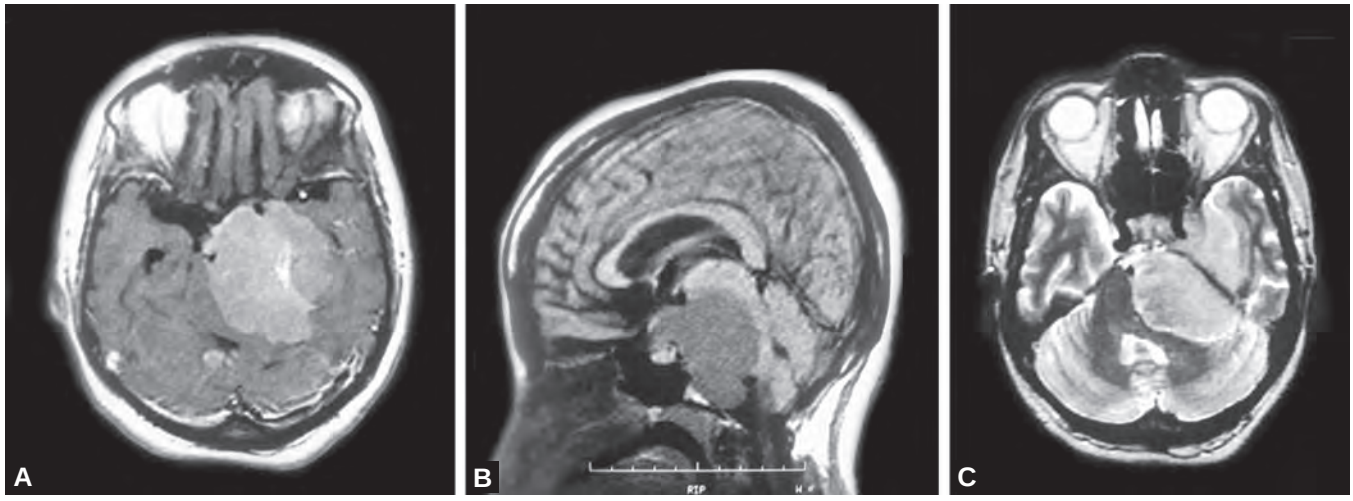
The presence of oedema on T2-weighted MR scans indicates a disruption of the blood-brain barrier and invasion or adherence of the tumour to the brainstem surface. Pial invasion of the tumour is indicated by the loss of the arachnoid plane on T1-weighted images and to the presence of blood supply to the tumour from the vertebrobasilar complex in the arterial phase of angiography.[15]

Patients may undergo cerebral angiography to study the vascular supply of the tumour and to plan the endovascular and surgical procedure. The tumour is principally fed by the meningohypophyseal trunk of the ICA, the posterior branch of the middle meningeal artery, the meningeal artery of the vertebral artery, the clivus artery originating from the carotid siphon, the petrosal branches of the meningeal arteries and the ascending pharyngeal branches of the external carotid artery. Preoperative embolisation should be performed through the main feeding vessels, which makes the surgical procedure easier.

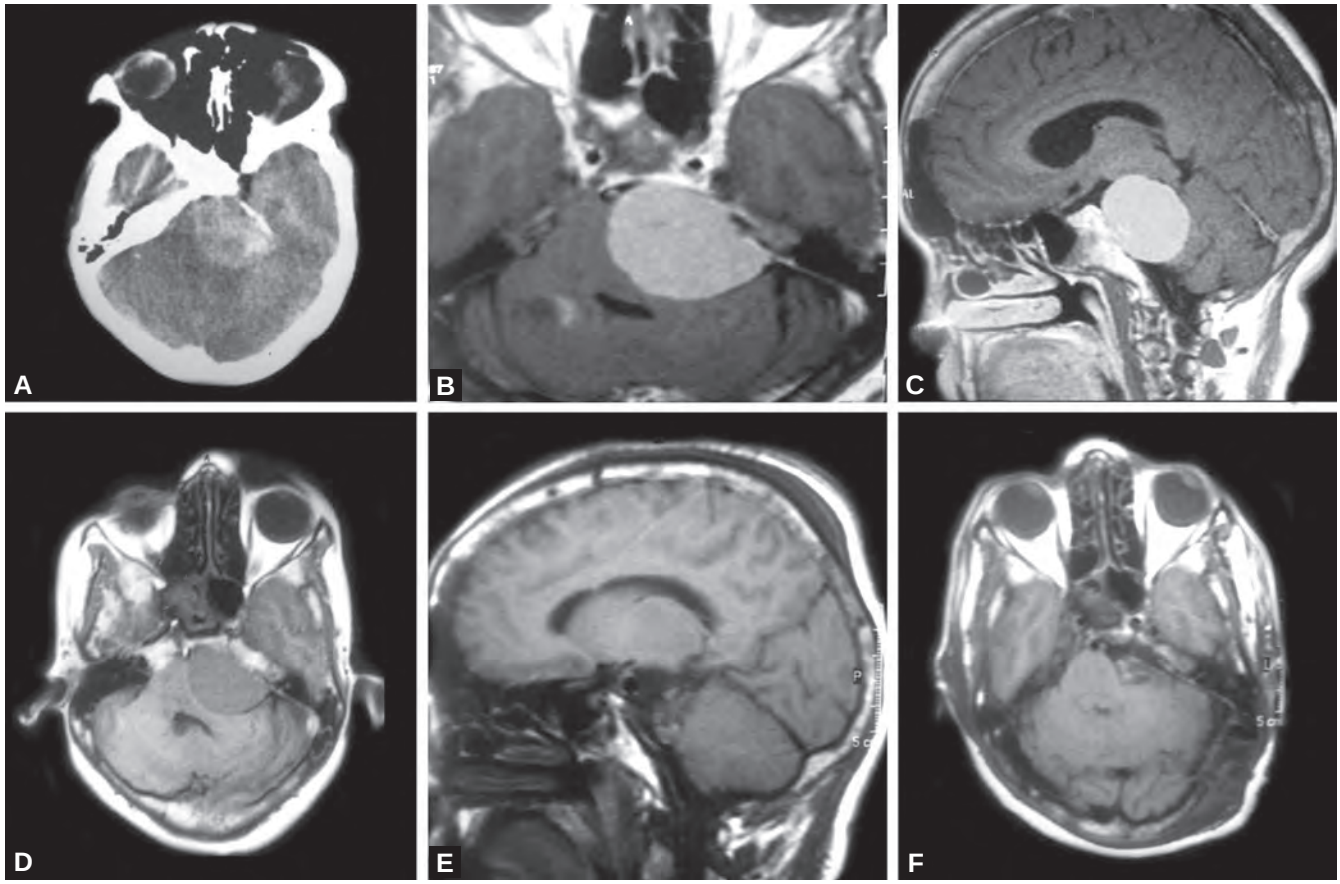
Encasement and narrowing of the main vascular channels may be noted. Venous anatomy should be studied, especially if ligature of a dural sinus is planned during the surgery. Temporal lobe venous anatomy is studied if the presigmoid petrosal approach is planned.

OPERATIVE DETAILS

Treatment strategies for difficult tumours, such as petroclival meningioma, are complex issues, because the



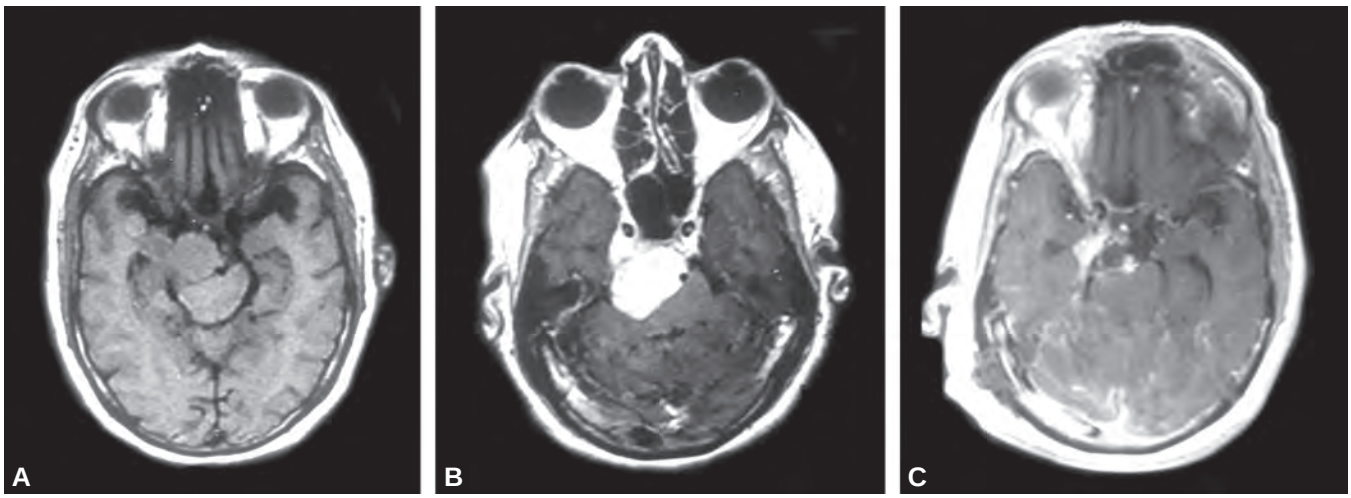
Figs 2A to C: (A) Post-contrast axial MR image shows a massive left petroclival meningioma. Both the basilar artery and supraclinoid carotid arteries are encased. (B) T1-weighted sagittal image shows the severe indentation of the brainstem. The tumour extends up to the sella. (C) T2-weighted MR axial image demonstrates the arachnoidal plane clearly between the tumour and the brainstem



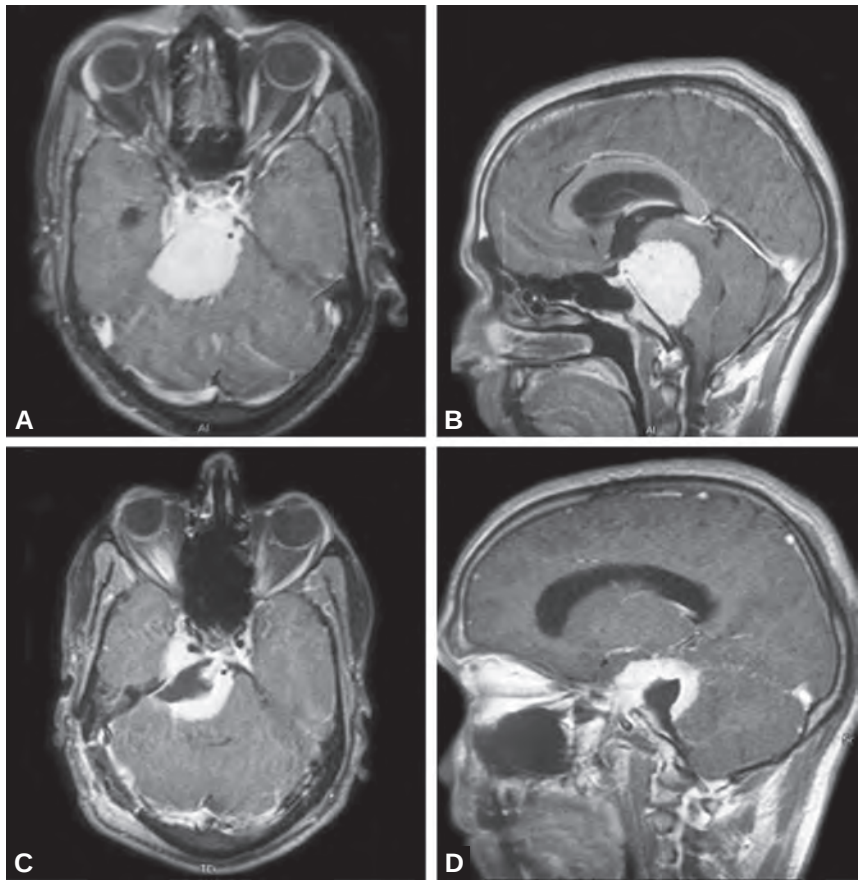
Figs 3A to F: Pre-operative. (A) Post-contrast axial CT image. (B) Post-contrast axial MR image. (C) Post-contrast MR sagittal image. (D) T1-weighted axial MR image shows a left petroclival meningioma. Post-operative. (E) Post-contrast sagittal MR image. (F) Axial MR image shows complete resection of the tumour. The retromastoid craniectomy is noted

patient may have a large tumour and minimal symptoms, the natural history is far from homogeneous and total removal is difficult to achieve. Theoretical considerations and pre-operative planning must be changed, depending on intra-operative findings. The collaboration of a neuron-otologist is sought when needed. Neurophysiological monitoring, when available, should be performed during surgery.

The surgical management of these tumours has been evolving, leading to better outcome and a marked reduction in surgical morbidity and mortality. A judicious evaluation should be done on a case-to-case basis as regards



Figs 4A to C: (A) T1-weighted axial MR image shows a right petroclival meningioma compressing the brainstem. (B) Post-contrast axial MR image shows the basilar artery outside the tumour capsule. A right cavernous sinus extension is noted. (C) Post-operative post-contrast axial MR image shows a small nubbin of tumour adherent to the basilar artery. A tumour remnant is noted in the right cavernous sinus



Figs 5A to D: (A) Post-contrast axial MR. (B) Post-contrast sagittal MR images show a large right petroclival tumour that has encased the basilar artery and invaded into the cavernous sinus. Post-operative imaging. (C) Post-contrast axial. (D) Post-contrast sagittal MR images show a thin rim of tumour residue along the brainstem including the encased basilar artery. Right cavernous sinus remnant is noted

extent of resection. Although gross total resection should be the goal of each surgical procedure, it is important to consider the quality of life of the operated patients. In this sense, the intra-operative decision of whether to continue dissection and removal or stop is crucial. It has to be noted that post-operative deterioration in KPS scores are likely to return to the baseline at one year and neurological function continues to improve with time.

The primary goal of surgery is to define and protect cranial nerves and vascular structures, as the tumour is progressively dissected free and debulked. Facial nerve stimulation with electromyography and brainstem auditory evoked potentials may be used. Meticulous haemostasis is maintained throughout the procedure to improve the visualisation of critical neurovascular structures. The selected approach should allow access to the vascular base during the initial stages of resection. Initial debulking of the exposed tumour and accessible core is followed by dissection of tumour capsule from surrounding structures. This series of debulking, capsule dissection and capsule removal is repeated until all resectable portions of the tumour have been removed. Due care should be taken to identify and protect en passage cranial nerves and arteries during central debulking. Portions of the tumour that are adherent to the brainstem pia, cranial nerve epineurium or arterial adventitia are left behind to protect the underlying structures.

The extent of surgical resection may be gross total, sub-total (more than 90% tumour volume resection) or partial (less than 90% tumour volume resection). This assessment is done on the basis of post-operative MR scan done at 3 months after surgery. Simpson Grades I and II resection include complete excision of the tumour, including dura and bone and reliable excision of the dural attachment including coagulation.[18]

The preferred approach for resection of petroclival meningiomas is controversial. Some surgeons prefer the retrosigmoid approach in the sitting position, arguing for simplicity of approach;[1,6,8,13,14] and others prefer the petrosal approaches.[5,7,12,17] The transpetrosal partial labyrinthectomy petrous apicoectomy approach or the orbitozygomatic frontotemporal approach takes a much longer time to perform than the retrosigmoid approach. The temporal lobe and cerebellum are retracted, respectively. The transpetrosal approach permits a direct view of the tumour, whilst in the retrosigmoid approach the cranial nerve traction is extensive. Transzygomatic approach may be used when the tumour involves the upper clivus. Tumours involving the lower and mid-clivus are approached by a presigmoid approach, occasionally with division of a non-dominant sinus. Skull base

reconstruction is essential in all approaches to avoid CSF leaks.

Editorial Comment: These tumours should not be handled unless the neurosurgeon has enough training and experience with techniques of skull-base surgery, microneurosurgery and support of a trained neuroanaesthetist.

Surgical Approaches

1. Combined petrosal
   - Transpetrosal partial labyrinthectomy petrous apicoectomy
   - Transpetrosal total petrosectomy
   - Transpetrosal translabyrinthine
2. Frontotemporal orbitozygomatic osteotomy (with transcavernous or pericavernous dissection)
3. Retrosigmoid (with or without combined transcondylar exposure)
4. Middle fossa (preauricular sub-temporal with anterior petrosectomy)

Adjunctive Procedures

Arterial bypass with saphenous vein graft after excision of encased ICA and sigmoid sinus division are the adjunctive procedures that may be required.

Tumour Characteristics

The term petroclival implies an involvement of the petrous apex and upper two-thirds of the clivus. Tumours may be classified on size as small (< 1 cm), medium (1–2.4 cm), large (2.5–4 cm) and giant (> 4 cm). These tumours extend from the petroclival region to the cavernous sinus, sphenoid, middle fossa, tentorium, Meckel's cave, cerebellopontine angle, jugular foramen and foramen magnum. There may be vascular encasement, which affects early post-operative neurological function negatively.

Little et al.[10] have described the following tumour characteristics. Vascular tumours were described as those with a rich blood supply and tendency towards persistent haemorrhage during resection that obscured the resection site. Adherent tumours are firmly attached to the pia, epineurium or vascular adventitia and cannot be dissected free or can be separated using sharp dissection. Fibrous tumours are described as hard or rubbery requiring resection with scissors and knife for most of the tumour removal. Engulfing tumours are those that encircle neurovascular structures with an identifiable intervening plane.

Adherent and fibrous tumours are often tethered to the brainstem and cranial nerves. Dissection of these tumours may lead to excessive manipulation of these vital neural structures resulting in morbidity. Tumour remnants are best left attached to neurovascular structures rather than risk direct injury. Factors that limit extent of resection include hypervasularity, tumour adhesion to neurovascular structures, tumour engulfment of neurovascular structures and firm tumour consistency.[10,12]

Post-Operative Radiotherapy

Residual tumours may be subjected to radiosurgery or radiotherapy. Stereotactic radiosurgery affords excellent tumour control with low morbidity of cavernous sinus remnants, rather than the high risk of cranial neuropathy associated with a cavernous sinus exploration.

Surgical Complications

- New onset/progressive cranial nerve palsies
- Long tract deficits
- Brain infarction/cerebral oedema
- Aspiration pneumonia
- Hydrocephalus
- Cerebrospinal fluid leak
- Brainstem haematoma
- Cerebellar haematoma
- Infection
- Stupor and coma
- Sinus thrombosis

The complex anatomy and difficult exposure of the petroclival region has led to the development of multiple techniques designed to minimise morbidity that may potentially obtain a surgical cure with complete resection. Complete resection is sometimes not possible because of the involvement of multiple regions, severe adherence to or invasion of the brainstem, or encasement of the vertebrobasilar circulation by a very firm tumour. Staged, multiple operations and combined approaches are used to achieve maximal tumour removal with a low rate of morbidity. Little et al.[10] have noted four significant operative risk factors: (1) history of prior operation; (2) pre-operative cranial nerve deficit; (3) tumour adhesiveness, and (4) tumour consistency (fibrous). At long-term follow-up, variables with a persistently negative impact on neurological function were: male sex, basilar artery blood supply, difficult dissection, sub-total resection and early post-operative dysfunction.

Even in the hands of the world's most experienced cranial base microsurgeons only in one third (32%) of the patients could the tumours (of which 80% were large) be removed completely.[12] Sub-total resection was achieved in 43% of the patients and partial resection in 25% of the patients. The real limitation in obtaining radical and safe removal is not inadequate exposure but rather the anatomicopathological characteristics of the tumour. Past experience has taught surgeons to be less aggressive in tumour removal in an effort to avoid injury to involved neurovascular structures.

A remarkable change has occurred in treatment strategies.[12] We have gone from a very aggressive approach that includes cavernous sinus dissection and carotid artery replacement to a less aggressive philosophy whereby tumour remnants are left behind for observation or radiosurgery. This change in surgical philosophy has led to a reduced percentage of patients with completely removed tumours but definitely, more importantly in individual patients, it has resulted in a high percentage of patients

with a satisfactory quality of life. Seventy-two per cent of the surviving patients were able to return to full time work or were retired from full-time work.

A complication rate of 27–73%, especially pertaining to cranial nerve deficits, has been reported. Natarajan et al. report the lowest complication rate of 22%.[12] Surgical mortality has varied between 0% and 17%.

Follow-Up and Survival

Natarajan et al.[12] report that during a mean follow-up period of 101[6] months, out of 150 patients, 87 patients (58%) were alive with disease and 45 (30%) had no evidence of disease. Eighteen patients died during the period of which only one death was the result of tumour recurrence. The majority of patients are able to return to their work with minimal disabilities and have a good quality of life without recurrence or progression.

Long-Term Disabilities

These include diplopia, hearing loss, facial numbness, imbalance, trigeminal neuralgia, diminution of vision, xerophthalmia, facial weakness, limb weakness, lower cranial nerve dysfunction and speech difficulties.

Recurrence and Progression

The recurrence rate of petroclival meningiomas, independent of the resection rate, is low and is uncertain, as observed from the long-term follow-up in the series of Natarajan et al.[12] Recurrence rates for published series have ranged from 0 to 42%.[1,4,7,9,10,13,14] Tumour recurrence seems to be negatively influenced by less extensive resection, malignant pathology and cavernous sinus involvement. The two important features of these tumours are the good outcomes and the low recurrence rates even in non-radically treated patients. The latter finding is intriguing and is at variance with previous detection of a high recurrence rate for surgically treated large cranial base meningiomas. This suggests that petroclival tumours may progress only at a slow rate.

Tumour recurrence after complete excision occurred in 4% of patients (2 out of 48), whereas tumour progression occurred in 5% (5 out of 105) after incomplete resection.[10,12] In only 3 out of 150 patients fatal tumour progression occurred, despite radiosurgery and repeat surgery.[12] Similar results have been observed in a series of 120 patients operated upon by Yasargil.[19] This data suggests that these tumours have a more benign nature than we have suspected. If the patient's symptoms are mild, observation may be the best treatment. This incidence is independent of the availability of gamma knife radiosurgery, which does not warrant tumour control in every case. Petroclival meningiomas have low MIB-1 indices[11] comparable to spinal meningiomas than to parasagittal tumours.

CONCLUSION

The ultimate goal of surgical treatment is a complete resection which is, however, not always possible due to the consistency of the tumour, multi-compartment involvement, adherence to the brainstem or encasement of vertebrobasilar branches. The excellent quality of life if the tumour is radically resected warrants aggressive but judicious tumour resection with or without radiosurgical treatment of tumour remnants.

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173 Foramen Magnum Meningiomas

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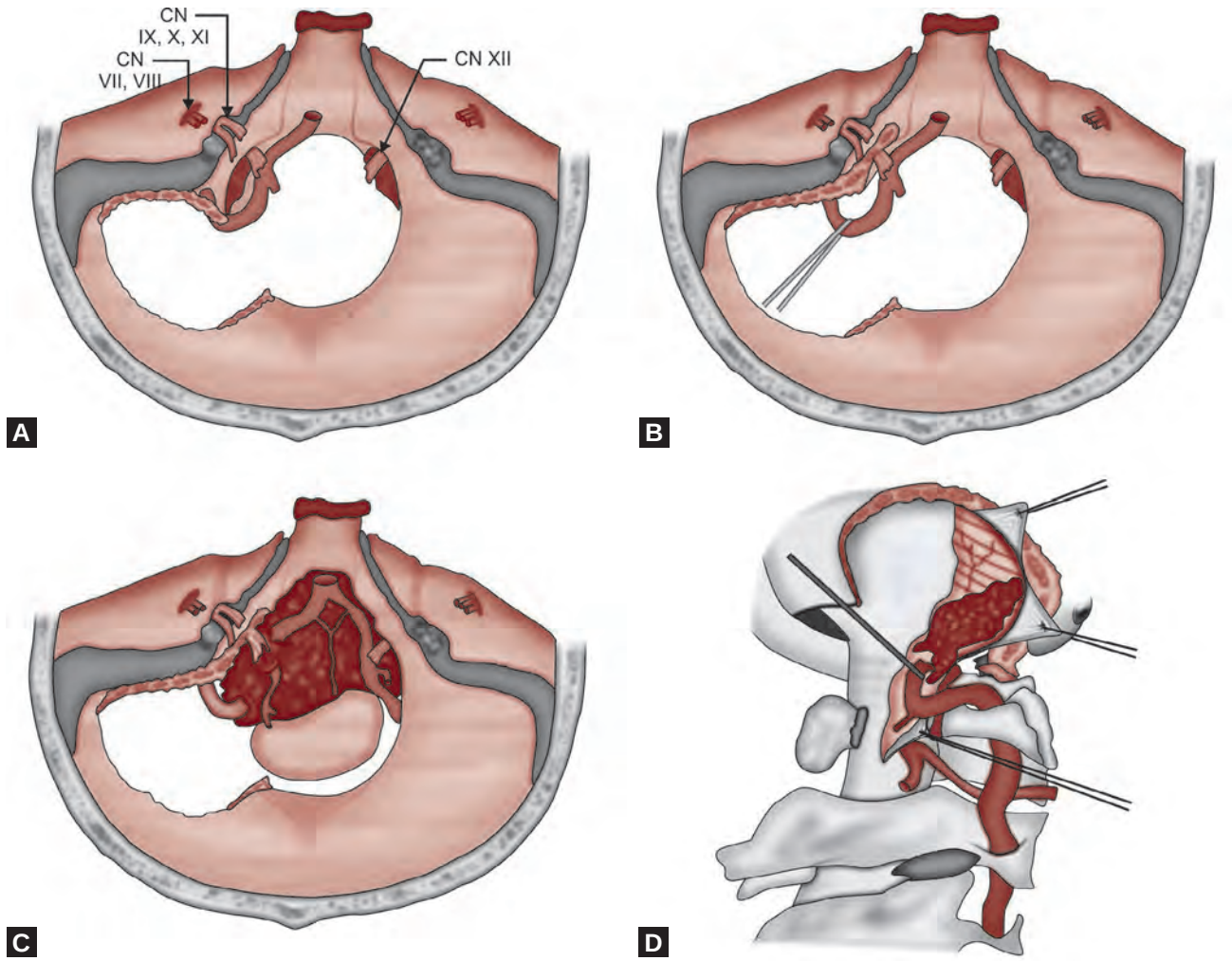
INTRODUCTION

Tumours at the foramen magnum comprise some of the most challenging and complex lesions that the neurosurgeon must contend with.[9] The anatomical area of the anterior foramen magnum is comprised of brainstem structures, cranial nerves and blood vessels all in a tight geometric arrangement. Added to this is the association of a variety of tumours that can further distort this anatomy, making a safe resection all the more challenging.[13] The recent development of microsurgical skull-base approaches has greatly opened up these once treacherous corridors for a more safe and successful surgical resection, over the more historical and traditional neurosurgical approaches (Figs 1A to D). Most tumours found at the foramen magnum are located anterolaterally,



Figs 1A to D: (A) An axial view of the standard lateral suboccipital craniectomy. (B) Same view, after partial medial condylar resection. This allows for mobilisation of the ipsilateral vertebral artery, enabling access to the lower clivus. (C) The same illustration, now with intradural tumour *in situ*. The advantage of partial condylar resection is demonstrated in enabling enhanced visualisation of the anterior portion of the tumour and its attachment after posterior mobilisation of the vertebral artery. (D) Lateral view of the same tumour again illustrating partial condylar resection with medial mobilisation of the vertebral artery as well

however, most approaches to these lesions have historically been strictly posterior. This review will briefly outline the three general approaches to the anterior foramen magnum that are employed by neurosurgeons:

1. Posterior/posterolateral suboccipital
2. Transoral
3. Extreme lateral transcondylar

While each approach has many technical modifications and many associated eponyms, the basic approach is the same within each category. Despite the specific pathology of the lesions at the anterior foramen magnum, the general surgical principles employed in their surgical resection are similar. Meningiomas at the foramen magnum will be used as the surgical model for the purposes of discussion in this review, as almost all large series reports and discussions have focused on these tumours. The remaining tumours are often described in anecdotal and case reports only.

The choice of surgical approach is determined by the unique pathological anatomy and each case is evaluated independently. Despite the variety of tumour pathology encountered, the general principles of a meticulous preoperative planning based on the microanatomical details of each patient, as well as an individualised tailoring of the surgical approach is similar for all cases. In the case of meningiomas, the risk of tumour recurrence is based on the tumour resection grade (whether Simpson grade[33] or the modified Kobayashi system). We as well as most authors have adopted the Simpson scale as applied to meningiomas to involve three categories:

1. Gross-total resection, including excision of the dural attachment and drilling of adjacent bone (Simpson I and II)
2. Near-total resection, in which a few millimetres of insulated and cauterised tumour were left on the vertebral artery (VA) or other vital structure if the arachnoid plane could not be established (Simpson grade III)
3. Subtotal removal of more than 50% of the tumour (Simpson grade IV)

The general surgical determinants are:

- Tumour location with respect to the foramen magnum
- Anterior-posterior relationship of the tumour with respect to the caudal medulla/spinal cord
- Rostral-caudal extent
- Laterality
- Encasement/involvement of the VA[35,39]

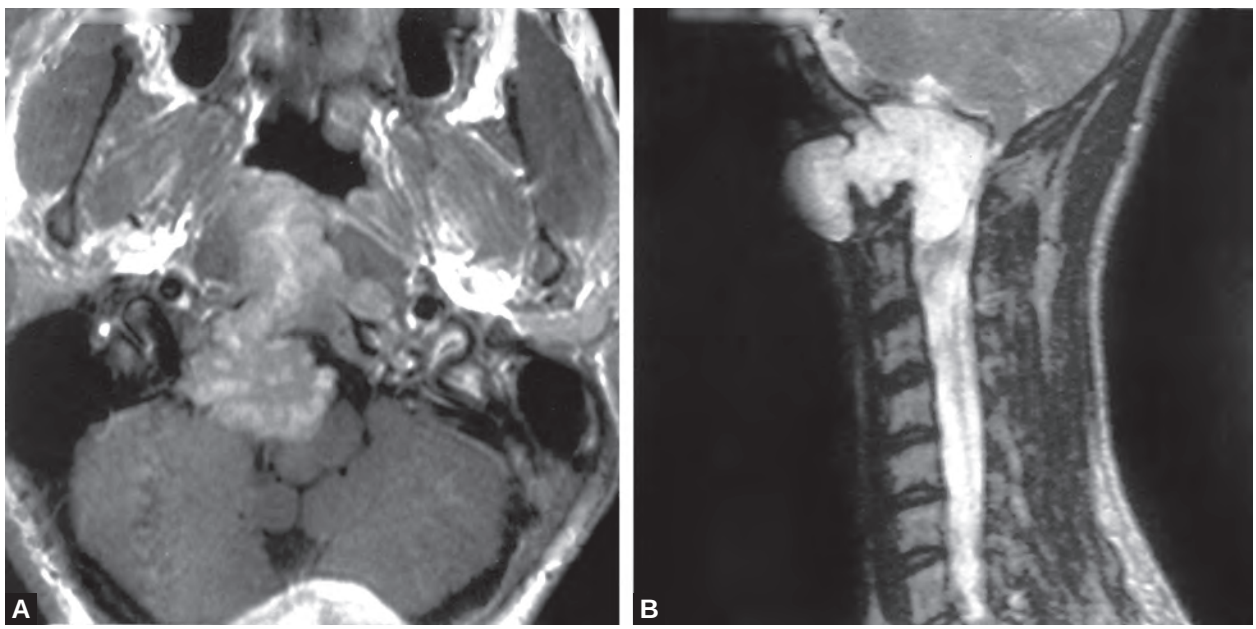
Individual surgeons have defined their surgical determinants more specifically based on their operative preferences in regards to the approaches that they employ. The surgical corridor involves the space between the lateral margin of the cervicomedullary junction and the medial aspect of the occipital condyle. Corridor is defined as "narrow" if it provides a diameter of access to the tumour of less than 1 cm; "adequate" if it is greater than 1 cm but less than 2 cm; and "large" if greater than 2 cm.

TUMOURS AT THE FORAMEN MAGNUM

Tumours at the foramen magnum are characteristically difficult to diagnose clinically. The wide spectrum of presenting signs and symptoms, combined with their often insidious onset have been known to mimic many more common neurological diseases, such as cervical spondylosis, multiple sclerosis, and other degenerating diseases.[13]

The differential diagnosis of extra-axial foramen magnum tumours include:

- Meningiomas as the most common chordomas (Figs 2A and B)



Figs 2A and B: (A) Magnetic resonance imaging T1 axial view with contrast. (B) T2 sagittal view demonstrating an extensive chordoma occupying multiple compartments including the occipital condyle, the lateral mass of C1, clivus, and retropharynx

- Neurilemmomas
- Epidermoids
- Chondroma
- Chondrosarcomas
- Metastatic lesions[32]

While meningiomas at the foramen magnum are the most common tumour at this location, they are still very rare lesions when compared to all intracranial tumours, and account for only 0.3–3.2% of all meningiomas and between 4% and 15% of all posterior fossa meningiomas altogether.[35,39]

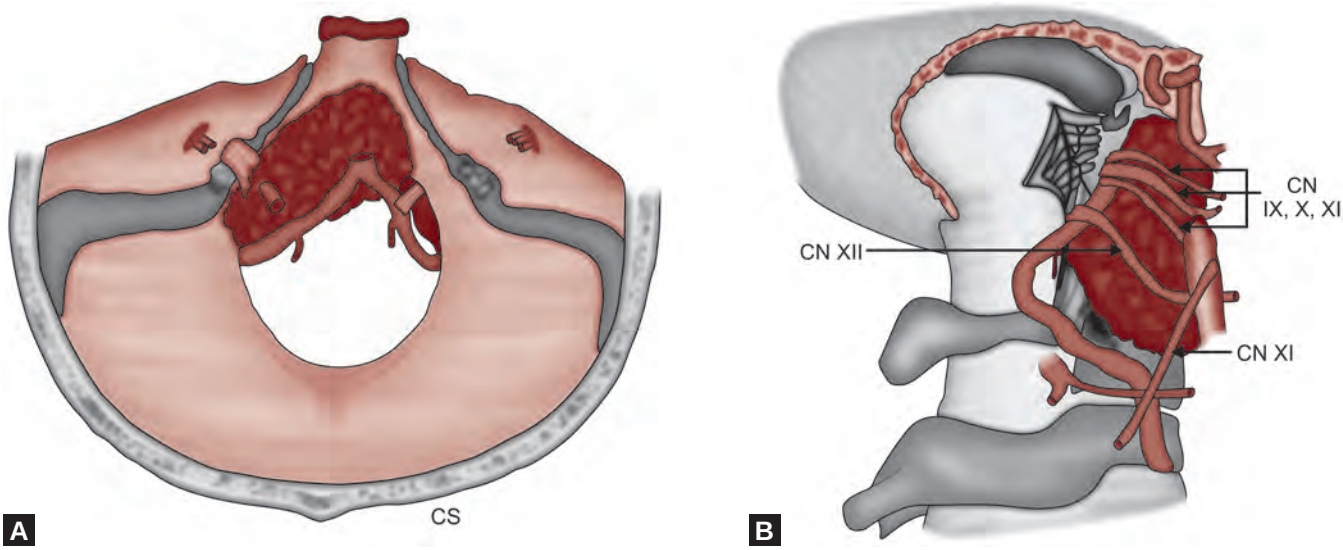
To understand the surgical approaches to the anterior foramen magnum, it is first crucial to define the anatomical terms that comprise the structures in this location. The foramen magnum is a skull base foramen that is composed of the occipital bone. The occipital bone surrounds the foramen magnum[26] and is composed of two parts: the posterior squamosal and the narrower anterior part (basal extension of the clivus). The anterolateral walls are formed by the occipital condyles.[38] The contents of the foramen magnum consist of the caudal medulla, cranial nerve XI (entering the skull), VA, and the anterior and posterior spinal arteries. The XI cranial nerve is the only cranial nerve that passes through the foramen magnum. Its spinal component arises as a series of rootlets midway between the ventral and dorsal rootlets of the upper cervical cord. The transition between medulla and spinal cord is arbitrarily set to be at the upper limit of the dorsal and ventral rootlets forming the first cervical nerve. The rootlets of the XII cranial nerve exit the anterior medulla and pass behind the VA to reach the hypoglossal canal just above and anterior to the occipital condyles. The specific orientation of the VA at this location and its course through the transverse foramina and through the intracranial dura is what corresponds to the landmarks to the surgical approaches to this region. The VA enters the dura inferior to the lateral edge of the foramen magnum through a tunnel approximately 5 mm in length. The posterior inferior cerebellar artery usually has an intradural origin, but may arise below the level of the foramen magnum. A detailed knowledge of this anatomy, practiced in cadaveric dissection, is crucial before attempting these operations for the first time.

GENERAL PERI-OPERATIVE CLINICAL EVALUATION AND NEUROPHYSIOLOGICAL MONITORING

Once the decision has been made to proceed with surgery, all patients should undergo a detailed study of their neurological function, independent of their clinical neurological examination. The critical location of these tumours to vital neurological and vascular structures necessitates a more detailed cranial nerve study. Ophthalmological, audiometric, and electromyographic studies can be supplemented to the pre-operative assessment of the patient's baseline function.[3] Cranial nerves IX through XII are especially important, and a detailed swallowing study and otolaryngological study of the vocal cords and the larynx are also useful as a pre-operative baseline. Careful assessment of the patient's ability to protect the airway is mandatory, and early tracheostomy may be advisable to avoid aspiration pneumonitis. The importance of preserving lower cranial nerve function is crucial in the intra-operative procedure. We employ intra-operative neurophysiological monitoring to prevent injury to the cranial nerves. Somatosensory evoked potentials and brainstem auditory evoked potentials are monitored bilaterally.[4,40] Electromyographic monitoring of the vagal, accessory and hypoglossal nerves are done on the ipsilateral side (or bilaterally if necessary). The vagal nerve can be monitored with an electromyography electrode-endotracheal tube or by laryngeal surface electrode that is placed after intubation. The accessory and hypoglossal nerves are monitored directly with electrodes placed on the ipsilateral trapezius and the inferior aspect of the tongue, respectively. We believe that this type of monitoring helps to preserve cranial nerve function during surgery. The use of intra-operative neurophysiological monitoring prevents the use of muscle relaxants during many stages of the operation. Occasionally, burst suppression with short-acting barbiturates can also be used for cerebral protection. We employ 24 hours of broad-spectrum IV antibiotics and peri-operative steroids at the time of surgery.

THE POSTERIOR/POSTEROLATERAL SUBOCCIPITAL APPROACH

The posterior suboccipital approach and its modifications (posterolateral) have been the traditional approach for lesions of the foramen magnum for many years (Figs 3A and B). The approach typically consists of a suboccipital craniectomy and partial to complete laminectomy of C1/C2 depending on the size of the tumour.[12] A vertical midline or hockey-stick suboccipital incision is used. The prone, three-quarter prone ("park bench") or semi-sitting ("slouch") may be utilised depending upon the surgeon's preference. The vertical incision is used for lesions situated in the upper spinal canal and posterolaterally at or above the foramen magnum. The hockey-stick incision is selected if the lesion extends anterior or anterolateral to the brainstem toward the jugular foramen or the cerebellopontine angle (CPA). This incision allows for removal of the full posterior rim of the foramen magnum, the posterior elements of the atlas and axis and in addition, a unilateral suboccipital craniectomy of sufficient size to expose the anterolateral surface of the brainstem and the nerves in the CPA. The actual amount of the suboccipital craniectomy and cervical laminectomy varies depending upon the rostral/caudal extent of the tumour. For anteriorly located tumours in this approach, the spinal cord is often displaced dorsally and rotated away from the side on which the bulk of the tumour mass is located.



Figs 3A and B: (A) An axial view of an extradural tumour demonstrating bony involvement. (B) Lateral view demonstrating suboccipital craniectomy with mastoidectomy, medial mobilisation of the ipsilateral vertebral artery (after opening the C1 transverse foramen), condylar resection, and ligation of the sigmoid sinus and internal jugular vein

The ventral cervical rootlets are usually displaced dorsally by these tumours. Early identification of these rootlets is crucial as they must be separated from the dorsal rootlets and dentate ligaments, as well as the spinal rootlets of the XI cranial nerve that can often be draped directly over the tumour. During the tumour removal it is also important not to injure the radicular vessels running with the upper cervical roots, since they supply blood to the spinal cord. An important landmark in the posterior approach to anteriorly placed tumours is the most rostral dentate ligament that lies at the level of the foramen magnum and more importantly indicates the point at which the VA pierces the dura. The upper 2–3 dentate ligaments may be sectioned with caution to reduce traction on the spinal cord and to allow for gentle rotation of the cord to facilitate tumour removal.

The advantage of the posterior suboccipital approach to anteriorly based tumours is the familiarity that most neurosurgeons feel with the anatomy and the technique, as this approach is employed for many lesions of the posterior fossa. A laminectomy and its extension into the pedicle may be sufficient to allow removal of ventral tumours when the tumour is not attached by a broad base and there is little adhesion between it and the anterior surface of the cord. The disadvantages of this technique are, however, the inability to safely reach the anterior midline or contralateral component of the tumour. In the case of recurrent or broad-based foramen magnum meningioma, however, the cord-tumour interface and the base of the tumour must be adequately visualised for safe or total removal. This technique relies on a good arachnoid plane existing between the tumour and the spinal cord and often does require division of the upper cervical rootlets and rotation of the spinal cord. The only technique used to help deliver the anterior portion of the tumour with this approach is to pull the lesion into the field along with the surgical debulking, which can be ineffective. The posterolateral modifications of the standard posterior approach as described by George[11] involve a lateral enlargement of the usual posterior opening via exposure of the sigmoid sinus via a posterior mastoidectomy down to the jugular foramen. In those cases in which the tumour extends laterally into the jugular foramen, the sigmoid sinus is sectioned between the vertical and horizontal portions. This technique requires exposure of the VA within its periosteal sheath from C2 to the intradural component. The exposure of the VA by this method allows for superior and lateral retraction of the VA, or medial displacement of the VA, requiring resection of the transverse foramen of C1 and giving access to the tumour lateral to the VA. Other modifications to the posterior approach have included a partial condylar resection,[12] or condylar drilling[25] to improve anterior exposure. These modifications, however, are still limited by those tumours in which there is arachnoid scarring, en plaque formation, and especially post-operative recurrence.[25]

TRANSORAL/TRANSPHARYNGEAL APPROACH

The direct anterior approaches consist of the transcervical or transoral which involve removal of the vertebral bodies to expose the intradural portion of the tumour. These approaches are most suitable for anterior extradural lesions, where direct midline exposure is the most relevant. The transoral route does provide for the most direct route to the clivus and the ventral foramen magnum, but it does have many limitations.

The patient can be positioned one of three ways:

1. Supine with slight neck extension
2. Modified lateral
3. Semi-sitting ("slouching")

A C-arm fluoroscope is often used to help identify bony landmarks during the operation. This surgery

has specialised transoral retractor systems (Crockard, Dingman, McGarver) that allow for tongue, pharyngeal and longus colli retraction. The surgical technique[8,18] generally involves early identification of the anterior tubercle of C1 and a vertical midline incision on the posterior wall of the pharynx. The incision extends from the inferior portion of the clivus to the base of the odontoid (and can be modified accordingly in lower lesions). The anterior arch of C1 is exposed, and the fascia-muscle layers are retracted laterally approximately 20 mm on either side. The VA is 33 mm from the midline at C1, and the hypoglossal foramen is 7.5 mm above the arch of C1 and 18 mm from the midline. The jugular foramen is 26 mm from the midline. After adequate exposure, self-retaining retractors are placed against the pre-vertebral fascia and opened, providing for a hexagonally-shaped opening. A fine-cutting burr is used to drill the anterior arch of C1 and the odontoid (from base to tip). Upon reaching the posterior cortex, the apical and lateral ligaments are visualised and sectioned. The posterior longitudinal ligament can be identified inferiorly and opened to expose the dura. The superoinferior extent of the exposure can be enlarged by the addition of maxillectomy above and mandibulotomy and glossotomy below. The lateral exposure is the limiting factor, as it is not safe to expose greater than 1 cm to either side of the midline. The lateral limitations are due to the pterygoid plates, the occipital condyles and the hypoglossal canals.

The closure in the transoral approach is especially crucial due to the issue of cerebrospinal fluid (CSF) leakage, fistula and post-operative infection because of the potentially contaminated avenue of exposure. The dura is the main determinant of the complexity of the closure, as a good dural closure is the best protection from post-operative meningitis. A multi-layered closure using fibrin glue plus abdominal fat and/or muscle is often employed with post-operative CSF diversion with either a spinal drain or a lumboperitoneal shunt.[8] The specific issue of airway management is the most important issue in the post-operative period, and the nasotracheal tube is often kept in place until pharyngeal swelling has reduced (facilitated by hydrocortisone cream applied locally). Poor wound healing of the pharyngeal incision or protracted CSF leak may also require a more extensive operation by a maxillotomy approach, with repair using a temporalis muscle flap or a microvascular free-flap transfer.[8]

THE EXTREME LATERAL TRANSCONDYLAR APPROACH

The extreme lateral approach[28,29,30] provides excellent exposure of the anterior foramen magnum and allows for proximal control of the VA. This approach has, over the years, taken on many names; however, it is essentially one approach in which there are variations in the patient's position, the skin incision, muscle reflection, the VA complex transposition, amount of condyle drilling and craniotomy. The extreme lateral transcondylar approach (ELTA) has evolved over the recent decades from the initial lateral modifications of the suboccipital approach.[14,16] The ELTA as described by Sen and Sekhar,[28] and Bertalanffy and Seeger[6] incorporates the medial mobilisation of the VA from the dural entrance point to C2, and the resection of the occipital condyle and the lateral mass of C1 (either partially or totally). The ELTA is suitable for both intradural and extradural lesions, allows control of the VA, permits dissection of the brainstem-tumour interface tangentially along this plane, and avoids traversing contaminated spaces. The approach has gained wide acceptance because it avoids entering the contaminated oral cavity, provides early visualisation of the VA and creates wider surgical exposure.[6,11]

Specific pre-operative studies are critical in surgical planning. Magnetic resonance imaging with magnetic resonance venography/magnetic resonance angiography (MRV/MRA) and computerised tomography scanning are routinely done. The MRV/MRA imaging provides information regarding the regional vascular anatomy, including the patency and dominance of the vertebral arteries and dural sinuses. We only use angiography for unresolved or aberrant findings on the MRV/MRA. The patient position can be either lateral or supine with the head turned away from the surgeon (preferred when other approaches are being incorporated). A detailed understanding of the suboccipital muscles (e.g. sternocleidomastoid, splenius capitis, semispinalis and longissimus capitis, superior and inferior obliques and the recti capitis major and minor) is crucial in the ELTA procedure, much more so than in a standard posterior midline approach.[35,38] We use either the inverted U-shaped incision or the C-shaped curvilinear incision. In the U-shaped incision the skin flap is completely away from the area of the operation and allows for the reflection of all the muscles as one large flap. We have used the C-shaped incision more commonly which begins in the retroauricular area and extends into the cervical area along the skin crease. The sternocleidomastoid muscle and fascia are reflected forward with the incision whenever possible, depending on the extent of exposure required. The surgical approach of ELTA essentially involves six steps:

1. C-1 hemilaminectomy and suboccipital craniectomy (small, extending 3 cm posterior to the sigmoid sinus) with unroofing of the sigmoid sinus
2. Partial resection of the occipital condyle (up to the hypoglossal canal)
3. Removal of the jugular tubercle
4. Mastoidectomy (limited to the labyrinth and the Fallopian canal) and retraction of the sigmoid sinus
5. Resection of the lateral mass of C1 with mobilisation of the VA (in the suboccipital triangle)
6. Resection of the remaining portion of the occipital condyle

The exposure involves removal of part of the occipital condyle and the C1 facet, to facilitate ventral exposure of the medullocervical junction with or without transposing the VA from the C1 transverse canal.[10] Condylectomy considerably shortens the distance to the anterior foramen magnum, especially in the superior corridor and widens both transverse and longitudinal planes in the inferior corridor allowing the surgeon to get greater access to work on these lesions.[2] Patterson[22] and Samii et al.[25] suggested that most lesions of the lower clivus can be removed without extensive dissection of the ELTA, which is time consuming. They also considered that condylar resection is unnecessary which may potentially contribute to the morbidity rate by requiring occipitocervical fusion.

To maximise exposure, suboccipital craniectomy, a lower mastoidectomy to skeletonise the lower part of the sigmoid sinus and a partial C1 laminectomy are necessary. The dura must be completely opened around the VA entry area before mobilising this vessel to work anterior to the artery during tumour resection. The dorsal ramus of C2 that runs posterior to the VA between C1 and C2 can serve as a guide to the artery as a landmark. A prominent venous plexus that connects with the condylar emissary vein and the epidural venous plexus surround the VA.[27,31] The presence of a patent jugular bulb can hinder tumour removal medial to this structure. When the jugular bulb is occluded (as is more often the case in an extradural tumour), the sigmoid sinus and the internal jugular vein are ligated above and below the bulb and the bulb is opened directly to remove tumour from the IX, X and XI cranial nerves. This particular technique allows for excellent exposure of the space anterior to the foramen magnum and whole craniocervical junction (from the level of the internal auditory canal to the upper cervical spine). For extradural tumours, the occipital condyle resection extends more anterior to excise the entire condyle. If the tumour extends into the lower clivus, one can resect it by working through the petrous bone and the inferior occipital area. Tumours that extend medially and superiorly can be resected with a combined subtemporal infratemporal approach. For intradural tumours, the dura is opened first vertically, just medial to the entrance of the VA. The arachnoid membrane of the cerebellomedullary cistern is opened and the intradural tumour is often easily visualised.[5] Resection of the C1 intradural rootlets and the upper dentate ligaments will facilitate tumour exposure to better resection. Suhardja did a cadaveric study and emphasised that ELTA provided a significantly greater area of exposure than the retrosigmoid approach.[36]

The dural closure in ETLA can be difficult, and a combination of dural graft and fibrin sealant is often used with the possible addition of local muscle/fat. A spinal drain is often used as a CSF diversion to facilitate wound closure. If more than a partial resection of the occipital condyle is performed, stabilisation may be needed. This occipital-cervical fusion and instrumentation can be performed at the same sitting or as a different stage. Occipitocervical fusion is recommended in condylar resections of 50% or greater.[37]

Complications in this approach are psuedo-meningocoele, CSF leakage, lower cranial nerve injury (especially IX, X and XI) and craniocervical instability.

EXTENDED ENDOSCOPIC ENDONASAL APPROACHES TO SKULL BASE

The standard transnasal endoscopic procedures have been recently expanded to remove lesions involving the skull base. These approaches to caudally located midline anterior skull base and cervicomedullary lesions are feasible and hold great potential for decreased morbidity.[17] The midline skull base is an anatomical area extending from the anterior limit of the anterior cranial fossa down to the anterior border of the foramen magnum. Resection of lesions involving this area requires a variety of innovative skull base approaches. These include anterior, anterolateral and posterolateral routes, performed either alone or in combination. These approaches provide a direct anatomical route to the lesion without traversing any major neurovascular structures, obviating brain retraction.[7]

Approach

The clivus can be localised by orienting the endoscope + 15 degrees rostrally. The inferior wall of the sphenoid sinus and vomer are resected and the overlying mucosa is retracted laterally till the Vidian nerve is seen. This provides sufficient exposure of the clivus. The safe lateral limit of the surgical corridor is the Vidian nerve. The clivus is then resected till the foramen magnum inferiorly. The safe lateral limit of the resection in this step is the proximal cavernous and the distal petrosal portions of the internal carotid artery (ICA). This resection provides a wide exposure of the clival dura. Care should be taken not to injure the basilar plexus, the abducens nerve which passes through the basilar plexus, and the paraclival portion of the ICA. After dural incision, the prepontine cistern and the basilar artery are exposed widely.[1] The disadvantages of this approach are a restricted field of surgery, danger of an inadequate dural repair with CSF leakage and potential for meningitis.[7] In tumours which extend laterally transcondylar and transjugular tubercle "far medial" expansions of the endoscopic endonasal approach to the inferior-third of the clivus provides a better corridor to the inferior clival and the ventrolateral surfaces of pontomedullary junction and cervicomedullary junction lesions.[19]

RADIOSURGERY

The ideal treatment of meningiomas is a safe and complete resection. If contraindications to surgery exist or if the patient elects not to undergo surgical

resection, then radiotherapy should be considered. Because of the vital and critical anatomy within the foramen magnum and the size of most tumours (less than 3 cm in maximum dimension), focused gamma knife surgery is recommended rather than standard conformal radiotherapy.[23] In patients with small residual tumours who are under observation, if the tumour grows, then gamma knife surgery is recommended.[15,20,21]

CONCLUSION

Advances in neurosurgical microsurgical techniques, detailed anatomical understanding, anaesthetic protocols and recent developments in skull-base surgery have dramatically reduced the once very high mortality associated with surgery for tumours located in the anterior foramen magnum. However, despite all these advancements this subset of tumour continues to remain one of the most challenging tumours to treat in all of neurosurgery. While the traditional posterior midline suboccipital approach is safe and useful in most tumours in the anterior foramen magnum, the additional benefits provided by the ELTA far outweigh most other approaches. We have reserved the transoral approach strictly for midline extradural lesions and do not use this approach for intradural lesions or for any lesion with lateral extensions beyond 30 mm from the midline. The other operative complications such as crossing of a contaminated operative field, CSF fistula, meningitis, difficult dural closure and destabilisation of the craniovertebral junction have all made the transoral approach less useful. In ETLA, there exists a wider surgical area of exposure of the tumour-cord/brainstem interface as well as the ventral dura without the need for retraction of the neural structures. The value of condylectomy alone both shortens the distance to the anterior foramen magnum and widens the lateral exposure for a better surgical angle for resection.[34] Control of the involved VA is possible and devascularisation of the tumour can be accomplished early in the operation. While variations of the ETLA procedure already exist and have been reported,[24] the final approach and its various modifications should always be tailored to the unique tumour presentation and the specific goals of surgery in the treatment of the individual patient. To totally resect type I foramen magnum tumours, the ELTA is an optimal choice. Type II foramen magnum tumours can be totally removed with a good prognosis.[41]

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174 Intraventricular Meningiomas

Harjinder S Bhatoe, Prakash Singh, Vibha Dutta

INTRODUCTION

Intraventricular meningiomas, together with deep Sylvian meningiomas, constitute the entity of "meningiomas without dural attachment." The cerebral ventricles are unusual sites for occurrence of tumours of the central nervous system. These intraventricular meningiomas, which are rare tumours, account for 0.5–5% of all intracranial meningiomas.[9] The rarity of these tumours underscores the lack of controlled studies and extensive experience and knowledge about the natural history and pathobiology of these tumours. The medical literature is peppered with a few case series of lateral ventricular meningiomas and still fewer case reports of meningiomas involving the third and fourth ventricles. The largest experience in managing these tumours is probably credited to Konovalov et al.[14]

ORIGIN

Meningiomas arise from arachnoid cap cells, which are specialised cells in arachnoid granulations. Intraventricular meningiomas too arise from arachnoid cells, found within the choroid plexus.[16] The presence of arachnoid cell nests in the normal choroid plexus stroma has been illustrated in the literature and a thorough examination of the choroid plexus will reveal a small or large collection of these cells.[8,12,20] The presence of these cells in the choroid plexus has been explained by various workers. The choroid plexus develops initially from an invagination of mesenchyme in the thin roof area of the myelencephalon, during the 6th week of intrauterine life.[22] In the 7–9 week human embryo, the telencephalic choroid plexus has started to develop a loose mesenchymal stroma, covered by a layer of cells derived from ependyma.[7] Arachnoid tissue is carried with the choroid plexus, as the ventricular system invaginates[15] and by 20–40 weeks of intrauterine life, the central stroma of the choroid plexus contains meningocytes, connective tissue and blood vessels.[20] Meningothelial inclusion bodies are normally found in the arachnoid and choroidal tela and meningiomas arise from this mesenchymal stroma of the choroid plexus.[18]

The ventricles are a rare site for occurrence of meningiomas. The incidence of meningiomas of lateral ventricles is variously reported 0.5–5% of all intracranial meningiomas, at least in adults.[1] For some unexplained reasons, meningiomas of the lateral ventricles occur more frequently in the left than in the right one (up to 60% of all lateral ventricular meningiomas).[6,9,10] Since the choroid plexus is more bulky in the lateral ventricles, the incidence of lateral ventricular meningiomas is higher, as compared to those in the third or fourth ventricle. In the lateral ventricles, the tumour originates from the choroid plexus in the region between the posterior portion of the body of the lateral ventricle and the entrance to the inferior horn.[14] This origin explains the predominant location of the tumour in the trigone. Tumour restricted to the frontal horn is extremely rare.[14] Meningiomas are rare in the third and fourth ventricle: an extensive review has shown 83 meningiomas in the third and only 35 meningiomas in the fourth ventricle.[17] Fourth ventricular meningiomas arise from the inferior tela, when they are partly intracerebellar, and from choroid plexus, when they are true intraventricular tumours.

PATHOLOGY AND CLINICAL COURSE

The ventricles of the brain provide space for tumour expansion, and till the CSF pathways are mechanically occluded, manifestations are mild and non-specific. Although Cushing described clinical features of intralateral ventricular tumours, diagnosis of these tumours is usually made after imaging procedures. Regardless of their location, most of the clinical symptoms are due to raised intracranial pressure.[4] Lesions grow into the ventricular cavity till they produce obstructive hydrocephalus. Visual field deficits may be seen in 25% of patients.[9] Seizures are rare.[21] Cerebellar signs may be seen in fourth ventricular tumours and hypothalamic features with or without endocrinopathy may be seen in third ventricular tumours. Manifestations of neurofibromatosis type 2 (NF2) syndrome may be evident on clinical and neurological evaluation. Meningiomas are more common in females, but Bhatoe et al.[4] saw only six out of fifteen female patients with intraventricular meningiomas; two of these patients had features of NF2. Although described to be common in childhood[9,13,21] also, Bhatoe et al. did not see any child with intraventricular meningioma.[4]

The rarity of intraventricular meningiomas, in contrast to those with dural attachment, may also be due to yet unknown factors. Multiple meningiomas arising

from the dura are regarded as due to inherent multicentricity of the dural foci, possibly influenced by hormonal factors.[19] Although there are no reports of multiple intraventricular meningiomas, they have been known to coexist with spinal meningiomas,[11] vestibular schwannomas and optic nerve sheath meningiomas as part of the NF2 syndrome. Meningiomas of the third ventricle, occurring primarily in young children, have a tendency to grow into both lateral ventricles as a trifoliate tumour.

HISTOPATHOLOGY

Intraventricular meningiomas can be of any of the histopathological types of the tumour, as per the WHO classification of meningiomas. These are predominantly either fibrous, fibroblastic or psammomatous.[1] Angiomatous type was the most common type seen in our series, followed by meningothelial, fibroblastic and psammomatous/osteoblastic types. The structure of psammoma bodies in the choroid plexus is very similar to that in meningiomas.[2] In general, meningiomas are diagnosed by morphological features alone. The expression of oestrogen receptor is low in these tumours, and two thirds of these patients are positive for progesterone receptors.[5] Whether these findings can be applicable to intraventricular meningiomas remains yet to be seen, as are the cytogenetic features, like deletion of chromosomes 1 and 14, seen in meningiomas at other sites. In our series, histopathology of the tumours was varied, as given below:[4]

Lateral ventricular tumours:

Psammomatous/osteoblastic	2
Macrocystic angiomatous	1
Angiomatous	5
Meningothelial	4
Papillary	1

Third ventricular tumour

Angiomatous	1

Fourth ventricular tumours

Fibroblastic	1
Meningothelial	1

Nine of these patients exhibited positivity for epithelial membrane antigen and vimentin. The psammomatous meningioma showed densely packed psammoma bodies in an ossified matrix. All sixteen patients have been followed up over 3–10 years, with no evidence of recurrence. Patients with NF2 have undergone surgery for associated tumours.

IMAGING

Lateral ventricular meningiomas are seen most commonly in the trigone or atrium of the ventricle (Fig. 1). Third ventricular meningiomas are seen in the anterior third ventricle, while fourth ventricular meningiomas can appear partially intracerebellar (when they arise from the inferior tela) and as tumours surrounded by CSF when they arise from the choroid plexus. Intraventricular meningiomas may occasionally be densely calcified so as to be visible on plain skull radiograph.[3] MRI is the most valuable imaging modality for evaluating intraventricular meningiomas. The tumour is generally lobulated and appears isointense on T1-weighted and T2-weighted images. Calcification, nodular or punctate, is seen as an area of signal loss. The tumour enhances uniformly with intravenous gadolinium (Fig. 2). Uncommonly, the tumour may be cystic. Cerebral oedema is unusual. The presence of other lesions, like optic nerve sheath tumour and vestibular schwannoma, indicate underlying NF2. Computed tomography supplements MRI by showing calcification. Digital subtraction angiography can be utilised for assessment of the vascularity and location of the principal feeder. Lateral ventricular tumours occurring in the body are fed by the lateral posterior choroidal vessels, while those in the temporal horn receive their blood supply from the anterior choroidal artery. Tumours in

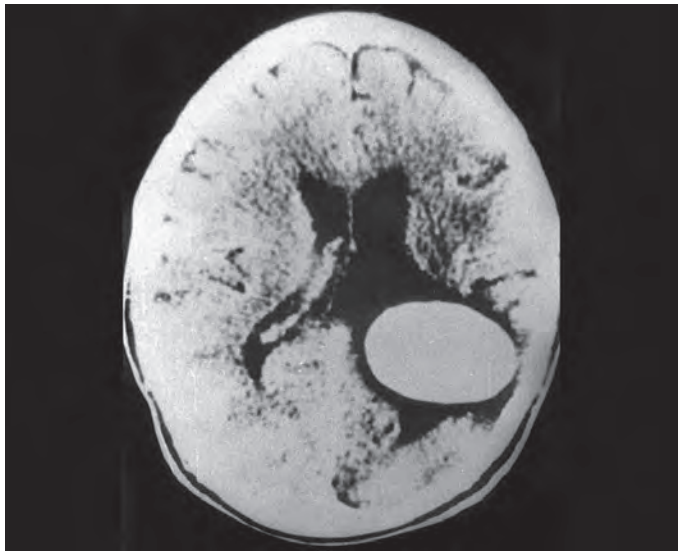

Fig. 1: CT scan of the brain shows well circumscribed lesion in the trigone of the lateral ventricle

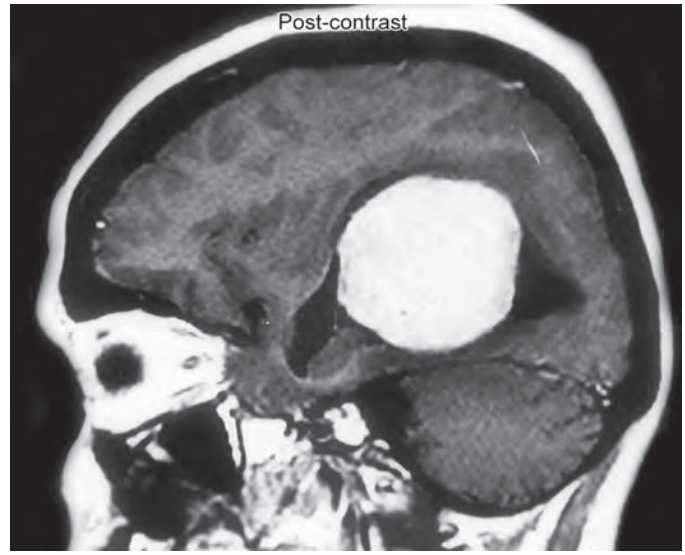

Fig. 2: MRI scan of the brain sagittal view showing uniformly enhancing lesion within the lateral ventricle

the atrium are supplied by both anterior and posterior choroidal arteries. Third ventricular tumours are supplied by the medial posterior choroidal vessels, while fourth ventricular tumours derive their blood supply from choroidal branches of the posterior inferior cerebellar artery (PICA).[14]

SURGICAL MANAGEMENT

Surgical management has to be individualised for each patient, depending upon the tumour location and its vascularity, involved ventricle and the presence of other tumours (as in NF2). Meningiomas are solid, discreet lesions that can be totally excised. The strategy should be to reach the blood supply with minimum neural section/retraction, coagulation of the tumour prior to incision, internal decompression and occluding of the feeding vessel(s). Magnification greatly aids in tumour excision. Since the surgical approach invariably means entry through neural tissue, neurological morbidity due to the approach has to be borne in mind.

Lateral Ventricular Tumours

The proximity of the optic radiation, left sided preponderance with potential for speech and cognitive deficits, the "C" shape of the lateral ventricle and aiming for early control of the vascular pedicle have led to a plethora of surgical approaches for meningiomas of the lateral ventricle. These approaches may be through the cerebral convexity (temporal, parietotemporal, parieto-occipital), involving occipital lobectomy, or through the corpus callosum.[9] Most of these approaches described lead to iatrogenic morbidity in the form of visual field deficit, disconnection syndrome or speech and cognitive deficits. The parieto-occipital approach follows a cranio-caudal orientation parallel to the optic radiation over the cerebral convexity, and is least likely to damage the optic radiation. Moreover, this is often the thinnest region overlying the trigone and the tumour. The capsule is extensively coagulated with bipolar cautery and the tumour is cored out through the area of coagulation, till it can be mobilised to expose its feeding vessel(s) from the posterior choroidal artery. These vessels are then coagulated and divided and the remaining tumour can then be excised in one piece. Initial debulking allows the tumour to be turned, so that the feeding choroidal vessel can be tackled effectively; early attempts to control the feeding vessel may result in undesirable brain retraction and its sequelae. While early control of the feeding vessel is desirable, it may not be possible till the tumour is debulked and turned to expose the vessel. The tumour can completely be excised and speech and cognitive deficits, if any, are mild and transient by this approach. A high cortical incision can be made in the dominant hemisphere, to avoid speech disturbances and frameless stereotaxy can be employed to secure a safe trajectory.[21]

Third Ventricular Tumour

A small third ventricular tumour can be approached by the transcortical transforaminal approach, while large tumours may require transcallosal exposure. There should be no traction on the tumour, so as to avoid hypothalamic injury. Large tumours lend themselves poorly to excision due to morbidity associated with neuroendocrine, hypothalamic dysfunction and deep venous system injury associated with surgery of large third ventricular tumours.

Fourth Ventricular Tumour

These tumours are exposed by suboccipital craniectomy and splitting of the vermis. There can be severe brainstem distortion and the PICA can be seen draped over the tumour. The artery is carefully mobilised and safeguarded. The tumour is coagulated and cored out and can be dissected out in the arachnoid plane and separated from the floor of the fourth ventricle. The dura is closed primarily or by duroplasty utilising pericranium or temporalis fascia.

Results

Lateral Ventricular Tumours

Recovery is smooth in the majority of the patients after tumour excision. However, a left-sided approach can result in cognitive deficits and speech disturbances that usually resolve within 2–4 weeks. Motor deficits can result in infiltrating tumours, when an attempt is made to separate them from the ventricular wall. Intraventricular haemorrhage can occur from choroidal vessels. Transient or persistent post-operative homonymous hemianopia may be seen.

Third Ventricular Tumours

Excision of third ventricular meningiomas carries a higher morbidity, due to neuroendocrine, osmotic and hypothalamic disturbances. The floor of the third ventricle has to be respected during surgery to avoid these complications.

Fourth Ventricular Tumours

Meticulous care of the fourth ventricular floor and PICA avoids potential post-operative respiratory dysrhythmias and oropharyngeal paralysis due to injury to the floor of the fourth ventricle.

CONCLUSION

Intraventricular meningiomas are rare tumours, occasionally seen as part of NF2 complex, most of them occurring in males. There are no unique clinical features in presentation and raised intracranial pressure is the usual presenting feature. Imaging is diagnostic and surgery requires planning to avoid eloquent area damage. Early control of vascular supply to the tumour is vital and the tumour can usually be removed intact

without damage to the vital areas around the ventricles. No recurrences have been reported after complete excision. Histology of these tumours is in no way different from meningiomas with dural attachment.

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175 Haemangioblastomas

Ravi Ramamurthi

Haemangioblastoma is a histologically benign tumour and has also been referred to as haemangioma, capillary haemangioendothelioma, Lindau's cyst, Lindau's tumour and angioreticuloma. The name haemangioblastoma was coined by Cushing and Bailey[14] and is widely accepted as preferable to the other names. These tumours may occur independently or may be part of Lindau's disease or von Hippel-Lindau complex (VHL).

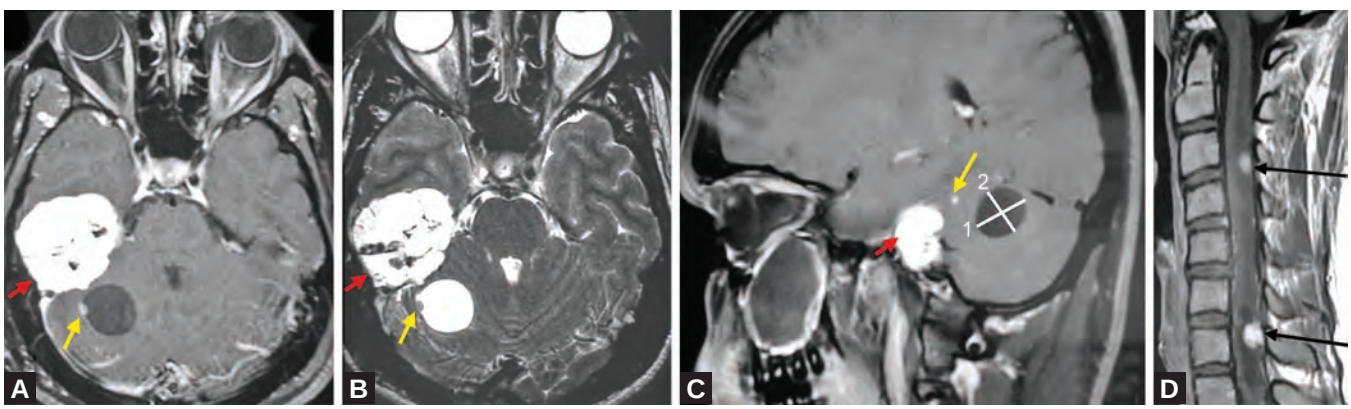
HISTORY[13,39,40,44,59,78]

In 1872, Hughlings Jackson reported in the Medical Times and Gazette the case of a 20-year-old woman and her sister who suffered from failing vision. An autopsy on the sister revealed a cerebellar cyst with clear yellow fluid and an angiomatous tumour in the cyst wall. Further reports by Vigla, Duchenne and Dolbeau (1864) and Paras and Remy (1879) soon followed. An accurate description of the ocular fundus picture was provided by Fuchs in 1882 and Laleyze in 1884. Pye Smith,[59] in 1885, reported the association of these cysts with pancreatic and renal cysts. In 1894, Treacher Collins gave a pathological description of the eye from a case of DJ Wood (1892).

In 1904, von Hippel published his classic paper in which he presented two patients with a retinal mass and retinal detachment and exudation. Seven years later, after becoming aware of Collin's work, he concluded that the retinal lesion was a haemangioblastoma. Lindau,[39] in 1926, wrote a classical monograph on the association of cerebellar cysts with other visceral manifestations. He presented the data on 40 cases, 16 of his own and 24 from the literature. Cushing and Bailey named it Lindau's disease.

GENETICS[6,7,29,30,74]

Haemangioblastomas may occur sporadically or as a part of VHL complex.[5] VHL complex is a familial disorder which has an autosomal dominant inheritance with variable penetrance and can be passed on by affected and unaffected members. This belongs to a group of disorders known as phakomatoses or neurocutaneous syndromes. Of 35 members of a family affected by VHL complex, nine had haemangioblastomas.[5] VHL complex is characterised by single or multiple haemangioblastomas in the neuraxis associated with one or more of the following visceral manifestations: Haemangioblastoma of the retina (von Hippel's tumour), renal carcinoma, renal cysts, pancreatic cysts, cysts and angiomas of the liver, epididymal cysts and adenomata and phaeochromocytoma[30] (Figs 1A to D). Extensive replacement of the spinal cord and brainstem by haemangioblastoma in a case of VHL complex has been reported.[64] Familial occurrence of solitary haemangioblastoma has been recorded without any stigmata of VHL disease.[5] Q-PCR is the method of choice for fast (within 3.5 hours), accurate and sensitive screening in routine DNA diagnosis of



Figs 1A to D: (A to C) MRI of the brain of a 24-year-old patient who was previously diagnosed to have pheochromocytoma showing glomus tumour (red arrow) arising from the middle ear along with cerebellar cystic haemagioblastoma on the same side with a mural nodule (yellow arrow). (D) Contrast MRI of the spine in the same patient showing multiple spinal haemangioblastomas

VHL disease.[27] Mosaicism could provide some genetic explanation for the clinical heterogeneity and variable severity of the VHL phenotype and should be considered as a possible event when evaluating sporadic cases of VHL or patients with isolated VHL-related tumours.[47] Renal cancer constitutes one of the main causes of death. The VHL gene, situated at 3p25–26, is a tumour suppressor gene, which plays a major role in regulation of VEGF transcription and expression. The germ cell mutation can be identified in 70% of patients. Somatic mutations of the VHL gene are also responsible for sporadic clear cell carcinomas. In the urological setting, any patient presenting with "sporadic" bilateral clear cell renal cancer or detected at an early age, or bilateral epididymal cystadenomas, should be investigated for the presence of VHL disease.[62] The von Hippel-Lindau (VHL) disease product is thought to down-regulate transcription, by antagonising elongin-enhanced transcriptional elongation. Germline VHL gene mutations predispose to the development of retinal, cerebellar and spinal haemangioblastomas, renal cell carcinoma and phaeochromocytoma. In addition, somatic inactivation of the VHL gene is frequent in sporadic renal cell carcinoma and haemangioblastoma. Regulation of transcript elongation is an important control mechanism for gene expression and the VHL gene might modify the expression of proto-oncogenes and growth suppressor genes during embryogenesis. VHL-mediated control of transcriptional elongation may have a role in normal human development.[63]

INCIDENCE

Haemangioblastomas constitute 1.5–2.5%[15,45,61,73,81] of intracranial tumours and 7–12%[15,21,45,55] of posterior fossa tumours. There is a complex relationship between CNS haemangioblastoma, retinal haemangioblastoma and Lindau's disease. About 20% of patients with CNS haemangioblastoma have VHL complex. Fifty per cent of patients with VHL complex have CNS haemangioblastoma.[7,30,42,50] The most common age at which they present are the third and fourth decades and there is a slight male preponderance. The age of onset of symptoms in VHL complex is earlier than in the sporadic variety. Cases have been reported in patients as young as 3 years and as old as 83 years.[32,37,42,45,54,55,68,70] Neumann et al.[50] have noted the mean age of onset of CNS symptoms in VHL complex as 39 years (12–73 years) and in the series of Maher et al.,[42] it was 29 years. Supratentorial haemangioblastomas are rare, forming 2–8% of all tumours of this type.[28,31,69] Haemangioblastomas may occur concurrently with other tumours like meningioma or with acoustic neurinoma or AV malformations.[43] Rarely, haemangioblastomas have been reported to occur in locations like the optic nerve, suprasellar region and the lateral ventricle.[25,35,57,58]

PATHOLOGY

Macroscopic Features

Haemangioblastomas occur most commonly in the cerebellar hemisphere. They may also occur in the vermis, brainstem, supratentorial compartment and in the spinal cord. In familial cases, the tumours tend to be multiple. Seventy per cent of haemangioblastomas in the cerebellum and about 20% in the brainstem and supratentorial location are cystic.[32,53,54]

Haemangioblastomas are pinkish or yellow and usually abut the pial surface. Dilated vessels may be seen on the cerebellar cortical surface. They do not have a true capsule, but are well circumscribed from the surrounding tissue. The cyst fluid is xanthochromic and the protein content may be up to 5 g/dl. The cyst wall is smooth and made up of glial cells and compressed cerebellar tissue. The solid portion is seen as a nubbin of varying sizes; the smallest may be even 2 mm and may be missed at surgery. The cut surface of the solid tumour is red in colour due to vascularity. Cavernous spaces and cysts may be seen and some areas may appear yellow from lipid deposition. Occasionally, the tumour may be totally solid as often happens in midline Vermian lesions.

Microscopic Features

The tumour consists of a mesh of vascular spaces lined by plump endothelial cells.[8,33,65] The vascular spaces are separated by numerous polygonal cells called interstitial or stromal cells. The capillary channels are surrounded by reticulin fibres which are demonstrated by reticulin stains. Pericytes, which lie just outside the periendothelial basement membrane and are themselves surrounded completely by a basement membrane, are best seen on electron microscopy. The origin of the stromal cells is still in doubt and various theories have been postulated.

The presence of histological variants of haemangioblastoma is well established. Clinical factors associated with histological subtypes, that is, of the cellular and reticular variant of haemangioblastoma, have been analysed in a series of 88 consecutive primary haemangioblastomas of the central nervous system. Ten haemangioblastomas were classified as 'cellular' according to Cushing and Bailey. As compared to the more common 'reticular' variant (n = 78), the proportion of tumours containing glial fibrillary acidic protein-positive tumour cells (80% vs 7%), as well as median Ki67 (MIB1) proliferation indices [4% (quartiles: 1–8%) vs less than 1% (< 1–2%)], was significantly higher in cellular haemangioblastomas ($p < 0.01$). Recurrences were more frequent in the cellular variant [2/8 (25%) vs 4/51 (8%)]. Kaplan-Meier analysis confirmed a significantly higher probability of recurrence in the cellular variant (Log-Rank test, $p < 0.01$). Cox regression analysis, not only confirmed the well established association of von Hippel-Lindau

disease with tumour recurrence ($p < 0.01$), but also revealed an independent effect of histological subtype on the probability of recurrence ($p < 0.05$), whereas no significant influence of age, sex or tumour location was observed. The results from this retrospective study suggest that histological subtyping of haemangioblastomas has prognostic implications and might contribute to identify patients at risk for recurrence.[24]

Astrocytomas are rarely found in von Hippel-Lindau disease and they may contain genetic changes common to both haemangioblastomas and some astrocytomas.[51] Malignant spread, distant metastases and subarachnoid seeding are very rare. Recurrence and extensive spread are excellently demonstrated by MRI.[23]

Histology of the cyst walls is consistent with reactive gliosis. CNS peritumoral cyst formation is initiated by increased tumour vascular permeability, increased interstitial pressure in the tumour and plasma extravasation with convective distribution into the surrounding tissue. When the delivery of plasma from the tumour exceeds the capacity of the surrounding tissue to absorb the extravasated fluid, oedema (with its associated increased interstitial pressure) and subsequent cyst formation occur.[41]

SYMPTOMS AND SIGNS[29,32,45,53-55]

The most common initial symptom is headache and other symptoms of raised intracranial pressure. Vertigo and diplopia may occur.[45,55] About 25% may have mental changes which may be caused by hydrocephalus. Rarely, they may present as subarachnoid or parenchymal haemorrhage. A full-term neonate presenting with supratentorial and infratentorial haemorrhagic lesions, which occurred as a result of congenital supratentorial haemangioblastoma bleeding has been reported.[36] The overall incidence of haemorrhage in patients with haemangioblastoma is low. An important indicator for the probability of haemorrhage is tumour size, as spontaneous or post-operative haemorrhage occurred exclusively in extraordinarily large tumours. Haemangioblastomas smaller than 1.5 cm (the vast majority of these tumours) harbour virtually no risk of spontaneous haemorrhage.[20] The average duration of symptoms is about 7 months and may extend longer.

Papilloedema occurs in a majority of patients (70%), although the percentage is less now than in earlier years, probably due to early diagnosis.[32,54] Depending on the location in the posterior fossa, there may be cerebellar or brainstem signs or both. Ataxia of gait, upper limb incoordination and nystagmus occur in about 60% of patients. If the tumour is located in the brainstem, cranial nerve and long tract signs may be present. Other presenting symptoms reported are adult cerebellar mutism and intractable hiccoughs.[1,48] Supratentorial lesions may mimic the clinical presentation of meningiomas. Paralysis of upward gaze may occur if the tumour is located in the roof of the fourth ventricle. It must be pointed out that these symptoms and signs are not specific for haemangioblastomas and are only dictated by the location of the tumour. Vascular engorgement of cerebellar haemangioblastomas during pregnancy may cause patients to become symptomatic.[49,76]

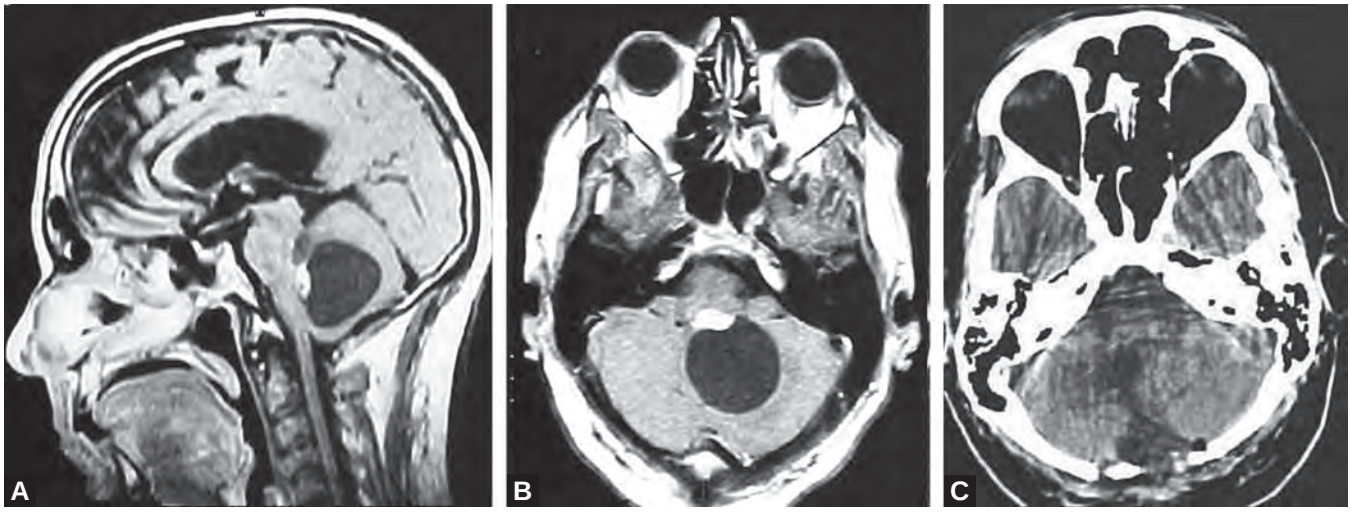
INVESTIGATIONS

The best screening test for haemangioblastomas is computed tomography in the axial and coronal planes.[19,67] The solid lesions generally appear isodense with the cerebellar tissue on plain scans, but enhance intensely with contrast injection. There is either homogenous enhancement or a mottled appearance, due to the presence of intratumoural cysts. The cystic lesion is seen as a sharply defined low density with attenuation values of CSF or slightly higher if the protein content is high. A mural nodule will enhance intensely with contrast, but the cyst wall does not. A small mural nodule may be missed on CT scanning.

Vertebral angiography is very useful, especially in patients with evidence of VHL complex, who have a cerebellar cyst with the mural nodule not visible on the CT. The following vascular patterns have been observed: (i) A vascular mural nodule within an avascular cyst; (ii) A doughnut ring of abnormal vessels surrounding an avascular space representing an intra-tumoural cyst; (iii) A large solid vascular mass and (iv) Multiple small widely separated vascular nodules.[67]

MRI is the most sensitive investigation for haemangioblastomas, especially those with small mural nodules and the ones near the base or the tentorium.[17,18,38,66] The cyst does not appear as hypointense as CSF on T1-weighted images and they may exceed the CSF signal on T2-weighted images. Occasionally, a cyst may show evidence of previous haemorrhage. On T1 and proton density weighted images, mural nodules stand out well against the darker background of cyst fluid (Figs 2A to C). With T2 images, the nodules may become less apparent, since their signal rises along with that of cyst fluid. Highly vascular lesions will remain low on T2 images and will be clearly visible. Prominent feeding arteries and draining veins are characterised by flow void. If larger vessels are present in the tumour, a 'salt and pepper' appearance may be seen. Solid tumours and mural nodules enhance brightly and homogenously after Gd-DTPA injection. Gd-DTPA enhancement is useful to detect multiple tumours, assure complete removal and detect possible recurrence.[3] The apparent diffusion coefficients are increased in haemangioblastomas. These findings may indicate rich vascular spaces of the haemangioblastomas. Diffusion-weighted imaging may be useful for distinguishing haemangioblastomas from other enhancing cerebellar tumours.[60]

Erythrocythaemia occurs in 9–49% of patients.[33,56] This is seen with posterior fossa or supratentorial tumours, but has not been reported in cases of purely spinal tumours. There is neither splenomegaly nor increase in white blood cells or platelets. The erythrocytes have a normal lifespan and the bone marrow may show



Figs 2A to C: (A and B) Pre-operative MRI of the brain sagittal and axial showing cystic haemangioblastoma of the cerebellum with ventrally placed mural nodule. (C) Post-operative CT scan showing total excision of the haemangioblastoma

erythroid hyperplasia. The erythrocytosis is due to secretion of erythropoietin by the tumour. Foci of extramedullary haematopoiesis can be found in some tumours.[10] Trimble et al.[75] have demonstrated erythropoietin RNA in the tumour cyst fluid by Northern blotting. Injection of the cyst fluid into experimental animals may cause erythrocythaemia. Immunohistochemical and electron microscopic studies have shown that the secreting cells are scattered in the vicinity of capillaries. Neither endothelial nor stromal cells were stained. In their morphology and distribution, the positively stained cells were identical to mast cells, as observed by electron microscopy.[34] After removal of the tumour, the polycythaemia regresses and may reappear with either recurrence of tumour or tumour occurring in another area. Estimation of haemoglobin, RBC count and PCV is useful during follow-up of these patients.

TREATMENT AND RESULTS

Surgery with total excision of the tumour leads to good results. The use of the operating microscope and bipolar coagulation are mandatory. Earlier series reported mortality rates of 25–30%.[4] Most current series report mortality rates of approximately 15%.[32,55,68,69,80] These, however, include patients operated upon in earlier years. In the past four decades, the mortality rates have come down to 4–6% and in one series there was zero mortality.[45,46,56] Surgical outcome for patients with CNS haemangioblastomas is favourable, however, management of haemangioblastomas is more difficult and prolonged for patients with VHL syndrome, as these patients present at younger ages and are at risk for development of new lesions, often multiple, and require lifelong follow-up.[11]

Ammerman et al.[2] in their study of 19 patients harbouring a total of 143 haemangioblastomas, concluded that these lesions exhibit a stuttering growth pattern, frequently remain asymptomatic and do not require treatment for long intervals. Unqualified radiographic progression is not an indication for treatment.

Surgery for posterior fossa haemangioblastomas is done through an appropriate craniectomy either midline, paramedian or retromastoid. The sitting, semi-sitting, prone or semiprone position is used, depending on the surgeon's preference. If the dura is tense due to a large cyst, the cyst must be aspirated before opening the dura. During such aspiration, needle injury to the underlying solid tumour should be carefully avoided. These tumours generally involve the pial surface. The location of the tumour can be made out by dilated pial vessels, especially in solid tumours. In cystic lesions, the cyst is entered through a cortical incision. The mural nodule should be looked for. Very often, this will be found superiorly and the superior pole may abut the tentorium. A thorough search must be made to locate the nodule, as this may sometimes be difficult to find. Evacuating the cyst alone, without removing the mural nodule is of no use, as the cyst will rapidly re-accumulate. No attempt should be made to biopsy the tumour or remove it piecemeal, as uncontrollable and catastrophic bleeding may occur. The nodule must be removed en masse by going around it in the cerebellar tissue adjacent to the tumour and coagulating the feeding arteries and veins like in an arteriovenous malformation. This technique is more important for solid tumours. Once a part of the tumour is seen, the dissection is carried out around the tumour. When the tumour is abutting the dorsal surface of the brainstem cardiorespiratory problems can occur during dissection. Those involving the cerebellar peduncles and the lateral surface of the brainstem can be removed without much difficulty and morbidity. Two types of brainstem haemangioblastomas (BSHs) can be identified. Patients with cystic BSH lesions could have an excellent outcome after surgery. Patients with giant or large solid BSHs remain a challenge to neurosurgeons. A combined strategy of pre-operative embolisation, mild hypothermia with or without hypotension, microsurgical

technique and intensive peri-operative management are mandatory for removal of these tumours with acceptable morbidity and mortality.[77] Particle embolisation is not recommended, as it can lead to acute tumour bleeding and death.[12]

Solid haemangioblastomas can be difficult to treat surgically because of their hypervascularity and requirement for circumferential dissection. They can be safely resected utilising wide transtemporal posterolateral skull-base exposures. Good tumour exposure was achieved with trans-cochlear approaches and division of the sigmoid sinus. For large tumours the added complexity of the approach was justified by providing a panoramic exposure to allow safe resection.[16]

A complete excision of the lesion has been achieved by means of endoscopy without any violation of the subarachnoidal space and complete cyst regression was observed on CT follow-up investigations.[52]

The need for pre-operative CSF diversion in patients with hydrocephalus depends on the surgeon's preference and is debatable.[22] Controlled ventilation is essential, except when the tumour is being dissected off the floor of the fourth ventricle, when respiratory monitoring is required. In a vascular cerebellar haemangioblastoma, Williams et al.[79] used profound hypothermia, cardiopulmonary bypass and circulatory arrest for successful removal.

Recurrence after total removal is rare. If there is evidence for recurrence of the tumour, it will most likely be a tumour arising at a different site. Radiation therapy in high doses may retard the growth of the tumour and reduce its size and vascularity. It is only palliative and should be used only in large solid tumours involving the brainstem which are inoperable.[26,71]

Radiosurgery often lends itself particularly well to these discrete lesions allowing highly focused treatment. For patients with multiple and metachronous cerebellar haemangioblastomas as part of the von Hippel-Lindau syndrome, the data support a policy of conventionally fractionated external beam radiotherapy to the whole cerebellum of 50–55 Gy followed, after a period of time, by radiosurgery to persisting lesions.[9,72,77]

The long-term prognosis is good in cystic and in non-familial tumours. The prognosis for tumours involving the brainstem is not very good, as the operative mortality and morbidity are high. In VHL complex, the prognosis depends on multiplicity of tumours and occurrence of carcinoma in the kidney.

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176 Primary Central Nervous System Lymphomas

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INTRODUCTION

Primary central nervous system lymphomas (PCNSLs) are the non-Hodgkin's lymphomas (NHL) arising in and within the central nervous system (CNS). These are extranodal malignant lymphomas arising within the CNS in the absence of obvious lymphoma outside the nervous system at the time of diagnosis. They are usually found in the brain parenchyma but may be present in the eyes, leptomeninges or rarely the spinal cord.[19] CNS lymphomas were first described by Bailey in 1929 as "perithelial sarcoma", since the tumours appeared to be reticuloendothelial in origin and perivascular in location. They have also been classified as reticulum cell sarcoma, microglioma or perivascular sarcoma in an effort to describe the cell of origin. In the 1970s, their lymphoid lineage and correct designation as lymphoma was accepted. An analysis of the tumour cell surface immunoglobulins in the 1980s revealed that PCNSLs were non-Hodgkin's lymphomas of B cell lineage with only 1–3% having a T cell phenotype. In the past two decades, their incidence has risen significantly in both immunocompromised and non-immunocompromised individuals.[3,17,25,27]

The disease has certain unique features. It is usually restricted to, yet disseminated within the CNS. Its radiological appearance, steroid responsiveness and the relative roles of surgery, chemotherapy and radiotherapy have distinctive features that make the management of this disease quite different from all other CNS tumours.

The source of the cell responsible for the development of PCNSLs is not known since the CNS lacks lymphatics and lymph nodes. Under normal circumstances, lymphocytes do move in and out of the CNS and may be the primary source of PCNSLs. However, it is the T cell lymphocytes that move through the CNS and B cells are usually not found there and yet PCNSLs are predominantly B cell tumours.

It has also been postulated that PCNSLs arise as metastasis from an occult systemic lymphoma. However, this is unlikely since PCNSLs are almost never associated with systemic NHL at diagnosis or autopsy; CNS spread of lymphoma usually occurs in patients with advanced systemic disease, a state never found in PCNSLs; and CNS metastasis from a peripheral NHL is usually leptomeningeal or spinal epidural and very rarely parenchymal. If a lymphoma at an extra CNS site is found coexisting with the lesion in the brain then, by definition, the brain lesion is no longer considered as a PCNL but a lesion that has metastasised to the CNS. Systemic lymphomas and leukaemias involve the CNS in approximately 5–35% of patients and their lesions are often confined to the leptomeninges and cranial or spinal nerve roots.

Another hypothesis postulates that since CNS is an immunologically privileged organ, lymphoma cells that arise elsewhere in the body migrate into and preferentially reside in the CNS. The normal immune system in the rest of the body would destroy these tumour cells. However, there is an absence of tumour cells in other immunologically privileged organs such as the testis.

The transformed tumour cells become receptors for the endothelium of cerebral blood vessels. This led to the postulation that the presence of unique cell surface markers would induce migration of these cells into the CNS. However, no specific adhesion molecule has been identified. Another hypothesis states that a B cell attracted to a CNS inflammatory lesion and targeting the organism responsible for inflammation, undergoes malignant transformation due to chronic antigenic stimulation within the CNS.[19] However, the incidence of PCNSLs is not increased in inflammatory disease like bacterial infections, multiple sclerosis or encephalitis. Moreover, no source of chronic antigenic stimulation coexists in the CNS of PCNSL patients.

Until the 1980s, PCNSLs represented 0.5–2% of intracranial neoplasms. Over the last two decades, there has been a 3–6 fold increase in its incidence. It now accounts for approximately 3% of all brain neoplasms and less than 1–4% of all non-Hodgkin's lymphomas.[15] This has been associated with an overall increase in the other systemic non-Hodgkin's lymphomas (NHL) as well as a higher prevalence of AIDS related PCNSLs.[27,39,40] PCNSLs may often be associated with other immunodeficiency states both congenital (e.g. hereditary immune deficiency, Wiskott-Aldrich syndrome, immunoglobulin A deficiency, hyperimmunoglobulin M syndrome or severe combined immune deficiency) and acquired (e.g. organ transplantation recipients or chronic pharmacologic immune suppression). The Ebstein-Barr virus (EBV) is an important cause in the genesis of PCNSLs in immunocompromised patients. However, EBV genome

has been identified in only a small portion of PCNSLs arising in immunocompetent patients.[26] Human herpes virus 8 (HHV-8) DNA has also been identified in PCNSLs in patients with or without AIDS. The other risk factors for PCNSLs include myasthenia gravis, vasculitis, autoimmune disease, rheumatoid arthritis, systemic lupus erythematosis, sarcoidosis and Sjogern's syndrome.

PCNSLs may occur in all age groups. Its peak incidence is in the sixth and seventh decades (mean approximately 58–60 years) in immunocompetent patients,[7] but it occurs in a much younger age group (mean approximately 37–43 years) in immunocompromised patients. Among the immunocompetent individuals, there is a 3:2 male-to-female ratio, but in the AIDS population, more than 90% of patients are men.

CLINICAL FEATURES

PCNSLs generally grow more rapidly than gliomas and may have a history of progression of only a few weeks to months. The presenting symptoms depend on the location of the tumour. Most PCNSLs present with pressure symptoms caused by the mass lesion. Focal cerebral deficits occur in nearly half of the patients. Behavioural and personality changes are also common presenting symptoms. PCNSLs often have a deep periventricular location and, therefore, seizures are less common (occurring in approximately 10% of patients). Diencephalon infiltration may cause hypothalamic syndromes including diabetes insipidus or the syndrome of inappropriate antidiuretic hormone secretion; altered sexual behaviour and eating disorders. Posterior fossa lesions may cause cerebellar syndromes and hydrocephalus. Brainstem lesions may produce long tract signs, internuclear ophthalmoplegia, vertigo and diplopia. Spinal cord lymphomas are rare and cause transverse myelopathies. The thoracic cord is usually involved, but lumbar infiltration with nerve root involvement may also occur. The leptomeningeal involvement is usually close to the site of the parenchymal lesions in the CNS and is usually asymptomatic. However, in an advanced stage, signs of meningism may occur.

Neurolymphomatosis is the painful or painless selective invasion of either cranial or peripheral nerves or the plexus they form. Sensory symptoms are common and include burning paraesthesias, allodynia, vibratory/position sense deficit or numbness. Cranial or peripheral nerve motor deficits, such as Bell's palsy, facial pain or limb weakness, are less common.

PCNSLs widely infiltrate the brain parenchyma. An autopsy usually shows microscopic disease even in areas that were appearing normal on magnetic resonance imaging (MRI).[29, 37] Multifocality is seen in nearly 40% of immunocompetent patients and in almost 100% of immunocompromised patients.[7] Due to the multiplicity of lesions in PCNSLs, the disease may often be mistaken for brain metastases, especially since approximately 13% of PCNSL patients already have a prior history of systemic malignancy. Most lesions are periventricular, allowing tumour cells to gain easy access into the cerebrospinal fluid (CSF). At least 40% of patients have demonstrable CSF seedling on examination or on MRI. The CSF spread of the disease is, however, often asymptomatic.

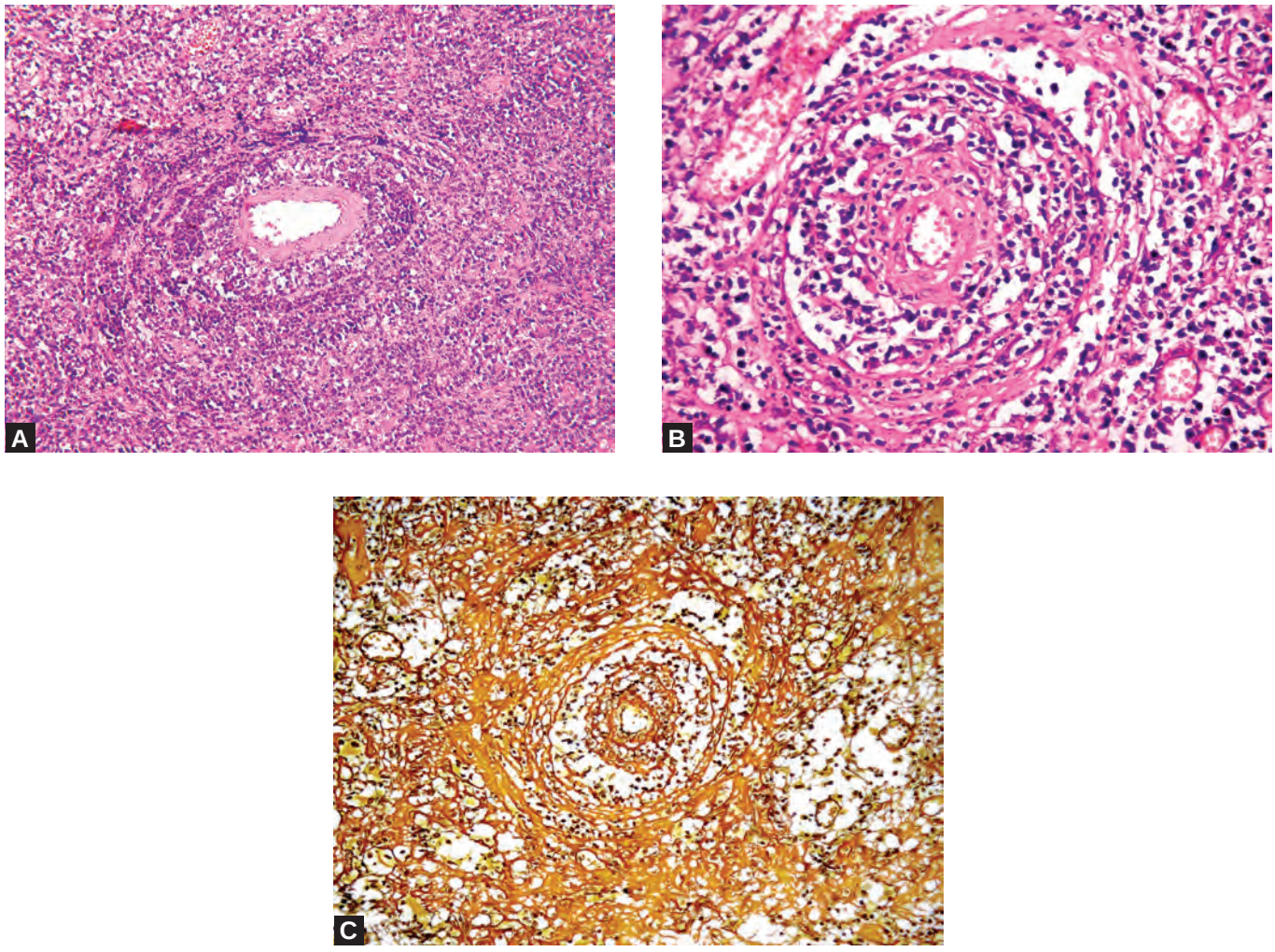
Ocular lymphoma involving either of the layers of the eye is a fairly common manifestation of PCNSL (in 12–18% of patients with cerebral PCNSLs). Fifty to eighty per cent of patients who present with ocular lymphoma develop PCNSLs over a period of time (median 9 months; range 2–94 months). This may cause visual deterioration, floaters in the eye fields, uveitis or retinitis. Indirect fundoscopy with slit lamp examination may be required to detect the ocular lymphoma.[9] An orbital lymphoma, on the other hand, is usually associated with metastatic NHL.

PATHOLOGY

About 60% of PCNSLs involve the supratentorial space, especially the cerebral hemispheres (52%) [frontal (15%), temporal (8%), parietal (7%), occipital (3%), basal ganglia/periventricular region (10%) and corpus callosum (5%)]. In the posterior fossa it occurs in the cerebellum in 11.5% and the brainstem in 2.3%. The spinal cord is involved in 0.6–1% patients. Approximately, 25–50% of lesions are multiple. Secondary meningeal spread is seen in 30–40% of PCNSLs, while leptomeningeal lymphoma may account for up to 8% of these tumours. The lesions are, however, solitary in 60–70% of cases. On the other hand, secondary CNS malignant lymphomas usually occur in the dura and leptomeniges but parenchymal lesions may also occur. Systemic dissemination occurs late in the course of the disease in 7–8% of cases, often in the lymph nodes in the abdomen and retroperitoneum. These metastatic lesions from PCNSLs do not usually cause any symptoms during the course of the disease and are usually found at autopsy.[29]

On gross examination, PCNSLs occur as single or multiple masses in the cerebral hemispheres. Commonly, they are deep seated and adjacent to the ventricular system. The tumours can be firm, friable, granular, centrally necrotic, focally haemorrhagic, grey, tan, yellow or virtually indistinguishable from the adjacent neuropil. Some tumours appear well-demarcated, like a metastatic lesion. When diffuse borders and architectural effacement are present, the lesions resemble gliomas. Macroscopically, meningeal lymphoma mimics a meningioma or meningitis.

On microscopic examination, a PCNSL diffusely infiltrates the brain parenchyma in an angiocentric pattern forming collars of tumour cells within concentric perivascular reticulin deposits (Figs 1A to C). Virtually, all PCNSLs show a diffusely infiltrating pattern. When tumours become confluent, geographic necrosis may be seen with perivascular islands of viable tumour cells surrounded by large regions of coagulative necrosis.

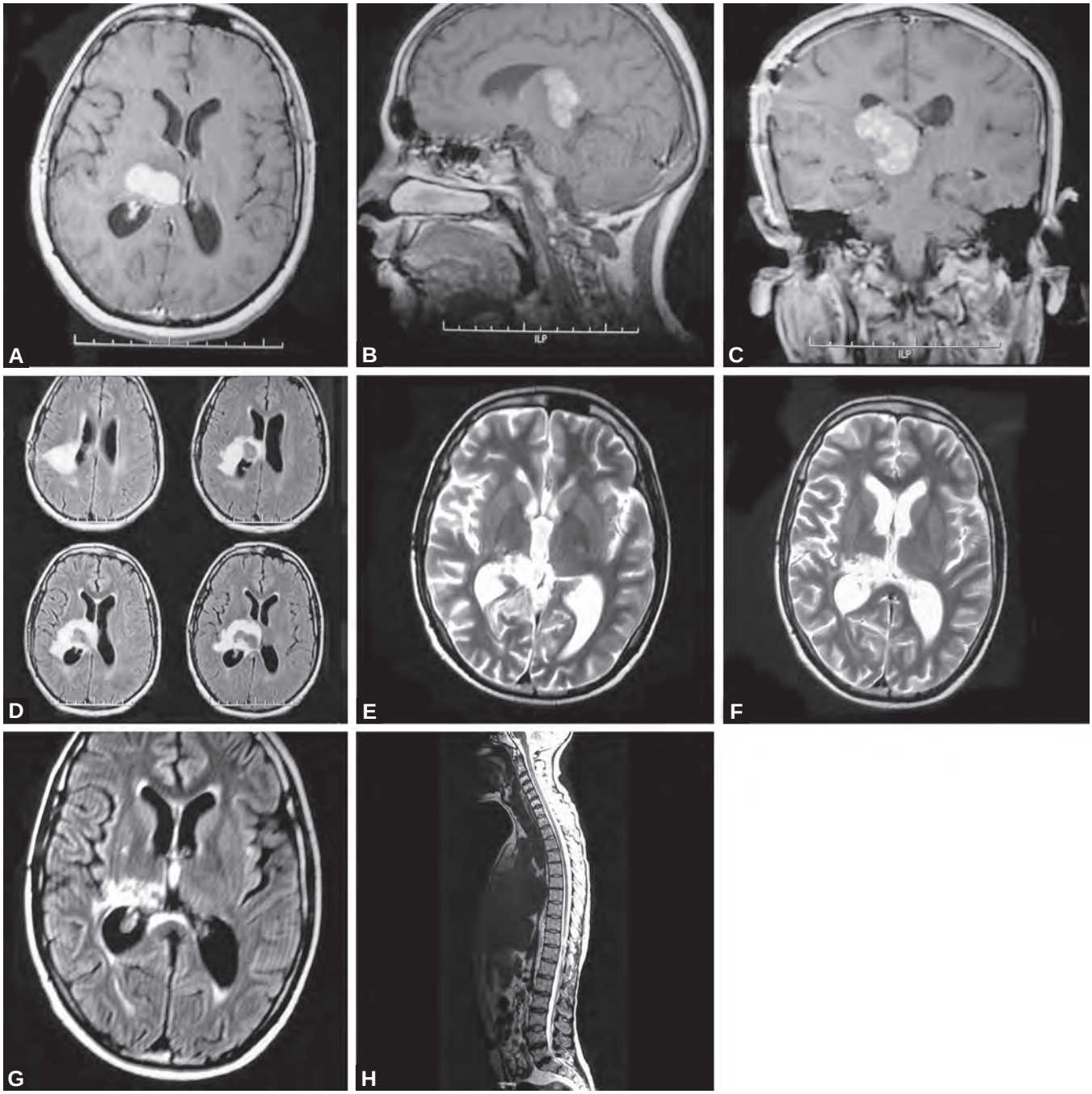


Figs 1A to C: (A) Malignant diffuse large cell lymphoma, diffusely infiltrating the brain and perivascular accumulation of neoplastic cells (H and E stain, Original Magnification x 40). (B) Malignant diffuse large cell lymphoma, perivascular accumulation of neoplastic cells (H and E stain, Original Magnification x 200). (C) Malignant diffuse large cell lymphoma, perivascular accumulation of lymphoma cells embedded in a concentric network of reticulin fibres (Reticulin stain, Original Magnification x 200)

A focally prominent astrocytic and microglial response, large macrophages and reactive lymphocytic infiltrates are common. On higher magnification, PCNSLs show lymphoid cells with a variable appearance.

Approximately 98% of PCNSLs are B-cell lymphomas with the immunohistochemical expression of pan-B markers, such as CD20 and CD79a, usually with IgM-κ production. According to a meta-analysis, sub-types of 590 sporadic PCNSLs were classified according to the working formulation, including diffuse large cell (43.4%), diffuse large cell immunoblastic (19.7%), diffuse small cleaved cell (9.5%), small non-cleaved cells/non-Burkitt (8.8%), atypical/unclassified (7.1%), diffuse mixed small and large cell (7.1%), lymphoblastic (2.9%) and small lymphocytic (1.5%). The major sub-types of HIV associated PCNSLs have been diffuse large cell immunoblastic (33.6%), diffuse large cell (32.7%) and small non-cleaved cell (21.6%). Revised European-American Lymphoma (REAL) classification and the WHO classification of lymphoma have greatly simplified the sub-typing of CNS lymphomas. Since the great majority of tumours can be classified as diffuse large B-cell lymphoma having large cells with round or lobulated nuclei with vesicular chromatin and prominent nucleoli typically mixed with reactive lymphocytes, histiocytes, microglia and astrocytes, supplemental immunohistochemistry (to determine the immunophenotype and to exclude the gliomas and carcinoma) is often necessary, especially with the limited biopsy from stereotactic procedures (Figs 2A to H and 3A to F).

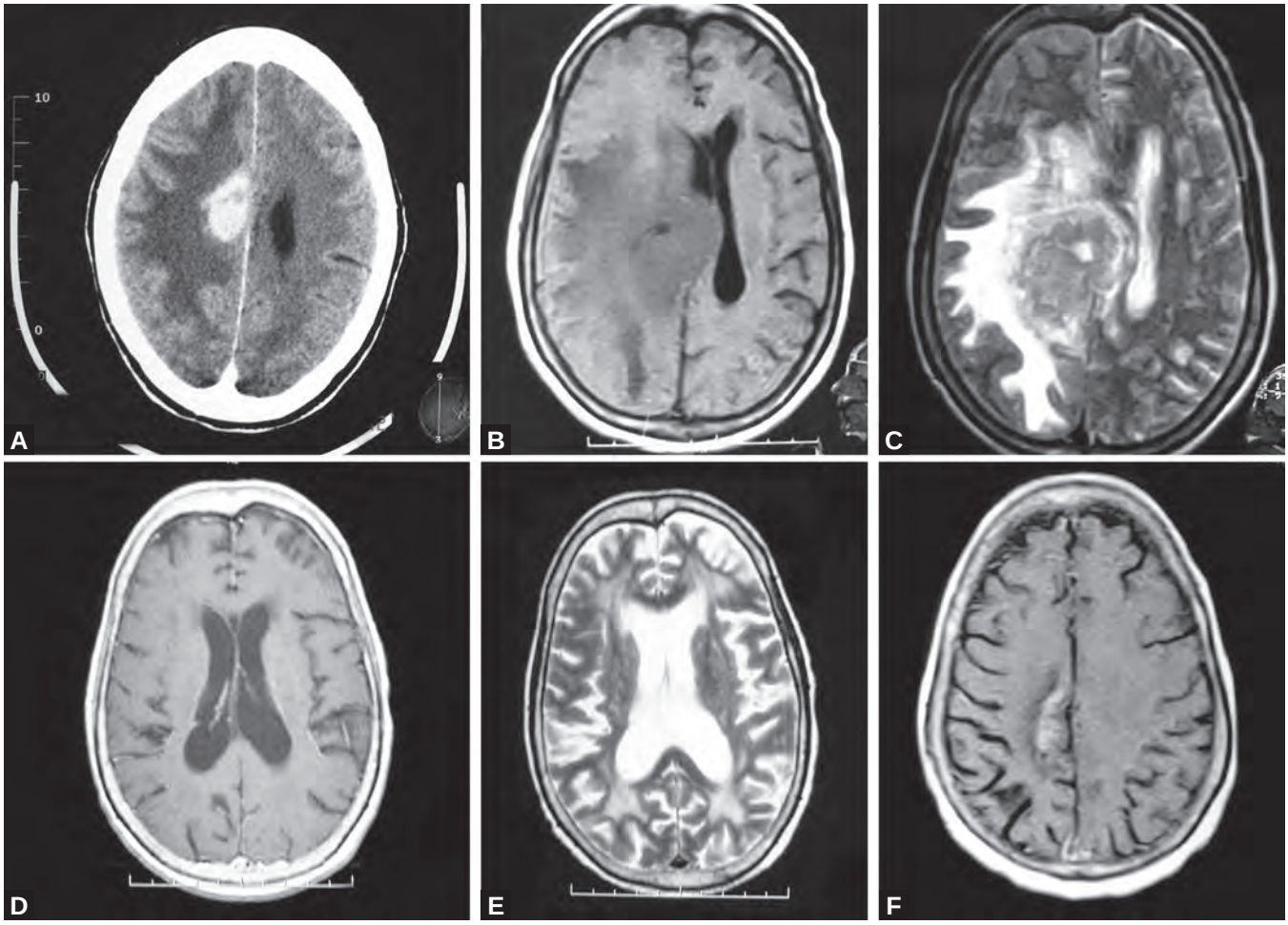
T-cell lymphomas constitute about 2% of PCNSLs and have mainly been seen in immunocompetent patients. They occur as solitary or multiple intraparenchymal masses, often having more frequent posterior fossa localisation, particularly in the cerebellum and with a propensity to arise in the leptomeninges.[7]



Figs 2A to H:. (A) Ti-weighted contrast axial image. (B) Sagittal image. (C) Coronal image showing a brilliantly enhancing thalamic lymphoma causing mild ventriculomegaly. The lesion is periventricular in location, extending to right caudate nucleus and causing effacement of right lateral and third ventricle and dilatation of contralateral lateral ventricle. (D) Axial flair images showing perifocal oedema around the lymphoma (E and F) T2-weighted axial MR images showing significant resolution of the lesion following radiotherapy chemotherapy. (G) Axial flair image showing significant decrease in perifocal oedema as well as tumour size and opening up of the ventricular system. (H) Whole spine T2-weighted MR sagittal image showing no evidence of spinal metastasis

Angiotropic lymphoma, also known as intravascular lymphoma, affects multiple organ systems. The CNS is involved in more than 30% of cases. Accumulation of large B-cells within small and medium vessels leads to vascular occlusion and disseminated small infarcts.

Hodgkin's disease is rare in the CNS and is most often seen in the setting of Grade III or IV systemic disease but primary CNS presentations have been described. Lesions are typically dural based but firm and well demarcated parenchymal tumours do occur. The diagnosis of Hodgkin's disease rests upon the identification of Reed-Sternberg cells or their variants in the background of appropriate non-neoplastic haematopoetic cells (lymphocytes, plasma cells, histiocyte and eosinophils).



Figs 3A to F: (A) Contrast enhanced axial CT scan showing a right hyperdense enhancing irregular lesion with significant perifocal oedema in centrum semiovale causing ipsilateral ventricular and gyral and sulcal effacement. (B) T1-weighted axial MR images showing hypointense right periventricular lesion causing effacement of body of lateral ventricle. (C) T2-weighted axial MR images showing intense perifocal oedema around the lesion. (D) T1-weighted. (E) T2-weighted. (F) Contrast enhanced T1-weighted axial MR images showing significant resolution of the lesion following radiotherapy and chemotherapy

Rare variants of PCNSLs have unusual sites of presentation and are uncommon pathological entities (e.g. neurolymphomatosis and primary leptomeningeal lymphoma). Neurolymphomatosis involves peripheral nerves and nerve roots in addition to systemic and CNS sites. The diagnosis requires a high index of suspicion and treatment incorporates the principles of therapy for systemic and CNS lymphoma. Primary leptomeningeal lymphoma can present with symptoms of raised intracranial pressure or cranial or spinal polyradiculopathies. Diagnosis can be made by examining CSF and incorporating immunophenotyping and molecular pathology techniques.

DIAGNOSTIC TESTS

Imaging Radiology

On non-contrast CT scans, these lesions are often hyperdense. They enhance brilliantly on contrast administration. The tumours are typically hypointense on T1-weighted images. On T2-weighted MR images, these lesions may be isointense to hyperintense due to their hypercellularity. Dense, homogeneous enhancement occurs on gadolinium administration. Only rarely are the lesions non-enhancing. The oedema is usually less than that seen in a malignant glioma of similar size. There may be multifocality in nearly 50% of tumours, especially in immunocompromised patients and calcification is not a feature of these lesions. They characteristically occur in the deep white matter of the centrum semiovale of the cerebral hemispheres and often have a periventricular location. There may be a subependymal spread or along the corpus callosum or they may occur as diffusely infiltrative lesions without a primary mass. In immunocompromised patients, they may show ring enhancement with significant oedema and a hyperintense signal on T2-weighted images reflecting the higher incidence of necrosis seen on pathological examination in this group. Spontaneous haemorrhage may also occur. PCNSLs lesions (as all other malignant lesions) show restriction in proton diffusion producing a hyperintense appearance on diffusion weighted images. MR spectroscopy reveals decreased N-acetylaspartate peak and an

increased ratio of choline to creatine (> 3:1). PCNSLs in immunocompromised individuals mimic infections and MRI may not be able to differentiate between the two. SPECT using Thallium-201 (a potassium analogue that only enters the region of disrupted blood-brain barrier proportional to the activity of the sodium-potassium adenosine triphosphatase pump)[2] or PET scans (using fluorodeoxyglucose) are usually effective in differentiating lymphoma from toxoplasmosis in immunocompromised patients since a PCNSL lesion shows a greater hypermetabolic state than is seen in infection.

Cerebrospinal Fluid Examination

The CSF cytology (consisting of reactive or malignant lymphocytes) may be positive in nearly 35–40% of the cases and may obviate the need for a brain biopsy. Immunohistochemistry may often demonstrate the monoclonal population of malignant cells. The protein concentration may be mildly elevated in 85% of patients (≤ 150 mg/dL). The glucose concentration is usually normal. However, low glucose concentrations with an increase in levels of tumour markers like β2-microglobulin, lactic dehydrogenase and β-glucuronidase may suggest a leptomeningeal invasion. In large supratentorial or posterior fossa lesions, performing a lumbar puncture may precipitate transtentorial or tonsillar herniation respectively or even both.

Vitreous Fluid Examination

Vitrectomy may also establish the diagnosis particularly in patients with isolated ocular lymphoma. Identification of interleukin 10 levels in the vitreous fluid and the immunophenotyping of vitreous cells may be done.

Systemic Evaluation

Staging for patients with PCNSLs includes CSF cytology, slit lamp examination of the eyes, CT scan of chest, abdomen and pelvis, bone marrow biopsy and serological testing for HIV. An extra CNS site is seen in less than 4% of patients with PCNSLs, so a comprehensive systemic evaluation may be eliminated. Since PCNSLs are frequently seen in AIDS patients, systemic evaluation for AIDS is recommended for these patients. In the immunodeficient patient, detection of Epstein Barr virus DNA by polymerase chain reaction of the CSF is a reliable indicator of PCNSLs.[2,4] The radiographical appearance of PCNSLs may resemble toxoplasmosis and therefore, most patients with AIDS and a cerebral mass lesion are initially treated with antitoxoplasmosis therapy. An early brain biopsy should be considered in patients who have negative toxoplasma titres and those who continue to deteriorate during the first week of antitoxoplasma therapy. Toxoplasmosis and other CNS infections, like tuberculosis, may also coexist with PCNSLs mass lesions. However, there is an increased risk of CNS haemorrhage during brain biopsy of immunocompromised patients, when compared to the procedure performed in immunocompetent patients.

Evaluation for systemic lymphoma is usually negative in immunocompetent patients but may often turn out to be positive for immunocompromised individuals where a high incidence of CNS metastatic lymphoma is seen.

RESPONSE TO CORTICOSTEROIDS

PCNSLs are corticosteroid responsive and may induce lysis of tumour cells. If the diagnosis of PCNSLs is suspected, then steroids should be avoided (unless impending herniation due to severe raised intracranial pressure makes their use mandatory) until a definitive diagnosis has been established since the biopsy may only yield reactive T cells after steroid administration. Astrocytomas, metastasis and multiple sclerosis plaques also respond to steroid therapy and so, steroid responsiveness of the lesion is not diagnostic of PCNSLs. If corticosteroids have been administered and the biopsy has proven to be inconclusive in a patient suspected to be having a PCNSL, the drug should be withdrawn and a re-biopsy of the lesion attempted. The patient should be kept under constant observation during the period of withdrawal of the corticosteroids because, occasionally, the tumour may enlarge rapidly.

PROGNOSTIC FACTORS

Correlation between the histological type and the survival in PCNSLs has led to conflicting opinions. Most authors have found no correlation, whereas others have maintained that histological sub-types have a direct correlation with survival. Like histological types, proliferation markers do not show any correlation with survival. The favourable prognostic factors include a single intracranial lesion, absence of meningeal or periventricular tumours, absence of immunodeficiency, age under 60 years and a pre-operative Karnofsky score of over 70. Absence of systemic B symptoms, like fever and weight loss and complete response to initial therapy, are also important prognostic markers. Amongst the tumour factors, Blay et al. report that a CSF protein concentration of more than 600 mg/dL is associated with a bad prognosis. They also report that after adjustment of the entire host and tumour factors, high dose MTX administration is the only treatment related factor that correlates with survival.

MANAGEMENT AND THERAPY

All PCNSLs are treated in the same manner regardless of the sub-type or the cell of origin, since the response to treatment and prognosis is not related to the pathological sub-type.

Using the clinical staging criteria for systemic lymphomas, PCNSLs correspond to stage IE (Ann Arbor staging system), that is, disease confined to a single

extra-nodal site. Systemic stage IE disease has a 100% complete response rate and at least a 70% 10-year survival rate with focal radiotherapy (RT). Despite the high responsiveness, the median survival with RT alone for PCNSLs is 12–18 months with a 3–4% 5-year survival rate. This is due to recurrence at other sites inside the fields, which may be distinct from the original site. The median survival, however, increases to 41–44.4 months with a combined modality treatment.

Immunocompetent Individuals

Corticosteroids

PCNSLs respond dramatically to steroids. At least 90% of patients improve clinically and 40% of patients have significant shrinkage or disappearance of tumour masses (as evident on MRI) after steroids. This is due to a direct cytotoxic effect of the steroids; biopsy after steroid administration often yields normal, necrotic or non-diagnostic tissue. The patients often become clinically asymptomatic after steroid administration for a short period of time. This may be due to regression in the mass or stabilisation of the blood-brain barrier without any detectable change in the tumour size. However, the steroid-induced remission is short-lived. Thus, steroids are generally used only for the first few weeks of treatment, often for symptomatic management of raised intracranial pressure and for prevention of oedema during radiotherapy.[7]

Surgery

Surgery is performed for these tumours to obtain a histological diagnosis. Tumour decompression has no therapeutic advantage. This is because of its multifocal and infiltrative nature. The mean survival of these patients after surgical resection is 3–5 months. Therefore, stereotactic biopsy is the diagnostic method of choice.[10] Excision of large lesions situated in deep periventricular locations is often associated with a high morbidity and, therefore, should not be attempted once a diagnosis of PCNSLs has been established by a minimally invasive technique. If a frozen section of a small surgical specimen reveals a PCNL, no further resection of the tumour is performed and the patient is treated with radiotherapy and chemotherapy.

Radiotherapy

Conventionally whole brain radiotherapy (WBRT) given under the cover of steroids is an effective modality for the treatment of PCNSLs. Although a complete response may be obtained, the median survival with RT alone has been between 12 and 18 months with only a 3–4% five-year survival rate. The dose-response relationship derived from retrospective data suggests that a dose of 40–50 Gy improved survival, when compared to smaller radiation doses. The Radiation Therapy Oncology Group (RTOG) conducted a prospective study of PCNSL patients treated with 40 Gy WBRT plus a 20 Gy boost to the involved area, to assess whether dose intensification improved outcome. The median survival was approximately 12 months in their study. Unfortunately, recurrences occurred within and outside the boost field. This suggested that local radiation boost did not enhance local control. The boosts are, therefore, limited to nodular subarachnoid deposits more bigger than 3 mm, symptomatic or painful nerve or root deposits or provided for palliation.[30]

The problem with whole brain radiation is that of delayed development of cognitive and intellectual deterioration. In patients treated with RT alone, this cognitive impairment may not be noticeable as patients often relapse within approximately a year after the diagnosis; however, patients receiving combined therapy, who have a prolonged disease-free interval, are often affected by this RT induced neurotoxicity.[11, 38]

Bessel et al. combined chemotherapy and RT, i.e. cyclophosphamide, doxorubicin and vincristine with dexamethasone plus carmustine, vincristine and cytarabine to two schedules of RT, i.e. WBRT of 45 Gy versus 30.60 Gy. In this study, it was seen that younger patients (< 60 years of age) showed a significantly superior survival. RTOG on the other hand, used a high-dose methotrexate-based regimen followed by 45 Gy WBRT. During this trial, the protocol was modified and the dose was reduced to 36 Gy delivered to whole brain by hyperfractionated RT. There was no difference in the disease-free or overall survival in the two groups. This trial suggested that when combined with chemotherapy, delivery of a lower RT dose is equally effective in achieving the desired response and with lesser risk of leukoencephalopathy. The use of high dose methotrexate as a pre-RT regime may also help in decreasing the whole brain RT dose and thereby in decreasing the risk of radiation related toxicity.[30] Shibamoto et al. reviewed the patients treated by partial brain RT to the local site. They observed that patients treated with RT, using margins of less than 4 cm around the tumours had higher out-field recurrences (83%) compared with those treated with 4 cm or more margins. This study suggested that large field RT is better than focal RT in prevention of recurrences.

It was initially believed that craniospinal irradiation (CSI) should be given in PCNSLs in view of the relatively high incidence of leptomeningeal involvement. However, this school of thought is no longer prevalent. This is because CSI compromises bone marrow and consequentially impairs the patient's ability to tolerate further systemic chemotherapy. Intrathecal chemotherapy may be used as an effective substitute for CSI under these circumstances.[12-14]

According to Lallana and DeAngelis,[25] the present recommendation is to include whole brain irradiation of 45 Gy without a boost. The eyes are not included in the port unless ocular involvement is present. The eyes receive approximately 36–40 Gy of radiation if ocular involvement is present.

Chemotherapy

In designing chemotherapy (ChT) regimens for PCNSLs, Freilich and DeAngelis[17] have enumerated the factors that must be considered. In systemic lymphomas, drug combinations are more effective than a single agent ChT. ChT must be administered before RT if its efficacy is to be assessed since PCNSLs usually respond very well to RT and the lesions often disappear. Preradiation ChT reduces the enhanced neurotoxicity of adding ChT to RT.[6] In PCNSLs, the blood-brain barrier needs to be overcome and the disease is widespread. Use of agents in high doses to enable them to penetrate the blood-brain barrier, the use of intrathecal therapy to deliver drug to the leptomeningeal tumour and the use of osmotic agents to disrupt the blood-brain barrier are methods for an efficacious drug delivery in PCNSLs.[8,12,13]

Commonly Used Drugs to Treat PCNSL

Methotrexate (MTX)I is the drug of choice for the initial treatment of PCNSLs. It inhibits dihydrofolate reductase, an essential coenzyme for folate reduction. Reduced folate is an essential coenzyme in the synthesis of purine and thymidine. This drug is poorly lipid soluble and, therefore, blood-brain barrier penetrance is poor. High dose MTX greater than 1 g/m^2 penetrates into the brain and CSF but therapeutic levels are only established in CSF at levels greater than 3 g/m^2. The latter is not sustainable for greater than 12 hours. The high doses are followed by leucovorin rescue. An Ommaya reservoir may deliver MTX into the CSF and achieve a sustained therapeutic level for 48 hours. Rapid infusion over 2–3 hours achieves a significantly higher CSF level than infusion over 24 hours, often obviating the need for intrathecal administration. MTX administration prior to RT may be protective against neurotoxicity. It is also nephrotoxic in high doses and should not be given if the creatinine clearance is below 60 mL/min. Intrathecal MTX may still be given when renal clearance is impaired.

Vincristine, Doxorubicin and Bleomycin are effective but do not cross the blood-brain barrier.

Procarbazine and Nitrosoureas (e.g. CCNU, lomustine) are lipophilic agents that cross the blood-brain barrier.

Cytarabine (ara-C) is a pyrimidine analogue that inhibits DNA synthesis by competitively inhibiting DNA polymerase with resultant inhibition of DNA chain elongation and template function. It may cross the blood-brain barrier and is also useful for ocular and leptomeningeal lymphomas. It may cause dementia and reversible cerebellar ataxia.

Alkylating agents, such as thio-TEPA, nitrogen mustards such as cyclophasphamide and ifosfamide, temozolamide or epipodophyllotoxin teniposide, a topoisomerase II inhibitor, are also used.[20]

Drugs available for subarachnoid application include MTX (12 mg twice weekly), cytosine arabinoside (30–50 mg once or twice weekly) and thio-TEPA (12 mg).

Systemic Lymphoma Protocols

The drugs used for treatment of systemic lymphomas, like CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone), CHOD (dexamethasone instead of prednisone) or MACOP-B (methotrexate, doxorubicin, cyclophospamide, vincristine, prednisone and bleomycin), for 3–4 cycles, followed by cranial irradiation may show a median survival between 8.5 and 14 months.[22, 23,36,41] The poor results may be due to the inability of the non-lipophilic drugs to cross the blood-brain barrier. The development of leukoencephalopathy and drug resistance may also play a role in treatment failure.[8,12,13]

Methotrexate Based Protocols

The recent protocol recommended is to use high dose (3.5 g/m^2) systemic MTX together with intrathecal MTX (12 g per dose) administered via an Ommaya reservoir followed by cranial irradiation (4500 cGy) and high dose ara-C (3 g/m^2). A higher median survival of approximately 42 months was seen. Dementia and ataxia were seen in patients older than 50 years but not in those less than that age.

The blood-brain barrier may be overcome by administering intra-arterial mannitol before ChT administration while avoiding cranial irradiation. Neuwelt et al.[31] used intra-arterial MTX (2.5 g) with intravenous cyclophosphamide, oral procarbazine and oral dexamethasone. The carotid and vertebrobasilar systems were used for drug administration and the treatment was given at monthly intervals for 12 months. There was a median survival of 44.5 months. The complications included infarction, arterial dissection, seizures and neuropsychological changes.

High dose intravenous MTX (3.5 g/m^2) followed by RT may also be given to overcome the blood-brain barrier with a good response and a median survival of 33 months.[18,21] PCV has also been tried with a good response.

In elderly patients, ChT may be administered without RT to avoid neurotoxicity. However, RT is eventually required in many patients due to a variable response. The patients with delayed RT died mostly of progressive disease, while those elderly patients who received RT after ChT died due to neurotoxicity.[21] In an effort to limit neurotoxicity in PCNSLs, a single trial of high dose ChT (MTX) with autologous stem cell rescue has been tried with a favourable response.[1,39]

In patients who have already received RT, high dose MTX and ara-C are avoided and, instead, 4–6 cycles of PCV are administered. Patients who relapse after the initial RT are given high dose MTX, as the recurrent disease carries a poor prognosis.[24]

Ocular lymphomas respond to RT and ara-C. Other drugs penetrate the vitreous poorly and the effect of MTX has not been established.

Despite combination therapy, 40–60% of patients eventually relapse. During recurrence, combination ChT

may be tried, based on the drugs previously received by the patients. Several systemic and intrathecal drugs used at relapse include procarbazine, lomustine and vincristine (PCV) combination, thiotepa, ara-C, ifosfamide, carboplatin and etoposide.[28] Intrathecal therapy with an Ommaya reservoir or a lumbar puncture may be tried in patients with leptomeningeal disease. In bulky leptomeningeal disease, a radioisotope CSF flow study is performed before the drug is administered into the subarachnoid space. Abnormal signals signify obstruction leading to inhomogeneous distribution of drug. If the drug is retained in the ventricular system, leakage may occur around the catheter resulting in localised necrotising leukoencephalopathy. Whole brain RT is an effective option for those patients not eligible for the toxic regimens and craniospinal RT for meningeal relapse that has failed to resolve with intrathecal and/or systemic ChT. The prognosis, however, is poor.

Among the newer therapies, rituximab, an anti-CD20 antibody that has an excellent activity against systemic follicular and diffuse large cell lymphoma may be used in PCNSLs, as an adjunct to MTX, as approximately 90% of PCNSLs express CD20 antigen. Temozolamide has a reasonable tolerance, minimal nephrotoxicity and penetrates the intact blood-brain barrier. Thus, it may be used in patients unable to receive high dose MTX because of poor performance status or renal insufficiency or as a good salvage regimen at relapse. In recurrent PCNSLs, high dose busulfan and thiotepa and autologous stem cell transplantation has also been tried. It may be useful in patients with a good performance status. Slow release drug formulations are also being used, such as cytosine arabinoside encapsulated in microsopic gelfoam particles that can be administered every 2 weeks.

In patients with immunocompromise, RT remains the primary treatment of PCNSLs. Patients with CD4 counts greater than or equal to 200/mm^3, a good performance status and no active co-morbid conditions may respond to additional ChT (often 3 cycles of PCV). Other cytotoxic drugs, such as zidovudine or gancyclovir (directed against EBV stimulated growth), must be avoided during ChT, unless there is recovery of blood counts. The response to RT is poor in immunocompromised patients with a median survival following RT alone being 2–5 months that increases to 16–28 months with combined treatment.[13,16]

THE INDIAN SCENARIO

Two large neurooncology (AIIMS, New Delhi and NIMHANS, Bangalore) units[35] together assessed the trend of incidence of PCNSL in India. PCNSLs constituted 0.95% of all intracranial neoplasms. This hospital based study did not reveal any increase in incidence of PCNSLs in India over the past 24 years. The association of PCNSLs with HIV/AIDS has been low in India, possibly due to early death in AIDS on account of opportunistic infections.

There are two audits from our centre, i.e. Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow. A combined modality approach, i.e. surgical resection and cranial RT (40–52 Gy + boost 10–16 Gy) was given along with chemotherapy. The median survival of 13 and 17 months suggests that the combined modality approach should be adopted, which includes surgery, RT and CT.[32,33] Another audit from Southern India using a similar combined modality approach reported a median survival of 19 months.[34] High dose methotrexate has not been tried in any of these centres.

All these retrospective audits reflect the need for more aggressive treatment to improve the outcomes.

The incidence of PCNSLs is showing a rising trend and they usually respond to multimodality ChT and RT based schedule. CNS dissemination, an intact blood-brain barrier, leptomeningeal and ocular involvement are factors that require consideration. In immunocompromised individuals, the prognosis is poor due to a more aggressive disease and, often, the presence of coexisting infections.[5]

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177 Intracranial Melanomas and Other Tumours

Bhawani S Sharma, Sumit Sinha

INTRODUCTION

Primary melanomas rarely affect the central nervous system. Intracranial melanomas derive from the proliferation of melanocytic elements normally present in the leptomeninges, which can assume neoplastic patterns. Melanin containing cells can develop melanoblastic activity, ranging between histologically benign and malignant patterns. These neoplasms are largely confined to the subarachnoid space with perivascular extension into brain parenchyma, depending on anaplastic features and the invasive potential of different clones.

The pigmented tumours of the CNS can be classified into:

- Primary pigmented lesions: Neoplasms derived from leptomeningeal melanocytes are uncommon lesions that present in localised or diffuse forms.[6] Localised lesions present sporadically as meningeal masses and range from well-differentiated melanocytomas to malignant, potentially disseminating melanomas.[17,33] The diffuse lesions (melanomatosis) generally occur in the setting of various dermatologic syndromes—Neurocutaneous melanosis syndrome and Nevus of Ota.[4,27]
- Metastasis: The CNS can be commonly affected by metastasis from a cutaneous melanoma. Among all the primary cancers, cutaneous melanomas have the highest propensity to metastasise to the brain, and in most of the reports is the third most common cause of metastatic brain tumours.[30]
- Primary CNS tumours with melanotic elements:
  - Meningiomas
  - Medulloblastomas
  - Astrocytoma
  - Acoustic neuromas
  - Pituitary tumours
  - Choroid plexus papillomas.

PRIMARY PIGMENTED LESIONS

Localised Melanocytic Neoplasms—Benign Melanocytomas and Malignant Melanomas

The term 'meningeal melanocytoma' was first proposed for 'pigmented meningioma' by Limas and Tio in 1972, on the basis of their ultrastructural characteristics: the presence of polar cytoplasmic processes, few zonula adherens and the presence of premelanosomes and melanosomes in the cells, to describe a tumour that had some of the histological characteristics of meningioma.[17] Since then, very few cases of intracranial and intraspinal meningeal melanocytomas have been described in the literature. Their epidemiological characteristics, natural history and response to treatment remain poorly understood.[18,22,23]

Melanocytes are derived from the neural crest during early embryonic development and are widely distributed throughout the normal leptomeninges. Meningeal melanocytomas probably arise from these cells, a hypothesis that appears to be confirmed by the reports of various authors.[37,39] Melanocytes occur in the highest concentration ventrolateral to the medulla oblongata, which accounts for the propensity of these lesions to occur in the cerebellopontine angle. The highest concentration of melanocytes in the spinal leptomeninges is found in the upper cervical levels, but spinal meningeal melanocytomas are not confined to the cervical region and have been described as far as the thoracolumbar junction. Both intracranial and intraspinal meningeal melanocytomas frequently arise in proximity to the cranial and spinal nerves, as they exit the brainstem and spinal cord.

Brat et al.[5] classified primary melanocytic neoplasms into: (a) low-grade well differentiated melanocytomas having an excellent prognosis; (b) intermediate or indeterminate differentiation category and (c) high-grade aggressive melanomas with cellular anaplasia and necrosis with unfavourable outcome (but better than metastatic melanoma). However, a clear distinction between them is not defined in the literature.[18,28,38,39]

Clinical Presentation

Meningeal melanocytomas are more common in females, with a female to male ratio of 2.2:1. The mean age at presentation is in the early fifth decade. The onset of symptoms is insidious over a period of several months to years.

Intracranial meningeal melanocytomas usually present with signs and symptoms of an expanding mass in the posterior fossa, sometimes compounded by obstructive hydrocephalus and cerebellar dysfunction. The tumour may grow to a significant size and the patient may present with single or multiple cranial nerve palsies.

Differential Diagnosis

Intracranial meningeal melanocytomas are rare lesions and the differential diagnosis includes pigmented meningiomas, melanotic schwannomas and primary or secondary malignant melanoma.[38] Radiological studies are of limited value in the diagnosis of the lesion and in differentiating them from other pigmented lesions and accurate diagnosis requires histological and immunohistochemical confirmation and also electron microscopy (Table 1).

The pre-operative diagnosis in meningeal melanocytomas is usually meningioma, because both the tumours have a long duration of symptoms, appearance of a dural-based extra-axial large mass, features of tight cellular nests or whorls with similar imaging features. The dark colour of the tumour pre-operatively and the presence of melanin in the tumour cells at frozen section suggest a diagnosis of melanocytoma. Electron microscopy is required to rule out meningioma, which shows many intermingling cell processes, not lined by the external lamina but joined by well-developed desmosomes, unlike the ultrastructure of meningeal melanocytes where the cell processes are surrounded by a single profile of external lamina. Electron microscopic demonstration of melanosomes and the presence of melanocytic antigens by immunohistochemistry are currently the only ways to differentiate between a pigmented meningioma and a melanocytic neoplasm.

Melanotic schwannomas contain spindle and epithelial cells with oval nuclei and cytoplasmic pseudoinclusions, in contrast to melanocytomas that show a tight nesting or a fascicular pattern of spindle cells. The schwannoma cells are individually surrounded by a basement membrane, especially at stromal surfaces, while melanocytomas show encirclement of nests or fascicles and not of individual cells. Ultrastructurally, only schwannomas contain electron dense accumulations of pericellular basal lamina.[8]

The differentiation between meningeal melanocytoma and primary or metastatic malignant melanoma[36] can be difficult. However, features suggestive of meningeal melanocytoma are duration of symptoms of more than one year, a radiological similarity to meningioma, uniform cytological features with abundant spindle cells and a low mitotic rate.[24]

Radiological Features

Meningeal melanocytomas may be confused with meningiomas because of their similar behaviour: they are solitary, attached to the dura and may be locally invasive. These tumours may be difficult to differentiate from acoustic neuromas, as they are commonly found in the posterior fossa and cerebellopontine angle.

On CT scan, they appear as well circumscribed, dural based iso- to high-density masses that enhance homogeneously on contrast, similar to meningiomas. Tumour calcification and hyperostosis of the adjacent bone are rare. The degree of melanisation strongly influences the CT pattern. There is usually sparing of the internal auditory canal and lack of haemorrhage.[22]

The MR imaging appearance of these rare tumours is not uniform and depends on the degree of melanisation, with more melanin causing greater shortening of T1 and T2 relaxation times. Thus, MR imaging of intracranial meningeal melanocytomas is not a very reliable or specific technique for the diagnosis of this rare tumour. On MR examination, they are isointense to hyperintense on T1-weighted images and isointense to hypointense on T2-weighted images with intense homogeneous contrast enhancement.[3,37]

Table 1: Differential diagnosis of localised pigmented tumours of meninges

	Meningioma	*Schwannoma*	*Melanocytoma*	*Melanoma*
IMMUNOHISTOCHEMISTRY				
Vimentin	+	+	+	-
S-100 Protein	-	+	+	+
HMB-45	-	-	+	++
Keratin	+	-	-	-
EMA	+	-	-	-
Leu-7	-	+	-	-
ULTRASTRUCTURE				
Basal Membrane	-	+	-	
Desmosomes	+	-	-	
Premelanosomes	-	-	+	
Long spacing collagen	-	+	-	
Prominent nucleoli	-	+	+	

Histopathology

On gross examination, these tumours are dark brown or black, heavily pigmented, and well-demarcated lesions that are firmly attached to the underlying leptomeninges. A meningioma may mimic this gross appearance if large amounts of haemosiderin are present within the lesion, as a result of previous episodes of haemorrhage.[35] Microscopically, the low-grade lesions have architectural and cytological features different from the high-grade aggressive tumours. The most specific feature of melanocytoma is the presence of melanocytes in tight nests with heavily pigmented cells at their periphery. Such a feature is not encountered in melanomas or in intermediate grade lesions. At high magnification, low-grade lesions reveal remarkably uniform oval or bean shaped nuclei with small regular, eosinophilic nucleoli, and the mitotic indices are low. The clinically aggressive melanomas differ from low-grade lesions in that they are highly cellular tumours with high nuclear to cytoplasmic ratio, increased mitotic activity, nuclear atypia and more basophilic in nature.

Immunohistochemistry can differentiate melanocytoma from other pigmented leptomeningeal lesions and must be done to arrive at a definitive diagnosis. It reveals a positive reaction to vimentin antibodies, S-100 protein and antimelanoma antibody (HMB-45) with absent response to epithelial Markers—EMA, NSE, GFAP and cytokeratin. Vimentin is rarely present in malignant melanoma; while meningioma cells lack the presence of HMB-45 and S-100 protein.[18,29,35]

Management

Most of the reports in literature indicate that the extent of surgical resection is the most important determinant of outcome and support the view that long-term patient survival is enhanced by complete tumour resection.[18,22,38,39] This may be impossible in up to half of the cases because of the large size of the tumour associated with vital structures, hypervascularity of the tumour and unfavourable tumour location. The role of radiotherapy in the management of these tumours is controversial;[7,23,39] however, it is worth considering for those patients with symptomatic residual, progressive or recurrent tumours not amenable for further resection.[13,23,34] According to some reports in the literature, adequate control of tumour re-growth can be achieved after partial resection, with the use of post-operative gamma knife therapy.[16] However, more cases with a longer follow-up period will help to define the adequate treatment protocol of these rare tumours.

Prognosis

Meningeal melanocytomas have a much better prognosis as compared to their malignant counterparts. These patients have a relatively good prognosis, with most of the patients surviving at least several years after the diagnosis. However, these tumours do locally recur. Despite various treatments including surgery and radiotherapy, there is a 71% recurrence rate at 5 years.

Diffuse Melanocytic Neoplasms

Neurocutaneous Melanosis

Neurocutaneous melanosis (NCM) is a rare congenital syndrome first described by Rokitansky in 1861. Van Bogaert, in 1948, named this condition as neurocutaneous melanosis. The criterion for the diagnosis of this syndrome are: (1) one or more congenital giant hairy nevi, multiple pigmented nevi or marked generalised brown cutaneous pigmentation that is unduly large (more than 20 cm); (2) there is no malignant melanoma transformation of the involved skin area; (3) diffuse thickening and brownish black melanin pigmentation of CNS pia mater, with no evidence of primary malignant melanoma in any organ other than the CNS. An autopsy or extensive surgical biopsy is essential to establish a correct diagnosis.[11,32] NCM is considered a phakomatosis because it is thought to arise from congenital dysplasia of the neuroectodermal melanocytic precursor. The disease affects both the sexes equally and occurs more frequently in Whites. The neurological symptoms usually appear within the first two years of life. Only a few cases have been reported in the second and third decades of life.

The cutaneous lesions of NCM are congenital melanocytic nevi. Most of the patients have giant nevi found in a 'bathing trunk' or lumbosacral distribution. The risk of malignant transformation of giant pigmented nevi ranges from 2 to 42% in various series.[25] Malignancy can occur at any age, but it occurs mostly during the first decade of life. It is not clear what percentage of patients with giant or multiple congenital melanocytic nevi could potentially develop NCM, but children with lesions in the head, neck or posterior midline seem to run an increased risk of leptomeningeal melanosis and should closely be monitored for the development of neurological symptoms.[15] Leptomeningeal pigmentation was present in over 85% of the cases analysed by Fox et al. and the areas most commonly affected were the pons, medulla, cerebellum, cerebral peduncles, interpeduncular fossa and the inferior surfaces of the frontal, temporal and occipital lobes.[11]

The clinical features are usually the result of raised intracranial pressure, vomiting, seizures, headache, increased head circumference or photophobia. The patient may develop ataxia with inability to walk, and show psychiatric symptoms with disease progression. Raised intracranial pressure is due to the presence of an abnormal mass of melanotic cells in the meninges or the presence of hydrocephalus. The majority of these lesions undergo malignant changes and show evidence of leptomeningeal melanoma.[14]

NCM must be differentiated from melanotic neuroectodermal tumour of the cranium of infancy and from melanotic nerve sheath tumour. MNET is a benign pigmented tumour arising from the neural crest cells and

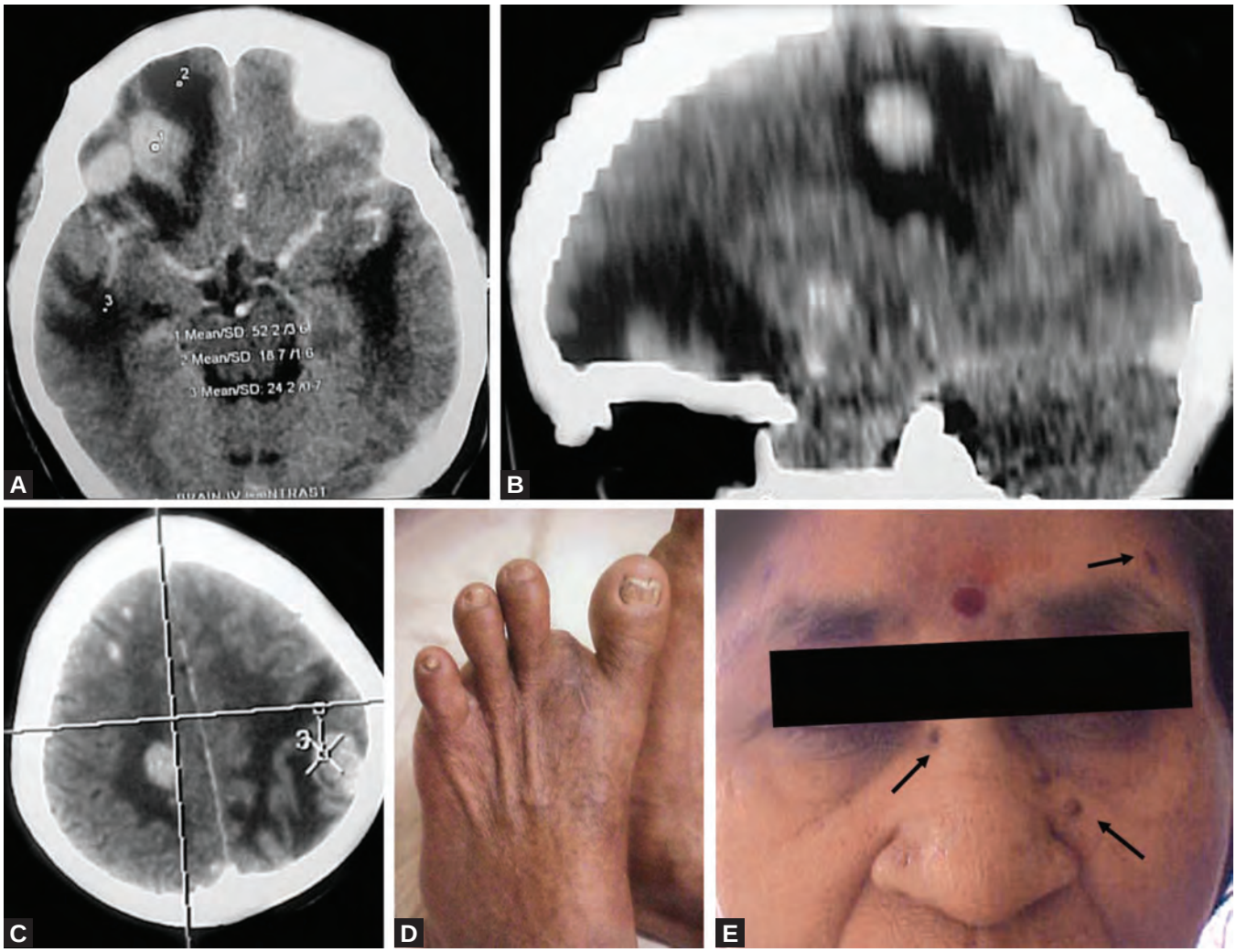
mostly occurs at the anterior fontanelle. They have an excellent prognosis with an early, complete excision and radiotherapy is reserved for incompletely resected lesions. Melanotic nerve sheath tumours are slow growing benign plexiform melanin containing neurofibromas found in young adults, which do not metastasise.

Secondary Malignant Melanoma

Melanoma has the highest tendency to metastasise to the brain among all the primary cancers. In many reports, it is the third most common cause of cerebral metastasis after breast and lung. Malignant melanomas commonly metastasise to lung and liver; however, the reported incidence of cerebral metastasis in patients with melanoma ranges from 6 to 43% in clinical series[1,2] and 12 to 74% in autopsy series.[9,33] Most of them are solitary but multiple metastases are not uncommon. Seventy-five percent of the patients with malignant melanoma with metastatic disease have intracranial involvement with the frontal and parietal lobes being the most common sites (Figs 1A to E). There is also a high incidence of extracerebral metastasis at the time of diagnosis of cerebral involvement. The time interval from the diagnosis of the primary lesion to cerebral metastasis varies from 6 to 60 months.

The clinical features depend on the site of cerebral involvement. Cerebral metastases carry the worst prognosis of all the visceral metastasis in patients with melanoma and are the cause of death in more than 50% of patients dying of malignant melanoma.

Various studies in the literature[20,31] have found an association between the development of brain metastasis and the following factors: (1) male gender; (2) head and neck primary lesions; (3) deeply invasive primary lesions; (4) primary lesions located on the mucosal surfaces; (5) ulcerated primary lesions; (6) lesions with a large diameter; (7) acral lentigenous and nodular histological types and (8) the presence of lymph nodes or visceral metastasis at the time of diagnosis. Thus,



Figs 1A to E: (A and C) Contrast CT axial and (B) sagittal reconstruction of the brain showing multiple enhancing lesions in the brain involving right basifrontal, right posterior frontal and left parietal regions in a patient who had undergone surgical amputation of (D) left second toe due a lesion, HPE of which was malignant melanoma and (E) pointed by black arrows also had evidence of multiple new naevi over the face and other parts of the body

patients with these clinical profiles should be followed more closely for the development of metastatic disease and would be candidates for prophylactic therapy.

Malignant melanomas have a characteristic appearance on CT and MRI and are classified according to their size into less than 1 cm, 1–4 cm and more than 4 cm. They are usually seen at the grey-white junction of the cerebrum and are slightly hyperdense with moderate contrast enhancement. Most of these lesions show moderate perilesional oedema and occasionally show a leptomeningeal spread. On MRI, T1 and T2 shortening is seen due to the presence of melanin.

The overall prognosis of patients with cerebral metastasis from melanoma remains dismal, regardless of the therapeutic intervention. The poor prognostic factors are the presence of more than one cerebral metastasis and disease in multiple sites, including the brain. The median survival, reported in the literature for surgically treated patients with brain metastasis from melanoma, ranges from 5 to 22 months, which compares favourably with 2–4 months median survival range for patients treated with whole brain radiotherapy alone, and the 2 weeks to 2 months median survival reported for patients treated with palliative therapy alone. Surgical treatment has also been evaluated for the treatment of cerebral metastasis from melanoma. Some studies have shown promising results following surgery with median survivals ranging from 5 to 10 months, although in most of these studies patients presented with a solitary metastasis.[40,41]

Several studies in the literature have identified a subset of patients with brain metastasis from melanoma who are expected to survive longer and they recommended the following guidelines for surgical therapy.[31]

Indications

- Single brain metastasis accessible to safe and complete resection without any other visceral metastasis
- Multiple brain metastasis with symptomatic or life threatening brain lesion accessible to safe and complete resection and no other visceral metastasis
- Single brain metastasis accessible to safe and complete resection and one other visceral metastasis accessible to complete resection or responding to systemic therapy
- Multiple brain metastasis all accessible to safe and complete resection and one other visceral metastasis accessible to complete resection or responding to systemic therapy
- Single symptomatic or life threatening brain metastasis accessible to safe and complete resection and one other untreatable visceral metastasis
- Multiple brain metastasis with a symptomatic or life threatening brain lesion accessible to safe and complete resection and one other untreatable visceral metastasis

Contraindications

- Brain metastasis not accessible to safe and complete resection
- More than one visceral metastasis in addition to the brain lesion
- Radiological or pathological evidence of leptomeningeal spread of tumour
- Surgical procedure likely to be life threatening

Malignant melanoma is relatively radioresistant. The use of radiotherapy in treating melanoma metastasis has given conflicting results; with some studies showing an increase in survival[19] and others showing no improvement.[12] Over the past decade, stereotactic radiosurgery has been found to provide control of cerebral metastasis from melanoma. Radbill et al. have supported the use of Gamma-knife radiosurgery in the initial treatment of melanoma brain metastasis, with the number and location of the lesions having significant prognostic value with respect to survival.[10,26] Mori et al. have reported that radiosurgery is effective therapy for the control of malignant melanoma metastasis. They did not find any notable benefit in combining WBRT with stereotactic radiosurgery in these patients.[21]

Other Pigmented CNS Lesions

Melanotic Medulloblastoma

These tumours show a typical histological appearance with pseudoepithelial-pigmented structures that are immunoreactive for S100 protein and vimentin. The treatment of choice is complete surgical excision and post-operative radiotherapy for any residual tumour.

Melanotic Cerebral Astrocytoma

These tumours clinically present with complex partial seizures as most of these lesions are located in the temporal lobe. Histologically, these tumours are benign and resemble pleomorphic xanthoastrocytomas, except for the presence of pigmentation. They are composed of two different regions: one consists of spindle shaped and pleomorphic cells with a foamy or vacuolated cytoplasm, while the other consists of fairly uniform spindle cells, many of which contain dark brown intracytoplasmic pigment, often with areas of desmoplasia. The features suggestive of malignancy, such as mitotic figures, necrosis and endothelial proliferation, are not found in these tumours. Immunohistochemically, the tumour cells in both the regions are positive for glial fibrillary acidic protein. On ultrastructural examination of the pigmented region, the presence of melanosomal melanin is found.

Melanotic Choroid Plexus Papilloma

These tumours show histological immunophenotypic and ultrastructural features of neoplastic choroid plexus epithelium. The pigment consists of lipofuchsin and

neuromelanin and autocatalytic peroxidation of lipofuchsin is thought to be the putative mechanism for melanogenesis.

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178 Benign Intracranial Tension

Nigel Peter Symss, Ravi Ramamurthi

The term benign intracranial hypertension (BIH) refers to a condition of increased intracranial pressure (ICP) in which the ventricles are not dilated and the cerebrospinal fluid (CSF) is normal. The patients present with symptoms and signs of increased ICP usually without any focal neurological deficit. Thorough investigations fail to reveal a space occupying lesion or any other specific cause for the raised ICP. Quincke, in 1897,[75] described this condition as a *serous meningitis*, and Nonne, in 1914, used the term *pseudotumour cerebri* (PTC) which is descriptive and was acceptable to many neurosurgeons. Symonds, in 1931,[94] first drew attention to a syndrome in which infection of the ear was followed by intracranial hypertension without any evidence of intracranial abscess or infection. This was described as *otitic hydrocephalus*. In 1936, Davidoff described cases of serous meningitis[23] and, in 1937, Dandy[21] reported on 22 cases of PTC. Since then, the condition of BIH has been recognised frequently. Evidence gathered over the years suggests that this condition is not a single clinical entity, but a syndrome resulting from a variety of causes.[11,33]

Although the term BIH has been accepted by common usage, it must be remembered that the condition is not always benign and may result in blindness or death in some patients, unless vigorously treated. The term idiopathic intracranial hypertension may be more suitable.

PATHOPHYSIOLOGY

The factors that may contribute to BIH are cerebral oedema, reduced CSF resorption, increased CSF production, increased cerebral blood volume and increased venous pressure.[86] The basic pathology is either an excess of accumulation of CSF in the intracranial subarachnoid space or an increase in the bulk of the brain parenchyma. In either case, the ventricles do not dilate and the biochemistry of the CSF remains normal. Thus, two main groups may be recognised, those with obstruction to the exit of the CSF from the cranial cavity and those without.

Absorption of CSF may be interfered with when there is thrombosis of the dural sinuses or the cerebral veins or an obstruction in the arachnoid villi. This may be caused by head injury, intracranial infections or thrombotic lesions. Mild injuries to the head with minimal bleeding in the subarachnoid space, as also mild infections, may block CSF absorption. More severe infections may lead to thrombosis of the major veins or sinuses. In these cases, the back pressure builds up initially in the subarachnoid space and then gets communicated to the ventricular system. Hence, although the ventricular pressure rises, the ventricles do not dilate; in fact they are often narrow, as the pressure in the subarachnoid space is already increased. The subarachnoid space often contains an excess of CSF. This group falls under the definition of communicating hydrocephalus and not BIH. CSF is thought to flow continuously from the site of production in the ventricles into interconnected spaces, i.e. cisterns and subarachnoid spaces (SASs). Since the SAS of the optic nerve is defined by a cul-de-sac anatomy, it is not evident how local CSF might recycle from that region to the general SAS. The concept of free communication of CSF has recently been challenged by the description of a concentration gradient of beta-trace protein, a lipocalin-like prostaglandin d-synthetase (L-PGDS), between the spinal CSF and that in the SAS of the optic nerve, indicating diminished local clearance or local overproduction of L-PGDS here. Computed cisternography, with a contrast agent in three patients with idiopathic intracranial hypertension and asymmetric papilloedema, demonstrated a lack of contrast-loaded CSF in the SAS of the optic nerve, despite it being present in the intracranial SAS, thus suggesting compartmentalisation of the SAS of the optic nerve. The concept of an optic nerve compartment syndrome is further supported by a concentration gradient of brain-derived L-PGDS between the spinal CSF and the CSF from the optic nerve SAS in the same patient.[54,59]

In the group without CSF obstruction are included conditions that cause fluid retention with electrolyte disturbances, resulting in cerebral oedema. Brain water self-diffusion was studied by Sorenson et al.,[90] who used the MR imaging technique of single spin echo pulse sequence with pulsed magnetic field gradients of different magnitudes. In BIH there were abnormal diffusion images, indicating increased water diffusion in the periventricular region or in the whole brain. A convective transependymal flow of water with increased outflow resistance resulted in interstitial brain oedema and intracellular brain water accumulation. CSF outflow resistance has been confirmed by lumbar steady state infusion tests[58] and by radioisotope cisternography.[72]

Greitz,[40] used gated MR imaging techniques and radionuclide cisternography in healthy volunteers and in patients with communicating hydrocephalus, BIH and venous vasculitis and suggested that the systolic expansion of the intracerebral arteries expels the CSF into a compliant spinal subarachnoid space, providing an alternating pressure gradient. The major portion of the CSF is transported to the bloodstream via the paravascular and extracellular spaces of the nervous system and not through pacchionian granulations. Greitz[40] suggested that an increase in pressure in the venous system is likely to be the cause of increased ICP in BIH.

Vasopressin has been implicated in the causation of BIH. Elevated vasopressin levels in the CSF of patients with BIH have been reported.[44] Whether the increased level of vasopressin is the cause or the result of increased ICP is disputed.

Kesler et al.[53] in a group of 33 women with BIH and the same number of women matched for age, body mass index, vascular risk factors and medications, found a significant ($p = 0.038$) increment in fibrinogen concentrations in the patients (341 ± 60.8 mg/dl) as opposed to the controls (307.9 ± 64.8). The same increment was noted for the aggregation of red blood cells (aggregation parameter of 8.7 ± 4.9 in patients vs 5.9 ± 3.2 in the controls, $p = 0.001$) was noted. Being associated with capillary slow flow, their findings might be relevant for the aetiopathogenesis of this disease.[53]

Global elevation of cerebral blood flow measurements has been noted in BIH.[41] By monitoring epidural ICP and middle cerebral blood flows simultaneously, Lundar and Nornes[58] also found a labile cerebral vasomotor state in BIH. Bateman found in patients with a clinical diagnosis of BIH and standard MRI with venography, there was cerebral hyperaemia suggesting a derangement of autoregulation.[8]

BIH is rarely seen in very young children or in old people. It is possible that the resistance to ventricular dilatation in the presence of decreased CSF absorption may be related to the volume and the state of maturity of the brain.[15,82] In elderly patients the ventricles may show minimal enlargement.

INFANTILE PRESENTATION OF BIH

These infants present with an enlarging head and a full fontanelle. The cranial sutures show separation. Apart from these, the infants do not show any abnormality and the milestones are normal. CT shows mild enlargement of the ventricles with enlarged SASs. The prognosis is good as the disease is self-limiting.[89] Similar to patients with BIH, children with hydrocephalus show a significant elevation in collateral venous flow, indicating that the same venous pathophysiological process may be operating in both conditions. Whether or not the ventricles dilate may depend on the differences in brain compliance between adults and children.[7]

AETIOLOGY

Many conditions and agents lead to the development of BIH. Hypervitaminosis,[30] hypoparathyroidism, prolonged steroid therapy, chronic adrenal insufficiency, severe anaemia and pregnancy may cause BIH.[55] Hypervitaminosis is known to produce hydrocephalus.[39,63,70] Higher levels of weight gain and BMI are associated with greater risk of BIH. Even non-obese patients (BMI < 30) are at greater risk for BIH in the setting of moderate weight gain. Vision-specific and overall health-related quality of life (HRQOL) is affected to a greater extent in BIH than in other neuro-ophthalmological disorders.[22]

Increased incidence of this condition in middle aged, obese, females and its association with pregnancy, menarche and menstrual dysfunction suggest a possible endocrinal aetiology.[36-38] Finsterer et al., for the first time, described the association of PTC, optic nerve demyelination, polycystic ovarian syndrome (PCOS), other endocrinological abnormalities, thrombophilia due to a factor V and prothrombin mutation in a 20-year-old obese lady. A causal relationship between these abnormalities remains elusive.[32] Familial occurrence has been reported in a mother and son who were both obese.[80] Simultaneous occurrence of BIH in male heterozygous twins has been reported.[95] Godefroid et al. reported a case of Gitelman syndrome (GS) in a dizygotic twin who, at 12 years of age, presented with growth delay, metabolic alkalosis, hypomagnesaemia and hypokalaemia with inappropriate kaliuresis and idiopathic intracranial hypertension with bilateral papilloedema. The patient, her twin sister and her mother also presented with cerebral cavernous malformations. Mutation analysis showed that the proband is a compound heterozygote for two mutations in SLC12A3: a substitution of serine by leucine at amino acid position 555 (p.Ser555Leu) and a novel guanine to cytosine transition at the 5′ splice site of intron 22 (c.2633+1G>C), providing the molecular diagnosis of GS. These mutations were not detected in 200 normal chromosomes and co-segregated within the family. Analysis of complementary DNA showed that the heterozygous nucleotide change c.2633+1G>C caused the appearance of two RNA molecules, one normal transcript and one skipping the entire exon 22 (r.2521_2634del). Supplementation with potassium and magnesium improved clinical symptoms and resulted in catch-up growth, but vision remained impaired. They found three similar associations of Bartter syndrome/GS with PTC in the literature, suggesting that electrolyte abnormalities and secondary aldosteronism may have a role in idiopathic intracranial hypertension.[35]

A defect in endogenous corticotrophin metabolism or of its release has been implicated as a cause of BIH. Patients with BIH did not show a response to metyrapone. The test became normal when clinical remission occurred. The use of oral contraceptives and the consequent water and sodium retention may cause BIH. BIH may also follow antibiotic therapy with tetracycline,[5,55] ampicillin,

Table 1: Conditions associated with benign intracranial hypertension

Drugs
Tetracycline
Oral contraceptives
Nitrofurantoin
Sulphamethoxazole
Systemic steroid withdrawal
Dietary conditions
Hypervitaminosis
Hypovitaminosis
Obesity
Systemic illnesses
Anaemia
Hypertension
Pregnancy
Heart failure with venous hypertension
Congenital heart disease
Renal disease
Multiple sclerosis
Systemic lupus erythematosus
Thrombocytopaenic purpura
Addison's disease
Sarcoidosis
Reye's syndrome
Familial Mediterranean fever
Chronic respiratory insufficiency

amphotericin B,[47] minocycline[26] and/or ciprofloxacin.[101] The aetiology of BIH also includes administration of eltroxin or growth hormone,[61,66] danazol[81] or of chemicals like cytosine arabinoside[29] and benzene hexachloride (Lindane)[98] (Table 1).

Peng et al. found ALZ-50 immunoreactivity to be elevated in the CSF of BIH patients; either the normal tau protein or its phosphorylated variant may be useful as a biomarker for the diagnosis of BIH. Since the ALZ-50 monoclonal antibody was generated against brain homogenate from Alzheimer's disease (AD) patients, their study suggests a possible link between BIH and AD.[73]

Cerebral and dural AVMs[79] may cause BIH. Myeloma,[100] typhoid,[67] sarcoidosis,[78] systemic lupus erythematosis[19,71] and Lyme disease (Borrebia infection)[12] may also cause BIH. The occurrence of BIH in a two-year-old female with HIV seropositivity has been reported.[96] Inferior tonsillar displacement (ITD) exists pre-surgically in a significant percentage of PTC patients and this subset of patients may actually represent a secondary form of PTC and may benefit from correction of ITD to restore normal ICP.[6]

CLINICAL DESCRIPTION

The condition is characteristically described in middle aged females who are usually obese. However, it affects all ages and both sexes. Ramamurthi,[77] reported on 75 patients of whom 49 were males and 26 females. Chatterjee and Chatterjee,[18] reported a higher incidence in males. The signs and symptoms are those of increased ICP with headache, vomiting and papilloedema. Headaches in BIH can be excruciating in some patients. They are usually pulsatile and the increasing intensity during sleep may waken the patient. Pain along the trigeminal or occipital nerve root distribution and retrocular pain often occur in BIH, unlike in other headaches.[99] There are no localising neurological signs. Some authors have reported varying incidence of diplopia, vertigo, tinnitus and ataxia,[18] and various cranial nerve palsies. Agarwal et al.[2] and Chari and Rao[17] reported cases of BIH with no papilloedema, unilateral papilloedema and III and VI nerve involvement. Bruce et al.[14] reported two patients with confirmed BIH, presenting with headache, diplopia and papilloedema. The first patient had bilateral sixth nerve palsies and a partial right third nerve palsy, which resolved rapidly after a CSF shunting procedure. The second patient had alternating skew deviation and upbeat nystagmus. Both cases had normal brain magnetic resonance imaging (MRI) and magnetic resonance venography (MRV) and normal CSF contents, ruling out a secondary cause of intracranial hypertension. They concluded that these exceptional vertical and horizontal ophthalmopareses in the setting of BIH may be related directly to very elevated CSF pressures and may be secondary to altered CSF flow in the posterior fossa.[14]

Pituitary deficiency and empty sella syndrome may occur in BIH.[25,76] Patients with chronic BIH may develop a secondary empty sella syndrome, characterised by extension of the subarachnoid space through an incompetent diaphragma sellae into the sella turcica.[10] There may be a history of ear infection in some cases. The EEG may show non-specific changes. Mani and Townsend,[62] reported that the EEG in the majority of patients appeared slightly abnormal and burst activity was a common feature. It is essential to exclude an intracranial lesion before diagnosing BIH. Imaging studies show a normal or narrowed ventricular system. Visual evoked potentials are useful in determining the state of visual function and in following up patients. Optical coherence tomography (OCT) shows increased peripapillary retinal nerve fibre layer (RNFL) and macular thickness in PTC and may be a useful clinical tool in children.[27] Heckmann et al., in their study, found laser scanning tomography (LST) measurements to be useful for evaluating the degree of papilloedema in patients with BIH and corresponded well with clinical data and measurements of CSF opening pressure. They concluded that, if a diagnosis of BIH is established, LST measurements may replace repeated CSF opening pressure measurements in follow-up monitoring.[46] Transcranial Doppler (TCD) parameters have no useful unique features for monitoring BIH patients.[43] Acquired choroidal folds and optic nerve subarachnoid space enlargement may be signs of BIH and their appearance depend on the level of ICP. They can be identified by OCT, fluorescein angiography and ocular fundus

photography. Nevertheless, the diagnosis should be confirmed by lumbar puncture.[56] Flavoprotein autofluorescence (FA) values averaged 60% greater in the more affected eyes of women with pseudotumour cerebri, but not between eyes of healthy women (control subjects), demonstrating the clinical utility of FA in the early detection and monitoring of retinal and optic nerve diseases.[28]

CT AND MR STUDIES

The diagnosis of BIH is one of exclusion and based on a series of diagnostic negatives. CT and MR help to exclude other possible causes of raised ICP. The scans are normal before and after contrast enhancement. In some patients, the subarachnoid space or the perioptic CSF space may be widened and there may be an empty sella. MR is more sensitive to exclude an intracranial lesion and to show sinus or venous thrombosis. The MR of patients with BIH shows a higher water index in the white matter, suggesting the presence of a low degree of white matter oedema.[68]

Agid and Farb, in a double blind controlled study, found that flattening of the posterior aspect of the globe is the only sign on cross-sectional imaging and, if present, strongly suggest the diagnosis of BIH. In addition, evaluation of extra-luminal and intra-luminal narrowing of the transverse and sigmoid dural sinuses, with contrast-enhanced MRV using a simple grading system, provides a highly sensitive and specific test for identifying patients with BIH.[4]

Vaphiades et al. analysed cranial and orbital MRI scans from 20 patients with BIH and 20 control subjects and found six neuroimaging signs to predict elevated ICP in these patients: flattening of the posterior sclera; optic nerve enhancement; perioptic subarachnoid space distension; optic nerve vertical tortuosity; empty sella and intraocular protrusion.[97]

The venous phase during angiography may reveal a block in a major venous sinus in an occasional case. Isotope cisternography may show abnormality of CSF absorption through the arachnoid villi in some cases,[9,72] while in many it may be normal.[50]

Pulsatile tinnitus, hearing loss and a feeling of fullness in the ear may be complained of by some patients. Brainstem auditory evoked response may show bilateral prolongation of peak latencies, which return to normal after treatment.[87,88] CSF pressure measurements are high and the composition of the CSF is normal.

DIFFERENTIAL DIAGNOSIS

In tropical countries, one should exclude cysticercosis, which may simulate BIH. The CT scan and MR are both diagnostic in cysticercosis; MR is more sensitive and may show the cysts even when the CT scan is negative.[85] Mild residual arachnoiditis following tuberculous meningitis usually causes hydrocephalus, but rarely may mimic the clinical picture of BIH. Toxic and lead encephalopathies may simulate BIH. Pseudopapilloedema[48] with headaches can be differentiated from BIH by careful ophthalmological examination, including fluorescein angiography and delineation of the blind spot. Bilateral disc drusen is an important differential diagnosis of PTC.[74]

TREATMENT

The aim of treatment is to relieve headaches and specially to prevent loss of vision. Conservative therapy is useful in most cases, but surgery is necessary when vision is threatened. Hence, a careful watch is necessary to detect deterioration in acuity of vision or in the visual fields. Visual evoked potentials and repeated quantitative perimetry are helpful in assessing the progress and in helping to decide on surgical treatment.[92,93]

Any detectable cause for BIH, e.g. hypervitaminosis, antibiotics or anaemia, requires suitable corrective measures. In other cases it is necessary to reduce the ICP. This may be done for a few days by intravenous mannitol or diuretics like furosemide. Dexamethasone, 12 mg a day, is administered for a few days in resistant cases. When the response is satisfactory, this may be followed by oral glycerol for some weeks. Topiramate seems to be effective in the treatment of BIH, weight reduction and the reduction of CSF formation being the possible mechanism of action.[16,31]

In many cases, it will be necessary to do frequent lumbar punctures to lower the ICP. Barbiturate augmented hypothermia has been used to reduce ICP.[57,84] In cases where the pressure is very high, the patient is ill or the vision is threatened, surgical therapy is indicated. Lumboperitoneal shunt is favoured by many surgeons, but has drawbacks like backache and persistent root pains. Cisternal shunting has been found useful.[51] Recent reports have shown promising short-term to medium-term results in patients with refractory idiopathic intracranial hypertension (BIH), treated using the stereotactic ventriculoperitoneal shunting (SVPS) technique. However, the long-term clinical efficacy of this technique remains questionable.[1]

Before appropriate shunts were available, subtemporal decompression has been done successfully on many patients and is still preferred by some surgeons to avoid problems associated with shunts.

Recently, endoluminal venous sinus stenting has been proposed as an effective and safe alternative treatment. It was performed under intravenous heparin administration and anti-platelet therapy was administered for 3 months post-treatment.[64,65]

OPTIC NERVE SHEATH DECOMPRESSION

Patients with BIH and progressive visual impairment have been shown to benefit from optic nerve sheath decompression.[3,13,34,49,83] It is desirable to perform the operation as soon as it is obvious that medical therapy is not effective in preventing progressive visual deterioration.[52] This operation is also known to provide relief from intractable headache.[20,83] Demonstration of

retrobulbar optic nerve sheath enlargement by CT or orbital echography is essential before making a decision to operate.

A variety of surgical approaches have been described for optic nerve sheath decompression.[24,34,49] However, the medial approach of Galbraith and Sullivan[34] remains the most frequently employed technique. The procedure is safe, with few complications. Gupta et al. found endoscopic endonasal optic nerve fenestration a safe, minimally invasive and extremely effective procedure for the management of BIH, with a 94.5% success rate and minimal morbidity.[42] Bariatric surgery and weight loss has been advocated for obese patients with BIH and stable visual symptoms to avoid shunt placement or optic nerve sheath fenestration.[57,69]

RESULTS

In the majority of cases, conservative treatment is beneficial. Risk factors identified for a bad visual outcome are the presence of atrophy of the optic discs, visual loss and marked field defects, delay in treatment, patients older than forty years and the presence of systemic hypertension.[93] In a long-term follow-up of cases, good prognosis has been reported after prolonged treatment.[60,102] Rarely, a few of the cases may turn out to have a tumour on investigations at a later date. Recurrence of BIH has been reported after a few years, especially in obese women whose obesity has not been corrected.[91] Long-term observation is advisable. Corneal contact lens-associated ophthalmodynamometry can be helpful for the monitoring of patients with intracranial idiopathic hypertension.[45]

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179 Tumours of the Cranial Vault

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The diagnosis and treatment of tumours of the skull come under the purview of the neurosurgeon, as they have the expertise in dealing with the cranial contents. Compared to the neurosurgical literature which consists of series of individual cases, more extensive reports of such tumours are found in the radiological journals. Vandenberg and Coley,[125] estimated that primary skull tumours accounted for 0.8% of all bone tumours.

The skull bones are affected by lesions similar to those seen in the other bony structures such as benign or malignant neoplasms or metastatic deposits, congenital dysplasias, metabolic disorders and haemopoietic diseases. Lesions that are primarily intracranial may involve the skull secondarily, and similarly, tumours arising in the skull bones can spread inside, producing raised intracranial pressure and focal neurological deficits. Malignant conditions from the paranasal sinuses, nasopharynx and orbit may spread to the base of skull and produce cranial nerve palsies.

ANATOMICAL CONSIDERATIONS

The vault of the skull is made up of membrane bones, whereas the base is of cartilaginous origin. This influences the type of pathological lesions that may develop in different parts of the skull. The deeper periosteum of the skull bones (the endosteum) is firmly incorporated with the dura mater. The dura forms an effective barrier against the intracranial spread of lesions of the skull. Dural lesions, however, often invade the inner table of the skull.

Classification

Tumours of the skull can be primary or secondary.

A. Primary tumours:

1. Benign
   - Osteoma
   - Haemangioma
   - Giant cell tumour
   - Dermoid
   - Epidermoid
   - Chondroma
   - Lipoma
   - Aneurysmal bone cyst
   - Ossifying fibroma
   - Cavernous haemangioma of the skull
   - Myxomas

2. Malignant
   - Chondrosarcoma
   - Osteogenic sarcoma
   - Fibrosarcoma
   - Carcinoma of the temporal bone
   - Fibrous histiocytoma[25]
   - Chordoma
   - Reticulum cell sarcoma
   - Angiosarcoma
   - Malignant sweat gland tumour
   - Benign osteoblastoma
   - Orbital rhabdomyosarcomas
   - Bone penetrating
   - Marjolin's ulcer of scalp
   - Ewing's sarcoma

B. Secondary tumours:

1. Contiguous spread
   - Meningioma
   - Glomus jugulare tumour
   - Nasopharyngeal tumours
   - Carcinoma of the paranasal air sinuses
   - Sinonasal melanoma
   - Nasal basal cell carcinoma

2. Haematogenous
   - Secondary metastases
   - Lymphoma
   - Leukaemic deposits

C. Conditions simulating skull tumours:

- Osteomyelitis
- Cephalhaematoma
- Leptomeningeal cyst
- Vascular disorders
- Vascular impression
- Sinus pericranii
- Histiocytosis X
- Pacchionian granulations
- Hyperostosis frontalis interna
- Sarcoidosis
- Paget's disease
- Fibrous dysplasia
- Hyperparathyroidism
- Mucocoele
- Neuroectodermal dysplasia
- Haemolytic anaemias
- Petrous apex cholesterol granuloma.

DIAGNOSTIC EVALUATION

The common presenting symptoms are swelling, deformity, disfigurement and local pain. A specific neurological deficit may also be found. Many skull tumours are detected incidentally on radiographical examination done for other reasons. The usual diagnostic procedures include plain films of the skull, computerised tomography, magnetic resonance imaging and cerebral angiography. Radionuclide bone scanning is occasionally done to detect metastases in bones from other primary malignancies.[63]

Plain Skull Films

After the invention of computerised tomography, the importance of plain X-ray films has declined. Routine views and tangential or edge-to-edge views are taken to detect the location, extent and the degree of involvement of the tables and diploe, and also to know whether the lesion is sclerotic, lytic or mixed (Figs 1A and B). When both the tables are involved, the lesions appear more lucent (punched out). Examination of the margins of the radiographic abnormality gives valuable information.[36,37,44]

Sharply defined and sclerotic edges indicate that the process is a slowly expanding one, permitting enough time for the adjacent bone to react by condensation and thus, the process is more likely to be benign. Irregular, poorly defined margins suggest a more aggressive process, either malignant or inflammatory.[67,124]

Computed Tomography

Computed tomography (CT) provides more accurate information regarding the extent of involvement of the skull bones as well as the soft tissues, both within and outside the skull. It is necessary to scan the bones of the skull as well as the soft tissues, using the appropriate settings on the CT machine[65,77,117] (Figs 2A and B). Such studies are also to be done after intravenous contrast infusion, to assess the degree of invasion of the dural venous sinuses, brain and extracranial soft tissues.

Magnetic Resonance Imaging

Signal intensity in magnetic resonance (MR) depends primarily on the concentration of mobile protons (hydrogen nuclei) in the tissue being imaged. As compact cortical bone lacks in unbound protons, the inner and outer tables of the skull appear as a signal void in the MR image. The diploe has abundant fat and hence images well, so also the pathological lesions arising in the diploe. Lesions at the base of the skull are better imaged by MR than CT, as the latter produces bone artefacts. Neoplasms have greater water content and hence are imaged with sharp contrast from the surrounding structures. The possibility of histological differentiation by MR is limited.

Cerebral Angiography

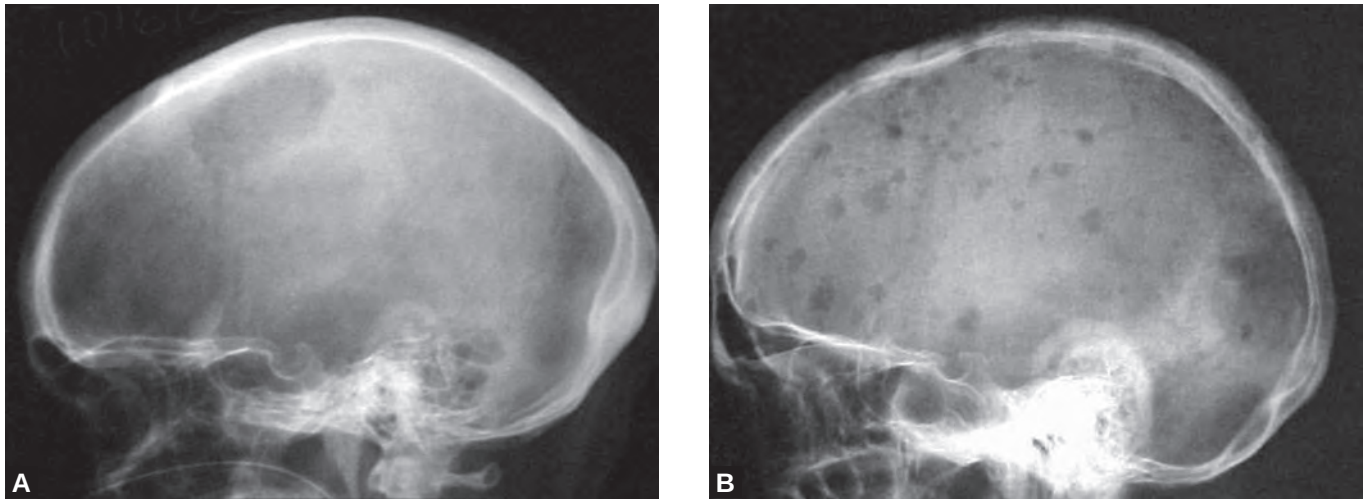
The indications for cerebral angiographic studies have become limited after the advent of CT. Assessment of possible intracranial extension when the CT and MR are not clear and the mapping out of the vascular supply of the neoplasm, before surgery, are some of the indications. Selective external and internal carotid studies are useful.

MANAGEMENT

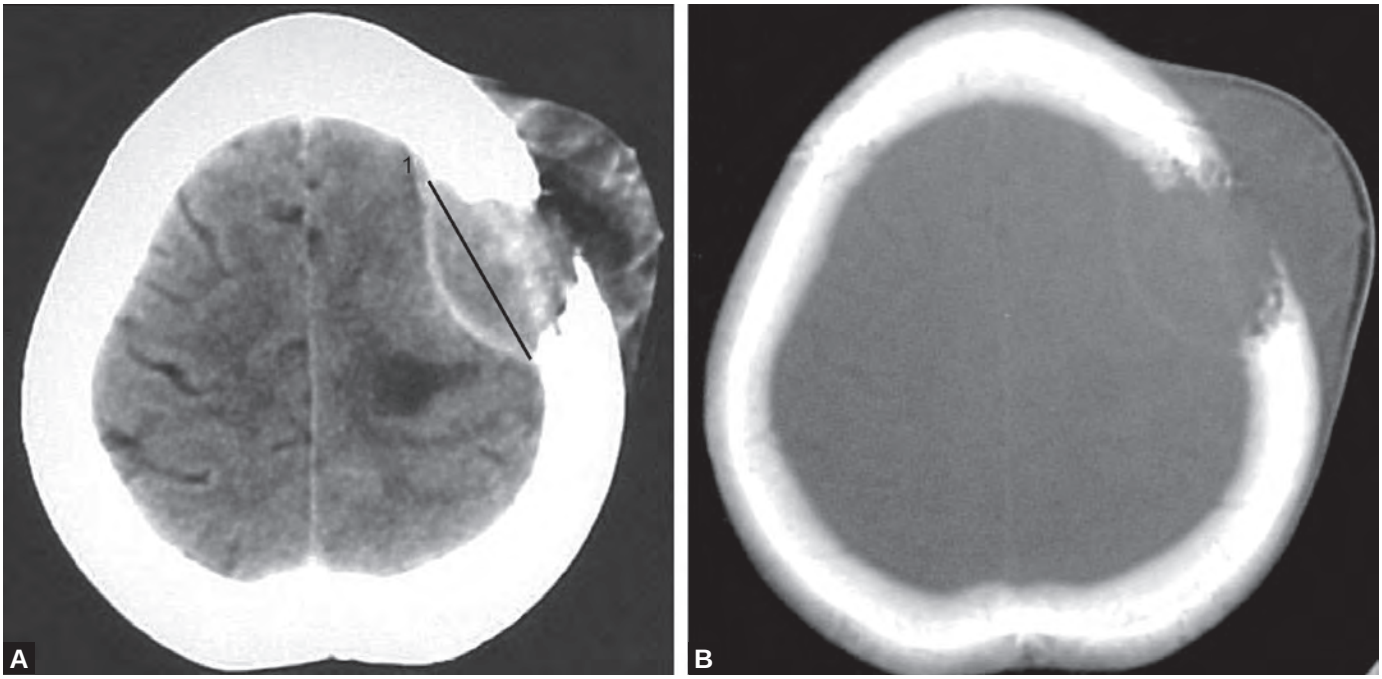
In principle, the treatment of neoplasms of the skull is similar to that of bone tumours elsewhere. The close proximity of the brain and other vital structures necessitates certain modifications in the therapy. Surgery, radiotherapy and chemotherapy are the modalities of treatment available and are often used in combination.

Operative Treatment

This depends on the suspected nature of the lesion, its location, single or multiple and whether neurological deficits are already present or are likely to result. A suspicious skull lesion, in the absence of any other demonstrable primary process, calls for a biopsy to determine the line of therapy. A needle biopsy may be adequate in some cases. In hard non-penetrable lesions, an open biopsy is done through an incision made at the circumference of the lesion, taking an adequate amount of tissue. The incision used for the biopsy should not interfere with any later scalp flap that may become necessary to excise the tumour.



Figs 1A and B: (A) X-ray skull lateral view showing osteolytic lesion in the frontoparietal region. (B) X-ray skull lateral view showing multiple osteolytic lesions, predominantly in the frontal and parietal bones



Figs 2A and B: CT scan bone cuts in the same patient, as in Fig. 1A, showing osteolytic lesion with soft tissue swelling

Primary tumours of the skull are excised completely whenever possible. This is especially important if the lesion produces neurological symptoms, causes cosmetic deformity or becomes infected. Cranioplasty may be done at the same sitting or at a later date. One must be prepared for full scale intracranial dissection, including dural grafting procedures. Modern imaging techniques give adequate warning to the surgeon to be prepared for such steps. Skull base lesions need special operative exposures and may need the co-operation of otorhinolaryngologists and plastic surgeons.[62,89,97] There has been remarkable progress in the treatment of these lesions with the advent of the speciality of skull base surgery. Lesions earlier considered inoperable are now being totally excised with good results.

Radiation Therapy

When deciding on radiation therapy, careful planning is necessary, taking into consideration the radiation sensitivities of adjacent normal structures such as the brain and eyes. In general, tissue response to radiation depends not only on the total dose but also the manner in which it is delivered. Multiple small fractionated doses per day spread out over a longer time, give a greater tumour killing response with less damage to normal structures.[88] Generally, the required dose is 55 Gray (Gy) or 5,500 rads in 30 fractions over 6 weeks utilising megavoltage photon radiation.[19,79,86]

Radiation damage to skull bones is uncommon with therapeutic doses; there is a 1% chance of delayed malignancy (sarcoma) in the irradiated bone.[14] Higher energy photon or electron beam therapy is the ideal treatment and can be tailored to the tumour volume by computerised techniques.

Adjuvant therapies, like the use of hyperthermia and hypoxic cell sensitisers, are being tried.[23,95] Palliative radiation to reduce the size of the mass may be advised, depending on the expected survival time and the probability of late adverse reactions.

Chemotherapy

Chemotherapy alone is useful in a few conditions like Hodgkin's disease, acute childhood lymphocytic leukaemia and testicular carcinoma.[30]

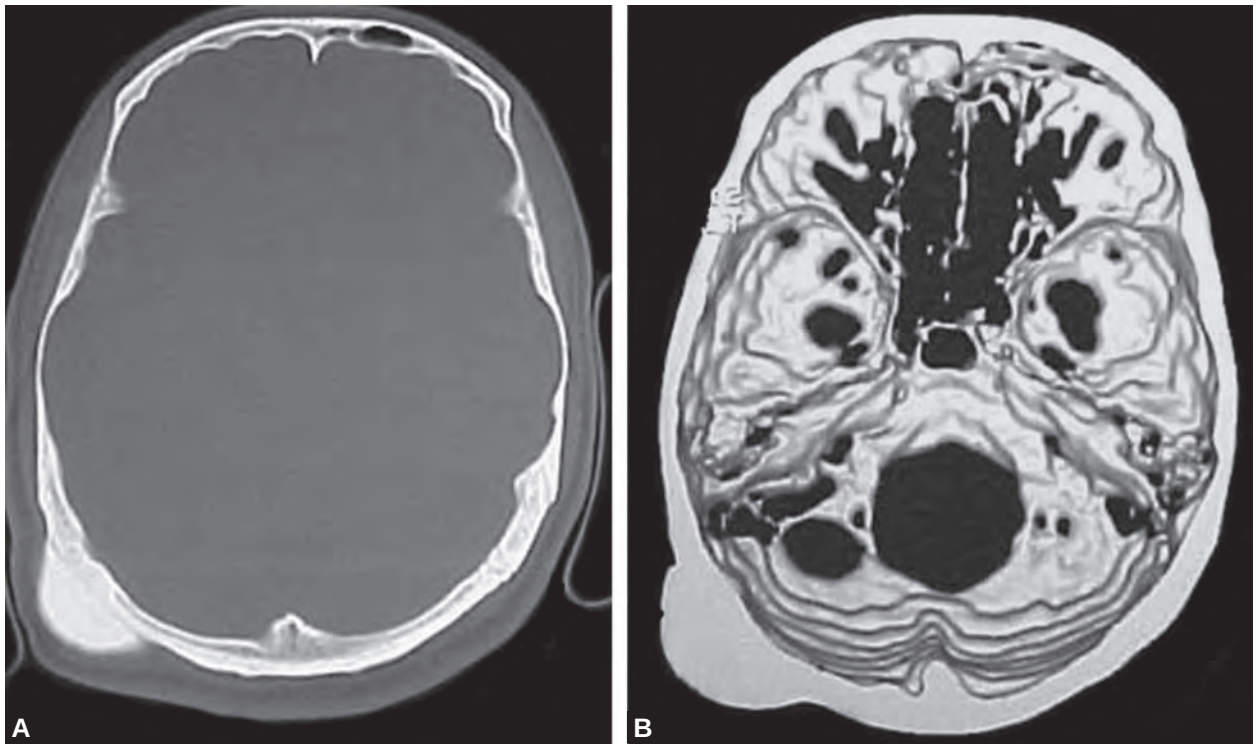
PRIMARY TUMOURS OF THE SKULL[91]

Benign Tumours

Osteoma

Osteomas are the most common of the benign neoplasms of the skull and facial bones. Bagchi,[4] reported osteomas to account for 32% of 31 skull tumours encountered by him. Usually solitary lesions are seen in the frontal region. They arise from membranous bone and proliferate into dense cortical bone or spongy cancellous bone. They commonly occur in the frontal sinus and in the mastoid air cells.[110] These slow growing tumours form an outward excrescence which is hard and painless and are usually noted while combing the hair. A compact osteoma may become hard like ivory. The attachment to the skull may be narrow or broad. Rarely, an osteoma may extend intracranially and cause seizures.

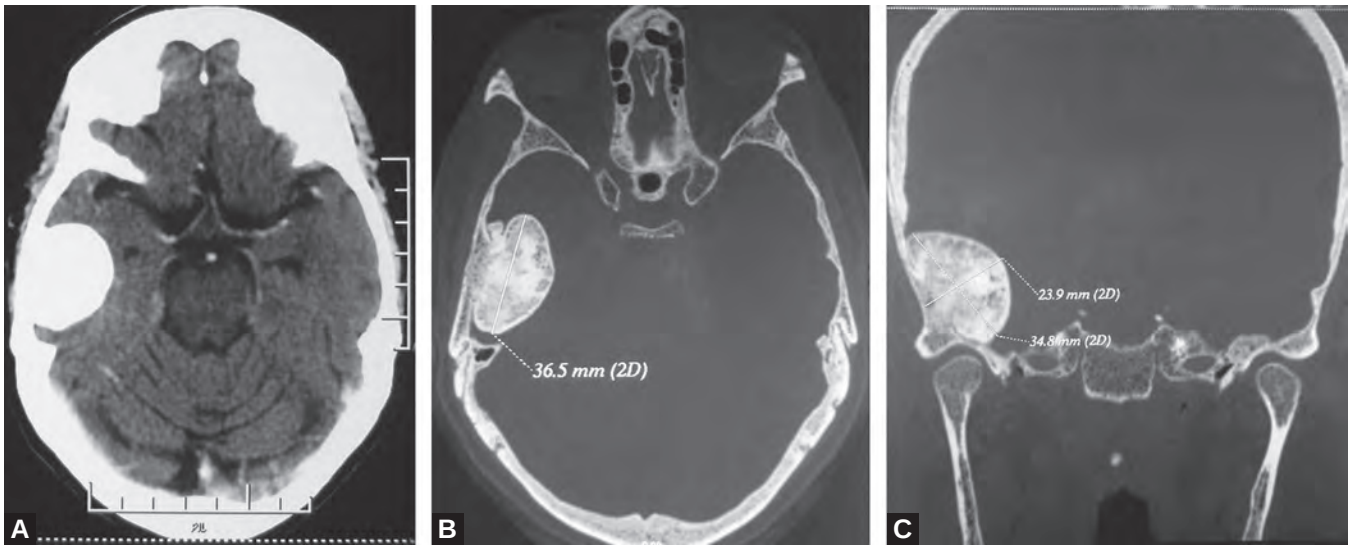
In plain X-rays, an osteoma is seen as a solid homogeneous bony shadow. There are no increased vascular channels. Tangential projections reveal the base and the



Figs 3A and B: CT bone cuts and reconstruction showing osteoma of the right occipital region

absence of involvement of the diploe and inner table. When the inner table is involved, differentiation from a meningioma becomes necessary. CT gives the precise diagnosis (Figs 3A and B and 4A to C). Multiple osteomas of the calvaria and mandible with soft tissue tumours of the skin and colonic polyposis form the triad of Gardner's syndrome.[22] Microscopically, the tumour is a nucleus of osteoid tissue in a background of osteoblastic connective tissue and is completely enclosed by reactive bone. Histological differentiation from fibrous dysplasia is difficult; but the presence of smooth, homogeneous and sharply defined sclerotic nodules is unusual in fibrous dysplasia.

Osteomas are surgically curable. The indications for removal are rapid growth, pain, obstruction to sinus outlets and noticeable deformity. Small osteomas of the outer table may be resected easily without destruction of the inner table. As these lesions are very hard, it is wiser to removed them by cutting around their base through the cancellous tissue. A large lesion needs removal of the entire bone as a flap and the defect is closed by cranioplasty. After excising the bone flap, the osteoma



Figs 4A to C: CT scan of the brain with bone cuts showing osteoma of the left temporal bone growing intracranially

can be excised from the flap and the flap can be used to close the defect primarily.[64]

Haemangiomas

Haemangiomas constitute about 7% of all skull tumours.[124] About two-thirds of haemangiomas of bone occur in the skull or the vertebral column. They arise from the vascular elements of the diploe, mainly in the vault of the skull and to a lesser extent in the roof of the orbit or petrous temporal bone. They are slow growing and may reach a large size. They are painless and the presence of a swelling is the chief complaint. The swelling is hard, but may be soft in some places. The skull is involved by erosion and the margins are imperceptible. Dilated veins may be present. In haemangiomas of the orbit, proptosis, blindness or extraocular palsies may be seen. Haemangioma of the petrous bone may present with deafness and cranial nerve palsies.

The plain X-rays show a swelling with a typical honeycombed or sunburst appearance. The diploe is enlarged and both tables of the skull bulge, outer more than the inner. Rarely, intracranial extension is seen.[104] The trabeculae are seen vertically oriented. The edges are well defined and a thin margin of bony condensation may be evident. CT images with 'bone window' show the hypodense matrix with discrete, thickened, sclerotic and widely separated trabeculae. Despite the vascular nature of the lesion, contrast enhancement is an exception rather than the rule. Carotid angiography shows enlargement of the external carotid artery branches.[104] Rarely, there may be an internal carotid supply to these tumours.[2] Calvarial haemangioma at a cranioplasty site presenting as scalp swelling has been reported by Kang et al.[60] which required total surgical removal along with cranioplasty.

Treatment is usually by en bloc excision or wide curettage. The tumour appears as a blue domed hard mass under the pericranium. Sometimes, the dural surface may bleed profusely in which case circumferential incision of the dura and resuturing will help. Radiotherapy is advisable in situations where excision is not feasible. Doses up to 30 Gy (3,000 rads), in 3 weeks, may be required.[88]

Giant Cell Tumours (Osteoclastoma)

Giant cell tumours arise from the cartilaginous bone in the sphenoid, mastoid or occipital areas.[104,105] They are extremely rare in the bones of the vault, as osteoclasts are usually not present in membrane bones. Their pathogenesis is unknown, although trauma and haemorrhage may precede their occurrence.

Osteoclastoma of the skull presents as a painless bony swelling and radiographs show evidence of rarefaction or destruction of bone. Excision is the treatment of choice; but it is often incomplete and needs supplementary radiotherapy to ensure freedom from recurrence. Occasionally, malignant changes have been reported after surgery and radiotherapy.[80] Considering the aggressive nature and potential malignancy of these lesions, careful long-term clinical and imaging follow-up is recommended.

Epidermoid and Dermoid Tumours

These tumours of developmental origin are derived from epithelial cell rests ectopically included in the bone during development. They are commonly seen in or near the midline at the vertex, the frontal or occipital regions or in the temporal bone. A posterior fossa dermoid associated with symptomatic syringomyelia has been reported.[121] However, they may occur anywhere in the calvarium. They originate in the diploe and enlarge in both directions expanding and thinning both the tables by continuous growth pressure. The bone at the edges of the lesion gets sclerosed. The lesion may break through the egg shell thin tables and expand under the scalp or extradurally. The swelling under the scalp is firm, rubbery and non-tender. Sometimes, a tract may extend through the inner table and dura to end in an intradural lesion. A lesion in the midline, especially over the torcula, may involve the venous sinuses.[81] Very large intracranial extensions may exist with surprisingly normal intracranial pressure and with no neurological deficits.[47] These are described as giant intradiploic epidermoids.[16,107] The larger lesions, especially epidermoids, tend to get infected and osteomyelitis may result.

Plain radiographs show a clear cut area of radiolucency in the skull with sclerosed margins, resembling an enlarged emissary foramen. Tangential views show expansion of the tables.[33,123] CT accurately delineates the bony defect and the size, location and extension of the soft tissue mass outside and inside the skull and dura. The lesion appears hypodense relative to the adjacent brain, due to contained keratinised debris and cholesterin.[68,129] They do not enhance with contrast, but adjacent compressed brain shows marginal enhancement. On MR, these lesions appear hyperintense in T2-weighted images and most often hypointense in T1-weighted images.

Treatment is by surgery. Pure extracranial lesions can be excised en bloc. A careful search must be made for any intradiploic or intracranial extension along a thin track which, if present, needs to be excised. While dealing with midline lesions, the surgeon must be prepared to do an extensive craniotomy and venous sinus repair, if necessary.[81]

Chondroma

These arise mainly in the cartilaginous bones of the base of the skull. They commonly occur between the ages of 20 and 40 years. The common sites are the paranasal sinuses and the sphenoethmoidal and spheno-occipital synchondroses. Depending on the site of origin, they may extend into the sellar or parasellar region, producing visual and ocular nerve palsies or endocrine dysfunction. The posterior lesions may compress the brainstem and involve the lower cranial nerves.[75] Radiographically, a chondroma appears as a lytic lesion at the base of the skull with fairly sharp margins. Areas of stippled calcification may be seen in more than 60%.[74,85,113] CT reveals well marginated bone destruction and an associated homogeneous, isodense and lobulated soft tissue mass with interspersed

calcification. Contrast enhancement is infrequent and when present is minimal. Differentiation from metastasis is based on the sharpness of the bony margin and the presence of calcification. Other lesions to be differentiated are chordoma and meningioma.[1,2,3,32,40,49,52,56,57,71,96,108,119]

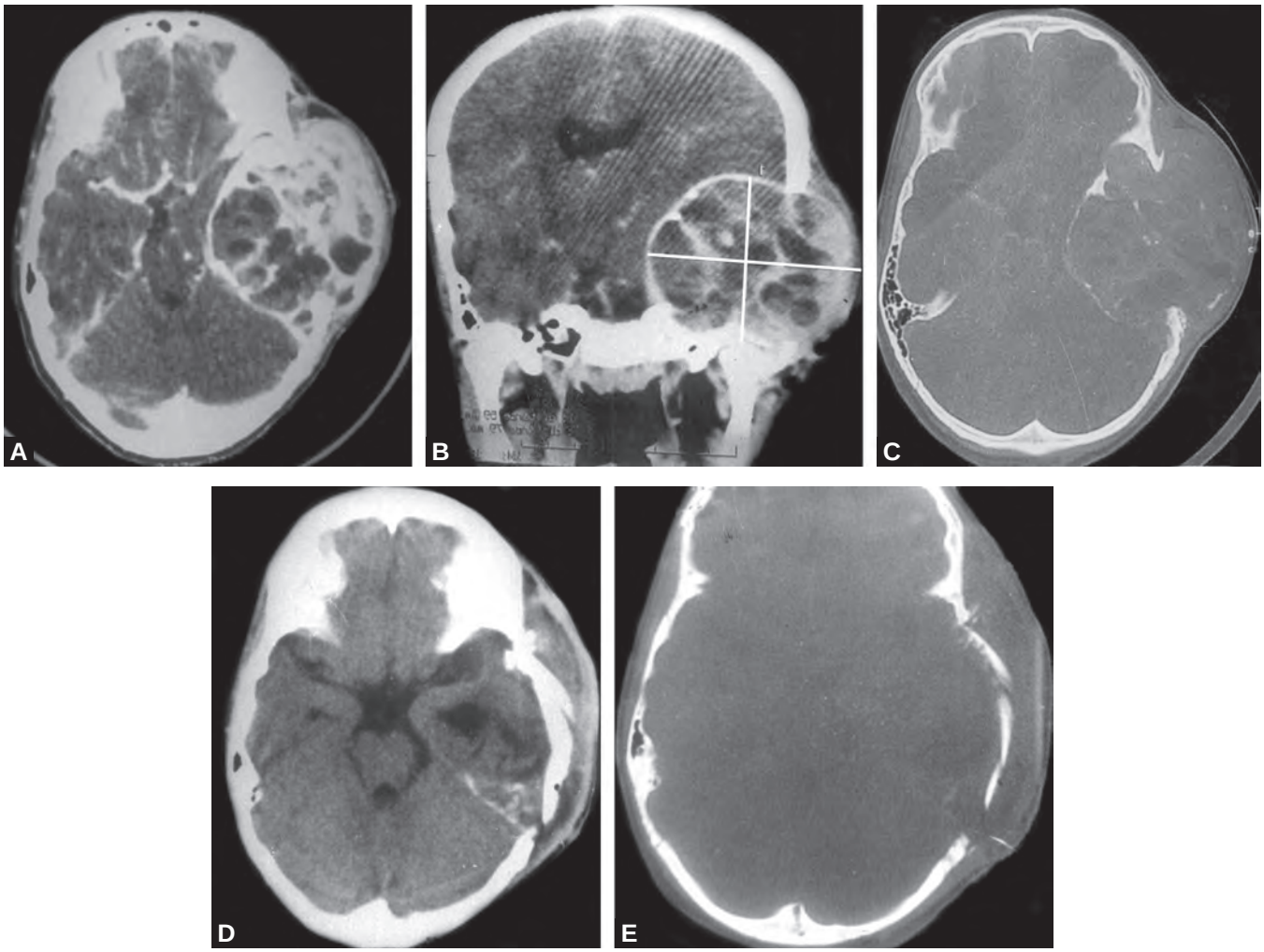
Sarcomatous changes occur in 1–2% of these tumours, more frequently in individuals with Maffucci's syndrome (multiple enchondromas and multiple subcutaneous haemangiomas).[8,72] Rapid growth indicates a malignant change. Histologically, malignancy is deduced by the presence of atypical cartilage cell nuclei in the actively growing peripheral portions of the neoplasm.[73] The treatment of a chondroma is total removal wherever possible. Most often, only partial removal is possible, especially at the skull base. Decompression of neural structures by such partial removal is often beneficial.[38]

Other Benign Tumours

Calvarial lipomas: They are rare. They present as painless, benign and slowly progressive lesions, often an incidental finding. These lesions appear hyperintense on both T1- and T2-weighted images. On CT scan, evidence of mixed bony destruction and proliferation are reported. Gross and histological features are like lipomas elsewhere. They are cured by excision.

Cavernous haemangioma of the skull: Despite their low incidence, cavernous haemangiomas must be included in the differential diagnosis of slow-growing osteolytic lesions located in the skull. The elective treatment of these tumours includes a complete resection by craniectomy, with safe bony margins. A large cranial cavernous haemangioma can be treated using embolisation and craniotomy with preservation of the outer cranial table.[18]

Aneurysmal bone cyst: It is a multiloculated expanding cystic tumour with a rich vascular network in the walls.[76] The encircling inner and outer tables are eroded to form thin bony shells. Some cysts show a central core of haemangioma and repeated haemorrhage may be the cause of the cystic expansion of the skull tables.[13] These lesions may either become symptomatic or enlarge during pregnancy.[21] On CT, the contents of the cyst may be of high or low density, depending on the protein content of the fluid (Figs 5A to E). The superficial temporal and



Figs 5A to E: (A to C) CT scan of the brain axial coronal and bone cuts showing aneurysmal bone cyst of the temporal bone. (D and E) Post-operative CT scan with bone windows of a patient with temporal aneurysmal bone cyst

middle meningeal arteries supply the tumour and this is made out well on selective external carotid angiography.

Ossifying fibromas or benign osteoblastoma: It is a rare tumour and has been described as a giant osteoid osteoma by Dahlin et al.[28] It is a solitary vascular tumour, predominantly osteolytic in character, with varying degrees of calcification and new bone formation. Treatment is by local excision.[103]

Osteoblastomas: They are occasionally seen in the base of the skull, but rarely in the vault. Most frequently, they occur in the midline in the clivus.[114,115] Depending on the site of origin, they produce signs of pressure on the optic nerves, the pituitary, the hypothalamus, the brainstem and the other cranial nerves. Radiologically, islands of erosion with normal bone in between are seen in the region of the clivus and sella. A suitable skull base approach enables excision of as much of the lesion as possible to ensure decompression of neural structures and the pituitary gland. Radiotherapy can be given post-operatively. A long-life span is usually expected. Malignant transformation after treatment has been occasionally reported.[80]

Myxomas: They are rare benign tumours arising from mesenchymal tissues throughout the body. Involvement of the skull base with intracranial extension has been reported but is extremely rare. It requires surgical excision. Despite radical surgery, the tumour may recur requiring re-surgery. The differential diagnosis frequently includes chondrosarcomas, chordoma, metastatic tumours of the skull, haemangiopericytoma, meningioma and other neoplasms of the dura and skull base in this location.[112]

Malignant Tumours

Chondrosarcoma and Osteogenic Sarcomas

They are the two primary malignant tumours of the skull and both are rare. Chondrosarcoma is a tumour of adult life, usually occurring as a malignant transformation in a benign chondroma. Chondrosarcomas form 0.1% of all intracranial tumours and 6% of skull base lesions. The common site is the base of the skull, in or around the sella, the cerebellopontine angle or the frontoethmoidal air sinuses.[5] They grow for a long time and produce pain, deformity and cranial nerve palsies in the advanced stages. Roentgenograms show destruction of bone with irregular poorly defined margins.[85] In more than 50% of cases, stippled calcification is seen, a fact used to differentiate these lesions from metastatic carcinoma, lymphoma and myeloma.[5] CT demonstrates an irregular destructive process with a soft tissue mass that is homogeneous and hyperdense. Areas of calcification are seen within the mass in more than 60% of cases. On contrast infusion, irregular and heterogeneous enhancement of moderate intensity is noted within the tumour.[46] They are locally invasive and tend to recur. Radical resection with supplemental radiation therapy is the treatment of choice. The five-year survival rate is usually in the range of 60–70%. Systemic chemotherapy is ineffective.[17,30,83]

Osteogenic Sarcoma

This rare tumour occurs usually in the vault and accounts for about 2% of all primary osteogenic sarcomas. It usually occurs in young persons, between the ages of 15 and 25 years. A second modest peak occurs in older patients with advanced Paget's disease of the skull.[29,106] Occasional cases have been reported as a late complication many years after radiotherapy to the calvarium.[7,45,59]

Osteogenic sarcomas grow rapidly and hence the history is quite brief. Pain and local swelling are the common symptoms. Early metastases to the lungs and other bones usually occur. On the plain radiographs they appear as a large lytic area with poorly defined margins.[33,42] Radiating bony spicules, in the form of sun rays, may be seen in some cases at the edge of the tumour. The calvarium is thickened at the advancing edge of the tumour due to subperiosteal extensions. CT shows irregular and prominent new bone formation within a large heterogeneous extradural mass showing irregular contrast enhancement.[6]

These tumours are extremely vascular and are sometimes referred to as bony aneurysms. Histological features are extremely variable with foci of new bone formation, necrosis, haemorrhage, telangiectasia and a frank sarcomatous stroma.[73] The reported incidence of osteogenic sarcoma in Paget's disease varies between 1% and 10%.[36,127] Radiographically, there is rapidly progressive lysis within the thickened and irregularly dense bone.[41,127] The usual treatment is complete excision followed by high doses of irradiation of 60–70 Gy (6,000–7,000 rads) post-operatively.[30] Adjuvant chemotherapy with methotrexate and leucovorin in high dose is administered. With this combination, a five year survival of 50% and even a cure may be achieved in some patients even with metastatic disease.

Fibrosarcoma

Fibrosarcoma may arise from the periosteum of the skull or from the dura. It presents as a rapidly growing painful tumour. In the early stages, X-rays show only a thinning of the outer table by an overlying soft tissue mass. In the later stages, there are large areas of complete destruction of both tables. The margins are irregular. The differential diagnosis is from other lytic tumours. Carcinomas are usually smaller and multiple. Meningiomas rarely cause an extracranial mass and other symptoms are likely to occur earlier. Osteogenic sarcoma without new bone formation at the periphery may cause difficulty in diagnosis on plain X-rays. Microscopic examination of a fibrosarcoma shows only a sarcomatous stroma without any new bone formation.

Fibrosarcomas are treated by radical resection, followed by high doses of post-operative radiation; 60–70 Gy (6,000–7,000 rads) in 6–7 weeks. Chemotherapy has

not been found to be advantageous. A five-year survival rate of 3% has been reported.

Ameloblastic Fibrosarcoma

It is a malignant odontogenic tumour that rarely affects the skull base and surrounding regions. This is due to a malignant transformation of a benign ameloblastic fibroma. The ameloblastic fibrosarcoma can extend from the site of origin to the orbit, anterior or middle cranial fossa, infratemporal fossa or to the cavernous sinus. Progressive proptosis with complete monocular vision loss was the presenting symptom. Multidisciplinary skull base approach, resection of all tumour except that in the cavernous sinus is recommended.[48]

Malignant Fibrous Histiocytoma

This is a pleomorphic sarcoma arising in the deep soft tissue of the extremities. It has also been found to arise from the bones and rarely from the skull. Hatashita et al.,[53] reported seven cases in the skull bones out of 177 such cases in the entire skeletal system. The frontal, temporal and occipital bones were seen to be involved, and there was a lesion in the clivus forming a retropharyngeal mass.[24,26,34] Metastases occur in the mediastinum, thoracic vertebrae and lungs. CT shows a large mass of low density with patchy enhancement, extending on the inner and the outer surfaces of the cranial bone with patchy enhancement. MR shows a bulky tumour with mottled enhancement with contrast.[109] Sometimes, local scalp tenderness and a skull defect in the plain film in the corresponding area may be present for several months, before the tumour becomes obvious.

The gross appearance and conventional histological examination do not show any specific features. There is a highly cellular pleomorphic picture consisting of spindle shaped cells of fibroblastic and histiocytic origin arranged in a spongiform pattern. The exact diagnosis can be made only by immunohistochemical methods to demonstrate intracytoplasmic granules, with staining of alpha-1 antichymotrypsin and alpha-1 antitrypsin. Eight to twelve months survival has been reported.[122]

Chordoma

See chapter on "Chordoma".

Ewing's Sarcoma

It is rarely seen as a primary lesion in the skull.[78] The most common site for primary Ewing's sarcoma of the cranium is the temporal bone followed by the frontal, parietal and occipital bones. The sphenoid and ethmoid are less commonly involved.[116] The patient usually complains of intermittent pain, more at night. The swelling appears later and may fluctuate in size, with increasing pain during periods of enlargement. Anaemia, leucocytosis and fever are common. The lesions are often multicentric in origin involving the tibia, ribs and vertebrae. Metastasis may occur in the liver.[82]

On plain X-rays, the lesion appears as an irregular area of bone destruction with poorly defined margins and an overlying soft tissue mass. A minor periosteal reaction may be present. CT and MR help to delineate the extent of bony involvement and the soft tissue mass, both extracranial and intracranial and will also demonstrate a diploic lesion. The venous phase of carotid angiography demonstrates depression of the superior sagittal sinus.

The lesion is composed of compact strikingly uniform cells with indistinct borders and large prominent nuclei. Differentiating this tumour from reticulum cell sarcoma and from neuroblastoma with skeletal metastases is difficult, but is very important to assess the prognosis.[78,130] Diagnosis can be confirmed by either immunohistochemistry or chromosomal abnormalities. Chromosomal abnormalities (translocation 11;22) can be detected by karyotyping and RT PCR.[17] Ewing's sarcoma is initially quite radiosensitive, so that radiation therapy with systemic chemotherapy is the treatment of choice. Recurrences are common and the prognosis is not good with any kind of treatment.

Other Malignant Tumours

Reticulum cell sarcoma is rare tumour of the skull. It appears as a lytic lesion and the diagnosis is made on histology. En bloc excision followed by radiotherapy has produced clinical cures. Angiosarcoma is occasionally seen in the skull as a soft, painful, rapidly enlarging tumour which may invade the adjacent scalp and dura. It is seen as a poorly demarcated osteolytic lesion in plain X-rays. Distant metastases are common. Microscopically, it consists of highly vascular channels, marked anaplasia and moderate mitotic activity. Wide en bloc excision followed by radiotherapy is recommended.

TUMOURS INVOLVING THE SKULL BY DIRECT EXTENSION

Meningiomas[27] may produce varying degrees of incidental bony changes in the overlying skull and may also invade the skull bone itself. The tumour may extend into the diploe and sometimes break through the outer table to form a subcutaneous palpable tumour. Such bony involvement may occur in the vault, the cribriform plate, the sphenoidal ridge or in the planum sphenoidale. While convexity meningiomas are large tumours, the dural involvement in basal lesions is often en plaque. These features and the bony involvement are seen well in CT scans. The bone involved by meningiomas can be highly vascular with tortuous arteries and large venous channels.

The bony changes caused by basal lesions may resemble those of fibrous dysplasia. The latter is usually bilateral, occurs at a younger age and angiography does not show enlarged external carotid artery branches. Sometimes, meningiomas may fail to produce a blastic response and may destroy the bone, giving an appearance very much like a metastasis in the plain skiagrams. Bone infiltrated by meningiomas is highly vascular.

Great care is needed in turning the bone flap which may have to be excised. Cranioplasty may be needed if the involved skull bone is excised. Sometimes, meningiomas remain completely intradiploic, expanding the two tables resulting in a doughnut like lesion in the plain skiagram. Total excision with repair of the bone defect gives good results.[99] Recurrent craniofacial meningiomas can usually be managed by using a lateral cranial base approach. A radical resection may prevent further recurrence with an acceptable quality of life.

Glomus Jugulare Tumour

See chapter "Jugular Foramen Lesions".

Nasopharyngeal Tumours

Benign tumours invading the base of skull are commonly angiofibroma and squamous cell papilloma. These tumours usually become symptomatic long before they invade the base of skull. When skull involvement is minimal, they can be removed through the nasopharynx. If there is marked intracranial extension, a combined approach will be necessary to ensure complete excision.

The incidence of nasopharyngeal carcinomas is low, being about 0.01% of all cancers. They are either epidermoid carcinomas or lymphoepitheliomas. The latter seems to be more prevalent among Mongoloid races. The tumour originates from the nasopharyngeal epithelium and invades the base of the skull through the foramina and also metastasises to the regional lymph nodes. Usually they are detected late, after intracranial extension has occurred. Almost all the cranial nerves may get involved.[39] Hard lymph node enlargement high in the neck may be the first symptom. Quite late in the disease, dysphagia, nasal obstruction and epistaxis may occur.

The diagnosis is made by local inspection and palpation of the nasopharynx and from evidence of erosion of the base of the skull in plain X-ray films. CT reveals the bony erosion and the soft tissue mass both intracranially and extracranially and the displacement of neural structures. SPECT is superior to CT in detecting early bone involvement by showing markedly increased focal radiotracer uptake in regions of bone involvement.[111] Differentiation from other similar lesions, e.g. chemodectoma or chondrosarcoma, is difficult and a biopsy is necessary. Nasopharyngeal carcinoma is primarily managed by radiation therapy with curative doses of 60–70 Gy (6,000–7,000 rads) delivered over a period of 6–7 weeks. Intensity modulated radiotherapy is being increasingly used in recent days along with chemotherapy for treating nasopharyngeal carcinoma. Better prognosis is seen in younger patients and those without lymph node metastasis at presentation.[50]

Oncocytic Schneiderian Papilloma

Epithelial cells of cylindrical cell papilloma are oncocytes, which arise from the sinonasal respiratory epithelium, hence the term oncocytic Schneiderian papilloma. This is a rare benign neoplasm of the nose and paranasal sinuses. Lesions arising from the nasoethmoidal space can extend to the anterior skull base through bone dehiscence with intradural invasion and orbital space involvement (Figs 6A to D). The clinical behaviour is comparable to inverted papillomas for local recurrence and malignancy co-existence. Surgical excision is the treatment of choice.[9]

Sinonasal Mucosal Melanoma

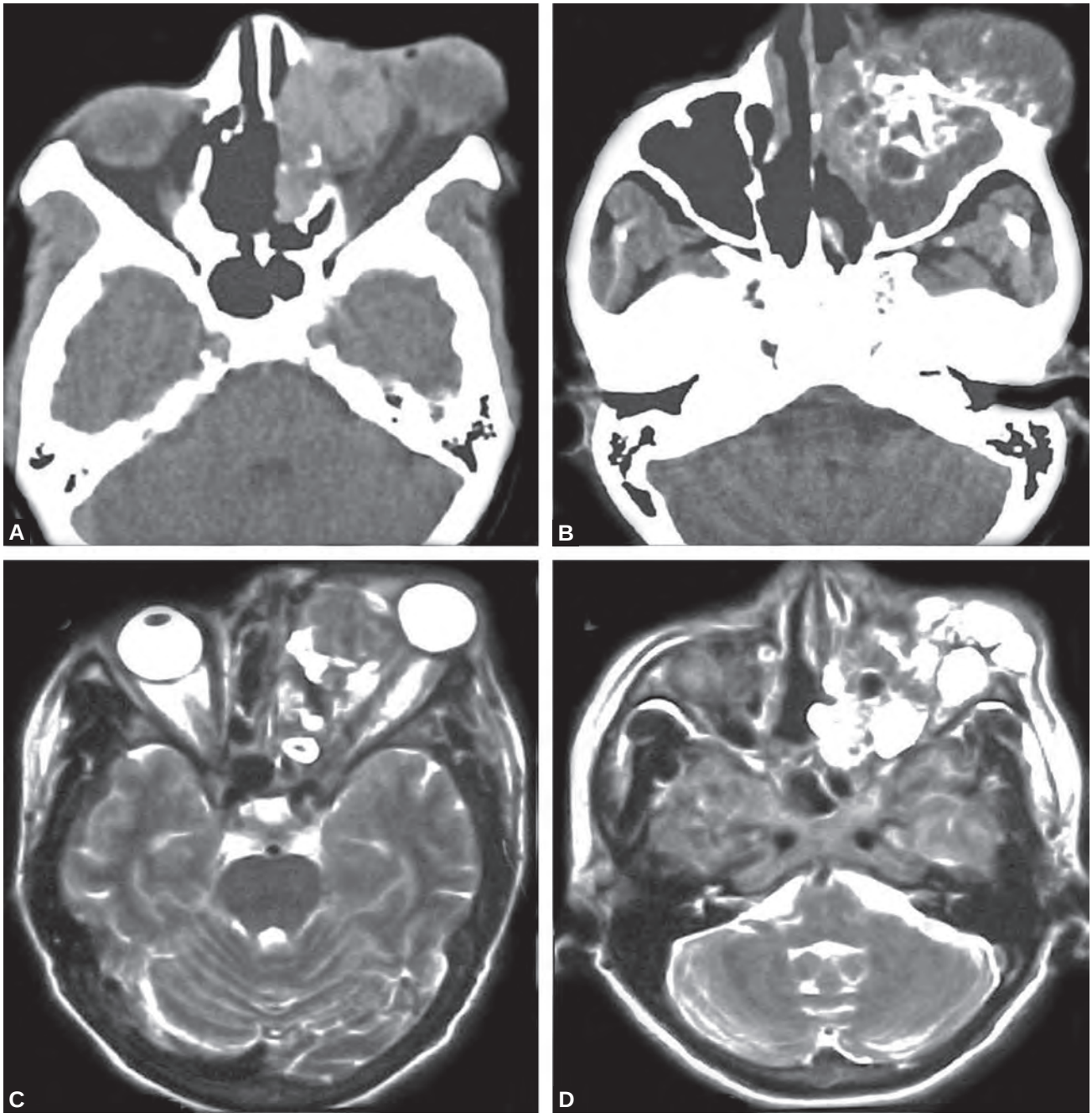
The most common presenting symptoms are epistaxis and facial pressure, mass lesion and obstruction. The most common anatomic locations are the maxillary sinus and nasal cavity. Seventy-two per cent of tumours extend to the skull base, frontal sinus, orbit or cranium. Tumour size ranging from 0.5 to 5.0 cm requires medial maxillectomy and an appropriate approach to the skull base is required to excise the tumour extending to the skull base. Chemotherapy with alpha interferon along with radiotherapy is an effective treatment.[90]

Carcinoma of the Paranasal Air Sinuses

These tumours involve the frontal, ethmoidal or the sphenoidal air sinuses and arise from the sinus epithelium. They invade the bony septae and adjacent walls and also the base of skull. Headache, epistaxis, rhinorrhoea, nasal obstruction and anosmia are the chief complaints. These tumours are best imaged by CT in the coronal plane and better still by MR.[98] Differentiation must be made from metastatic carcinoma, lymphoma, myeloma, osteosarcoma, chondrosarcoma and esthesioneuroblastoma.[12] Survival depends on the histopathological type of the tumour. Squamous cell carcinoma has the worst outcome, whereas adenocarcinoma and glandular carcinoma have better outcome and low recurrence after treatment. Patients with undifferentiated carcinoma exhibited an intermediate survival. Meta-analysis by Dulguerov et al. confirmed that surgery alone or surgery with radiotherapy has better local control and cure rates than with radiotherapy alone. Patients with skull base extension have a worse prognosis. In patients with high nasal and ethmoid carcinoma, craniofacial resection by combined cranial and transfacial approaches has become a routine procedure in a few institutions.[17]

Malignant Sweat Gland Tumour (Hidradenocarcinoma)

Malignant sweat gland tumours are rare neoplasms with high recurrence and metastasis rates. Nearly 50% of dural based hidradenocarcinoma have local brain invasion. The pathogenesis of these tumours is thought to be from ectopic sweat gland cells entrapped in the dura mater, as there is no scalp or skull bone involvement at presentation. Magnetic resonance imaging reveals a heterogeneous intense dural-based lesion in both T1- and T2-weighted images.[69]



Figs 6A to D: CT scan and MRI of a patient suffering from papilloma, arising from the paranasal sinuses, with extension into the orbit, causing proptosis

Orbital Rhabdomyosarcomas

Orbital rhabdomyosarcomas, being the most common primary orbital malignancy in children, form 8% of all childhood malignancies. They have a propensity for local spread to the skull base and parameningeal spread often resulting in a worse prognosis. MRI shows the extent of the lesion while CT scan shows bony erosion. In patients with limited disease, multimodality treatment including surgery, chemotherapy and radiotherapy need to be given to improve the outcome and quality of life. In patients with extensive skull base involvement metastatic workup needs to be done and a decision has to be taken on an individual basis.[120]

Haematogenous Metastasis

The usual primary sites for skull metastases are the breast, the lungs, the prostate, the thyroid and the kidneys. The skull metastases are osteoblastic when the primary is in the prostate, breast or gastrointestinal tract or osteolytic when they arise from carcinoma of the lung, uterus, thyroid, pancreas and kidney or from malignant melanoma.[33,123] Since the close attachment of the dura mater to the cranial bones, malignant deposits in the skull may invade the dura.

Osteolytic metastases to the skull are typically seen in plain X-ray films as multiple radiolucent areas with poorly defined margins. The size and degree of

radiolucency is variable and it is estimated that more than 50% demineralisation must occur before a lesion could become radiographically evident.[63] The larger lesions are quite typical in appearance, but lesions less than 5 mm and confined to the diploe are very much like multiple myeloma. Osteomyelitis of the skull may also have a similar radiographic appearance, but bone destruction appears later in the disease and clinical manifestations of severe pain, a soft tender swelling and constitutional symptoms occur earlier.

Osteoblastic metastases appear radiographically as multiple, poorly marginated areas of slightly increased density. On CT, the bone shows slight thickening. In some cases, mixed lucent and sclerotic areas appear, e.g. metastases from carcinoma of the breast. Although metastases can affect any part of the skull, they are found to be common in the vault. In the base, the common sites are the dorsum sellae and the clivus, where the radiographical appearance may be mistaken for demineralisation due to chronic raised intracranial pressure.

Conventional radiographs are positive only in 60% of cases of calvarial metastases and CT in 85%.[122] It is important to view the images at "bone window" setting and intravenous contrast infusion is necessary to show extradural and scalp extension[101] (Figs 7A to D). Although radionuclide bone scanning is more sensitive, it lacks the specificity and anatomical configuration. Biopsy of the skull lesions may be needed to establish a diagnosis. A complete excision of the lesion can be done and the treatment correlated with that of the primary disease. Local palliative radiation may be useful to relieve pain and symptoms of nerve compression at the base of the skull.

Lymphoma

Involvement of bone is a common late feature in disseminated lymphomas and occurs in 10–15% in Hodgkin's and 7–25% in non-Hodgkin's lymphoma.[55] Skull radiography shows areas of osteolysis and it is not uncommon to find an admixture of sclerotic areas also. CT shows the lesions at the stage of diploic permeation and also delineates extradural and scalp extension.[55] The more aggressive lymphosarcoma and reticulum cell sarcoma rarely involve the skull. Treatment consists of local radiotherapy 30–40 Gy (3,000–4,000 rads) over 3–4 weeks, with chemotherapy for wide spread disease.

Leukaemia

Leukaemia in childhood manifests with skeletal pain, anaemia and fever. Calvarial lesions are uncommon and, when they occur, they appear as ill-defined areas of rarefaction with peripheral new bone formation similar to a neuroblastoma.[33] Low dosage radiation may give rise to symptomatic resolution. Chemotherapy of the systemic disease produces a more effective remission.

Myeloma

Multiple myeloma is the most common primary malignancy of the skeletal system. It affects males more commonly and occurs between the ages of 40–60 years. The skull is a common site for these lesions. Pain, weight loss, palpable tumours, anaemia, hypercalcaemia, hyperglobulinaemia and Bence Jones proteinuria are the usual features. Biopsy of the lesion or bone marrow biopsy will usually clinch the diagnosis. Skull radiography usually shows multiple punched out areas of bone destruction of different sizes and density. Less commonly, a solitary tumour about 2–3 cm in diameter may occur. In more than 80% of cases the solitary type lesion eventually becomes multiple.[66] Solitary plasmacytomas are treated with radiotherapy in curative doses of 50 Gy spread over 5 weeks. Multiple myeloma is treated with chemotherapy, melphalan and prednisone being the most commonly used drugs. Frequently, skull involvement is treated palliatively with radiation doses of 30 Gy in 2 weeks.[30,88]

Neuroblastoma

It is a common tumour of childhood. Skull metastases often precede detection of the primary adrenal tumour. Typically, the child presents with periorbital ecchymosis and an associated abdominal mass. Diffuse nodular lucencies are seen in radiographs.[33] The lesions are highly vascular and they lift up the periosteum, thus producing radial bone speculation extending into the soft tissues. A similar spread occurs on the inner aspect of the skull and the cranial sutures get invaded producing diastasis of sutures.[20] Although the dura often resists the spread of the lesion, spontaneous intratumoural haemorrhage may rupture through the dura into the brain parenchyma (Figs 8A and B). CT is useful in detecting the gross thickening of the skull, the extent of the intracranial mass and also complications like haemorrhage and compression of dural venous sinuses.

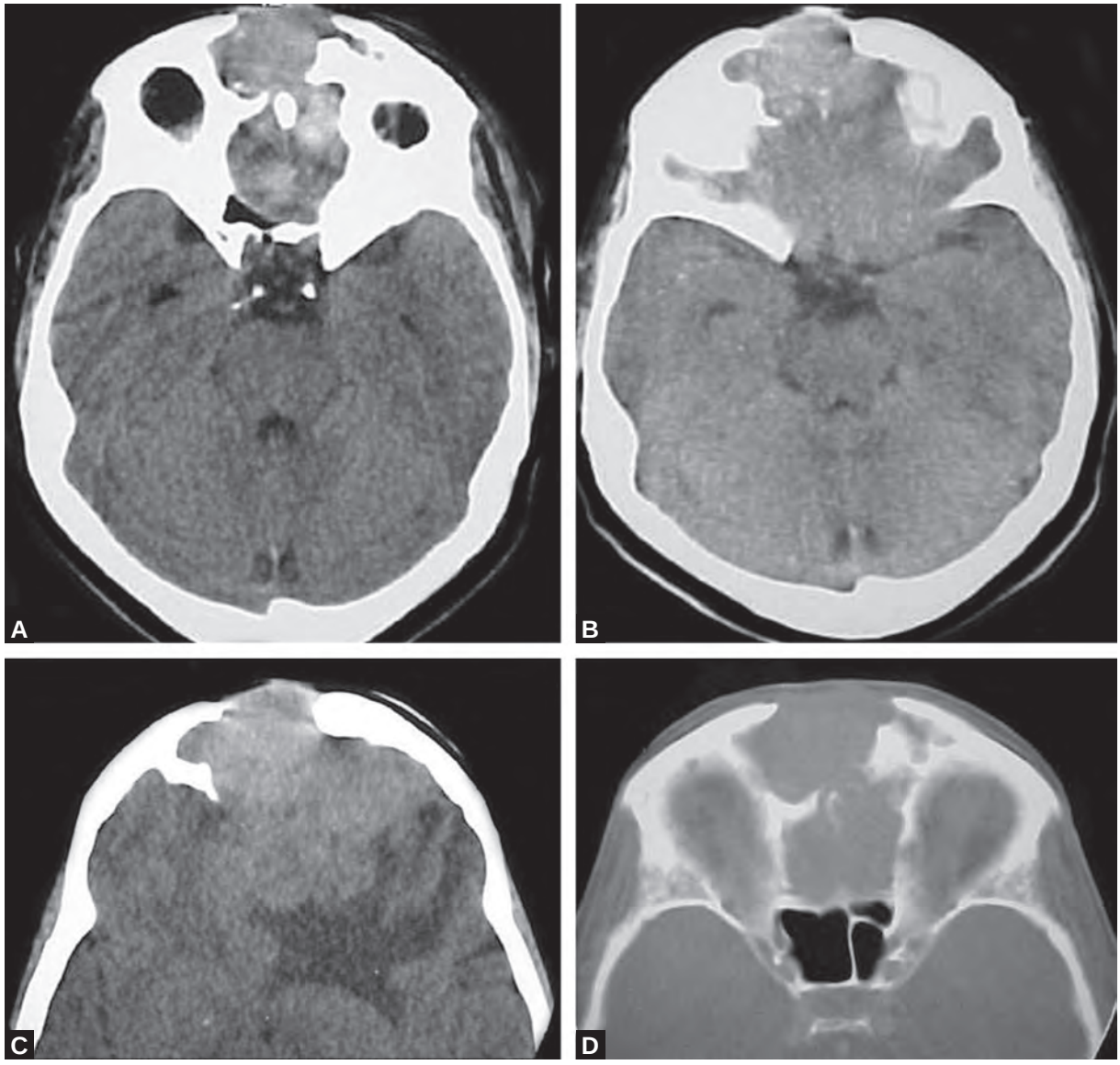
Spontaneous resolution of a neuroblastoma into more benign forms has been known to occur occasionally, as the patient matures; but involvement of the skull suggests a poor prognosis. Local irradiation and systemic chemotherapy are the treatment of choice.

CONDITIONS SIMULATING SKULL NEOPLASMS

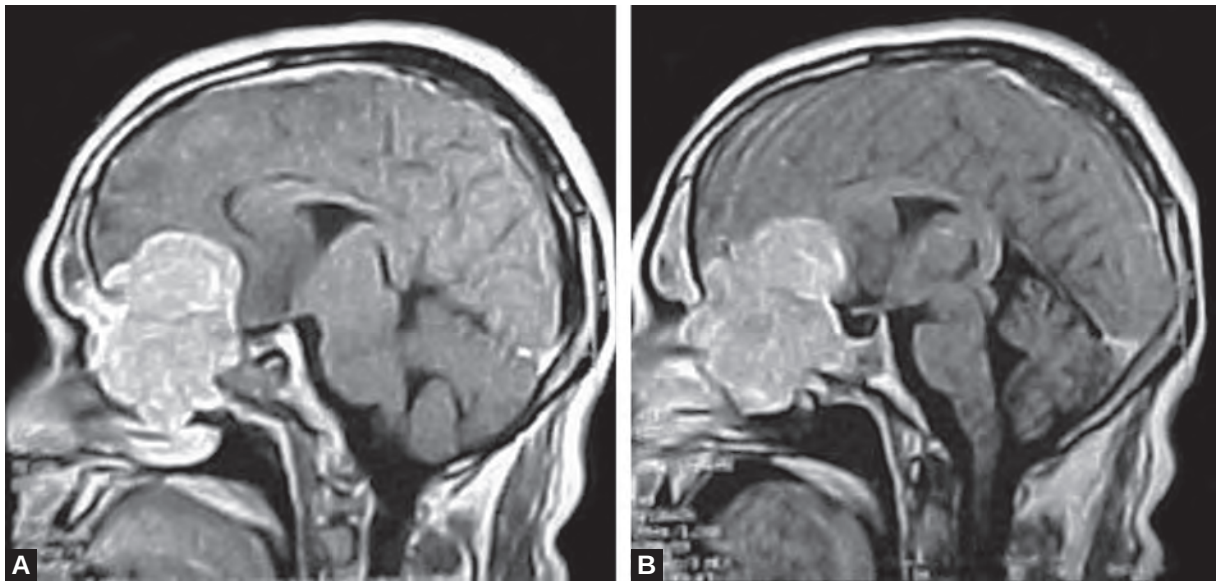
It is not uncommon to find lucent defects in plain films that are clinically insignificant and not neoplastic. On the contrary, in many neoplasms of the skull, in the early stages, symptoms are either absent or of non-specific nature. Therefore, it is important to understand and recognise the conditions which may simulate neoplasms.

Osteomyelitis

Radiological changes appear long after the onset of clinical signs and symptoms.[33,123] In the plain films, multiple nodular areas of lucencies appear in the outer table or



Figs 7A to D: CT scan of the brain with bone cuts showing osteolytic metastatic lesion in the frontal region in a patient who was treated for breast carcinoma



Figs 8A and B: Contrast MRI of the brain showing contrast enhancing lesion involving the anterior skull base and causing erosion with extension to the sinuses and intracranially. Transnasal biopsy done; HPE: Neuroblastoma

diploe.[123] CT demonstrates these early lesions clearly. In young children, the sutures usually limit the process, but in adults contiguous spread to adjacent bones is common. In course of time, the nodular lucencies condense into a large defect and visible and palpable oedema of the scalp (Pott's puffy tumour) occurs. Inward spread leads to an extradural empyema or granuloma. CT shows this as a biconvex extradural hyperdense mass with marked peripheral contrast enhancement. Poorly defined sclerosis occurs at the edges of the bone. Practically no subperiosteal new bone formation occurs. Sequestrum formation is uncommon, as the skull is very vascular. Their radiological appearance may remain stable or endosteal regeneration may continue to occur in healed osteomyelitis.

Tuberculosis, syphilis and other low grade chronic infections appear on radiographs as irregular, poorly defined areas of sclerosis. Sometimes, a central area of lysis may be present. Soft tissue thickening may be minimal or absent.

Traumatic Conditions

Cephal Haematoma

In the newborn, it results from birth injury due to forceps delivery and is commonly seen in the parietal bone and is limited by the sutures.[35] Initially, the X-rays show a soft tissue shadow overlying the bone. About a week later, calcific edges are seen arising from the sutural areas and these gradually project into the soft tissues of the scalp, resulting in a shell-like calcification completely bridging the mass.[123] Simultaneously, there is gradual resorption of the inner table with progressive remodelling. Rarely, a deformity persists with a radiographic appearance not unlike fibrous dysplasia or epidermoid tumour.[16] A review of previous skull radiographs and clinical history should aid in the differential diagnosis.

Leptomeningeal Cyst (Growing Fracture of the Skull)

A linear fracture of the skull in infants may be associated with a laceration of the dura and the brain pulsations may herniate a pouch of arachnoid, which may enlarge and widen the fracture and form a cystic collection under the scalp. Varying degrees of pressure atrophy of the brain occurs, resulting in a subdural cystic collection. The plain films show an area of lucency in the skull with scalloped margins and a soft tissue shadow outside the skull.[92] CT shows the intracranial porencephalic cyst and atrophic changes in the ventricles. Occasionally, these cysts cause expansion between the tables of the skull bone, producing an intraosseous leptomeningeal cyst.[54] This condition requires surgery and the results are often rewarding if the surgical principles are strictly followed.[118]

Vascular Diseases

Vascular Impressions in the Skull

Normal vascular structures and vascular tumours of the scalp, dura and brain produce impressions on the skull and may simulate the radiographic appearances of skull tumours. Pacchionian granulations produce focal thinning of the inner table with slightly lobulated margins. Venous lakes are wider and they invade the inner table with sloping margins. The arachnoid granulations occasionally involve the outer table also. They are commonly seen in the parietal parasagittal regions and in the occipital squama and occasionally, more laterally.

Sinus Pericranii

It is a congenital defect involving the skull, containing abnormal emissary veins which connect an intracranial venous sinus, commonly the superior sagittal sinus in the frontal region with a cluster of veins or a venous angioma in the extracranial space. Typically, the veins bulge as a swelling in the recumbent posture and disappear in the erect posture.[92] A cluster of smooth sharply marginated circular defects in the midline of the frontal region, seen in plain skiagrams, should suggest the diagnosis.

Histiocytosis X

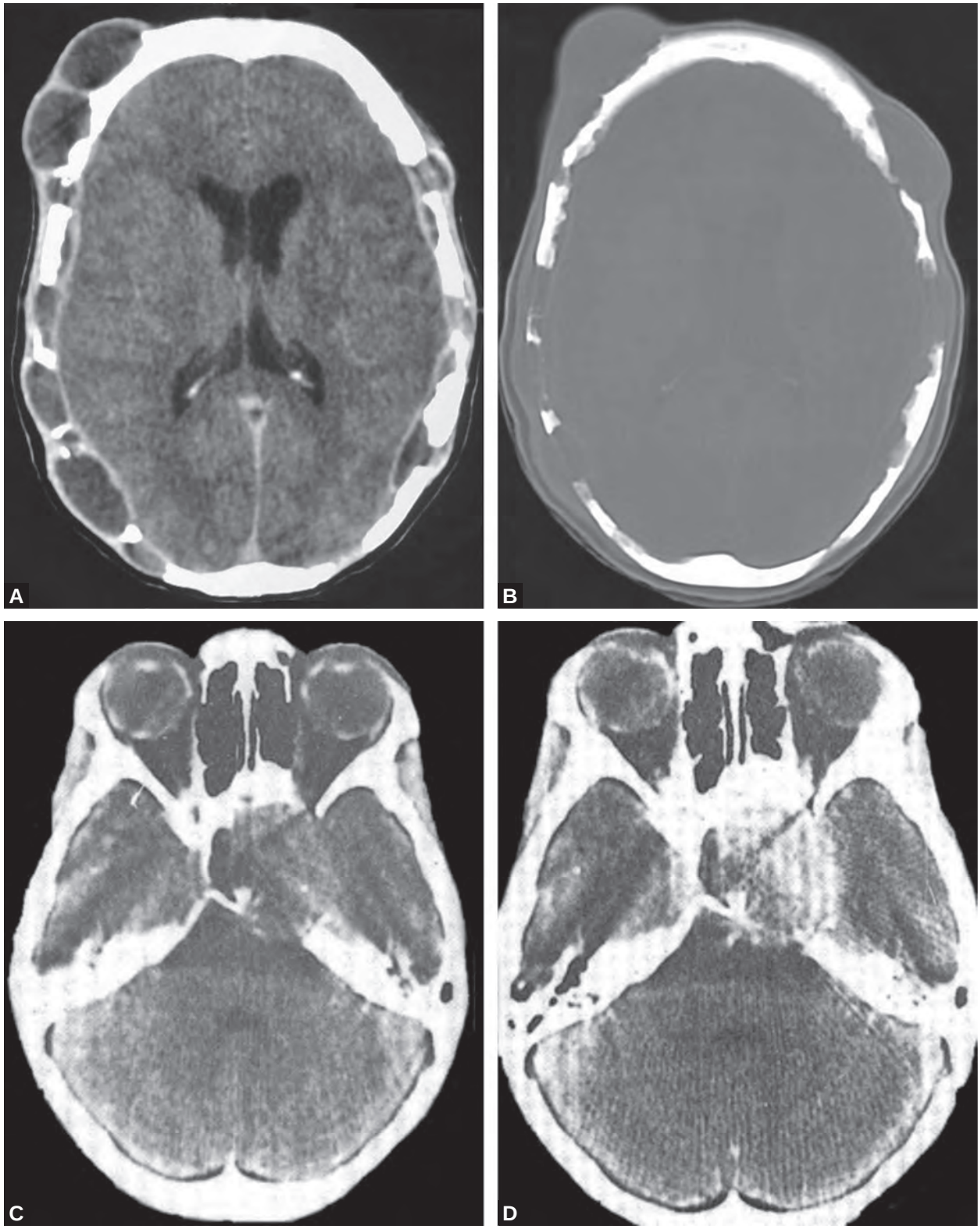
This disease complex comprises of Hand-Schuller-Christian syndrome which has associated diabetes insipidus, Letterer-Siwe disease and eosinophilic granuloma.[73,74] The first two occur in young children as multiple recurrent areas of skull involvement. Eosinophilic granuloma occurs as a solitary non-recurring lesion in older children and young adults. Co-existence of psoriatic arthritis and eosinophilic granuloma has been observed and an autoimmune mechanism is thought to be an aetiological factor.

Eosinophilic granuloma is manifested by local tenderness and pain. Skull radiographs show an irregular area of rarefaction without any sclerosis. Tangential views of the skull and the CT scan show the edges of the lesion to be bevelled, due to differential involvement of the outer and inner tables.[33,123] Sclerosis is, however, seen at the time of healing of the lesion. The solitary lucent lesion may be difficult to differentiate from myeloma or a metastatic deposit. Hence, it is important to establish a diagnosis by complete excision and histopathological examination. Radiation therapy in small doses, 10 Gy (1,000 rads) over 1 week is curative.

The multiple recurrent type of lesion seen in younger children often involves the frontal bone and spreads extensively, showing clear cut but irregular edges described as "map like" or "geographic skull" (Figs 9A and B). Soft tissue masses may become palpable, when the outer table gets perforated. Orbital involvement produces proptosis. The facial bones and paranasal sinuses eventually get involved[33,123] (Figs 9C and D). Other parts of the skeleton are involved simultaneously. Following diagnostic biopsy, systemic chemotherapy with prednisone, vincristine and cyclophosphamide is usually given. Local radiation is given as palliation.[30]

Sarcoidosis

This is another condition which destroys multiple areas of bone. Skull involvement is rare and is seen as multiple punched out areas of bone rarefaction.[94] The growth of such lesions is very slow and may remain unchanged for several years.



Figs 9A to D: (A and B) CT scan of the brain with bone cuts of a patient with histiocytosis X showing multiple osteolytic lesions with beveled edges and soft tissue swellings. (C and D) Plain and contrast axial CT scan of a child with histiocytosis X showing an enhancing lesion in the sella and the right para sellar region

Osteitis Deformans (Paget's Disease)

This disease was first described by Sir James Paget in 1877. The aetiology is still not known. The patients are usually of middle age, men being more frequently affected than women. The disease is multicentric, affecting the pelvis, the femora, the vertebral column and more commonly the skull.[31,93] It starts as a diffuse mottled thickening of bone in the frontal or occipital area or as irregular patches or lysis which give the appearance of a geographical skull when viewed on radiographs. After some months or years, patchy sclerosis develops, gradually progressing to produce gross thickening of the skull.

The new bone is soft and the involvement of the base of skull leads to invagination. The skull loses its three tabled architecture in the late stages (Figs 10A and B). Differential diagnosis includes fibrous dysplasia of mixed type, mixed blastic and lytic metastases and healing stage of hyperparathyroidism. Widespread involvement of the vault and the base, gross thickening and distortion of the normal bony architecture and the much older age of the patients help in differentiation.[39,123]

Pain and asymmetric enlargement of the skull and deafness and blindness due to foraminal involvement may occur. Involvement of the axial skeleton may produce an ape-like appearance. When there is widespread bony involvement, the level of serum alkaline phosphatase is considerably raised. Except for neural decompression, this condition usually does not need treatment. Osteogenic sarcoma may occur as an infrequent sequel.[127]

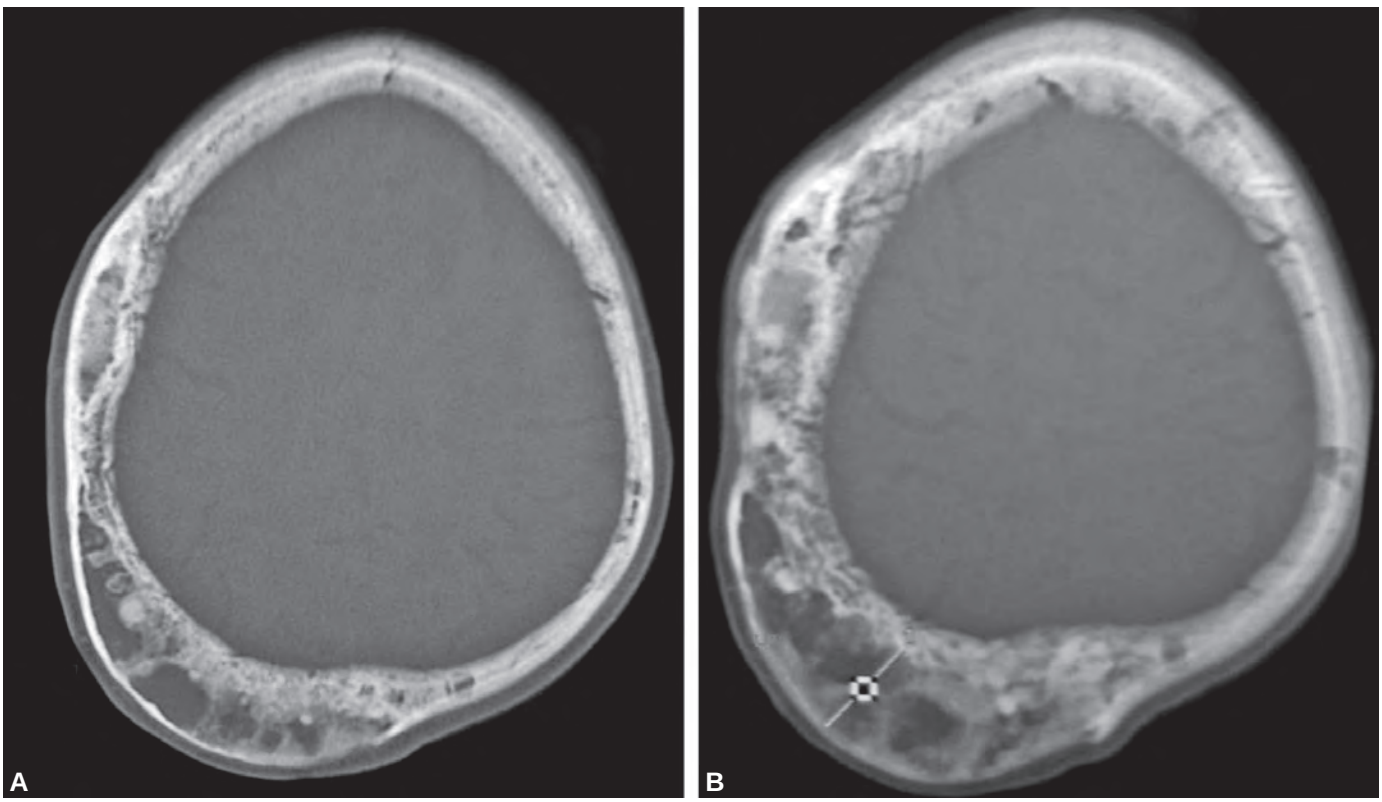
Fibrous Dysplasia

It is a benign disorder of bone commonly seen from childhood to the third decade. Normal bone is replaced by fibrous connective tissue with varying degrees of osseous metaplasia. The skull alone may be involved, but usually other parts of the skeleton are also affected.[84] The radiographic pattern may be cystic, sclerotic or mixed.[70] The cystic type mainly affects the cranial vault. It is seen in plain films or CT as a focal homogeneous widening of the diploic layer with gross thinning of the outer table and relatively less involvement of the inner table. The margins of the lesion are ill defined and gradually taper into the surrounding of the skull.

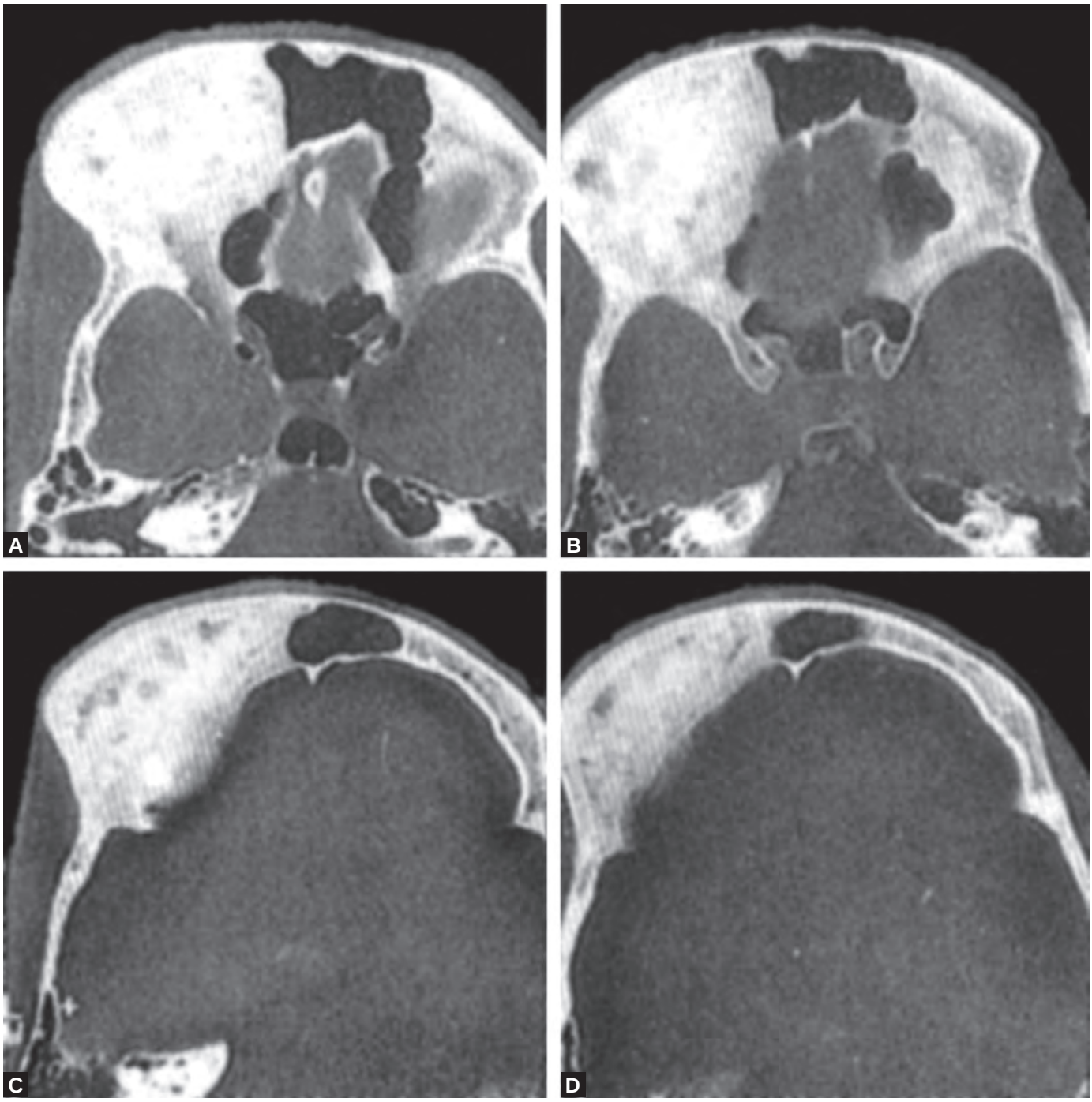
The sclerotic variety involves the skull base and facial bones, causing diffuse bilateral thickening of the floor of the anterior and middle cranial fossae. Despite gross involvement of the bones of the base of skull, neural structures are rarely compressed. The optic nerve may be compressed when the optic foramen is involved. When unilateral, the bone thickening may be difficult to differentiate from the hyperostosis due to a meningioma (Figs 11A to D).

The mixed type is least common and it involves the vault of the skull more often. The diploe is widened and the outer table is thinned. There are patches of lucent and dense areas as in Paget's disease, but they are more sharply defined and well localised.

Histologically, fibrous dysplasia appears as multiple areas of fibrous tissue contained within islands of bone with evidence of both blastic and clastic activity. The condition tends to stabilise at a certain stage with few instances of progression after adolescence.[70,84] Usually, no treatment is advised except in the case of orbital compression or neural involvement. Sarcomatous change rarely occurs. If active enlargement or local inflammation occurs, excision and cranioplasty is advised. It is important to remember that the involved bone may be vascular and one must be prepared to encounter considerable blood loss during the operative procedure. When it is localised some authors call it ossifying fibroma.[126]



Figs 10A and B: CT bone cuts in a patient with Paget's disease



Figs 11A to D: Axial CT scan bone windows showing the thickened bone in a patient with fibrous dysplasia

Hyperparathyroidism

This metabolic abnormality of calcium and phosphorus is characterised by elevated blood calcium and lowered blood phosphorus, and there is increased loss of both ions from the body. Bony changes generally occur. In the skull, wide areas of granular osteoporosis occur. These may coalesce to form large areas of lysis forming "Brown Tumours" (osteitis fibrosa cystica).[15,33] During the healing process, patchy areas of sclerosis occur superimposed on the diffuse granular osteoporosis. Patients with secondary hyperparathyroidism due to renal failure may also show such patchy sclerosis.[128]

Mucocoele

This condition occurs in any one of the paranasal air sinuses, frontal, frontoethmoidal or sphenoidal sinuses in that order. As a result of obstruction to the outflow tract, the mucoid secretions collect in the sinus cavity and gradually enlarge, thinning out the walls of the sinus. In the case of the frontal sinus, a small osteoma at the frontonasal duct may be the obstructing agent.[100] The anterior wall bulges out forming a visible swelling on the forehead (Figs 12 and 13A to D). The posterior wall may also bulge and compress the dura. Sometimes the mucocoele may burst through the dura. Ethmoidal sinus mucocoele may occur alone or in conjunction

with frontal sinus mucocoele. It produces proptosis. Mucocoeles of the sphenoidal sinus are rare and they erode into the sella and parasellar regions, the optic foramen and the superior orbital fissure. In certain instances, with spontaneous drainage, regression of the mucocoele and later recurrence of the swelling may occur. When infected, it may form a pyocoele.

Plain skiagram shows enlargement and opacification of the sinus and a soft tissue swelling. A sphenoidal lesion may erode the optic foramen and enlarge the superior orbital fissure.[11] The floor of the sella may bulge upwards and appear eroded. The location and extent of the lesion are seen well on the CT. The cystic contents, however, appear denser than the usual cysts in the cranium, due to the high protein content of the fluid.[87] Treatment consists of complete excision of the mucocoele, along with all the sinus lining and obliteration of the cavity. Where the skull defect is large, it is better to close it with autogenous bone graft than with acrylic material, as the mucocoele is often potentially infected. Even if it is not infected, care must be taken not to spill the contents into the subarachnoid space as this may result in chemical meningitis. Mucocoeles of the sphenoidal sinus are better treated through the transnasal route.

Neuroectodermal Dysplasias

Skull bone involvement in neurofibromatosis is common and may manifest as a deficiency in the orbital wall due to the local erosive effect of an overlying tumour, or as a sharply marginated round or oval defect in the lesser wing of the sphenoid or in the region of the lambdoid suture due to bone dysplasia.[10,36,58,61] The lesions may rarely mimic skull neoplasms and a CT scan clearly shows the margins of the lesion and the absence of a soft tissue mass.

Osteosclerotic nodules may be seen on plain films in cases of tuberose sclerosis.[37] These may be mistaken for the peripherally located calcified glial nodules which are so typical of this disease. CT clearly defines the location and nature of the process.

Haemolytic Anaemias

In infants with severe anaemia, the cranial diploe provide a major source of red blood cell production. The abnormalities are marked in thalassaemia or Cooley's Mediterranean anaemia. The diploe widens with resultant atrophy of the outer table. The trabeculae of the diploe assume a radial striated pattern and are seen perpendicular to the inner table which remains intact. The occipital bone inferior to the internal occipital protuberance is spared, as marrow is absent at this site. The tremendous enlargement of the marrow prevents pneumatisation of the air sinuses. Similar changes have been observed in chronic iron deficiency anaemia and in infants with congenital cyanotic heart disease.[102]

Hyperostosis Frontalis Interna

This is an idiopathic benign condition seen in the skiagrams of middle aged and elderly women. There is

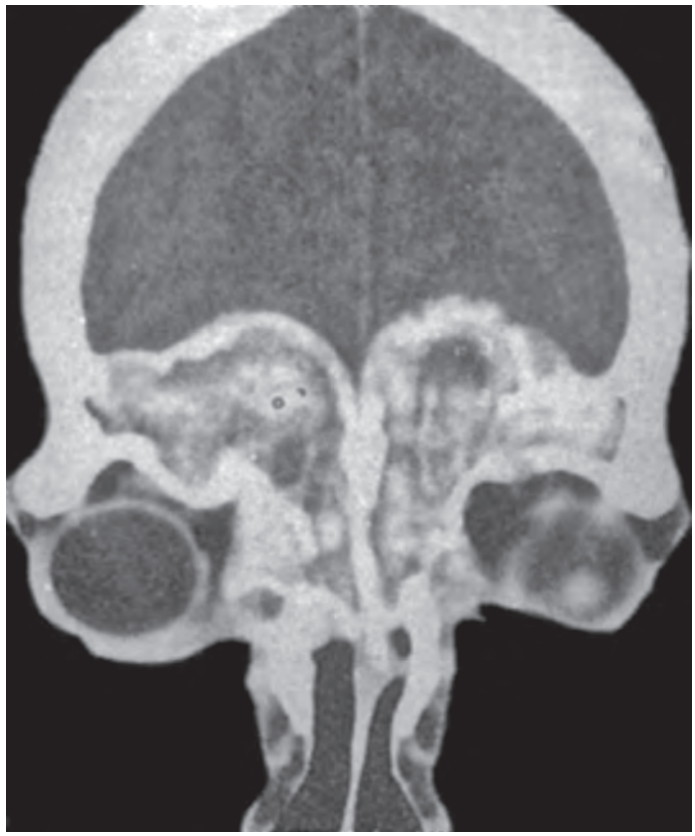
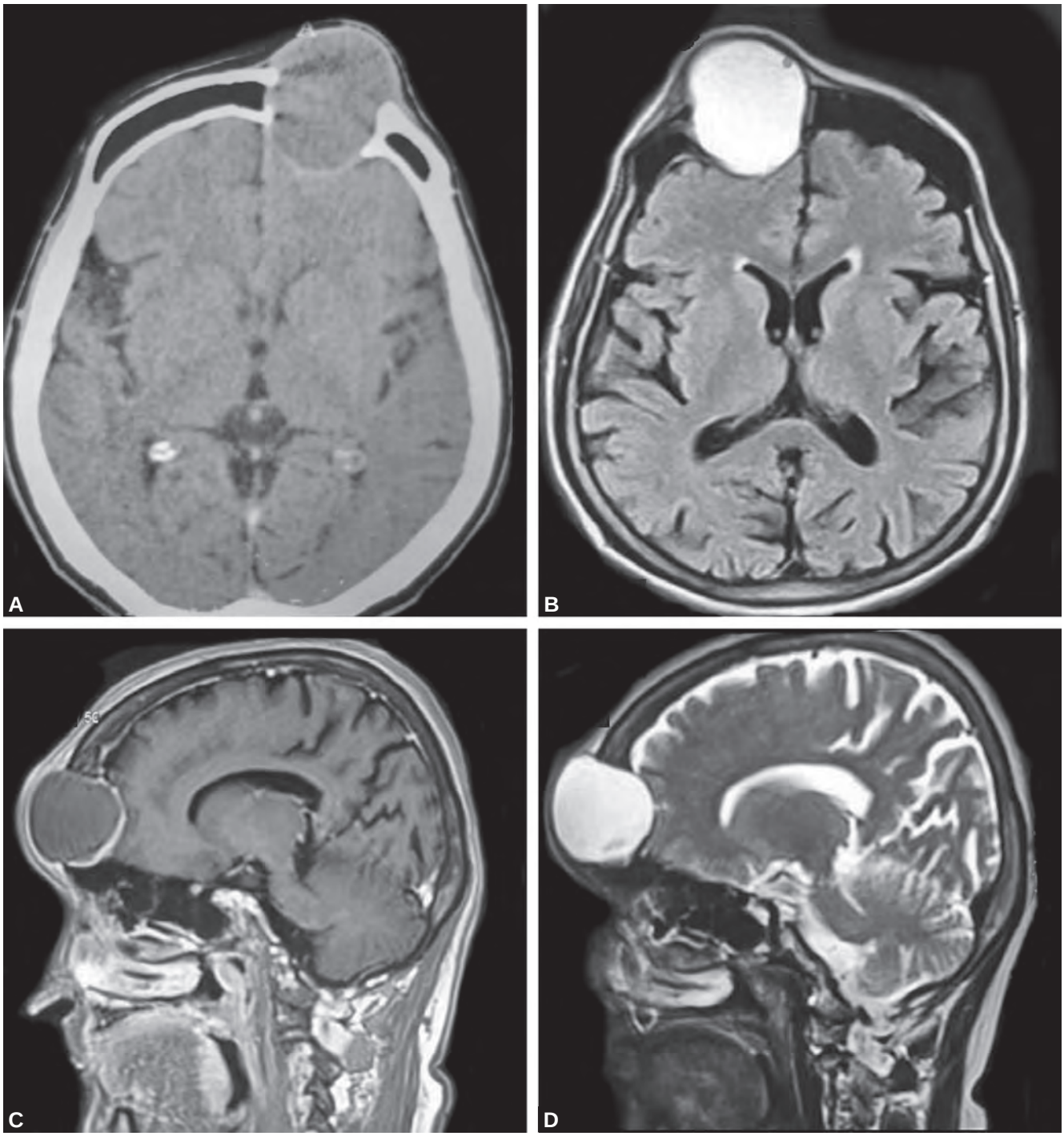


Fig. 12: Coronal CT scan showing frontal mucocoele



Figs 13A to D: (A) CT scan of the brain showing frontal mucocoele. (B to D) MRI axial T2, sagittal T1, T2 showing frontal mucocoele

diffuse hypertrophy of the inner table, commonly seen in the frontal bone, but sparing the midline. It is not of any clinical significance. When it occurs on one side, the differentiation from meningeal hyperostosis of the inner table becomes difficult. CT will help to elucidate the condition.

Petrous Apex Cholesterol Granuloma

Cholesterol granuloma produces symptoms of trigeminal, facial and abducens nerve palsy and may not affect the auditory nerve. CT shows a non-enhancing, smooth-walled, expansile isodense lesion at the petrous apex with bilaterally well pneumatised mastoids. Asymptomatic patients can be observed till the condition becomes symptomatic. Drainage and permanent ventilation are the goals of treatment in symptomatic patients. Those with good hearing can be treated by the infralabyrinthine approach. The infratemporal fossa approach is advocated in patients with extensive disease and internal carotid artery involvement. Complete removal is indicated in selected cases where placement of a drainage tube is not feasible.[43,51]

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SECTION

13

Skull Base Surgery

Deepu Banerji

180 Clival Chordomas

Chandranath Sen

INTRODUCTION

Chordomas are rare primary malignant bone tumours that arise in the axial skeleton. They are believed to originate from remnants of embryologic notochordal cell rests and thus manifest epithelial as well as mesenchymal features.[27,35] Although chordomas are found throughout the axial skeleton, they are much more frequent at either end. It has been reported that 25–39% of chordomas arise in the clivus.[7,10,14,25,43] They are slightly more prevalent in males and can be found at any age, but the mean age incidence is 40 years. The incidence of chordomas in the clival location is 1/2,000,000 per year.[5,25]

These tumours are generally slow growing but are locally aggressive, due to the fact that the clinical course of a patient is typically punctuated by multiple local recurrences. Metastases are uncommon. Local recurrence is usually the cause of the patient's death.

NATURAL HISTORY

Untreated skull-base chordoma has a dismal outlook for survival. A Swedish epidemiological study reported that the survival of untreated chordomas at the skull base from the time of diagnosis is 6–28 months.[10] Among the 15 patients with skull-base chordomas, Dahlin reported only 2 surviving beyond 5 years after surgery and radiation.[7] Forsyth et al. reported on 51 patients treated with surgical debulking and radiation at the Mayo Clinic, between 1960 and 1984.[12] Overall, 5-year survival was 51% and 10-year survival was 35%. Patients who were younger than 40 years of age had a better survival with aggressive surgery and radiation. In a Scottish epidemiological study, O'Neill et al. found a mean 7.7 year survival of patients with clival chordomas.[29] McMaster et al. conducted a large US epidemiological study and reported 5-year survival of chordoma at 67.6% and it dropped to 13.1% by 20 years.[25] Although metastases have been reported in up to 43% of patients studied, most large surgical series that were reviewed indicate a much lower rate.[15,23]

PATHOLOGICAL FEATURES

These tumours are characterised by a lobular growth pattern of tumour cells that are arranged in clusters, chords and strands. The cells are large and contain abundant eosinophilic cytoplasm. Many of them contain large clear vacuoles and hence the name, "physaliferous". The nuclei may vary from small and hyperchromatic to large and vesicular. They are usually surrounded by a myxoid matrix. Three variants have been described on the basis of the histology: conventional chordoma, chondroid chordoma and dedifferentiated chordoma. Chondroid chordomas contain conventional chordomas surrounded by neoplastic hyaline cartilage occupying up to 75% of the tumour area.[2] The dedifferentiated tumours have tumour cells arranged in irregular nests in a collagenous fibrous stroma and resemble a poorly differentiated carcinoma. Immunohistochemistry is essential in confirming a diagnosis of chordoma. They stain positively for cytokeratin, epithelial membrane antigen, S-100 protein and vimentin.

CLINICAL FEATURES

The clinical features depend on the anatomical location of the lesion. Chordomas are classified as upper, middle, lower or craniovertebral junction and the symptoms and signs depend on the spread of the lesion. They have also been classified as basisphenoidal and basioccipital, depending on whether they arise above or below the spheno-occipital synchondrosis. Diplopia due to abducens paralysis is the most common symptom. The other clinical features that may be present are visual loss, pituitary endocrinopathy, chiasmal syndrome, cavernous sinus syndrome, nasopharyngeal mass, multiple cranial nerve involvement, brainstem signs, cerebellopontine angle involvement, hydrocephalus and lower cranial nerve palsies.[32]

IMAGING FEATURES

MRI and CT scans are the most important imaging studies for evaluating chordomas at the skull base. On the MRI scans, they usually appear as lobulated masses arising from the clivus. They manifest low signal intensity on T1-weighted images and have high signal intensity on T2-weighted images. They do enhance with the administration of gadolinium, but this occurs to a variable degree.[26] They can vary greatly in size and distribution. They often extend intracranially as well as extracranially into adjacent anatomical areas and also, sometimes,

intradurally. On CT images, they appear isointense on the non-contrast studies. There is irregular bone destruction at its site of origin, which may be in the midline of the clivus or eccentrically located. The tumour may also show areas of calcification. Differentiating chordomas from chondrosarcomas is often difficult due to the identical imaging appearance. Chondrosarcomas usually arise eccentrically at the petroclival synchondrosis.

PRINCIPLES OF SURGICAL MANAGEMENT

Radical surgical excision is the primary treatment of choice. Neoplastic location at the clivus, however, poses limitations to this goal. The tumour is often located in close proximity to many critical neurovascular structures and at a considerable depth from the surface. The tumours often reach a relatively large size by the time they are diagnosed and thus have a propensity to involve many contiguous anatomical areas such as the cavernous sinuses, retropharyngeal space, the occipital condyle and its articulation with C1. There may be substantial intradural extension with variable degrees of brainstem compression. The internal carotid arteries and the vertebrobasilar system are often intimately involved by the tumour. Not a single surgical approach provides access to all the regions of the skull base.

Thus, a variety of surgical approaches have been described. Since these are primarily extradural tumours, the surgical approaches are directed to this area. A single surgical approach may not be enough to achieve a radical excision. Depending on the size and anatomical extensions of the tumour, a combination of more than one approach may be needed, either at the same or separate sittings.[13]

The surgical approaches to this area are broadly divided into anterior midline and lateral approaches (Table 1).

Anterior midline approaches:

- Extended subfrontal
- Trans-sphenoidal[20,22]
- Endonasal endoscopic with image guidance[18,33]
- Transfacial
- Transoral[8]
- Transmandibular circumglossal retropharyngea[l9]

Lateral approaches:

- Frontotemporal with orbitozygomatic osteotomy
- Preauricular subtemporal and infratemporal[37,38]
- Presigmoid combined supratentorial and infratentorial
- Extreme lateral transcondylar.[34,39]

It is important for the surgeon to be familiar with all of these approaches. Each approach has its advantages and disadvantages. Each approach often permits access to a very specific area and thus requires detailed planning based on the imaging studies and the clinical status of the patient. Because of the location of major arterial and venous structures and also the passage of many cranial nerves, the approaches need to be carefully selected and tailored to the specific tumour in a patient. This is important in order to minimise the exposure and unnecessary manipulation of these structures. The surgical procedure usually involves three components: (1) surgical approach; (2) tumour resection and (3) reconstruction of the skull base. Each of these components has to be carefully planned and executed to ensure a successful outcome. Since these operations are complex and involve access through facial, pharyngeal and temporal bone structures, close collaboration with an otolaryngologist is very helpful.[21,22,24]

Table 1: Surgical approaches

	Approach	*Areas exposed*
Anterior midline approaches	Trans-sphenoidal	Sphenoid sinus, upper clivus
	Transoral	Lower clivus, foramen magnum, C1, C2
	Le Fort maxillotomy	Middle clivus with lateral extensions
	Mandibulotomy and glossotomy	Lower clivus, foramen magnum and upper 3 vertebrae
	Extended subfrontal (transnasal)	Sphenoid sinus, middle and lower clivus
	Endoscopic endonasal	Entire midline clivus from sella and upper clivus, down to foramen magnum
Lateral approaches	Frontotemporal, orbitozygomatic (anterior transpetrosal)	Upper clivus, parasellar
	Presigmoid transpetrosal (retrolabyrinthine or ranslabyrinthine)	Midclivus
	Subtemporal and preauricular infratemporal	
	Extreme lateral transcondylar	Lower clivus, jugular foramen, C1, C2

Surgical Approach

Based on the imaging studies, the location of the main tumour bulk is determined. The surgeon must determine the most efficient approach to this area that would provide direct access and then establish adequate visualisation and control of critical adjacent structures and thus allow radical tumour removal. Although tumour

removal is done in a piece-meal fashion, all the soft portions of the tumour, the surrounding bone and involved dura need to be removed. The incisions, bone exposures and removal are performed, also keeping in mind that an additional procedure may be needed if the entire tumour cannot be removed by this approach. Also, in the future, if there is tumour recurrence, additional surgery may be needed. These options should be kept open at this time. It is also important to note that the initial operation is usually the best opportunity that will ever exist for achieving a radical tumour removal.

Tumour Resection

These tumours are usually soft and gelatinous in consistency and can easily be removed by suction and curettage. They usually push soft tissue boundaries but have an indistinct border with the bone, which is the clivus in this area. Actual invasion of the arteries and cranial nerves is unusual, but the course of these structures can be markedly altered by the tumour. The cranial nerves may also get severely attenuated by the chronic tumour compression, to the extent that they may be difficult to identify and preserve. These tumours can also be compartmentalised by fibrous septae and may also extend in between the layers of the dura.

These extensions may be difficult to identify and can result in portions of tumour being left behind. It is, therefore, important to remove the tumour in a systematic manner starting in one area and then progressing to other areas, moving along certain landmarks that have been determined on the imaging studies. This strategy not only allows the possibility of radical tumour removal but also is beneficial for planning the radiation therapy. If any tumour is left behind, it is best to have this remnant in a localised area instead of being scattered throughout the surgical bed. This allows the radiation to be aimed at a specific area rather than spread out over a large area. Occasionally, the tumour may be vascular and fibrous or contain portions of calcification. Special precautions have to be exercised here, so that inadvertent injury to nearby structures is avoided. Although intra-operative stereotactic navigation and image guidance can be helpful, it is not a substitute for thorough anatomical knowledge.[40,41]

Reconstruction of the Skull Base and Potential Complications

After removal of these tumours, there is often communication into the pneumatic sinuses at the skull base, nasopharynx, the temporal bone, etc. There may also be a substantial dural defect that will need to be covered. The facial skeleton may have been disassembled for the approach. All these factors predispose to the development of cerebrospinal fluid fistulae and post-operative infections. Reconstruction is also aimed at the function and appearance of the patient. It is, therefore, extremely important to devote special attention and effort in reconstruction and closure of the wound. Much of this is already planned out at the time of the surgical approach and review of the pre-operative imaging studies.

If there is a dural defect, it should either be closed primarily or a dural graft should be used. Watertight closure is often not possible and, therefore, soft tissue layers are a helpful adjunct. This is in the form of free-fat graft or rotation flaps such as the pericranial flap, the temporalis muscle flap and the temporo-parietal fascial flap. Free-fat graft is preferred to free-muscle graft, since it is easily visible in the post-operative imaging studies. If the reconstruction is performed in a systematic manner, future recurrence of the tumour can be detected more readily in the subsequent MRI studies.

Bony reconstruction of the clivus or the central skull base is not necessary, provided a secure layered soft-tissue reconstruction has been performed. Loss of bone around the orbit will need to be reconstructed in order to prevent enophthalmos. Loss of bone from the external surface should be reconstructed to restore the contour and appearance of the patient. Usually, commercially available titanium mesh and plating systems are excellent for this purpose. Cerebrospinal fluid diversion by a lumbar spinal drain or an external ventriculostomy is often used during the early post-operative phase.

RADIATION TREATMENT

Historically, radiation has been used throughout the management of chordomas. Catton et al. in a series of 48 patients with cranial and spinal chordomas had a 100% failure rate with a median survival of 62 months using doses of 40–60 Gy.[3] Pearlman and Friedman showed that doses less than 40 Gy are inadequate and proposed that doses higher than 70 Gy were needed to control the tumour.[31] The optic nerves, chiasm, the brainstem and the pituitary gland represent limitations to such doses when the tumour is in proximity to these structures.

Although megavoltage fractionated photon radiation, as well as stereotactic radiosurgery has been used for the treatment of these tumours, the largest body of data exists for proton beam therapy.[16,19] The "Bragg Peak" effect allows a high dose to be delivered to the precise target site with no exit dose, making it an attractive modality for chordomas. Proton-beam irradiation seems to add to the length of survival of the chordoma patient. Its benefit is clearly seen in patients with residual tumour, but its effect on the patients with no obvious residual tumour is not definitely shown. The volume and distribution of the tumour are critical for the dose planning, as well as efficacy of the treatment.[17,28] The proton radiation data are quite encouraging with an excellent effect on tumour control. Fagundes et al. studied the patterns of disease recurrence after proton-beam treatment.[11] These investigators found only 1% lymph node metastasis and a 6% distant metastatic progression in their series. Surgical pathway seeding occurred in only 5% of cases. Local recurrence is by far the leading reason for failure of treatment in chordomas. This could be explained on the basis of undetected microscopic tumour that may have escaped the full radiation

dose or a biologically aggressive tumour. They found that the mean time to local failure was 24 months, which is in keeping with our findings in the present series.

It is important for the surgeon to plan the surgery in a way that the tumour is removed in a systematic fashion, such that the residual tumour, if any, is of a small volume and confined to a small region, to be ideally suited for the proton-beam therapy. In my personal experience of treating 71 patients, 56% of the patients who are alive without evidence of tumour recurrence have not received any form of radiation therapy. Among the 19 patients who have died, 14 patients (74%) received radiation after their surgery. Although most of the patients received proton-beam radiation, they represented a mixed group treated with a variety of radiation modalities. In actual practice, the use of radiation has varied amongst the authors. Al-Mefty[1] has advocated using proton therapy routinely after surgery, while Sekhar[36] and Crockard[5] have reserved use of radiation only when there was residual tumour identified in the post-operative scans.

CONTEMPORARY CASE SERIES AND SURVIVAL

We have treated 65 patients harbouring histologically proven clival chordomas between 1991 and 2005. Of these documented cases, 47 patients had typical chordomas, 8 patients had chondroid chordomas and 10 patients had dedifferentiated chordomas. There were 45 patients with tumours in the clivus and 20 patients with tumours at the craniovertebral junction (lower clivus, C1 and C2). The male to female ratio of patients was 1.8:1. The mean age of the patients at the first operation was 40.7 years (range 7–78 years). Forty-two patients were operated upon primarily and 23 patients had had prior surgery elsewhere. Considering both initial and recurrent operations 80 operations were performed by us on this group of 65 patients. The median time to follow-up from our first operation was 53 months (range 3–174 months).

Survival was significantly not influenced by age, sex or location of the tumour. It was, however, influenced by the degree of resection. The 5-year survival was 90% with radical resection compared to 52% with incomplete resection. Radical resection of tumour (no visible tumour in post-operative scans) was achieved in 59% and incomplete removal in 41%. Factors influencing the degree of resection achieved at surgery included tumour location (clivus vs CVJ), prior surgery, surgical approach (anterior, lateral or combined) and single- or double-staged operation. None of these showed a statistically significant association with degree of resection in our experience. It should be noted that the decision to use an anterior, lateral or combined approach and also whether to perform the operation in a single- or double-stage manner was made based on the size and distribution of the tumour.

Pre-operative tumour volume and the number of anatomical areas that were involved by the tumour had a statistically significant, inverse relationship to the likelihood of achieving radical resection. The median length of follow-up of the patients in the present series was 53 months. In this time, 19 (29%) patients have died from the tumour. Twenty-five patients (38%) are alive without evidence of residual disease and the remaining 21 patients (32%) are alive with residual tumour. We achieved radical resection in 38 patients (58%) at our initial operation, 33 of these (87%) are alive with 25 of those (66%) without recurrent tumour at the time of our writing. Thirteen (48%) of the 27 patients who had incomplete tumour resection are alive. Tumour recurrence has a poor prognosis.[11] There were 14 patients who had tumour recurrence after radical resection (37%), while 15 patients with incomplete tumour resection (55%) had regrowth of the tumour. Four patients developed local seeding of tumour and one patient had distant metastasis. Three other patients had both local seeding as well as distant metastases. Radical resection thus had a significantly favourable effect on the overall survival as well as the recurrence rate.

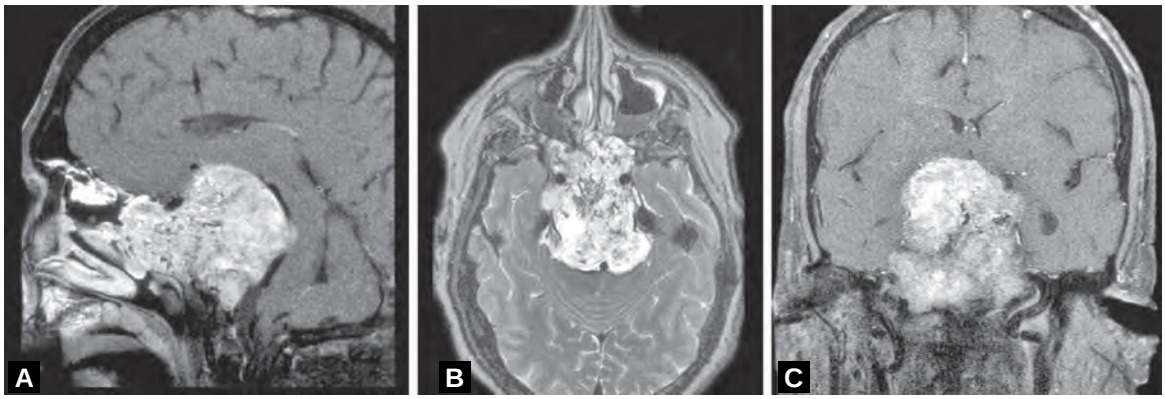
Tzortzidis reported their findings of treating 74 patients by skull base surgical techniques.[43] In his cohort, 32% of patients survived without evidence of disease at a mean follow-up of 96 months, after a gross total resection achieved in 71.6% patients. At follow-up, 50% of the group was alive with residual tumour and 17% had died.

Colli and Al-Mefty classified the degree of tumour resection as more than 90% tumour resection ("radical", "subtotal") and less than 90% resection ("partial").[4] Radical resection was achieved in 45.3% of chordomas. At five years, the recurrence free survival (RFS) was 65.9% for subtotal resection or better, compared to 23.1% for patients with partial resection. In this report, 17% (9 patients) of their chordoma patients died in the post-operative follow-up period (mean 49 months). Also in this follow-up period, 6 patients died in 3 years or less after their first operation, while 3 others died at 7, 8 and 10 years after the first operation. These data suggest a difference in the tumour biology in individual patients.

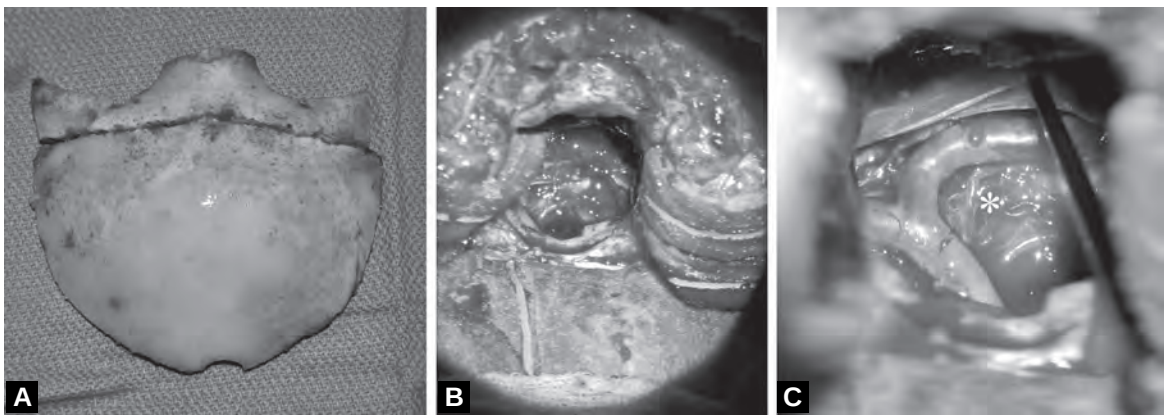
Crockard et al. reported a 4.2% surgical mortality in 42 patients with clival chordomas.[5] Tumour resection was classified as complete excision (i.e. no post-operative evidence of residual tumour), radical (i.e. more than 90% tumour removed), partial (i.e. 50–90% tumour removed) and biopsy (i.e. less than 50% tumour removed). Of the 32 patients who had radical or better tumour resection, 100% survived at 5 years. In the subgroup of patients who had less than radical tumour removal (10 patients), all received post-operative radiation therapy and had a 65% survival at 5 years. The greatest incidence of mortality was within 40 months after the operation. The overall survival for the entire group was 77% at 10 years. Pamir et al. treated 26 patients with a mean follow-up of 48.5 months.[30] In this study, about 25% of patients had radical tumour resection, 57.7% patients experienced recurrence of tumour and there was 23% mortality from tumour progression.

ILLUSTRATIVE CASES

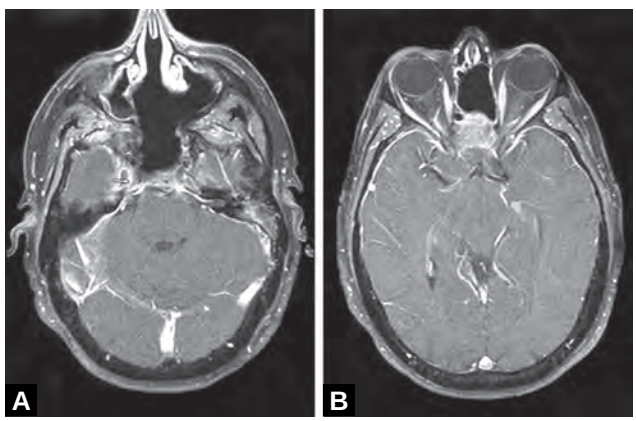
1. JD: This 43-year-old man had presented with difficulty in walking, vertigo and right sided weakness and numbness. MRI scan showed a large tumour (Figs 1A to C) at the skull base producing hydrocephalus. A ventriculoperitoneal shunt and a transnasal biopsy were done at another institution and he was then referred to us. The first operation was done through an extended subfrontal approach combined with an endonasal endoscopic approach. The optic canals were fully unroofed, in order to allow manipulation of the optic nerves while removing the tumour (Figs 2A to C). Reconstruction of the skull base was performed using a pericranial flap and autologous fat graft. After his operation, he lost hearing in his left ear. Five months later, he had surgery through a purely endoscopic endonasal approach to remove some residual tumour. He is being monitored with MRI scans on an annual basis (Figs 3A and B).
2. PB: This 11-year-old boy presented with gradual onset of left sided hemiparesis. MRI showed a large clival tumour with severe brainstem compression



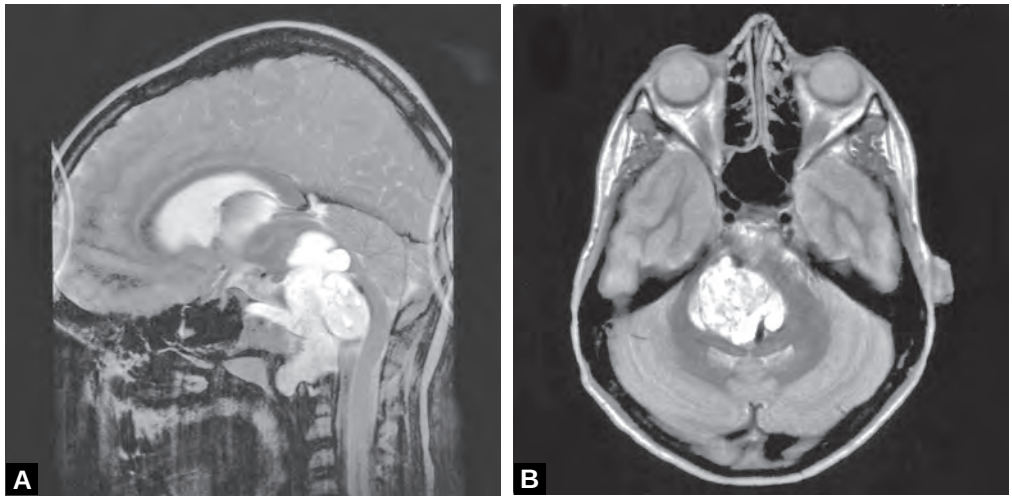
Figs 1A to C: MRI scan of 43-year-old man showing a large clival chordoma at the skull base



Figs 2A to C: (A) Bone flap of an extended subfrontal approach. (B) Operative view of extended subfrontal approach. (C) Endoscopic view showing basilar artery bifurcation and the tumour posterior to the vessels



Figs 3A and B: Post-operative MRI scans



Figs 4A and B: MRI scans showing a large clival tumour with severe brainstem compression

(Figs 4A and B), and the CT scans showed areas of bone destruction in the clivus (Fig. 5). He underwent surgery through a right-sided subtemporal and preauricular infratemporal approach. This approach consisted of an extradural subtemporal exposure and unroofing with translocation of the entire petrous segment of the internal carotid artery, in order to provide an approach to the clivus. A substantial amount of the tumour was found to be intradural. After removal of the soft portion of the tumour, the clival bone was drilled away in the affected areas. The post-operative MRI scans suggested some residual tumour and he underwent proton beam radiation (Figs 6A to D). He had temporary 6th nerve palsy immediately after surgery but recovered fully and remains functioning normally at 7 years post-operatively without any recurrence (Figs 7A and B). He does have hypopituitarism from the radiation treatment.

3. RS: This 37-year-old man suffered from severe occipital headaches. He had no neurological deficits. MRI scans showed a midline mass with bone destruction in the clivus (Figs 8A to C). The tumour was removed by a purely endoscopic endonasal approach using intra-operative navigation (Fig. 9). The tumour had invaded the dura and the tumour along with the involved bone and dura was removed (Fig. 10). The skull base was reconstructed using fascia lata and fat graft. He developed cerebrospinal fluid rhinorrhoea and required re-exploration and repair. He remains normal and has not received any post-operative radiation.
4. RR: This 16-year-old boy had developed tingling and numbness involving both upper extremities. MRI scans showed a large tumour involving the lower clivus and the craniocervical junction (Figs 11A and B). It intimately involved the vertebral artery on the right side and extended intracranially as well as extracranially. The tumour was approached through a right sided extreme lateral transcondylar approach (Figs 12A and B). The tumour was removed including the involved bone and dura (Figs 13A and B). Since the occipital condyle was also removed, he had an occipito-cervical fusion with titanium rods performed the following day[42] (Fig. 14). A few months after this he was treated with proton-beam radiation receiving 79.4 CGE.

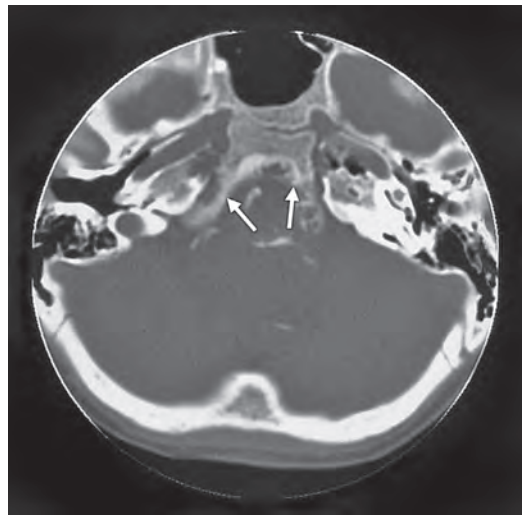
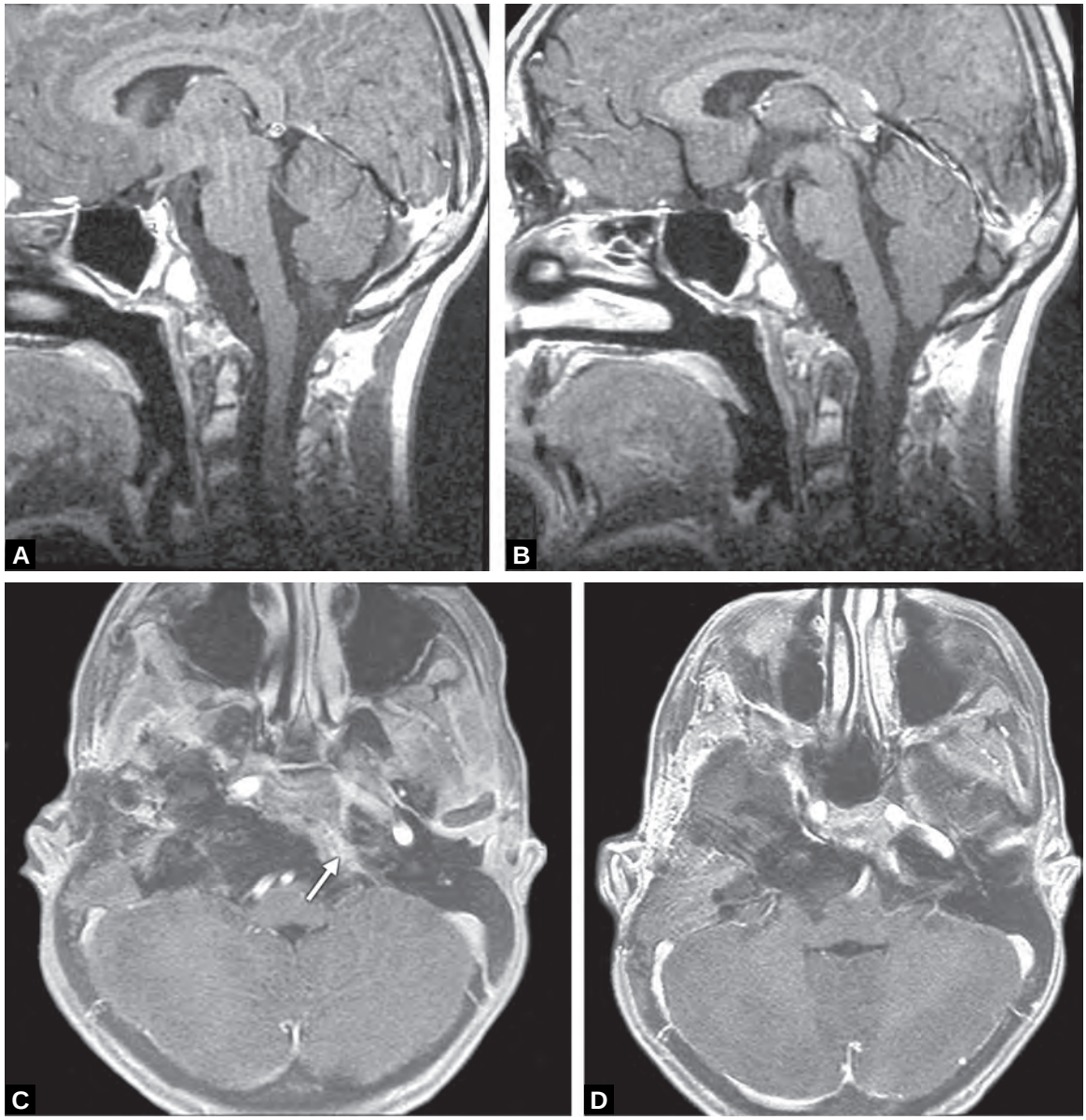
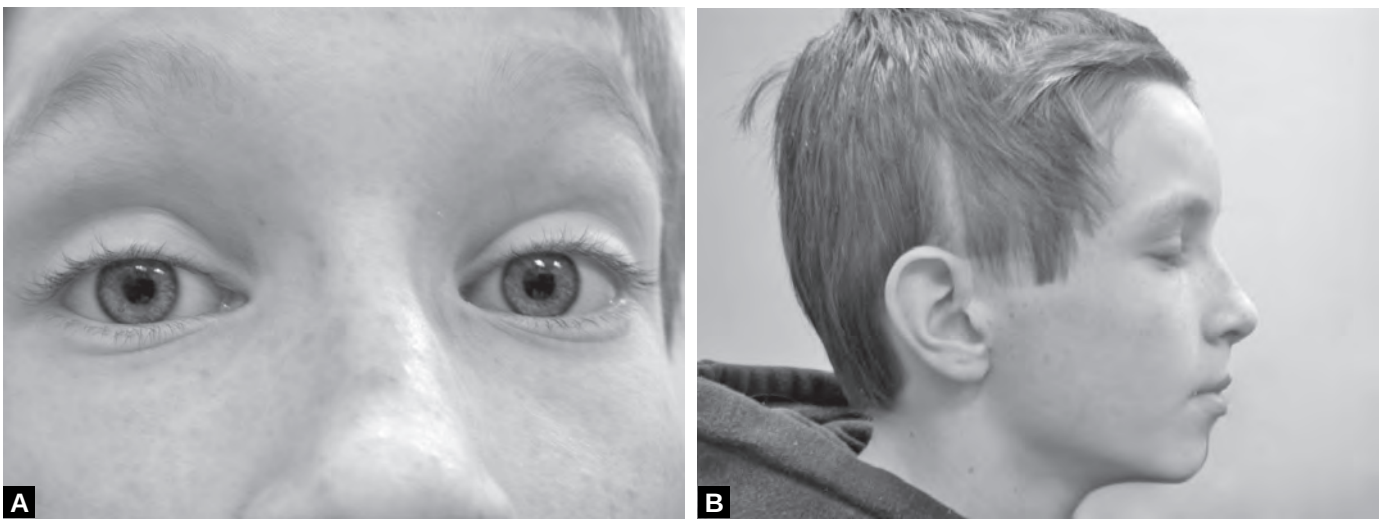


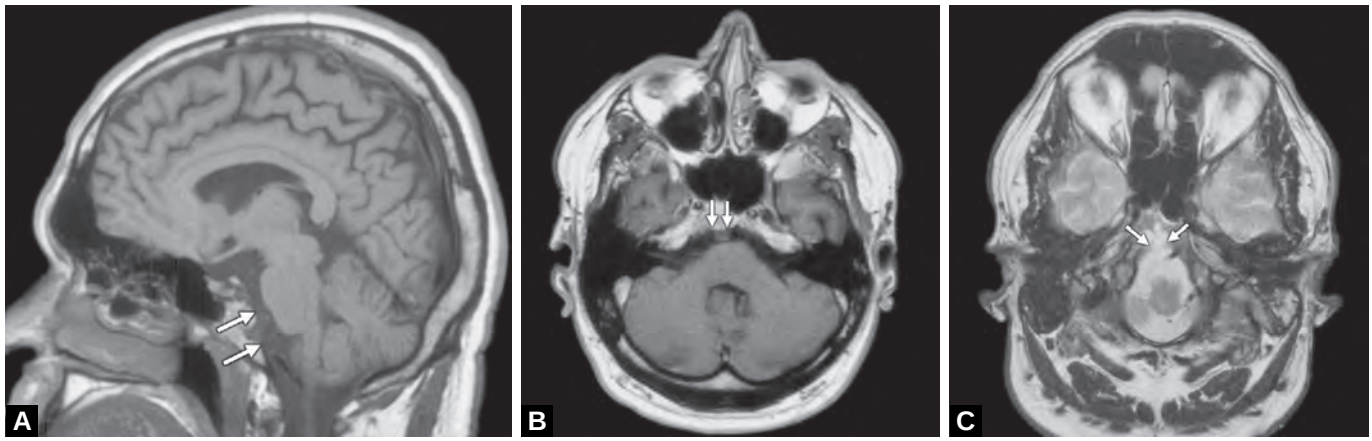
Fig. 5: CT scan showing areas of bone destruction in the clivus



Figs 6A to D: Post-operative MRI scans. Solid white arrow showing the residual tumour after surgery



Figs 7A and B: Clinical photograph 7 years after the surgery with normal functions, without any recurrence of 6th cranial nerve palsy



Figs 8A to C: MRI scans of a 37-year-old man showed a midline mass with bone destruction in the clivus. Bone destruction is shown by the solid white arrows

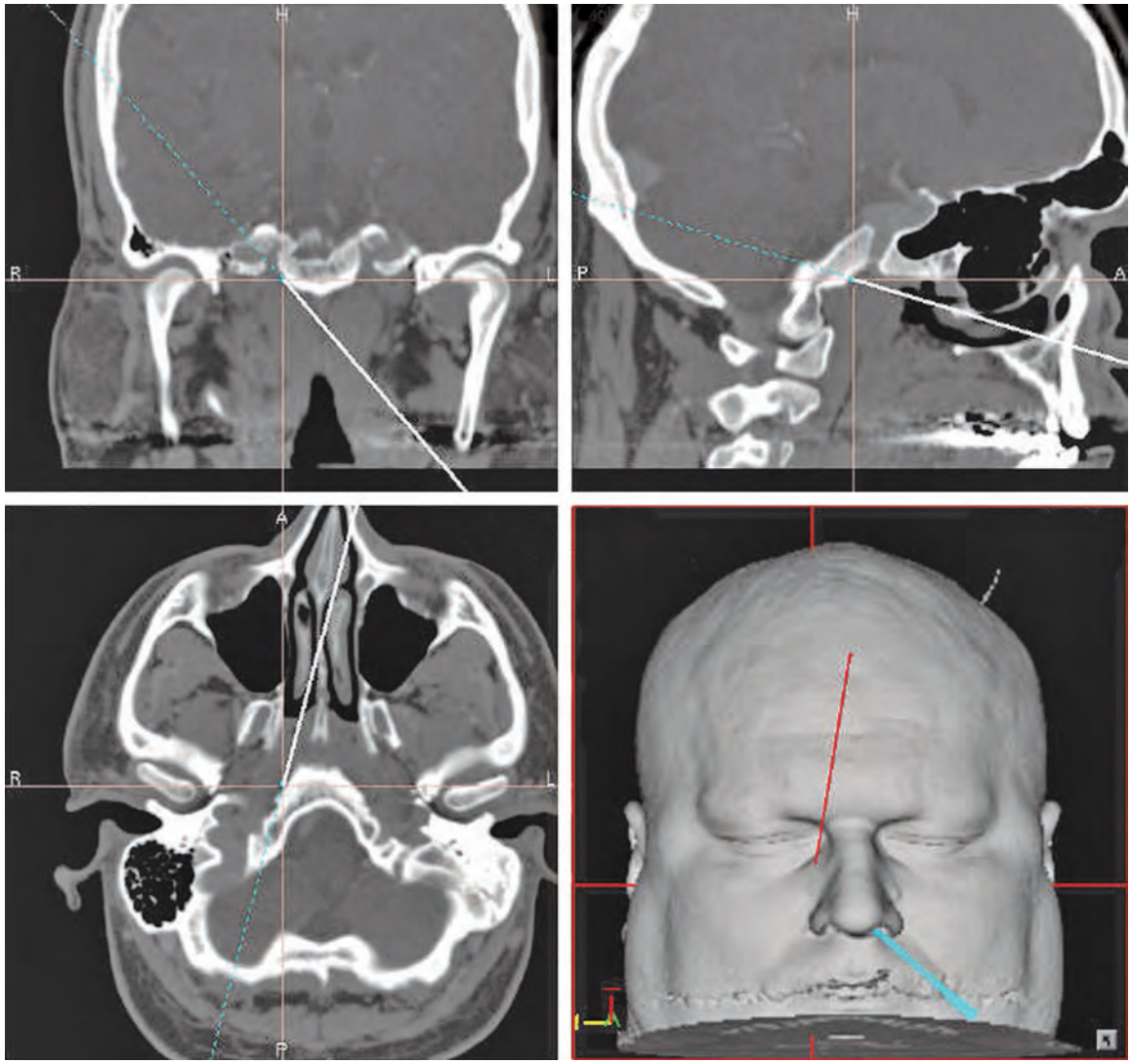


Fig. 9: Intra-operative navigation co-ordinates used for the endoscopic endonasal approach for removal of the tumour described in Figures 8A to C

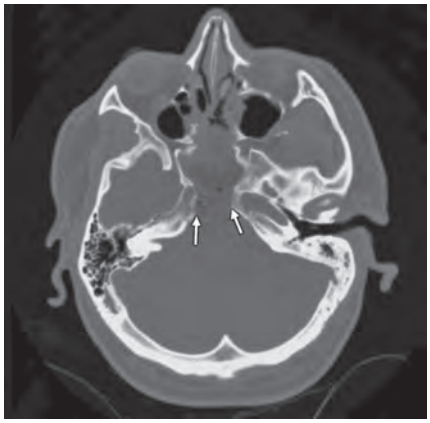
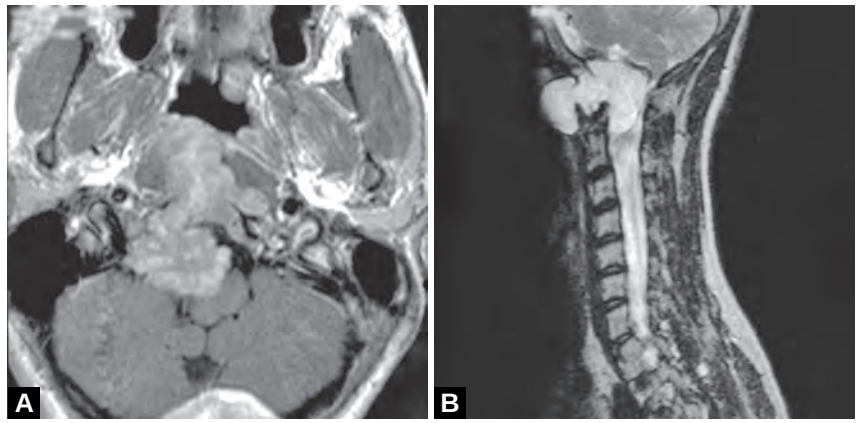
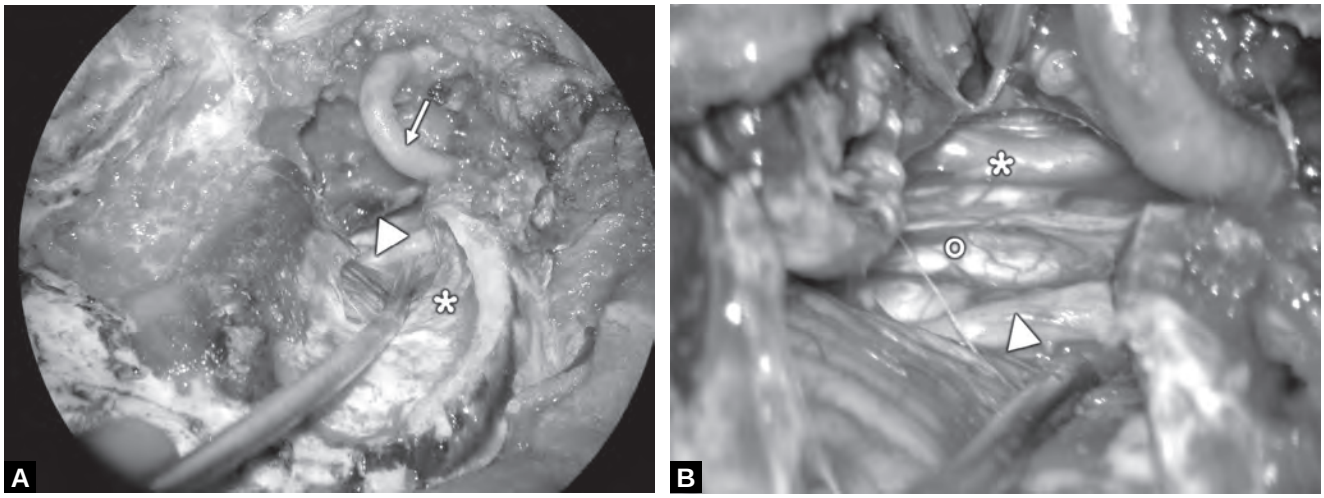


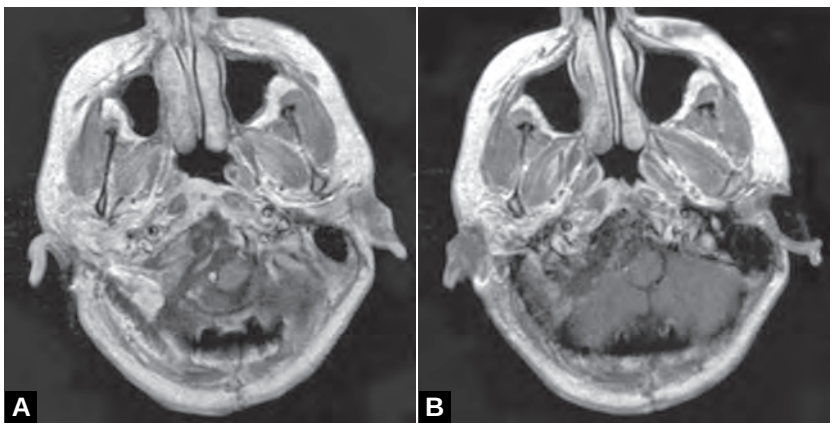
Fig. 10: Post-operative CT bone images showing bone removal



Figs 11A and B: MRI scans of a 16-year-old boy showing a large tumour involving the lower clivus and the craniocervical junction



Figs 12A and B: Surgical procedure (for removal of tumour shown in Figures 11A and B) using right sided extreme lateral transcondylar approach



Figs 13A and B: Removal of tumour including the involved bone and dura

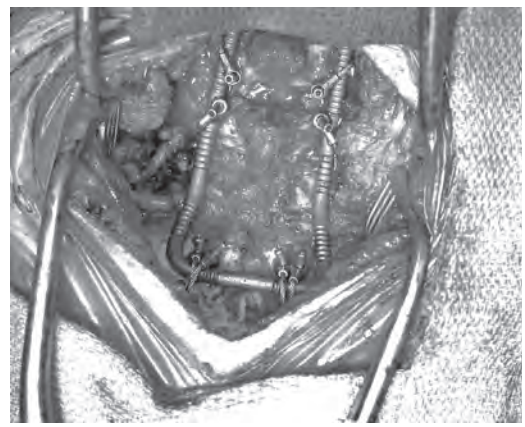


Fig. 14: Occipito-cervical fusion with titanium rods

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181 Trans-facial Transmaxillary Approaches to Anterior Skull Base

Sojan Ipe, Bobby Jose

INTRODUCTION

With the evolution of skull base surgery, transfacial approaches have gained popularity for the surgical resection of lesions located anterior to the neurocranium because of the anteroinferior anatomic relationship of the facial viscerocranium to the cranial base. The intimate relationship of the anterior and midskull base to the facial structures as well as the cranium requires mobilisation of one of these, for approaching pathology in this region. The term transfacial is used to describe any procedure that mobilises the midface skeleton, through a facial skin incision irrespective of the extent of midface disassembly employed. The nasal bone, maxilla and zygoma may be mobilised alone or in combination unilaterally or bilaterally and either as an osteoplastic flap or as free bone fragments.

The surgical disarticulation of the craniofacial skeleton can be used to gain access to otherwise inaccessible sites in the skull base. These approaches allow access to the anterior and middle cranial fossa, cavernous sinus, clivus, craniovertebral junction, upper cervical vertebrae up to the level of C4, infratemporal and pterygopalatine fossa, nasopharynx, paranasal sinuses and the orbit.

The facts to be considered, while selecting an approach, should be the ease of approach, the consequences due to alterations in the affected as well as the surrounding normal structures due to the operative approach and the post-operative patient quality of life. In selecting the transfacial approaches, the variable consequences, such as post-operative swelling of the facial tissue which is short-term and self-limiting, are more desirable than a similar swelling in the neural tissue which may be fatal or debilitating.

HISTORY

The first report of bilateral horizontal maxillotomy was by Von Langenbeck in 1859.[33] He also reported a case where he used this technique to remove fibroids of the pterygopalatine fossa.[34] Later, in 1867, Cheever used the approach for removal of a nasopharyngeal tumour.[7,20] In 1893, Lanz described division of the maxilla in the midline in addition to the horizontal maxillotomy.[10,18] In 1901, Le Fort classified the variants of fractures of the maxilla. Subsequently, Martin Wassmund performed a Le Fort I osteotomy for correction of congenital malocclusion in 1927 and the operation was reported in his textbook of 1935.[10,20] Paul Tessier,[31] in his landmark paper, demonstrated that intracranial and extracranial exposures could be combined without undue risk of infection. He also showed that the facial bones can be stripped of periosteum, osteotomised and would still survive. Numerous other reports followed this in the otolaryngological and maxillofacial literature in the use of the transmaxillary approach for removal of various nasopharyngeal tumours and correction of deformity. The approach gained popularity in neurosurgical circles after the applications of this were rediscovered following the advent of skull base surgery in the late 1980s. These principles have proven valuable for achieving wide exposure of the skull base through facial routes, which allowed complete resection of tumours previously considered unresectable.[8,33]

INDICATIONS

The basic principles of anterior skull base surgery are as follows:

- Identify the epicentre of the mass.
- Take the shortest route from the skin to the target lesion.
- Bypass the vital structures essential for satisfactory functional outcome.
- Use pre-existing spaces in the face and the skull bones.
- Plan reconstruction depending upon the approach.
- Reconstruct aesthetically with best cosmetic end result.
- Maintain compartmentalisation—segregate neurocranium and viscerocranium.
- Evaluation of tumour biology and appropriate pretreatment to downgrade the tumour.

The transfacial transmaxillary approach is useful for a variety of lesions from the paranasal sinuses to the clivus. It can be extended with mandible splitting procedures, to reach up to the upper cervical spine. This approach is ideal for lesions arising from the paranasal sinuses with or without intracranial extension, anterior skull base lesions, extradural lesions of the upper and middle third of the clivus such as clival chordoma and chondrosarcoma. Other potential lesions that can be treated with this approach are fibrous dysplasia, inverting

papilloma, osteoma and ossifying fibroma.[19] It can also be used for the removal of small to moderately sized nasopharyngeal lesions, such as juvenile angiofibromas, with limited lateral extension, esthesioneuroblastoma (olfactory neuroblastoma), adenocarcinoma and adenoid cystic carcinoma.[4,5,26,28,30,32] Many of these tumours to a greater or lesser degree are malignant. Inverting papilloma is an example of a tumour that is locally invasive, does not metastasise but must be resected aggressively to avoid recurrence. Esthesioneuroblastoma varies from a very sluggish to highly aggressive tumour. Most tumours of nasal or paranasal sinus origin are squamous cell or adenocarcinoma of the maxillary or ethmoid sinuses. Transfacial approaches also provide access to the deformed skull base in patients with basilar invagination and marked neuraxial compression.[13,27] There are reports of this approach being used for treating vertebrobasilar junction aneurysms,[2,9,21] but, with the advent of interventional treatment for such lesions, surgery is almost never done considering the risk factors of the surgery. This approach has also been used for intradural lesions in this region. We use the anterior transfacial approaches mainly for extradural lesions and extradural lesions that have transgressed the dura secondarily. Combined craniofacial resections are recommended when there is tumour extension beyond the anterior skull base and if there is frank intradural extension of the tumour. Purely intradural lesions, such as basal meningiomas, are also approached by combining this with transcranial approaches for the ease of repair of the dural defect and thus to avoid potential complications. The transmaxillary approach has the advantage of being an extradural anterior inferior midline approach with a relatively low risk of injury to the cranial nerves and the major blood vessels.[19] Also, for extensive lesions, these transfacial approaches can be combined with other intracranial approaches simultaneously or staged.[11,12]

The advantages[15] of the transfacial approaches are the following:

- Facial anatomy has developed from embryonic fusion of nasofrontal, maxillary and mandibular processes. Normally the fusion takes place in the midline or in the paramedian region, thus logically presenting the optimal lines of separation of facial units for surgical approaches and facilitating the least traumatic displacement.
- The primary blood supply to the facial units is through the external carotid system which also has a lateral to medial direction of flow, thus ensuring viability of displaced surgical units.
- The midface contains multiple hollow anatomical spaces (oronasal cavity, nasopharynx and paranasal sinuses) that facilitate the ease of surgical access to the central skull base.
- Displacement of facial units for approach to the central skull base offers much greater tolerance to the post-operative surgical swelling, as opposed to similar displacement of the contents of the neurocranium.
- Re-establishment of the normal anatomy, following repositioning of the reconstructive phase of surgery, leads to good functional as well as aesthetic results.

The disadvantages[15] of transfacial approaches are the following:

- Contamination of the surgical wound with oropharyngeal bacterial flora.
- The need for facial incisions with subsequent scar formation.
- Emotional consideration of the patient related to surgical facial disassembly.
- The potential need for supplementary airway management like post-operative endotracheal intubation, temporary tracheotomy, etc.

SURGICAL ANATOMY[1,23,25]

The cranium is sub-divided into the cranial vault and the cranial base which consists of the floor of the cranial cavity intracranially and the inferior surface of the skull extracranially and the facial skeleton which includes the orbital cavities, the nasal fossae and the jaws. The base of the cranial cavity is divided into three distinct fossae—the anterior, middle and posterior.

The floor of the anterior cranial fossa is at a higher level than the others. The anterior cranial fossa occupies less than the anterior one-third of base of the skull.

Skeletal surface landmarks of the face are sometimes palpable. It is important to have an idea of the surface relationship of the underlying structures to plan the transfacial approach. The superciliary arches are palpable above the orbit with a horizontal ridge in the midline called the glabella. The supraorbital margin lies beneath the upper margin of the eyebrow. The supraorbital notch is palpable 2 fingers breadth from the midline at the junction of the rounded medial 1/3rd and the sharp lateral 2/3rds of the supraorbital margin, which at times may be converted into a foramen. It is worth noting that the supraorbital, infraorbital and the mental foramina all lie approximately in the same vertical plane (Fig. 1). The median mental tubercle of the mandible is palpable. The mental foramen lies below the premolar tooth, 2 fingers breadth lateral to the mental tubercle and midway between the upper and lower borders of the mandible. A vertical line drawn from the supraorbital notch to the base of the mandible passing over the canine fossa crosses the infraorbital foramen 5 mm below the infraorbital margin and a finger breadth from the side of the nose. The canine fossa is posterior to the canine eminence overlying the root of the canine tooth.

The relevant osteological details alone will be discussed here. For a detailed account of the anatomy, the reader is advised to refer to specialised anatomical textbooks. The superciliary arch is a rounded curved elevation situated just above the medial part of each orbit. The glabella is the horizontal median elevation connecting the two superciliary arches. The nasion is the median

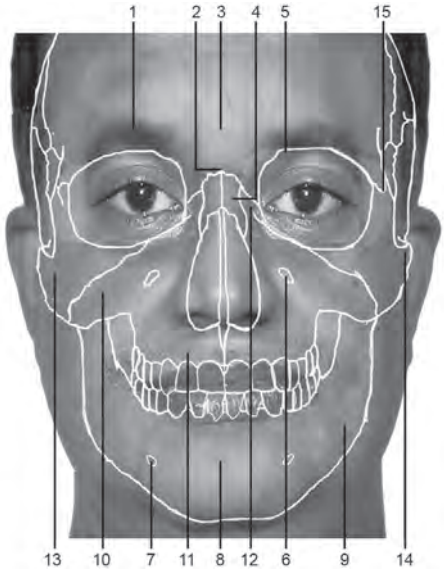


Fig. 1: Surface landmarks: (1) Superciliary arch; (2) Nasion; (3) Glabella; (4) Nasal bone; (5) Supraorbital notch; (6) Infraorbital foramen; (7) Mental foramen; (8) Mental tubercle; (9) Mandible; (10) Maxilla; (11) Alveolar process; (12) Frontal process of maxilla; (13) Zygomatic bone; (14) Zygomatic arch and (15) Fronto-zygomatic suture

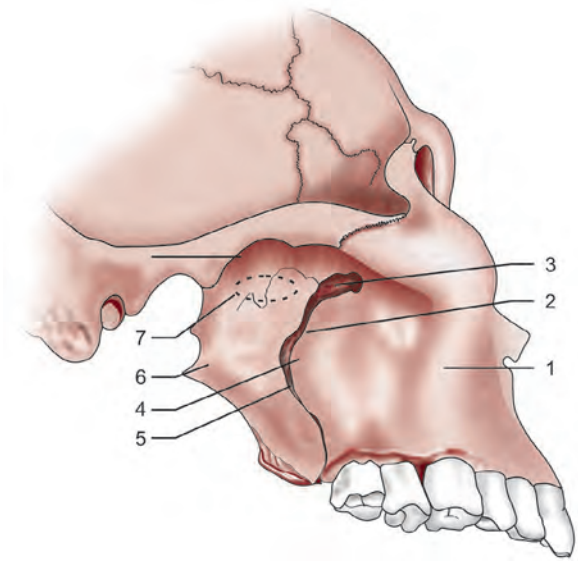


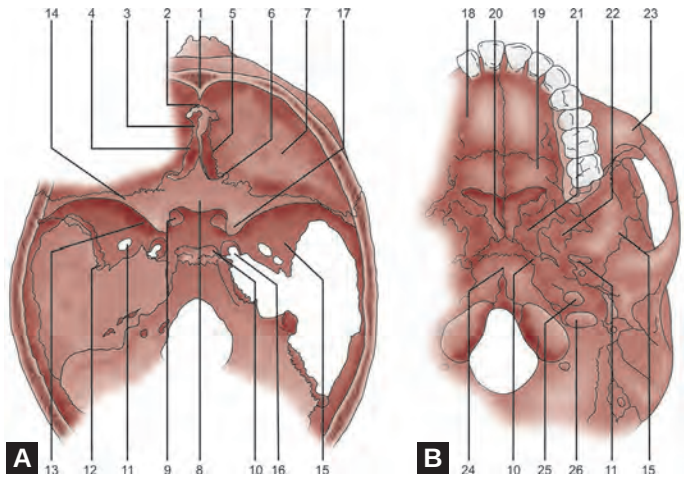
Fig. 2: Right inferiolateral view: (1) Zygomatic crest; (2) Pterygopalatine fossa; (3) Inferior orbital fissure; (4) Maxillary tuberosity; (5) Pterygomaxillary fissure; (6) Lateral pterygoid plate and (7) Infratemporal fossa

point of the root of the nose where the internasal suture meets with the frontonasal suture below the glabella.

The central part of the face is mainly occupied by the maxillary bones and the anterior nasal aperture. Each maxilla contributes to the upper jaw, the bridge of the nose, the floor of the orbit, the nasal aperture and the bone of the cheek. The maxilla has a body and four processes. The body encloses the maxillary sinus. The anterior aspect of the maxilla has the following landmarks: the alveolar process is socketted for the maxillary teeth, the frontal process projects posterosuperiorly between the nasal and the lacrimal bones, connecting the frontal bone and the nasal bone (Fig. 1). The lateral surface of the frontal process gives attachment to the medial palpebral ligament and the zygomatic process connects to the zygomatic bone. The infraorbital foramen contains the infraorbital nerves and vessels. The lateral aspect of the maxilla has the zygomatic crest between the lateral pointing zygomatic process superiorly and the second molar inferiorly. The posterior convexity of the maxillary body is the maxillary tuberosity which forms the anterior wall of the infratemporal fossa (Fig. 2). The superior aspect of the maxilla forms the nasal floor medially and the greater part of the orbital floor laterally.

The palatine process, which forms a large part of the nasal floor and the hard palate, arises as a horizontal plate from the body of the maxilla at the boundary between the body and the alveolar process. The hard palate is formed by the paired palatine processes of the maxilla and the horizontal plates of the palatine bones posteriorly (Figs 3A and B). The pterygomaxillary suture defines the connection between the maxilla and the lateral pterygoid plate of the sphenoid bone.

The piriform apertures contain the nasal septum, which is formed by the cartilaginous septum anteroinferiorly, by the vomer posteroinferiorly and by the perpendicular plate of the ethmoid bone superior to both these structures. The lateral wall of each nasal cavity supports the curved bony plates of the nasal conchae. The pterygoid process of the sphenoid bone consists



Figs 3A and B: (A) Interior of the base of skull and (B) Inferior view: (1) Frontal crest; (2) Foramen caecum; (3) Crista galli; (4) Cribriform plate; (5) Anterior ethmoidal foramen; (6) Posterior ethmoidal foramen; (7) Orbital plate of frontal bone; (8) Jugum sphenoidale; (9) Carotid groove; (10) Foramen lacerum; (11) Foramen ovale; (12) Foramen spinosum; (13) Foramen rotundum; (14) Lesser wing of sphenoid; (15) Greater wing of sphenoid; (16) Posterior clinoid process; (17) Anterior clinoid process; (18) Palatine process of maxilla; (19) Horizontal plate of palatine bone; (20) Insertion of vomer on sphenoid; (21) Medial pterygoid plate; (22) Lateral pterygoid plate; (23) Zygoma; (24) Clivus; (25) Carotid canal and (26) Jugular foramen

of the lateral and medial pterygoid plates and extends inferiorly on each side of the sphenoid (Fig. 3B). The foramen lacerum is immediately posterior to the medial pterygoid plate and its upper half houses the internal carotid artery. The internal carotid artery limits the lateral exposure in this area. The anterior margin of the pterygoid process is adjacent to the horizontal plate of the palatine bone. The lateral pterygoid plate forms the posterior aspect of the pterygomaxillary fissure, adjacent to the maxillary tuberosity (Fig. 2). The maxilla, thus, forms the anterior wall of the pterygopalatine fossa as well as that of the infratemporal fossa.

The anterior cranial fossa is formed at the front and sides by the frontal bone while its floor is formed in the median plane anteriorly by the cribriform plate and the crista galli of the ethmoid bone and posteriorly by the superior surface of the anterior part of the body of the sphenoid (Fig. 3A). On either side, the floor is formed by the orbital plate of the frontal bone and the lesser wing of the sphenoid posteriorly. The medial end of the lesser wing forms the anterior clinoid process. The inferior surface is related to the roofs of the orbits on each side and the roof of the nasal cavity.

The cribriform plate spreads across the midline between the orbital plates of the frontal bones and is depressed below them, forming part of the roof of the nasal cavity. The olfactory nerves pass from the nasal mucosa to the olfactory bulb through numerous foramina in the cribriform plate. The anterior margin articulates with the frontal bone at the frontoethmoidal suture, which is marked in the median plane by the foramen caecum. The cribriform plate has the crista galli anteriorly, which projects upwards like a tooth and provides attachment to the falx cerebri. The lateral margins articulate with the orbital plate of the frontal bone and the suture has the anterior ethmoidal canal which transmits the anterior ethmoidal nerve and vessels. The nerve then passes into the roof of the nose by the side of the crista galli via a foramen. The posterior margin articulates with the jugum sphenoidale and the posterolateral corners present the posterior ethmoidal canals, which transmit the posterior ethmoidal vessels.

Jugum sphenoidale separates the anterior cranial fossa from the sphenoid sinuses. The orbital plate of the frontal bone separates the anterior cranial fossa from the orbit and supports the orbital surface of the frontal lobe. The medial margin covers the labyrinth of the ethmoid and the posterior margin articulates with the lesser wing of the sphenoid.

PRE-OPERATIVE EVALUATION

The patient is evaluated with high resolution CT scan and MRI to define the anatomical extent of the lesion. Angiography may be done in selected cases. Some cases may benefit with pre-operative embolisation. Adjuvant pre-operative chemotherapy and\or radiotherapy may be planned in some cases to down size the tumour. The decision on the approach is based on the anatomical site and the extent of the lesion, experience and familiarity of the surgeon, and the age and overall prognosis of the patient and the presumptive biological characteristics of the lesion. The dental hygiene of the patient should be evaluated and any infection should be treated to avoid post-operative complications. A dental splint is fabricated to reproduce normal occlusion after surgery, depending on the type of osteotomy planned. Culture of the nasal and throat flora should be obtained pre-operatively. Appropriate antibiotics should be started with the induction of anaesthesia, to be continued post-operatively.

ANAESTHESIA

The airway is maintained either with orotracheal intubation or with tracheotomy. We prefer orotracheal intubation and have not anytime encountered excessive swelling of the orofacial tissues compromising the airway in the post-operative period. Arterial and central venous pressure lines and a precordial stethoscope to detect venous air embolism are desirable. Hypotensive anaesthesia is not mandatory. A spinal drain may be used if dural breach is expected.

PATIENT POSITIONING

The patient is positioned supine with the head resting on a head ring or rigid fixation as per the surgeon's preference. Then complete preparation of the face and neck is performed with povidone iodine solution and the oropharynx is irrigated with appropriately diluted solution, the area is then draped. In addition, the lateral thigh is prepared and draped as a fascia lata donor site.

OPERATIVE TECHNIQUE

The transfacial approach relies on the principle that the facial anatomy can be divided into composite units along key neurovascular units and aesthetic lines.[15] These individual units merge into larger composite units without compromising their individual function. Although there are numerous terminologies for the various transfacial approaches, all are based on the general principle of disassembling the face along these units depending on the location and extent of the lesion.

Classification of Transfacial Transmaxillary Approaches

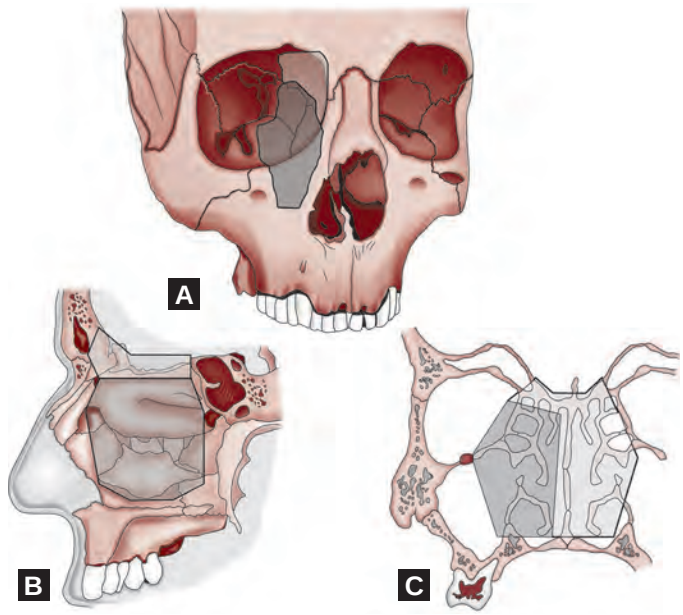
I. Medial
   1. Medial maxillectomy[29]
   2. Medial mini-facial translocation[15]

II. Lateral
   1. Total maxillectomy[22]
   2. Standard facial translocation[15]
   3. Extended osteoplastic maxillotomy[6]

III. Combined (Medial and Lateral)[15]
   1. Medial extended facial translocation (Le Fort I)
   2. Medial and inferior extended facial translocation

IV. Bilateral
   1. Bilateral facial translocation[15]
   2. Extended transfacial subcranial[24]
   3. Facial degloving[16]
   4. Transmaxillary approaches of Beals and Joganic[3]

This classification was based on the extent of bone removal and the limits of anatomical exposure gained by each approach. Several approaches have been described by different authors, from which we have selected certain standard procedures described in the literature, which will help the reader to understand the various concepts. The choice of employing the appropriate approach for an anterior skull base tumour is dependent on patient factors such as age, general health of the patient, tumour characteristics, extent of involvement, nature of growth (whether benign or malignant) and the surgeon's personal preference and experience.



Figs 4A to C: Medial maxillectomy extent of excision

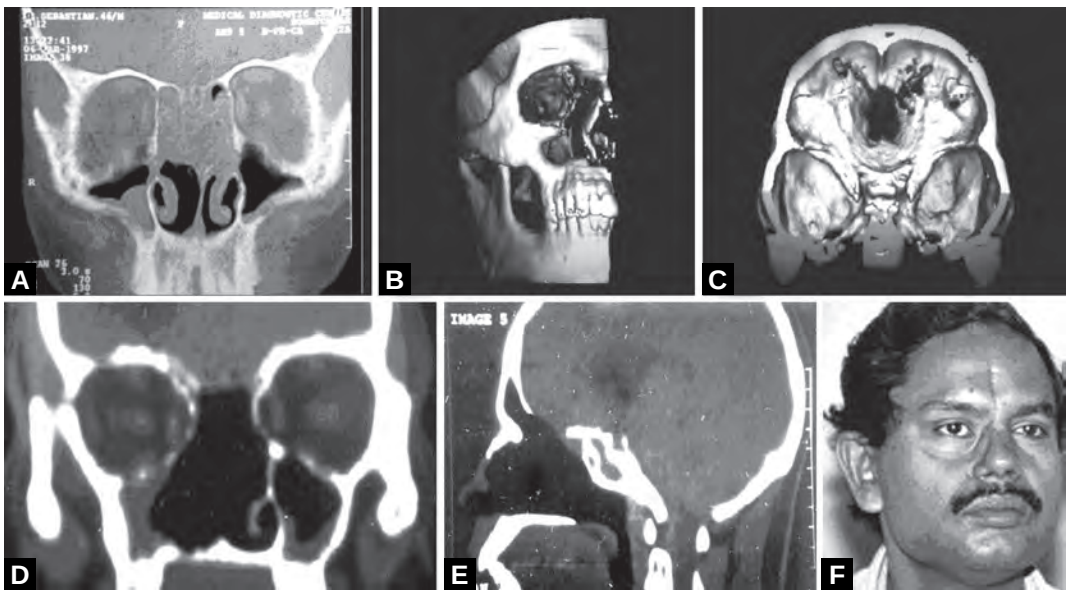
Medial

Medial Maxillectomy

The technique of medial maxillectomy, as described by Sessions and Larson in 1977,[29] requires excision of the medial maxillary sinus wall and turbinates, ethmoids and lamina papyracea, lacrimal bone and the orbital wall medial to the infraorbital nerve [Figs 4A to C (shaded areas in views)]. This procedure is an extension of the lateral rhinotomy approach made in the side of the nose for surgical exposure.

Medial maxillectomy is indicated for benign and malignant neoplasms limited to the nasal walls, medial wall of the maxillary sinus and adjacent ethmoid sinus. When a component of the neoplasm extends intracranially, the medial maxillectomy can be combined with a frontal craniotomy to allow en bloc craniofacial resection of the lesion.[17] A number of modifications of medial maxillectomy are possible including the medial orbital rim, in combination with frontal sinusotomy for lesions of the ethmoid roof extending to involve the anterior cranial base [Figs 4A to C (shaded areas with lighter tone)]. Under magnification, the entire median aspect of the floor of the anterior cranial fossa can be removed with the infiltrating tumour mass (Figs 5A to F).

Medial maxillectomy approach gives better physical quality of life index (PQLI) after surgery, early feeding with good dental occlusion and early mobilisation and



Figs 5A to F: (A to C) Clinical example of modified medial maxillectomy employed to excise a squamous cell carcinoma filling the upper nasal cavity and infiltrating the floor of the anterior cranial fossa. (D to F) 18 months follow-up CT scan showing the extent of bone removal and the cosmetic end result

rehabilitation of the patient. It minimises intracranial complications that would occur with combined transcranial approaches such as brain retraction related contusions of the frontal lobes, intracranial haematomas, dural tears, CSF leaks, pneumocephalus and meningitis.

Medial Mini-Facial Translocation[15]

This approach is designed to reach the medial orbit, sphenoid and ethmoid sinus and inferior clivus as described by Janecka (Figs 6A and B). The port of entry is through the displaced ipsilateral nasal bone and the nasal process of the maxilla with attached medial canthal ligament, lacrimal duct and skin. The skin incision is made along the lateral aspect of the nose and the inferior aspect of the eyebrow with a triangular design at the level of the medial canthal ligament. The lateral extent of the osteotomy is just medial to the infraorbital nerve. The entire unit can be displaced laterally for surgical exposure.

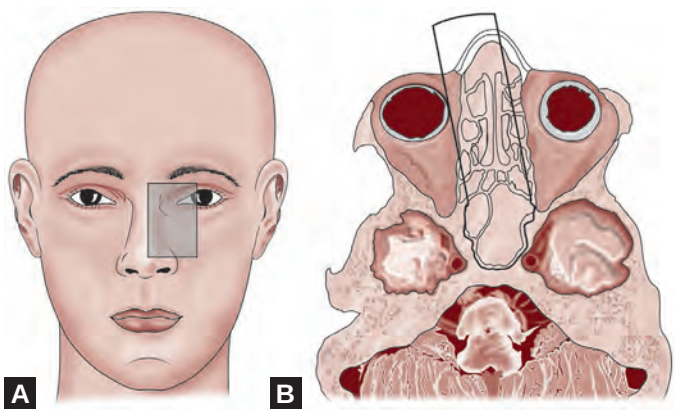
Lateral

Total Maxillectomy

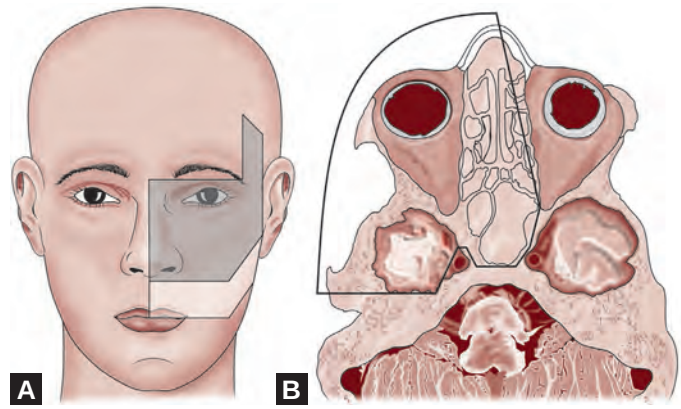
Classical total maxillectomy procedures are described in plastic surgery,[22] which gives clear cut details of this procedure which becomes part of the extended procedures described by others. The classical Weber-Ferguson-Longmire skin incision and the soft tissue dissection involved in exposing the anterior surface of the maxilla have to be followed. An in depth understanding of this step is important before learning various levels of osteotomies involved in the extended procedures.

Standard Facial Translocation

With this technique of translocation, good exposure of the anterolateral skull base is achieved, especially when the infratemporal fossa is involved as well. This was originally described by Janecka.[15] The ipsilateral facial skin including the lower eyelid is displaced laterally and inferiorly with the underlying maxilla, with or without the hard palate (Figs 7A and B). The nasal incision may extend inferiorly to include an upper lip split. The superior incision continues from the nose to the inferior fornix of the lower eyelid through the lateral canthus horizontally to the preauricular area. Osteotomies correlate to Le Fort I-II or the mid-palatal lines when the entire maxilla is being displaced.



Figs 6A and B: (A) Basic plan for medial mini-facial translocation. (B) Axial outline of surgical view

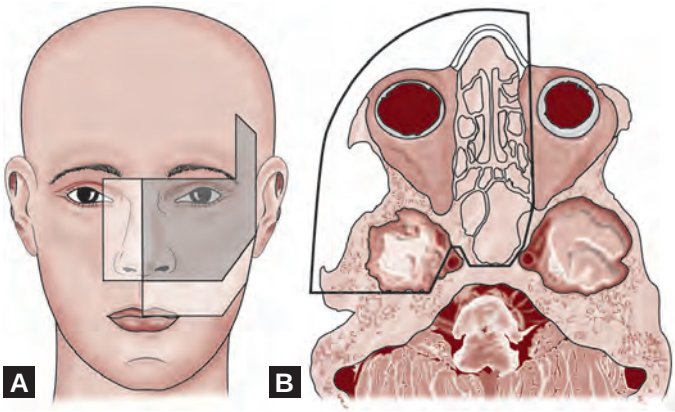


Figs 7A and B: (A) Basic plan of standard facial translocation with palatal extension shown in the lightly shaded area. (B) Axial outline of surgical view

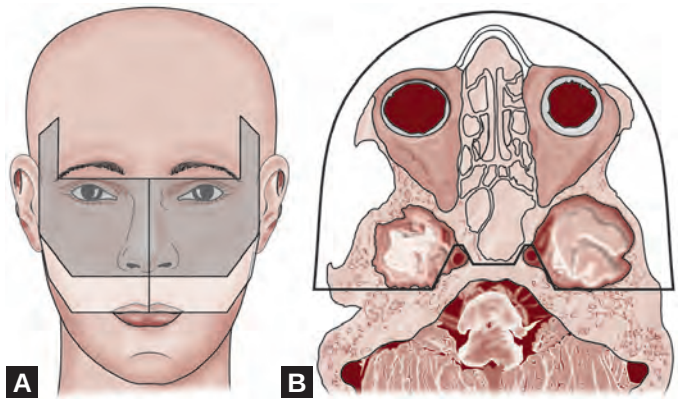
Extended Osteoplastic Maxillotomy

This technique, originally described by Catalano,[6] provides wide, direct exposure of the lateral and/or central skull base. It is indicated for benign or malignant lesions that involve two or more of the following anatomic areas: pterygopalatine fossa; sphenoid sinus; nasopharynx; infratemporal fossa; cavernous sinus and/or floor of the middle fossa and clivus. The maxillofacial skeleton is exposed via a Weber-Ferguson incision. Osteotomies in the maxilla and zygoma disengage the maxilla from the facial skeleton. The maxilla is mobilised on the skin and the soft tissues of the ipsilateral cheek, thereby maintaining its blood supply. Due to this osteoplastic technique, the untoward effects of adjuvant radiation therapy and/or chemotherapy are minimal. By varying the position of the facial osteotomies, this approach is very flexible. Medial positioning of the anterior osteotomy of the maxilla determines the extent of exposure of the nasopharynx and the positioning of the lateral osteotomy determines the extent of exposure of the infratemporal fossa. Pterional or temporal craniotomy can be combined to gain access to the corresponding cranial cavity. Miniplate fixation of the maxilla and the zygoma re-establishes the contour of the facial skeleton functionally and cosmetically.

Catalano's technique of osteoplastic maxillotomy has many similarities to the techniques described by Janecka et al.[14] and Wei et al.[35] The basis of osteoplastic maxillotomy is the pedicled osteoplastic unit, comprised of vascularised bone, muscle, skin and mucosa, whose design can be tailored to the desired skull base exposure.



Figs 8A and B: (A) Scheme. (B) Axial extent of the exposure



Figs 10A and B: (A) Scheme. (B) Axial extent of the bilateral facial translocation

Combined (Medial and Lateral)

Medial Extended Facial Translocation (Le Fort I)[15]

This approach incorporates the standard translocation unit of Janecka plus the nose and the medial one-half of the opposite face up to the infraorbital nerve. It can be rotated at the Le Fort I level or include the ipsilateral palate and upper lip split (Figs 8A and B). The skin incisions are similar to the standard technique, except that the paranasal incision is made on the contralateral side. The surgical exposure involves the ipsilateral infratemporal fossa and central and paracentral skull base bilaterally. The entire clivus, optic nerves, precavernous internal carotid arteries and nasopharynx are accessible. Reconstruction is with the temporalis muscle flap. Occlusion plane is re-established with an orthognathic splint.

Medial and Inferior Extended Facial Translocation[15]

This exposure is the same as the medial extended facial translocation with an inferior extension by a mandibular split (Fig. 9). The lower lip incision is performed in a zigzag fashion to conform to the tension lines of the skin. Mandibular osteotomy is performed just medial to the mental foramen. Prior to osteotomy, it is wise to select an appropriate miniplate for eventual fixation, contour it to the mandible and create drill holes. This assists in post-operative re-establishment of normal occlusion. This inferior extension adds a significant inferior cranial as well as upper cervical surgical access.

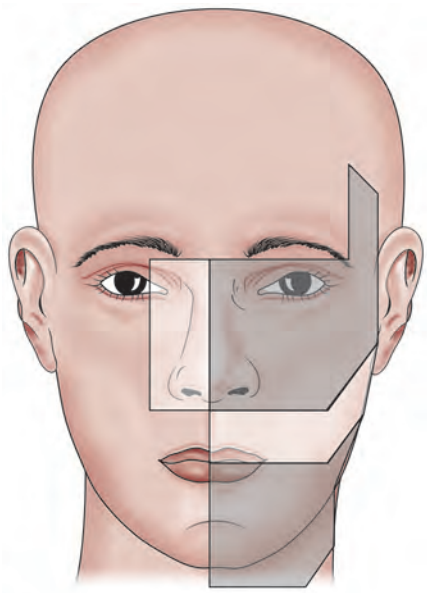


Fig. 9: Scheme of medial and inferior extended facial translocation

Bilateral

Bilateral Facial Translocation[15]

This approach combines complete right and left standard facial translocation units of Janecka with or without palatal split (Figs 10A and B). The exposure incorporates both infratemporal fossae and the central and the entire paracentral skull base. Both distal cervical internal carotid arteries and the clivus are in view. The palatal split permits a reach to the level of C2-3 and an added mandibular split adds a vertical reach to C3-4. The surgical defect is repaired with a single temporalis flap.

Extended Transfacial Subcranial Approach[24]

Raveh, in 1993, described an en bloc bifrontal craniotomy including the supraorbital ridges and the nasal bones. He proposed the extended subcranial approach to the anterior skull base, which is an extended exposure of the anterior, middle and posterior planes of the anterior fossa. With only one operating field, this technique provides a wider angle of approach to the skull base. The other advantage of this method is that only minimum retraction of the frontal lobes is required. The perfect fit of the free bone flap and the fact that there is no facial incision ensure a satisfactory cosmetic result.

The first step of the procedure is designing a bicoronal flap. The pericranial flap is taken down, and care is taken not to injure the supraorbital pedicle with the nerve and vessels. A pneumatic tool or a chisel should be used to remove the nerve from its channel. A meticulous dissection is made entering the orbit and both orbits are dissected medially, superiorly and laterally. The anterior ethmoid artery is ligated and the flap is cut down to the

tip of the nasal bone. The lacrimal duct is taken out of its bony channel.

The next step of the procedure is to decide what type of osteotomy is needed. The type A would include the anterior frontal sinus wall along with the nasal bones. The type B osteotomy involves taking off the posterior frontal sinus wall just anterior to the crista galli. Before doing this, however, a radical ethmoidectomy is performed. In the type B osteotomy, after both orbits have been dissected, the anterior ethmoidal arteries ligated, and radical ethmoidectomies have been performed bilaterally, the whole fronto-naso-orbital segment is taken out and this will include the posterior frontal sinus wall as well. If the tumour is unilateral, it is possible to preserve the olfactory filaments on the contralateral side. This is very rare, but can be done in some cases, since anosmia is the major inconvenience of the procedure. There is a large defect at the end of this procedure. The posterior sinus wall and the entire area that is left after the resection of the tumour need to be reconstructed. This is done with very large and generous pieces of fascia lata. The first layer of fascia lata is sutured to the edges of the resected dura and a second layer of fascia lata is introduced under the edges of the bone. Telecanthus is prevented by bilateral fixation. A thread is passed through the medial canthal ligament and fixed on the contralateral side. After the reconstruction of the skull base, the last step of the procedure is the application of the naso-frontal-orbital segment in its original anatomic place and its fixation by titanium plates. The plates were formed pre-operatively in order to replace the bone in its original anatomical position at the end of the operation. With the subcranial approach, a medial maxillectomy can be done to only a limited extent. When the tumour is above the inferior turbinates, the subcranial approach alone is sufficient, but if it reaches the inferior walls of the maxilla, a transfacial approach or a formal maxillectomy will be needed in addition.

Facial Degloving[16]

This is performed to prevent surgical incision on the face. First, a midface degloving procedure is done and then the regular osteotomies as per requirements are done for excision of the lesion. For the degloving procedure, the medial palpebral ligament is first dissected and wired after making a small incision near the medial angle of both eyes. These wires are tied under the nasal skin at the end of the surgery.

Bilateral circumferential mucosal incisions are made in the nares. A transfixation incision is connected bilaterally with intercartilaginous, pyriform and nasal floor incisions. The soft tissues of the nasal dorsum are separated from the upper lateral cartilages and nasal bones through the intercartilaginous incisions bilaterally in a subperiosteal plane. All fibrous attachments between the septum and the skin of the nasal tip area are divided. Thus, the nasal tip including the lower lateral nasal cartilage is separated. Extension of the incision circumferentially within the nasal vestibule at the skin mucosal junction completes the release of the nasal soft tissue at the pyriform aperture. A sublabial incision is made 4–5 mm above the labiogingival sulcus. It may extend up to or beyond the first molar tooth on both sides. The skin and soft tissue of the face is then dissected in the subperiosteal plane, sparing each infraorbital nerve. Facial soft tissues including lip, cheeks, nasal tips and alae, columella and nasal skin are then reflected superiorly. The elevation is extended as high as the infraorbital rim and the glabella as per the requirement. Then the necessary nasomaxillary and Le Fort I osteotomies, as required, are performed.

Transmaxillary Approaches of Beals and Joganic[3]

The system is based on selecting the most appropriate angle and exposure to the anatomic site of the tumour. Six levels of exposures are described. The upper three approaches are transfrontal approaches incorporating a supraorbital bar, either alone or with nasal and medial orbital walls; and further extended by including the lateral orbital walls.

The lower three levels of approaches provide exposure to the midline skull base through the maxilla. The transnasomaxillary approach (level IV) achieves a wide exposure of the entire central skull base but requires a Weber-Ferguson incision and a Le Fort II osteotomy. The level V transmaxillary approach requires a midfacial degloving and a Le Fort I osteotomy. It is mainly indicated for extradural lesions of the upper two-thirds of the clivus. Level VI is a transpalatal approach (Fig. 11).

Level IV: Transnasomaxillary approach: This approach can be used for nasopharyngeal lesions or for large clival lesions that extend in any direction. This technique requires a modified Weber-Ferguson incision, which extends across the radix and along the subciliary margin of the opposite lower lid. The nasomaxillary area is exposed and a Le Fort II osteotomy is performed. The osteotomy skirts along the infraorbital

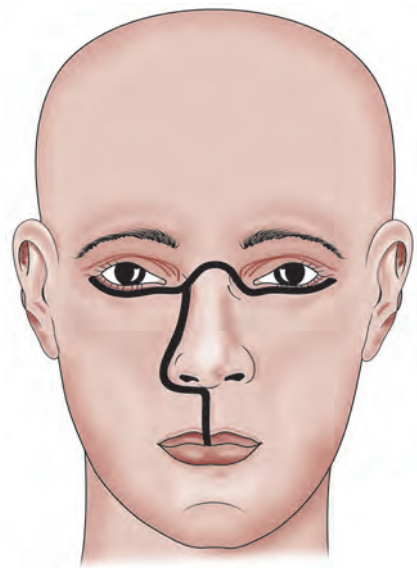
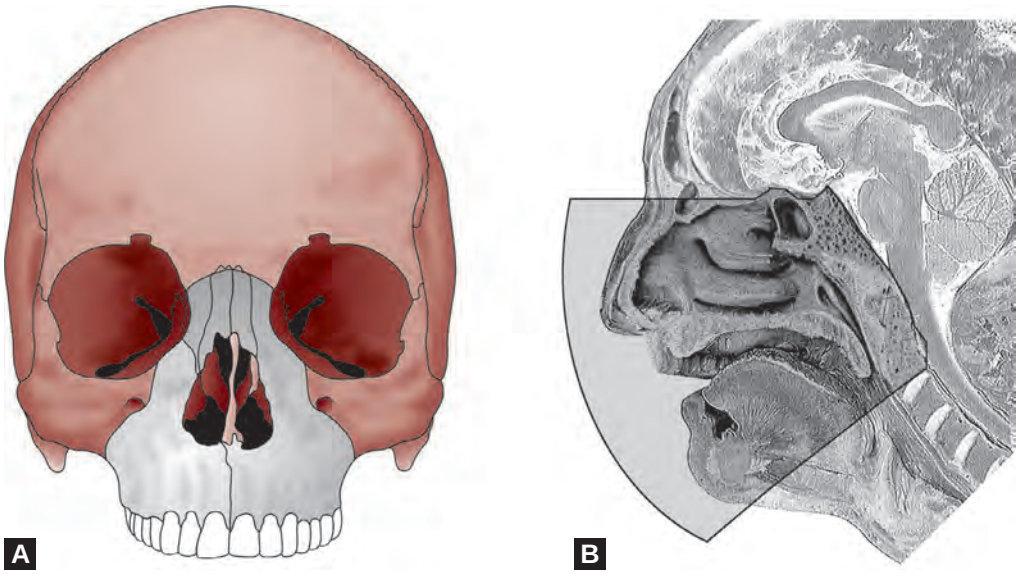


Fig. 11: Modified Weber-Fergusons incision



Figs 12A and B: (A) Scheme of Le Fort II osteotomies for level IV transmaxillary approach. (B) The sagittal extent of surgical view

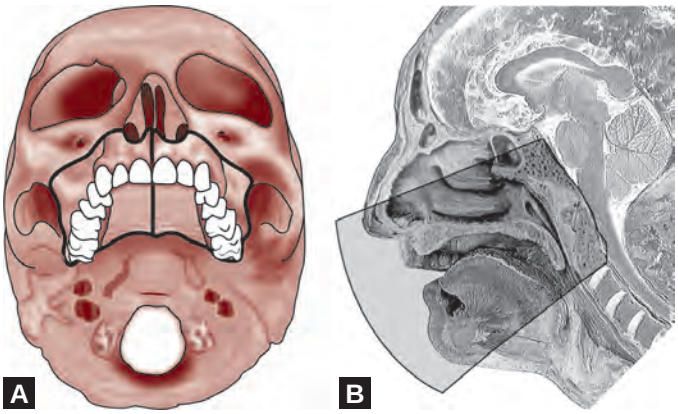
foramen anteriorly and along the nasolacrimal canal at the medial aspect of the inferior orbital rim (Figs 12A and B). The fragment is split at the nasal process of the maxilla on one side and the palate is split at the midline. The nasal complex remains on any one side of the fragment, depending on the best angle for exposure of the tumour and is retracted with it.

Level V: Transmaxillary approach: This exposure is ideally suited for moderately sized nasopharyngeal lesions as well as for clival lesions with superior or inferior extensions. An intraoral approach using an upper buccal sulcus incision is used as for midface degloving. Le Fort I osteotomy is performed along with a midline split (Figs 13A and B) and each half is retracted. After tumour resection, reassembly is done using an interdental splint.

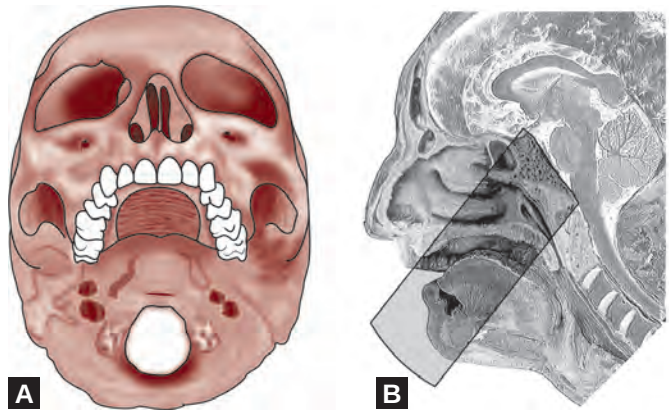
Level VI: Transpalatal approach: This approach gives access to the lower clival region. A midline incision is made from one side of the uvula towards the incisive foramen. A separate incision is made in the upper labial sulcus and the floor of the nasal mucosa is lifted from the palatal surface and then the osteotomies are performed (Figs 14A and B).

POST-OPERATIVE MANAGEMENT

Most patients are extubated immediately after surgery. Only rarely tracheotomy is necessary, especially in patients with palatal splitting procedures. Suction drains are kept in the operative bed. Parenteral antibiotics are continued until all the drains are removed and then oral antibiotics are continued for a week. A short course of steroids is also administered to minimise soft tissue inflammation. Tube feeding can be started after 24 hrs, once bowel activity returns. The patient is maintained on tube feeding for 5 days and then oral intake is resumed. If a spinal drain is in place, it is removed after 3–4 days. CT scan is performed after 24 hours to ascertain immediate post-surgical changes.



Figs 13A and B: (A) Scheme of Le Fort I osteotomy for level V transmaxillary approach. (B) The sagittal extent of surgical view



Figs 14A and B: (A) Scheme for level VI transpalatal approach. (B) The sagittal extent of surgical view

COMPLICATIONS

Complications fall in three main categories: (1) bleeding; (2) infection and (3) wound healing and can be quite hazardous.

Venous bleeding is often encountered, which can be quite bothersome and may be controlled with bone wax or with gelfoam. Inadvertent injury to the vertebral or the carotid artery may be fatal and repair should be attempted after application of temporary clips.

Infection is often due to the presence of non-vascularised tissue or post-surgical dead space or due to inadequate dural repair leading to CSF leak and meningitis. Wound healing problems are more common in patients who had previous surgery or radiotherapy.

Attention to certain details, such as the assurance of the displaced tissue viability, judicial use of electrocautery, detailed and thorough knowledge of the vascular anatomy along with judicious use of vascularised flaps, lessens the potential for complications.

Above all, in planning and treating by the transfacial approach, the surgeon has to keep in mind that the post-procedure quality of life should not be worse than the natural course of the disease.

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182 Approaches to the Lateral Skull Base

Atul Goel, Muzumdar D

INTRODUCTION

Lateral approaches to clival, petroclival and posterior cavernous sinus tumours have been used for a long time. Advances in skull base surgery have resulted in development and refinements in these approaches.[2,6,7,21,23,27,47,52,55,58,63,72,73,78,81,87,90,93,94,96] With the availability of modern radiology, in most cases, the histological nature of the lesion can be made out frequently. The surgery is, therefore, undertaken with the aim of radical excision and decompression of the region, helping in the alleviation of symptoms and aiming for a cure. To achieve this goal, the planning and execution of the surgery should be meticulous and should take advantage of the advancing technology in radiology, neurophysiology, operative instrumentation and neurointensive care. Wherever necessary, a combined effort of a neurosurgeon and an otolaryngologist could prove to be helpful.

IDEAL APPROACH

It is necessary to consider various issues while selecting an ideal approach for a particular tumour. The ideal approach has the following features:

- The working distance between the surgeon and the tumour should possibly be the minimum. The direction of the approach selected should therefore be such that the tumour is closest to the surface. Temporal bone drilling could be done on some occasions only to reduce the operating distance.
- The approach should be quick to perform. The time factor is of less consideration when safety of the patient and radicality of tumour excision could be compromised. If by reduction of bone work and limitation of the exposure safe excision can be performed, such an approach could be selected. The bone work can be extended after the tumour is exposed and its nature assessed.
- The approach should be least difficult. Manoeuvres, like exposure and mobilisation of the petrous carotid artery, unroofing and mobilisation of the sigmoid sinus, transposition of the facial nerve, are difficult and potentially dangerous and time consuming procedures and should be avoided as much as possible. Such endeavours could be done in desperate cases and only after adequate assessment of the nature of the tumour.
- The exposure should be low which could avoid retraction of brain. The exposure should be wide enough such that the entire lesion can be excised in one single operative field. The exposure should provide access to the base of the tumour so that in cases of meningiomas, the tumour could be devascularised early in the operation. The exposure should be such that the tumour and the normal surrounding structures are exposed in the same field so that dissection under vision is possible.
- As far as possible, an approach through a potentially infective field should be avoided.
- Reconstruction should be easy, safe and with a vascularised pedicle graft.

SURGICAL CONSIDERATIONS

The following important characters of the tumour determine the nature of approach:

1. *Size of the tumour, its relationship to arteries and nerves, and to the adjacent bone*: The larger size of the tumour, the more difficult is the surgery and consequently the outcome can be affected. The vertical height of the tumour in relationship to the petrous bone and tentorium is also an important consideration. In cases of large tumours, the approach itself may not extremely be wide, as the tumour makes space for itself and, when the initial intratumoural debulking is started, more working space can be obtained around the area.
2. *Nature of the tumour*: In most cases the arterial displacements, as a result of growth of the tumour, differentiate meningiomas from other tumours. A trigeminal neurinoma displaces the intracavernous carotid medially, while chordomas and chondrosarcomas displace the internal carotid artery at the petrous apex anteriorly. Soft tumours, like the chordomas and pituitary tumours, displace the artery but only rarely narrow its lumen. On the other hand, firmer tumours, like meningiomas, rarely encase the artery and when they do, they frequently narrow its lumen. Such and other characters help in histologically classifying the tumours and thus assist in deciding the route of approach and the extent of resectability and for prognosticating the ultimate outcome.
3. *Consistency of the tumour*: On the basis of radiological imaging and presenting clinical features a reasonable idea

regarding the consistency of the tumour can be made. Long-standing symptoms and symptomatic involvement of adjacent nerves suggest the presence of a firm tumour. Signal characters on T1- and T2-weighted MR images help in diagnosing the nature of the tumour. These characteristics determine to a considerable extent the ease of surgical resection and the extent of exposure that may be necessary to resect the lesion. The consistency of the tumour and its vascularity are important variables on which the course of surgery depends. Encasement of the vessels signals difficulties in resection. Narrowing of the encased vessels suggests the firm nature of the tumour. Resection of such tumours could be a formidable surgical problem.

4. *Vascularity of the lesion*: Vascularity of the lesion can be observed on angiography. Multiple punctate spots in the tumour on MRI also suggest high vascularity. More vascular the lesion, the larger is the exposure that is necessary.

5. *Presence of arachnoidal plane of dissection around the tumour*: It can be determined on MRI scanning. Such information can critically be important. The presence of arachnoidal lakes around the tumour should carefully be analysed.

6. *Patient related factors like age, presence of other major illnesses*: It can also guide towards the extent of the surgery that would be necessary.

Operative Technique

The direction of the approach should be towards the base or site of the attachment of the tumour in an attempt to devascularise it early. In larger tumours, frequently, approaching the base may be difficult due to the presence of the tumour bulk and the stretched adjoining nerves and vessels. In the majority of cases, intratumoural debulking near the base, devascularising the lesion by coagulating at the site of attachment to the dura, followed by further debulking and later removal of the thin residual shell by carefully separating the adjacent structures under vision can lead to successful resection of the lesion. In cases where the tumour has encased a particular major vessel, the first aim is to either isolate the parent artery early in the operation, or debulk the tumour with the primary aim to isolate the parent artery and the tumour encased vessel. Once the artery is isolated and dissected the rest of the clear plane of cleavage between the artery and the tumour can be made out and the dissection can proceed in that plane. In case the arachnoidal plane is lost, one should consider the risks of further dissection vis-à-vis problems of leaving residual tumour behind. Extensive dissection around arteries is wrought with risks of vascular occlusion by laceration or thrombosis. It is usually safer to avoid prolonged dissection of the tumour from the arteries. Tumoural coagulation should be avoided as such a procedure makes the tumour firmer and resection more difficult. A combination of sharp and blunt dissection with the help of bipolar cautery (with irrigation) and graded suction is necessary in the proximity of major arterial channels. Traction over the tumour should be avoided during the entire operation. Leaving tumour residue remote from the site of attachment and origin is safer than leaving tumour in the region of attachment (or origin), as regards possibility of recurrence. In selected cases, lumbar puncture and drainage of CSF is an important pre-operative adjuvant to help relaxation of the brain and to permit safe and adequate exposure of the lesion. In subtemporal approaches, retraction of the temporal lobe is much easier and safer when CSF drainage is performed. CSF drainage could always be considered when a bulging brain restricts manipulation. For this reason a complete lateral position is better than a supine position with head turned to the other side. The lumbar drainage of CSF can be done with ease whenever it is indicated in this position. CSF drainage for facilitating retraction of the brain should be avoided prior to craniotomy in cases of large tumours where herniation may occur.

Bone Work

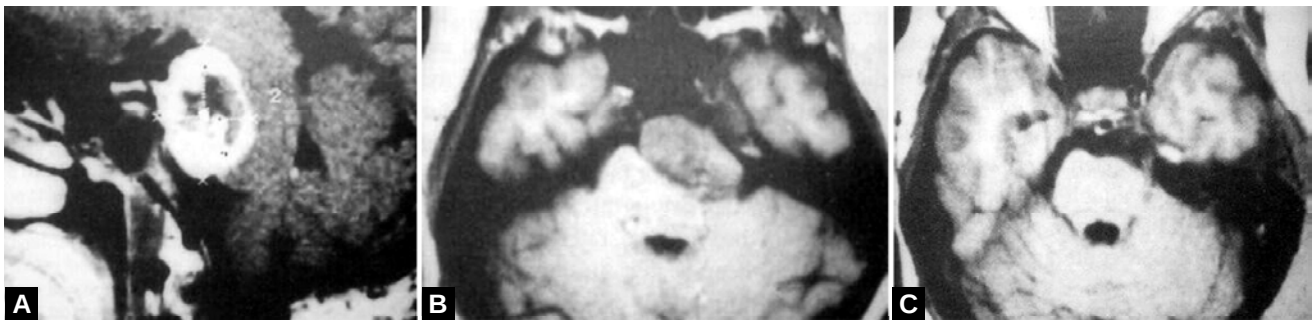
Drilling of the petrous bone to obtain basal and wider exposure is frequently necessary. However, such a procedure should be done only when it is absolutely necessary. The drilling should be minimal and only at sites where it is necessary to expand the exposure. In more difficult lesions, extensive temporal bone drilling may be required.

SURGICAL APPROACHES TO LATERAL SKULL BASE

Anterior Subtemporal Approaches

Anterior subtemporal approach is indicated when a majority of the tumour is in the middle fossa in the region of the cavernous sinus. Basal extension of the anterior subtemporal approach is frequently necessary to avoid retraction of the temporal pole.

Anterior extension of the temporal craniotomy can be done by removal of the posterior part of the lateral and, whenever indicated, the superior wall of the orbit. Removal of the orbital rim is seldom necessary but can be done in complex cases. The inferior extension of the conventional temporal craniotomy can be done by caudal displacement of the temporalis muscle facilitated by zygomatic osteotomy. The zygomatic arch can even be cut and displaced inferiorly by leaving the attachment to the masseteric fascia intact. The infratemporal muscles are dissected off from the base of the middle fossa bone by sharp subperiosteal dissection. The middle fossa basal bone is removed to expose the superior orbital fissure, foramen rotundum and foramen ovale. These manoeuvres provide an inferior angle of approach to the basal middle fossa structures. The horizontal portion of



Figs 1A to C: (A) Contrast-enhanced MRI shows a large clival meningioma. (B) Transverse cut showing the tumour indenting into the pons. (C) Post-operative scan showing complete resection of the tumour. Basal extension of the subtemporal craniotomy was used to resect the tumour. Resection of the rest of the petrous bone was not necessary

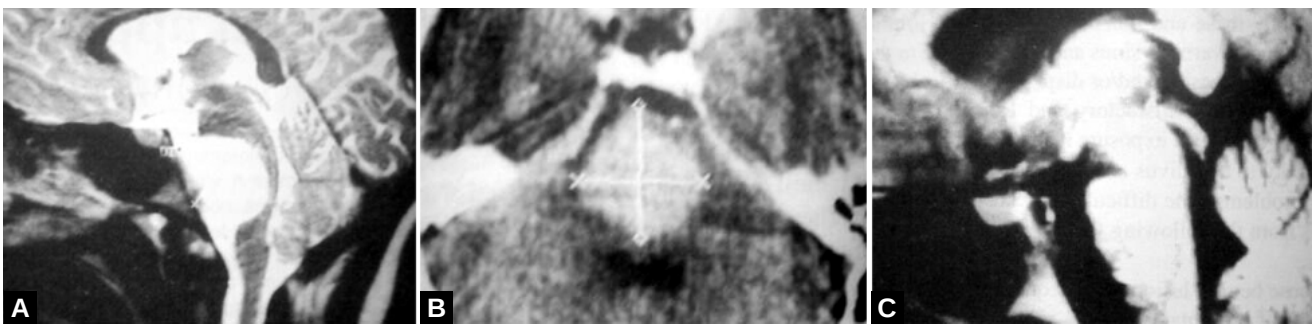
the intrapetrous carotid artery can be exposed. Exposure of the entire intrapetrous carotid artery (horizontal segment, genu and the vertical segment of the carotid artery) can be done. However, exposure of the vertical segment (a procedure which is seldom necessary) can be done more easily after resection of the condyle of the temporomandibular joint. The Eustachian tube and the tenser tympani muscle are in the way during the exposure of the genu of the carotid artery. After the exposure of the horizontal segment of the intrapetrous segment of the carotid artery, the petrous apex can be drilled safely and more radically to expose the upper clivus. Familiarity with the anatomy is crucial to perform petrous apex drilling. Arcuate eminence, greater superficial petrosal nerve (GSPN), lateral border of the Gasserian ganglion, third trigeminal nerve division and foramen ovale and spinosum are important landmarks of the petrous apex. The GSPN lies superior to the internal carotid artery in the petrous apex. Drilling in Kawase's triangle and widening of the exposure according to the requirements can crucially expand the exposure at the petrous apex.

Combined approaches, which involve utilisation of a posterior fossa craniotomy as well, with or without sigmoid sinus ligation, are seldom necessary. Inferior temporal gyrus resection and anterior temporal polectomy can help in expanding the superior exposure. Such a corticectomy is safer than resorting to prolonged retraction of the temporal lobe.

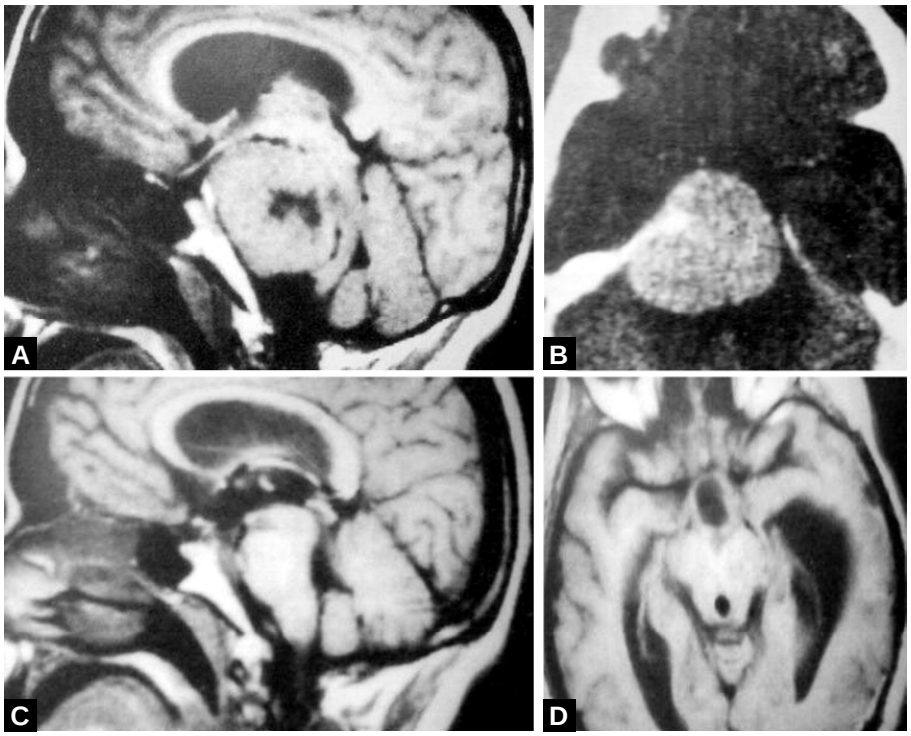
Transtemporal Approaches

The petrous bone has been considered an obstructing 'hump' by neurosurgeons, during the approach to clival or petroclival lesions. In the various recently described skull base surgical approaches, the petrous part of the temporal bone has been 'exploited' to enhance the exposure to deep seated lesions which were difficult to excise by the conventional neurosurgical approaches. Transpetrous approaches not only provide better exposure of the tumour in the cerebellopontine angle and petroclival regions, but also expose the intrapetrous extensions of the tumour and cranial nerves in healthy areas, so that their function can be better preserved. However, petrous bone drilling should highly be calculative and precise. Indiscriminate or overenthusiastic drilling of this important bone should be avoided. In some instances, it may be better to expose the lesion, analyse its consistency and vascularity before starting the petrous bone drilling procedure.

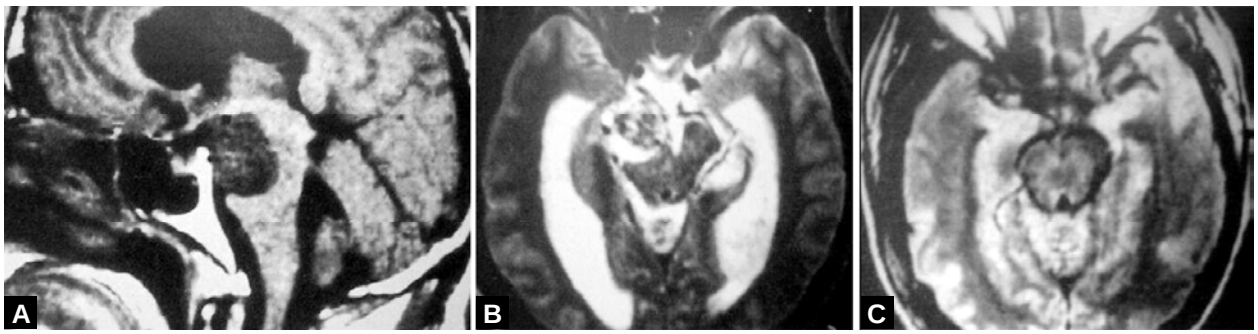
Most of the lesions situated in the petroclival region can be approached and safely resected by conventional neurosurgical operations, like the subtemporal and retrosigmoid, or combined subtemporal and retrosigmoid approaches. However, some tumours are hidden behind bony protuberances and in the angle of the petrous bone and the clivus (Figs 1 to 6) and various 'transpetrosal' approaches have been adopted (Figs 7 and 8).



Figs 2A to C: (A) T2-weighted MRI shows a large hyperintense midclival tumour deeply indenting the pons. (B) Contrast-enhanced CT scan shows the large tumour involving the pons. (C) Post-operative MRI showing complete resection of the tumour



Figs 3A to D: (A) MRI scan shows the massive petroclival meningioma. The tumour was vascular being fed by the branches of the meningohypophyseal trunk and middle meningeal artery. (B) Contrast enhanced CT scan showing the large petroclival meningioma. (C) Extended middle fossa approach was used to resect this tumour completely. (D) Axial scan showing resection of the tumour



Figs 4A to C: (A) Sagittal view of T1-weighted MRI showing the large hypointense tumour located on the anterior surface of the pons. (B) T2-weighted image showing the hyperintense tumour indenting the pons. (C) Post-operative scan demonstrating tumour excision. Basal extension of the subtemporal craniotomy was used to resect the tumour

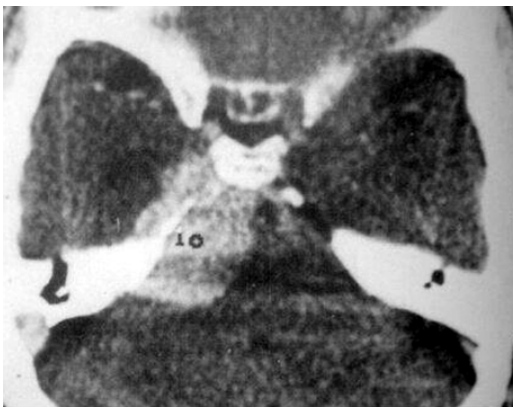


Fig. 5: CT scan showing the more usual extensions of a petroclival tumour. Note the involvement of the cavernous sinus and extension along the petrous apex. The histopathology of the tumour was meningeal sarcoma

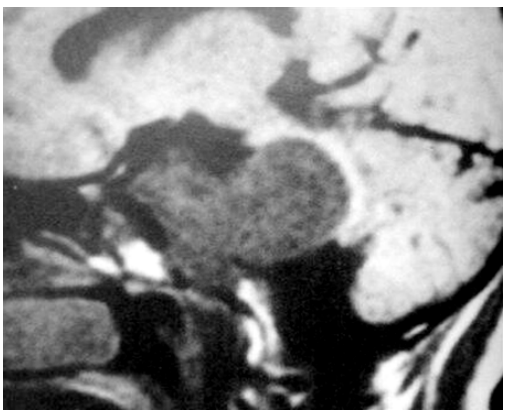


Fig. 6: MRI showing a large clival chordoma. Extended middle fossa approach was used to radically resect this tumour

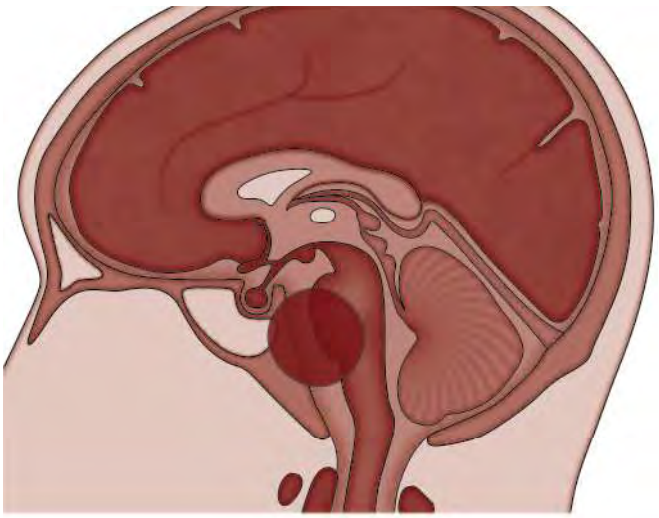


Fig. 7: Schematic drawing showing the midclival tumour. Apart from other parameters, the sight of the tumour in relationship to the clivus is important in determining the approach to the tumour and to determine the extent of exposure necessary

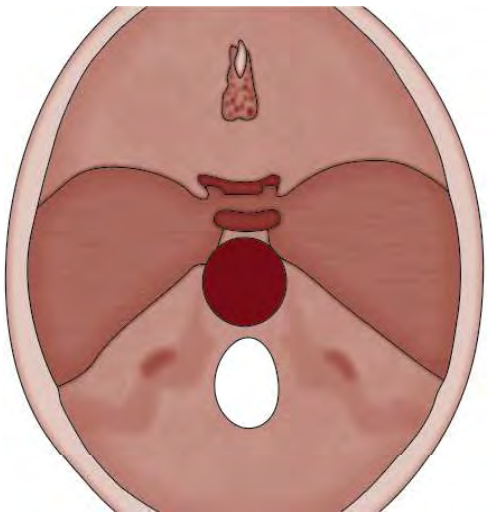


Fig 8: Transverse view of the midclival tumour. The lesion is located in front of the brainstem. The site of the tumour, relationship to the brainstem and pressure or absence of the arachnoid planes will determine the extent of the bone drilling necessary for a particular case

Spetzler et al.[90] summarised 'neurosurgical' approaches through the temporal bone into three groups:

Group 1: Approach preserving hearing.

Group 2: Approach where hearing is sacrificed.

Group 3: Approach that involves transposition of the facial nerve.

The petrous bone is situated at an angle of 40 degrees from the horizontal plane. On the other hand, the external ear canal is almost transversely placed. These angles should carefully be taken into account when one is planning the operation and more importantly while positioning the patient. The line drawn along the external ear canal meets the petroclival region and the approach along this line is the shortest from the surface. The petrous bone contains the vestibulocochlear apparatus and the facial nerve. At the anterior end of the bone lies the intrapetrous carotid artery and at the posterolateral end lies the sigmoid sinus. Apart from these structures, from the neurosurgical standpoint and for simplifying the study of the approaches, the rest of the petrous bone is described to be made up of packing material.

Petrous Apex

The Gasserian ganglion is situated in a shallow groove of the Meckel's dural cave at the petrous apex. The GSPN lies on the anterior face of the petrous apex. This nerve forms an important landmark for surgery in this region, as it is relatively easily identified and isolated during an extradural operation due to its location in a long shallow groove. GSPN originates from the geniculate ganglion and becomes extradural after its exit from the petrous bone through a small opening called facial hiatus. In some cases, the geniculate ganglion itself is without a bony cover and lies in an extradural location. Often there is another orifice situated slightly anteriorly and medially called the accessory hiatus from where emerges the lesser petrosal nerve. During surgery, which involves extensive manipulation in the region of the petrous apex, it is sometimes advisable to section the GSPN early in the operation as traction on this nerve may result in facial nerve palsy. There is a small branch of the middle meningeal artery, which courses along the GSPN supplying the facial nerve and geniculate ganglion. The horizontal portion of the intrapetrous carotid artery lies parallel and underneath the GSPN. The tensor tympani muscle and the Eustachian tube are located in small grooves on the anteromedial aspect of the inferior surface of the petrous bone. The Eustachian tube is osteocartilaginous in nature and about 35 mm in its length. It connects the middle ear cavity to the pharynx.

The intrapetrous carotid artery lies in the carotid canal and has been divided into three segments: (1) the vertical segment; (2) genu and (3) the horizontal segment. In its entire intrapetrous course, the artery is covered by a 'periosteal' sheath in which are enmeshed a large number of sympathetic nerve fibres. The carotid artery enters into the carotid canal after its cervical course. There is a firm fibrous ring at the site of the entry of the artery into the canal, which fixes the artery at this point. The temporomandibular joint is lateral to the vertical segment of the carotid artery. The genu of the intrapetrous carotid artery has a close relationship to the middle ear cavity. Anteriorly, the tenser tympani muscle and Eustachian tube travel in close proximity to the genu. Sometimes, the Eustachian tube and the tenser tympani muscle lie directly over the genu of the intrapetrous carotid artery, without any intervening bone. The horizontal segment of the carotid artery lies parallel to the GSPN. Posteriorly, this segment is in close relationship to the basal turn of the cochlea.

Mobilisation of the Intrapetrous Carotid Artery

Sometimes this difficult and precise procedure may be necessary to widen the exposure through the petrous apex and occasionally the segment of the artery needs to be exposed for the purpose of bypass graft, particularly whilst dealing with intracavernous tumours or lesions. Exposure of the horizontal segment of the carotid artery is frequently necessary for the purpose of proximal control of the artery during cavernous sinus surgery. The medial end of the horizontal segment of the artery lies under the Gasserian ganglion at the site where it gives off the third division of the nerve, which traverses through the foramen ovale. A very thin film of bone under the Gasserian ganglion covers the artery and sometimes the bony divide is absent and the ganglion lies directly over the artery, separated from it by a layer of fibrous connective tissue. It is easier to begin isolation of the artery from the medial side where the thin bone can be gently removed. The drilling can then continue laterally. The GSPN can be saved when only the horizontal segment of the artery needs to be exposed. Complete anterior mobilisation of the carotid artery is necessary for obtaining a wide anterior exposure through the petrous apex for lesions located in the mid or lower clivus region. This procedure necessarily involves sectioning of the Eustachian tube and tenser tympani muscle. Whenever there is a need to section the Eustachian tube or when it is accidentally opened, it should be denuded of mucosa, packed firmly with fat and later stitched to prevent cerebrospinal fluid (CSF) leakage. As the artery is firmly fixed by a thick fibrous ring at the site of its entry into the petrous bone, the ring has to be sectioned before satisfactory mobilisation of the artery is possible. The temporomandibular joint lies laterally to the vertical segment of the artery. The condyle of the joint can be either inferiorly displaced or sectioned to expose this part of the artery. Sectioning of the condyle is easier and the procedure is less painful to the patient in the post-operative phase.

The superior petrosal sinus lies in a shallow groove on the petrous ridge. The leaves of the tentorium are attached to the petrous ridge and divide to enclose the superior petrosal sinus. The superior petrosal sinus either courses over the root of the fifth nerve or rarely divides to enclose it. The superior petrosal sinus drains in close proximity to the junction of the transverse and the sigmoid sinus. The 'vein of Labbe' drains a large part of the temporal lobe of the brain into the transverse sinus. This vein needs to be preserved as sectioning it has been reported to result in temporal lobe haemorrhagic infarcts. The dissection of the vein from the arachnoid and from the surface of the temporal lobe can result in the relaxation and mobilisation of the vein, which can assist in enhancing the room for retraction of the temporal lobe. The sigmoid sinus marks the posterolateral limit of the petrous bone. More often, the right side sinus drains into the right jugular vein and the right atrium is larger than the left. Various presigmoid approaches have been described. Often the exposure obtained by this route can be restricted and there arises the need for posterior mobilisation of the sigmoid sinus to enhance the exposure. The mobilisation of the sinus is a technically challenging manoeuvre and should be done slowly and carefully. There can be profuse bleeding and sometimes sacrifice of the sinus may be necessary. For mobilisation of the sigmoid sinus, a long segment or the entire vertical length of the sinus needs to be exposed. The presigmoid dura (dura of the posterior fossa), retrosigmoid dura, tentorium and superior petrosal sinus also have to be adequately exposed. Sigmoid sinus unroofing is more difficult in the elderly due to dural adhesions to the bone. The sinus wall is very thin at the site of the bend from the transverse to the sigmoid sinus. The endolymphatic sac is sectioned during the process of cutting the presigmoid dura for posterior mobilisation of the sigmoid sinus. The superior petrosal sinus is isolated, clipped and sectioned. Sectioning of the superior petrosal sinus is safe as there is a large alternative channel for venous drainage from the basilar venous plexus. This procedure has never been reported to result in problems related to venous infarction. Ligation of the sigmoid sinus to enhance the exposure is seldom used in modern neurosurgery. However, the non-dominant sigmoid sinus can be ligated after confirming the adequacy of flow in the contralateral sinus. The sinus can also be sectioned after application of proximal and distal temporary clips. The sinus can then be repaired by application of sutures to the walls circumferentially at the end of the procedure to maintain the blood flow. The dominant sigmoid sinus should not be ligated.

Facial Nerve

This nerve has the longest intraosseous course (28–30 mm) of all the cranial nerves. With the various acute bends during its course the shape of the nerve resembles that of a 'Z'. There are three segments of the facial nerve in the bone. The labyrinthine segment is the one with which a neurosurgeon is familiar due to its proximity to the more commonly encountered lesion—the acoustic neurinoma. This segment is in close relationship with the superior semicircular canal, which presents on the superior surface of the petrous bone, as a well-defined bony elevation called the arcuate eminence. The labyrinthine segment of the facial nerve ends in the geniculate ganglion from where arise the greater and lesser superficial petrosal nerves. The tympanic segment of the facial nerve begins as an acute bend after the geniculate ganglion and is in close proximity to the middle ear cavity. Only a thin shell of bone covers the segment of the nerve in relationship to the middle ear cavity. The mastoid segment of the facial nerve lies firmly fixed in a bony canal. Some air cells may surround the nerve in this segment. The nerve exits from the stylomastoid foramen and the stylomastoid branch of the external carotid artery supplying the facial nerve enters through

the foramen. The digastric muscle groove forms an important landmark for the identification and isolation of the facial nerve.

Mobilisation of the Facial Nerve

During any transtemporal approach the facial nerve must adequately be protected. The intraosseous facial nerve rarely needs to be mobilised as it forms an obstructing band in any transpetrous approach. However, such mobilisation is wrought with the dangers of affecting the functional integrity of this important nerve and should be done only as a 'last resort'. Segments of the facial nerve can be unroofed and mobilised for enhancing the exposure. The mastoid segment of the facial nerve can be selectively mobilised for the exposure of the region in a glomus jugulare tumour. Some transpetrous approaches involve decompression and complete mobilisation of the facial nerve. The unroofing of the facial nerve is more difficult in the region of the geniculate ganglion due to the relationship with the thick bones of the semicircular canals and the cochlea and the relative thinness of the nerve (bottleneck of the nerve) in this region. The labyrinthine segment of the nerve is accompanied by three other nerves (cochlear, superior and inferior vestibular nerves); thus rendering the dissection of the facial nerve relatively safe. The mastoid segment of the facial nerve is also difficult to unroof due to its relatively long course in the firm surrounding bone. Any attempt towards mobilisation of the facial nerve involves tedious dissection. Mobilisation necessarily involves sacrifice of blood vessels supplying the nerve. There is an inherent risk of precipitating a partial paresis after mobilisation of the nerve. The temporomandibular joint is directly anterior to the external ear canal. The glenoid fossa bulges in the middle fossa floor. The posterior end of the root of the zygomatic arch divides to form the external landmark of the condyle.

Approaches Preserving Hearing

The petrous apex and the mastoid bone are two major areas deprived of neural or vascular structures. The presigmoid-retrolabyrinthine-transmastoid approach has been used to approach petroclival lesions. However, on some occasions the labyrinth forms an obstructing bulge in the field, restricting the exposure and resulting in a posteriorly and inferiorly directed approach. Injury to the labyrinth often results in an immediate hearing loss. Some authors have recently suggested the use of partial labyrinthectomy to widen the exposure from the presigmoid route. Such a procedure has been shown not to affect hearing. Superior projection of the jugular bulb (high jugular bulb) can also limit the exposure obtained by the transmastoid (or translabyrinthine) approach. Posterior mobilisation of the sigmoid sinus can be used to enhance the exposure. The presigmoid transmastoid exposure is combined with the subtemporal exposure for widening the exposure.

Kawase described a triangle (named after him) in the petrous apex lateral to the root of the trigeminal and medial to the internal auditory meatus.[55] This part of the petrous bone can be drilled in a middle fossa approach providing a crucial window to lesions located in the region of the mid clivus. The exposure can be enhanced underneath the Gasserian ganglion. The cochlea is the lateral limit, while the horizontal segment of the petrous carotid artery is the medial limit. The exposure can be increased by the anterior displacement of the carotid artery or by drilling the cochlea.

Approaches Involving Sacrifice of Hearing

The presigmoid translabyrinthine approach is an anterior extension of the presigmoid retrolabyrinthine approach. The approach involves removal of the semicircular canals, thus enhancing the exposure. The facial nerve comes in the way during this approach while exposing petroclival region tumours. The transcochlear approach is the anterior extension of the translabyrinthine approach.

Approaches Involving Mobilisation of the Facial Nerve

Elaborate transpetrous approaches have been described for petroclival lesions some of which involve mobilisation of the facial nerve. Approaches involving extensive resection of the petrous bone with or without translocation of the facial nerve include transcochlear and total petrosectomy approaches.[82,90,97] The total petrosectomy approach has been described by Sekhar et al.[90] The approach involves unroofing of the entire facial nerve and its posterior mobilisation. The petrous carotid artery is displaced anteriorly. The unroofing of the entire petrous segment of the facial nerve is a time consuming procedure and involves a high possibility of jeopardising facial nerve function. The transcochlear approach can be modified and segments of the facial nerve can be mobilised.

Extended Middle Fossa Approach[27]

The author has found the approach relatively quick, safe for the facial nerve and results in an extensive manoeuvrable exposure. It involves unroofing and depression of the external ear canal, removal of the glenoid cavity of the temporomandibular joint, exentration of the middle ear ossicles, posterior mobilisation of the labyrinthine and tympanic segments of the facial nerve and drilling of the petrous bone from an entirely lateral perspective. An extensive and low exposure of the petroclival region, posterior aspect of the cavernous sinus, upper and mid clivus and the cerebellopontine angle is obtained. The anterior surface of the brainstem up to the pontomedullary junction is exposed with minimal

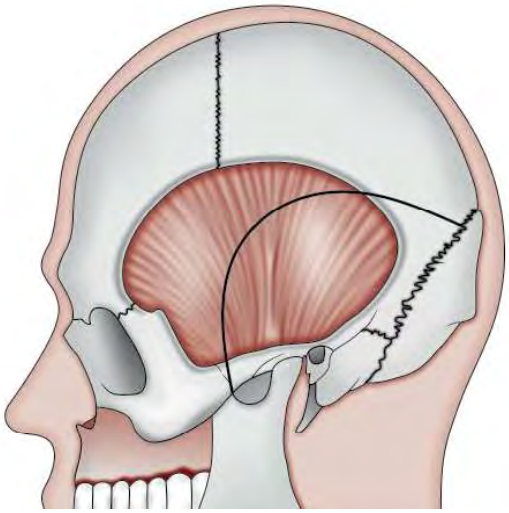


Fig 9: Line drawing showing the scalp incision. The incision starts anterior to the tragus and then traverses superiorly over the middle of the zygomatic arch and then posteriorly in the occipital region. The centre of the operative activity is in the line of the external ear canal

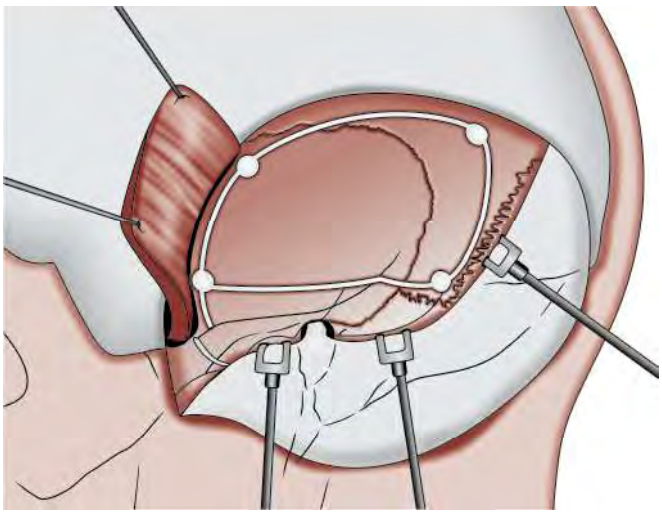


Fig. 10: The root of the zygomatic arch, roof of the external ear canal and the superior half of the mastoid bone are exposed. The part of the temporalis muscle exposed is reflected anteriorly. The sites for burr holes and the craniotomy are seen

or no retraction of the temporal brain (Figs 9 to 27). The vein of Labbe and the sigmoid sinus drainage are unhampered. Anterior and posterior extension of the exposure is possible. Only a limited mastoidectomy and labyrinthectomy, necessary to facilitate exposure and mobilisation of the facial nerve, is required. The dome of the jugular bulb sets the inferior limit of the exposure. Hearing is sacrificed.

Operative Technique

The patient is placed in a lateral position. Under continuous external lumbar CSF drainage, a low temporal craniotomy with the base centred on the external ear canal is performed (Figs 9 to 13). This is followed by unroofing of the superior half of the bony external auditory canal and removal of the glenoid fossa and the root of the zygomatic bone, taking care to preserve the meniscus of the joint (if a larger exposure is necessary, the external ear canal may be exenterated and closed and the mandibular condyle resected).[23,80,90] Drilling of air cells in the upper and middle half of the mastoid bone remaining anterior to the sigmoid sinus and wide opening of the antrum is carried out. The external ear canal is depressed inferiorly with the tympanic membrane after removing the ossicles of the middle ear, thus preserving the sterility of the field. The dura is elevated off the petrous bone and the GSPN and the foramen of the middle meningeal artery are identified.

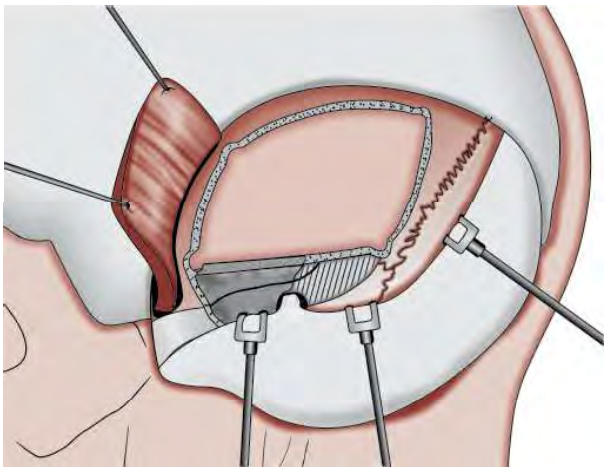


Fig. 11: Low temporal craniotomy. The roots of the zygomatic arch and the glenoid fossa are preferably removed in one piece with the help of an electric saw. The shaded angled lines depict the area of mastoid bone and the roof of the external ear canal that can be removed with the help of an electric drill. Note that the centre of the basal exposure is on the external ear canal

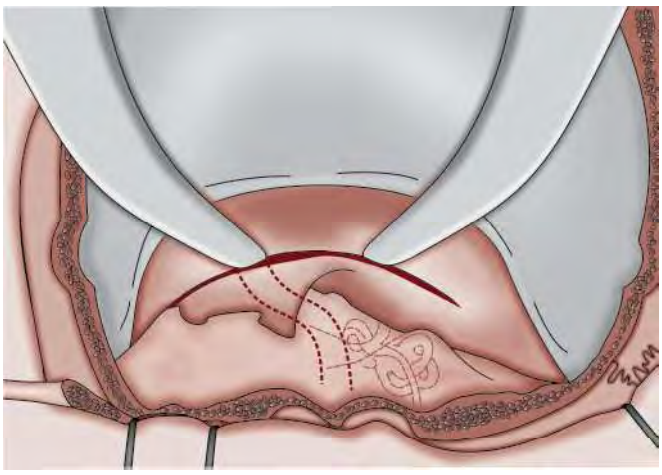


Fig. 12: The condyle and the superior half of the external ear canal are unroofed and the superior half of the mastoid air cells has been drilled to obtain a basal exposure. Elevation of the middle fossa dura and exposure of the Gasserian ganglion, foramen spinosum, foramen ovale, foramen rotundum and the anterior face of the petrous bone

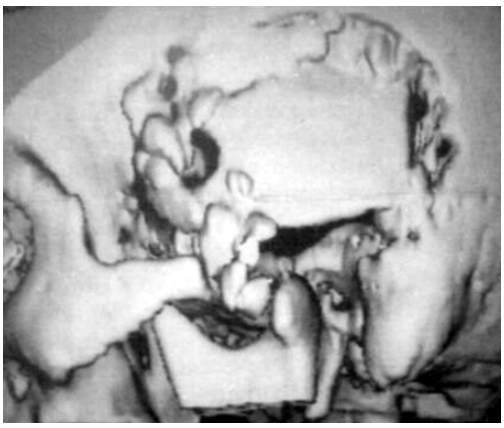


Fig. 13: Post-operative three-dimensional CT image showing removal of the posterior aspect of the zygomatic arch, roof of the condyle and the external ear and the superior part of the mastoid air cells. The basal exposure available to the petrous apex can be appreciated

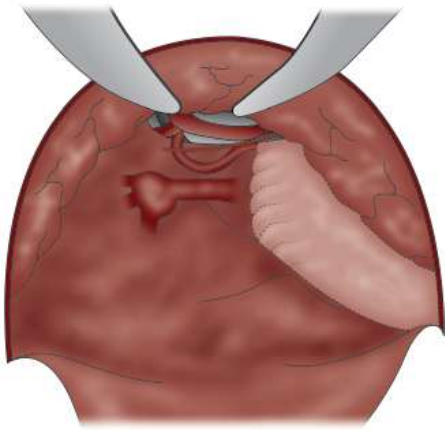


Fig. 14: After the basal bone work, the dura is opened, the temporal lobe is retracted and the edge of the tentorium and the brainstem are exposed

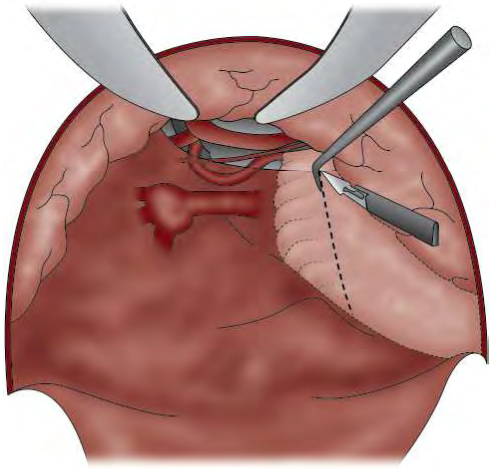


Fig. 15: Tentorial dural flap is being made. A blunt hook is used to elevate the tentorium. The hook and the knife are being used (as described in the text) to make the tentorial incision

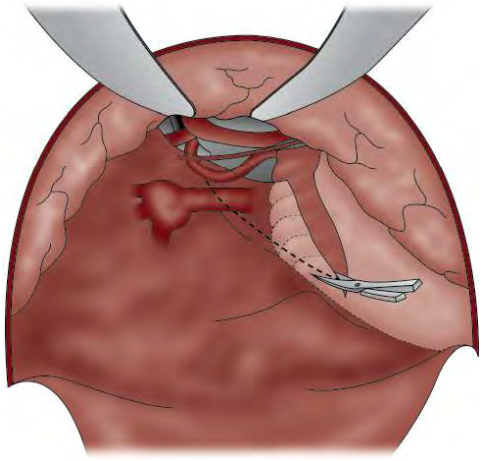


Fig. 16: The tentorial incision has been completed and the tentorial dural flap is elevated. The tentorial flap can be resected by cutting along the superior pertrosal sinus or can be rotated anteriorly over the middle fossa floor. Brainstem, cerebellum, superior cerebellar artery, posterior cerebral artery, petrosal vein and cranial nerves third to eighth are exposed widely

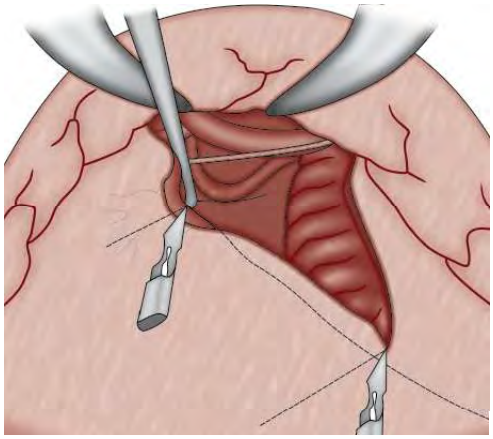


Fig. 17: Drawing showing the incision over the roof of Meckel's cave (after application of haemostatic clip to the superior petrosal sinus). An incision of the middle fossa dura can also be made, a procedure, which connects the extradural with intradural compartments

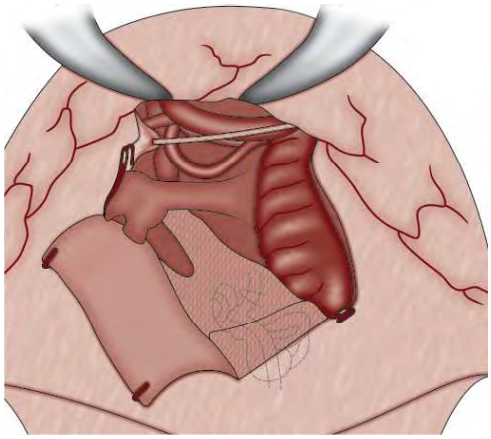


Fig. 18: The superior petrosal sinus is clipped with the help of two sets of clips, one over Meckel's cave and the other laterally in the region of the arcuate eminence. The fifth nerve root, posterior half of the Gasserian ganglion and the cerebellopontine angle are now exposed

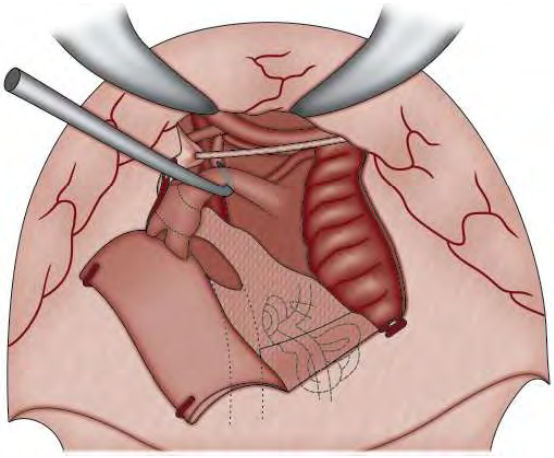


Fig. 19: The root of the fifth nerve can be lifted superiorly (after its adequate mobilisation in the region of Meckel's cave dura) to expose part of the brainstem and basilar artery

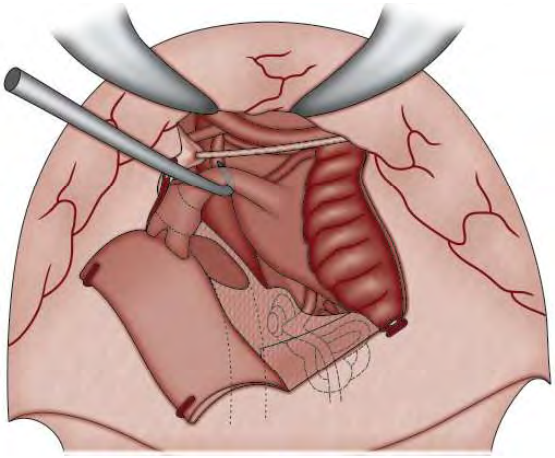


Fig. 20: The petrous apex posterior to the course of the carotid artery (horizontal petrous and precavernous sinus segment) and medial to the cochea is resected to enhance the exposure of the brainstem

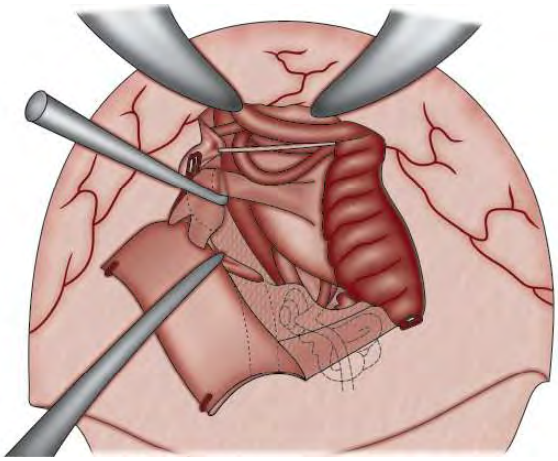


Fig. 21: The petrous carotid artery is depressed anteriorly to expose an additional segment of the petrous apex, which can be drilled to improve the exposure

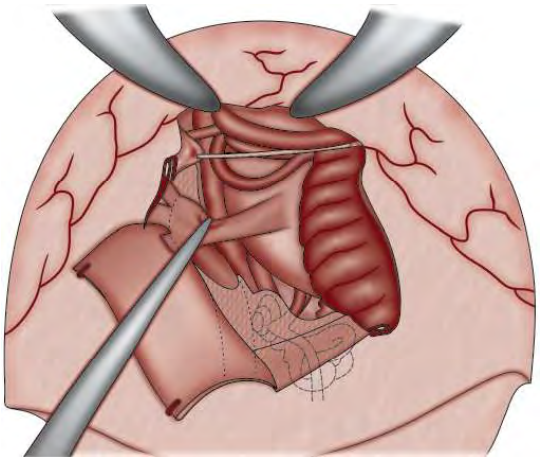


Fig. 22: The fifth nerve root and the Gasserian ganglion can be depressed inferiorly to expose the petroclival region bone, which can be drilled

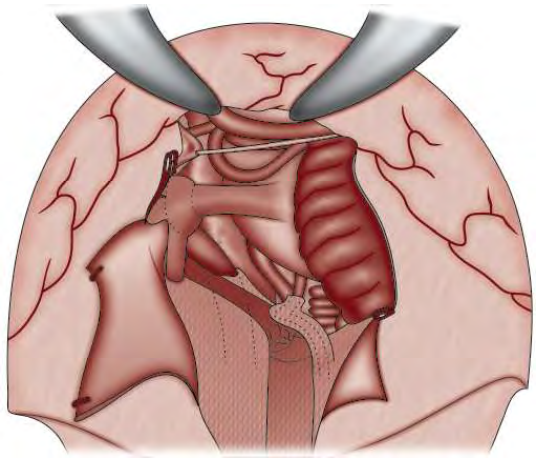


Fig. 23: Bony unroofing of the horizontal segment of the petrous carotid artery. The bone medial to the labyrinthine segment of the seventh cranial nerve (in its course in the internal auditory canal up to the geniculate ganglion) is removed, including the cochlea and the labyrinth in the bone drilling. The exposure is thus widened. Such bone drilling also exposes the lateral aspect of the cerebellopontine angle

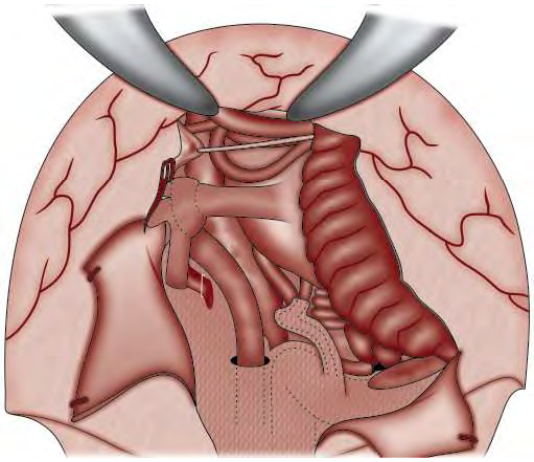


Fig. 24: Further drilling of the petrous bone. The Eustachian tube is sectioned and clipped, and the middle ear contents are exenterated and removed. The vertical segment, genu and the horizontal segments of the intrapetrous carotid artery are unroofed of the bony cover. The tympanic segment of the facial nerve is also unroofed of the bony cover

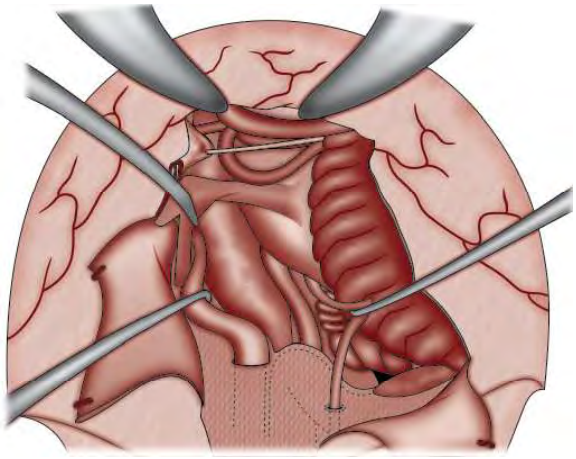


Fig. 25: The entire intrapetrous carotid artery is mobilised anteriorly, the tympanic and labyrinthine segments of the facial nerve are mobilised posteriorly and the petrous bone is resected entirely in a lateral perspective. The mastoid segment of the facial nerve is not yet unroofed. A large portion of the brainstem is now exposed. The inferior limit of the exposure is set by the dome of the jugular bulb

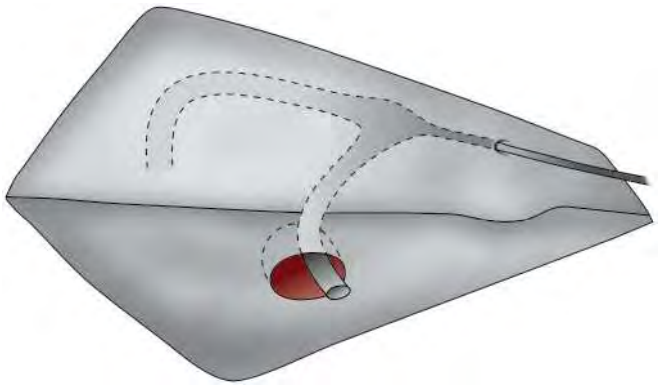
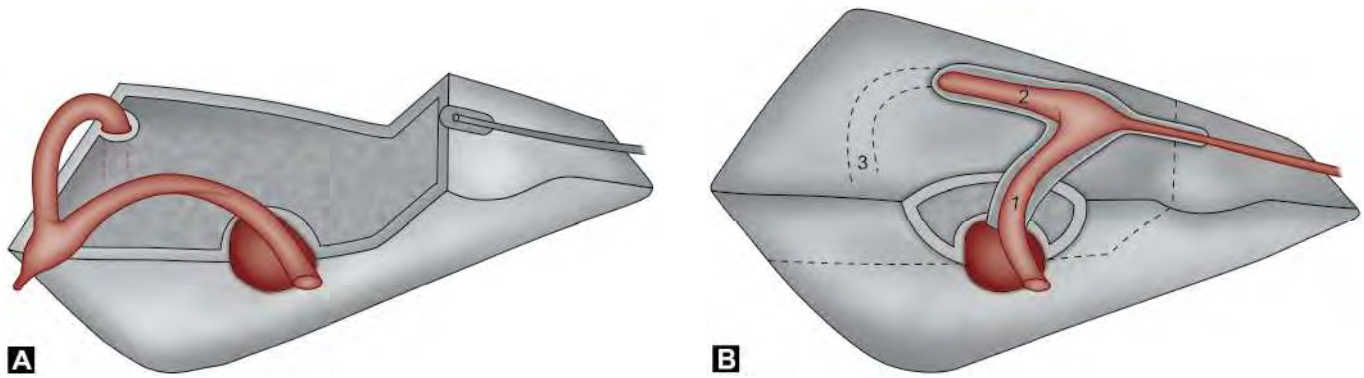


Fig. 26: Simplified figure depicting the winding course of the seventh nerve. Number 1 is the labyrinthine segment; number 2 is the tympanic segment and number 3 is the mastoid segment of the facial nerve. The nerve lies in a bony canal

The middle meningeal artery is coagulated and cut. The GSPN is followed laterally and the geniculate ganglion is unroofed of its thin bony cover (Figs 26 and 27). Partial superior labyrinthectomy is carried out to expose the dura of the internal auditory meatus. The thin bony shell covering the tympanic segment of the facial nerve is removed by gentle drilling. The 1st and 2nd segments of the facial nerve are dissected. The facial nerve now hangs freely from the brainstem up to its external genu and is mobilised posteriorly, after sectioning the GSPN sharply (Figs 25 to 27). After the mobilisation of the nerve, radical resection of the petrous bone is carried out avoiding the petrous segment of the internal carotid situated anteromedially and jugular bulb inferiorly. The petrous carotid artery is under control and can be mobilised for obtaining further anterior exposure. The Eustachian tube is closed (Fig. 24).[79] Widening of the anterior and posterior exposure as necessary is carried out. For intradural lesions, the temporal dura is opened and the lobe retracted superiorly. The edge of the tentorium is cut parallel to the petrous ridge preserving the fourth nerve and the root of the fifth nerve. The superior petrosal sinus is clipped. An approach directed inferomedially to the upper and mid clivus, petroclival area and the posterior cavernous sinus is now available (Figs 24 and 25).

The procedure is an approach from the middle cranial fossa and occipital craniotomy is not necessary. Unroofing of the sigmoid sinus and decompression of the mastoid segments of the facial nerve and their mobilisation as required in other similar approaches can be time consuming procedures. Tears in the sigmoid sinus can complicate the operation. Facial nerve decompression in the tight bony mastoid canal can be difficult, and important blood supply to the nerve from the stylomastoid foramen may be jeopardised. These manoeuvres are avoided in this operation. The approach being relatively quick when compared to other similar approaches can be more frequently utilised. The procedure involves posterior mobilisation of the tympanic and labyrinthine segments of the facial nerve. A small branch of the middle



Figs 27A and B: (A) Partial unroofing of the labyrinthine and tympanic segments of the facial nerve. (B) The labyrinthine (1) and the tympanic segments (2) of the facial nerve which have been mobilised posteriorly after sectioning of the greater petrosal nerve. The nerve now hangs freely from the brainstem to the point of the external genu of the nerve (3)

meningeal artery, which accompanies the GSPN, rarely of critical importance in its vascular supply to the geniculate ganglion, needs to be sacrificed. The mobilisation of the facial nerve from the brainstem to the external genu provides a large area of petrous bone for resection. Since the major blood supply is preserved, its function can be retained. The approach to the clivus is directly lateral. The height of the external and middle ear is utilised to provide the critical basal exposure minimising the need for temporal lobe retraction. Clival meningiomas can be devascularised from the base early in the operation. Control of the internal carotid artery in the petrous bone can be obtained whilst dealing with lesions involving the posterior cavernous sinus. The approach is particularly useful in situations where the facial and eighth nerve functions are already compromised.

Basal Extension of Lateral Subtemporal Craniotomy

The temporal line (supramastoid ridge) forms the inferior limit while the zygomatic arch is the anterior limit of a conventional neurosurgical basal craniotomy. Zygomatic osteotomy, inferior displacement of the temporalis muscle and resection of the floor of the middle fossa have been employed to improve the basal exposure. Partial unroofing of the external ear canal has also been recommended for enhancing the inferior angle of vision.[88] Resection of the root of the zygomatic arch, including the glenoid fossa, roof of the external ear and superior third of the mastoid process, was seen to improve the basal exposure for lateral subtemporal middle fossa approaches. The enhanced exposure helps in reducing the extent of brain retraction and improves the working space for manipulation of the instruments.

Operative Technique

The scalp incision starts about 1.5 cm anterior to the tragus and about 1.5 cm inferior to the mid-point of the zygomatic arch (Fig. 9). Initially it curves superiorly and then posteriorly. The incision exposes the squamous temporal and posterior parieto-occipital bone, posterior aspect of the temporalis muscle, roots of the zygomatic arch, supramastoid crest and the base of the mastoid process (Fig. 10). The posterior aspect of the temporalis muscle is mobilised in the subperiosteal plane from the temporal bone and the sharp superior border of the zygomatic arch. The muscle is then rotated anteriorly. A low temporal craniotomy with the base centred on the external ear canal is performed (Fig. 11). The anterior and posterior roots of the zygomatic arch, the glenoid fossa and lateral half of the roof of the external ear canal are removed preferably with the help of an electric saw in one piece (Figs 12 and 13). Rongeurs may also be used. The external ear canal is protected by sharp subperiosteal separation of the canal from the bony roof. The meniscus of the temporomandibular joint is exposed but not removed. The superior third of the mastoid air cells are drilled. The mastoid antrum and the sigmoid sinus are not exposed. After the procedure the mastoid air cells are packed with bone wax, free muscle or fat graft. The posterior third of the temporalis muscle along with its fascia can be rotated to the base for strengthening the reconstruction. The bone piece harbouring the roots of the zygomatic arch, glenoid fossa and the lateral aspect of the roof of the external ear is replaced and sutured along with the craniotomy bone flap. The external auditory meatus is packed with cotton pledgets to avoid cicatricial stenosis.

Most of the described skull basal techniques employ zygomatic osteotomy, facilitating inferior displacement of the temporalis muscle. Some reports indicate the usefulness of resection of the middle fossa floor.[79] However, such approaches are anterior subtemporal and the working angle to the petrous apex is about 40–60 degree from the horizontal plane in the line of the external ear canal. The posterior subtemporal approach is performed after mastoidectomy. In such a posterior subtemporal approach, the vein of Labbe obstructs the exposure. The direct lateral approach, as described, is the shortest route to the petrous apex and has an additional advantage of ease of working in the infratentorial compartment.

The technique of extension of the temporal craniotomy, as described, improves the horizontally wide basal exposure directly in line with the petrous apex. It does not affect hearing and the function of the temporomandibular joint. The procedure is technically easy. There is no need to expose the superior bend of the sigmoid sinus, which is posterior in the line of the operative direction. This makes the exposure relatively quick and safe. The temporalis muscle is displaced anteriorly and is thus away from the operative field. Resection of the entire zygomatic arch is unnecessary. Whenever indicated, the basal exposure could further be widened both horizontally and inferiorly. The condyle of the temporomandibular joint can be removed, the external ear canal can be depressed (after it is entirely unroofed) along with the tympanic membrane (by removal of the ossicles of the middle ear) or it can be exenterated and closed, mastoidectomy could be widened and the sigmoid sinus can be displaced posteriorly, whenever indicated. The petrous bone resection can be done as much as is necessary. The external ear canal has loose fibrous connections to the bony and cartilaginous wall. It is more firmly attached to the spine of Henle, where sharp dissection may be necessary to dissect the canal. In an occasional case, where a radical transpetrous approach is being adopted, the superior half of the external ear canal can be unroofed up to the tympanic membrane and middle ear cavity. After the section of the head of the malleus, the external ear canal with the tympanic membrane can be depressed inferiorly, thus adding to inferior exposure and maintaining sterility of the surgical field.

Middle Fossa Sub-Gasserian Ganglion Approach[29]

Most of the lateral procedures described for resection of clival chordomas involve relatively complex and extensive skull basal dissection, exposure and mobilisation

of the carotid artery,[79,85] facial nerve,[23,54] sigmoid sinus[2] and temporomandibular joint.[23,79,85]

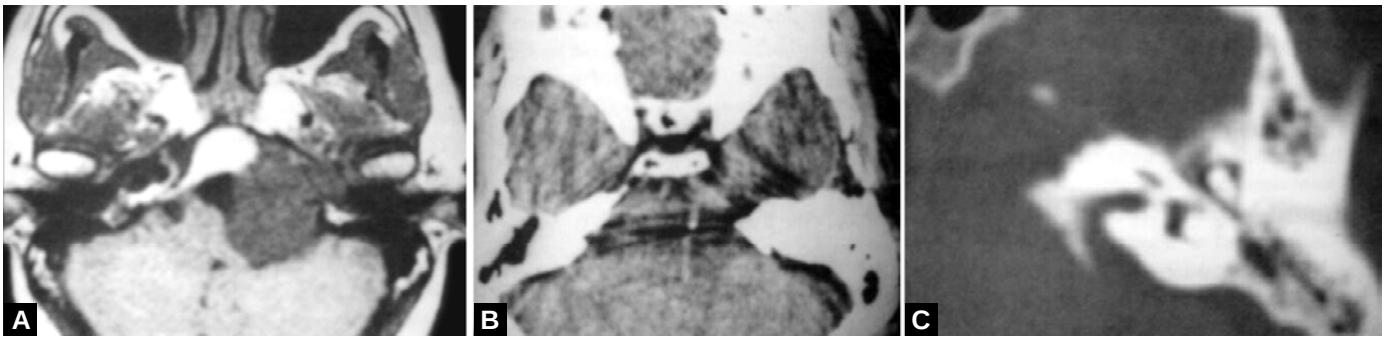
A modified lateral subtemporal, transpetrous apex and sub-Gasserian ganglion approach is suitable for clival chordomas. The approach selection is based on the typical anatomic relationship of chordomas in terms of site of origin, pattern of growth, bone destruction and neural and vascular displacements. The approach is suitable for dealing with tumour anterior and lateral to the brainstem, clival part of the tumour and its subcavernous sinus extensions. The carotid artery is under control. The approach has the advantage of being simple and relatively quick and its familiarity to general neurosurgeons. The tumour can be excised radically and extension of the anterior, posterior and inferior exposure is possible.

Operative Technique

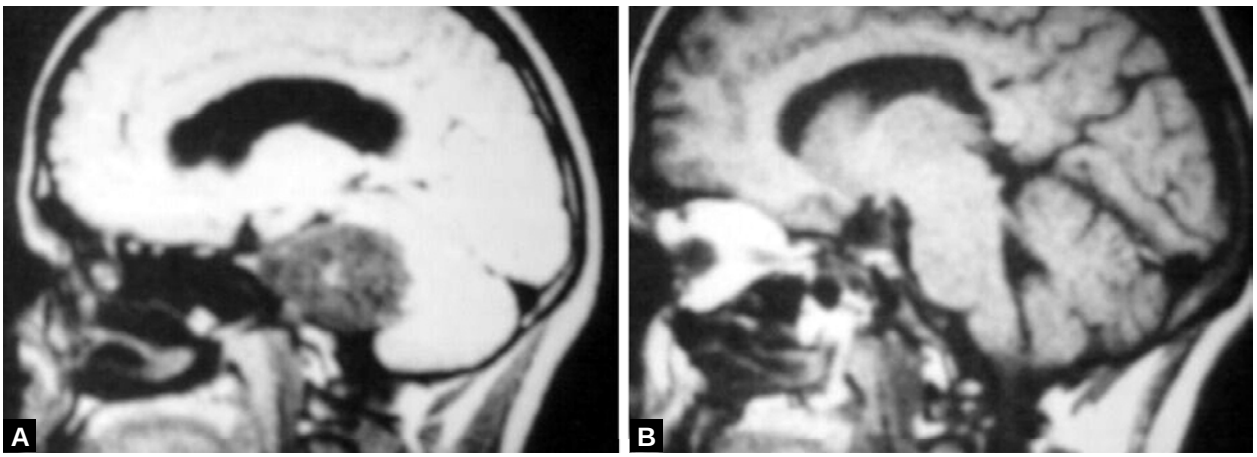
The patient is placed in the lateral position and a continuous external drainage of CSF by lumbar subarachnoid catheter placement is established. The approach is by a subtemporal route centred on the external canal. A low temporal craniotomy is done and a basal exposure is obtained along the anterior face of the petrous bone. In cases where a large middle fossa extension of the tumour is present, zygomatic arch osteotomy can be done to elevate the temporalis muscle out of the exposure.[31]

The approach is initially intradural where the temporal lobe is elevated off the middle fossa floor. By an intradural exposure and tentorial incision, the root of the trigeminal nerve and the Gasserian ganglion are unroofed and mobilised superiorly.[26] Underneath the medial and inferior dural cover of the Gasserian ganglion is the most prominent bulge of the tumour. An incision is made along the root of the fifth nerve over the dura of Meckel's cave. It is sometimes difficult to identify the fifth nerve. Identification of the nerve after an initial tumour debulking or following the nerve along its intradural segment is advocated. The tumour is seen immediately underneath Meckel's cave. The petrous apex is drilled laterally as required, more frequently up to the medial end of the internal auditory meatus, taking care to preserve the cochlea. The internal carotid artery is identified in the petrous apex and is exposed and protected. The soft, relatively avascular and extradural nature of the tumour helps in expanding the exposure. The tumour is removed by an initial intratumoural debulking procedure that releases the stretch on the neural and vascular structures, which are then dissected free. Remaining intratumourally and debulking is the safest way to preserve the adjoining critical structures. Anterior extension of the exposure by removal of the middle fossa base, condyle of the temporomandibular joint and mobilisation of the petrous carotid artery, and lateral and inferior extension by additional drilling of the petrous bone and whenever necessary mobilisation of the labyrinthine and tympanic segments of the facial nerve is possible. The clivus is directly in the line of the exposure and can be drilled widely.

It was observed that combined intradural and extradural exposure makes dissection of the tumour from the cranial nerves and brainstem relatively safe and under direct vision. A basal temporal exposure and lumbar drainage of CSF make temporal lobe elevation off the base relatively safe. The inclusion of the intradural route for a primarily extradural tumour, although against the principles of skull base surgery, significantly increases the exposure, which is critical for the safety of the patient and radical resection of the tumour. Direct lateral and basal exposure is the shortest surgical route to the tumour located in the clivus and adjacent areas. As the tumour displaces the adjoining segments of the internal carotid artery anteriorly, the direct lateral route is more appropriate for its safety. The arteries and nerves are relatively easily dissected free from the tumour, probably because their involvement is only compressive and not invasive in nature. The petrous apex and clival bone are eroded, precavernous and cavernous segments of the internal carotid artery are displaced anteriorly and the Gasserian ganglion is elevated on the dome of the tumour in all cases. These anatomical features are utilised in developing a sub-Gasserian ganglion exposure. The tumour, being soft and relatively avascular, is removed by debulking and blunt dissection (Figs 28 and 29). The dura protects the brainstem and cranial nerves and an intact periosteal sheath protects the internal



Figs 28A to C: (A) T1-weighted MRI shows the large hypointense petroclival chordoma. (B) Post-operative CT showing resection of the tumour. Part of the petrous apex is destroyed by the tumour and part was drilled during surgery. (C) Bone window of the post-operative scan showing the petrous apex medial to the internal acoustic meatus drilled during surgery. The part of the petrous apex harbouring the cochlea is left undisturbed



Figs 29A and B: (A) T1-weighted MRI showing the large clival chordoma displacing the internal carotid artery along its anterior surface. (B) Post-operative scan showing complete tumour resection

carotid artery. Reconstruction of the region is easy and safe.

The described middle fossa approach appears to be ideal for dealing surgically with the more characteristic form of clival chordomas. This approach could be used and exposure widened depending upon the extensions of the tumour.

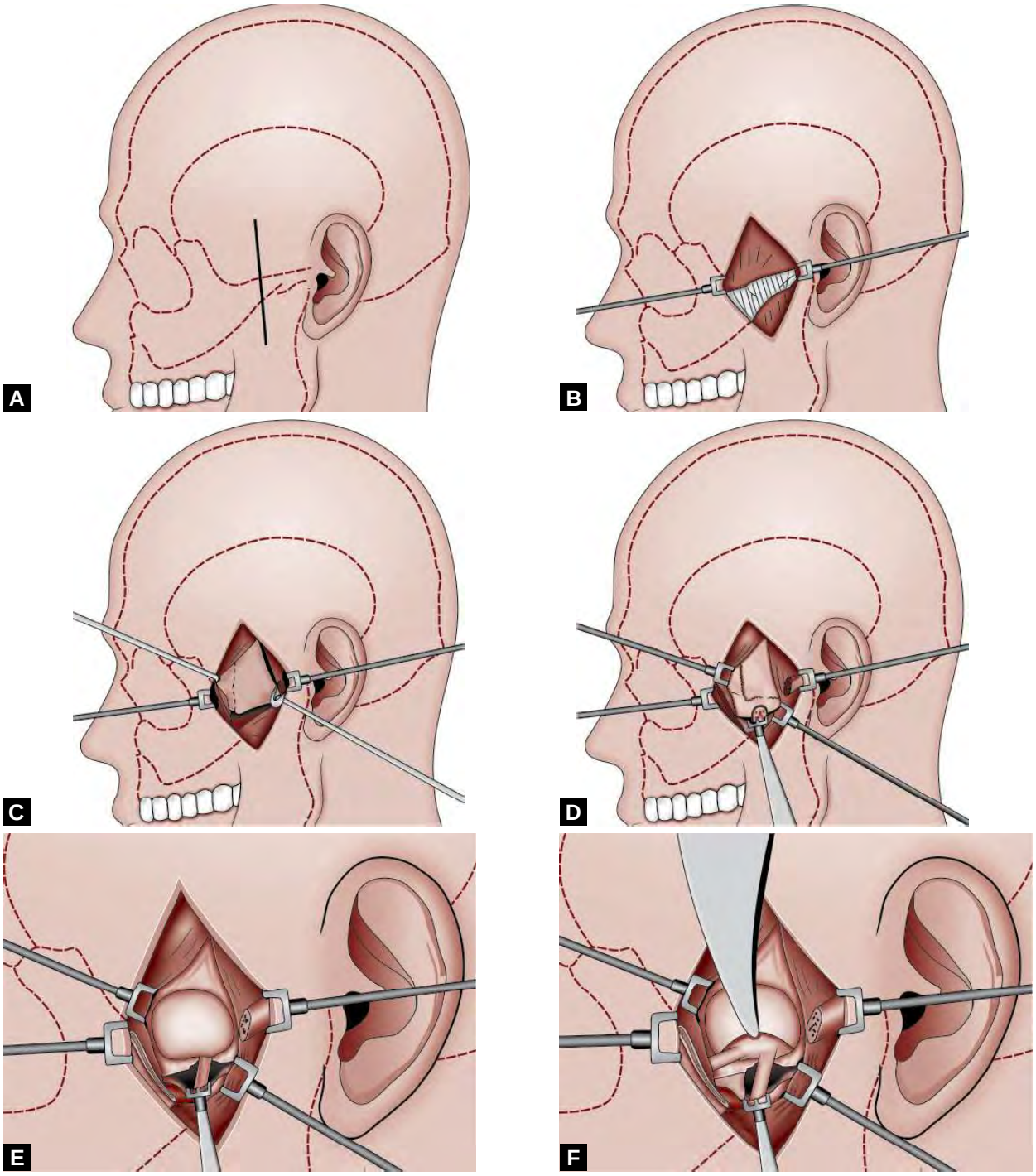
Infratemporal Fossa Interdural Approach[28]

A small craniectomy in the infratemporal fossa incorporating the foramen ovale can be used to resect even large trigeminal neurinomas with extensions from the posterior cranial fossa into Meckel's cave and the lateral wall of the cavernous sinus. After the bone cut the dural sheath around the mandibular nerve and Gasserian ganglion is opened. By progressive tumour debulking, the entire lesion can be exposed and safely excised. The head position and the surgeon's view of the tumour are modified to obtain a basal view. The craniectomy at this strategic site provides an avenue for control of the carotid artery at the petrous apex, avoids the need for brain retraction and permits safe and complete resection of the tumour. The approach appears to be ideal for selected cases of trigeminal neurinomas.

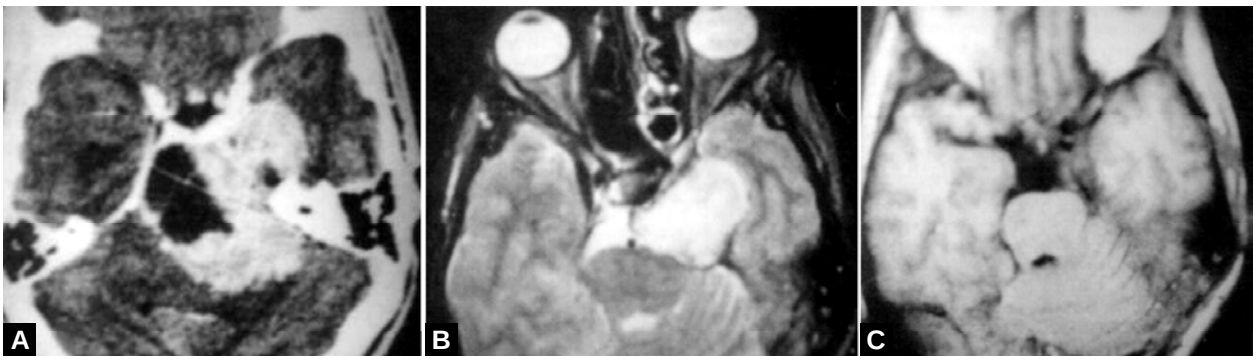
Operative Technique

Operative technique has been depicted in Figures 30A to G. The patient is positioned so that the head is extended and turned to the contralateral side. The right-handed surgeon stands on the right side at the level of the chest of the patient irrespective of the side of the lesion and suitably alters the angle of the rotation of the head (Fig. 30G). A linear incision is made over the zygomatic arch, which is completely resected (Figs 30A to C). The temporalis muscle is either split in the direction of the incision (Fig. 30C) or can be reflected either superiorly or inferiorly. The muscles of the infratemporal fossa are dissected from the bone by sharp subperiosteal dissection and the foramen ovale is exposed (Fig. 30D). With a microdrill, a small craniectomy, measuring approximately 3 x 3 cm is made in the infratemporal fossa, incorporating the foramen ovale (Figs 30E to G and 31). An incision is made on the lateral surface of the dural sheath of the mandibular nerve at the level of the foramen ovale and extended posteriorly to the inferior and lateral surface of the dural sheaths covering the Gasserian ganglion. Usually the tumour is palpable in the region of the ganglion. The dura over the Gasserian ganglion and the lateral wall of the cavernous sinus is reflected exposing the middle fossa part of the tumour (temporal lobe exposure and middle fossa floor durotomy is avoided). The bulk of the tumour usually dilates the dural sheaths in each case and a large exposure can be obtained. After debulking the tumour, the exposure can be further widened. A large tumour in the region of the Gasserian ganglion is seen to dilate Meckel's cave, thus providing sufficient exposure to the part anterior to the brainstem. The inner membranous dural layer separates the tumour from the venous channels of the cavernous sinus. The cavernous sinus part of the tumour can usually be resected by anterior angulation of the microscope. The tumour is followed in the posterior fossa along Meckel's cave. The operation is thus carried out in the infratentorial compartment. Tumour resection in the posterior cranial fossa can be carried out only if the tumour is small or is very soft and amenable to suction debulking and subsequent resection (Figs 31A to C).

A modification of the above-described interdural approach is suitable in some cases, particularly those with small tumours (Figs 32A and B). The patient is placed in the lateral position. Lumbar drainage of CSF is carried out. A limited subtemporal craniotomy in the line of the external ear canal is done. Zygomatic osteotomy is avoided. The temporalis muscle is displaced anteriorly. Extradural exposure of the foramen ovale is done. Dissection is done between the dural sleeves of the third division of the trigeminal nerve and the tumour is resected.



Figs 30A to G: (A) Incision for infratemporal fossa interdural approach to trigeminal neurinoma. (B) The incision has been made and the wound opened to expose the zygomatic arch widely. (C) The zygomatic arch has been resected and the lateral aspect of the infratemporal fossa is exposed. The temporalis muscle has been split in the line of the incision. (D) Exposure of the third division of the trigeminal nerve and foramen ovale. (E) A small craniectomy or craniotomy is made around the foramen ovale in the infratremporal fossa. (F) If necessary more of the Gasserian ganglion and the fifth nerve divisions can be exposed prior to opening the dural layers of the Gasserian ganglion to enter into the tumour mass. (G) Surgeon's hands showing the direction of approach. Shaded ipsilateral zygomatic arch and infratemporal fossa bone depict the extent of bone removal for trigeminal neurinoma shown by oblique lines. The zygomatic arch will be replaced at the end of operation



Figs 31A to C: (A) Contrast CT showing the massive trigeminal neurinoma. (B) MRI showing the middle fossa residue after a retrosigmoid approach tumour resection. (C) Post-operative scan following tumour resection after an infratemporal fossa interdural approach

Presigmoid Approach

Presigmoid approaches are advocated to provide an anterior line of vision to the cerebellopontine angle or clival tumours. The working distance between the surgeon and the tumour can be minimised by this approach. However, there are the following various disadvantages in the approach:

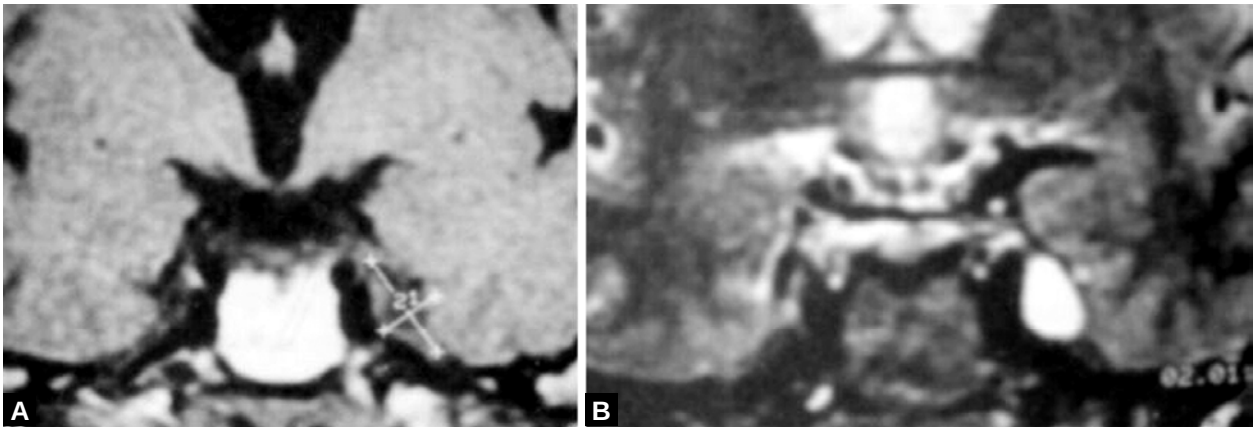
1. The working space between the anterior surface of the sigmoid sinus and the external ear canal is small. The space can be extended by posterior mobilisation of the sigmoid sinus, but complete unroofing and mobilisation of the sigmoid sinus is not always an easy procedure and can sometimes lead to tears in the sinus with its attendant problems.
2. The line of vision to the tumour in the presigmoid transmastoid approach can severely be limited by the posterior semicircular canal. Partial labyrinthectomy can help in improving the exposure. Although some authors report preservation of hearing after partial labyrinthectomy, such results are difficult to achieve.
3. The line of vision by a selective presigmoid approach is in the inferior and posterior direction of the cerebellopontine angle.

Retrosigmoid Approach

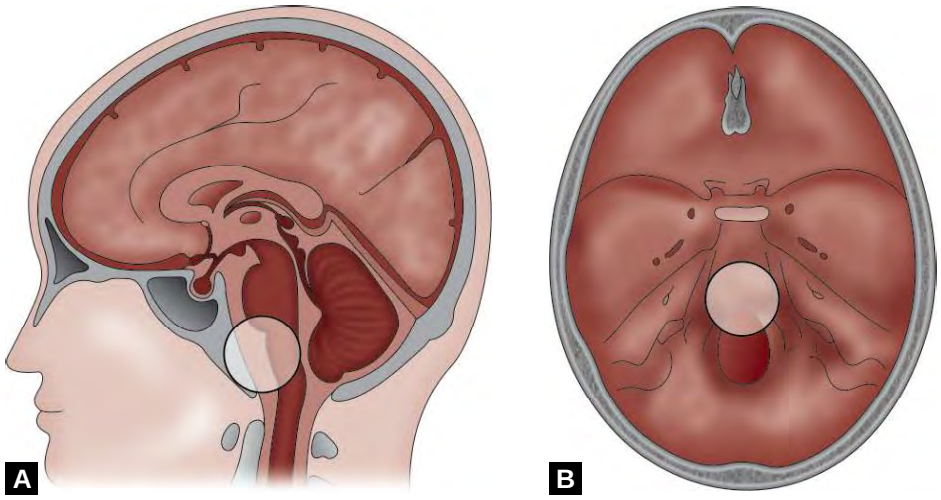
In some situations, a selective retrosigmoid approach may be appropriate. Lateral extensions into the cerebellopontine angle and inferior extensions of the lesions along the clivus are indications for such an approach.

Surgical Technique

The patient is placed in a semi-sitting position with the head suitably turned. Routine precautions necessary for surgery in the sitting position are taken. A conventional retrosigmoid approach adopted for large acoustic neurinomas is used. The lateral aspect of the transverse sinus and the sigmoid sinus are exposed widely. The cisterna magna is exposed early in the operation to drain CSF and relax the brain. The initial exposure of the tumour is through a lateral supracerebellar infratentorial avenue. The nature of the tumour as regards its arachnoid planes, consistency and vascularity is assessed. The tumour is first debulked towards the site of its attachment. Once the region is significantly relaxed, the cerebellum is retracted away from the petrous bone and the exposure is then done through the cerebellopontine angle. The tumour resection is further performed using careful microsurgical dissection techniques, by working



Figs 32A and B: (A) T1-weighted MRI showing a small hypointense trigeminal neurinoma in relationship to the cavernous sinus. (B) T2-weighted MRI showing a markedly hyperintense trigeminal neurinoma



Figs 33A and B: (A) Schematic drawing showing a low clival tumour. (B) Transverse view of the low clival tumour

in both the lateral retrosigmoid and the supracerebellar infratentorial avenues. Drilling the petrous apex medial and superior to the seventh-eighth-nerve complex can access extensions of the tumour into the middle cranial fossa. A tentorial incision is performed whenever a superior angle is needed.

Transcondylar Transclival Approach

An anterior approach is rarely needed for lesions located in the pontomedullary region. An approach which involves unroofing of the jugular bulb followed by either its superior mobilisation or packing, drilling off of the condyle and continuing the drilling to resect part of the clivus provides a considerably anterior view to lesions anterior to the lower brainstem (Figs 33A and B).

Supracondylar Infrajugular Bulb Keyhole Approach to Anterior Medullary Lesions[32]

Lesions located anterior to the brainstem in the lower clival and foramen magnum region pose a formidable surgical challenge. Various lateral approaches have been suggested to widely expose anterior medullary lesions. An alternative approach is suggested, which involves resection of the subsigmoid and retrosigmoid sinus, lateral occipital squamous bone, lateral border of the foramen magnum and a small area of bone between the jugular bulb and the condyle. Exposure, manipulation or mobilisation of the extradural vertebral artery is avoided. Condylar resection is not necessary. The exposure is relatively quick and significantly anterior. After an adequate inspection of the nature of the lesion, the exposure could be widened in all directions.

Operative Technique

The patient is placed in a lateral position and the head is flexed and turned to the contralateral side (inferiorly). A low occipital and retromastoid incision is made, which extends inferiorly into the upper cervical region. The lateral rim of the foramen magnum and the occipital squama are exposed. The part of the occipital squama including the rim of the foramen magnum is carefully removed (Fig. 34). The bone removal is extended anteriorly to include the bone of the supracondylar and infrajugular bulb region. The condylar vein can sometimes result in troublesome bleeding and has to be adequately dealt with. The exposure obtained is of a key shape (Fig. 35). A dural incision is made as shown in Figure 36. The lateral edge of the cisterna magna is opened. The intradural segment of the vertebral artery is identified and its relationship to the tumour analysed. No additional exposure may be necessary if the tumour is soft and suckable. The exposure may be widened inferiorly by drilling off the condyle as necessary, preserving the hypoglossal nerve, which travels in the superior half of the condyle. The bone on the inferior aspect of the jugular bulb can widely be removed. In cases where the dura of the jugular bulb is thick, the jugular bulb can be compressed superiorly and the exposure widened (Fig. 37). In most of the cases, no significant further increase in exposure is necessary. Whenever necessary,

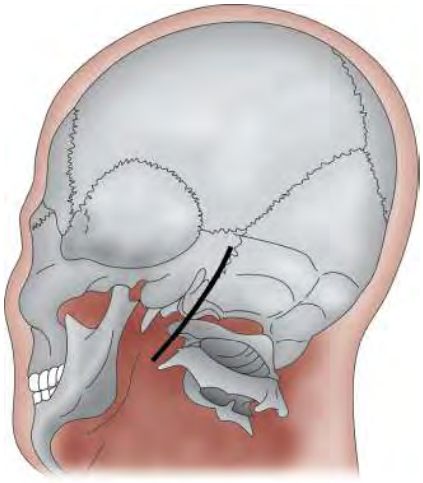


Fig. 34: Line drawing showing the incision for supracondylar infrajugular bulb keyhole approach to anterior medullary, low clival lesions

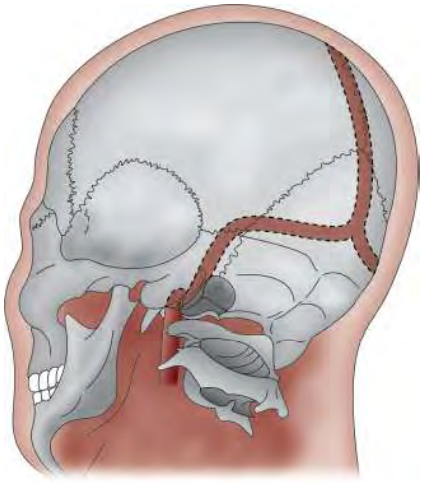


Fig. 35: The shaded area shows the site of keyhole exposure. The bone lying between the condyle and the jugular bulb is removed. Bone removal is extended posteriorly to include the anteroinferior part of the occipital squama

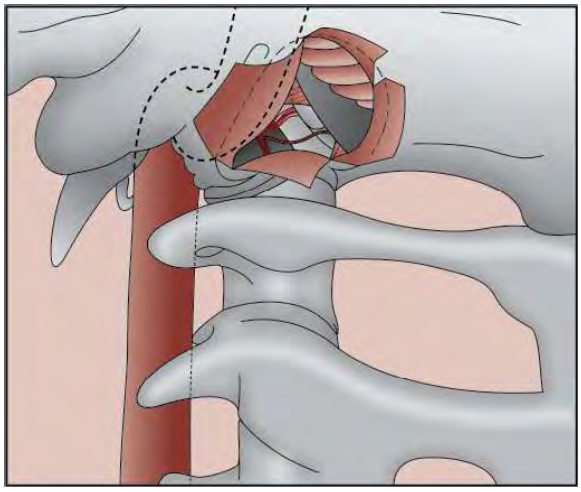


Fig. 36: The supracondylar and the infrajugular bulb area are exposed after making a cruciate dural incision and reflecting the dural flaps. A large condylar vein can sometimes cause troublesome bleeding

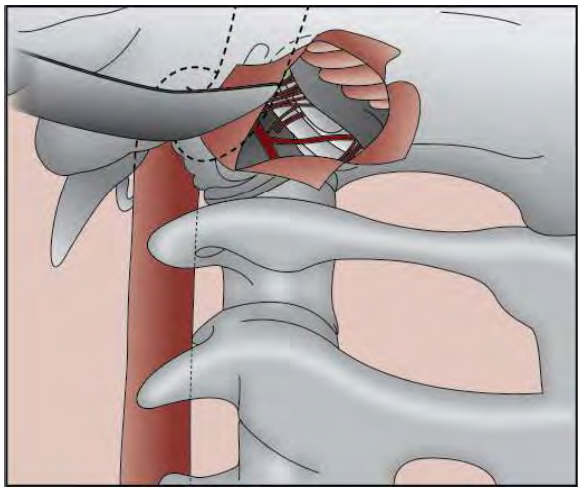
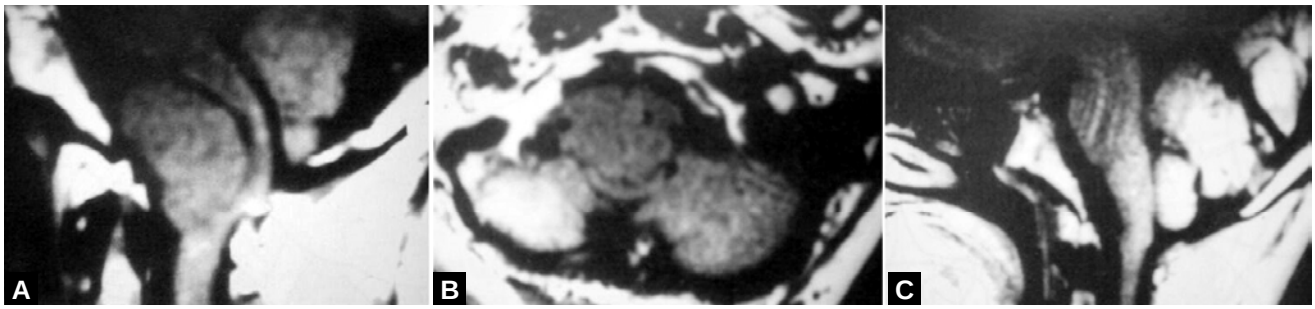


Fig. 37: The jugular bulb is being retracted superiorly to enhance the exposure. In cases where additional exposure is required the jugular bulb can be sacrificed and packed after adequate preparations

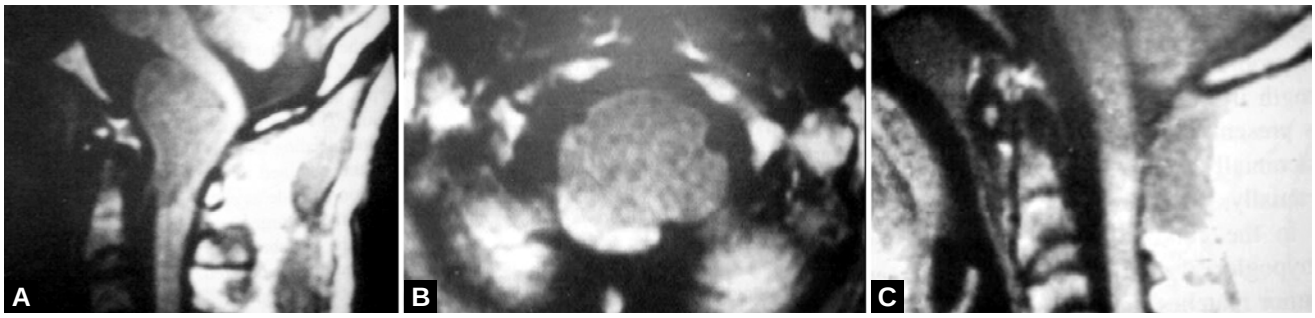
various complex manoeuvres like exposure of the extradural vertebral artery, its mobilisation, condylar resection, obliteration of the jugular bulb and other such procedures may be employed (Figs 38 to 40).

Splitting of the Temporalis Muscle[33]

There are various methods recently described to enhance the middle fossa basal exposure circumventing the obstruction to the visual field, imposed by the



Figs 38A to C: (A) T1-weighted MRI shows a large anterior medullary meningioma. (B) Transverse cut showing partial encasement of both vertebral arteries. (C) Post-operative scan showing complete resection of the tumour. A lateral suboccipital subsigmoid sinus approach was used to resect the tumour



Figs 39A to C: (A) T1-weighted MRI shows the low clival meningioma. (B) Transverse section shows the midline location of the tumour, involvement of both vertebral arteries and deep indentation of the medulla. (C) Post-operative scan shows complete resection of the tumour. A supracondylar, infrajugular bulb keyhole approach was used to resect the lesion

temporalis muscle bulk (Figs 41 and 42). Spiller has employed splitting of the temporalis muscle to improve the caudal exposure in various subtemporal approaches including the classic one described.

Anatomical and Technical Considerations

The temporalis muscle is a fan shaped muscle. The muscle arises from a large area of squamous temporal bone and adjoining frontal, parietal and occipital bones and the fibres converge towards a relatively smaller area over the coronoid process of the mandible. The muscle fibres are vertically oriented and directed towards the site of insertion. There is abundant vascular supply to the muscle through the anterior, middle and posterior sets of deep temporal arteries and a large superficial temporal artery. The nerve supply to the muscle is through deep temporal branches of the mandibular division of the trigeminal nerve. Vertical splitting of the temporalis muscle into half or one third would still preserve the main feeding vessels and the nerves. The splitting will not adversely affect the circulation and will not significantly disturb the function of the temporalis muscle. Retraction of the split segments of the temporalis muscle can be carried out after its adequate mobilisation. The zygomatic arch is anatomically inferior in relation to the middle fossa floor. In most instances, zygomatic arch osteotomy is performed principally to facilitate the inferior displacement of the temporalis muscle, as its bulk limits the basal exposure. By splitting the temporalis muscle, zygomatic arch osteotomy could be avoided in some cases (Figs 43 and 44). The split in the muscle is done directing the incision towards the coronoid process to minimise the transection of the muscle fibres. The split may predominantly be anterior or posterior depending upon the desired area of the exposure. In cases requiring exposure of the infratemporal fossa, splitting of the temporalis muscle can be performed after zygomatic osteotomy. This manoeuvre helps in obtaining a significantly improved inferior exposure of the infratemporal fossa.

The variety of vascular lesions and tumours involving the cavernous sinus, petroclival region, infratemporal and sphenopalatine fossa are treated by a basal subtemporal and infratemporal fossa approach. In most of the described approaches, the temporalis muscle is completely detached from its insertion in the temporal fossa[13,62,69,79] and its caudal displacement is facilitated by

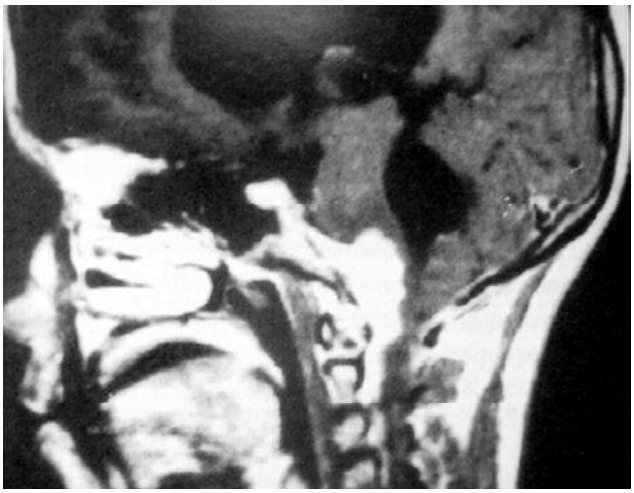


Fig. 40: Contrast-enhanced MRI shows the large premedullary lesion

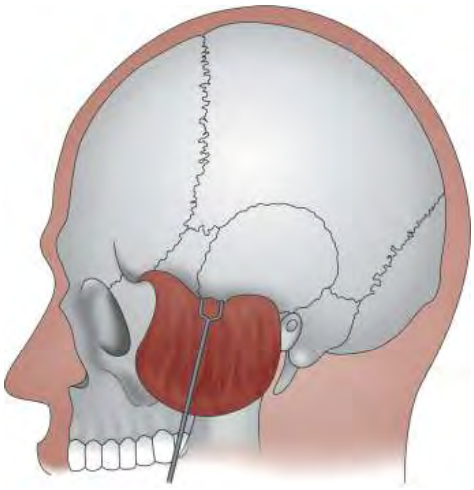


Fig. 41: The temporalis muscle is reflected inferiorly. Zygomatic osteotomy is not done. The muscle bulk limits the extent of basal exposure

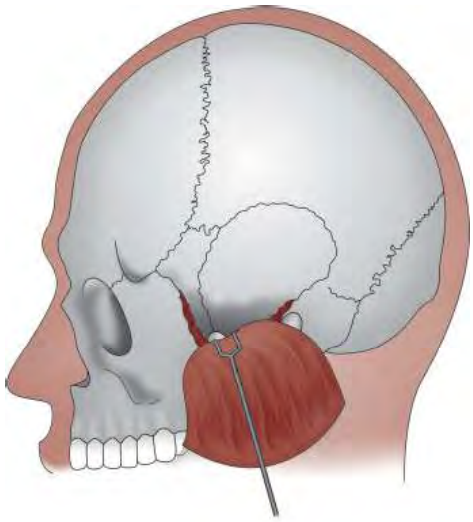


Fig. 42: Zygomatic osteotomy is done to caudally retract the muscle and obtain an improved middle fossa basal exposure

either temporary resection or mobilisation of the zygomatic arch. Al-Mefty et al. suggested superior retraction of the temporalis muscle along with its coronoid insertion.[3] Splitting of the temporalis muscle as described in this report appears to be a simple alternative to the other described procedures to obtain a basal subtemporal exposure. The obstacle to the surgical exposure imposed by the muscle bulk is minimised. In selected cases, zygomatic osteotomy is not necessary. The problems of denervation and devascularisation of the temporalis muscle are avoided.

Tentorial Dural Flap[26]

For a subtemporal transtentorial approach to the anterior part of the posterior fossa, a tentorial incision has to be made. Various methods of retraction of the edge and incisions over the tentorium have been described. The fourth nerve travels along the edge of the tentorium. The nerve is closer to the edge of the tentorium in its distal segment as it comes closer to the posterior clinoid process. In the terminal segment, the nerve travels within the fold of the tentorial dura for about 1 cm. An incision made in the tentorium about 1.5 cm posterior to the posterior clinoid process, keeping the nerve under vision by retracting the tentorial edge, is usually safe as regards the fourth nerve. The root of the fifth cranial nerve and the petrosal vein lie directly underneath the tentorium. During surgery, the location of the superior petrosal sinus cannot be adequately ascertained and an inadvertent incision into it could lead to profuse bleeding which could be difficult to control due to the inadequate space available underneath the retracted temporal lobe. Bleeding from the superior petrosal sinus occurs from both sides of the cut. Packing of the sinus, after widely opening the mouth of the sinus, with oxidised cellulose and pressure with the help of cotton patties can adequately control the bleeding. Removal of extra oxidised cellulose can then be carried out, so that it does not obstruct the operative field. Sometimes, an incision into the venous sinuses in the tentorium could lead to troublesome bleeding. The incision, travelling parallel to the superior petrosal sinus and terminating in the tentorial dural edge posterior to the entry of the fourth nerve, is the most commonly employed incision. Such an incision is appropriate in cases where a large part of the tentorium cannot be exposed due to the limited working space (Figs 15 and 16). Adequate relaxation of the brain is necessary for the described incision and eversion of the tentorial dural flap. An incision is begun at the free edge of the tentorium at the level of the posterior edge

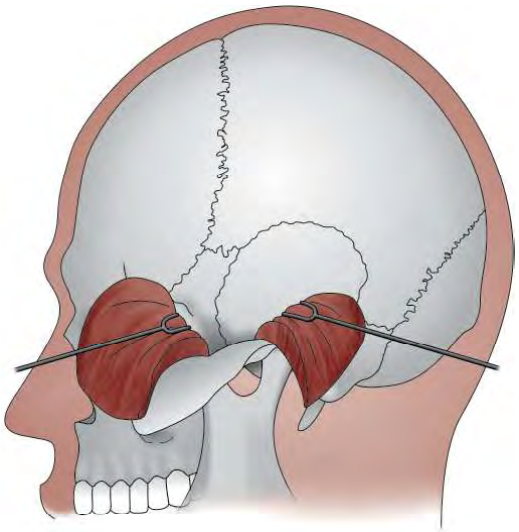


Fig. 43: Splitting of the temporalis muscle. The shaded area depicts the extent of enhancement of basal exposure

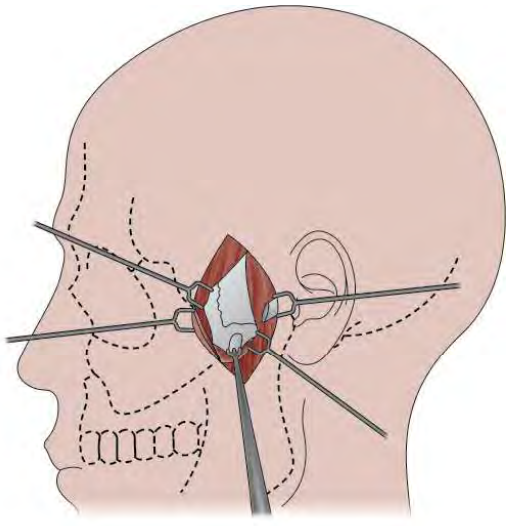


Fig. 44: Splitting of the temporalis muscle is done after zygomatic osteotomy. The infratemporal fossa muscles are retracted inferiorly. The basal exposure is enhanced by these procedures. The mandibular division of the fifth cranial nerve can be exposed extracranially

of the cerebral peduncle and is then directed anterolaterally towards the superior petrosal sinus. A triangular flap of the tentorial dura is everted over the superior petrosal sinus. The flap has the advantage of being simple and safe and provides a wide window to the infratentorial structures. In addition, the occasional troublesome bleeding from the superior petrosal sinus and the petrosal vein is avoided. The fourth and fifth cranial nerves are protected and exposed widely. The 40 degree angle of the petrous bone in relation to the transverse plane is used in making the incision over the tentorium.

Operative Technique

A blunt hook is used to elevate the tentorial edge and the number 11 scalpel is used to advance the incision anterolaterally in the tentorium. The knife cuts the tentorium onto the base of the hook, which protects underlying structures (Figs 14 and 15). The incision starts from the edge of the tentorium at approximately the posterior edge of the cerebral peduncle and traverses towards the base of the petrous pyramid and superior petrosal sinus. As the hook advances laterally, its path is obstructed by the edge of the petrous bone. In this fashion, a triangular flap of tentorium is obtained which can be everted over the superior petrosal sinus. Thus, a wide exposure of the infratentorial compartment is obtained (Fig. 16). The described incision starts much posterior to the conventional incisions, which begin or terminate just posterior to the dural entry point of the fourth nerve. Thus, it results in better protection of the fourth nerve. On eversion of this flap based on the superior petrosal sinus, a wide exposure to the infratentorial compartment is obtained. The need to make an incision on the tentorium superior to the fifth nerve and petrosal vein is avoided. As the incision is directed anterolaterally, the edge of the petrous bone obstructs the passage of the hook, which therefore helps prevent an inadvertent injury to the superior petrosal sinus. If felt necessary, the tentorium can be sutured at the termination of the surgery.

SELECTION OF APPROACHES

Petroclival Meningiomas

There are various approaches described to deal with lesions present in this location.[2,8,9,11,15,17,23,27,34,36,46,53,67,83,90,97] However, for a particular tumour, there is only one approach, which is ideal and best and can be performed. It is up to the surgeon to decide the ideal route of approach for a particular lesion. The familiarity with all the available approaches is, therefore, essential so that the best possible route could be selected.[35] Expertise in one particular route and an attempt towards performing surgery on all lesions with the same approach could sometimes lead to problems. Some modifications of the described approaches may be appropriate for a particular case to be operated upon. The issues in the decision regarding the approach should include considerations for the approach, which could be performed in the shortest time, is least difficult and safest for the patient. The exposure must be wide and it must also provide with avenues for dealing with disasters like major arterial tears, and for reconstruction of nerves and arteries whenever necessary. A secure basal reconstruction is vital to prevent CSF leakage.[25,30]

Petroclival meningiomas are described as those which arise from the dura in the region medial to the entry of the trigeminal root into Meckel's cave.[83,84] Frequently, these and other lesions situated in this region involve the cavernous sinus and extend down to the mid-clivus, encasing and/or displacing critical arteries and perforators.[38,40,42,43] For satisfactory and safe excision of these tumours, an adequate exposure is necessary. Meningiomas in proximity to the clivus are amongst the most difficult surgical problems. The difficulty in resection of these lesions stems from the following facts:

- These benign lesions are frequently of large size at the time of presentation.
- Patients present with relatively subtle neurological symptoms and signs.
- Tumours may encase vital major arteries and perforators, sacrifice of which could result in permanent neurological deficit or even death. Such an eventuality could have taken years in the natural course of tumour growth.
- Alternative methods of treatment, like radiosurgery, chemotherapy, photodynamic therapy, etc. are of no proven value in the management of these cases.
- If left alone, in all probability, the tumour will grow and lead to a slow and crippling death. Once the decision regarding surgery is made, one has to understand that in most cases the operation is not being carried out to obtain a histological confirmation regarding the nature of the lesion as such information is usually available with reasonable certainty on radiological studies. The approach to the lesion involves retraction of vital brain structures and the operation needs prolonged microsurgical dissection to isolate the lesion from vital structures. A low or basal approach that could avoid or limit retraction is necessary as prolonged and excessive retraction may not be well tolerated by the brain. A small or limited excision may be of very little help to the patient. It only means that clival lesions should be approached when the operating team is reasonably confident that a total or a radical excision could be made on the basis of their experience and level of confidence.

The extensions of the tumour and the site of its attachment into the supratentorial compartment, cavernous sinus and cerebellopontine angle are common. A variety of transpetrous and middle fossa approaches have recently been described and successfully employed for surgical resection of petroclival meningiomas. Some authors believe that the conventional retrosigmoid approach is suitable for some of these tumours.[8,73,74]

The selection of a surgical approach for petroclival meningiomas will depend on a large number of variables. The nature of tumour extensions, its relationship with the petrous bone, clivus, tentorium and cavernous sinus and the adjoining critical neural and vascular structures, generally determine the surgical approach. However, personal preferences, experience and the nature of surgical technique of tumour resection of an individual surgeon will be some crucial factors that can affect the decision making, regarding the surgical approach. The variability of extensions and relationship with adjoining structures in petroclival meningiomas, unlike a fixed location and specific extensions of tumours, like acoustic neurinoma, makes it impossible to specify that one particular surgical route is the best or the only option in all of these cases. A posterior fossa approach is generally suitable for large sized tumours, those having majority of their bulk in the posterior cranial fossa and those 'pointing' into the cerebellopontine angle. The approach is suitable for tumours having a lateral extension beyond the internal auditory canal and an inferior extension below the level of the pontomedullary junction. Smaller, superior clival tumours, tumours with predominant location in the tentorial hiatus, and those with significant extension into the supratentorial compartment or in the cavernous sinus may be suitable for an alternative basal subtemporal approach. A lateral surgical position and a basal subtemporal approach could be selected in cases where the anticipated tumour resection is expected to be a more difficult and a time-consuming process, as long operations with the patient in the sitting position can be stressful both for the patient and for the surgeon's hands.

The posterior fossa approach is far easier, safer and quicker and the exposure of the tumour is wider, as compared to the transpetrous or basal subtemporal approaches. It avoids any major arterial or venous or venous sinus handling, manipulation or sectioning, petrous bone drilling and temporal lobe retraction related problems. The authors of the earlier reports recommending a posterior cranial fossa route for these tumours also recommended a sitting surgical position for the patient.[8,15,21,89] Utilising both supracerebellar and cerebellopontine angle routes provide a circumferential exposure of the tumour. The extent of petrous bone drilling could be determined after the nature of the tumour is ascertained. This is in variation of the predetermined bone drilling necessary for all transpetrous and basal subtemporal approaches. The site of the tumour attachment is in direct line of vision and can be widely exposed. Dural and wound closure is easy and safe. The approach has the additional advantage of its familiarity to general neurosurgeons. Although it is possible to resect middle cranial fossa extension of the tumour by a posterior cranial fossa route by a limited petrous apex drilling, the exposure of this part of the tumour is cumbersome and the angle available for tumour resection is inadequate.[73,74] The control of venous haemorrhage from the superior petrosal sinus and the cavernous sinus is more difficult through the posterior fossa route. Proximal or local control of the carotid artery is not possible and control of supratentorial arterial bleeding is more difficult by the posterior cranial fossa route.

Recurrence rate of a relatively small residual tumour after a radical surgical resection has been seen to be distinctly low.[59,73,74] Due to this reason, and the possibility of disabling morbidity or even death as a result of injury to blood vessels and neural structures, various authors have stressed the need of a safe dissection and cautioned against extensive dissection around the perforators and cranial nerves.

Out of the total 84 petroclival meningiomas treated in our institution over 12 years, we found a posterior fossa approach suitable in 28 cases. After using extensive[36] and limited petrous dissection,[31,36,94] and also using a conventional posterior fossa approach for a number of years, the percentage of these tumours dealt with by a posterior fossa route have increased in the later part of the series. The tumours treated by different surgical routes in our series had varying degree of complexities and the extent of tumour resection and the overall patient outcome varied and was not comparable.

Trigeminal Schwannomas

Surgery for trigeminal schwannomas has evolved along with the evolution of skull base surgical techniques.[95] Various operative approaches have been described for the surgical resection of trigeminal neurinomas.[77,98] The anatomy of the tumour and its dural covering, anatomy of the region and anatomy of various approach routes are now better understood. Trigeminal schwannomas can now be removed by relatively small and straightforward exposures with minimum brain handling. Most recent papers show a higher percentage of tumour resection, low surgical morbidity rate and a lower rate of recurrence.[60,71,75,98] Various reports have stressed the need for radical surgery, as total resection leads to cure from the tumour and the recurrence rate for cases with partial resection is relatively higher with trigeminal schwannomas than acoustic schwannomas.[4,28,41]

On the basis of the presenting clinical features and characteristic radiological signs, a diagnosis of a trigeminal schwannoma could be made in a majority of cases. Such a diagnosis is crucially important in planning the surgical strategy for the cavernous sinus related lesion. The relationship of the dura and the adjoining structures, which is characteristic in trigeminal schwannomas, may not be for other tumours in the location. The major impediment to complete removal is an inadequate exposure.[18,71,77,79] Due to the location in the depth, close proximity to vital neural and vascular structures; the ideal surgical approach should be the shortest and most direct, it must be wide and low, avoiding the need for prolonged and excessive brain retraction. Considering

the location within the layers of the dura in the middle fossa, there is no specific need to have proximal control of the carotid artery as would probably be necessary for some other lesions in this location.[48] The layers of the dura also form a relatively thick barrier that facilitates surgery. A large proportion of these tumours are soft, necrotic and only moderately vascular. Frontotemporal craniotomy with or without orbitozygomatic osteotomy and the petrosal approaches were used in the early part of the series but were later not preferred. For small tumours in the middle fossa and those having a relatively small extension into the posterior fossa, an infratemporal fossa interdural approach as described by us was found safe, quick and provided adequate exposure.[28] Al-Mefty et al. described section of the temporalis muscle at its insertion at the coronoid process and superior displacement of the muscle.[3] The temporalis muscle can also be either split in the direction of its fibres or reflected inferiorly and later used for basal reconstruction.[31,33] The tumour is followed into the posterior fossa along the dilated Meckel's cave. The presence of atrophy of the temporalis and pterygoid muscles makes the infratemporal fossa exposure relatively easy. The Meckel's cave is exposed after drilling and widening of the foramen ovale and the tumour is resected by dissection between the layers of the dura. The direction of approach and the surgeon's position in relation to the patient can be altered, to provide a direct and low access to the lesion. The approach is interdural, avoiding the need to expose the temporal lobe and thus, limiting the extent of temporal lobe retraction to the minimum. The possibility of anatomically dissecting the layers of the dura in cases of trigeminal neurinoma has been described earlier.[19,68] Although the carotid artery at the petrous apex is not exposed, as it is usually covered by the dural sheath, it is close in the field and can be exposed relatively easily.[49] The tumour bulk widens Meckel's cave and a large window can be obtained for resection of the posterior fossa portion of the tumour. The soft nature of the tumour can be used to circumvent the disadvantage of confronting the tumour prior to exposure of the brainstem. The approach to the tumour anterior to the brainstem is entirely infratentorial. In our series, the exposure obtained by such an approach was seen to be adequate for safe and complete resection of the tumour. In none of the cases was there any need to extend the exposure for tumour removal. The entire procedure could be performed in a significantly shorter time and is cosmetically appealing.

In larger tumours located in the middle fossa, a basal lateral subtemporal exposure is suitable.[31,37,41] Extradural exposure for relatively smaller tumours and intradural exposure for larger tumours is appropriate. The approach is found to be suitable to deal with the middle fossa component or both the middle fossa and the posterior fossa component of the tumour. The basal extension of the exposure is achieved by resection of the roots of the zygomatic arch, roof of the external ear canal and superior third of the mastoid bone.[88,94] The temporalis muscle is rotated anteriorly and is thus away from the field.[31,65] The exposure is centred over the external ear canal in line with the petrous apex. The direction of the approach to the tumour is the shortest and perpendicular from the surface and avoids any neural or vascular manipulation. Inclusion of mastoidectomy in the exposure added to the advantages of the petrosal approach.[3] In tumours located in the posterior cranial fossa, a retrosigmoid exposure is satisfactory. The tumour does not involve all the fibres of the fifth nerve and some fibres were invariably spared. At least some fibres of the nerve are preserved in the majority of cases. Working within the tumour, using blunt dissection with the help of suction or cavitron ultrasonic aspirator (CUSA) and avoiding coagulation, as much as possible, probably avoids injury to these fibres. The inferolateral approach to the tumour helps in preserving the more crucial first division of the trigeminal nerve than the frontotemporal approach, which provides an anterolateral trajectory. In the posterior cranial fossa, the sixth cranial nerve and the seventh-eighth-nerve complex are most likely to be injured during the dissection and need to be protected. Superior cerebellar and posterior cerebral arteries and their branches are critically located and need to be protected. However, in the majority of cases, the dissection of the cranial nerves and vessels off the tumour is relatively simple due to the presence of a well-defined arachnoidal plane of dissection from the tumour capsule. In the subtemporal intradural approaches, protection of the 'vein of Labbe' forms a crucial part of the operation. Pre-operative lumbar drainage of CSF can be used to great advantage. In patients with large tumours, resection of the inferior temporal gyrus helps in increasing the exposure and avoidance of excessive retraction. In tumours having an extracranial extension, the infratemporal or orbital exposure is obtained depending on the extensions.

Foramen Magnum Meningiomas

Meningiomas in the region of the foramen magnum are relatively rare.[1] A large proportion of foramen magnum meningiomas are located anterior to the brainstem and have a close relationship to vital neural, vascular and bone structures. Meningiomas with en-plaque extension and extradural growth have been reported.[24,44,45,76] The clinical course is slowly progressive, leading to dysaesthesia, asymmetric motor weakness, gait ataxia and relatively less commonly, lower cranial nerve affection. Misdiagnosis due to uncommon symptoms, leading to wrong decisions and inappropriate treatment has frequently been observed with these lesions. MRI has provided a significant advancement in the diagnosis.[10] It clearly delineates the exact tumour size, location, site of dural attachment and relationship to vascular and neural structures, and provides an opportunity to assess its consistency and vascularity. Recovery after a successful tumour resection is almost instantaneous and recurrence rates have been

seen to be extremely low.[22] Injury to the brainstem, cranial nerves or vertebral artery or its branches can lead to a disastrous outcome for the patient and the family.[12,61,66] Surgery on meningiomas located in the region of the foramen magnum anterior or anterolateral to the brainstem constitutes a formidable challenge and has been evaluated by various authors over many years. Anterior transoral,[16,64] anterolateral transcervical,[57,92] extreme lateral,[86] far lateral[16] and lateral approaches[5,14,24,32,50,51,70,76] have been advocated and have been preferred over the conventional posterior approach.[39,70,76,91] Whilst there are certain obvious advantages of a lateral or an anterior approach to these lesions, a posterior approach used by various surgeons over a century also has a distinct set of advantages.[20] The meningiomas located in the region 'anterior' to the brainstem in the region of the foramen magnum are only rarely strictly anterior. Despite their varied sizes, most of these tumours point laterally on one side of the midline and the brainstem is displaced or twisted posterolaterally rather than posteriorly.

A midline skin incision and exposure of the region of the foramen magnum, occipital bone, arch of atlas and axis is far easier, safer, quicker and wider, when compared to any anterior or lateral approach. Extensive drilling of the occipital condyle,[5,56,76,86] lateral mass of the atlas[5] or anterior spinal elements[16] is not involved, avoiding the possibility of injury to the hypoglossal nerve and vertebral artery and spinal instability. The vertebral artery is easily exposed in the region of the arch of the atlas, at the site of its entry into the dura by a midline approach and proximal control is possible. Exposure of the extradural vertebral artery, its manipulation[86] and mobilisation amidst large venous plexuses necessary in some lateral approaches, involves considerable degree of effort and possible risks.[45] By a slightly larger midline skin incision and an additional retraction of muscles, a significant lateral exposure is obtained by the conventional midline posterior approach. The extent of additional bone removal necessary is determined, after ascertaining the nature of the tumour consistency, vascularity and the extent and site of dural attachment.

Additional drilling of the condyle is possible for a more lateral exposure in cases of directly anteriorly placed meningiomas. The condylar drilling is safer, as the vertebral artery and nerves are already exposed. The brainstem, cranial nerves, vertebral artery and the tumour are exposed in the same field and the dissection is carried out with all structures under vision. The exposure is improved after retracting the cerebellum and the operation can be done in the cerebellomedullary angle from a lateral perspective, employing appropriate angulation of the microscope. The exposure is wide and not 'deep', when compared to that obtained by transcervical, transoral and even lateral approaches.

Most of the meningiomas encountered are relatively soft and have moderate vascularity. They have a well-defined plane of arachnoid cleavage, which make the resection easier even with a relatively small exposure. The tumours are resected after performing an initial debulking and then by working within the planes provided by tumour growth. The tumour debulking provides additional working space for dissection. Debulking of larger tumours provides more space anterior to the brainstem, making it unnecessary to operate from a more lateral angle. The exposure of the anterolateral and anterior foramen magnum and clival dura is direct and in line of the exposure, which makes the coagulation and resection of the involved dura easily possible after tumour resection. Such a direct exposure is difficult or impossible by a strictly lateral approach and could be obtained only if the entire condyle is resected. Total and radical removal of the tumour should be attempted but, if dissection of the tumour from the vertebral artery, its branches, or any cranial nerve entails risk of damage, a small portion of the tumour can be left behind.

Clival Chordoma

Most of the lateral procedures, described for resection of clival chordomas, involve relatively complex and extensive skull basal dissection, exposure and mobilisation of the carotid artery,[85,79] facial nerve,[23,54] sigmoid sinus[2] and temporomandibular joint.[23,79,85]

A modified lateral subtemporal, transpetrous apex and sub-Gasserian ganglion approach is suitable for clival chordomas.[29] The approach selection is based on the typical anatomic relationship of chordomas in terms of site of origin, pattern of growth, bone destruction and neural and vascular displacements. The approach is suitable for dealing with tumour anterior and lateral to the brainstem, clival part of the tumour and its sub-cavernous sinus extensions. The carotid artery is under control. The approach has the advantage of being simple and relatively quick and its familiarity to general neurosurgeons. The tumour is excised radically and extension of the anterior, posterior and inferior exposure is possible.

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183 Transpharyngeal Approach to the Cranio Vertebral Junction

AH Menezes

The transoral approach to the ventral craniocervical border is the most direct route for decompression of irreducible extradural pathology. These procedures encompass the transoropharyngeal, the transpalatal and the median mandibulotomy with glossotomy (Fig. 1).[9] The author's experience of 730 patients treated via the transoropharyngeal-transpalatopharyngeal route is shared with the readership. Since 1977, the procedure has evolved into a safe and direct approach with minimum morbidity and mortality.[5] The author's technique is elaborated here. Ninety-seven per cent of patients will require craniocervical stabilisation which is now carried out under the same anaesthetic as the transpharyngeal procedure.[10]

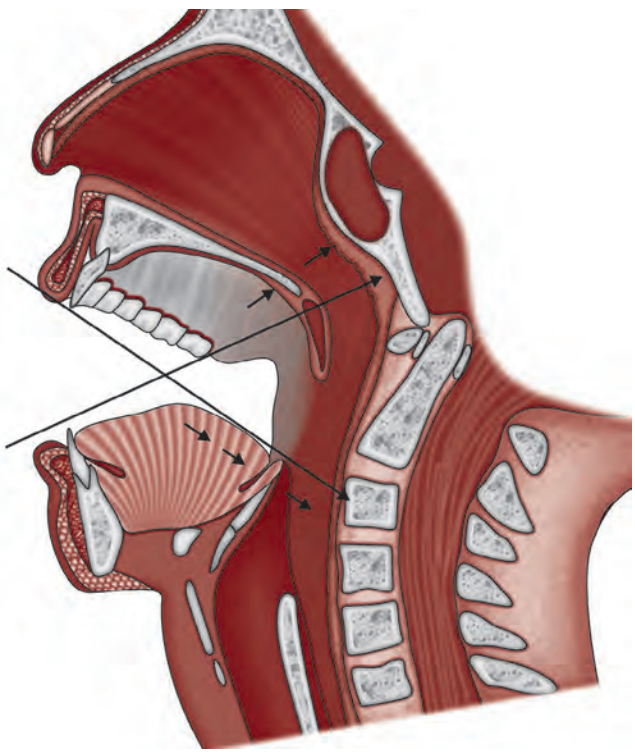


Fig. 1: Mid-sagittal line drawing of the face and neck to include the craniocervical junction. A soft palate elevation or a soft palate split with tongue depression allows exposure between the long arrows. The open areas identify the extent of exposure with removal of the distal hard palate. This brings one to the mid clivus. A midline glossotomy as indicated by the arrowheads, allows exposure to the C3-C4 vertebral body

INTRODUCTION

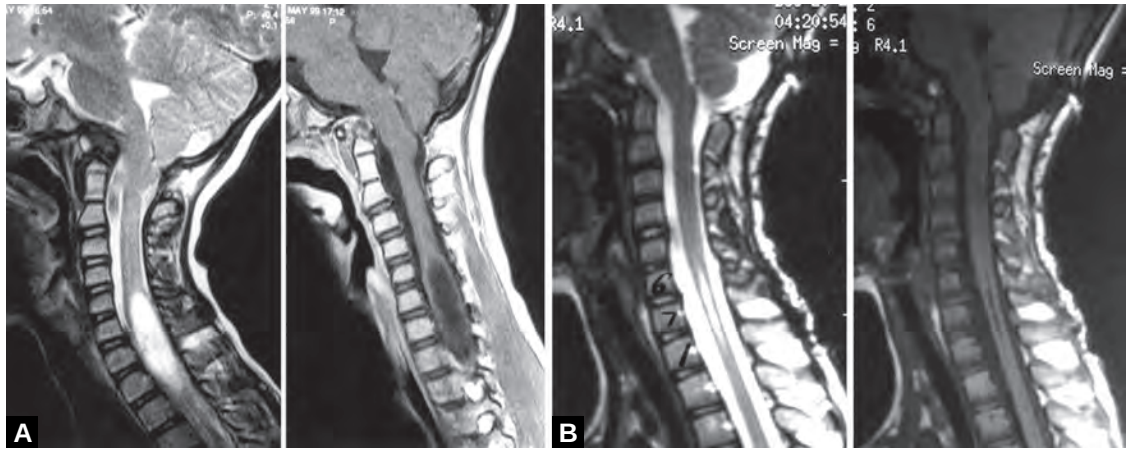
The relevant diagnostic imaging for abnormalities of the craniocervical junction consists of plain radiographs of the region which should include the skull and cervical spine. Dynamic studies with the flexed and extended position are made to assess the stability and the need for possible reduction.[8] The cervical spine radiographs should include the mandible so that the relationship of the craniovertebral border to the hard palate can be judged, including its accessibility. In patients with normal anatomy, the configuration of the clivus is normal (almost vertical). Thus, with the transoral approach, elevation of the soft palate suffices to provide anterior exposure of the craniocervical junction.[3,9] On the other hand, in patients with congenital abnormalities associated with hypoplasia of the clivus, this now tend to become horizontal. It appears as though the upper cervical spine has "ascended". Consequently, the soft and the hard palate must be sectioned.

Magnetic resonance imaging (MRI) is the mainstay of the neurodiagnostic armamentarium. The T1- and T2-weighted mid-sagittal MRI should be done in both the flexed and extended positions. This modality provides information about the neural structures, as well as their relationship to the bony abnormality and vascularity (Figs 2A and B). Magnetic resonance angiography should be performed when neurological dysfunction cannot be fully explained. In that circumstance, it is done with the patient in the rotated, flexed and extended positions, to identify vascular occlusions that can appear when the patient changes position.

Computed tomography (CT) of the craniocervical junction is an integral part of this author's assessment of the bony pathology. Conventional CT (2D CT) is further augmented by 3-dimensional CT reconstructions. This modality shows the location of the occipital condyles, the lateral atlantal masses and the axis body, as well as the lateral masses. The odontoid process is visualised and, in congenital abnormalities, it is very frequent that the odontoid process is actually smaller than in normal adults, because of segmentation abnormalities.

ASSESSMENT OF NUTRITIONAL STATUS

This issue is particularly important in patients who have had difficulty with swallowing and failure to thrive. It is also important in patients with rheumatoid arthritis,



Figs 2A and B: (A) Mid-sagittal T1- and T2-weighted MRI of craniocervical junction and cervical spine in a patient where the clivus-odontoid articulation indents into the mid medulla. Note the hindbrain herniation and the cervical syringohydromyelia. This individual will require a transpalatal approach. (B) Post-operative MRI in mid-sagittal plane of the same patient as in Figure 2A. A transpalatopharyngeal decompression of the ventral medulla has been performed. Note the reduction of the syrinx and the medullary decompression

atlantoaxial dislocation, tuberculosis and rheumatoid vertical migration of the odontoid process that compresses the brainstem.[4,7] Thus, pre-operative nutritional support is mandatory before operative intervention. Failure to do so results in wound dehiscence and non-fusion.[9]

Dental Hygiene

Dental hygiene is addressed to remove causes of bacterial contamination such as pyorrhoea, gingivitis or dental caries. This author has custom-built dental guards made so as to provide protection of the upper and lower dentition during surgery.

Assessment of Co-morbidities

Abnormalities of the lower cranial nerves can cause brainstem dysfunction. It then becomes necessary to perform pulmonary function studies and to assess for sleep apnoea. Significant loss of glossopharyngeal, vagal and hypoglossal nerve function mandates a tracheostomy before proceeding with surgery. Likewise, the cardiac status assessment is crucial.

Oropharyngeal Cultures

Oropharyngeal cultures are obtained 3–4 days before surgical intervention. The cultures must be from the oral cavity as well as from the nasal passages. In this author's experience, no antibiotics are instituted, if normal nasal flora is present. As a precaution, Nystatin rinses and Peridex gargles are performed three times a day before the procedure.

DECISION TREE FOR TREATMENT OF CRANIOCERVICAL JUNCTION ABNORMALITIES

Bony abnormalities of the craniocervical junction can be divided into those that are reducible and the irreducible categories (Flow chart 1). Stabilisation is the primary treatment for reducible craniovertebral junction lesions. Surgical decompression of the ventral cervicomedullary junction is necessary, whe n irreducible pathology is encountered. This decompression must be made in the direction in which encroachment has occurred. Thus, the transoral-transpalatopharyngeal route is utilised when a lesion is ventrally situated.[5] The other possible approaches to the craniovertebral border are the lateral extrapharyngeal and the maxillary dropdown procedures.[11] In lateral compressions, a lateral or posterolateral approach is utilised. When dorsal compression is seen, a posterior approach is made. If instability exists following any of the situations, it is mandated that the posterior fixation be made. Thus, the factors that guide the surgical approaches to lesions of the craniovertebral junction are: (1) the reducibility of the lesion; (2) the direction of the encroachment and (3) the type of lesion.

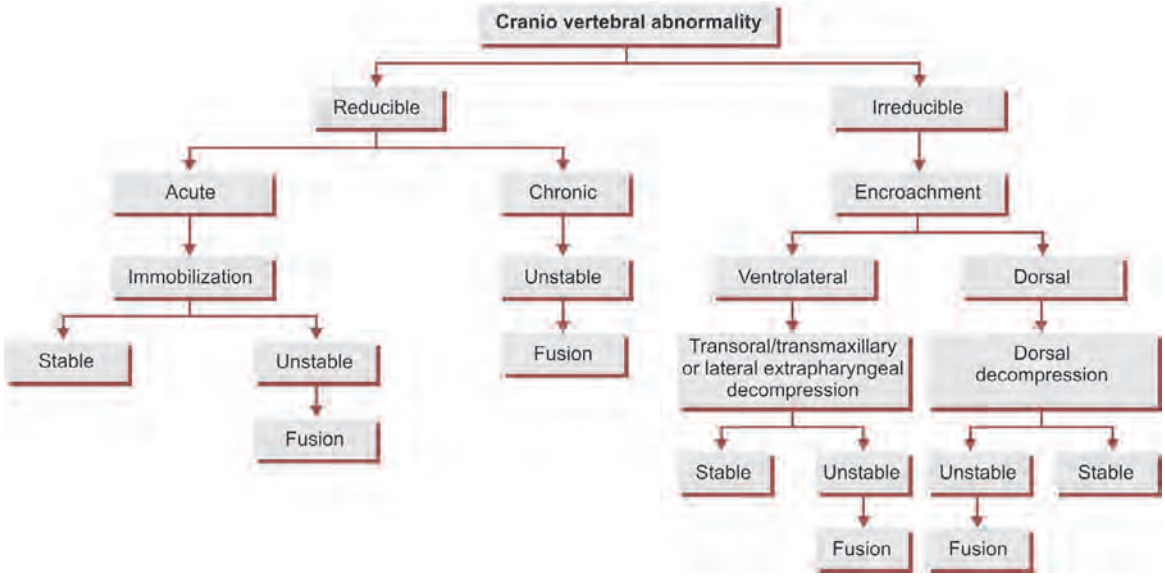
The main indication for the transoral-transpalatopharyngeal approach to the ventral cervicomedullary junction is extradural pathology and, rarely, intradural tumours.

PRE-OPERATIVE CERVICAL TRACTION

Skeletal traction is applied with an MRI compatible halo device, so as to assess the reducibility of the bony lesions. This is usually instituted 3–4 days prior to the operative procedure. Should the lesion be reducible, a dorsal fixation is all that is necessary. On the other hand, if it is irreducible, both the ventral and the dorsal procedures are carried out under the same anaesthetic. In other situations, where one knows that a grossly irreducible lesion is going to be present, the crown halo traction is placed only after the induction of general anaesthesia to stabilise the craniovertebral junction.

This author has evaluated over 5,200 patients symptomatic with craniovertebral junction abnormalities. More than 730 have undergone the ventral transoral-transpalatopharyngeal route for decompression of the

Flow chart 1: Decision tree for treatment of craniocervical junction abnormalities



cervicomedullary junction. The infection rate for this operation has been less than 1%. A dorsal occipitocervical fusion has been necessary in all individuals. Preoperative antibiotics consist of 1 gm of penicillin G started 2 hours before commencement of the transoral procedure.

A median glossotomy allows caudal exposure to the vertebral body of C4.[1,11] The lateral extent of this exposure is between the condylar canals of the hypoglossal nerve (18 mm to either side of the midline), the Eustachian tubes and the vertebral artery before it enters the intradural space. When a tumour, such as chordoma, has created the dissection, the exposure may extend as far laterally as the medial aspect of the jugular foramen. By this time, reduction of a bony lesion has already been attempted and the patient is recognised as having an irreducible ventral bony abnormality.

The ability to open the mouth and the space between the incisor teeth must be at least 3 cm. Achieving this opening is facilitated by the use of paralysing agents during the general anaesthesia.

OPERATIVE TECHNIQUE OF THE TRANSORAL-TRANSPALATOPHARYNGEAL APPROACH TO THE VENTRAL CRANIOCERVICAL BORDER

The patient is brought into the operating suite with a cervical collar in place as a precaution for the intubating manoeuvres as well as positioning. Topical oropharyngeal and nasopharyngeal analgesia is utilised and at times may be supplemented by bilateral superior laryngeal nerve blocks to facilitate fibreoptic intubation. The patient's position is guided by pre-operative dynamic studies (Fig. 3). Once the intubation is performed, the neurological status is checked in the awake patient. General anaesthesia is then administered. This author prefers not to have nasopharyngeal intubation, since it can disrupt the integrity of the high nasopharynx and obstruct the operative field.

The patient is positioned supine on the operating table with the head resting on a padded Mayfield horseshoe headrest with mild extension. Cervical traction is made at 7 lbs in the adult and 4–5 lbs in children (Fig. 4). The endotracheal tube is now secured. The nasal passages are topically anaesthetised with 4% cocaine. The laryngopharynx is occluded with a throat pack and cleansing of the oral cavity and pharynx commences.

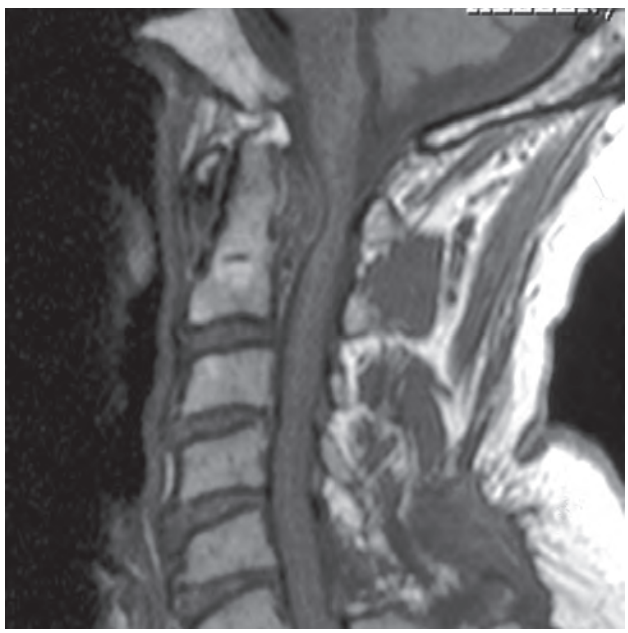


Fig. 3: Mid-sagittal T1-weighted MRI of craniocervical junction in an adult with a retro-odontoid mass, causing significant compression of the ventral cervicomedullary junction. The anatomy of the clivus and the upper cervical spine is normal. Elevation of the soft palate allows exposure from the craniocervical border to the C3 vertebral body. This patient underwent a palatal elevation and a transoral procedure

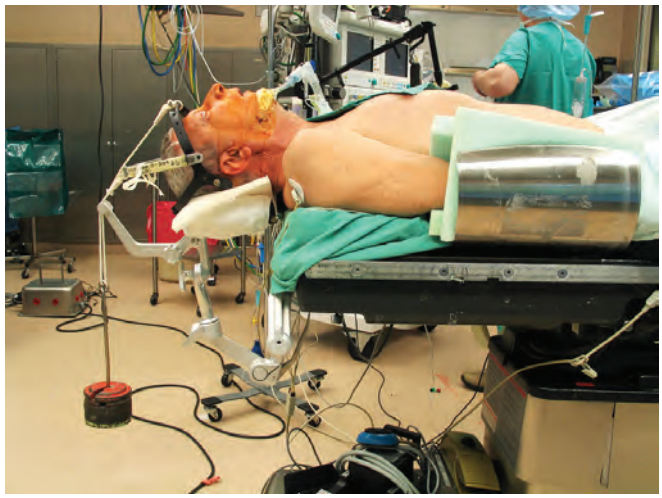


Fig. 4: The operative positioning viewed from the side. Cervical traction was applied at 7 lbs with the head resting on a horseshoe headrest and mild extension of the craniocervical junction

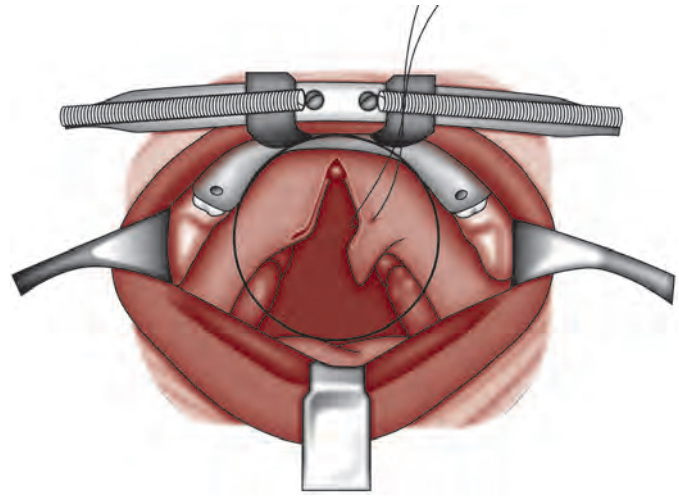


Fig. 5: Artist illustration of the transoral-transpalatopharyngeal approach. The Dingman mouth retractor is in place and the tongue blade depresses the tongue. The operative procedure through the microscope will be carried out within the circle. The soft palate has been incised

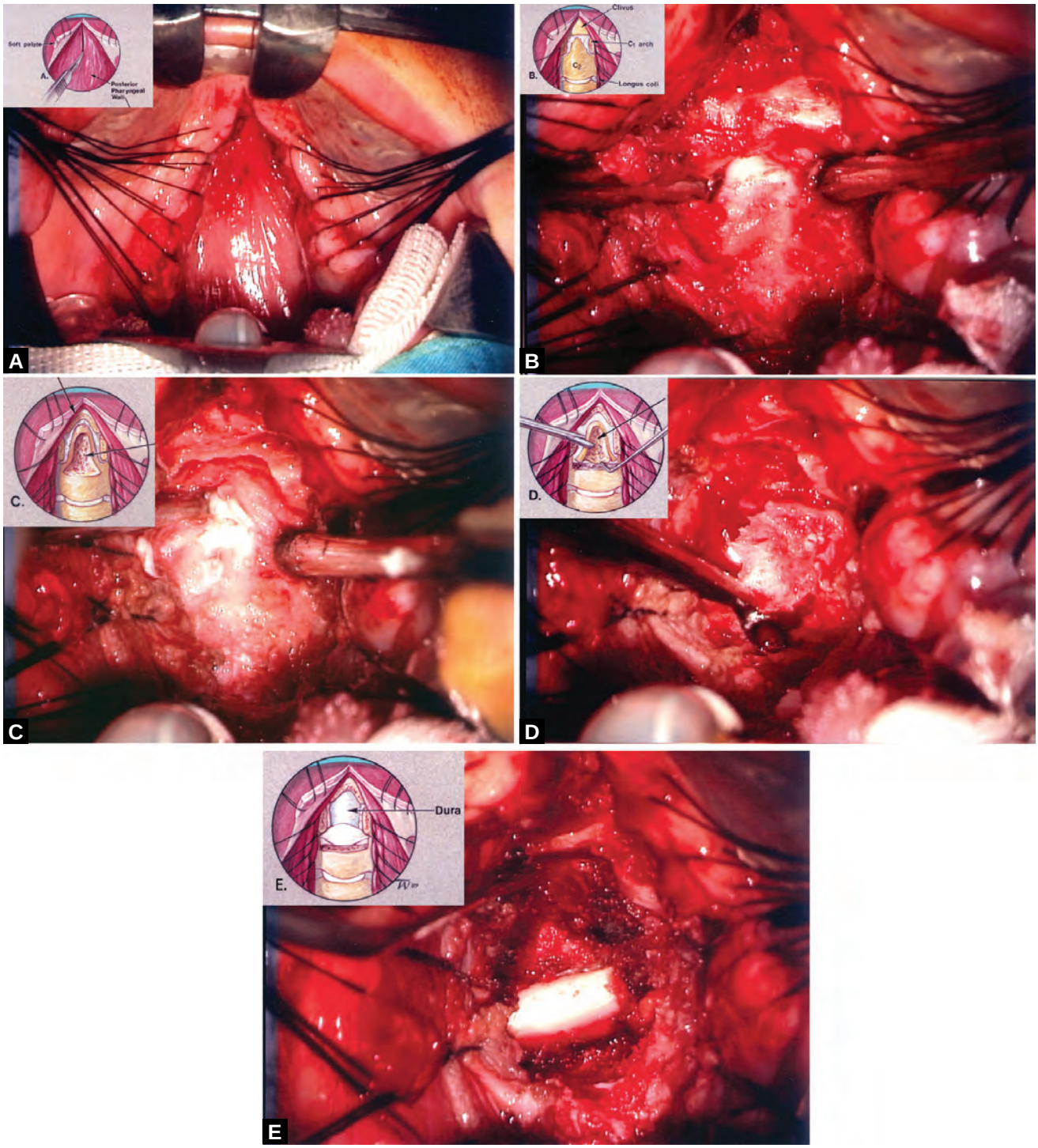
This is done with successive rinses of 10% povidone-iodine, followed by saline and then hydrogen peroxide and subsequently saline. The previously mentioned dental guards are now used over the upper and lower dentition to protect them during the operative procedure. This author prepares the right anterior abdominal wall for possible harvesting of donor external oblique aponeurosis and fat, should this be necessary, if the dura is violated during the operation. The circumoral area as well as the anterior abdominal wall are prepared and draped in a sterile fashion.

The pharyngeal exposure is accomplished with a modified Dingman mouth retractor, which has an incorporated tongue blade for automatic exposure.[6] In circumstances where the operative procedure is at the foramen magnum and above, it will be necessary to split the soft palate and at times the hard palate (Fig. 5). On the other hand, if the procedure is limited to the level of the atlas and the axis vertebra, the soft palate may be elevated by catheters attached to the soft palate via the nasal passages and secured to the soft palate on either side of the base of the uvula. The catheters are then withdrawn into the high nasopharynx to allow for exposure. A gauze pack is used to occlude the laryngopharynx. 0.5% Lidocaine solution with 1:200,000 epinephrine is injected into the median raphe of the soft palate. The microscope is now brought into the operative field for the operative dissection. The soft palate incision, when performed, starts at the base of the uvula to one side of the midline and ascends into the median raphe towards the hard palate. This author utilises stay sutures to hold apart the leaves of the soft palate and these stay sutures are attached to the Dingman mouth retractor (Fig. 6A). When exposure of the lower clivus is necessary, an extension of the midline incision is made onto the hard palate and a subperiosteal exposure of the midline hard palate is then made. The posterior pharyngeal wall is now topically anaesthetised with 2% cocaine and the midline raphe is infiltrated with 0.5% lidocaine solution with 1:200,000 epinephrine. A midline incision is then made into the posterior pharyngeal median raphe, extending from the mid clivus to the upper border of the C3 vertebra. The leaves of the posterior pharyngeal wall are now reflected laterally and folded upon themselves with stay sutures. This prevents damage to the orifices of the Eustachian tube. The prevertebral fascia with the longus colli and the longus capitis muscles are now freed so as to expose the lower clivus, the ventral surface of the atlas and the axis vertebrae (Fig. 6B). The anterior longitudinal ligament and the occipital ligaments are now, dissected free of their bony attachments. This exposes the caudal clivus, the anterior arch of the atlas, and the anterior surface of the axis body. The width of the exposure is about 3 cm. Further lateral exposure is not advised.

The anterior arch of the atlas is now removed with a high-speed drill for a width of about 20 mm. A 4 mm cutting burr is then substituted for a diamond burr using the electric drill. In situations where the odontoid process has invaginated into the posterior fossa, the inferior portion of the hard palate may require resection. This is accomplished with fine Kerrison rongeurs.

The inferior portion of the clivus is now removed by thinning of the anterior surface with the diamond burr and defining the inferior border. This now allows for separation of the circular venous sinus and the dura, as well as the tectorial membrane. It is needless to say that great care needs to be taken so as to prevent damage to the circular sinus or producing a CSF leak. The author prefers the use of fine Kerrison rongeurs for clivus resection after the thinning out has been done.

The odontoid process removal is accomplished by starting at the tip and proceeding downward. The



Figs 6A to E: (A) Stay sutures hold apart the soft palate and the posterior pharyngeal wall is now exposed. A midline incision is demarcated in the drawing to the left. (B) The longus colli and the longus capitis muscles have been retracted laterally to expose the anterior atlas arch and the base of the odontoid process underneath it. (C) The anterior arch of the atlas is now removed and a coring out of the odontoid process starts. (D) The odontoid shell is now being removed. (E) Tectorial membrane and the dura are decompressed. The odontoid removal is complete. The bright structure at the bottom of the operative procedure is the transverse portion of the cruciate ligament

odontoid process is first cored out and subsequently the lateral margins are defined using sharp curettes and rongeurs (Fig. 6C). It is essential to sharply divide the apical ligament as well as the alar ligaments with curettes. Resection of the odontoid process starts at the apex and extends into the axis body. The extent of this is dictated by pre-operative studies. Removal of the odontoid process is facilitated by the use of fine Kerrison rongeurs, as well as microcurettes and microbiopsy forceps (Fig. 6D). The removal of the pannus from behind the odontoid process and the posterior fossa is only done in a piecemeal fashion after bipolar cauterisation.

The cruciate ligament now comes into view (Fig. 6E). This author prefers to leave the cruciate ligament intact, unless it is frayed by tumour or rheumatoid arthritis. The tectorial membrane should be preserved. Cervical traction is maintained during the operation for potential, as well as inherent instability. When pannus or granulation tissue acts as a mass, this should be removed. However, once bony decompression has been accomplished, the entire removal of granulation tissue is unnecessary. This will ultimately fibrose and can aid in the healing process.

At the end of the resection, anaerobic and aerobic bacterial cultures are obtained from the depths of the wound. This author has routinely used a combination of bacitracin powder and microfibrillar collagen to layer the resection bed. The longus colli and the longus capitis muscles are now approximated in the midline with 3-0 polyglycolic sutures. A similar suture is used to bring together the pharyngeal constrictor muscles and, separately, the posterior pharyngeal mucosa.

The mucosa over the clivus is friable and delicate. There is also no muscle underneath this. In these circumstances, where the clivus is exposed, it is important to bring together the closure starting inferiorly coming up to the clivus, so that the mucosa can be brought together. A blanket of Gelfoam® is then placed over the reconstituted pharyngeal wall. At this point the throat pack is removed.

A previously tested nasogastric feeding tube is then passed via the nostril into the pharynx and thence into the oesophagus and stomach. The tube should then be secured to the ala of the nostril.

The closure of the soft palate must be made in a layered fashion. It is done by bringing together the nasal mucosa with 3-0 polyglycolic interrupted sutures. The muscle layer and the oral mucosa of the soft palate are then approximated with interrupted vertical mattress sutures. The tension in these latter sutures must be carefully assessed, so as not to be too snug. Otherwise, one will be faced with dehiscence.

A dorsal occipitocervical fusion combined with posterior fossa decompression is usually mandated and is accomplished with the same anaesthetic.[2,9]

SPECIAL CIRCUMSTANCES

Transpalatal Route

This is used routinely to treat congenital abnormalities where the clivus is foreshortened and seems to be more horizontally oriented than vertical. Removal of 1 cm of the posterior hard palate in the sagittal plane and about 8 mm to either side of the midline exposes a sufficient amount of nasopharynx and clivus. The posterior edge of the vomer is exposed. The soft palate should then be closed in a layered fashion at the end of the procedure. The author has used this exposure to get up to the mid clivus.

Median Glossotomy Combined with Transoral-Transpalatopharyngeal Approach

This procedure provides a wide caudal exposure down to the vertebral body of C4.[1,11] If combined with mandibular split, the exposure is significant along the ventral and rostral caudal dimensions. The cosmetic outcome is excellent.

Intradural Extension for Tumour and Repair of Cerebrospinal Fluid Leak

An intradural lesion at the upper cervical spine, craniocervical border or behind the clivus necessitates pre-operative recognition of the dural extension and placement of a lumbar subarachnoid drain prior to the commencement of the operation. The dural turgidity may be reduced by draining cerebrospinal fluid during the procedure. The incision in the dura is made in a cruciate fashion. The vertical component of this starts inferiorly and proceeds upwards in a rostral direction with careful cauterisation and clipping of the circular sinus at the foramen magnum. Once the intradural operation is complete, it is essential to bring the dural leaves together as much as possible. This is done with 4-0 polyglycolic sutures. It is then covered with an external oblique aponeurosis graft which is sutured to the dura. This prevents migration of the graft. Fibrin glue is now used over this. This is then backed with fat obtained from the anterior abdominal wall after which the posterior pharyngeal closure is made in the earlier described layered fashion.[7,10]

CSF tension is reduced by drainage from the lumbar subarachnoid space during and after the operative procedure. Triple antibiotic therapy consisting of methicillin, metronidazole and cefotaxime are continued for the first 5 days after operation. If no bacterial flora is present on CSF examination, the third generation cephalosporin is discontinued and the antibiotic terminated at the end of 10 days. At this point, CSF drainage is discontinued.

POST-OPERATIVE MANAGEMENT

The endotracheal tube is maintained in place for post-operative convalescence until the swelling in the oral cavity has receded. This usually stays for 3–4 days in the non-rheumatoid patient and may be longer in advanced rheumatoid arthritis. It is important to maintain caloric intake of 2,500 calories by the 3rd or 4th day. Earlier experience using intravenous parenteral hyperalimentation has led to our use of nasogastric tube feedings and has reduced our co-morbidities.

The post-operative management comprises of ventilator and respiratory care and nutrition, antibiotic regimen, pain management and immobilisation.

The vast majority of patients who have undergone the ventral procedure will leave the operating suite with an endotracheal tube in place secured to the circumoral area, intra-venous and intra-arterial lines that have been

required for intra-operative care and nasogastric feeding tube. In addition, the patient should have had a dorsal stabilisation. These individuals are then transported to the intensive care location with a soft collar in place. The halo ring that was utilised intra-operatively for traction and stabilisation is left in place if it is to be connected to a halo vest later. Otherwise this is removed.

Intra-venous penicillin G is administered for 48 hours and then discontinued. However, if wound cultures grow pathological flora, appropriate antibiotics are instituted. The Peridex and Nystatin rinses that were instituted pre-operatively now, are done at 8-hour intervals to minimise bacterial flora, especially in light of the operative procedure and prolonged intubation necessary. The dental guards are left in place to prevent inadvertent biting of the endotracheal tube. The cuffed endotracheal tube is intermittently deflated only after proper oral care is accomplished.

The tongue swelling usually recedes by the 2nd or 3rd day. The soft tissues of the retropharyngeal space are monitored with a lateral cervical radiograph. By the end of the 3rd or 4th day, when tongue swelling has receded and the pharyngeal oedema has resolved, an attempt at endotracheal extubation is made. This is carried out only with an experienced intensivist in attendance and a neurosurgeon. Prior to this, the nasogastric feedings are discontinued for at least 6 hours and the endotracheal tube cuff is deflated to detect leakage of air around the tubing. Our policy is to attempt extubation only with utilisation of a "tube exchanger", replacing the endotracheal tube. This smaller diameter exchange tube allows for satisfactory ventilation and, should it be necessary, the tube exchanger is used as a stylet for rapid reintubation.

The position of the nasogastric feeding tube placed during the operation is confirmed with appropriate chest and abdominal radiographs. It is preferable to have the feeding tube in a transpyloric location. Enteral feedings are instituted in a graduated manner at the end of 24 hours. A clear liquid oral intake is initiated by the fifth post-operative day and converted to a full liquid diet by the 10th day. By this time, the patient's caloric intake has been 2,500–3,000 calories per day. A soft diet is started at the end of the 15th day.

Post-operative immobilisation is accomplished in a soft collar until a final decision is made to either use a halo vest or an occipitocervical brace. An immediate placement of a halo vest hampers post-operative oral care as well as jeopardises extubation.

PREVENTION AND MANAGEMENT OF COMPLICATIONS

The prevention of peri-operative complications as well as delayed adverse events is described in Tables 1 and 2, respectively.

Table 1: Peri-operative complications of transoropharyngeal surgery at the craniovertebral junction; prevention and management

Complication	*Prevention/Management*
Unnecessary ventral procedure	Pre-operative reduction, if possible
Too small an oral aperture	Distance between incisors must be >25 mm May improve with administration of IV paralysing agents. May need mandible and/or tongue split or another approach
Damage to Eustachian tubes and hypoglossal nerves	Limit lateral exposure to 2 cm from midline
Inability to reach clivus for resection due to platybasia	Divide soft palate and possibly hard palate. Intra-operative fluoroscopy
Lost—cannot reach distal dens or epidural masses	Fluoroscopy. Novice may use "frameless stereotaxy". Start resection of dens from rostral end
Persistent bleeding at clivus	Bleeding from circular sinus needs fibrillar collagen/ oxidised cellulose. Else clip both leaves of dura. Pannus and arterial bleeding must be coagulated
Intra-arachnoid lodgment. CSF leakage	Pre-operative lumbar drain. Attempt dural closure. Fascia + fat + plasma glue. CSF drainage. 1 week antibiotics

Table 2: Delayed complications of transoropharyngeal surgery at the craniocervical junction; prevention and management

Complication	*Prevention/Management*
Severe tongue swelling	IV Dexamethasone; intermittent release of tongue depressor. Retain dental guards in children
Meningitis	CSF exam. Lumbar drainage. No oral intake. Antibiotics. Close CSF leak
Palatal dehiscence	Inadequate closure. Must be reclosed
Pharyngeal dehiscence	<1 week–reclosure >1 week–hyperalimentation, antibiotics
Neurological worsening	Check alignment → traction Reassess ?meningitis, ?abscess,?retained lesion. Vascular compromise ? MRI and MRA
Retropharyngeal abscess	Check for osteomyelitis and meningitis. Extrapharyngeal drainage

Contd...

Complication	*Prevention/Management*
Delayed pharyngeal bleeding	Secondary infection. Exclude osteomyelitis and vertebral artery erosion and false aneurysm MRI, CT and angiography necessary!
Velopalatine incompetence	Usually appears 4–6 months post-operative Pharyngeal retraining/prosthesis Retropharyngeal fat injection. May need pharyngeal flap
Persistent hoarseness of voice	Appears 4–6 weeks after surgery. Needs visualisation of vocal cords. Likely granulomas on cords. Needs vocal cord rest and proton pump inhibitors

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184 Reconstruction of the Skull Convexity and Base

Atul Goel, Muzumdar D

INTRODUCTION

Reconstruction is an integral part of any neurosurgical operation and must adequately be planned and performed. Pre-operative planning of the reconstruction methodology and suitably altering the operating steps is crucially important for success of the surgical procedure. Adequate reconstructive procedures are necessary to provide for rigid compartmentalisation after an elaborate skull base operation.

HISTORY

The repair of skull defects paralleled the practice of trepanation from the prehistoric neolithic time (10000–7000 BC). Gold and silver pieces corresponding to the size and shape of the skull defects have been found in the graves in Peru and skull allografts (rondells, round discs) in Neolithic Celt remains. Coconut shells were used by South Sea Islanders to repair skull defects. J. van Meekren (1670) used the first bone graft in history to repair a skull defect in a Russian with a canine bone; however, he had to remove the implant under the threat of excommunication by the church. In 1821, P. von Walther performed the first human autogenic bone graft. Macewen, in 1873, re-implanted calvarial bone, after treating them with mercury bichloride and, in 1878, he was the first to transplant a human bone allograft. In 1889, Senn wrote on repair of cranial defects with antiseptic decalcified bone. Seydel transplanted a tibial autograft with attached periosteum to repair a parietal defect. Muller and Konig, in 1890, advocated a flap of scalp periosteum and outer skull table to be swung over a skull defect. Bunge (1903) first used a fresh osteoperiosteal homograft skull. Kappis (1915) used whole ribs, Brown (1917) used split ribs and Mauclaire (1914) used ilium for cranioplasty.

The use of alloplastic material for the repair of cranial defects was popularised after the availability of various plastics and metals from the end of the 19th past century. Fraenkel (1890) used celluloid, but it was later abandoned due to cellular reactions and biodegradation over a period of time. Booth and Curtis (1893) first used aluminium, followed by Gersten (1895) using gold. Many metals have been tried since then including vitallium alloy (cobalt, chromium and molybdenum) by Geib (1941); tantalum (Pudenz and Odom—1942); stainless steel mesh used by Boldrey (1944); stainless steel used by Scott, Wycis and Murtagh (1956) and titanium used by Simpson (1965) and Gordon and Blair (1974). Black (1978) reintroduced aluminium because of its malleability, radiolucency and low tissue reactivity.

Acrylic resins became available in 1937 and Zander introduced methyl methacrylate for human cranioplasty in 1940. Spence (1954) described the one stage acrylic cranioplasty, which was widely used. Galicich and Hovind (1967) incorporated stainless steel mesh within methyl methacrylate which increased its toughness. Habal and colleagues have reconstructed cranial defects with an alloplastic combination of polyurethane terphthalate filled with autogeneic cancellous bone. Plaster of Paris (calcium sulfate hemihydrate, $CaSO_4$) has been used as a bone substitute for repair of extracranial defects since 1892. It can be used in areas of infection, is absorbable, resorbs as bone grows and acts as a binder for ceramic hydroxylapatite, which is osteoconductive and bonds to adjacent bone. However, it is brittle and has low impact resistance and tensile strength. The combination of plaster of Paris and hydroxylapatite has successfully been used to close frontal sinus defects. However, the variable resorption and limited mechanical strength of hydroxylapatite make less reliable biomaterial for cranioplasty.

Reconstruction of the skull base is a formidable task due to its location and proximity to vital vascular and neural structures. However, recent advances in craniofacial and skull base surgery have allowed surgeons to safely approach these lesions. The reconstruction of the head and neck was limited to local scalp flaps and distal pedicle flaps, such as a deltopectoral flap. The temporalis, sternocleidomastoid, trapezius and pectoralis muscle flaps have also enhanced the feasibility of basal skull reconstruction. The use of locally available materials, like the galea and pericranium, are effective measures for adequate closure. The most important advance in recent times is microsurgical transplantation using free flaps. This has allowed aggressive and complete removal of basal skull tumours without the fear of inadequate reconstruction.

ANATOMICAL CONSIDERATIONS

There are various inherent problems involved in skull base reconstruction, especially the proximity of the skull

base to potentially infective spaces like the paranasal sinuses, nasal, oral and pharyngeal pathways, external ear canal and other such spaces. After the surgery, it is important to seal off the cranial cavity from these spaces to avoid ascending infections. The basal dura is relatively thin, friable and densely stuck to the bone. Approximation of the edges and watertight suturing often may not be possible, especially in areas of vessel and nerve transit. Occasionally, following a surgical procedure, the site of CSF fistula cannot be deciphered. It is pertinent, therefore, that all the potential sites of CSF leakage be recognised during the surgery and adequately taken care of. Some tumours involve the basal bone and dura, and for achieving a radical resection these structures have to be removed deliberately. Opening up of the paranasal air sinuses, middle ear cavity and Eustachian tube, can subject the patient to risks of cerebrospinal fluid fistula. Frequently, there are large dead spaces that need to be filled in after basal bone, soft tissue and tumour resection. Many skull base procedures are of long duration. Many surgeons are involved in the operation and extensive instrumentation is used. All these factors add to the risk of infection. The reconstruction begins at the end of a relatively long operation when the operative team may be exhausted and errors of omission may be made. Some prefer a plastic and reconstructive surgical team to assist in the reconstruction.

Sometimes, persistent post-surgical or traumatic cerebrospinal fluid fistula can pose a formidable surgical challenge and super-added infection can be a life threatening condition. Familiarity with various methods of reconstruction and their satisfactory performance can be gratifying. These methods should relatively be simple to perform by the operating surgeon.

SURGICAL CONSIDERATIONS

Reconstruction of Bone Defects

Reconstruction of bone defects following skull base surgery is a controversial subject. All bone defects do not require reconstruction. The size of the defect, extent of resection of the associated structures, history of previous operative procedures, endovascular and radiation treatment are important variables that determine the appropriate reconstructive procedure. The site and volume of tumour extirpation are also important determinants in the method of reconstruction. Various methods of reconstruction of basal bone have been described. Reconstruction of bone defects in the cranial base should preferably be done with the help of bone. In sterile fields, free small or large bone pieces can be used for this purpose. Ribs, iliac crest and scapular grafts have successfully been used. Acrylic and metal plates can also be used in such a situation. Autogenous tissue such as fascia lata or allografts can be used for some tumours, which require excision of the overlying dura. In situations where there is limited bone resection for access to basal tumours, the surrounding structures will collapse and obliterate the dead space. However, if the defect is very large, there is less chance of collapse of these rigid structures and these areas will require addition of bulk for adequate obliteration. Fat grafts have been used to obliterate small defects. These grafts are devoid of vascular supply upon transplantation. Moreover, up to 60–70% of the transplanted fat can get absorbed. Necrosis is also a potential problem if the mass of the graft exceeds the ability for vascularisation. Hence, fat, as a reconstructive material, should be used only for relatively small defects. In potentially infective fields, which are more frequently encountered after a skull base operation, use of a bone flap based on a vascularised pedicle is recommended.

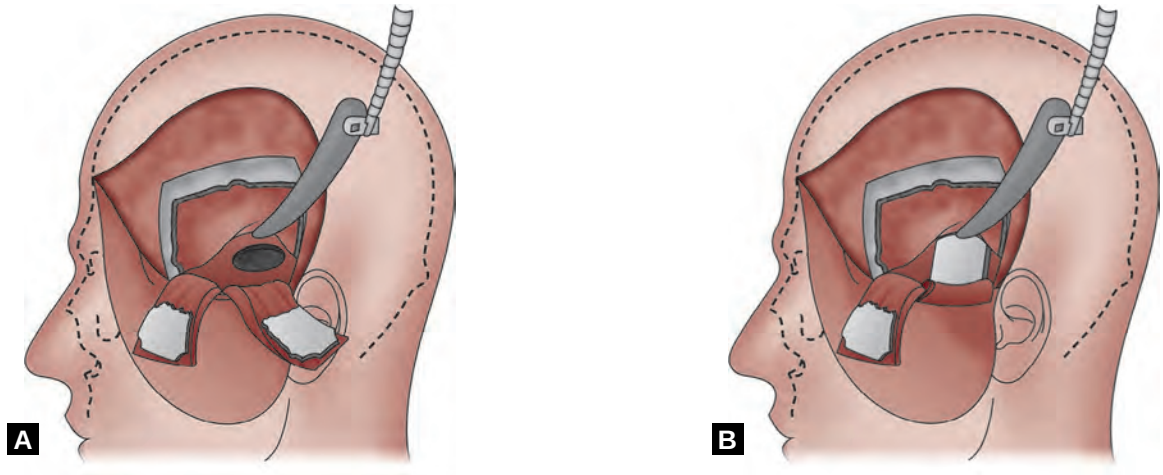
As the question of cosmesis, arthrodesis and stability are not applicable in basal reconstruction, the principle purpose of reconstructing bone defects is to avoid possible herniation of the brain matter into the aerodigestive tracts, ear, orbit or in the space resulting following resection of a large tumour or after treating a basal encephalocoele. The possibility of such an eventuality is rare and the decision regarding reconstruction of basal bone should be a calculated one. In the presence of intact basal dura even large bone defects can be tolerated without any consequence. One third to half of the orbital roof can be removed without any problem of pulsating exophthalmos. Large clival, petrous and sphenoid bone defects can safely be left unrepaired. Often it is safer not to perform bone reconstruction at the end of a long surgical procedure for the fear of infection and consequently complicating the entire surgical procedure.

Larger defects over the tegmen tympani and orbital roof should preferably be replaced with bone, as the dura in these regions is relatively thin and the region is devoid of large basal cerebrospinal fluid cisterns and consequently initially the brain pulsations can be transmitted and later the brain can herniate into these spaces. Support for brain tissue may be necessary, where large bone defects are created following the operation. Reconstruction of the bone is also carried out to support the dura and help in the provision of watertight sealing of the base and avoiding formation of cerebrospinal fluid fistulae. Protection of the brain from future injury and restoration of a reasonable appearance and quality of life are other important objectives.

Flaps

Vascularised Osteomyoplastic Flap[9]

Various experimental studies have been conducted on the use of temporalis osteomuscular flaps, as compared to calvarial free bone grafts.[1,5,7] The studies confirmed that vascularised bone flaps remain viable and are characterised by normal evolution, while free bone grafts show typical signs of necrosis and resorption. Such vascularised bone flaps based on a muscle pedicle have been used in cosmetic facial surgery and mandibular, maxillary and palatal reconstruction and mastoid

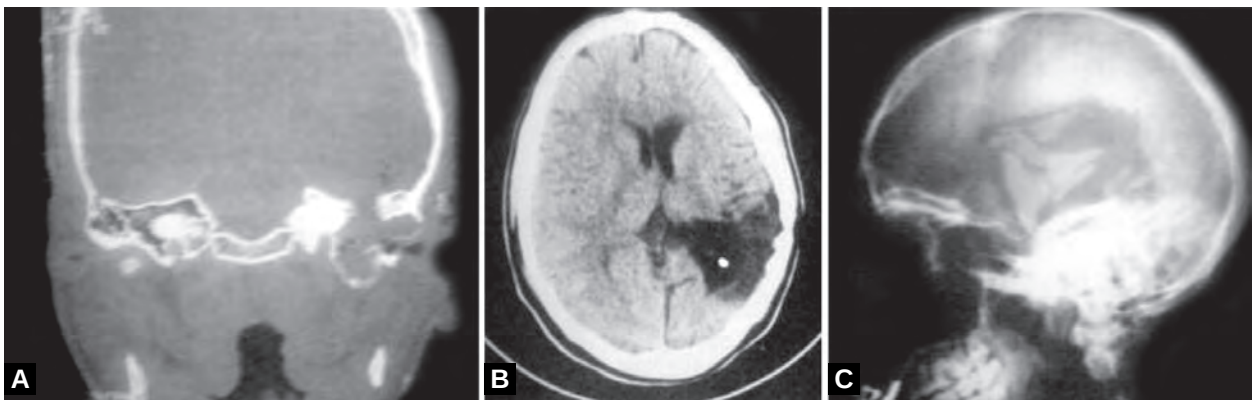


Figs 1A and B: (A) Bone defect in the middle cranial fossa on retracting the temporal brain. The temporal brain is split into two, each piece being placed on temporalis muscle pedicle. (B) The posterior piece of the temporal bone flap is rotated to fill the defect. This forms the osteomyolastic flap. The anterior piece of the temporal bone flap is replaced in the convexity

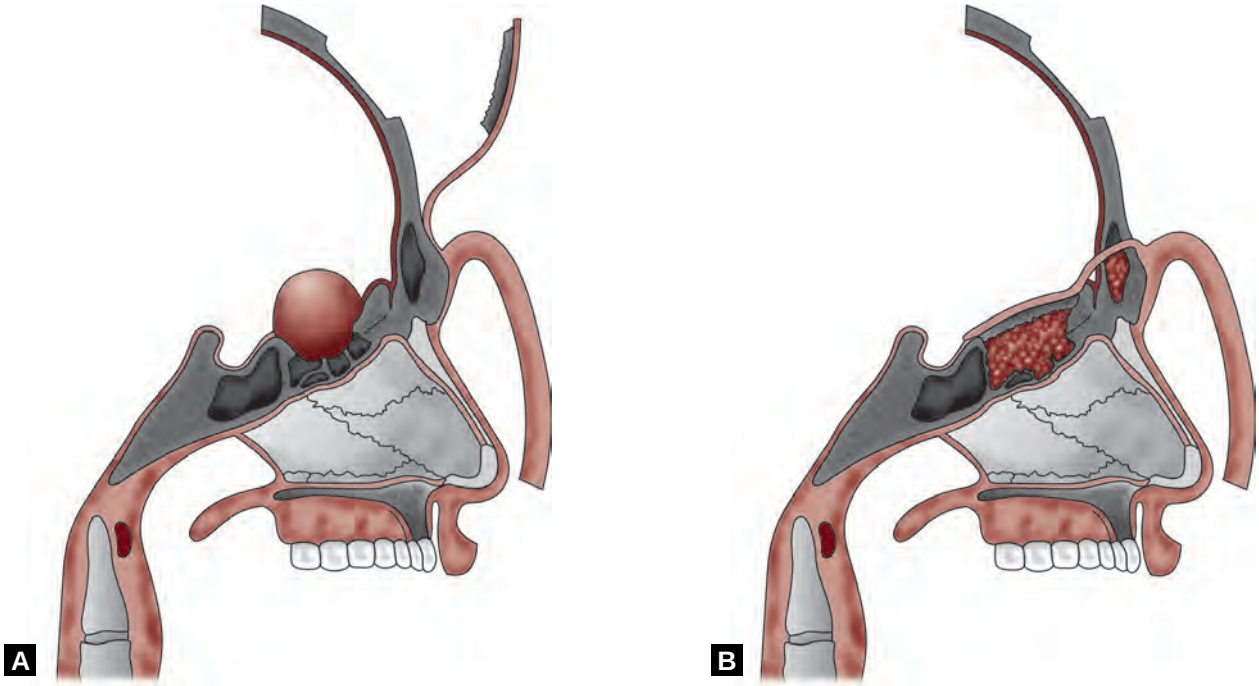
cavity obliteration.[2,4] The temporalis muscle, being in close proximity to the skull base and also the ease with which it could be rotated in various directions, can be used effectively for such an osteomyoplastic flap for skull base reconstruction (Figs 1 and 2). The temporalis muscle has an extensive blood supply to the calvarium through multiple perforators. Elevation of the bone flap with wide attachment to the muscle pedicle results in a well-vascularised flap. A vascularised bone flap can also be based on muscles of the nape of the neck. Judicious use of split cranial grafts can fill-up the resulting defects in the skull. Osteomyoplastic flaps can be used for reconstruction of middle fossa and petrous bone defects with relative ease. The fascial layers covering the temporalis muscle can be used to seal the defects in the basal dura while the muscle and bone occupy the area of bone defect. Unlike pericranial and galeal flaps, which can be raised either before or after the surgical resection, osteomyoplastic flaps, on most occasions, have to be planned and fashioned in the exposure stage of the operation. The incisions and dissection in the muscle and fascial planes are modified to avoid transection of blood supply, which could be crucial to sustain the bone flap.[13]

Pericranium Based Bone Flaps[9,10]

Pericranial and galeal flaps have been described for reconstruction of anterior cranial base and craniofacial deformities. The pericranium comprises of an outer layer of loose areolar tissue and an inner layer of osteoblasts and contains an extensive vascular network. The pericranium derives blood supply anteriorly from the supratrochlear and supraorbital arteries and laterally from the superficial temporal arteries. Pericranial layer pedicled flaps can be based on either of these vessels, and accordingly rotated anteriorly or laterally. The pericranium can sustain the calvarial flap by means of multiple small, vertical perforators. Studies have shown that calvarial flaps can safely be pedicled on the pericranial layer or



Figs 2A to C: (A) Bone window of the CT scan showing a bone defect in the tegmen. Soft tissue shadow in the petrous bone is seen. Also note air spaces in the external ear canal, petrous bone and intracranially. (B) A plain CT scan shows encephalomalacia of the parietotemporal brain and ipsilateral enlargement of the lateral ventricle. (C) Post-operative skull X-ray showing the large temporal squamous bone flap (seen end on) over the petrous bone. Bone pieces fill the bone defect created. No evidence of intracranial air is seen

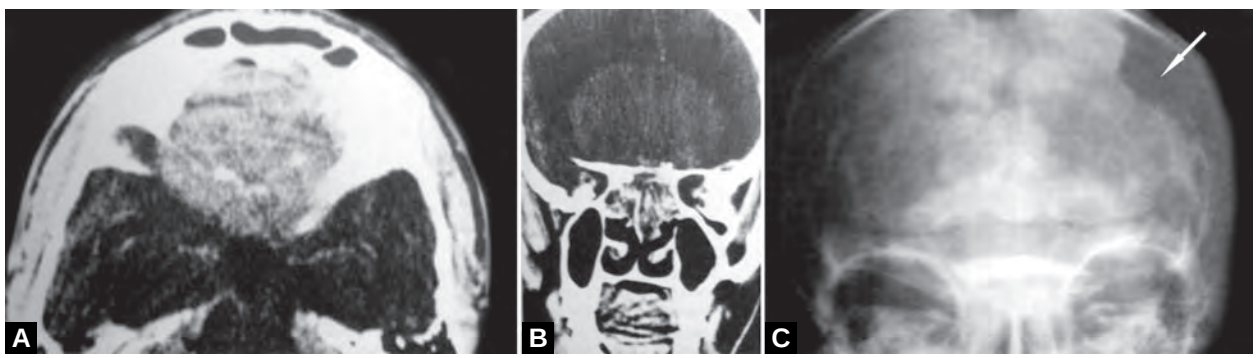


Figs 3A and B: Anterior cranial base tumour. (A) A split thickness calvarial graft pedicled on the galeopericranial layer is taken. (B) The tumour has been resected. The bone graft is placed in the resultant basal defect. Fat occupies the opened sinuses

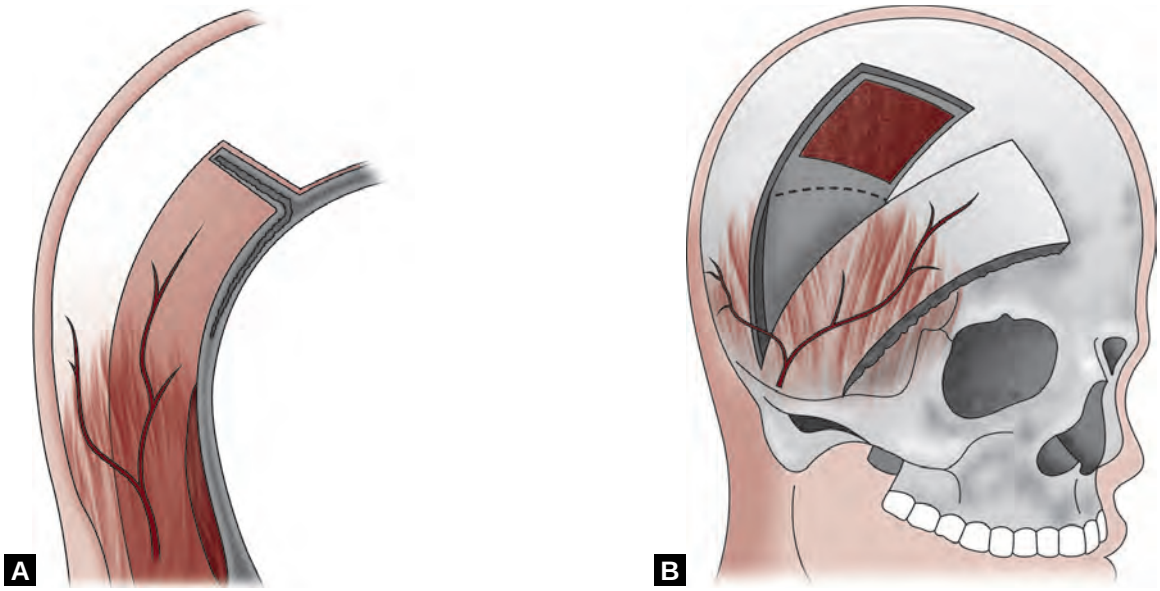
galeopericranial layer.[3,6,23,27,28] The flap can be harvested as far posteriorly as the auricular plane, giving a length of 10–12 cm. Bone flaps of the calvarium can be either of full thickness or only of the outer table. A split thickness osteo-galeopericranial flap as shown in Figures 3 and 4 can be used to reconstruct the anterior cranial fossa base. Easy availability, rotational capability, long length and close proximity to the operative area of such vascularised flaps make them ideally suited for skull base reconstruction. The bone piece can be pedicled on a large base of pericranium and can additionally be nourished by the galeal flaps. Whenever necessary, the bone flap can be turned upside down so that the bone surface is not directly exposed to the paranasal sinuses. The flap can even be sandwiched between the pericranial layers. In cases with extensive defects, an extended subgaleal fascia-pericranial temporalis flap can be first placed in the region of the defect over which the described bone flap can be placed.[12,17] Reconstruction can thus be with multiple layers of vascularised tissue. The bone piece can be fractured into two or more pieces retaining its attachment to the pericranium so that its contour can be adjusted to suit the local environment. Such vascularised flaps are more resistant to infection, tolerate radiation therapy better, are mechanically stronger, contract less and survive better in a poorly vascularised bed, when compared to free bone grafts. It is presumed that such flaps would be ideal while treating basal encephalocoeles.[20]

Long Vascular Pedicle Composite Cranial Flap[14]

The flap described is a split or full thickness cranial bone flap based on the pericranial layer, which receives its vascular nourishment from the temporalis muscle and its overlying fascial layers. The outer table of the skull bone is split, as shown in the Figure 5A, preserving the overlying pericranium. A part of the temporalis muscle

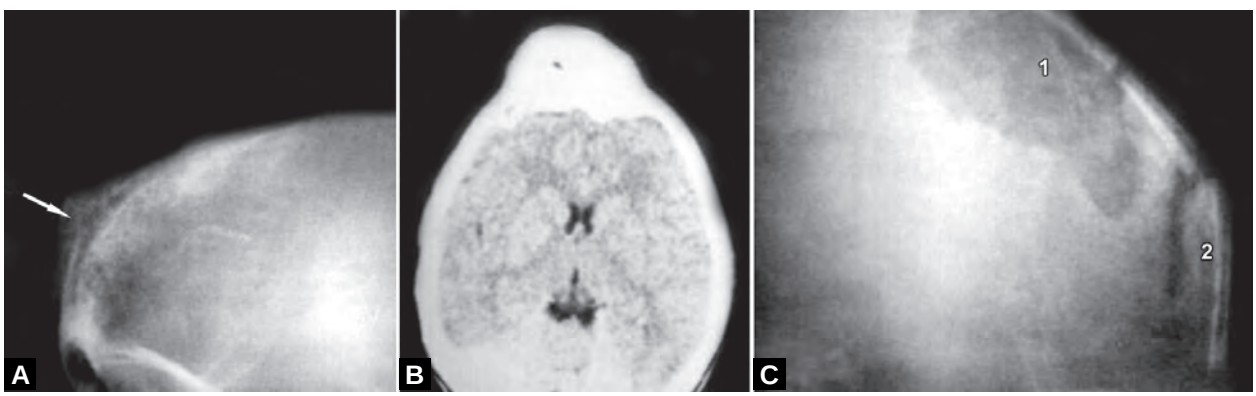


Figs 4A to C: (A) CT showing the large olfactory groove meningioma. (B) Note the involvement of the ethmoid sinuses by the tumour. (C) Post-operative skull X-ray shows that the bone flap occupies the region of the resected tumour. Arrow shows the site from where the partial-thickness split cranial graft was taken

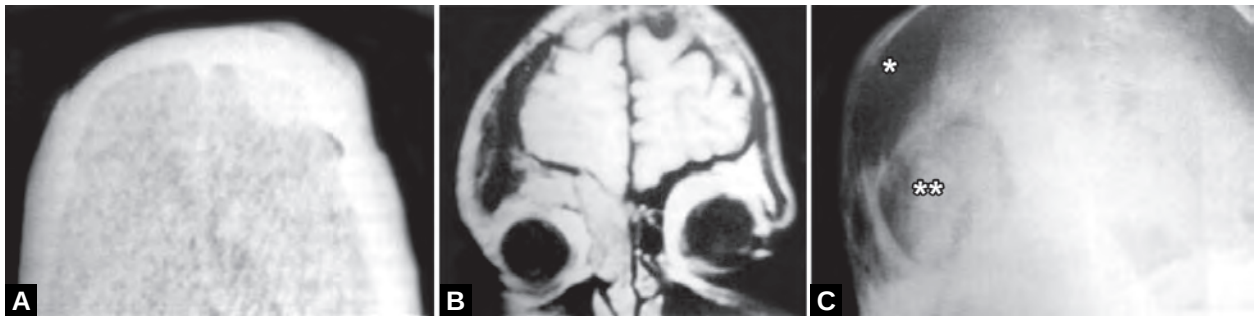


Figs 5A and B: (A) Splitting of the cranial bone. The bone flap is being elevated along with the pericranium. The temporalis muscle and its fascial envelope form the pedicle of the flap. (B) Drawing shows how the described flap will be harvested and rotated towards the site of the bone defect. The temporalis muscle had been split vertically

(and fascial layers) along with the pericranium is elevated and rotated as required (Fig. 5B). The superficial fascial layer over the temporalis muscle is a part of the pericranial aponeurosis, whilst the deep temporal fascial layer completely invests the superficial aspect of the temporalis muscle. The temporalis muscle and its fascial envelope and the pericranium receive their blood supply from the anterior, middle and posterior deep temporal and superficial temporal arteries. Subperiosteal elevation of the temporalis muscle along with the fascial layers preserves the integrity of all the major vascular supply. The split or full thickness cranial bone based on the pericranial layer and the temporalis musculofascial layer as described, results in a viable flap with abundance of vascular supply. Vertical splitting of the temporalis muscle into half or one third would still preserve at least one or two of the main feeding vessels. This splitting would not adversely affect the circulation to the flap and could help in preservation of the function of the temporalis muscle. The skull bone is thicker superior to the temporal line, which marks the attachment of the temporalis muscle. Splitting of the skull bone is easier in the paramedian parietal bone, due to the well-formed diploic channels. The split thickness graft can be broken into pieces and can be suitably contoured, preserving the attachment of the pericranium. The long length and local availability and manoeuvrability of the flap make it versatile, with great potential for reconstruction of the skull convexity and basal defects. The other advantages of such a flap include harvesting of grafts of adequate size, ease of access within the same operative field, and no or minimal post-operative morbidity and discomfort for the patient. The described flap can be used to reconstruct cranial defects where there is poor local nourishment and potentially infective fields and areas, which are cosmetically crucial (Figs 6 and 7).



Figs 6A to C: (A) Plain X-ray showing the frontal bone lesion with sunray appearance. (B) CT scan showing the large frontal bone lesion. (C) Post-operative photograph showing the transfer of the cranial bone flap from site 1 to site 2



Figs 7A to C: (A) CT scan showing the extracerebral enhancing meningioma in the frontal region with hyperostotic bone changes. (B) MRI shows the frontal lesion and its extension into the ethmoid sinus. (C) Radiograph with (*) suggesting the donor site where the cranial bone was slit and (**) showing the receptor area

Use of Bone Dust and Debris

With the use of modern craniotomes for making burr holes, a large amount of bone dust can be obtained. The bone dust can be flattened and placed in the form of a sheet over the site of defect. Small bone chips and bone debris, which is generally available during a craniotomy, can be placed interspersed in the bone dust. This forms a template over which new bone and fibrous tissue is laid and a firm, strong and resistant barrier is formed (Fig. 8).

Reconstruction of Skull Base with Free Bone Flap

Whenever possible, bone defects should be filled up with a vascularised pedicle bone flap. However, such a vascularised bone flap is sometimes not available and in this situation a free bone flap may be required. A free bone flap should not directly be exposed to the paranasal sinuses or mucosal surfaces. Whenever such a free bone flap is placed in the skull base, it should be as small in size as possible and care should be taken that it is covered on both sides with vascularised and viable soft tissue.[18,19] Such a 'sandwich' free bone flap can be placed between muscle and fascial-pericranial layers. Post-operative collection of haematoma around the bone flap should also be avoided and whenever necessary external drains can be placed. Tenting scalp stitches can be used[8] whenever possible and indicated.

Fig. 8: The bone dust obtained after drilling one burr hole has been collected in a bowl and spread into a sheet

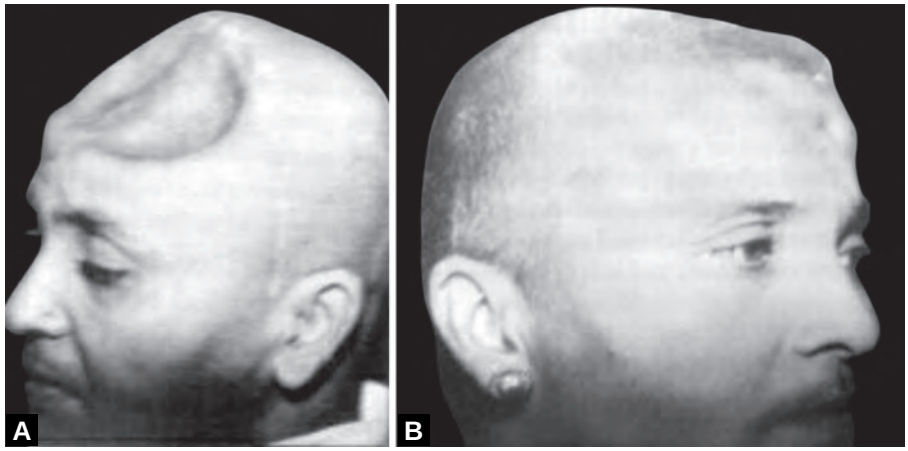
Suturing of Bone Pieces

Small bone pieces usually obtained after zygomatic and orbital osteotomy should be sutured preferably with thin wires, unbraided silk or nylon stitches. The use of miniplates, screws and an excessive volume of metal can be avoided. Placement of soft tissue in place of bone, although not consistent with the generally taught principles of reconstruction, can form a firm barrier of fibrous tissue and serve the purpose, in cases of basal bone defects. Rotation of a vascularised pedicle muscle, pericranial or fascia flap or free fat graft or muscle can be performed to occupy the area of bone defect and empty spaces.[9,10,11]

Subgaleal Preservation of Bone Flaps[15]

Convexity and basal bone flaps can be preserved in some rare situations, like brain swelling, potentially infective operative field and other such conditions, and can be replaced to the original site after a period of time. Various techniques of preservation of bone flaps have been described both inside and outside the body. The flaps have been more frequently and successfully stored in the subcutaneous plane of the abdominal wall or in the thigh (Figs 9A and B). External storage methods include deep freezing, autoclaving it while replacing, storing after radiation treatment and using antibiotic solutions.

An alternative method of preservation of the skull bone flap in the subgaleal space was found to be effective. The subgaleal plane adjacent to the site of operation is exposed widely, using blunt dissection. The bone flap is placed in this plane taking care that the curvature of the bone flap does not excessively elevate the scalp or cause tension over the scalp edges. In cases where larger bone flaps are placed in the subgaleal space, the curvature may necessitate fracturing of the bone flap in two or more pieces. The relative avascularity of the subgaleal plane helps in limiting the rate of reabsorption of the bone. The subgaleal space can be easily exposed widely, providing a large area for bone placement. Such a large and avascular space is not available elsewhere in the body. Frequently, the curvature of the bone flap matches that of the adjacent bone, which assists in the



Figs 9A and B: (A) Profile of the patient with large anterior skull base defect. The bone flap was placed in the subcutaneous fat layer of the abdomen. (B) After 18 months, the bone flap was replaced into the area of the defect resulting in satisfactory cosmetic outcome

ease of placement. The flap is placed and replaced to the original site in one operative field. As no additional incision is necessary, the procedure is quick to perform.

Use of Synthetic Material in Skull Base Reconstruction

Synthetic material is rarely required and advocated to reconstruct basal bone. Issues of biocompatibility, corrosion characteristics and metallurgic properties of the implant, its hardness and malleability and suitability of the host area to adjust to the foreign intrusion and various other factors have to be adequately analysed prior to selection of such material. Various substances including acrylic casts, plastics, glassionomer cement, silicone bars, prolene mesh and stainless steel have been used. Recently there has been a renewed interest in titanium miniplates, screws and wires. These are more commonly advocated for reconstruction of cosmetically sensitive areas such as the orbital rim, zygomatic arch and facial contour defects. Adequate reconstruction and prosthesis is necessary in patients with large and complex bone defects presenting with major functional and aesthetic disability. Adequate reconstruction is necessary and important to restore them to their accustomed way of life.

Reconstruction of Dural and Soft Tissue Defects

Fat and Free Muscle As a Packing Material

Small or large pieces of fat have been effectively used for this purpose. The fat globules get vascularised early from the surrounding tissues. Whenever free muscle is being used as packing material, it should be ground into small pieces, so that these pieces can get vascularised from the surrounding tissues. If large pieces of muscle are placed, it gets vascularised from the periphery and the central portions of the tissue can get necrosed. Such necrosed tissue can get absorbed or even pose a problem of infection. Free tissue should never be placed over free tissue, as this procedure can lead to ischaemic necrosis of the tissue most distant from the vascularised structures.

Lyophilised Dura, Gelfoam® and Fascia Lata

These dural substitutes have been used extensively and successfully for basal reconstruction. However, whenever possible, live and vascularised pedicle fascial material should be used to obtain a compact closure.

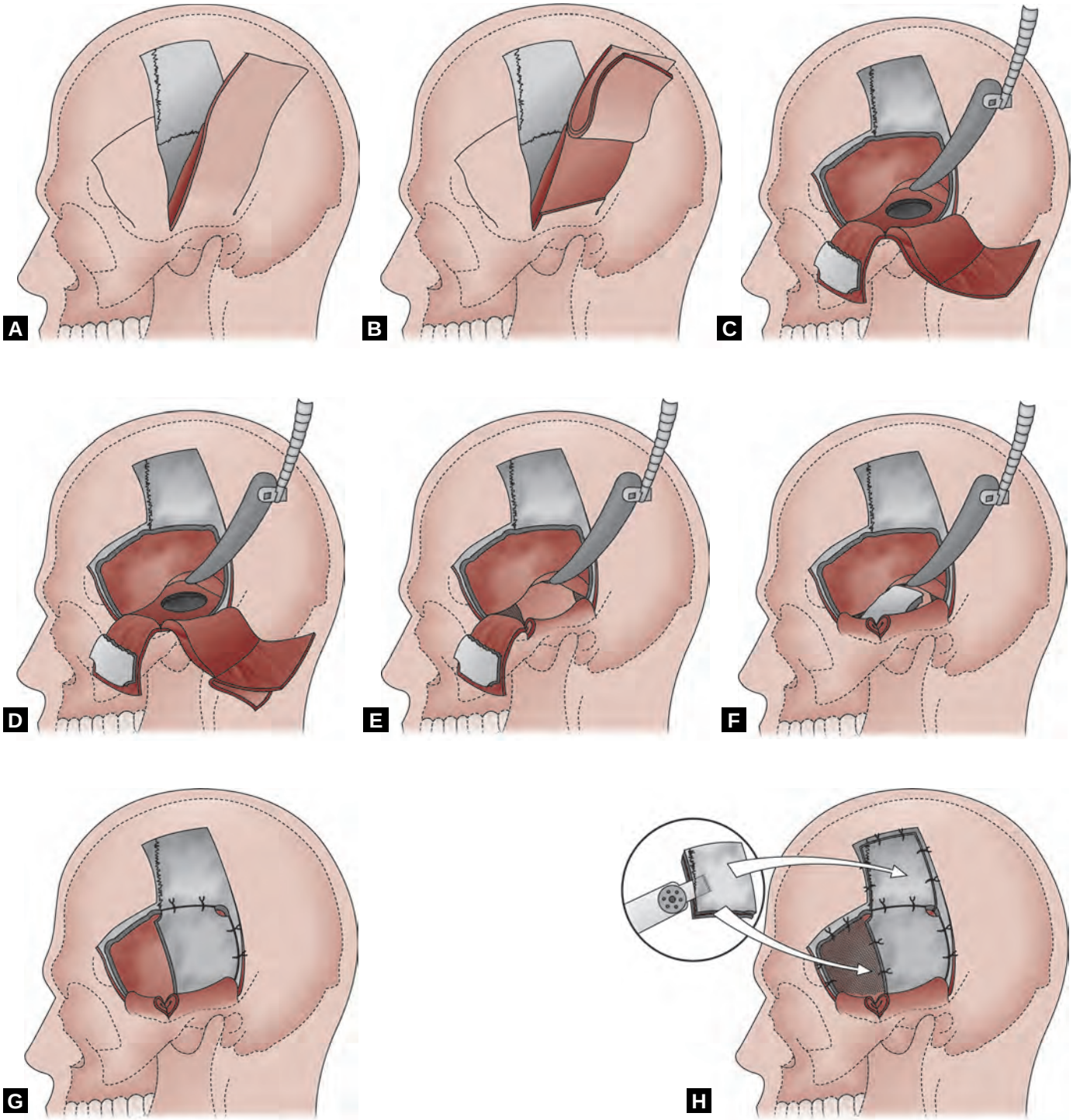
Use of Pericranial and Galeal Flaps

Pericranial and galeal flaps have extensively been used for reconstruction of basal defects. Their use is more effectively possible for reconstruction of bone and dural defects in the anterior cranial base.

Use of Rotation of Muscle Flap

Extended Vascularised Temporalis Muscle-Fascia Flap[11]

The deep layer of the temporalis fascia is everted partially over the temporalis muscle, preserving its vascularity (Figs 10A to H). A composite flap, comprising of temporalis muscle and its fascia attached along its superior border, is rotated for reconstruction of post-operative defects in the middle cranial fossa floor and mastoidectomy cavities (Fig. 10C). Partial eversion of the temporalis fascia over the muscle increases the length of the flap, while retaining its vascular pedicle. The long length vascularised pedicle flap can be used to cover defects, may be folded for bulk and may be used to carry blood supply to poorly vascularised recipient sites. The deep layer of the temporalis fascia is nourished by multiple small branches, which traverse through the muscle. Similar flaps using the thinner superficial layer of temporalis fascia have been used in craniofacial reconstruction,[3] filling up post-traumatic defects in the anterior cranial fossa and for facial reanimation.[22,24] As discussed above, the superficial temporal fascial layer is part of the pericranial aponeurosis, whilst the deep temporal fascial layer invests the superficial aspects of the temporalis muscle down to the zygomatic arch. These fascial layers have a separate arterial and venous supply and have been used as a homograft, a rotation flap or free



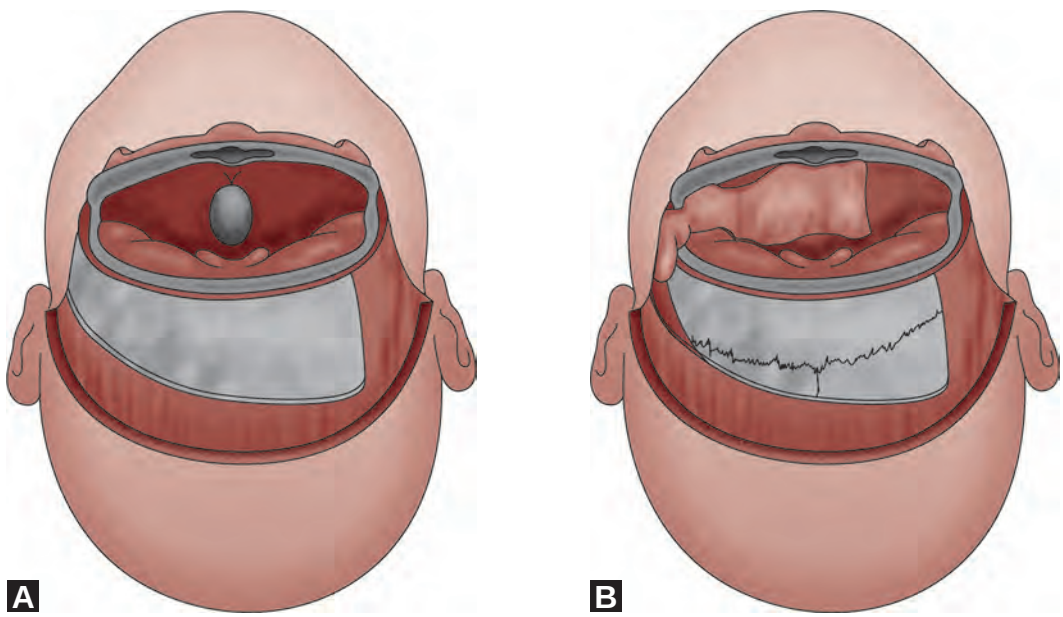
Figs 10A to H: Multilayered vascularised flap. (A) Fashioning of the flap. The temporalis muscle is split into two parts. The anterior part is used to harvest an osteomyoplastic flap (secondary flap) while in the posterior part the temporalis muscle and its fascial envelope are elevated along with the pericranial layer of the parietal bone (primary flap). This forms a long vascularised pedicled temporalis muscle-pericranial flap. (B) The deep and superficial fascial layers of the temporalis muscle are cut at the inferior aspect and rotated superiorly towards the pericranial layer. This procedure makes the distal segment of the vascularised flap relatively thick (primary flap). (C) Craniectomy. The temporal brain is retracted to expose the middle cranial fossa bone defect. The anterior half of the flap is an osteomyoplastic flap (secondary flap), while the posterior half of the flap is a long temporalis muscle-fascia-pericranial flap (primary flap). (D) The primary flap is a thick muscle fascia flap. (E) The primary flap is rotated first towards the middle fossa floor defect. (F) The secondary osteomyoplastic flap is then rotated so that it lies on the previously laid primary flap. This results in the formation of multilayer construct with vascularised pedicle falps. (G) The posterior half of the free squamous temporal bone is replaced at its original site after basal reconstruction. The anterior half of the temporal bone defect remains. (H) Parietal bone flap (from where the pericranium is harvested) is elevated and split into two halves. The temporal bone defect is reconstructed with the inner table of the bone flap (as shown in the inset) and sutured *in situ*

microvascular flap. The deep temporalis fascia is separated from the superficial by a plane of loose areolar tissue (subgaleal fascia-discussed later). The temporalis muscle and the deep layer of the fascia receive their blood supply from the anterior, middle and posterior deep temporal arteries. These vessels run between the muscle and the periosteum, and subperiosteal elevation of this fan-shaped muscle results in a viable muscle flap. The deep layer of the temporalis fascia is nourished by multiple small branches, which traverse through the muscle. Partial eversion of the deep layer of fascia with an attempt to preserve small vascular connections can result in a long vascularised flap.

Fat and free muscles have effectively been used as packing material for mastoidectomy defects. However, in some cases, particularly where there is infection in the receptor area, a vascularised pedicle graft may be necessary. Temporalis muscle can be easily rotated to cover the mastoid defects. However, the length of the muscle is not sufficient for it to be used to pack large mastoid bone defects. Also, often the thickness of the muscle restricts its rotation and it is not possible to lay it on the middle fossa base. Rotation of the muscle flap from the neck or provision of a distant muscle flap (e.g. rectus abdominis) with microvascular anastomosis, can be used in such a situation. However, an extended temporalis-muscle fascia flap provides a simple, easily manoeuvrable and locally available alternative. A similar flap can also be used for reconstruction of large defects in the middle cranial fossa base (Fig. 8).

Extended Subgaleal Fascia-Pericranial Temporalis Flap[12]

A long pericranial flap can be used to line an anterior skull base defect. The temporalis muscle is rotated along the pericranial flap and forms the vascular pedicle of the flap. Subgaleal fascia is preserved to enhance the vascularity of this long flap. Subgaleal fascia, known previously as 'loose areolar tissue layer' of the scalp and believed to be a relatively avascular zone has now been shown to have its independent and extensive blood supply entering into it at the base of the cranial vault circumferentially.[25] Casanova et al.[3] called the same layer as innominate fascia. It is a thin but well-defined trilaminar fibrous structure and discretely separable layer. The superficial temporal artery and its branches, which supply the galea, also give minute but many branches[26,27] to the subgaleal fascia, which is closely approximated to the pericranial layer. The blood supply to the subgaleal fascia is also enhanced by the vascular connections with the branches of the deep temporal arteries which supply the temporalis muscle and its fascial coverings. The pericranial layer and subgaleal fascia are continuous laterally with the superficial layer of the temporalis muscle. The pericranial layer is supplied by the perforating branches of the superficial temporal artery which traverse the subgaleal fascia and those of deep temporal arteries, which traverse through the temporalis muscle and its fascial envelope. Preservation of the subgaleal fascia and subperiosteal elevation of the temporalis muscle, along with the fascial layers, preserves the integrity of the major vascular supply to the pericranial layer. It is presumed that such a twin source of vascular supply could sustain a long length of pericranial flap. Although laterally based pericranial flaps are described for covering anterior central skull base defects, successful usage of such a flap taken beyond the midline has not been reported (Figs 11 and 12). While elevating the pericranial flap, some of the subgaleal fascia is almost always included. A specific attempt to preserve this layer by conscious and careful dissection from the galea, in an



Figs 11A and B: (A) The site from where a long subgaleal fascia pericranial flap will be harvested. (B) After rotation of the long subgaleal fascia-pericranial flap it adequately covers the site of the anterior cranial floor defect

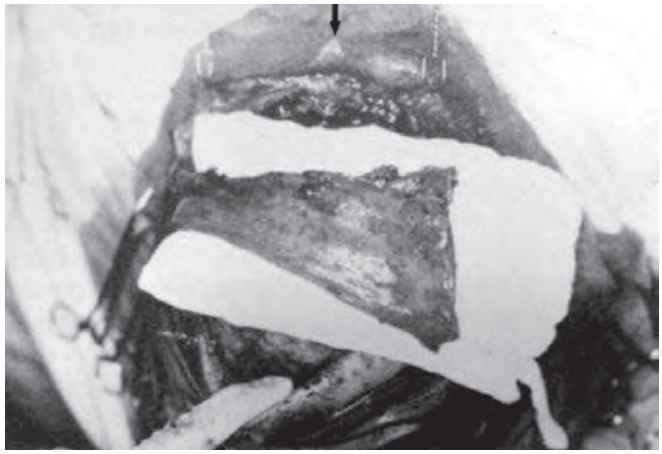


Fig. 12: Intra-operative photograph showing the extended subgaleal fascia-pericranial temporalis flap placed over the surgical mop. The exposure is basal frontal. Anteriorly, the scalp flap is everted by hooks. Posteriorly, the surgeon's index finger is retracting the scalp flap, exposing the cranial bone from where the flap is raised. Arrow indicates the midline

attempt to preserve additional vascular supply to the pericranial layer, could be critically important in long pericranial flaps, as described. Although the temporalis muscle can be used in its entirety, vertical splitting of the temporalis muscle into half or one-third would preserve at least one or two of the main feeding vessels. The described flaps can be used to reconstruct cranial defects, where there is poor local nourishment and in potentially infective fields. Relative ease of harvesting and the ability to alter the arc of rotation of this flap can be effectively used.

Temporalis Muscle and Temporoparietal Fascia

The temporalis muscle has been used for head and neck reconstruction and is a suitable muscle for lateral and anterior defects. The vascular supply to the temporalis muscle is from the internal maxillary artery. It can be used for defects in the infratemporal fossa, anterolateral skull base, orbit and maxillary regions. It is limited by its inability to reach the midline. It can be split longitudinally or rotated by subperiosteal dissection and fracturing of the coronoid process. Maintaining its muscular attachment to its insertion should preserve the venous drainage of the flap. The temporalis muscle along with its fascial coverings can be rotated along with the pericranium to form a long flap. The fascial cover of the temporalis muscle can be everted to form a thick peripheral flap. The temporalis muscle can be effectively rotated to cover middle fossa defects. The sternocleidomastoid and other muscles of the nape of the neck can be rotated superiorly to cover defects in the posterior cranial base.

Myocutaneous Flaps

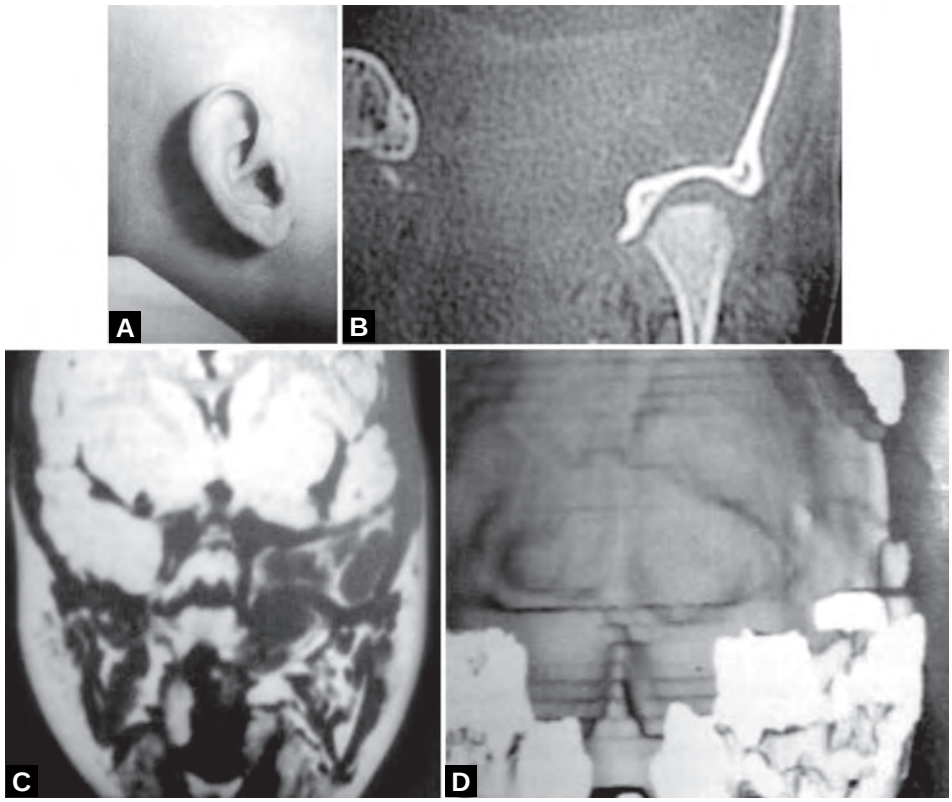
The pectoralis, latissimus and trapezius muscle can be used to raise a myocutaneous flap based on their vascular pedicles. The pectoralis muscle flap is based on the thoracoacromial vascular pedicle as it crosses under the clavicle just medial to the pectoralis minor muscle. A line, drawn from the mid portion of the clavicle to the xiphoid, delineates the path of these vessels. The clavicle can be transacted for the pedicle to gain its reach up to the cranial base. The latissimus muscle is based on the thoracodorsal vessels, which are the branches of the axillary artery. The skin paddle is designed at the anterior border of the muscle since the vascularity of the flap is safely assured at that point. The arc of rotation of the flap can be extended by transection of the humeral insertion. The pectoralis and the latissimus muscle flap have a limitation that they can deliver only a limited volume of tissue above the zygomatic arch and infraorbital rim. The trapezius flap is a versatile flap fed by the descending branch of the transverse cervical artery. The vertical part of the muscle is raised since the transverse part is required to maintain shoulder shrugging. The paravertebral perforators, which additionally supply the vertical part of the muscle, should be ligated whilst harvesting the flap. Tunnelling of the flap is avoided to prevent undue pressure on the pedicle and strangulation or kinking of the blood supply. The skin paddle is based over the muscle and can be extended past the muscle in a random manner for several centimetres. The flap is bulky and has a considerable length. Hence, it is the flap of choice for coverage over the posterior temporal fossa and the lateral and posterior skull base. It can reach up to the vertex without any difficulty.

Free Tissue Transfer/Free Flaps

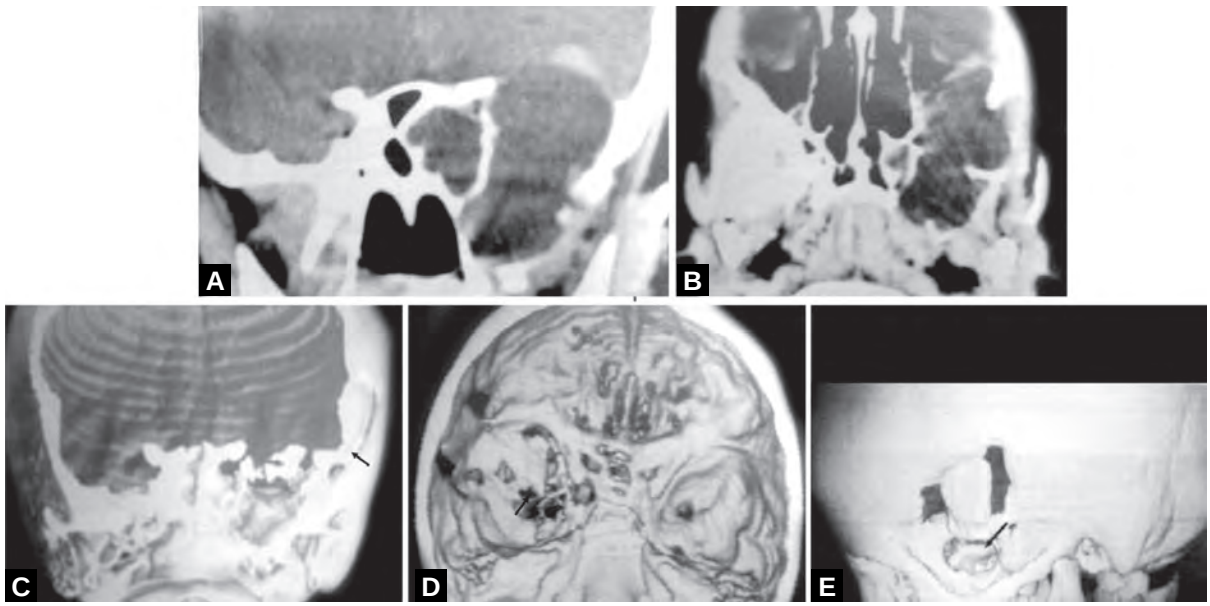
Free transfer of tissue or flaps is indicated in patients who have large geometrically complex defects of soft tissue, bone or dura following craniofacial resection, extended transtemporal bone surgery or excision of recurrent tumours. Usually they require a large volume of tissue for reconstruction. The site of defect, patient positioning for harvesting, donor morbidity, recipient vasculature and the need for an adequate pedicle length are factors to be considered. Moderate to large defects can be reconstructed using the rectus muscle or the latissimus muscle myocutaneous flap. The rectus muscle free flap is a natural choice. It is based on the deep inferior epigastric vessels which are branches from the external iliac artery and vein proximal to the inguinal ligament. The pedicle is large, usually 4–6 cm in length with an arterial diameter of 3–4 mm. The overlying skin or subcutaneous tissue provides additional bulk, if required, especially for central and irregular defects. The latissimus myocutaneous flap has less subcutaneous fat, as compared to the rectus myocutaneous flap. The radial free forearm flap is ideal for defects requiring thin tissue and enhanced vascularity. It is based on the radial artery subcutaneous perforators to the overlying forearm skin and fascia. If more bulk is required, the lower three slips of the serratus muscle can be transferred, based on the thoracodorsal vessels. Both these flaps can provide pedicle lengths of 10–12 cm.

Multilayer Reconstruction of Middle Fossa Base

Frequently there are large spaces that need to be filled after basal bone, soft tissue and tumour resection. Such spaces can be a site for haematoma or CSF loculation. Both these events may enhance the possibilities of infection and CSF fistulae (Figs 10, 13 and 14). Use of multiple layers of vascularised tissue for reconstruction not only provides a compact sealing of the defect, but by



Figs 13A to D: (A) A small swelling is seen in the external ear canal. The photograph does not clearly show the leaking CSF. (B) CT showing the large defect in the middle cranial fossa floor. (C) MRI showing the herniation of a multicystic temporal lobe into the infratemporal fossa. (D) Post-operative three dimensional CT scan showing the large defect in the petrous bone roofed almost completely by the rotated bone flap



Figs 14A to E: (A) CT showing a large defect in the middle cranial fossa floor as a result of a large epidermal cyst. (B) Axial cut showing the extent of the cyst and the bone defect. (C) Three dimensional CT, the arrow showing the rotated temporal bone flap in a multilayer construct. (D) Arrow shows the middle fossa defect covered by the temporal squamous bone flap. (E) Arrow shows the basally displaced temporal squamous bone flap

virtue of its volume helps in reducing the dead space. Two methods of multiplayer reconstruction of middle cranial base defects are shown in Fig. 10. The procedure involves use of an osteomyoplastic flap, which is placed over one of the two described types of temporalis muscle-fascia flap.

Elevation of the pericranial layer along with the temporalis muscle and fascial layers, as shown in Figures 10A and B, results in a viable flap with abundance of vascular supply. In situations where this flap is sufficiently thick, it can be used as the primary flap. Whenever the pericranial part of the flap is not very thick or for some reason cannot be harvested, a muscle-fascia flap (described earlier) can be rotated. In this method, partial eversion of the superficial and the deep layers of the temporalis fascia by cutting these two layers just above the zygomatic arch (Figs 10B to D), is performed. The peripheral part of the flap now has three fascial layers, comprising of pericranium and superficial and deep layers of temporalis fascia. This makes the distal end of the flap relatively thick. The proximal end of the flap is formed by the full thickness of the muscle. The result is a long and thick flap. This splitting would not adversely affect the circulation to the flap. The anterior or the posterior part of the split temporalis muscle can be used to harvest a vascularised pedicle osteomyoplastic flap (Figs 10A to D). This forms the secondary flap. Split or full-thickness bone can be used. The bone piece can be fractured into two or more pieces, retaining its attachment to the muscle so that its contour can be adjusted to suit the local environment. The primary flap consisting of either of the two types of muscle-fascial flap is first placed over the site of the middle fossa bone defect over which the secondary osteomyoplastic flap is placed (Fig. 10F). This forms a compact and multilayered construct of vascularised pedicle flaps. Whenever it is felt that bone replacement over the site of the defect is not essential, only soft tissue flaps could be used. The temporal bone defect resulting from basal rotation can be reconstructed with a split cranial flap, as shown in Figures 10G and H.

In most cases of middle fossa defects, a simpler method of reconstruction may suffice. However, in occasional cases with a complex defect, information about the feasibility of the described method of reconstruction may be a useful adjunct. The multilayered reconstruction, as discussed, could be performed as a radical measure, in situations where problems of CSF fistula or those related to herniation of the brain matter are anticipated or where earlier attempts at reconstruction have failed. Such a multilayered flap fashioned entirely with vascularised pedicles, by virtue of its bulk and long length can be used to cover bone defects, may be folded for bulk and may be used to carry blood supply to poorly vascularised recipient sites. In an occasional case of CSF otorrhoea, such an elaborate reconstruction could be a life saving procedure.

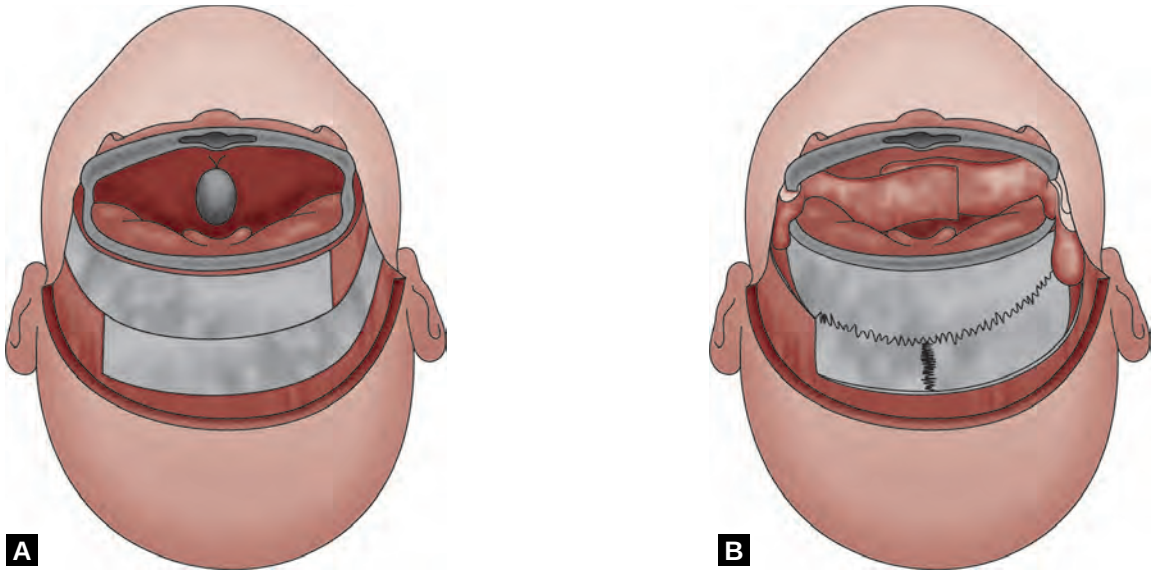
Anterior Cranial Base Reconstruction

Repair of large post-operative defects in the anterior cranial fossa is strongly recommended in the following circumstances, namely a large medial dead space, a large lateral orbital removal, thereby avoiding enophthalmos and pulsation of the eyeball, resection of the orbitofrontal rim, supraorbital margins and the frontal area for cosmetic reasons. Autogenous bone is recommended for closure of air-filled cavities of the face that have widely been opened and are predisposed to contamination. Iliac graft or split calvarial grafts have been used. Bone-dust harvested from the partial thickness burr holes behind the posterior margin of the bifrontal free flap can also be used. In reconstruction of a large portion of the anterior cranial fossa, following extensive resection of fibrous dysplasia, the dead space should be packed with cancellous bone. A cortical graft should be placed between the nasion and the clivus beneath the horizontal portion of the sellar floor, to close the ethmoidosphenoidal area. If the clivus has been removed, the graft should be placed between the floor of the sella and anterior margin of the foramen magnum or anterior arch of the atlas. Bone-dust should be packed intracranially to provide a tight closure.

Multilayer Reconstruction of the Anterior Cranial Fossa Floor[21]

Multiple combinations of flaps can be used to cover anterior cranial basal defects. Two multilayer flaps are shown in Figures 15 to 17. The flaps could comprise only of soft tissues (Fig. 15) or may include a bone piece (Fig. 16). A bicoronal incision is made and scalp flaps are reflected both anteriorly and posteriorly in the subgaleal plane. The pericranium over the frontal bosses is relatively thin and harvesting an intact pericranial flap could be difficult. Whenever such an elevation is possible, the frontal pericranium can be rotated over the defect in the anterior cranial base. Everting the posterior part of the scalp results in a wide exposure of the pericranium over the parietal or even occipital region. Harvesting a long pericranial flap, based on the temporalis muscle and its fascial cover from both sides and rotating them over the anterior cranial fossa defect, can result in a multilayer closure. The long length of the flaps can be useful in placing the flaps loosely or even double-breasting it over the defect.

Whenever it is felt that addition of bone is necessary for adequate reconstruction, a vascularised pericranial based bone flap, as described earlier, can be used. The split or full thickness bone flap can also be pedicled on a laterally based pericranial flap. A long pericranial flap is harvested from the contralateral side, as shown in Figures 15 and 16. Both these pericranial flaps (one containing bone piece) are then rotated along with the temporalis muscle and its fascial coverings. On both sides, the temporalis muscle can be split vertically to retain its function. On one side, the anterior portion of

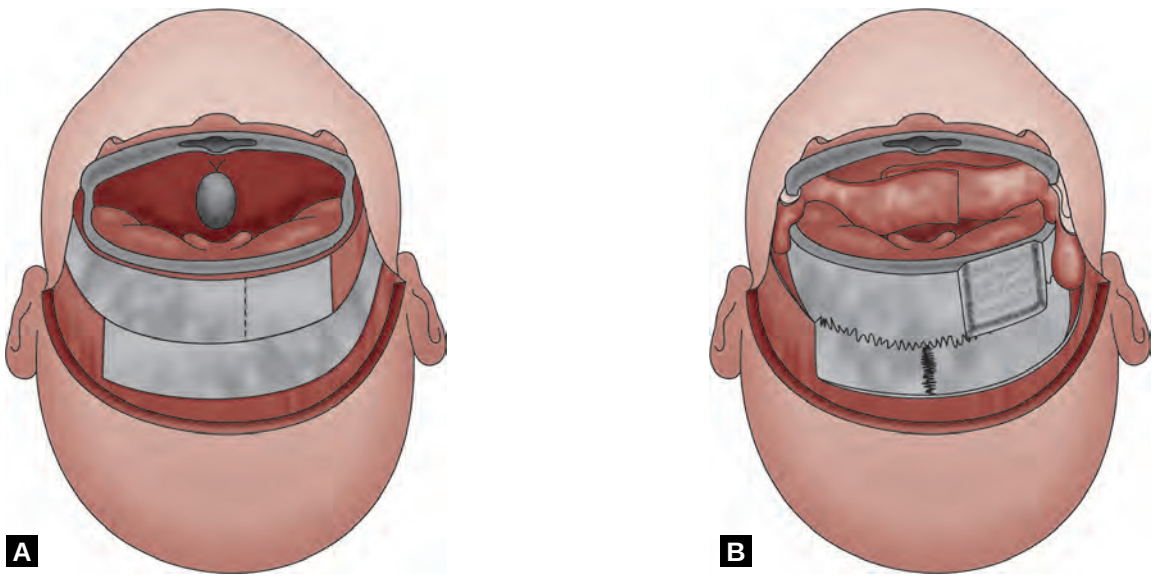


Figs 15A and B: (A) Bifrontal craniotomy. The shaded area shows the pericranial cover of the skull bone. The transverse lines show the sites of the pericranial layer incision for the purpose of harvesting the flaps. (B) The two pericranial flaps from the both sides are harvested and rotated along with the temporalis muscle towards the defect in the anterior skull base, one over the other, forming a multilayer reconstruction

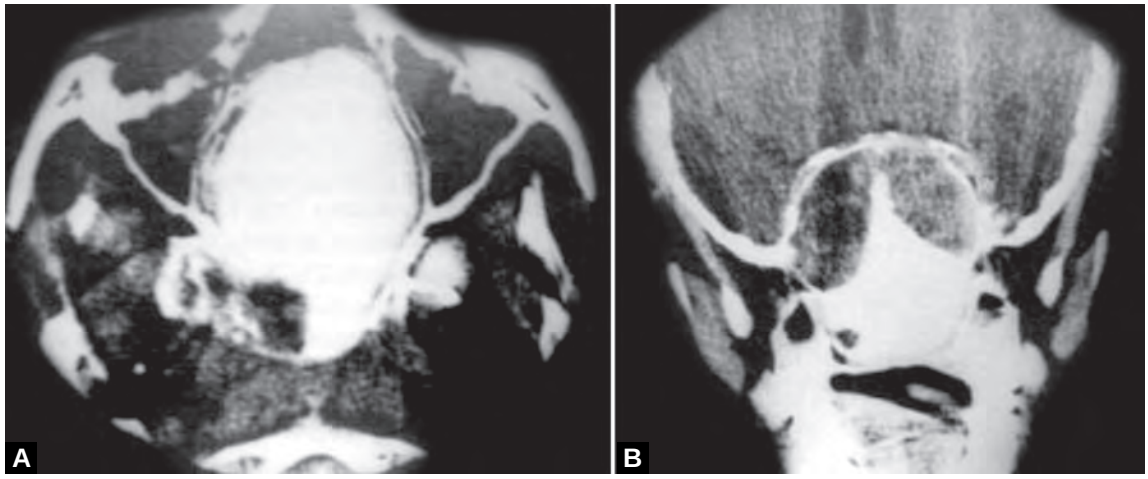
the split muscle is used as the base of the pericranial flap over the anterior parietal region, while on the other side the posterior portion of the split muscle forms the base of the pericranial flap over the posterior parietal region. A specific attempt is made to preserve the subgaleal fascia to enhance the vascularity of the designed flaps. Both these flaps are rotated anteriorly and laid down one over the other in the region of the defect in the base. The vascularised pedicle bone flap is placed superior to these flaps, so as to avoid direct exposure of the bone to the paranasal sinuses.

Use of Outer Layer of Dura As a Pedicled Flap[16]

Cranial dura is formed by two layers: (1) the outer endosteal layer and (2) the inner meningeal layer. These layers are well defined and 'separable' by manual dissection, particularly in younger individuals. Multiple small and medium sized arteries supply the dura circumferentially. The meningeal blood vessels are largely located in the endosteal layer. When preserved intact, the outer endosteal layer can be rotated and used to cover defects in the proximity. The principle advantage of using such material is that it may be used as a vascularised pedicle



Figs 16A and B: (A) The incisions over the pericranial layer. Bifrontal craniotomy is seen. Note the skull bone is split on the right side so that it can be rotated along with the pericranuim to form a vascularised pedicled bone flap. (B) Anterior cranial base multilayer reconstruction



Figs 17A and B: (A) CT showing a massive bony tumour occupying the nasopharynx, sphenoid and posterior ethmoid sinuses, which displaced the anterior cranial fossa floor including the sella, planum sphenoidale superiorly and stretched the optic nerves laterally. Multilayer reconstruction was used to repair the skull defect after tumour excision. (B) Axial view showing the large bony tumour

flap or a free graft (Fig. 18). The consistency and quality of the material matches that of the adjacent dura. Local availability and ease of rotation of this flap are the other advantages. Despite the limitations in using this flap, due to technical difficulties in separating the layers, it can be useful only in an occasional patient.

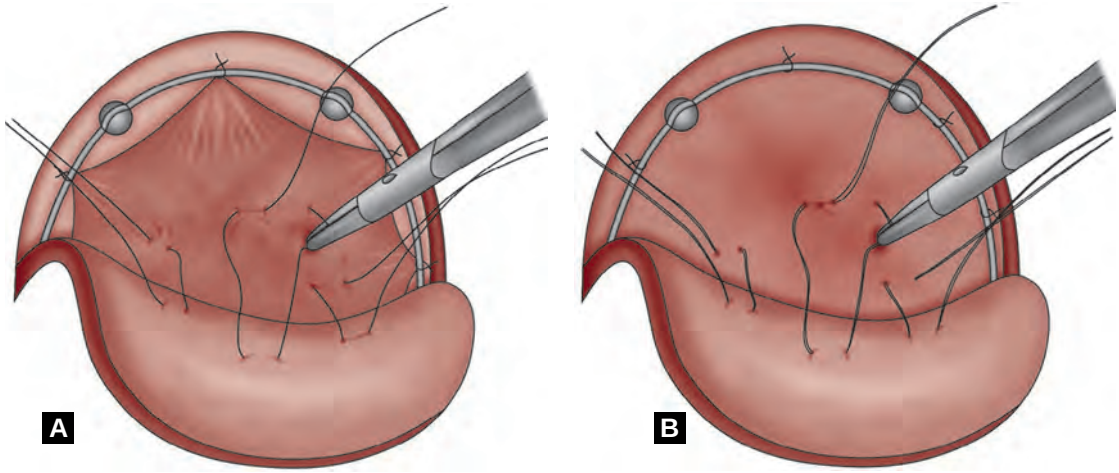
Tenting Scalp Stitches[8]

Post-operative collections underneath the scalp are common, although usually no more than a nuisance to the surgeon and the patient. However, sometimes these collections can be a source of secondary complications, such as wound breakdown and infection. Such complications are particularly relevant after a long skull base operation. The problem can occur after an osteoplastic craniotomy, when the collection develops between the galea and the pericranium or following free bone flap exposure in which case the collection is between the pericranial layer and the bone flap. Suction drains and tight head dressings are frequently used at the time of closure, to avoid this problem. Occasionally, there is a need to drain the collection and approximate the scalp layers by a large bore needle and sometimes lumbar drainage of CSF may be necessary. Suction or gravity drains often become clogged, or only approximate the layers of the scalp in a limited area. They cannot be used for long periods because of the risk of infection. Tight head dressings loosen over a period of time, can be a source of discomfort to the patient, and occasionally compromise the blood supply of the skin flap.

Fig. 18: Operative picture showing the two slit dural layers. The layer held by the stay suture is the cerebral layer, while that held by the forceps is the endosteal layer. The endosteal layer was rotated to cover the mastoid air cells

'Tenting' sutures of the dura are routine after every craniotomy. These stitches help to prevent the occurrence and expansion of extradural collections. The stitches shown in Figure 18 are similar in principle and action for the scalp. This is a simple and non-time consuming technique. The sutures help to seal surgically created space between the layers of the scalp and act as internal compression. The closer approximation of the scalp to the bone improves the vascularity of the bone, by providing an additional pathway for blood supply in the initial post-operative phase.

Technique: After adequate haemostasis, when the scalp is reflected back for closure, three to four (or more) sutures are placed between the galea and the pericranium, as shown in Figures 19A and B. The site of the sutures is carefully judged so that the scalp wound can approximate closely. It is usually easier to place the sutures at a distance of about 5 cm from the scalp incision. The greater the number of sutures placed, the more compact is the closure of the layers. It is easier to tie knots after all the sutures have traversed the layers. In case of a free bone flap, the pericranial layer is sutured to the bone flap after drilling holes in the bone. The holes used for tenting the dura in the centre of the bone flap can be used for this purpose.



Figs 19A and B: (A) Galea to pericranium stitches. (B) Galea-pericranial layer bone flap stitches. Note that the dural tenting sutures have already been placed and tied in the central bone holes

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185 Orbital Tumours

Aadil S Chagla

INTRODUCTION

- Orbital tumours are rare
- They have a wide histological variance
- Benign tumours are far more common in children
- Difficult surgical challenge despite advances
- Safe access to the orbit via the cranium.

Orbital tumours arise from several locations within the orbit and have varied aetiologies. Each of these locations is associated with its own symptomatology, epidemiology, management problems and prognostic factors. However, orbital tumours may have overlapping features in the clinical presentation and imaging findings. In order to narrow down the differential diagnosis and derive an appropriate management plan, one must have a clear understanding of the gross and microsurgical anatomy of the orbit and appreciate the displacement and involvement of various intraorbital structures in relation to the tumour. One must also have a comprehensive knowledge of pathologies of different orbital tumours, in order to treat these lesions. It may be mentioned that the term tumour here is not restricted to neoplasms but includes all space-occupying lesions.

GROSS SURGICAL ANATOMY

The orbits are highly compact three-dimensional structures, which contain vital neuromuscular structures related to the eyes suspended in a sea of fat. The orbits are cone or pyramidal shaped bony cavities, each situated on either side of the root of the nose and taper posteromedially towards the cavernous sinus and optic canal. The base of the orbital 'cone' faces anteriorly and has a very strong lateral wall. The orbits protect the eyes by providing sockets for each eyeball. The orbit can be divided into four anatomical compartments: (1) bony orbit; (2) extraconal orbit; (3) intraconal orbit and (4) globe.

Bony Orbit

The skeletal framework is made up of seven bones (Fig. 1). The lateral wall is composed of the zygomatic and frontal bones anteriorly and the greater wing of the sphenoid posteriorly (Fig. 2). The medial wall consists of thin ethmoidal, nasal, frontal and lacrimal bones, a small part of the lesser wing of the sphenoid and the

Fig. 1: Cadaveric specimen of the skull showing the right orbit

tip of the maxilla. The floor is formed predominantly by the orbital process of the maxilla. The roof of the orbit is formed by the lesser wing of the sphenoid and the frontal bone (Fig. 3). If the roof is deficient, the brain

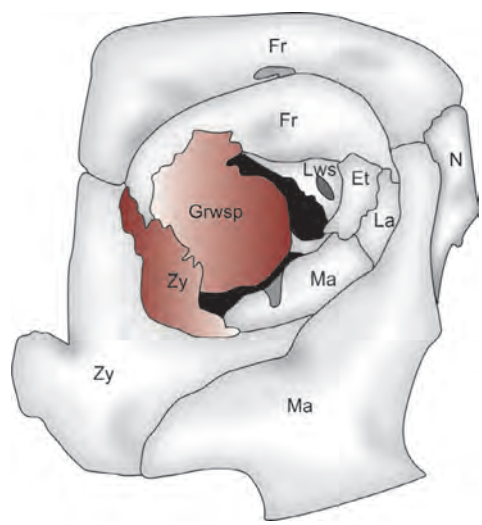


Fig. 2: Diagrammatic representation of the bony orbit showing various bones that form the orbit (Zy—Zygoma, Fr—Frontal bone, Grwsp—Greater wing of sphenoid, Et—Ethmoid, La—Lacrimal bone, Lws—Lesser wing of sphenoid, Ma—Maxilla)

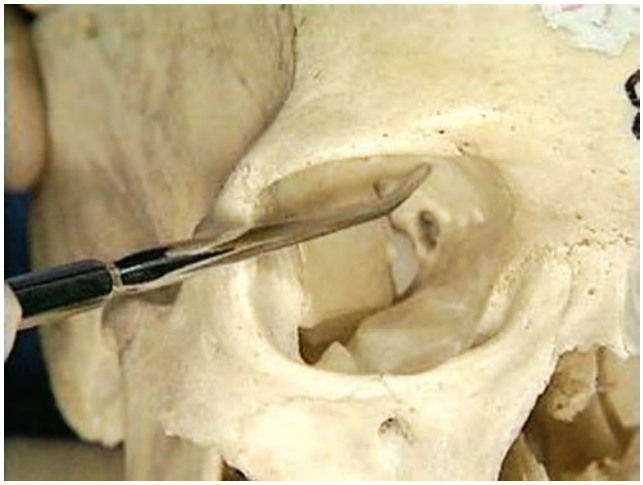


Fig. 3: Roof of the orbit; the frontal bone anteriorly and the sphenoid lesser wing posteriorly

pulsations will translate on the orbit and the pulsations will be quite evident to the clinician and the patient. The long axis of each orbit passes medially and backwards, so that their medial walls lie parallel to each other and the lateral walls are set at right angles to each other (Fig. 4).

The orbital walls are perforated by the superior orbital fissure (SOF), inferior orbital fissure (IOF), the ethmoidal foramina, the zygomaticotemporal and zygomaticofacial canals, the nasolacrimal canal and the optic canal.

The optic canal measures between 5 mm and 10 mm in length and is approximately 5 mm in height.[25] The roof of the canal is approximately 2 mm thick. The proximal opening of the canal is formed by the falciform process, a thin fold of dura overlying the optic nerve. This process is also about 5 mm long. The optic canal lies between two 'struts' or roots of the lesser wing of the sphenoid, laterally the anterior clinoid process and medially the thinner portion of the sphenoid strut. The optic nerve is approximately 30 mm in length which is 5 mm longer than the distance of the orbital apex to the posterior margin of the globe and this redundancy in the nerve allows normal movements of the globe. This laxity also allows the nerve to course around the tumour and helps preserve its function. This important anatomical fact helps protect vision and sometimes even large tumours of the orbit have little or no visual impairment.

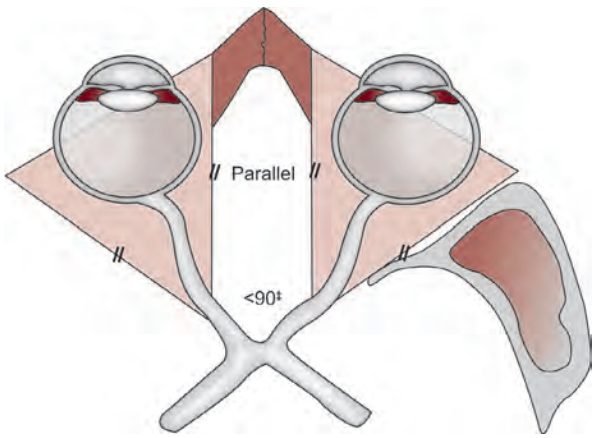


Fig. 4: The medial walls lie parallel to each other and the lateral walls are set at right angles

The SOF is bound by the lesser wing of the sphenoid bone along the superomedial margin and by the greater wing of the sphenoid on the inferolateral margin. The superior head of the lateral rectus splits this fissure into an upper part and a lower part, which is termed oculomotor foramen. The SOF is retort shaped. The bulbous end of the retort is medially placed and the thin neck directs laterally and superiorly. A fibrous ring called the annulus of Zinn surrounds the optic canal and the medial portion of the SOF. This gives rise to the four recti muscles of the orbit along with the levator palpebrae superioris and the superior oblique. These muscles pass anteriorly and attach on to the eyeball in the form of a 'cone'. The optic nerve and the ophthalmic artery enter the orbit through the optic canal. The lacrimal and frontal branches of the ophthalmic division of the trigeminal nerve, along with the trochlear nerve, enter the orbit lateral to the annulus in the SOF. The superior division of the oculomotor nerve, the nasociliary nerve (division of the ophthalmic nerve), the abducent nerve and the inferior division of the oculomotor nerve enter through the annulus (Fig. 5).

The IOF originates at the apex and extends anteroinferiorly and transmits vessels and nerves into the infratemporal and pterygopalatine fossae.

Periorbita

The periorbita is the periosteum of the orbit and separates the bony orbit from the extraconal orbit. The periosteum of the orbit lines the orbital bone from within and is continuous with the intracranial dura. The pia and arachnoid of the optic nerve are fused with the dura

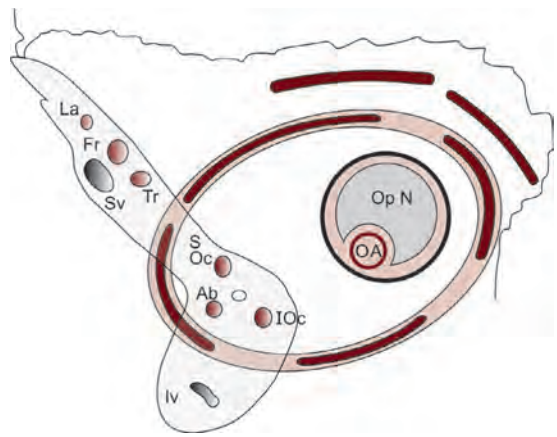


Fig. 5: Diagrammatic representation of the superior orbital fissure (SOF) (La—Lacrimal nerve, Fr—Frontal nerve, Sv—Superior ophthalmic vein, Tr—Trochlear nerve, SOc—Superior division of oculomotor nerve, Ab—Abducent nerve, Nc—Nasociliary nerve, IOc—Inferior division of oculomotor nerve, Iv—Inferior ophthalmic vein, Op N—Optic nerve, OA—Ophthalmic artery)

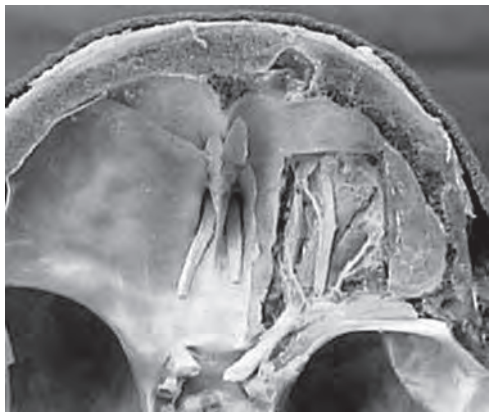


Fig. 6: Cadaveric specimen showing the structures of the extraconal orbit

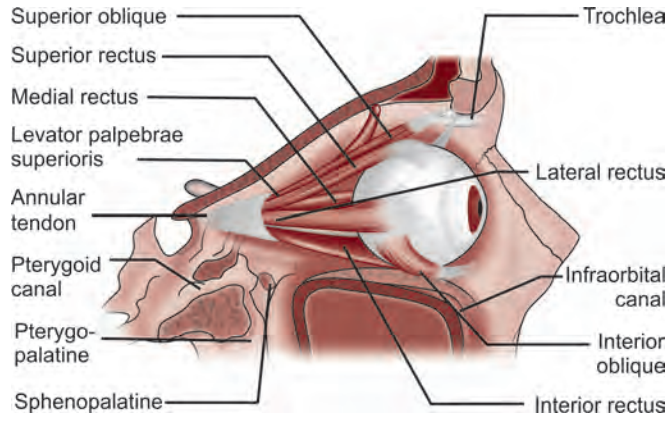


Fig. 7: Muscles forming the intraconal orbit

at the fibrous annulus of Zinn dorsomedially and ventrally. Since the dura is continuous with the periorbita at the SOF, it is difficult to eradicate tumours at the orbital apex which are adherent to the dura/periorbita without compromising neural functions.

Extraconal Orbit

The principal content of this compartment (Fig. 6) is the orbital fat. The frontal nerve and the lacrimal nerve, which pass through the SOF lie on the superior surface of the levator palpebrae superioris. The trochlear nerve is the only nerve which supplies an extraocular muscle and is extraconal in location. It enters the muscle as a series of branches quite posteriorly. This compartment also contains the lacrimal gland. It is divided into a larger orbital and a smaller palpebral part. The orbital part is encased superiorly by the lacrimal fossa and inferiorly by the aponeurosis of the levator and the lateral rectus. The palpebral part lies under the aponeurosis of the levator and over the conjunctiva of the superior fornix.

Intraconal Orbit

The orbital apex is the most posterior part of this compartment (Fig. 7) and contains the most important structures passing through it. The external ocular muscles originate from the common tendinous ring or the annulus of Zinn. The annulus encloses the optic canal and the oculomotor foramen. Various structures which enter through the optic canal include the optic nerve with its meningeal and arachnoid coverings, the ophthalmic artery and a sympathetic plexus. At first, the ophthalmic artery is below and lateral to the optic nerve. Within the orbit, it first lies between the lateral rectus and the optic nerve. It then crosses over the nerve and lies below the superior rectus muscle. As it reaches the medial wall of the orbit, it is accompanied by the nasociliary nerve. It then divides into various branches. The central retinal artery is the most important branch and is given off 5–10 mm behind the globe and enters the optic nerve from its inferomedial side.

The blood supply of the intraorbital portion of the optic nerve is from the tight vascular plexus in the pia matter. This pial network arises primarily from the arterial perforating branches from the posterior ciliary arteries, which are posterior to the entry of the central retinal artery into the optic nerve. A second contribution to the pial network is from the recurrent branches of the long and short posterior ciliary arteries. A third contribution is from the central retinal artery.[12]

The structures entering through the oculomotor foramen include the superior branch of the oculomotor nerve, abducent nerve, nasociliary nerve and the inferior branch of the oculomotor nerve, in that order. The superior division supplies the levator and superior rectus, while the inferior division crosses below the optic nerve to supply the medial and the inferior rectus. This arrangement of the nerve supply makes the approach to the optic nerve from the medial compartment extremely safe and easy. All nerves supplying the muscles enter the internal surface of the muscles at their posterior third. The ciliary ganglion lies between the lateral aspect of the optic nerve and the lateral rectus in the posterior orbit.

The optic nerve is the principal constituent of this compartment. It is 4.5–5 cm long and about 4 mm in diameter. It has four portions, namely intraocular, intraorbital, intracanalicular and intracranial.

Globe

The globe is the "raison d'être" of the orbit. All constituents of the orbit ultimately contribute to the optimal function of the globe. There is a fascial sheath, Tenon's capsule which invests the globe snugly. A third of the globe lies outside the orbit. There is a connective tissue network spanning the entire orbit. The anterior part is the Tenon's capsule which surrounds the globe. The connective tissue septa around this condense into various suspensory ligaments and also get attached to the periorbita. The orbital septum is the anatomic boundary of the anterior orbit and originates from the thick periorbita of the orbital rim called arcus marginalis. The orbital fat is held in its posterior position by this septum.

The orbital spaces are divided into: (a) sub-periosteal space; (b) the peripheral surgical space; (c) the central surgical space and (d) Tenon's space. These spaces correspond with the compartments defined above. This concept of compartmentalisation of the orbit is immensely helpful in dealing with orbital tumours and planning the surgical approaches.[22]

TYPES AND INCIDENCE OF ORBITAL TUMOURS

Orbital tumours are rare. Table 1 describes histologically proven primary orbital tumours, operated upon from 1995 to 2007 at the King Edward VII Memorial Hospital, Mumbai. The list of tumours is only of primary orbital tumours. Not included in this list are pseudo-tumours and skull base malignant tumours, such as sinonasal carcinomas and other tumours that have secondarily invaded the orbit. The most common malignant tumour in an adult population in any large series of orbital tumours is a metastatic tumour.[27] In our series, metastatic tumours are far less due to the referral pattern. The low incidence of optic nerve gliomas and capillary haemangiomas, noted in this series, is because these patients are often observed and have not undergone surgery (Table 2).

Table 1: Total number of cases operated at the King Edward VII Memorial Hospital, Mumbai, Maharashtra, India

Year	*Total number of cases*
1995 to 2007	148

Sex distribution

Sex of the patient	*Number of cases*
Male	79
Female	69

Table 2: Histological distribution (Surgically treated patients at King Edward VII Memorial Hospital, Mumbai, Maharashtra, India between 1995 and 2007)

Histopathology	*Cases*	*Percentage*
Benign Tumours		
Neurofibroma	25	16.89%
Meningioma	21	14.18%
Haemangioma	15	10.13%
Lymphangioma	09	06.08%
Optic nerve glioma	09	06.08%
Granuloma-Tuberculoma	07	04.72%
Lacrimal gland adenoma	06	04.05%
Fibrous dysplasia	05	03.37%
Dermoid/Epidermoid cyst	05	03.37%
Fungal granuloma	04	02.70%
Haemangiopericytoma	03	02.02%
Eosinophilic granuloma	02	01.35%
Juvenile ossifying fibroma	02	01.35%
Capillary haemangioma	01	0.67%
Total	114	77.02%

Contd...

Contd...

Histopathology	*Cases*	*Percentage*
Malignant Tumours		
Adenoid cystic carcinoma	08	05.40%
Lymphoma	06	04.05%
Rhabdomyosarcoma	05	03.37%
Squamous cell carcinoma	04	02.70%
Non-Hodgkin's lymphoma	02	01.35%
Malignant invasive meningioma	02	01.35%
Retinoblastoma	02	01.35%
Neuroblastoma	01	0.67%
Granulocytic sarcoma	01	0.67%
Mesenchymal sarcoma	01	0.67%
PNET	01	0.67%
Germinoma	01	0.67%
	34	22.97%
Total	**148**	

CLINICAL FEATURES OF ORBITAL TUMOURS

Orbital tumours produce symptoms and signs by compression, infiltration and/or infarction of the orbital structures. Sometimes, they act as mass lesions producing only proptosis. Occasionally, they may produce limitation of eye movements. They may also produce neuro-ophthalmological symptoms and signs through their effect on:

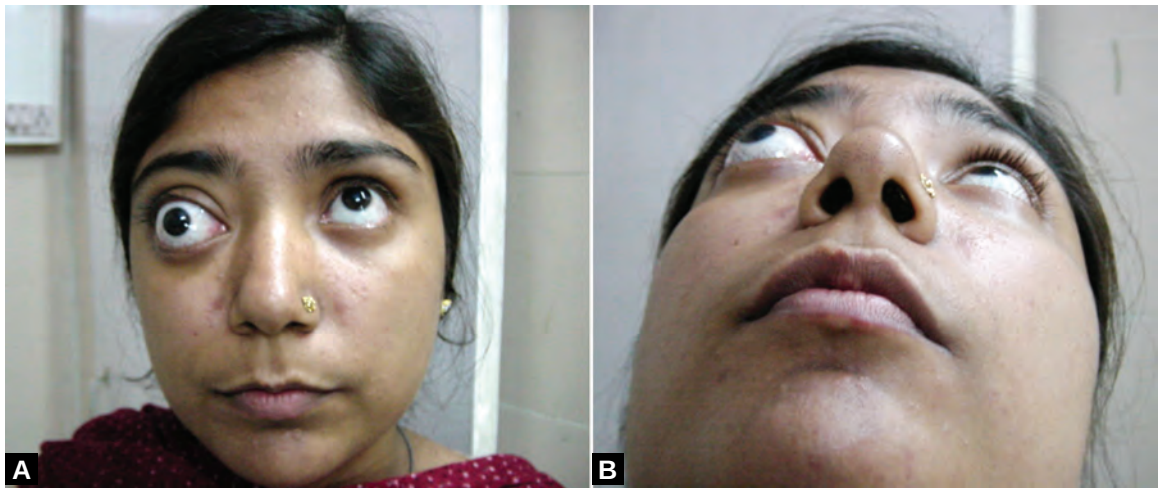
- The optic nerve.
- The ocular motor nerves.
- The orbital branches of the ophthalmic division of the trigeminal nerve.
- The nerve supply to the iris sphincter and dilator muscles.

Proptosis

Most orbital tumours produce some degree of proptosis (Figs 8A and B). Optic sheath meningiomas may take up little room in the orbit and may produce minimal proptosis but present early with visual complaints. On the other hand, vascular tumours, which are soft in consistency and can become quite large, produce significant proptosis. Tumours located within the extraocular muscle cone, e.g. haemangioma, optic nerve glioma, meningioma, are more likely to produce axial proptosis (the eye is pushed directly forwards), while tumours outside the muscle cone, e.g. dermoid cyst, neurinoma, lacrimal gland tumour, tend to push the eye out or in a direction opposite to that of the lesion. Proptosis can also be caused by lesions outside the orbit, e.g. cavernous sinus, when the venous flow is impaired. Pulsatile proptosis may occur in vascular lesions or when the roof of the orbit or the sphenoid bone is deficient.

Optic Neuropathy

Vision is generally impaired with tumours involving the optic nerve namely optic sheath meningiomas[35,42] and optic nerve gliomas.[43] Benign tumours of the orbit, such



Figs 8A and B: Proptosis

as neurofibromas and haemangiomas tend to produce visual deficits only when they are of large size and have been symptomatic and have been present for a while.[11] Malignant lesions often produce visual deficits.

Visual field involvement may be subtle, i.e. enlargement of the blind spot and slight peripheral field constriction. The optic disc will show swelling and would appear similar to unilateral "papilloedema" from increased intracranial pressure (ICP). Hence, the term unilateral optic disc swelling is preferred and the term papilloedema restricted to disc swelling which results from raised ICP.[28]

A second form of presentation of orbital tumours is that of unilateral transient visual loss.[4,39] This may occur only in certain positions of gaze and immediately clears when the direction of gaze is changed. Either direct pressure on the optic nerve or interruption of the blood supply is the explanation for this phenomenon. Chronic compression of the intraorbital portion of the optic nerve will produce:

- Loss of vision.
- Optic disc swelling that resolves into optic atrophy.
- The appearance of optociliary shunts veins.

This is often seen in spheno-orbital meningiomas,[1,9,44] but may also occur in cases with optic nerve gliomas.[14,17]

Ocular Motor Nerve Paresis

The three ocular motor nerves enter the orbit through the SOF. Each of these nerves may be involved resulting in varying degrees of diplopia. Tumours that are located at the orbital apex may involve the ocular motor nerves early, before they are large enough to produce proptosis. The ophthalmoparesis that is produced by orbital tumours is indistinguishable from that produced by intracranial lesions. Ophthalmoplegias are most common in malignant tumours of the orbit, metastatic carcinomas or lymphomas, although optic nerve gliomas, neurinomas, haemangiomas and lymphangiomas can also produce it.

To differentiate diplopia due to oculomotor nerve paresis and muscle involvement due to mechanical restriction of ocular movement can be gauged by the following:

- Intraocular pressure increases substantially when the patient attempts to look in the direction of gaze limitation[32,34,45] The intraocular pressure measurements are performed using a pneumatic tonometer,[34] although any instrument may be used.
- Forced duction (or traction) testing can also be used to detect mechanical limitation of motion. An attempt is made to move the eye forcibly in the direction of gaze limitation. As described by Jaensch,[18] this test is performed as follows. The cornea is anaesthetised using several drops of a topical anaesthetic such as proparacaine or tetracaine hydrochloride. The conjunctiva is further anaesthetised by holding a cotton swab or cotton-tipped applicator soaked with 5–10% cocaine against it for about 30 seconds. The conjunctiva is then grasped with a fine toothed forceps near the limbus on the side opposite to the direction in which it is to be moved. The patient is instructed to try and look in the direction of limitation and an attempt is made to move the eye in that direction (i.e. opposite that in which mechanical restriction is suspected). If no resistance is encountered, the motility defect is not restrictive; however, if resistance is encountered, then mechanical restriction does exist. In some patients, particularly those who are co-operative and have substantial limitation of movement, the forced duction test can be performed simply by asking the patient to look in the direction of limitation and then attempting to move the eye, by placing a cotton-tipped applicator stick against the eye on the opposite side, just prior to the limbus.[37]

Pain

Tumours that involve the orbit are generally not painful. Neoplasms causing pain are likely to be malignant.

Inflammation causes severe pain and one can confidently predict neural infiltration at the orbital apex and cavernous sinus, when there is ophthalmoplegia and pain together.[2,29,30,38,40,41]

Pupillary Abnormalities

It is theoretically possible that patients with an orbital tumour could develop either a Horner's syndrome from damage to the oculosympathetic pathway that supplies the iris dilator muscle or a tonic pupil from damage to the ciliary ganglion or short ciliary nerves that supply the iris sphincter muscle. Such abnormalities do not occur in isolation and if they are present, they are usually masked by the oculomotor nerve palsy.

Chemosis and Bruit

Chemosis is often seen in tumours that cause obliteration of the venous outflow of the orbit. It is generally seen in inflammatory or malignant tumours and also seen in carotico-cavernous fistulae (CCF), due to the back pressure in the veins secondary to the arteriovenous shunt.

Bruit is sometimes audible on auscultation which should be routinely carried out in all patients with proptosis and suspected arteriovenous malformations (AVMs). A bruit that disappears on carotid compression is characteristic of CCF. Opto ciliary shunts and retro-ocular striae may be seen on fundus examination.[15]

INVESTIGATIONS

Plain X-ray

Plain X-rays (Fig. 9) have lost their place of importance in the pre-operative investigations of proptosis. Plain X-ray films are important to detect:

- **Bony erosions:** Bony erosions are seen on the superolateral margins of the orbit. Erosions may occur at this site which suggests a lacrimal gland neoplasm.
- **Sclerosis:** Sclerosis of the bones may suggest an intraorbital meningioma or metastatic disease. But when sclerosis is associated with an expanded bony contour, the diagnosis of fibrous dysplasia must be entertained.
- **Calcification:** Osteomas of the paranasal air sinus are extremely dense and diagnostic on plain X-ray.

Plain radiographs also demonstrate enlargement and changes in the bony wall. The optic canal may be widened in optic nerve gliomas and sometimes the posterior lateral wall is deficient in neurofibromatosis.

Computed Tomography Scan

With recent advances in technology, the computed tomography (CT) (Fig. 10A) images are excellent and provide a wealth of information in the diagnosis of orbital tumours. Axial scans along with coronal images help in localisation of tumours, show the bony changes, calcification and various enhancing patterns of different tumours (Fig. 10B).

High Resolution Magnetic Resonance Imaging Scan

Magnetic Resonance Imaging (MRI) is the investigation of choice for orbital tumours. It not only shows the soft tissue structures well but also gives us the most important relationships of the tumour with various structures

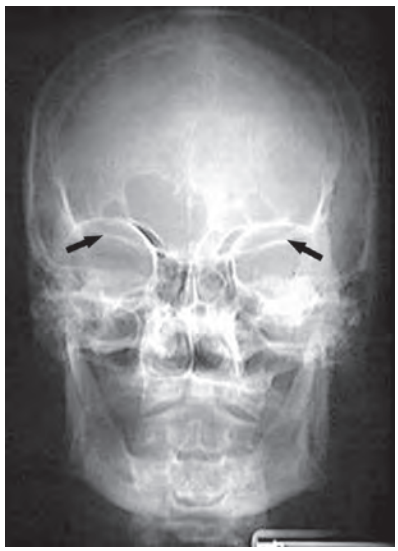
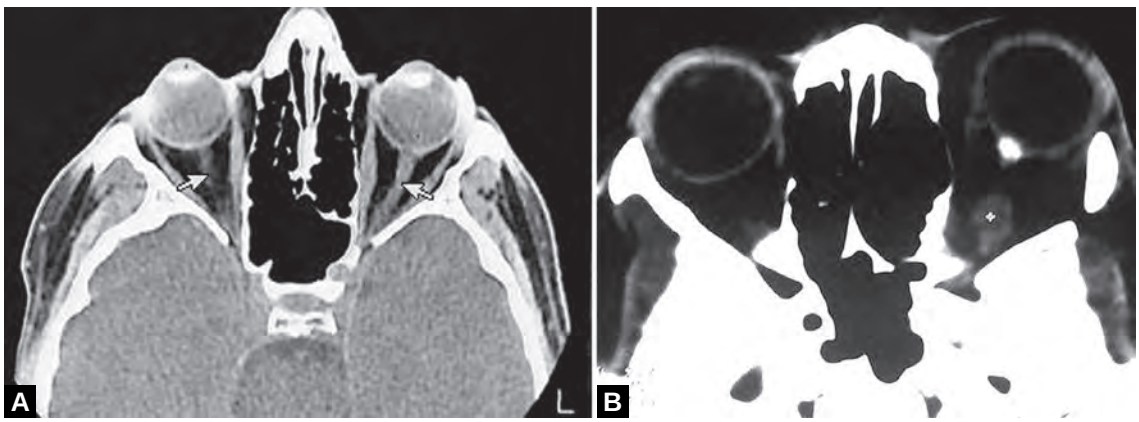


Fig. 9: Plain X-ray of the orbit; arrows showing the lesser wing of the sphenoid on either side



Figs 10A and B: (A) Computed tomography (CT) scan showing the optic nerves. (B) CT scan showing left optic sheath meningioma

within the orbit and most importantly the optic nerve. Gadolinium enhanced MRI also shows the varied enhancing patterns of orbital tumours. The location of the tumour in the orbit in the extraconal, in the intraorbital but outside the periorbita, inside the periorbita but extraconal and intraconal is easily delineated. Infiltration of various intraorbital structures in malignant and inflammatory conditions is also seen. Non-tumourous conditions, such as Grave's disease and inflammatory myositis, are also picked up (Figs 11A and B).

Angiography

Angiography is sometimes required when tumours are suspected to have increased vascularity in cases of:

- Meningiomas
- Haemangiopericytomas
- Retro-orbital pial or dural arteriovenous malformations (AVMs)
- Carotid cavernous fistula

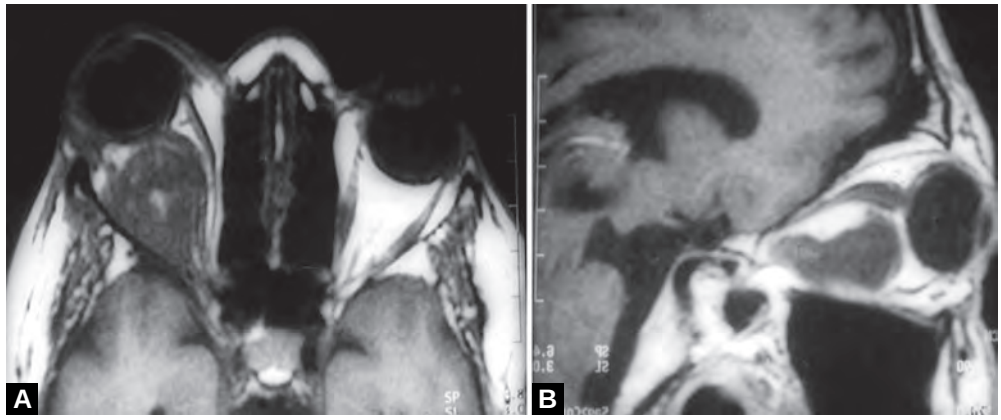
Angiography is sometimes coupled with embolisation techniques to prevent excessive blood loss during surgery. Orbital venography was a common diagnostic procedure in the past, but with more sophisticated imaging facilities available. This angiographic technique is rarely used today. It is still a good tool to diagnose and treat intraorbital varix and other developmental vascular lesions (Figs 12A and B).

Ultrasonography

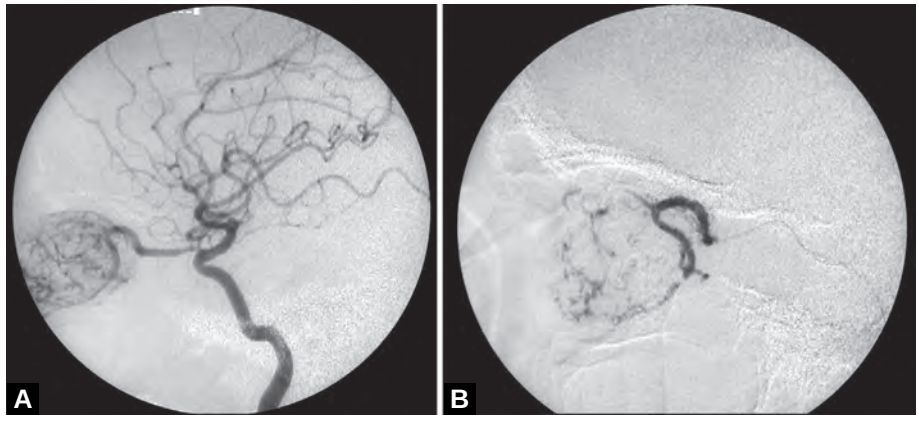
Ultrasound is particularly useful in evaluating intraocular lesions by ophthalmologists and in diseases involving the anterior portion of the retrobulbar space. At times, intra-operative ultrasound may be required to locate small tumours.

MANAGEMENT OF ORBITAL TUMOURS

The orbit is a meeting place for numerous surgical specialties, to focus their skills in order to achieve good results. The neurosurgeon, the ophthalmologist, the maxillofacial surgeon, the head and neck oncosurgeon and at times the otolaryngologist may share their knowledge and to derive the best cosmetic results the plastic surgeon too is involved in the resection of certain tumours. Orbital tumours are a difficult surgical challenge despite various advances in techniques and radio imaging. The cranium provides a safe access to the orbit and, therefore, it is imperative for neurosurgeons to have sufficient knowledge of tumours in this region.



Figs 11A and B: (A) Medial displacement of the optic nerve. (B) Superior displacement of the optic nerve



Figs 12A and B: (A) Pre-operative digital subtraction angiogram (DSA) showing vascular tumour of the orbit (haemangiopericytoma). (B) Post-embolisation DSA image on the same patient

Principles in the Treatment of Orbital Tumours

- The essence is to achieve safe "total" excision of benign tumours.
- "En bloc" excision in malignant tumours.
- Use "safe" orbital spaces to access the tumour.
- Attack the tumour from the base of the cone.
- Avoid bipolar coagulation.
- Gentle handling of the intraorbital structures.
- No fat to be sacrificed.
- Reconstruction of the walls of the orbit.

History of Surgical Approaches to the Orbit

Tumours of the orbit are of interest to various surgical specialties. Neurosurgeons too have shown great interest in orbital tumours over the years (Table 3).

Table 3: Choice of operative approach for orbital tumours

Subfrontal approach with superior orbitotomy	• Superiorly and medially placed moderate and small-sized tumours • Intraconal tumours medial to optic nerve
Fronto-orbito-zygomatic craniotomy	• Superiorly and medially placed large size tumours • All tumours with involvement of the apex
Fronto-orbito-zygomatico-temporal craniotomy	• All tumours with middle fossa extension • All tumours with infratemporal extension
Lateral orbitotomy	• Laterally placed extraconal tumours • Intraconal tumours lateral or inferior to the optic nerve

Bartisch (1583) described one of the earliest approaches to the orbit. He attempted a subtotal exenteration with preservation of the eyelids. Thomas Hope (1744) reported one of the first orbital eyeball sparing procedures. On the other hand, Foster (1948) stated that the only accepted method of treating orbital tumours was to 'iodise and temporise—irradiate and exenterate'.

Extracranial Approach

Anterior orbitotomy was first described by Hermann Knapp in 1847. It was rediscovered by Benedict in 1949. Inferior orbitotomy was described by Davis in 1940. The frontal trans-sinusoidal approach was used by Colohan in 1941. Niho described transethmoidal orbitotomy in 1961.[27]

Lateral Orbitotomy

Gustav Passavant was the first person to use the lateral approach to remove a vascular malformation in 1866. However, its name is associated with Kronlein who first described the process in great detail in 1889. Stalard rediscovered the same in 1947. Rowbotham furthered the approach in 1949. Berke improved upon it in 1953 and Krayenbuhl and Brihaye improved upon the technique in 1967 and 1968, respectively. Kennerdell and Maroon further added variations in 1976.[27]

Transcranial Approach

Durante (1887) was the first person to adopt a transcranial route for treating orbital tumours. However, it was Walter Dandy who popularised this approach (subfrontal approach) with his classical paper in 1941. Poppen was another strong proponent of this approach in 1943. This was furthered upon by Housepain in 1969 and 1978. Iliff restudied the Dandy series and concluded that surgery of orbital tumours properly lay within the province of ophthalmology. The frontolateral (without sphenoid bone resection) approach was popularised by Naffziger in 1948 and further refined by Maroon and Kennerdell in 1984. The frontotemporal (pterional) approach was described by Welti and Offret in 1943 and later by Hamby in 1964, then by Seeger in 1983 and further by Hassler and Eggert in 1985. The fronto-orbital approach was described by Tym in 1961 which was furthered upon by Brihaye in 1968 and then by Jane in 1982.[27]

Other Approaches

Rollet in 1907, Elscnig in 1927 and Golovine in 1930 advocated a transpalpebral route through the superior orbital margin.

Davis, in 1940, described an approach through an incision along the inferior orbital border to remove an optic nerve glioma. Callaham in 1948 and Vergez in 1958 used it for other pathologies.

The transconjunctival approach was introduced by Hermann Knapp in 1974.

I prefer to include lateral orbitotomy as a transcranial approach rather than an extracranial one. In fact, micro-orbitotomy should be described as a minimally invasive "cranial" access to the orbit.

Various Areas in the Orbit may be Approached in the Following Manner

Extracranial approaches are generally reserved for tumours that involve the anterior two-thirds of the orbit. Medially placed lesions may be tackled by transethmoidal, anteromedial orbitotomies, whereas lateral lesions may be tackled by an anterolateral orbitotomy. The subfrontal approach is generally used to tackle superiorly placed tumours or tumours medial to the optic nerve. The frontolateral approaches provide greater access into the orbit and are used for tumours that are superolateral in the orbit and may encroach into the orbital apex or SOF. The fronto-temporo-zygomatic approaches are used to access tumours superiorly and laterally placed in

the orbit, extending into the intracranial region involving the SOF, IOF, orbital apex and inferior orbit as well.

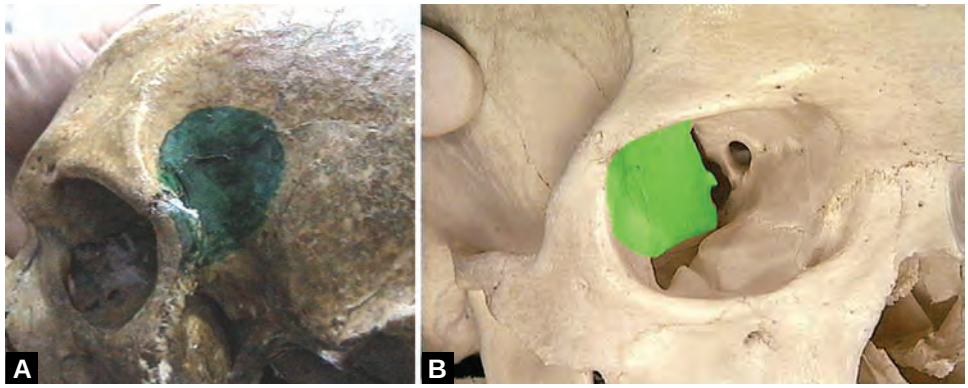
Surgical Approaches

Lateral Orbitotomy

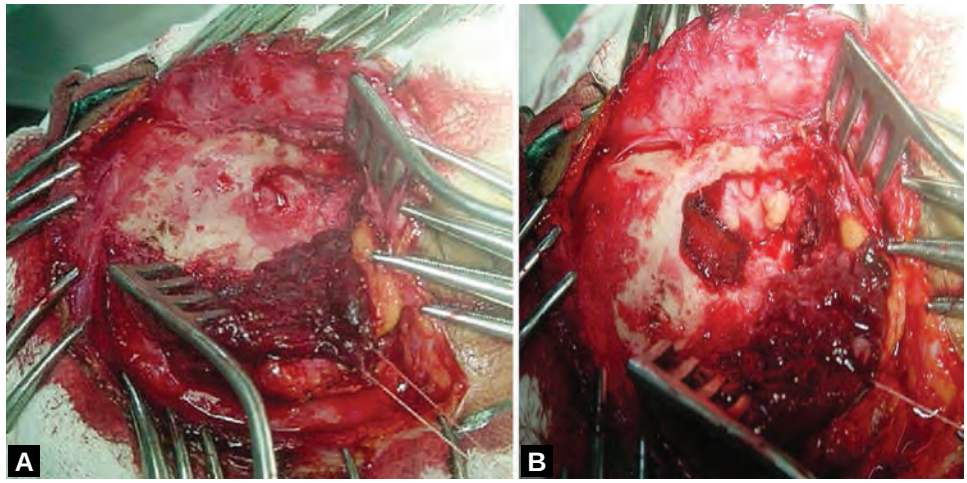
This is the most popular approach (Figs 13A and B) to orbital tumours today. A skin incision, which is curvilinear and follows the hairline, is used. As the skin flap is elevated, dissection is carried out to the lateral orbital rim, completely exposing it. The temporalis muscle is dissected off the lateral wall. A burr hole is placed in the lateral orbital wall, exposing the periorbita (Figs 14A and B). The zygomatic bone may be divided using a Gigli saw for greater exposure. At times, the zygoma may be nibbled to widen the exposure, without excising the lateral rim of the orbit. Additional exposure is achieved by removing the lateral wall of the orbit till the apex. If needed, the temporal dura can also be exposed by removing a part of the sphenoid bone. A cruciate incision is made on the exposed periorbita and periorbital fat is encountered. Extraconal tumours lie in this space and can be removed safely. If the tumour is intraconal, the lateral rectus muscle has to be identified and dissection is carried out either above or below it, as needed. Exploration of the intraconal space should be done using microneurosurgical techniques and principles to avoid injuries to vital structures. Minimal use of bipolar coagulation is recommended. After the lesion is excised, haemostasis is achieved and the periorbita closed with 3-0 Vicryl. The lateral orbital margin should be reconstructed and the temporalis muscle sutured back. It is not necessary to reconstruct the entire lateral wall. However, as there is always plenty of bone pieces and bone dust, it is easy to reconstruct the lateral wall as well. The temporalis muscle and fascia are anchored and sutured in position and the wound is closed in layers.[5,6] Figures 15A and B are pre- and post-operative images of a haemangiopericytoma excised using a microlateral orbitotomy.

Subfrontal Approach

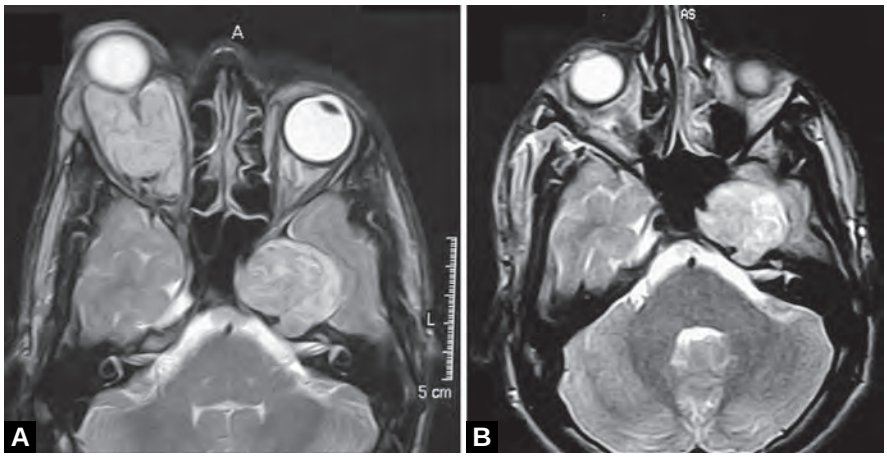
A "key hole" burr hole is placed and unifrontal craniotomy is performed (Fig. 16A). The supratrochlear nerve



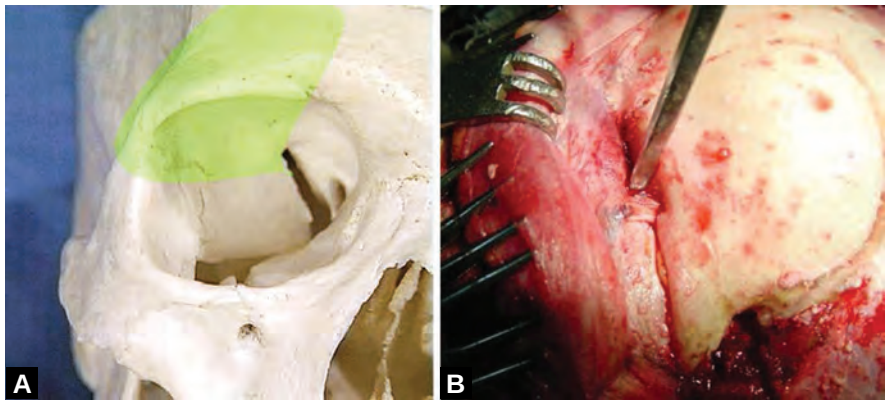
Figs 13A and B: (A) Bony exposure required for a microlateral orbitotomy. (B) Wide exposure available through the lateral wall. This diagram clearly shows that inferiorly placed tumours (that displace the optic nerve superiorly) can safely be approached from this route as well



Figs 14A and B: Intra-operative image of the exposure provided by microlateral orbitotomy (in this case the lateral rim of the orbit is preserved). The skin and subcutaneous tissue is reflected anteriorly and the temporalis muscle and fascia are seen reflected posteriorly. The orbitotomy is widened to the extent, to allow safe access to the tumour



Figs 15A and B: Examples of (A) pre-operative. (B) post-operative images of a haemangiopericytoma excised using a microlateral orbitotomy

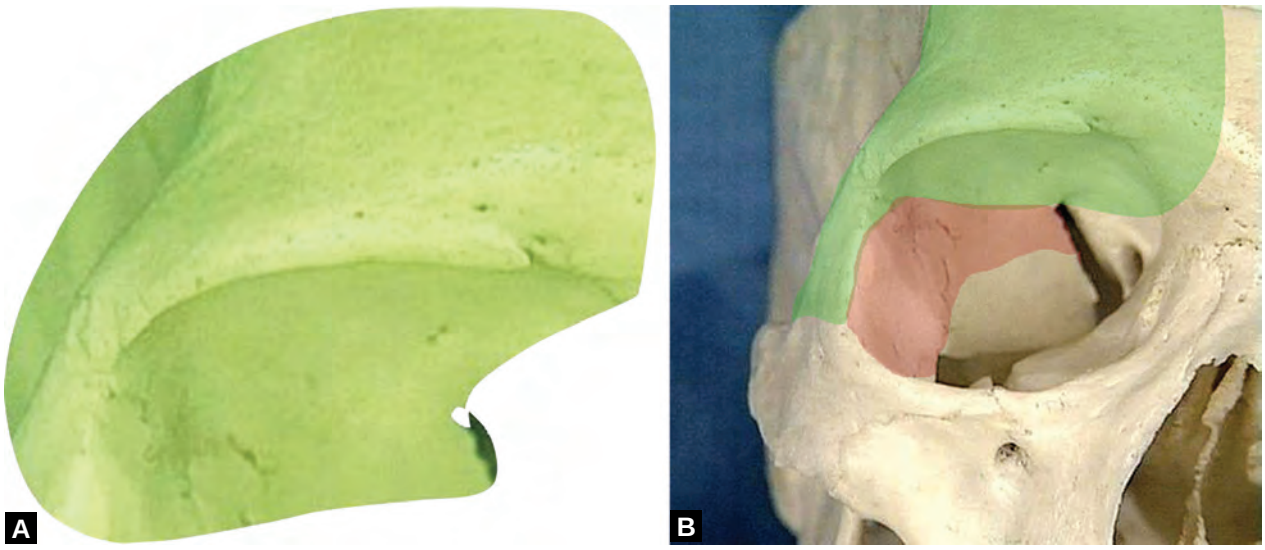


Figs 16A and B: (A) Superior orbitotomy for the subfrontal approach. (B) How to preserve the supratrochlear nerve by breaking the bony strut which anchors the nerve using a fine osteotome

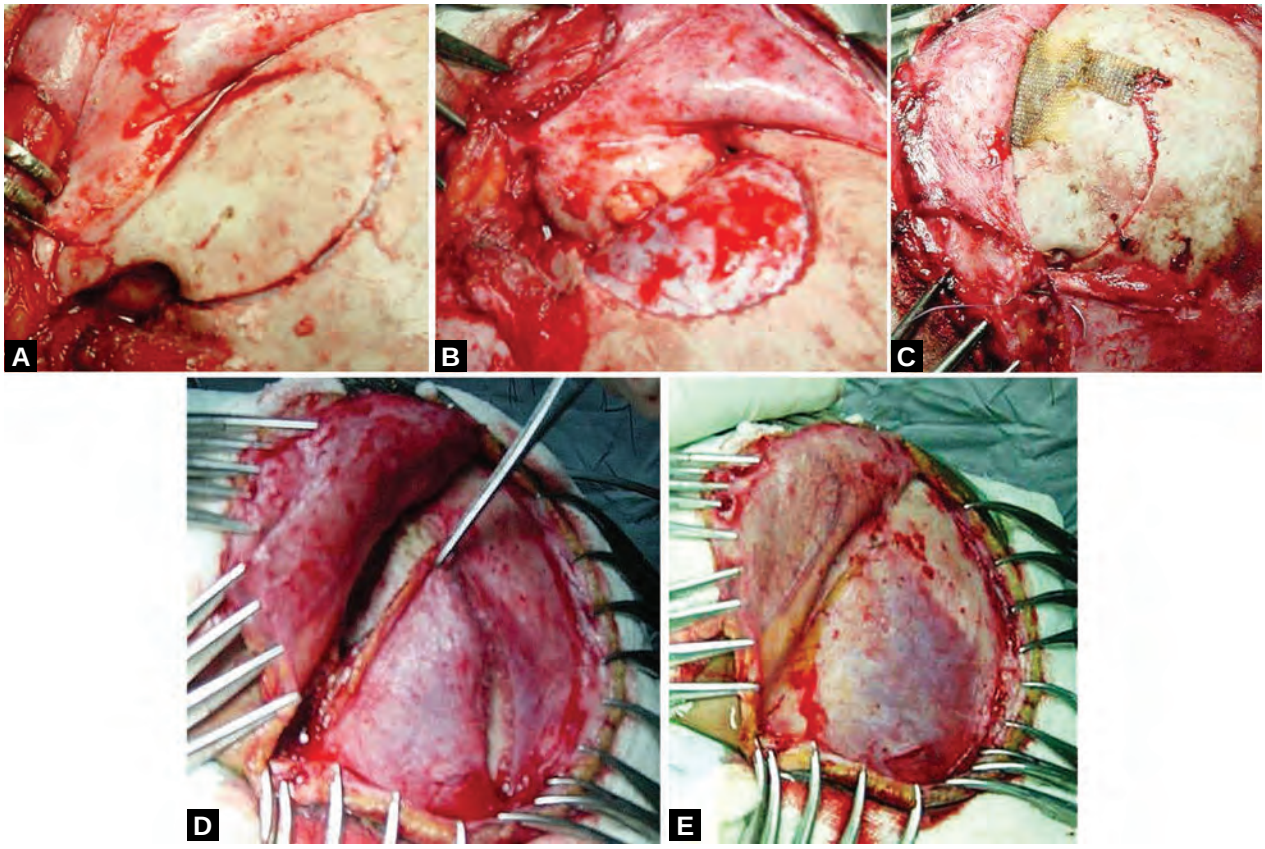
is preserved as shown (Fig. 16B). The roof of the orbit is excised, along with the bone flap. In this manner, no loss of bone occurs and the reconstruction is quick and cosmetically and functionally perfect. Orbital exploration demands a minimal backward retraction of the dura. The periorbita is cut in a cruciate manner. Once a small opening is made, the opening can be enlarged by using a roungeur. The optic canal can be unroofed using orbital micro-punches (House). The periorbita is incised in a cruciate fashion with a no.11 blade. Micro-neurosurgical techniques are used to excise the tumour. The approach to the tumour should be preferably between the superior rectus and medial rectus muscles, to avoid any injury to the branches of the oculomotor nerve. This is particularly useful for tumours of the optic nerve. A meticulous reconstruction is done after this and wound closed in layers.

Fronto-orbito-zygomatic Craniotomy

This approach (Figs 17A and B) was popularised by Maroon. A bi-coronal hairline incision is used. It starts just in front of the tragus and extends to the superior temporal line of the opposite side. The entire scalp flap and temporalis muscle are dissected subperiosteally. The supraorbital nerve is freed from the superior orbital margin. The dissection is carried out along the orbital roof to displace the periorbita away from it. Dissection is carried out laterally to clear the lateral periorbita away from the lateral orbital margin. The temporalis muscle is dissected down to the zygomaticotemporal suture. A frontal craniotomy is planned. The first burr hole is placed in the anterior most part of the lateral wall of the orbit. The other hole is made just inferior to the superior temporal line. These are connected with the craniotome cutter. The roof of the orbit and the zygoma are removed in one piece; the thin orbital roof is broken posteriorly, using an osteotome. The optic canal should be thinned with a diamond drill and then exposed with a small curette. The periorbita is excised in a cruciate fashion. The approach to the tumour should be preferably between the superior rectus and medial rectus muscles, to avoid any injury to the branches of the oculomotor nerve. This is particularly useful for tumours of the optic nerve.[7] A meticulous reconstruction is done after this and wound closed in layers (Figs 18A to E).



Figs 17A and B: Diagrammatic representations of the superolateral approach also called the orbitozygomatic craniotomy



Figs 18A to E: (A) Operative photograph showing the craniotomy, roof of the orbit and the inferior cut on the zygoma, all removed in one piece. (B) Exposure after the bone flap is removed. (C) Bone flap anchored and bone dust and oxidised cellulose placed to produce the best cosmetic results. (D) Temporalis muscle and fascia repositioned. (E) Sutured

Fronto-temporal-orbito-zygomatic Craniotomy

It is similar to the above procedure however the temporal burr hole is also placed posteriorly so that after the craniotomy the temporal dura is also exposed (Fig. 19). The sphenoid ridge and the lesser wing of the sphenoid are removed to expose the SOF and the middle fossa skull base (Figs 20A and B).

Fig. 19: Bony exposure on a cadaveric skull

DIFFERENT ORBITAL TUMOURS

Neurofibroma

Neurofibromas (Figs 21A and B) of the orbit are common tumours which occur in the latter half of the second decade to the fourth decade of life. Multiple neurofibromas occur in the younger age group and may also have a diffuse or plexiform appearance and may be a part of Neurofibromatosis Type I. The tumour is seen in both sexes with a slight pre-prominence in the female sex.

These tumours have an excellent plane of cleavage and are distinct from the surrounding orbital tissue. There are a few, however, which are adherent to the posterior aspect of the globe, tumours which are of long standing duration and larger tumours. Unless the tumour is totally excised, there is always a possibility of recurrence and at times the recurrence may be cystic. Recurrent tumours are difficult to excise completely, making it a difficult management problem. These tumours often arise from sensory twigs of the ophthalmic division within the orbit. These tumours are intraconal and often can be tackled using the microlateral orbitotomy. The plexiform variety of tumours are more diffuse and spread extraconal and at times outside the orbit as well, making it difficult to excise the tumour completely. These tumours, however, pursue a more indolent course.

Meningioma

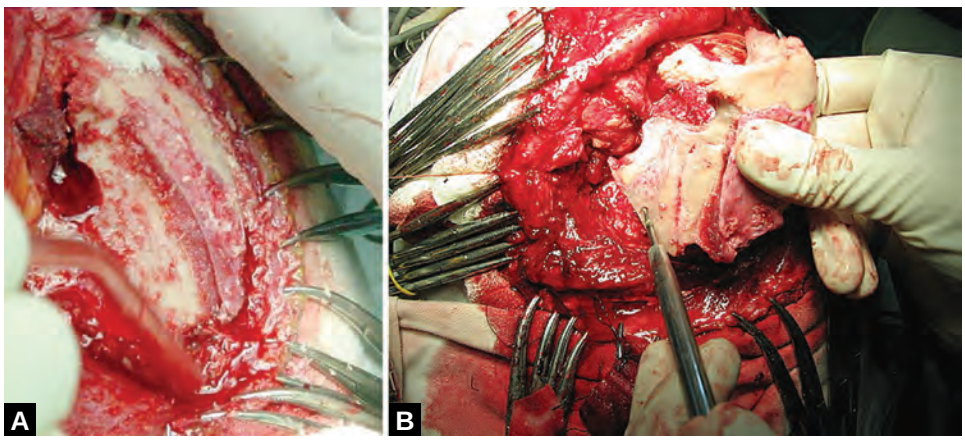
There are three types of meningiomas that involve the orbit:

(1) Optic sheath meningioma (Fig. 10B).
(2) Tumours arising from the arachnoid cap cells involving the periorbita or the dura around the orbital fissure or optic canal (Figs 22A and B).
(3) Meningiomatosis that involves the dura extensively in and around the orbit (Fig. 22C).

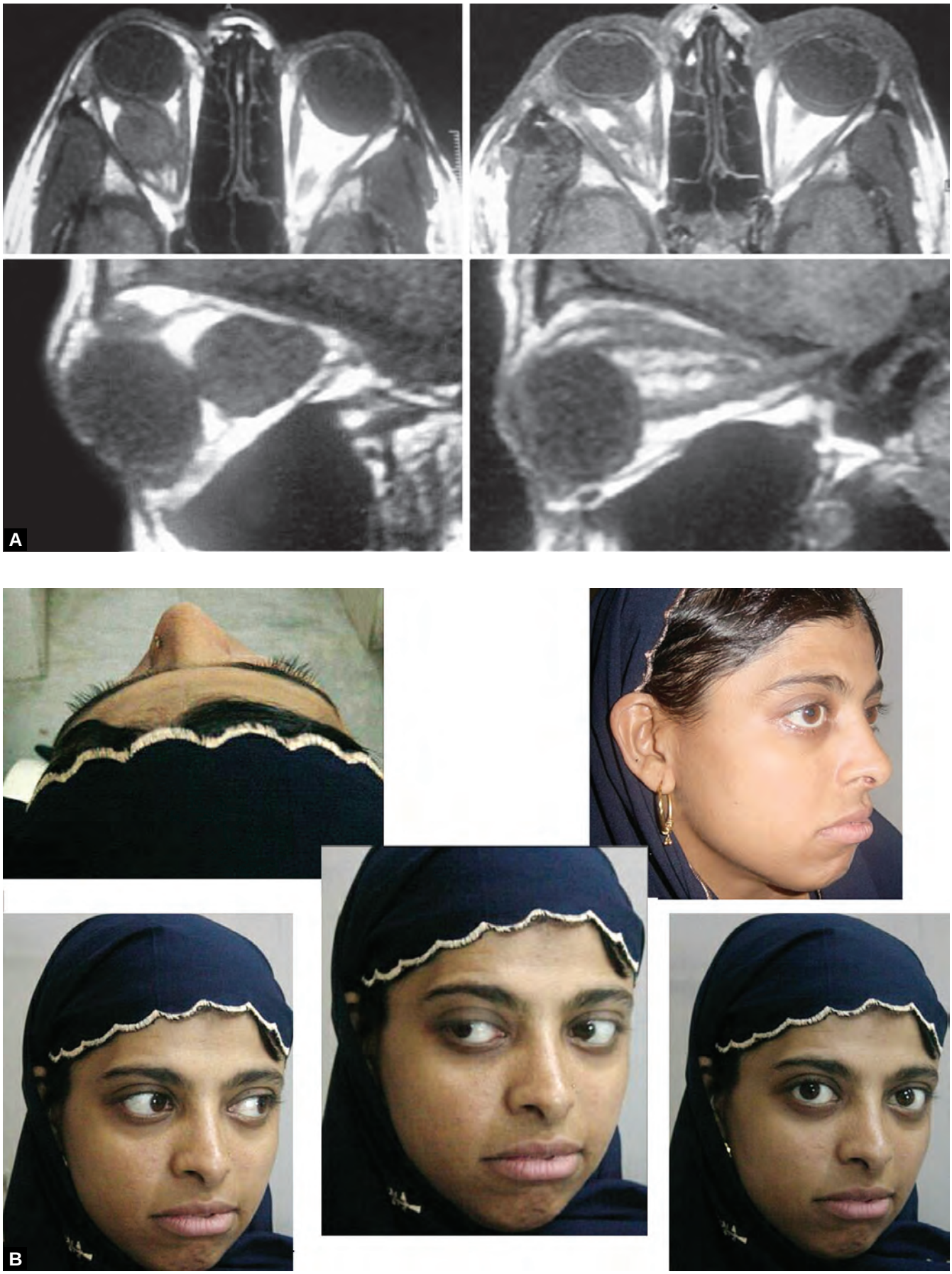
(1) Optic sheath meningiomas comprise about 5–7% of primary orbital tumours.[33] Our incidence is higher due to the referral pattern, 6 out of 21 meningiomas (28.5%). Optic sheath meningiomas are either:
   a. within the optic nerve sheath encircling the optic nerve.
   b. within as well as outside of the optic sheath, causing an exophytic growth adjacent to the optic nerve.
   c. purely exophytic growth of tumour outside the optic nerve sheath.[26]

Although these tumours are benign tumours and generally are meningothelial, transitional or fibromatous in their histological types, they produce profound visual loss, as these tumours are firm and they may encircle the optic nerve. There are some tumours that have exophytic extensions and are favourable for surgery. However, most of them are difficult to excise completely. They occur around the latter half of the third and fourth decades of life. In addition to the above symptoms, impaired movement of the globe, disc swelling or optic atrophy with shunt vessels and an afferent papillary defect may occur.[1]

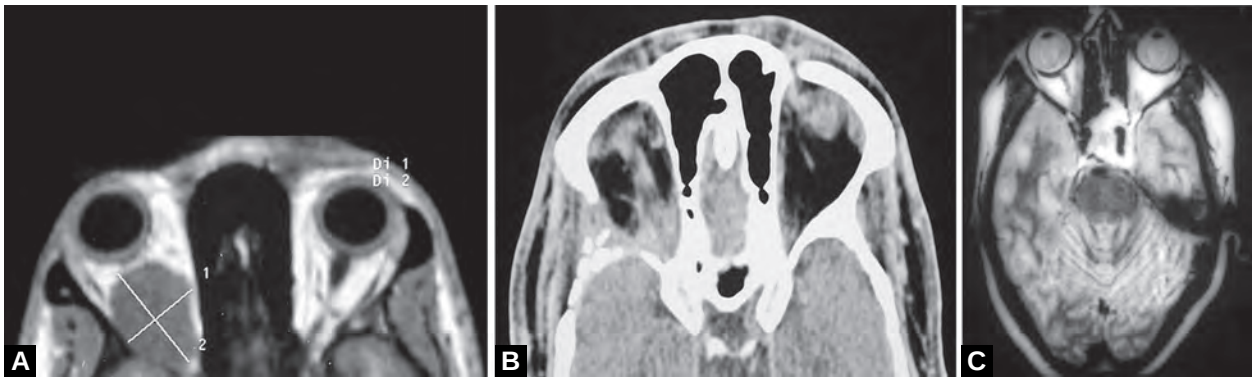
As these tumours are firm, although friable and well encapsulated, dissection sometimes is tedious at the orbital apex. At times, the dura of the optic sheath is infiltrated with tumour densely stuck to the periosteum



Figs 20A and B: Intra-operative images of the same technique



Figs 21A and B: Pre-operative and post-operative MRI of neurofibroma. (B) Three months post-operative clinical images of neurofibroma patient



Figs 22A to C: (A) Tumour arising from the arachnoid cap cells involving the periorbita or the dura around the orbital fissure or optic canal. (B) Intracranial as well as (C) Intraorbital meningioma

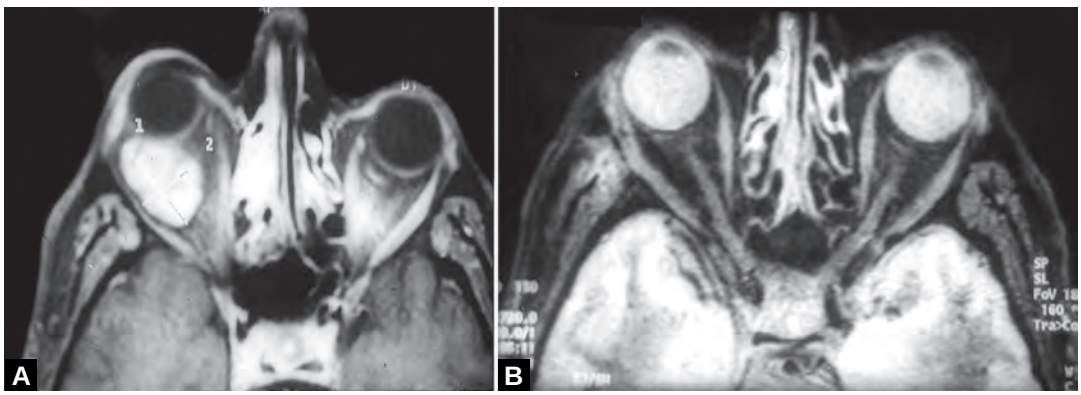
of the bone at the orbital apex, optic canal and orbital fissure. Optic sheath meningiomas are vascular and derive their blood supply from the ophthalmic artery as well. There remains considerable controversy regarding management of these lesions.[1,42] When the vision is well preserved it may be best to follow these tumours as some of them have long indolent courses. Radiotherapy proponents have claimed excellent results in control of these tumours.[36]

(2) Orbital meningiomas not arising from the optic sheath pose less surgical challenges in terms of compromised visual function. However, these tumours are generally close to the optic fissures and tend to produce oculomotor deficits. It is safer, therefore, to leave a small cuff of tumour at the orbital apex, if there is no compromise of oculomotor nerve function pre-operatively. These tumours are firm to hard and have indolent courses and can be closely observed. The unpredictable and relatively slow growth rate of a meningioma allows the surgeon to practice sub-total removal and decompression, in order to preserve vision and oculomotor function.[21,20,27]

(3) Meningiomas with a more diffuse dural involvement are most common in women and may be associated with tumours spread intradurally to involve the planum sphenoidale, tuberculum sella and the sellar region. These tumours need to be excised early so that they may cause compromise of vision on the opposite side as well. The surgical approach often entails a wide fronto-temporal-zygomatic craniotomy. The bone flap also comprises of the roof of the orbit taken as one piece. The exophytic variety may produce proptosis with relatively less visual deterioration. When the tumour is within the optic sheath, even small tumours produce dense visual impairment. Early disc swelling is recognised. If the vision is completely lost at the time of presentation, radical excision of the tumour is feasible and the aim is to prevent intradural spread of tumour and correct the proptosis. If the patient's eye movements are intact, using microsurgical techniques it is possible to preserve the same after surgery. Total excision of these tumours is difficult; in order to preserve oculomotor function it may be advisable to leave a cuff of tumour at the apex of the cone, so as to prevent handling of the nerves and muscles, as they crowd together at the orbital apex.

Cavernous Haemangioma

These are among the common benign tumours in adults involving the orbit (Figs 23A and B). They are often intraconal; however, some of them may have extraconal



Figs 23A and B: (A) Pre-scans. (B) Post-scans of a cavernous haemangioma

extensions as well. They present with painless proptosis with remarkably well preserved vision and normal eye movements, in spite of their huge size. They occur from the second to the fourth decades of life and have a female pre-ponderance.[13]

These tumours are well encapsulated. They have variable consistency and although they bleed at surgery, the bleeding is never difficult to control. They have a typical bluish hue, due to the stagnant blood filled cavernous spaces. At times, they may also show micro calcification. These tumours have the best prognosis following surgery and are often tackled by microlateral orbitotomy.

Lymphangioma

These tumours are similar to haemangiomas; however, they are far more extensive and infiltrative and often involve the intraconal and extraconal spaces simultaneously. Total eradication of tumour is difficult. If microneurosurgical principles are adhered to and no aggressive surgical options are undertaken, remarkable clinical results can be achieved. These tumours pursue a relatively benign course.

Optic Nerve Glioma

Optic nerve gliomas arise from the anterior visual pathway and may involve the optic nerve, chiasm or tract (Figs 24 and 25). They generally manifest in the latter half of the first decade or second decade of life. They are often associated with neurofibromatosis. Most of these tumours have an indolent course; however, there are some tumours that are aggressive in nature. Tumours that are associated with neurofibromatosis have a more indolent course.[16] They are common with neurofibromatosis type I (NF 1).

Tumours involving the optic nerve present with blindness and proptosis.[19] The typical imaging finding shows enlargement of the optic foramina. These tumours progress and grow intracranially and can involve the chiasm. The general principle of management is close observation and regular follow-up. Tumours that demonstrate progression are excised when the vision is completely compromised. It is important to cut the optic nerve beyond the tumour to prevent the spread of the tumour into the chiasm. Tumours that involve the chiasm are generally biopsied and given radiotherapy. Although western literature favours chemotherapy, most of the patients we deal with are in the age group of 10 years and over (paediatric age group) and can tolerate radiotherapy better than chemotherapy. The surgical approach for these tumours would often entail a frontotemporal craniotomy coupled with a subfrontal approach to the orbit.

The histology of these tumours shows a predominantly fibrillar pattern with microcystic changes sometimes. Rosenthal fibres are commonly seen. As the tumour enlarges, reactive proliferation of the meninges occurs, contributing to the increased size of the tumour.[43]

Lacrimal Gland Tumours

Lacrimal gland tumours make-up 35% of lesions involving the lacrimal gland and the rest being inflammatory lesions. The most common tumour is the benign mixed tumour which accounts for approximately 50–60%. The malignant mixed tumours account for 5–10%, adenoid cystic carcinomas for 20–30% and other carcinomas for about 5–10%.[8,23,31] Microlateral orbitotomies may suffice for benign tumours, however, "en bloc" resection of malignant tumours is required.

Fibrous Dysplasia

These are not actually tumours; however, these are lesions of childhood and adolescence which can cause significant deformity of the orbit, frontal, zygomatic, ethmoid or sphenoid bones. The fibrous dysplasias are generally of two varieties:

(1) The mono-osteotic variety where only one bone is involved.
(2) The polyosteotic where many bones in the orbit are involved.

They produce unsightly proptosis and distortion of the face. Often, the patient has no other complaints besides cosmesis. However, there are times when the optic nerve is compressed in its canal and surgery becomes mandatory. Surgical removal of the roof of the canal and the optic struts provide relief of compression.

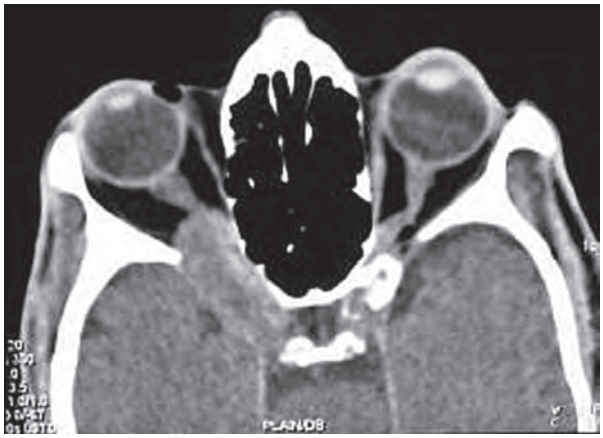


Fig. 24: Optic nerve glioma

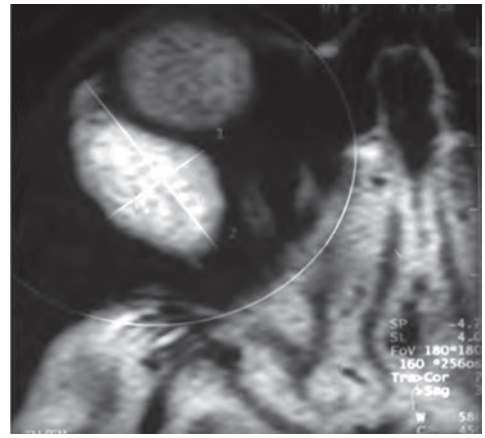


Fig. 25: Dermoid and epidermoid cyst

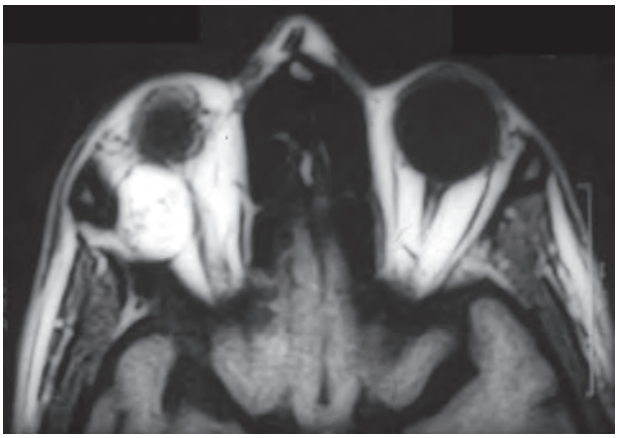


Fig. 26: Simple reconstruction using a metal plate contoured to the shape of the rim of the orbit and screwed into the buttress of the maxilla

Dermoid and Epidermoid Cysts

Dermoids (Fig. 26) are the most frequent developmental cysts. They are found usually in the latter half of the first decade or first half of the second decade. However, as they are slow growing and innocuous in their presentation, they can be encountered in late adult age. They are usually located at the lateral canthus and are almost always extraconal and extraperiosteal in location. These tumours may sometimes cause scalloping of the bone due to prolonged and slow growth and may produce radiolucent bone defects with well corticated margins on X-ray or CT scans. They usually are painless, generally produce cosmetic disfigurement of the face and cause little or hardly any displacement of the globe. They can be completely excised by various approaches; a lateral orbitotomy would suffice in most cases.

Osteoma

These are commonly found in the frontal or ethmoid sinuses. They are hard lesions which displace the globe laterally and produce a bulge superior to the medial canthus. These are usually present in the second decade of life. They may also have intracranial extensions. Depending on the location and the extent, transcranial or extracranial approaches may be used. The excision is greatly simplified by using high speed pen drills. It is important to excise the entire osteoma or else recurrences are known.

Mucocoele

This is a cystic collection of obstructed mucous lined by the mucous membrane, arising either from the frontal or from ethmoidal air sinus and, occasionally, from a pneumatised roof of the orbit. The blockage may be secondary to chronic inflammation, scarring due to trauma or surgery and at times polyps or bony tumours (Osteoma). The radiology shows "ballooning" of the sinus walls, producing a characteristic "eggshell" appearance. Patients can present with proptosis, pain, visual discomfort, headache and, at times, a palpable mass. Often a transcranial approach would provide a better cosmetic result, however, direct eyebrow incision with excision of the mucocoele by using an anterior approach may also be used.

Metastatic Tumours

Neuroblastoma and Ewing's tumours are common in childhood and may metastasise to the orbit. These malignant tumours of the orbit have a short history with ecchymosis, pain and swelling. The most common malignant tumour of the orbit in an adult is a metastatic tumour and common primary sites are testicular tumours, breast, lung and some skin tumours. When malignant tumours are suspected, a fine needle aspiration biopsy is preferred so that the treatment protocol may be planned.[21] "En Bloc" resection must be performed whenever surgery is indicated.

Vascular Lesions

CCF: The fistula causes increased venous pressure in the veins of the orbit, particularly the superior ophthalmic vein. This leads to increased orbital volume and produces proptosis. At times, muscle thickening is also seen due to the increased venous pressure. All these features are reversible on treatment of CCF, which is now only performed by the interventional neuroradiologist.

Venous Varix

It is a congenital condition where a venous pouch is present in the orbit and any increase in venous pressure produces exophthalmos. Valsalva manoeuvre, dependency of the head and straining tend to fill the venous pouch and produce the characteristic symptoms. Today, such lesions are treated by the neurointerventional team.

Arteriovenous Malformations

AVMs may be located within the orbit and are diagnosed with a bruit audible over the eye and verified by characteristic scan and angiogram findings.

Intraorbital Ophthalmic Artery Aneurysms

These are extremely rare. More commonly, the aneurysms from the cavernous and clinoidal segments of the internal carotid artery encroach upon the orbit and orbital structures.

Pseudotumours

Inflammatory pseudotumours of the orbit are far more frequent than specific granulomas, such as tubercular or cysticercus. They represent a heterogeneous group.[3,24] At times, they have extensive spread of disease with involvement of the paranasal air sinuses. They have the following characteristics: there is a dense tissue reaction due to mobilisation of chronic inflammatory cells,

vascular proliferation and hyperplasia of connective tissue forming an indurated orbital mass, which often surrounds the optic nerve and also incorporates one or more extraocular muscles. There is absence of any aetiologic agent and, at times, histological verification may be required to rule out:

- Specific granulomas
- Hodgkin's lymphoma
- Lupus erythematosus among other diseases[10]

Besides the MRI and CT findings the per-operative gross features are also quite pathognomonic. The treatment of choice is dexamethasone which is given over a period of 3–6 weeks in tapering doses.

RESULTS

Remarkable results can be achieved using microsurgical techniques. As a rule, results, such as the case shown in Figures 21A and B, are what we can achieve using the techniques described above. The only patients who have worsened in vision were two cases of optic sheath meningioma, as described earlier. At times, reconstruction of the lateral rim of the orbit may be necessary and implants may be needed. Figure 27 shows a simple reconstruction using a metal plate contoured to the shape of the rim of the orbit and screwed into the buttress of the maxilla. An 'en bloc' excision for an adenoid cystic carcinoma (cylindroma) had been carried out, prior to the reconstruction at the same operation. Complications are uncommon if the above techniques and general microneurosurgical principles are meticulously followed.

The key to successful orbital surgery is a proper knowledge and understanding of the surgical anatomy, proper selection of the approach for a given patient and pathology; adequate exposure to allow safe tumour excision. To conclude, excellent results are possible using standard microsurgical techniques.

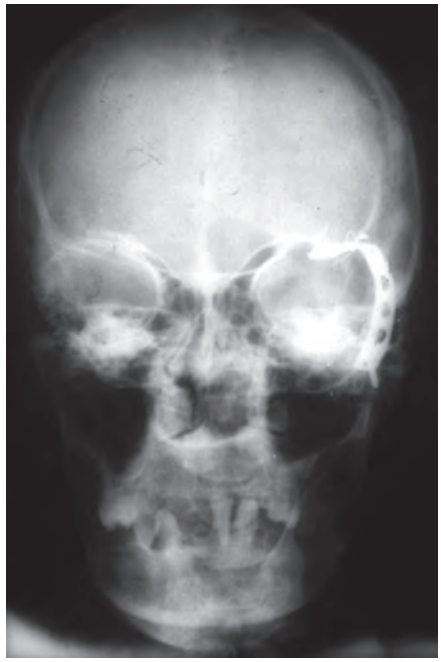


Fig. 27: Simple reconstruction using a metal plate contoured to the shape of the rim of the orbit and screwed into the buttress of the maxilla

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SECTION

14

Stereotaxy

Ravi Ramamurthi

186 Stereotaxy: General Principles

Ravi Ramamurthi, Vikram M

The ability to reach any desired depth of the brain and to stimulate or make lesions in predetermined areas has been a notable advancement in modern neurosurgery. The development of stereotaxic surgery has given this capacity to the surgeon to operate in the depth of the brain, without undue mortality or morbidity. It has led to advancement in knowledge about the functioning of the deep areas of the human brain and has helped to provide relief in diverse types of neurological disabilities, apart from the diagnosis of deep-seated lesions.

Although the idea of reaching the deep structures in various areas of the brain is more than a century old, its real development for human use has been only after World War II. At the end of the 19th century, Sir Victor Horsley,[15] with the help of his physicist Mr Clarke, devised an apparatus, which could be fixed on the head of animals, to enable him to introduce a probe into a desired area of the brain. At the conclusion of the experiment, the animal was sacrificed and the brain examined to confirm the correct placement of the probe. Only 50 years later the technique of stereotaxic placement of lesions was introduced for human neurosurgery, by the efforts of Spiegel and Wycis in Philadelphia, who modified the Horsley-Clarke apparatus for human use[43] (Fig. 1). For therapeutic purposes in the human, an extreme degree of accuracy was essential and this could not be achieved by calculation from external landmarks commonly used in animal experiments. The idea of using internal landmarks in the centre of the brain increased the accuracy of the placement of the electrode. The nearer these landmarks are to the target aimed at, the greater is the accuracy. The foramen of Monro and the pineal gland were used initially as guides but the variability of the pineal shadow and of the width of the foramen of Monro reduced the degree of accuracy. The anterior and posterior commissures of the brain, as outlined by air or contrast studies or recently by special CT or MR, have been found to be more accurate. Most of the measurements in stereotaxic terminology refer to the line connecting the anterior and posterior commissures in the midline and these calculations ensure anatomical accuracy of the placement. When the technique is used for other indications with other targets to be reached, the landmarks will naturally vary, e.g. tip of the temporal horn for amygdalotomy, anterior horns of the lateral ventricle for cingulotomy and the fourth ventricle for dentatectomy.

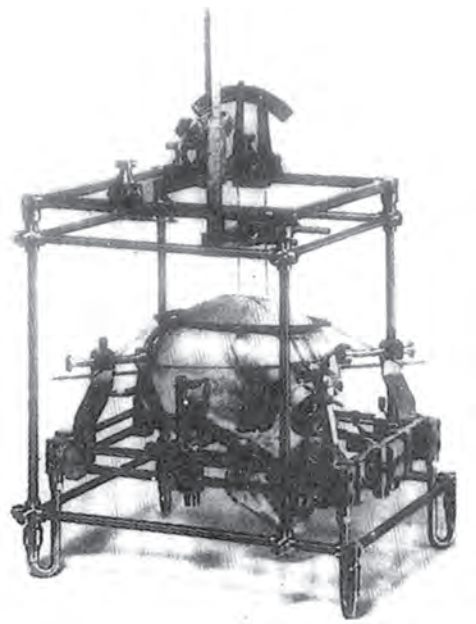

Fig. 1: Spiegel and Wycis stereotaxy apparatus

The modern techniques that are being used in stereotaxic surgery ensure a safe degree of accuracy for therapeutic purposes. Generally, there is a close correlation between the planned site of the lesion and the actual site, in the brains of Parkinson's patients examined postmortem. For finer neuropsychological determinations, a greater degree of accuracy would be desirable and necessary. One limiting factor in achieving such extreme accuracy is the variation seen in different human brains. This difference is not only seen between the sexes but also in different individuals belonging to the same ethnic group. This variation makes electrical stimulation studies necessary as a method of accurate localisation of the target. Recording of the electrical activity from the deep structures, as also a study of the evoked potentials, further help in the accurate localisation and assessment of the target. After such physiological studies, the desired area of the brain could be destroyed by heat, cold, wire loop, alcohol, wax, etc. It is also possible to focus an energy beam into a desired area of the brain, after making the necessary calculations.[25] The latter obviates the need for open surgery in the form of burr holes. This energy beam at a lower intensity can be used as a stimulus for neurophysiological studies and later, at a higher intensity, for making a lesion.

An important achievement of stereotaxic surgery, in the early years, has been the treatment of involuntary movements, chiefly Parkinsonism. Deliberate placement of a lesion initially in the globus pallidus and later in the thalamus[13] led to marked amelioration of symptoms in patients suffering from Parkinson's disease. The success attending this procedure encouraged further advancement in the science of stereotaxic surgery and the scope of such surgery has been widened to include other involuntary movements like dystonia, hemiballismus and choreoathetosis. The other condition for which the technique has been utilised with success is the relief of intractable pain. A few centres, notably in Japan and the Madras group,[20,21] have advanced the study further and have included cerebral palsy and behaviour disorders in the realm of stereotaxic surgery.[33,35,36] Further progress has included surgery for epilepsy and for some well defined psychotic conditions. The stereotactic technique can also be used in many other situations, e.g. clipping a deep aneurysm, introducing radioactive seeds into a pituitary adenoma or pineal tumours, biopsy of deep seated tumours, removal of deep lying foreign bodies, radiosurgery and draining of cysts and haematomas. Thus, stereotaxic surgery has increased our ability to give relief to patients, simultaneously providing a tool for neurophysiological investigations on the structures in the depth of the brain.

Apparently, there seems to be great scope for these forms of surgery, especially as more and more of the functions of the deep-lying nuclei in the human brain are unravelled. In addition to giving us an idea of the function of each area of the brain, stereotaxic surgery would also help us to know more about the association of functions between various areas of the brain and to understand how the human brain works as an integrated whole.

PRINCIPLES AND TECHNIQUES

Numerous apparatuses and guides are now available to approach accurately the desired target in the brain. All ensure a good degree of accuracy, whilst some provide ease and variety of manoeuvrability.

All the instruments use internal landmarks as guides from which one can determine the exact location of the target. During the past three decades, many stereotactic instruments, which are CT compatible, have been introduced. These instruments, while accurate enough for biopsy, do not provide enough accuracy to locate physiological targets in the depths of the brain. Special CT images are needed or the CT scan has to be done with positive contrast ventriculography, to provide clear delineation of the internal landmarks. MR compatible machines provide accurate visualisation of the needed landmarks in the centre of the brain. When such machines are not available, stereotaxic surgery can still be done accurately with air or non-ionic water-soluble contrast X-ray studies. The position of the anterior and posterior commissures and the midline of the brain, which are the common landmarks used, are determined by contrast studies.

Air may be introduced into the ventricles through a lumbar puncture (pneumoencephalography) or through a burr hole (ventriculography). Some workers introduce a water-soluble positive contrast medium into the ventricular system through a burr hole, so as to get a better definition of the third ventricle. In the sagittal and the horizontal planes of reference, the line joining the anterior and posterior commissures is used as the guide. The target point is calculated as so many millimetres above or below the inter-commissural line and as so many millimetres in front of or behind the midpoint of the same line. In the coronal plane, the site of the target is calculated with reference to the midline of the brain, as determined by the centre of the third ventricle demonstrated in the AP view. Although the commissures and the ventricles can be well demonstrated both by ventriculography as well as by PEG, the latter may induce some error in calculation, if air enters the subarachnoid space as this tends to displace the deep brain structures. Such difficulties were encountered in about 14% of cases by Schmidt et al.[41]

To reach accurately the predetermined subcortical target, calculations are necessary which enable one to adjust the direction and the depth of the electrode in relation to the constant reference points. The aim is to get the calculations accurate for each individual brain. In the CT and MR guided machines, once the target is defined, the calculations are made by the computer. In the older technique, it was necessary to use measurements to obviate the centrifugal enlargement of the X-ray pictures obtained by a near X-ray tube with divergent beams.

To fix the measurements of the required anatomical target points in each brain is difficult. Hence, model brain charts are prepared, taking the average of measurements taken from a large number of brains. Racial differences have been identified in brain measurements and separate charts have been prepared from Japanese brains. In general, the experience of more than 1,700 stereotactic operations done at The Institute of Neurology, Madras confirm the belief that Indian brain measurements are similar to European measurements. Kalyanaraman and Ramamurthi[18] found that the length of the third ventricle in patients of Parkinsonism, operated upon in Edinburgh and Madras, did not differ significantly, whereas there was a difference in the measurements of the width of the ventricle, the size being smaller in the Madras population. No autopsy-based accurate measurements are available as yet for Indian brains. Using the average or the model brain chart and calculating for X-ray magnification, the x, y and z co-ordinates are determined to fix the target accurately and also to determine the angle of inclination of the electrode.

There are two types of stereotactic apparatuses that are commonly used; in one type (Spiegel and Wycis)

horizontal co-ordinates are used and in the other polar co-ordinates are used (Leksell, Talairach, Riechert, Sugita and the Brown Todd-Wells apparatus, Cosman-Roberts-Wells apparatus).

In the linear type, the measurement of the target is taken in three planes and then the electrode is introduced in one of the three planes. Adjustment is possible for the needle (electrode) only in the three planes. It is not possible to incline the needle (electrode), as calculations for angle are not included. Hence, to reach different targets, the burr hole has to be made at different sites. In the apparatus that utilises polar co-ordinates, the needle (electrode) can be tilted to the required angle to reach the target. Thus, through one burr hole, different structures can be reached.

Cooper used an instrument which he called a guide. In this apparatus, movement of the needle in various planes is possible. Under X-ray control the needle is advanced to the desired target, the position of the needle being checked by repeated X-rays. Guiot and Gillingham, Bertrand, Narabayashi, Sano, Mackinley, Sehgal and Patil have devised their own machines. The principles used in these apparatuses include those explained above.

STIMULATION AND DEPTH RECORDING

In stereotactic surgery aimed at physiological targets, achievement of anatomical accuracy alone is not enough to ensure a good result. Tasker et al.[45] in a review, found deviations in a significant number of patients between the intended target and the target decided upon by anatomical calculations. Hence, a physiological check is essential to test the accuracy of placement of the electrode. In Parkinsonism, when the proper site is stimulated, there may be an arrest of the tremor for a few seconds. Depending on the frequency of the stimulus, the tremors may also get accentuated. If the tip of the electrode happens to be in the motor part of the internal capsule, motor phenomena resulting from stimulation would indicate that the electrode is not correctly placed. In such a case, it can be withdrawn and reinserted correctly. In temporal lobe epilepsy, a seizure may be induced by stimulation of the target.[47] Stimulation of the amygdala may cause apnoea, or sympathomimetic effects may be obtained from the hypothalamus[3,38] or from the lateral thalamus.[34] This stimulation serves as a method of physiological control. This is the most popular method of physiological localisation. The stimulation is performed at the tip of radiofrequency lesioning electrodes. Stimulation is performed at low current levels (less than 1 mA) and low frequency (2–5 Hz) and the current is increased until an effect is seen. The current is then reduced to sub-threshold levels and the frequency increased until a response is seen. Monopolar stimulation results in greater current spread than bipolar stimulation; the optimal probe is a 1.1 mm bipolar concentric electrode with 0.5 mm pole separation.[45]

Recording of evoked potentials from the nuclei during stimulation of the target is another way of identifying and delimiting the target. The modern technique of using the averaging computer to analyse the evoked potentials has increased the value of such studies. Similarly, evoked potentials recorded from the target on stimulation of peripheral structures are also useful in determining the accuracy of placement. The target in the depth may also be localised by recording the impedance of various areas of the brain.[24]

It is also possible to record the electrical discharges from these deep areas of the brain and the information utilised for locating the various nuclei. Such depth recording is especially useful in surgery for epilepsy. Microelectrodes may be used to record the response from single cells or from a small group of cells to peripheral stimuli (evoked responses). Some groups of cells in the thalamus and subthalamic nucleus fire in unison with the tremor of the limbs, while others precede the muscle contraction. A study of such activity contributes to the accuracy of placement[21] and adds to our understanding of the functioning of those nuclear groups.[4,10,19]

METHODS OF MAKING THE LESION

Temporary Lesions

Once the correct target is decided upon, it is necessary to make a lesion which will be permanent but circumscribed. Before making a permanent lesion, a temporary lesion may be made to enable one to know whether the correct target has been reached and whether benefit will accrue from placing the lesion in the particular area. The original technique of Cooper of inflating a balloon at the tip of the needle was one such procedure. In the techniques that use electrodes, similar temporary lesions can be made by heating the electrode tip to about 40°C for about 20–30 seconds to a level when function would be interrupted. If the placement is satisfactory, then the electrode is heated to coagulation levels. Similarly, when using cold as the lesion-making agent, the cryoprobe can be cooled to about 0°C for 30 seconds to make a temporary lesion, which may later be made permanent by cooling to minus 80°C.

Chemical Lesions

Chemicals have been used for many years to produce lesions during stereotaxic procedures. Alcohol or a mixture of alcohol with myodil or cellulose or bees wax has commonly been used. The danger of these chemicals seeping along the various tissue planes is always present. One can also not be absolutely sure about the shape of the lesion and its direction of spread.

Electrolytic Lesions

By using a diathermy current and coagulating the tissues, precise radiofrequency lesions can be made in the various deep nuclei. Special arrangements have to

be made in the diathermy machine, to make sure that there is no sudden voltage change which would make the lesion inconsistent. With the help of a thermocouple fixed to the tip of the electrode, the temperature at the tip may be increased to the desired level (62.5°C for 2 minutes) so that a constant lesion could be made.[48,50] Radio-frequency lesion-makers are available and help to create a predictable lesion. The optimum size of the lesion is 100–150 mm.[11,49]

Cold Lesions (Cryogenic Lesions)

By using vacuum-insulated probes conducting liquid nitrogen gas, the tip of the probe may be cooled to minus 80°C.[9] After the accuracy of the probe placement has been confirmed by a temporary lesion, by cooling the tip of the probe to 0°C, the temperature of the tip is brought down to minus 80°C and kept down at that level for 3 minutes. This usually produces a frozen lesion about 8 mm in diameter. The size of the lesion depends on the temperature of the tip and the duration of cooling and can be accurately monitored.[27] The tip of the probe is warmed to 20°C before being withdrawn. The temporary post-operative disturbances are minimal when cold lesions are used.

Mechanical Lesions

Mechanical lesion-makers are useful, as one can be sure of the exact extent of the lesion. Small wire leucotomes have been used successfully in may centres.[5] When the needle is in the correct position, the wire is protruded to the required extent (2–4 mm). The leucotome is turned around 45 degrees on each side. The wire is now withdrawn into the leucotome, the direction of the leucotome rotated to 90 degrees and the process is repeated. Such a procedure prevents accidental tearing of any blood vessel that may lie near the tip of the needle.

Lesions can be made by using radioactive substances like radioactive gold or yttrium. It is also possible to make the lesion by using high-energy proton beams. The use of the proton beam obviates the need for a burr hole. The high speed accelerator is so adjusted that the concentration of the protons would be at the target area whose co-ordinates are calculated in the usual manner. Tym and Weynad[46] have used external alpha particle radiation to create lesions. Leksell's group has used gamma rays from a radiocobalt source to make functional lesions.[26]

STEREOTAXIC BIOPSY

Before making a permanent lesion and after one is satisfied regarding the accuracy of placement of the electrodes, it is possible to take a small biopsy from the area of the lesion[11] to study the morphology of the site of the lesion. Histochemical and electron microscopic studies of such biopsy specimens add to our knowledge of the pathological anatomy of the diseased area.

Biopsy Instrumentation

A variety of instruments are available that include cup forceps, spiral needle, side-cutting aspirator, and needle core device. The needle core device is a 14-gauge cannula with a stylet for entry. A core is aspirated at the target site but greatly depends on lesion texture. The side-cutting aspirator is a modification of the needle coring device. It provides a 1.5 × {times} 10 mm cylindrical specimen, but the result also depends on lesion consistency. The cup forceps provides about 1.5 mm specimens and depends less on lesion characteristics. It also provides some assessment of tissue firmness as judged by resistance to palpation of the lesion with the probe tip.

POST-OPERATIVE STUDY OF THE SITE OF THE LESION

As the procedure of stereotaxic surgery is an accurate neurophysiological exercise, it is essential to have an idea of where exactly the lesion has been placed and to correlate it with the results. Only thus can further knowledge be gained. After the permanent lesion is made, to mark the site of the lesion, a small stainless steel ball or an MR compatible radio-opaque marker is introduced through a cannula and pushed into the area of the lesion. By studying the position of the marker on the X-rays, it is possible to chart accurately the site of the lesion on anatomical charts of the brain.[39,40,45] In case myodil wax is used as in amygdalotomy, the insertion of the radio-opaque marker is not necessary.

ASPIRATION OF CYSTS AND HAEMATOMAS

Using stereotactic localisation, a number of cysts, neoplastic and non-neoplastic may be biopsied for diagnosis and then drain them to relieve compression on the brain. When a predominantly cystic craniopharyngioma is encountered in the third ventricle, stereotactic biopsy of the enhancing margin for diagnosis, followed by placement of a catheter into the cyst attached to a large Ommaya reservoir for serial aspirations, is a surgical option. The cyst wall commonly is very thick and resists puncture by conventional biopsy probes, which may result in deviation of the catheter around the cyst wall. To prevent this, the blunt probe is advanced to the wall of the cyst and a sharp inner cannula is used to puncture the cyst wall. The outer probe is then advanced over the inner probe into the cyst cavity. An alternative treatment for recurrent cystic craniopharyngiomas is the use of beta-emitting radioisotopes. Phosphorus-32 is a pure beta emitter with penetration of several millimetres that has shown efficacy in treating cystic tumours,[22,29] provided the cyst wall is competent before isotope instillation; as leakage of isotope into surrounding cisterns may be disastrous. A computed tomography scan with contrast injected into the cyst is sufficient to demonstrate competence. Colloid cysts are amenable to similar

surgical aspiration and, as with craniopharyngiomas, a sharp probe may be needed to puncture the cyst.[12]

A stereotactically guided Archimedes screw-type device has been advocated to evacuate organised deep brain haematomas,[1,7] as well endoscopes may be used to irrigate and evacuate haematomas. Catheter reservoirs may be implanted into the haematoma, followed with streptokinase or tissue plasminogen activator injections to lyse the clot with periodic aspiration.

STEREOTACTIC CRANIOTOMY

Image-guided stereotaxis can be used to guide the surgeon to deep-seated or small tumours that need to be resected. Vascular lesions, such as cavernous malformations and small arteriovenous malformations, can be localised and removed as well. Use of an arc-centred system, such as the Cosman-Roberts-Wells system, allows the surgeon to tailor the incision and bone flap to the lesion, as the pointing device can be rotated out of the field while the craniotomy is performed. After the dura is opened, the probe can be used to guide or create a corridor to the lesion. Tumour-brain interfaces can be detected more easily by correlating the intra-operative position with the stereotactic co-ordinates.

CHRONIC IMPLANTATION

Instead of making an acute lesion, fine electrodes can be left in the desired target in the brain (chronic electrodes) and periodic stimulation and recording may be done. As indicated, small incremental lesions could be made. Such chronic implanted electrodes have to be made of special alloy or stainless steel to diminish tissue reaction.[23,37] Similarly, a chemode can be inserted into a desired area and chemical agents may be delivered to focal areas in the depth of the brain for the relief of seizures, pain, abnormal movements or behaviour disorders.[32]

STEREOTACTIC ANGIOGRAPHY

There are several applications for stereotactic angiography: vessels to be avoided during biopsy or implantation procedures can be visualised, localisation of arteriovenous malformations for radiosurgery or open procedures can be done and specific cortical gyri and sulci can be identified by the positions of cortical arteries and veins.[44] The angiogram is performed with the patient in the stereotactic head frame in the lateral and anteroposterior projections. The referencing system consists of nine points on a radiolucent plate that fits on the four sides surrounding the patient's head. Each film contains 18 points that are related by the degree of separation between them and the divergence of the X-ray beams. Structures located between the two plates can be described in stereotactic space after the appropriate computer programme transformations.

Fig. 2: Leksell's stereotaxy apparatus

TECHNIQUE USING THE LEKSELL'S APPARATUS

The Leksell's apparatus (Fig. 2) has a square frame with opaque markings that help in calculating the co-ordinates. On this, a semicircular frame with an electrode carrier is fitted, so that the electrode may be introduced into the target from any angle. This is one of the simplest and most accurate stereotactic apparatuses and the technique is easily learnt. The apparatus can be modified suitably for further sophisticated use.

The Leksell frame may also be used for spinal stereotactic surgery, but the technical difficulties are too many. Hence, it is better to use a specially made spinal stereotaxic apparatus to make lesions in the upper cervical cord and the brainstem[14] (details about the BRW frame are given in the chapter "Stereotaxy for Brain Tumours").

COSMAN-ROBERTS-WELLS SYSTEM

The head ring, localiser ring and phantom frame of the Cosman-Roberts-Wells system are identical to those of the Brown-Roberts-Wells system. The difference rests in the design of the arc guidance frame. An arc-centred frame similar to those of the Todd-Wells and Leksell systems is used. The four angles of movement and the need for separate entry point calculation are avoided. Anteroposterior, lateral and vertical co-ordinates are accounted for in the arc, placing the lesion in the centre of the sphere with a fixed radius. Consequently, the depth of the probe is fixed and the target is always accessed, regardless of the choice of entry point. The design of the frame allows removal of the arc ring from its base for a 90 degree transposition before placement onto the head ring. This allows a lateral trajectory to the head, useful for acquisition of temporal lobe lesions. Posterior fossa targets can be reached by angling the posterior portion of the head ring inferiorly. This allows a nearly horizontal approach to biopsy infratentorial lesions. The simplicity, flexibility and accuracy of the Cosman-Roberts-Wells frame have made it the preferred stereotactic system.

PHANTOM INSTRUMENTS

Some stereotactic instruments, like Riechert's and Sugita, use the principle of phantom apparatus; the calculations and the adjustments are all made in the phantom set-up

from which they are directly transferred to the frame on the patient's head.

TWO MACHINE STEREOTAXY

It is possible to approach various regions on both sides of the brain by using two stereotaxic apparatuses simultaneously. However, there are instruments available now which facilitate the introduction of electrodes into both halves of the brain. With this technique, it is possible to record and stimulate from one hemisphere while recording from the opposite side. This helps in further understanding of the deep neural mechanisms.[17] However, the CRW system allows lesioning on multiple sites, on either side of the brain in the same sitting without removal of the frame and recalculations, as the system is arc centred.

Simultaneous bilateral lesions in the thalamus have been described by Kalyanaraman and Ramamurthi.[16] It is found that such lesions can be made without lasting side-effects in younger patients, but these are better avoided in the older ones. Making simultaneous lesions in the amygdaloid nucleus for behaviour disorders is a common practice.

Although stereotaxic surgery was initially performed only in adults, it is possible to operate on young children. This becomes necessary for cerebral palsy as well as for behaviour disorders. The Madras group has operated upon patients as young as three years of age.[2]

STEREOTACTIC EXTERNAL BEAM RADIATION THERAPY

General Concepts

Ideal radiation therapy would subject the lesion to very high levels of ionising radiation sparing all normal tissue. This ideal can be approximated with the use of interstitial brachytherapy or external beam radiation (teletherapy). With the advent of computed tomography-guided stereotaxis, radiation may be targeted and focused onto lesions within the brain at a much higher dose than is possible with conventional radiotherapy.

Three methods can deliver this type of radiation. The Gamma knife uses fixed cobalt-60 sources that emit gamma rays (photons) to a focal point 403 mm away.[25,30] A collimator helmet with various diameters is used to alter the volume of radiation emitted. The stereotactic device allows accurate targeting from imaging and places the target at the focal point of the converging gamma rays. The second system that uses photons as an energy source is a modification of the standard linear accelerator (Linac).[6,8,51] Secondary collimators are fitted to the head of the machine, which rotates with intersecting arcs to produce a high concentration of radiation at the isocentre. A stereotactic frame is used to place the target at the isocentre. The last method uses collimated beams of charged heavy particles, such as protons (hydrogen ions) or helium ions.[28] Charged particles have several properties that make them ideal for radiotherapy. They penetrate through matter with a low initial dose, followed by a very high dose at the end of the range of the beam (the Bragg peak), which is well defined for each particle.[18] Immediately after the Bragg peak, the dose steeply falls off. The shape of the radiation field is controlled by specially designed collimators. The width and depth of the Bragg peak can also be modified with tissue compensation techniques. Only a few beams of radiation are required because of the unique physical qualities of charged particles. This mode of therapy is restricted to a few research centres because of the expense required in setting up and running a cyclotron to generate the charged particles.

Clinical Applications

Stereotactic radiosurgery has found its greatest application in the treatment of small, deep-seated arteriovenous malformations, small benign tumours of the cerebellopontine angle and metastatic disease.[42] Obliteration of arteriovenous malformations after radiosurgery is a result of radiation-induced vascular injury, resulting in the thrombosis of vessels and ultimately of the nidus. This effect is delayed, often not seen for as long as 2 years. Although surgical resection is still the mainstay of therapy for acoustic neuromas, stereotactic radiosurgery is gaining popularity, especially in elderly patients with medical illnesses that preclude surgery. Growth arrest of the tumour is seen in most cases, but long-term follow-up is lacking. Tumour shrinkage from radiosurgery usually is minimal, although central necrosis may be seen. The risk of developing a delayed facial neuropathy is 33%, but some degree of recovery is seen in most cases.[31] Following Kelly's development of the technology that made volumetric sterotactic guidance for tumour resection, the targets are being defined as a volume in space rather than a point in space. The stereotactic arc holds a cylindrical retractor aimed at the centre of rotation, which is used to direct the surgeon's view line along the same trajectory as the computer reconstruction. Similar techniques were used for volumetric reconstruction to guide craniotomy, tumour resection and endoscopy.

FRAMELESS STEREOTAXY

With the introduction of computers, frameless stereotactic systems have been developed. These are based on the co-registration of an instrument or a pointer relative to the patient's anatomy, as demonstrated by CT or MRI scans. They are more useful as a guide during craniotomy and are not accurate enough for functional neurosurgical procedures. The first commercial frameless system was developed using a multi-articulated arm attached to the operating table or head holder. With advances in the system, there is no longer a need to use the multi-articulated arm. The use of ultrasonography, light emitting diodes, or video "machine vision" to

localise hand held pointers or instruments in stereotactic space has made them more user friendly.

SPINAL STEREOTAXIC SURGERY

The principles of cranial stereotaxic surgery can be extended to the spinal cord, thus facilitating the placing of accurate small lesions in the various tracts. A simple electrode carrier to make a spinal cord lesion in animals was devised by Clarke in 1920.[14]

As cordotomy after laminectomy carries a good amount of risk for debilitated patients, the technique of percutaneous cordotomy was developed. Spinal stereotaxic surgery is a further step in this direction.

A special stereotaxic frame suitable for spinal surgery was devised by Hitchcock.[14] The midline is found in relation to the AP view of the frame, using co-ordinates based on either the odontoid process or the third and fourth ventricle. By suitable adjustments of the frame, the spinal target in the lateral view can be related to the radio-opaque markings on the horizontal and vertical bars. The vertical and horizontal bars are then rearranged, so they lie within the plane of the target, at the desired laterality from the midline and at the required depth below the frame. An electrode carrier fitted with a Vernier scale is attached to the vertical bars, thus permitting the movement of the electrode tip by 0.1 mm distances. This technique can be used for various types of tractotomy in the medulla and for cordotomy in the upper cervical cord.

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187 Stereotaxy: Brain Tumours

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INTRODUCTION

The fundamentals of stereotactic surgery lie in the understanding of the brain as a three-dimensional structure and the application of the Cartesian co-ordinate system to define a specific region of interest. Any geometric volume can be divided by three imaginary intersecting spatial planes, orthogonal to each other, based on the Cartesian co-ordinate system. The brain is considered as a geometric volume and can thus be defined in the horizontal, frontal and sagittal planes. With reference to the centre point of intersection of these orthogonal planes, any point within the brain can further be defined by precise numerical values termed as co-ordinates. From its conception in the late 19th century, the concept of stereotaxy has evolved from frame-based applications to frameless stereotaxy. Further, the concept has been utilised in the field of radiation therapy to administer a high dose of concentrated radiation to a precise target, termed as stereotactic radiosurgery. In recent times, the addition of stereotactic techniques to endoscopy has added to precision and safety of the procedure.

Classically, stereotactic surgeries are performed using a stereotactic frame, the popular frames are the Leksell, Brown-Roberts-Wells, Patil and Cosman-Roberts-Wells frame. The basic principle of nearly all current stereotactic equipment is firm fixation of the stereotactic apparatus to the patient's skull vault with metal pins. Once the head frame is attached under local anaesthesia, the patient is shifted to obtain magnetic resonance (MR) or computed tomography (CT) images with the reference frame in place. The patient is then returned to the operation theatre, where the procedure is performed. Frame-based fiducials and target points are entered into a computer that calculates the entry points and trajectory.

In the frameless stereotactic technique, the surgeon can navigate through the spine and cranium with image guidance. The CT or MR images of the surgical field are imported into the computer software. A digitising camera senses the position of the surgeon's instruments in space and indicates the position of the instrument on the image displayed on the computer monitor in real time by referencing the co-ordinate system of the brain with a parallel co-ordinate system of the three-dimensional image data of the patient that is recorded earlier. The spatial accuracy of frameless stereotaxy has been further enhanced with the introduction of intra-operative MR imaging (MRI) that provides real-time images to document the residual lesion and to assess brain shift during surgery as the operation proceeds.

Frameless stereotaxy and stereotactic radiosurgery have been dealt with in detail in other chapters. This chapter deals with the application of stereotaxy for brain tumours using the stereotactic frame. Stereotactic techniques, though commonly used in functional neurosurgery, have been widely utilised for brain tumour surgeries mainly biopsy and aspiration of critically located masses or combined with craniotomy for excision of lesions.[32,33,51]

STEREOTACTIC BIOPSY

Stereotactic biopsy is the most common stereotactic neurosurgical procedure performed. Considerable experience has accumulated all over the world with different systems. An obvious limitation of stereotactic biopsy is the small amount of tissue obtained. Several studies have shown good diagnostic yield using combined cytological and histological techniques.[12,17,24,50]

Stereotactic biopsies are generally performed for the following intracranial masses:

- Suspected malignant intraparenchymal tumours in eloquent areas
- Deep-seated lesions
- Multiple lesions
- Patients reluctant for open surgery.

Stereotactic biopsies are avoided in the following conditions:

- Extra-axial lesions
- Superficial (grey-white junction) lesions
- Suspected vascular malformations/vascular lesions.

Stereotactic brainstem biopsy sampling needs special mention. It was first reported by Gleason and his colleagues in 1978 in a series of eight adult patients.[28] Proponents of this procedure claimed that stereotactic biopsies of brainstem lesions were safe, had a high diagnostic yield, and carried low morbidity and mortality rates.[65,70,75] It has also been reported that brainstem tumours were better managed once a definitive tissue diagnosis had been established.[42] More recently, however, with the improved resolution of MRI it has

been recommended that diffuse pontine lesions do not need to undergo routine biopsy sampling and that the procedures should be reserved for patients with a focal mass lesion.[1,14,59,72] Because of the increasing diagnostic capabilities of neuroimaging modalities, the role of stereotactic biopsy sampling for brainstem masses has been refined. In patients in whom a biopsy procedure is indicated, it remains a safe option with excellent diagnostic and prognostic value. Currently the use of biopsy sampling is reserved for a specific subset of patients, particularly those with the following:

- A focal, enhancing, peripontine mass in the midbrain, medulla or peduncle
- A posteriorly exophytic tumour protruding into the fourth ventricle
- A tumour exhibiting an uncharacteristic MRI pattern and is probably non-glial
- Focal, enhancing (especially ring-enhancing) lesions (to identify patients with benign non-neoplastic lesions)
- Clinical or neuroimaging evidence of disease progression in tectal masses.[1,18,58,60]

Procedure

The majority of operations are done under local anaesthesia. General anaesthesia is used only for children and uncooperative adults. Shaving of the head is not necessary. The sites where the pins are to be fixed are cleaned with povidone-iodine topical solution. The head ring is then fixed to the head with the help of pins, after infiltrating the sites with 2% lignocaine. In fully conscious, co-operative patients, the head ring is fixed in the sitting position. While fixing, care is taken to make sure that the likely target is not in the plane of the head ring or the pins so that pin/head ring artifacts do not interfere with the target selection. Then, the patient is transferred to the CT/MR scan table.

The patient is given intravenous contrast medium for the contrast CT scan. Usual slice thickness of CT scan of 8–10 mm is taken. However, for smaller lesions scans are obtained at 1–2 mm thickness. The target chosen is from a contrast-enhancing region, in an area away from ventricular or cisternal spaces. Once the target is chosen, the co-ordinates are obtained from the CT scan monitor depending upon the stereotactic system used. The patient is then shifted to the operation theatre. After sterile cleaning and draping, the stereotactic arc is attached to the head frame and using the co-ordinates the entry point is marked. Local anaesthetic agent is then infiltrated to the area. A burr hole or a craniostomy is done using a twist drill. Once the drill has gone through the bone, care is taken to just puncture the dura without damaging the brain. Care is taken to prevent excess cerebrospinal fluid (CSF) drainage as it may result in shift of the brain and hence the target. Then the arc system is placed over the head ring and co-ordinates are adjusted in such a way that the probe can enter perpendicularly through the centre of the burr hole. The probe is then guided in up to the predetermined depth. The sleeve is withdrawn. About 3–4 bits of tissue are obtained using a biopsy forceps introduced through the outer sheath. The tissue smear is made immediately. If the consistency of the tissue precludes a smear preparation, more than one target is biopsied. In case of cystic lesions, care is taken to obtain the biopsy sample prior to decompressing the cyst. There are several types of biopsy instruments:

- Cup forceps
- Spiral needles
- Side-cutting instruments
- Needle core devices.

Spiral needles and Sedan-type side-cutting instruments have a higher risk for morbidity.[6]

Although stereotactic biopsy is a safe, efficient and valuable procedure. It has a morbidity rate ranging from 0.9 to 15% and mortality rate between 0% and 4.2% in reported series (Table 1). After the stereotactic procedure, a plain CT scan is done after 4 hours to rule out haematoma at the biopsy site or along the course of the probe tract. The site of the biopsy can also be made out by the presence of a dot of air in most of the cases. The relief of pressure effects following decompression of cystic lesions can also be demonstrated by the post-procedure CT scan.

Stereotactic brain biopsies can be performed using frameless stereotaxy, which provides several advantages.[19] The MRI or CT can be obtained any time before the procedure. This flexibility is convenient for scheduling of operation and avoids issues related to transporting the patient after the frame has been fixed. The image guidance workstations can be configured to view the trajectory in which the biopsy needle will travel. The risk of injuring an artery or vein can be minimised by selecting an appropriate entry point and trajectory. The ability to change biopsy targets in the operation theatre is yet another benefit of frameless image guidance. If non-diagnostic tissue is obtained, the target can easily be readjusted without reimaging or arithmetic calculations. This advantage is lacking during a conventional stereotactic biopsy. One potential drawback to using frameless stereotaxy for biopsy is the lack of a rigid frame to serve as a structural support for the biopsy needle. The freehand image-guided advancement of the biopsy needle can increase movement of the needle and decrease accuracy.

Results

Several series of stereotactic biopsies have reported a positive yield between 90% and 96%.[5,15,37,44,45,53,71,75] The non-specific diagnostic biopsies could be classified into two categories:

1. Negative biopsy in which the tissue obtained failed to indicate the nature of the lesion.
2. Inconclusive biopsy in which a representative tissue was obtained, but the definitive diagnosis could not be made.[61]

Table 1: Outcome of stereotactic biopsy in various series

Series	*Year*	*Number*	*Negative biopsy (%)*	*Morbidity (%)*	*Mortality (%)*
Ostertag et al.[52]	1980	302	10.0	3.0	2.3
Edner[20]	1981	345	9.0	2.3	0.9
Mundinger et al.[50]	1985	815	NR	3	0.6
Bernstein et al.[8]	1986–94	300	NR	6.3	1.7
Apuzzo et al.[2]	1987	500	4.4	1.0	0.2
Kelly et al.[35]	1987	261	1.14	0.76	0.38
Thomas et al.[69]	1989	292	7.2	4.7	0.3
Lee et al.[42]	1991	153	7.9	1.3	2.6
Ranjan et al.[61]	1995	390	4.87	3.9	0.4
Regis et al.[60]	1996	370	2.3	0.8	1.3
Ulm and Friedman[71]	2001	200	1.5	2	0
Smith et al.[66]	2005	213	10	2	0
Woodworth et al.[76]	2006	160	9	13	1
Linskey et al.[54]	2009	106	4	4	0

Although experience of the pathologist is the most important factor in the diagnostic yield, the small size of the samples is the major disadvantage of stereotactic biopsy.[27,74] Because it is a two-step procedure that includes interpretation of smear preparations intraoperatively and paraffin preparations post-operatively, there could be some discrepancies between the results of smear and paraffin preparations. In the literature, discordance between smear and paraffin preparations has been reported as ranging from 5 to 38.46%. The presence of massive necrosis and the absence of a diagnostic histological component in the small biopsies were the reported causes of the discordance in those studies.[12,15,27,54] Ostertag et al.[54] reported 5% discrepancy between the diagnosis from the smear preparation and the subsequent histological diagnosis. In cases where only necrosis is detected in smear, the pathologist should acquire additional samples. If the presence of only necrosis persists, the case must be deferred for the paraffin preparations to evaluate the other samples taken for paraffin section. If the only finding is necrosis in the final paraffin sections, rebiopsy or resective surgery must be offered.[6]

The quality of the smears is one of the most important factors in evaluating the cytological details. Improper quality causes difficulties in diagnosis of a glial tumour versus metastasis and gliosis and in the diagnosis between tumours having cytological similarities such as pineocytoma and oligodendroglioma.[6]

The specific method of tissue biopsy likely plays a key role in determining diagnostic accuracy and yield. Earlier series appear to be relatively evenly divided between the use of biopsy forceps or a side-cutting biopsy needle, while many report using both and other surgeons still use needle aspiration techniques.[3,9,25,30,54,62,73] More recent series tend to favour a side-cutting needle exclusively, which has the advantage of preserving a core of intact cross-sectional tissue architecture which facilitates histological interpretation.[25,68,78]

Linskey and Owen[56] used a relatively aggressive biopsy technique which would minimise sampling error and increase the likelihood of an accurate diagnosis. Multiple sections were taken with the side-cutting needle at serial depths along the track to obtain ''geologic core'' with a single needle trajectory, providing samples of normal brain, lesion edge and central contents. The utility of this approach is reflected in the accurate grading of all but one of the gliomas in their series, and in the low number (three) of necrosis—only results in glioblastoma multiforme biopsies. In another series of 407 cases of intracranial masses, there were 19 (4.87%) negative biopsies and three (0.76%) inconclusive biopsies, thus giving a total of 5.64% of non-diagnostic biopsies.[61] Stereotactic biopsy has also been shown to have a high specificity. The diagnostic yield in CT-guided stereotactic biopsy of gliomas is highest at the enhancing margin.[29] The CT morphology of intracranial masses does not seem to influence the positive yield, although a negative biopsy may be more likely with hypodense non-enhancing masses than with enhancing masses. Similarly, an increase in operator experience in stereotactic biopsies does not seem to correlate with a significant increase in positive biopsies.[61] The mortality after stereotactic biopsy has been variously reported as 0.6–2.6%.[44,52,54] Ranjan et al.[61] in their series of 407 patients (this includes all the non-neoplastic lesions as well) who underwent biopsy and aspiration, had two deaths due to procedure related complications. In both there was bleeding at the biopsy and aspiration site. The procedure related morbidity has been reported to be between 1% and 5.9%. Various authors[25,49] have reported that brainstem, pineal and deep-seated lesions are associated with increased

morbidity. Shastri-Hurst et al.[66] have noted the finding of blood intra-operatively in seven cases out of 203 cases as having a positive predictive value of 57% for post-operative deterioration but a sensitivity of only 30%. In Linskey's series,[56] 19% of patients who had persistent intra-operative bleeding which persisted beyond two needle irrigations had significant haemorrhage in the post-operative scan. In general, a morbidity rate of less than 4% (temporary or permanent neurologic deficit) has been reported in various large series (Table 1), hence an aggressive sampling technique can be employed without compromising patient safety. McGirt et al.[49] found that increasing the number of biopsy samples did not independently impact morbidity if the samples were collected along a single needle trajectory.

STEREOTACTIC ASPIRATION

Primary and metastatic brain tumours often have associated cystic components. Conventionally, the presence of a single, large and cystic brain tumour has been regarded as an indication for surgery.[26] Yoshida and Morii advocated surgical treatment for patients with large cystic lesions, providing rapid relief of neurological symptoms caused by mass effect.[79] However, if the lesion is deep within the brain or located adjacent to eloquent areas, surgical procedures may result in severe neurologic deficits. In addition, surgical procedures are not effective or safe for patients in poor general condition or those with multiple lesions. Stereotactic cyst aspiration with or without Ommaya reservoir insertion is a safe and effective alternative procedure in these patients. Possible complications include haemorrhage, focal neurosurgical deficits, seizures and infection.[77]

In cystic lesions, the most dependent portion is chosen as the target and the wall of the cyst is targeted for biopsy. If possible, the biopsy of the wall is obtained before aspirating the cyst, because decompression of the cyst would change the position of the biopsy target. A cannula with a stylet is inserted through the probe holder and at the appropriate depth the sylet is removed and gentle suction applied through the cannula. In cases where a large amount of fluid is aspirated from a cystic lesion, care is taken to prevent entry of air into the cavity. Stereotactic implantation of an intracystic catheter with an Ommaya reservoir placed in the subgaleal space can be used to instil therapeutic agents and to perform frequent aspirations where necessary.[63]

In metastatic tumours located in the eloquent areas or in deep locations with a large cystic volume, it is difficult to remove the tumour completely or subject them for radiosurgery. Because the volume of the lesion is the limiting factor for radiosurgery given that it correlates with the risk of radionecrosis and the cystic component of a metastatic lesion is unresponsive to radiation, the therapeutic effect of gamma knife radio-surgery (GKRS) is reduced. In such situations, stereotactic cyst aspiration followed by radiosurgery could be the better treatment modality than surgical resection. Stereotactic cyst aspiration with or without Ommaya reservoir insertion and GKRS can be performed with a single frame application on the same day in large cystic brain metastases that do not appear suitable for radiosurgery alone.[80]

In order to avoid invasive procedures (transfrontal, transcallosal) in the surgical treatment of colloid cysts the stereotactic aspiration technique was introduced by Bosch, Rahn and Backlund in 1978.[10] Colloid cyst of the third ventricle can be aspirated obviating the need for open surgery. A high incidence of early recurrence was reported by various authors.[48,67] Stereotactic partial cyst wall disruption and content aspiration was then suggested to limit recurrence of colloid cysts, thus offering an advantage over simple stereotactic aspiration alone.[43] The major factor that is predictive of difficulties during percutaneous procedures concerns the high viscosity of the cyst's content, which is correlated with the hyperdensity of the cyst noted in CT scans.[40,46] T2-weighted sequences are useful for predicting the difficulty of aspiration of colloid cysts during percutaneous procedures by stereotactic aspiration. A significant correlation between low signal on T2-weighted fast spin-echo sequences and viscosity (and therefore hard or impossible-to-evacuate) of cysts has been reported by EL Khoury et al.[13] However, with conflicting reports in the literature, it has been suggested that radical removal by open or stereotactically guided microsurgery is the method of choice since stereotactic aspiration fails to offer a radical or permanent treatment for colloid cysts of the third ventricle. Stereotactically placed precise and limited craniotomy, a small cortical opening (10–20 mm), a precise trajectory to the foramen of Monro and standard microsurgical resection has been reported as safe and effective management of patients with colloid cysts.[8,21,41]

In unresectable craniopharyngiomas, the goal of treatment is tumour control and improved length of survival, while maintaining quality of life. The most commonly used alternative treatments have been a biopsy, cyst drainage, or planned partial resection, followed by radiotherapy. One of the typical characteristics of craniopharyngiomas is the presence of a cyst within the tumour. Recurrent collection of fluid in cystic craniopharyngiomas can be periodically aspirated. The aspirated fluid is of prognostic significance as well. Instillation of antineoplastic agents into the tumour, including beta-emitting radionuclides, bleomycin and IFNα into the cyst is an effective option. Bleomycin has been used for intracystic treatment of craniopharyngiomas, both initially and at the time of recurrence. In general, bleomycin has been used for temporary tumour control with the expectation that other therapies, such as resection or radiotherapy, will be required for longer term tumour control. Bleomycin is usually injected into the craniopharyngioma cyst via a subgaleal Ommaya reservoir attached to a catheter, with its tip located in the cyst. One of the concerns with the transventricular route is that there may be toxic effects from spillage of the cyst

contents into the ventricular system. As an alternative to bleomycin, intracystic IFNα has been used for patients with craniopharyngiomas. It is similar to bleomycin in that it provides short-term control of a predominantly cystic tumour and delays more definitive treatment aimed at longer term control. Unlike bleomycin, IFNα does not appear to have any significant major toxicity, even if it spills into the subarachnoid space.[23,31,69]

STEREOTACTIC BRACHYTHERAPY

In conventional external beam radiation therapy (EBRT) for cerebral tumours, the total radiation dose is limited by the potential for damage to the overlying brain. Stereotactic brachytherapy, the temporary or permanent implantation of radioisotopes into brain tumours, is one method of overcoming the limitation of conventional teletherapy. Another advantage is that this mode of therapy can also be employed in recurrent tumours which already have received the maximum tolerated dose of EBRT.[16] For solid tumours, 125 or 1921r sources are most commonly used.[7] The most often used dose rate is of the order of 40–60 rads/hour. At these levels, interstitial irradiation is supposed to achieve a therapeutic ratio superior to conventional teletherapy.[16] For cystic tumours such as craniopharyngioma, 90 Yt or 32P has been used. The beta-emitting radionuclides are instilled after stereotactic puncture of the cyst and the appropriate dose is calculated on the basis of the size of the cyst. The goals of intracavitary radiotherapy are reduction of the cyst and long-term control of the tumour, in many respects similar to the goals of EBRT. Regardless of the beta-emitting radionuclide used, intracavitary radiotherapy reduces the size of the cyst in 50–100% of cases, according to different case series.[11,36,57]

Iodine-125 interstitial irradiation has been used for gliomas, pinealomas, brainstem tumours, recurrent meningiomas, solid craniopharyngiomas and metastases. Due to financial reasons, gamma knife and Linac are not available widely in many countries and neurosurgical institutes. In the absence of the above mentioned radiosurgical methods, brachytherapy is an alternative solution in the treatment of different types of inoperable or recurrent brain tumours. One of the negative aspects of intracavitary radiotherapy is the difficulty in accessing the radioisotopes and the complexity of the process for instillation of such materials into the cyst.

STEREOTACTIC CRANIOTOMY

The stereotactic system can be effectively combined with conventional neurosurgical craniotomies for treating smaller lesions located in deeper or eloquent areas and helps in reducing morbidity. Stereotactic and computer-assisted techniques have revolutionised the diagnosis and treatment of many brain disorders, enabling the surgeon to adopt the least traumatic approach. These stereotactic methods were initially introduced by Kelly, using a frame-based stereotactic system.[37] Frame-based systems are designed to mechanically constrain instrumentation to a direct path to tumour tissue. Stereotactic craniotomy is most useful for small, deep-seated lesions where reliance on surface anatomic landmarks can be misleading. Furthermore, for convexity lesions, stereotactic guidance can allow for smaller, more localised craniotomies than would be possible with the use of surface landmarks. Normally for this procedure seven targets are chosen—lesion centre, lateral edge, medial edge, posterior edge, anterior edge—these five are calculated from the same axial slice, and the superior edge and inferior edge—these are calculated from slices showing the upper and lower limits of the lesion. The calculation of multiple target co-ordinates enables a more accurate planning of the craniotomy as well as aiding in volumetric excision. The initial procedure is similar to stereotactic biopsy. It can be carried out under conscious sedation (awake craniotomy) or under general anaesthesia. The posterior, anterior, superior and inferior edges of the lesion are marked out on the skin using the sterile pointer—this procedure outlines the lesion. Generally the centre target is used to plan the trajectory. Once the outlining is over, the arc is swung away and craniotomy performed. Before opening the dura, the arc is swung back and the trajectory confirmed. Further surgery is the standard procedure of tumour excision. In deep-seated lesions the sterile pointer may be passed directly into the target and locked in position. This will act as a guide to the target, with dissection being carried around the pointer. There is inevitably some movement of the brain on performing a craniotomy, even under stereotactic conditions, and this will affect the accuracy.[22,34,51,64]

STEREOTACTIC ENDOSCOPY

Cerebral endoscopy has been used to approach an intracerebral tumour for visualisation, irrigation, tumour cyst wall puncture, aspiration and biopsy.[2,4,5] The use of endoscopy for the management of intraventricular brain tumours has evolved from simply treating the associated hydrocephalus, to sampling of tumour tissue, to tumour resection. Planning the entry point and trajectory is often the most crucial aspect of the surgical procedure; this step can be guided by stereotaxy. An entry site must be selected that provides a direct, linear route to the cyst to accomplish two distinct goals:

1. One is to minimise any torque on the cortical or intraventricular neural tissue.
2. The second is to allow direct, inline access to the distal edge of the cyst wall; the edge abutting the CSF-containing cistern into which the cyst will be fenestrated.[47]

The application of stereotactic techniques to endoscopy enhances both precision and safety. The custom made modifications in the endoscope can provide multiple capabilities to bring about such functions.[2,38,39] Stereotactic endoscopy has the advantage of control over depth penetration and precise trajectory to deep-seated lesions under direct vision.

In colloid cysts stereotactic aspiration may at times be unsuccessful due to the viscosity of the intracystic colloid and the displacement of the cyst away from the aspiration needle. The CT/MR-guided stereotactic endoscopic technique gives the opportunity to fenestrate the cyst wall under direct visual control. After CT-guided stereotactic puncture of the right lateral ventricle with the foramen of Monro as the target, a steerable endoscope is introduced and the foramen of Monro is passed. The wall of the cyst is fenestrated and coagulated by means of monopolar (or laser) coagulation. Continuous rinsing is mandatory to preserve clear vision.[20]

Stereotactic endoscopic resection of intra-axial brain tumours using an endoscopic system consisting of a stereotactic guiding tube and a fine endoscope was reported by Otsuki et al.[55] The stereotactically inserted guiding tube acts in the place of brain retractors to expose deep-seated pathological lesions, which are then visualised by means of a fine endoscope. The lesion was then treated by various microsurgical techniques such as laser vaporisation. This system was reported to be particularly useful for removing small intra-axial tumours in deep or eloquent areas which are difficult to resect using ordinary surgical techniques. Johnathan et al.[35] developed a minimally invasive microsurgical technique for intraventricular surgery using parallel endoscopy to visualise the lesion. Surgical resection was performed via an 11.5 mm transparent conduit (neuroendoport) deployed under stereotactic guidance, termed as stereotactically guided endoscopic port (SEP) surgery. They reported that this technique was not limited by the vascularity, friability or size of the lesions. They concluded that SEP surgery for colloid cysts and intraventricular tumours was a safe and effective alternative to conventional microsurgical resection.

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188 Involuntary Movements: Anatomy and Pathophysiology

Srinivasan AV

INTRODUCTION

The extrapyramidal system (EPS) is more of a functional concept derived primarily from the study of patients with neurological disease than an anatomical or physiological entity. The term "extrapyramidal" was first used by Wilson while describing Wilson's disease.

Extrapyramidal disorders lead to a category of neurologic illnesses now more often referred to as movement disorders. Such a disturbance may cause excessive movements—Huntington's disease (HD) or a poverty of movements—Parkinson's disease (PD), or a disturbance of tone, posture or other manifestations.[1]

The EPS is phylogenetically old. Much of its functions are confined to modulation of the pyramidal system rather than by direct projection to the spinal cord. The term basal ganglia (BG) is given to the grey nuclear masses that are located subcortically and are derived from the telencephalic ganglionic hill of the embryo.[4]

These ganglia consist of the caudate nucleus (CN), putamen, globus pallidum, claustrum and amygdaloid nuclear complex. In addition, the related structures, i.e. substantia nigra (SN), subthalamic nucleus (STN) and red nucleus (RN) are also included.[13] The CN and putamen are functionally related as also the SN and globus pallidum.

The caudate, putamen and pallidum are known as corpus striatum. The caudate and putamen are together called neostriatum and the phylogenetically older globus pallidus (GP) or pallidum carries the name paleostriatum. For purposes of discussion, striatum refers to the neostriatum. The putamen and GP are commonly spoken of as one unit using the term lentiform nucleus or lenticular nucleus with the putamen lateral to the GP, which lies like a wedge between the internal and external capsules.[9]

The putamen develops from the telecephalon while the pallidum develops from the diencephalon. The caudate and putamen are identical histologically. They contain few large and many small neurons with the small cells predominating in the ratio of 20:1. The dendrites may be spiny or aspiny.[13]

The most common cell type in the striatum is small and spiny and contains GABAergic neurons along with either substance P (SP) or enkephalin (ENK). The small spiny neurons are the primary source of striatal efferents. The small aspiny neurons are cholinergic.[5]

The microstructure of the striatum consists of a matrix and striosomes. In the CN the matrix contains cholinergic neurons while the striosomes primarily contain SP neurons (D1 dopamine receptors) and ENK neurons (D2 dopamine receptors).

The striosome—matrix is not evident in the putamen as in the caudate and consists mostly of matrix. The cholinergic neurons of the matrix are facilitatory to the projection neurons and are inhibited by dopamine.[4]

The GP is medial to the putamen and separated by the external medullary lamina. Internally, the GP is divided by the internal medullary lamina into a lateral part [globus pallidus externa (GPe)] and a medial part [globus pallidus interna (GPi)].[13]

The GP contains only about 5% as many cells as the striatum and all are large neurons. Neurons throughout the GP use primarily gamma-aminobutyric acid (GABA) as a neurotransmitter and less use Ach. The associated neuropeptide is SP in the GPi and ENK in the GPe.[4]

The SN consists of the substantia nigra compacta (SNc) which contains large melanin containing dopaminergic neurons and substantia nigra reticulata (SNr) which contains large, multipolar, non-pigmented GABAergic neurons similar to those in the GPi.[5] The SNr is closely related functionally to GPi.

Other important structures involved in the extrapyramidal motor control system include the thalamus, RN, the brainstem reticular formation, the inferior olivary nucleus in the medulla, zona incerta, the pedunculopontine nucleus (PPN), and the grey matter of the quadrigeminal plate.[10,13]

The PPN is a cholinergic nucleus that lies caudal to the SN in the brainstem tegmentum, partially buried in the superior cerebellar peduncle. It receives afferents from GPi and sends cholinergic projections to the dopaminergic neurons in the SNc. This may be involved in locomotion, and dysfunction of the PPN may be important in the pathophysiology of the locomotor and postural disturbances of Parkinsonism.

The BG have rich connections with one another and also with brainstem structures, the cerebral cortex and with lower centres. In essence, the cerebral cortex projects to the striatum which in turn projects to the GP and SNr; efferents go to the thalamus, which projects back to the cerebral cortex primarily to the motor areas.

MAJOR BASAL GANGLIA PATHWAYS

Connections of the Basal Ganglia

The BG is part of a complex network of neuronal circuits organised in parallel to integrate activity from different cortical regions.[7,13]

Striatal Afferents

Striatum forms the main input zone of the BG.

Corticostriate fibres: The major inputs to CN are from the entire ipsilateral neocortex which is arranged somatotopically. The head of the CN receives afferents from the frontal lobe, the body from the parietal and occipital lobes and the tail from the temporal lobe.

The putamen (mainly medium spiny neurons) receives projections from areas 4 and 6, the parietal lobe and perirolandic motor areas.

Thalamostriate fibres: The striatum receives afferents from the dorsomedial and ventral anterior nucleus of the thalamus.[13]

Nigrostriate fibres: The SNc sends fibres to the striatum which liberate dopamine at their terminals and are inhibitory in function.[6]

Brainstem striatal fibres: Brainstem raphe nuclei from the locus ceruleus also send ascending fibres to the striatum.[7,13]

Striatal Efferents

The primary efferent fibres project to the GPi. They have GABA as their neurotransmitter. The CN also sends fibres to the putamen and to the thalamus.[4]

Striatonigral fibres: Fibres pass from the CN and putamen to the SN. Some of the fibres use GABA or Ach as the neurotransmitter while others use SP.[3]

Pallidal Afferent

Striatopallidal fibres: The principle afferents to GP are from the CN and putamen. They have GABA as their neurotransmitter.

There are also afferents from STN, thalamus, SNc and from areas 6 and 4.

Pallidal Efferent

The pallidal efferents are the principal outflow of the BG. They are:

- Fasciculus lenticularis
- Ansa lenticularis
- Pallidotegmental fibres which arise from GPi
- Pallidosubthalamic fibres which arise from GPe.

Both the ansa lenticularis and fasciculus lenticularis have the same origin, the GPi, the same destination, the thalamus; the difference is that the fasciculus penetrates through and the ansa curves around the internal capsule.

Pallidofugal fibres are often discussed in terms of their relationships to the "fields of Forel".

Pallidofugal fibres stream into the prerubral field (lies just rostral to the RN, Forel fields H) and as they ascend towards the thalamus, they divide into a dorsal stream (consist of the lenticular fasciculus, Forel field H2) and ventral stream (consist of the thalamic fasciculus, Forel field H).[1,4]

Subthalamic Nucleus

The connection to STN is the only pallidal efferent to arise from GPE, all others arise from GPi. The STN sends back fibres to GPe and to GPi through the subthalamic fasciculus.

Substantia Nigra

Afferents: This includes:

- Striatonigral fibres: SNr receives fibres from the striatum, Gp and STN

Efferents: This includes:

- Nigrostriatal fibres
- Nigrothalamic fibres
- Nigrotectal fibres: It connects SN with the ipsilateral superior colliculus and is concerned with the control of eye movements. There are also connections between SN and PPN and reticular formation.[4]

FUNCTIONAL ORGANISATION OF THE BASAL GANGLIA AND OTHER PATHWAYS

Afferent projections to the striatum arise from all areas of the cerebral cortex, the intralaminar nuclei of the thalamus, mesencephalic SN, and from the locus ceruleus and raphe nuclei. There is also a projection from the cerebral cortex to the STN. The major efferent projections are from the GPi and SNr to the thalamus and brainstem nuclei such as PPN. The GPi and SNr project to ventral anterior and ventrolateral thalamic nuclei. The GPi also projects to the centromedian thalamic nuclei and the SNr projects to the mediodorsal thalamic nuclei and superior colliculus. The ventral anterior and ventrolateral thalamic nuclei then project to the motor and premotor cortex. This circuit is somatotopically organised throughout the loop so that the leg is represented dorsally, the face ventrally and the arm in between. Movement related neurons are found mainly in the posterolateral region of BG.

The BG have dense internuclear connections exemplified by the box and line circuit diagrams that have become entrenched in the literature. Five parallel and separate closed circuits through the BG have been proposed. These are the motor, oculomotor, dorsolateral prefrontal, lateral orbitofrontal and limbic loops. It is now generally agreed that these loops form three major divisions—sensorimotor, associative, and limbic, that are related to motor, cognitive and emotional functions, respectively.[9]

The functions of the sensorimotor striatum are subserved mainly by the putamen, which derives its afferent cortical inputs from both motor cortices. Sensorimotor pathways are somatotopically organised and the pathway ultimately terminates in the premotor and primary

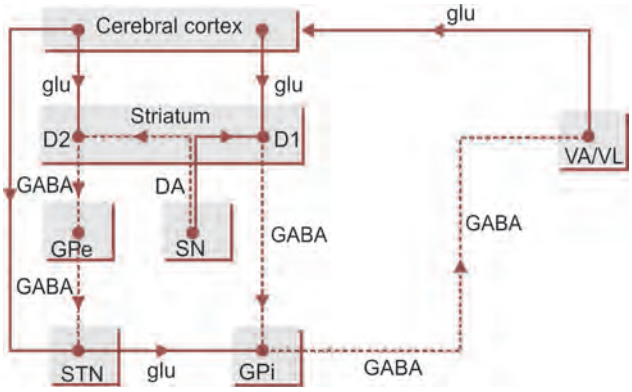

Fig. 1: Modified schematic drawing of the internuclear connections of the basal ganglia, including (A) direct and indirect pathways and depicting (B) the direct pathway. (See figure 2 for a depiction of the indirect pathway). Excitatory pathways in solid lines, inhibitory pathways in dotted lines. GPe = external segment of the globus pallidus; SN = substantia nigra; STN = subthalamic nucleus; GPi = internal segment of the globus pallidus; VA/VL = ventral anterior/ventrolateral thalamic nuclei; glu = glutamate; GABA = γ-aminobutyric acid; D2 = dopamine D receptor; D1 = dopamine D receptor; DA = dopamine

motor cortices and the supplementary motor area. Cognitive functions are managed by the associative striatum. In this pathway, the dorsal CN receives afferent input from the homolateral frontal, parietal, temporal and occipital cortices. Projections from this pathway ultimately terminate in the prefrontal cortex. The limbic striatum subserves emotional and motivational functions. Its input derives from the cingulate, temporal, and orbitofrontal cortices, the hippocampus, and the amygdala. It comprises mainly the ventral striatum with ultimate projections to the anterior cingulate and medial orbitofrontal cortices. Whether these divisions are interconnected or organised in parallel remains a topic of debate.[13]

Within each BG circuit lies an additional level of complexity. Each circuit contains two pathways by which striatal activity is translated into pallidal output. These two pathways are named the direct and indirect pathways, depending on whether striatal outflow connects directly with the GPi or first traverses the GPe and STN (Fig. 1). The direct and indirect pathways have opposite effects on outflow neurons of the GPi and SNr. A closer look at the motor circuit illustrates this principle.

In the motor direct pathway, excitatory neurons from the cerebral cortex synapse on putaminal neurons, which in turn send inhibitory projections to the GPi and its homologue, the SNr. The GPi/SNr sends an inhibitory outflow to the thalamus. Activity in the direct pathway disinhibits the thalamus, facilitating the excitatory thalamocortical pathway and enhancing activity in its target, the motor cortices. Thus, the direct pathway constitutes part of an excitatory cortical-cortical circuit that functions to maintain ongoing motor activity.

In the indirect pathway, excitatory axons from the cerebral cortex synapse on putaminal neurons. These neurons send inhibitory projections to the GPe. The GPe sends an inhibitory projection to the STN. The net effect of these projections is disinhibition of the STN. The STN in turn has an excitatory projection to the GPi. Activity in the indirect pathway thus excites the GPi/SNr, which in turn inhibits the thalamocortical pathway.[1,4,9,13]

Thus, the net effect of increased activity in the indirect pathway is cortical inhibition. The striatum also receives a robust afferent input from the SNc. This projection, from the SNc, an important modifier of striatal activity, facilitates activity in the direct pathway and inhibits activity in the indirect pathway, thus promoting cortical excitation through both pathways.

In addition to these pathways there are other closed loop circuits, which seem designed to modulate and regulate the excitability of the BG themselves.[9,13] Several circuits may be recognised which are as follows:

- The centromedian/parafascicular (CM-Pf) thalamic nuclei striatum GPi CM-Pf circuit, which is probably a positive feedback loop leading to increased neuronal activity
- The CM-Pf STN GPi CM-Pf circuit, which is probably a negative loop leading to reduced neuronal activity
- The STN GPe STN circuit, which is an excitatory-inhibitory loop with "autostabilising" characteristics
- The STN-GPe/GPi dual projection, which is an "open" but inter-connected loop by which the STN might induce excitation and inhibition of the same GPi neurons within less than 5 ms
- The primary motor cortex (area 4) STN GPi motor thalamus area 4 loop, which is perfectly suited to provide inhibitory feedback signalling to the cortex and probably very relevant for the termination of movement.

The dopaminergic system innervates all BG nuclei and probably exerts a powerful modulatory control of the above-summarised circuits. The mesencephalic dopaminergic system stems from three main cellular groups known as areas A8, A9 and A10. Mesencephalic dopaminergic neurons are now divided according to their topographical distribution and chemical characteristics.[13] Neurons in the dorsal tier of the SN mesencephalic region (including some SN cells, VTA, and retro rubral area) are loosely spaced and are positive for calbindin D. These neurons project mainly to the limbic and associative areas of the striatum. On the other hand, cells from the ventral region of the SN mesencephalic region, which are calbindin D negative but rich in dopamine transporter, give rise to the major dopaminergic projection to the motor regions of the BG.[7,13]

Two different types of axonal projections have been recently distinguished:

1. Neurons with a long axon travelling directly to the striatum and emitting no collaterals, which mainly innervate specific zones of the striatum known as "patches" or striosomes.

2. Neurons producing axons that are profusely arborised and mainly innervate extrastriatal nuclei such as the GPe, GPi, STN and even the thalamus. The latter type of cells in the ventrolateral tier of the SN, which appear arranged in columns penetrating into the SNr, seems to be the first to degenerate in PD.[4,11]

Disorders of the BG result in prominent motor dysfunction, though not generally in frank weakness. The absence of direct primary or secondary sensory input and the lack of a major descending pathway below the level of the brainstem suggest that the BG moderates rather than controls movement. In the simplest sense, the direct and indirect pathways have opposite effects on the cerebral cortex. The direct pathway is important in initiation and maintenance of movement and the indirect pathway helps with suppression of extraneous movement.[7] From this model of BG connectivity, hypotheses about the motor function of the BG have been proposed. One hypothesis is that the relative activities of the direct and indirect pathways serve to balance the facilitation and inhibition of the same population of thalamocortical neurons, thus controlling the scale of movement. A second hypothesis proposes that direct pathway mediated facilitation and indirect pathway mediated inhibition of different populations of thalamocortical neurons serve to focus movement in an organisation reminiscent of centre surround inhibition. These hypotheses related activity in the direct and indirect pathways mainly to rates of firing in the STN and GPi.[7,12,13] Thus, death of neurons in the SNc decreases activity in the direct pathway and increases activity in the indirect pathway (Fig. 2). These changes cause an increased rate of firing of subthalamic and GPi neurons with excessive inhibition of thalamocortical pathways and produce the behavioural manifestations of bradykinesia in PD. On the other hand, selective loss of indirect pathway neurons, as in HD, interferes with suppression of involuntary movements.[12] Choreic involuntary movements are the usual result. Direct electrophysiological recordings of the STN and GP during stereotactic functional neurosurgical procedures confirm that the GPi and STN are overly active in patients with PD. The activity of these nuclei returns toward normal with effective pharmacotherapy, and chorea is associated with lower firing rates of neurons in these nuclei. Unfortunately, this model does not completely explain some important features of movement disorders. For example, bradykinesia and chorea coexist in HD and in treated PD.[2,8] Thalamic lesions that might be expected to worsen Parkinsonism by reducing excitatory activity do not do so. Pallidal lesions that might be expected to worsen chorea by decreasing inhibition in thalamocortical pathways instead are dramatically effective at reducing chorea. The model is even more problematic when applied to dystonia. It has been suggested that, in dystonia, there is overactivity of both the direct and indirect pathways. Yet, intra-operative recordings in dystonia show low rates and abnormal patterns of neuronal activity in the GPI.[2,8,14] A simple change in firing rate of the STN or GPi is thus insufficient to explain the underlying physiology of dystonia. It is likely that disordered patterns and synchrony of pallidal firing as well as changes in sensorimotor integration and the control of spinal and brainstem reflexes are important.

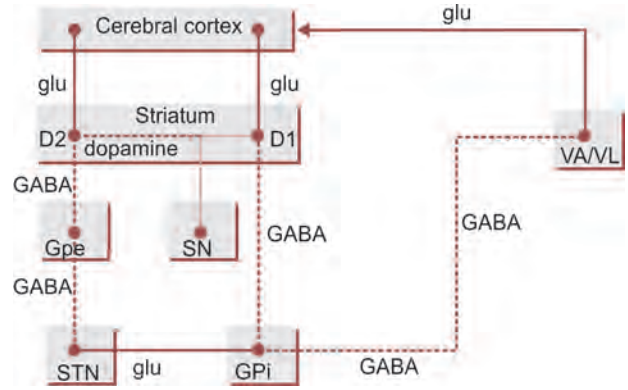

Fig. 2: Modified schematic drawing of the functional activities of the direct and indirect pathways in Parkinson's disease. Reduced dopaminergic facilitation of the direct pathway and inhibition of the indirect pathway due to death of dopaminergic neurons causes increased firing and increased inhibition of thalamocortical pathways, causing reduced inhibition in thalamocortical pathways with the production of excessive or involuntary movements

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190 Surgery for Movement Disorders

Paresh K Doshi, Animesh Upadhyay

INTRODUCTION

Movement disorders, such as Parkinson's disease (PD), tremor and dystonia, are among the most common neurological conditions, and affect millions of patients. Although medication is the mainstay of therapy for movement disorders, neurosurgery has played an important role in their management for the past 60 years. Surgery is now a viable and safe option for patients with medically intractable PD, essential tremor and dystonia.

HISTORY OF MOVEMENT DISORDER SURGERY IN INDIA

Stereotactic surgery started in India as early as 1960. Balasubramaniam and Ramamurthi performed chemopallidectomy using Cooper's balloon in 1962.[18] From 1964 they used the Leksell's apparatus to perform thermal lesions for movement disorders.[5] Kalyanaraman performed bilateral simultaneous thalamotomies in patients with various movement disorders using two different stereotactic apparatus (Sehgal frame and Leksell frame). They observed that the complication rate was acceptable and no greater than staged procedures in patients with advanced PD. In patients with bilateral intention tremors this formed a good surgical option as it avoided two hospitalisations.[32]

Another area of interest was cerebral palsy. Following the work of Narabayashi,[56] Balasubramaniam and his colleagues operated upon a large number of cerebral palsy patients. As their experience evolved they chose different targets depending on the predominant symptom complex. For rigidity they made a lesion in the area below the ventrolateral nucleus (VL); for dyskinesias they used a variety of targets including the ventralis intermedius nucleus (Vim), the centromedian nucleus (CM) and the dentate nucleus of the cerebellum. As most of these surgeries were done under general anaesthesia verification of the electrode placement by stimulation as done in PD was not possible. Stimulation was still done to exclude electrode placement in the corticospinal tract.[33] They later on introduced stereotactic dentatectomy for patients with predominant spasticity. They found that VL and sub-VL lesions were effective for rigidity, whereas for patients with a mix of rigidity and spasticity these lesions had to be supplemented by dentatectomy. Patients with sensory induced involuntary movements benefited from centromedian thalamotomy.[3]

For severe hyperkinetic disorders, Kanaka found hypothalamotomy to play a distinct role in their management. She observed that it works because the area destroyed forms part of the limbic system. It seemed to be more on the "effector" side. It does not cause any morbidity. However, in the management of hyperkinetic behaviour disorders the first target to be destroyed used to be the amygdaloid nucleus. If this operation failed hypothalamotomy was performed.[4]

HISTORY OF MOVEMENT DISORDER SURGERY—WORLD (EXCLUDING INDIA)

Various surgical approaches, such as resection, lesioning, stimulation and others, have been used to treat patients with movement disorders. Craniotomies were performed for the resection of the motor cortex,[17] cerebral peduncles,[81,82] and a variety of subcortical lesioning procedures.[70] Irving Cooper[19] first reported the effects of ligation of the anterior choroidal artery for PD in 1953. Six patients were treated with eight ligations, which resulted in significant alleviation of rest tremor, rigidity and contralateral cogwheeling. It was not until the introduction of stereotaxis by Spiegel et al.[69] in 1947, and later by Leksell[46] in 1949, that a more accurate, less invasive and more consistent placement of lesions in various subcortical locations became feasible. The development of stereotaxy led to a variety of lesioning procedures of the basal ganglia and the thalamus for the treatment of rigidity and tremor in the 1950s and 1960s. The motor thalamus and the pallidal targets in the ventral and posterior portions of the globus pallidus internus (GPi) as well as the pallidal projections were considered to be the most effective targets. However, it was the advent of L-dopa in the mid-1960s and its significant clinical benefits that led to a dramatic decrease in surgery for PD. For the next 20 years, surgery for movement disorders was predominantly limited to thalamotomy[2] for the treatment of tremor and pallidotomy and thalamotomy for dystonia.[50,59]

It was not until the late 1980s that there was a re-emergence of interest in the neurosurgical treatment for PD due to the increasing realisation of the limitations of PD medications and the side effects of L-dopa. This led

to a resurgence of lesioning surgeries such as pallidotomies for PD. The initial Leksell[72] target of pallidal lesions for treatment of PD was modified and repopularised by Laitinen et al.[42,43]

Original analytical descriptions of thalamic nuclei and circuitry by Hassler,[29] Hassler et al.[28] and Macchi and Jones[52] and basal ganglia circuitry by Delong et al.[21,22] also served as a foundational substrate for newer targets for therapeutic interventions using stereotactic techniques. The ability of electrical impulses to modify functional outcome in certain brain regions was identified more than 200 years ago, in 1809, by Rolando.[25] The use of electrical stimulation to understand and map the function of the human brain and its circuitry became commonplace in the 20th century.[15,16] Early explorations by Hassler et al. revealed that acute low-frequency stimulation during stereotactic exploration for ablation of the pallidum could augment tremor, whereas high-frequency stimulation at 25–100 Hz had the opposite effect.[15] These observations paved the way for the future development of chronic electrical stimulation therapies for the management of movement disorders. The first systematic use of chronic deep brain stimulation (DBS) for the treatment of movement disorders is attributed to Bechtereva et al.[6] from Russia. Beginning in 1967, they reported benefits with chronic DBS of the thalamus, striatum and pallidum. But it was not until the 1980s that Brice and McLellan,[11] Blond and Siegfried,[10] Siegfried and Shulman[66] and Benabid et al.[9] published reports of the use of chronic electrical stimulation or DBS for the treatment of movement disorders, thus ushering in a new era of functional neurosurgery for movement disorders. DBS has similar efficacy as that reported with various lesioning procedures (e.g. pallidotomy and thalamotomy). However, the superior safety profile of DBS relative to lesioning procedures, particularly bilateral thalamotomy and pallidotomy, has made it the procedure of choice in countries where access to this technology is available. DBS, with its inherent features of reversibility and adjustability, has gained popularity and emerged as the neurosurgical standard of care for movement disorders, such as PD, dystonia and essential tremor, over the past 20 years.[1]

Movement disorders can be classified according to the predominant motor manifestations (Table 1). For this chapter we have reviewed the therapies for more common movement disorders, i.e. tremors and various forms of dystonias. Surgical treatment for PD is reviewed elsewhere.

Table 1: Clinical classification of movement disorders

Akinetic—rigid form
Parkinsonism: Parkinson's disease; Parkinsonian syndromes
Stiff man syndrome
Hyperkinetic forms
Chorea syndromes
Dystonias
Myoclonus
Ballism
Tics
Atactic movement disorders
Cerebellar ataxias
Spinocerebellar degeneration

Table 2: Tremor classification and treatment

Tremors classification
Parkinson's disease
Essential tremor
Post-traumatic and Post-hemiplegic tremors
Tremors from multiple sclerosis
• STN is the target of choice for PD tremor
• Vim nucleus of thalamus is the target of choice for other tremors
• Thalamotomy for unilateral cases/thalamic stimulation for unilateral or bilateral cases
• Bilateral thalamotomy has high morbidity
• More than 90% success rate in relieving tremors by either procedure
• Major morbidity is less than 5%

TREMORS

Tremor is an unintentional (involuntary), rhythmical alternating movement that may affect the muscles of any part of the body. Tremor is caused by the rapid alternating contraction and relaxation of muscles (Table 2).

The thalamus is involved in the genesis of various types of tremors. It functions as a relay nucleus in the cortico-basal ganglia-thalamocortical loop in Parkinsonian tremor, the premotor cortex and cerebellar thalamic connections in cerebellar types of tremors, and the premotor cortex and connections with the triangle of Mollaret[27] in essential tremor and brainstem tremor, or Holmes tremor.[23] Although part of the motor thalamus [ventralis oralis posterior (Vop) and ventralis intermedius] is considered as the target of choice for tremor relief by stereotactic neurosurgery[67] recently, tremor suppression in PD was also demonstrated after surgery of the globus pallidus[51,54] and subthalamic nucleus (STN).[37,63] Tremor can be objectively evaluated using –NIH essential tremor consortium diagnostic criteria for essential tremor[12] and Fahn-Tolosa-Martin tremor rating scale for tremor outcome.[71] Good control of tremor is defined as more than 66% control; moderate is 33–66% and poor outcome is defined as tremor control less than 33%.

The most common types of tremor amenable to stereotactic neurosurgery are PD tremor, essential tremor, tremors due to multiple sclerosis (MS), stroke and post-traumatic tremor. The Vim nucleus of the thalamus, as defined by Hassler, is the currently preferred target for tremor suppression (Fig. 1). Thalamotomy or thalamic stimulation can be offered for unilateral tremor. However, bilateral thalamotomy carries a significant risk of morbidity of speech and cognition and hence is not

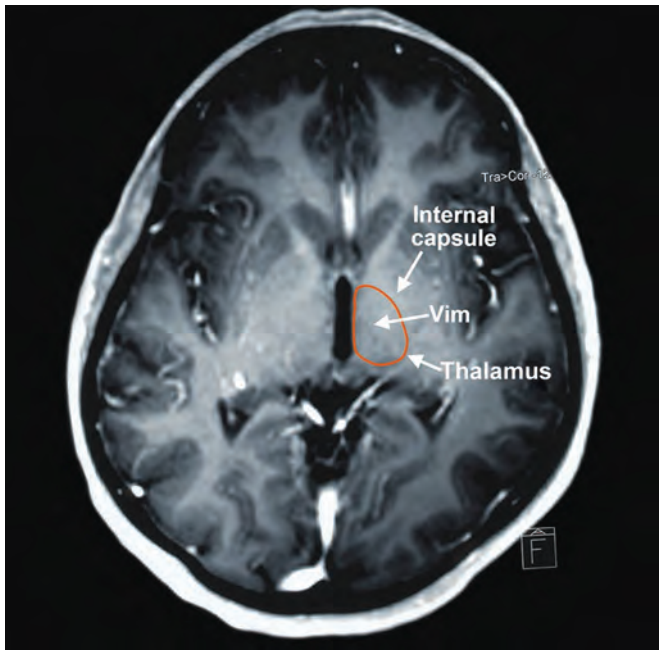

Fig. 1: MRI at the level of AC-PC showing different thalamic nuclei including Vim

currently practiced. The results of thalamotomy and thalamic stimulation are dependent on the type of tremor aetiology and are discussed separately.

Parkinsonian Tremor

Unilateral thalamotomy results in a permanent significant improvement of Parkinsonian tremor in approximately 80% of the patients. Permanent morbidity is 4–47% and mortality is below 1%.[31,34,55,64,77] In 1991, Benabid and his co-workers reported tremor suppression in 88% in 26 patients undergoing thalamic stimulation with very low morbidity, making bilateral surgery possible.[8] These findings were confirmed in a multicentre European study.[47] Lozano and associates described an improvement of tremor after unilateral pallidotomy in patients with advanced PD.[51]

Pallidal and STN stimulation may give both striking and lasting suppression of Parkinsonian tremor. Permanent adverse events are less frequent and less severe with these targets after bilateral stimulation as compared to the thalamic target. Another advantage of this procedure is simultaneous reduction in rigidity and dyskinesia with improvement in bradykinesia. These procedures have replaced thalamic surgery in patients with advanced PD even with severe tremor. STN is the target of choice for advanced PD, including patients with severe tremor. We prefer to perform bilateral surgeries (especially DBS) in PD patients as we feel that PD is a bilateral disease and will eventually need bilateral control to improve quality of life. However, there are some exceptions, for example, in a small proportion of Parkinsonian patients with a long history of tremor and a slight bradykinesia, well-controlled by medication, a unilateral STN stimulation can be considered. Patients who cannot afford DBS can also be offered STN lesioning with good outcome.

We have performed nine thalamotomies, one thalamic stimulation, one unilateral subthalamic stimulation and three bilateral subthalamic stimulation for pure PD tremors. Of the patients undergoing thalamic surgery, six had good control of tremors whereas four had moderate control. However, all patients undergoing subthalamic surgeries had good tremor control.

Essential Tremor

Essential tremor is also known as familial tremor as it runs in families. It is characterised by tremors on action or posturing. There are no tremors at rest. Usually, they remain under control for long years up to 10–15 years. When the tremors become severe, the patient can be considered for surgical intervention.

The number of patients referred for surgery is rather small as compared to PD. Vim nucleus of the thalamus is the preferred target by most workers. A permanent satisfying tremor relief was demonstrated in the contralateral extremities of 68.7% and 95% for coagulation and stimulation.[68] Schurman demonstrated that, after 2 years follow-up, thalamotomy and thalamic stimulation were equally effective in tremor suppression, but thalamic stimulation had considerably less adverse effects and made bilateral surgery possible.[64,65]

We have performed one thalamotomy and five bilateral thalamic stimulations for essential tremor. Of this, four patients had good control whereas one patient has moderate control of tremor and the other has poor tremor control. We have not been able to evaluate the cause of these failures as they have been lost to follow-up. It could be possible that reprogramming using a different set of stimulation parameters may achieve better tremor control.

Post-Traumatic and Post-Hemiplegic Tremor

These tremors are mainly postural and action tremor. They are more violent in nature as compared to the essential or Parkinsonian tremors. They manifest following recovery from the original cerebral insult and can be of considerable disability to the patient. Pharmacotherapy is generally not effective. The surgical target for their treatment is once again the Vim nucleus. Various workers, for the treatment of this disabling tremor,[83] have performed thalamic stimulation or thalamotomy. The results have been variable as far as tremor control was concerned, but they all reported significant improvement in the quality of daily living.

We have performed six thalamotomies and one thalamic stimulation for this indication. Five patients had good tremor control and two had moderate control.

Multiple Sclerosis Tremors

Of the various disabilities from MS, tremor also forms one important component. The tremors are coarse and

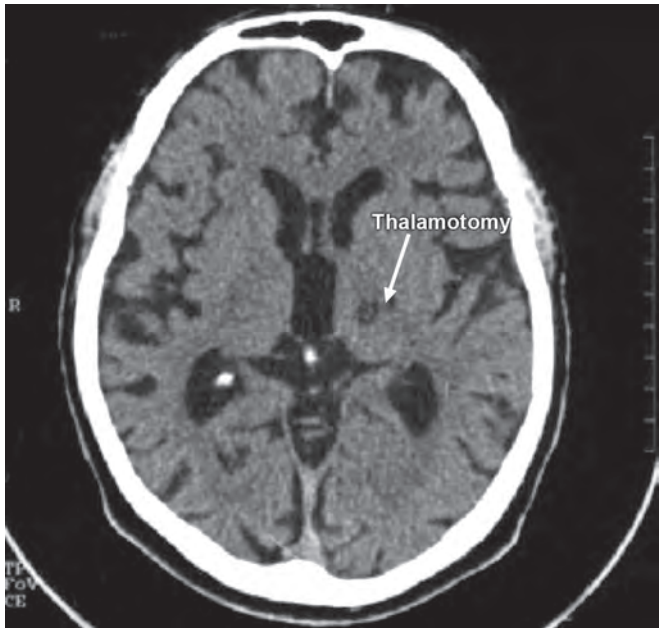

Fig. 2: Left sided thalamotomy for essential tremor (arrow)

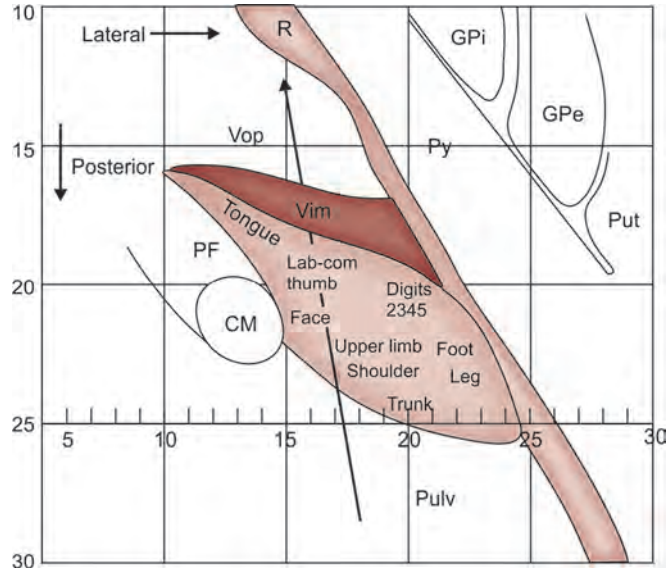

Fig. 3: Somatotopic organisation of Vim target (marked in red)

have a large amplitude proximal component. They are also associated with neck tremors or dysarthria. These tremors are very difficult to control, especially the proximal component. Besides, they also have very low side effect thresholds precluding use of higher stimulation parameters.[49,83] We have performed one surgery for MS tremors with only partial improvement.

The Vim Target

The Vim nucleus is the common lesioning and DBS target used for the treatment of tremors (Figs 1 to 3).[7,57] In the somatotopic organisation of the Vim nucleus the face area lies medially, followed by the upper extremity laterally and the lower extremity is the most lateral situated close to the internal capsule (Fig. 3). The Vim nucleus of the thalamus has neurons that fire in synchronous bursts with the tremor frequency and are called tremor cells (TCs). The TCs are believed by some to act as tremorigenic pacemakers.[38] The DBS target for tremor control is the electrophysiologically defined Vim. This electrophysiologically defined motor thalamus (Vim) has TCs and kinesthetic cells, and it lies immediately anterior to the cutaneous receptive cells, which lie in the sensory thalamus.[1] The somatosensory relay nucleus ventralis caudalis (VC) of the thalamus lies immediately posterior to Vim. The VC has specific neurons that respond to tactile stimulation in small, receptive fields. The Vop nucleus lies immediately anterior to the Vim. The internal capsule lies lateral to the Vim. The Vop receives afferents from pallidal neurons and the Vim receives afferents from the cerebellar neurons (cerebellothalamic fibres). There is some degree of overlap and interdigitation between these two nuclei.[38] Vim is not visible as a separate nucleus on routine MRI sequences. We base our targeting on CT scan. As we use a CRW stereotactic system, which is gantry independent, we can align the anterior commissure (AC) and posterior commissure (PC) on the same plane. We base our target 2/10–3/10 anterior to PC and ½ of AC-PC length. We thereafter examine its relationship to the internal capsule. Microelectrode recordings (MER) are used to identify TCs and stimulation-based responses to finally find the target. Usually tremor control is seen on the operating table itself. If the tremors are not controlled alternative trajectories are explored depending on the MER and stimulation responses.

DYSTONIA

Dystonia is defined as an involuntary movement disorder characterised by repetitive, patterned or sustained muscle contractions causing twisting movements or abnormal postures.

Dystonia is classified as primary or secondary. Primary dystonia is the classical familial dystonia described by Oppenheim. It is also known as dystonia musculorum deformans (DMD). DMD is a disease of young people, with most cases commencing in childhood (Age: 0–12 years), although some do not appear till the age of 10 years; adult onset is rare.[53] Primary idiopathic dystonia refers to dystonia with no discernible aetiological factor responsible for its onset. Patients with primary idiopathic dystonia have normal imaging findings, cerebrospinal fluid composition and laboratory test examinations. A subset of patients with primary dystonia have a DYT-1 mutation on chromosome 9q,[44] whereas others are sporadic cases. Secondary dystonia occurs due to a variety of disorders ranging from hereditary neurological syndromes, like Wilson's disease and Huntington's disease, to perinatal cerebral injury causing cerebral palsy or later on in life secondary to head

trauma, brainstem lesions or brain tumours. Tardive dyskinesia is another subset of dystonia that results from super-sensitivity of the post-synaptic dopamine striatal receptors due to long-term administration of dopamine receptor blocking agents such as neuroleptics.[35] The most common drugs implicated are metoclopramide, olanzapine and risperidone. Risperidone appears to have fewer dystonic effects, only clozapine has been shown to have a lower risk of tardive dyskinesia than older antipsychotics. These are commonly used to treat psychiatric conditions. Another form of dystonia that is amenable to surgical treatment is a focal dystonia known as Writer's cramp. This is a task specific dystonia. Patients develop abnormal posturing during performance of a particular task like writing, playing a musical instrument, drawing, etc. whereas they are completely normal during rest and with other activities.

Dystonia can also be classified according to the affected body part. In focal dystonia, a single region of the body is affected, such as in blepharospasm (eyes), cervical dystonia/torticollis (neck) and spasmodic dysphonia or laryngeal dystonia.[39] In segmental dystonia, two or more adjacent body parts are affected, such as cranial-cervical dystonia, or brachial dystonia. Generalised dystonia refers to dystonia involving most body parts. Currently accepted clinical rating scales for dystonia include physicians global dystonia rating scale (PGDS), The Burke-Fahn-Marsden (BFM)[14] scale, and the unified dystonia rating scale (UDRS). We use the BFM score for our pre-operative and post-operative work up.

Primary, generalised dystonia of DYT-1-positive[44] or non-DYT-1 types, as well as patients with idiopathic cervical dystonia can obtain the best motor benefits with bilateral GPi DBS.[79] Patients with juvenile-onset idiopathic dystonia whose age of onset is older than 5 years and who do not have multiple orthopaedic deformities also have a good response to surgery.[60] Appendicular symptoms (e.g. those affecting the limbs) appear to respond better than axial symptoms. With regard to focal dystonia, ideal surgical candidates are those with cervical dystonia.[45] The results of DBS for secondary dystonia are inconsistent. In general, DBS for secondary dystonia is less effective than for primary generalised dystonia, particularly in those patients with an identifiable structural brain abnormality. The only exception is tardive dystonia, which has been reported to respond well to surgery in a small number of patients[24] (Table 3).

Table 3: Classification of dystonia

Dystonia
Primary/Secondary
• Usually for hemidystonia or generalised dystonia
• GPi is the target of choice
• Pallidotomy in hemidystonia/pallidal stimulation for hemidystonia or generalised dystonia
• Results are variable

Indications for Surgical Treatment of Dystonia

It is difficult to define surgical indications for dystonia; the clinical picture varies enormously and there are many different causes. Surgery does not alter the progress of dystonia or the underlying neurological deficits. Thus, not withstanding how successful the surgery is, the eventual outcome is determined by the subsequent disease progress and the underlying neurological deficit. Selection of suitable candidates for dystonia surgery is extremely crucial. Patients with primary generalised dystonia, also those who are DYT1 gene positive, are the best surgical candidates. Primary dystonia of sporadic variety also benefits from surgery. Secondary dystonia, especially hemi-dystonia, which has been stabilised, can be offered a surgical option. Patients whose progress has halted and have been stable for the last 6 months or more could also be offered surgical treatment. Severe pain from dystonia also forms one of the indications for surgical intervention. It is important to exclude the primary dystonias that are responsive to medical treatment with trihexyphenidyl hydrochloride or Levodopa.

Surgical Options in Dystonia

The GPi is currently the most common target for treating dystonia[76] although, earlier, the thalamus (Voa, ventrolateral)[73] and subthalamus have been used. The GPi DBS target is the posteroventrolateral GPi, which is the predominant motor territory of the nucleus (Fig. 4). The Gpi is well-visualised on MRI (inversion recovery and T2 sequences) and we routinely use MRI to define the surgical target and identify the internal capsule and the optic tracts (Figs 5 and 6). The globus pallidus is divided into two anatomic segments: (1) internal (GPi) and (2) external (GPe). Although these segments are separated

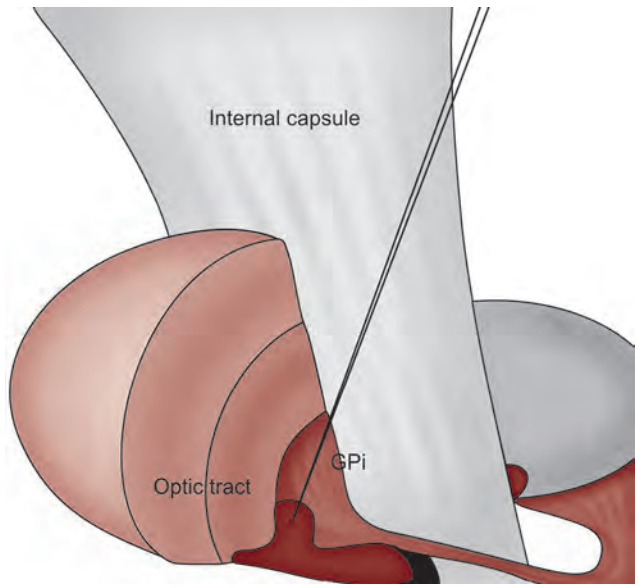

Fig. 4: GPi target and its relationship with optic tract

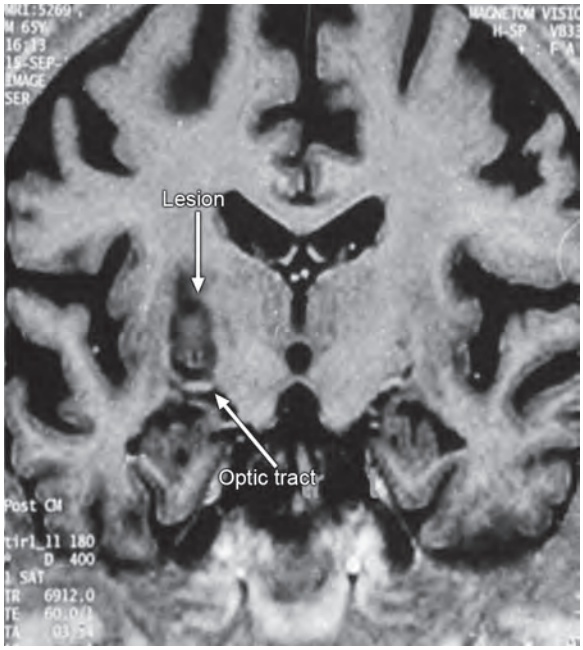

Fig. 5: IR coronal MRI showing GPi lesion (note the relationship to the optic tract)

by the medial medullary lamina, the pallidal neurons from each segment are similar and, for the most part, morphologically indistinguishable. The GPi is bound laterally and dorsally by the GPe. Medially the GPi is bound by the internal capsule. Ventrally it is close to the optic tracts. The therapeutic sensorimotor territory of the GPi is ventral and posterior, and the somatotopy places the face and arm posterior and ventral, and the leg central and more dorsal.[74] Pallidal stimulation is a better alternative to pallidotomy. This has the advantage of being completely reversible and chances of

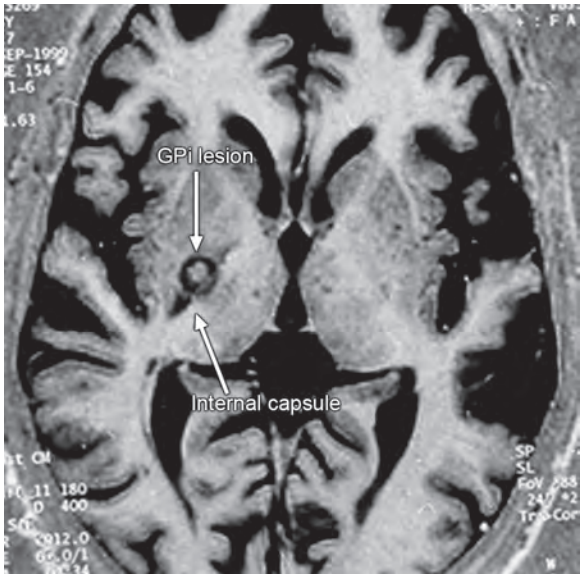

Fig. 6: IR axial MRI showing GPi lesion (note the relationship with internal capsule)

cognitive deficits are much less. Bilateral pallidotomy does carry a risk of cognitive impairment[26,50] and hence in bilateral cases only pallidal stimulation should be performed. However, pallidotomy is a useful adjunct for treating focal and unilateral dystonias.

Results

Results of pallidotomy or pallidal stimulation are both comparable. However, pallidal stimulation offers an added advantage of post-operative titration. The current requirements for the stimulation are considerably high and hence it affects the battery life used for the pulse generator. Typically the battery lasts for 5–6 years, if it is used to stimulate for PD. However, with the currently available batteries they would require to be replaced within 3 years or less, if used for stimulation of the pallidum for dystonia. It may take months for the full effect of pallidal stimulation to develop. Mild improvement in "mobile" dystonia is often seen within the first few hours after the initial programming of the stimulators and is a good predictor for continuing improvement.[40]

There are several case reports about dramatic improvement of generalised dystonia after bilateral pallidotomy.[30,41,48,51,58] The most striking effect was the clear benefit of axial dystonia without side effects, such as hypophonia, known to be associated with bilateral pallidal lesioning in PD. It has been reported that the BFM DRS scores improve approximately by 80%.[20,75,80]

For secondary generalised dystonia, reported results are highly variable, ranging from no benefit at all to significant improvement in some cases. However, the numbers are too small to give any meaningful comment about predictive factors.[78]

DBS offers a therapeutically viable option for patients with severe, primary dystonia and also for a small subset of patients with secondary dystonia. The key to favourable responses after DBS in patients with dystonia is proper patient selection. Patients who are refractory to all conservative measures, including medication trials (anticholinergics, baclofen, benzodiazepines or other muscle relaxants) and botulinum toxin injections are potential candidates.

We have performed six unilateral pallidotomies and nine bilateral GPi stimulations for dystonia. Good response was found in 6, moderate benefit was found in 5, poor in 1, 2 cases were explanted and 1 abandoned. There was no major visual or motor deficit. The explanation was done because of delayed infection in one due to poor hygiene and the second one due to self inflicted injury post-operatively leading to infection.

COMPLICATIONS

Complications of pallidotomy and thalamotomy are uncommon. Both procedures are designed to create defined lesions in deeply seated and critically located brain nuclei. Haemorrhage is the primary concern in both procedures. Since the electrode is small and no tissue is

Table 4: Symptomatic complications of stereotactic pallidotomy

Series	*No of cases*	*Haemorrhage*	*Non-haemorrhage deficit*	*Seizure*	*Infection*	*Death*
Laitinen et al.	42	0	16.7	0	0	0
Iacono et al.	194	3.2	2.1	0	0.5	0
Dogali et al.	18	0	6	0	0	0
Kondziolka et al.	40	0	8	0	0	0
Doshi et al.	9 stimulation 6 lesion	0	0	0	2*	0

*The two cases where electrodes were explanted were due to delayed infection by poor hygiene and self inflicted injuries

Data taken from

1. Dogali M, Fazzine E, Kolodry E, et al. Stereotactic ventral pallidotomy for Parkinson's disease. Neurology. 1995;45:753–61.
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removed during such procedures, the haemorrhage rate is low (Table 4). The second common complication is infection. Minor infection presenting as inflammation can be conservatively managed with antibiotics; however, if there is an implant, any evidence of discharge or pus formation warrants removal of the implant. If the infection is at the pacemaker site, the pacemaker and the connecting extension needs to be removed. If it is at the burr hole site the intracranial electrodes have to be removed. We had to explant the system completely in two patients developing infection, one due to poor hygiene and another due to self mutilation.

Pallidotomy Complications

Neurologic deficits may be produced by the lesion itself. The most common neurologic deficits after pallidotomy include visual field deficit, hemiparesis and dysarthria. Such symptoms are usually temporary. The close approximation of the globus pallidus interna to the internal capsule and optic tract are the basis for these deficits. Radiofrequency lesion generation causes focal tissue necrosis surrounded by a zone of oedema. This peripheral oedema may cause transient deficits. The mainstays of complication avoidance for pallidotomy surgery are appropriate patient selection and target planning, the use of test lesions and visual evoked potential monitoring, physiologic evaluation, careful intra-operative neurologic examinations and judicious lesion generation. Attention to each of these steps reduces complications of pallidotomy procedures; each is addressed subsequently. We had no lesion related complications in pallidotomy for dystonia.

Thalamotomy Complications

Common complications following thalamic surgery include dysarthria and pyramidal and cognitive deficits. Bilateral thalamotomies have the highest risk of these complications followed by unilateral lesioning and then stimulation procedures. Bilateral thalamotomies are rather contraindicated in present day functional neurosurgery. Putzke et al.[62] reported on the outcomes of 22 patients with head, voice or trunk tremor undergoing bilateral, staged, DBS thalamic implants. Bilateral stimulation was more effective than unilateral stimulation in alleviating axial tremors; however, as for bilateral thalamotomies, the rate of neurological complications was higher in patients who underwent bilateral stimulation. Dysarthria was observed in 27% of patients with bilateral stimulation, whereas none of those undergoing unilateral stimulation experienced the same problem. Likewise, disequilibrium was more common during bilateral stimulation. These stimulation settings varied minimally during this period, further corroborating the stability of the effects. Although staged bilateral procedures are often preferred for axial symptoms, they may not be safer than simultaneous implantation procedures.[61] Thalamotomy results were comparable to thalamic stimulation as per Pahwa et al. and tremor suppression was very similar in both groups. Complications, particularly intracerebral haemorrhages, were more common among patients with thalamotomies (35% vs 0%). Likewise, cognitive deterioration and hemiparesis occurred respectively, in 29% and 12% of patients who had undergone thalamotomies, but in none of those with thalamic stimulation. Although thalamic stimulation is chronically effective for most patients,[13] reductions in efficacy during longer-term follow-up periods have been reported.[36]

SURGERY FOR MOVEMENT DISORDERS: FUTURE DIRECTIONS

The field of functional neurosurgery has witnessed a renaissance over the past 20 years. This development has been fuelled by progress in understanding the

neurobiology of movement disorders, surgical technical advancements, therapeutic device developments and innovative approaches. The growth in our understanding of the neural circuitry of the disease has determined and refined our surgical targets. This increased understanding of the neurobiology of movement disorders will guide the discovery of additional targets for surgical exploration and translational clinical research. The evolution of stereotactic surgical tools and techniques is facilitating safe and minimally invasive approaches that enable neurosurgeons to target various brain structures with reliable accuracy. This, coupled with rapid advances in imaging technology, will play an important role in improving our capability to visualise brain structures and function with unparalleled resolution. At present, DBS is the standard therapy of choice for movement disorder patients who are medically intractable and meet the surgical selection criteria. DBS has a proven safety and efficacy profile and long-term outcomes have been demonstrated by prospective, randomised studies. Technological advances in DBS systems have already resulted in improvement and will continue to do so. The next generation DBS systems will be smaller and rechargeable, with current steering features and built-in sensing capabilities. A number of clinical trials are under way to explore the utility of gene therapy and cell transplantation and stem cell approaches with promising preliminary outcomes. In the near future, these technologies will provide additional options for neurosurgical management of movement disorders.

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191 Gamma Knife Radiosurgery

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The introduction of gamma knife radiosurgery (GKS) in the mid 20th century has heralded a quiet revolution which has changed the way neurosurgery is practiced, at levels which perhaps could not be contemplated as early as two decades ago. Gamma knife is actually a misnomer. There is no knife. It is a platform used to deliver highly focused beams of gamma radiation onto an immobilised intracranial target within a frame, using the age-old principles of stereotaxy.

HISTORY

The gamma knife was the brainchild of Dr Lars Leksell, the Swedish neurosurgeon, who succeeded Professor Herbert Olivecrona as the Chairman of the Department of Neurosurgery at the Karolinska Institute in Stockholm. The first procedure was performed in October 1967 for a patient with a craniophayngioma, previously treated with intracavitary radiation with yttrium 90 at the private hospital Sophiahemmet in Stockholm. A single lesion using a maximum dose of 20 Gy was created. Success in the form of tumour necrosis was documented on autopsy 4 months later when the patient expired due to shunt obstruction.[2] In 1970, Steiner and Backlund treated the first intracranial arteriovenous malformation (AVM) with astounding success.[58] Since then, the platform has evolved from a model U (University) to B, C, 4C and a revolutionary new platform called Perfexion™. Initially devised to treat benign tumours, movement disorders and intractable pain with gammathalamotomy, the scope of GKS has seen a radical diversification. It is now considered the most accurate and reliable means of delivering radiation to precisely delineated intracranial targets, without exposing the normal brain tissue around the lesion.

MEDICAL PHYSICS

The Leksell Gamma Knife™ (LGK) contains 201 cobalt-60 sources of approximately 30 curies (1.11 TBq) each, placed in a heavily shielded assembly. A combination of helmets with pores (collimators) focuses the gamma rays into the centre of a circular array where the patient's head is placed. Gamma rays are ionising rays in that they have the capability to generate secondary electrons, by removing outer shell electrons from atoms, thus creating a positive ion. This is made possible by the fact that the energy of the gamma ray exceeds the binding energy of the outer shell electron. This binding energy depends on the proximity of the electron shell to the nucleus and the number of protons within the same. In biological tissues, this varies from 13.6 eV for hydrogen atoms to 4 KeV for the calcium atom.

Co-60 is produced in nuclear reactors by adding a neutron to the naturally occurring isotope Co-59. This decays as follows:

Co-60 $\rightarrow$ Ni-60 + β radiation $\rightarrow$ Co-59 + 2 γ rays (1.17 MeV + 1.33 MeV)

The half-life of Co-60 is about 5.26 years which means that the radioactivity of the source becomes half its original activity in this span of time. Sources can be used up to a maximum of 10 years before they need to be reloaded and the spent source disposed. The danger in waiting this long lies in the fact that the treatment time gets prolonged and the unwanted scatter radiation to which the patient is exposed increases. The advantage of Co-60 is its relatively high radioactivity for a small volume (specific activity), ruggedness, reliability and output stability. The disadvantages are that the radiation is always 'on' unlike Linear Accelerators (LINAC), the half-life is relatively short and the sources need to be reloaded.

There are two basic principles in radiosurgery:

1. *Conformity:* This implies that the isodose at which the radiation is prescribed (prescription isodose) should hug the margin of the tumour target as closely as possible. Conformity is achieved in GK by using multiple isocentres ("shots"), changing the position of the isocentres, adjusting the beam diameter (by using 4, 8, 14 and 18 mm collimators), adjusting the weight of the beams (which determines the time spent by the patient within the gantry) and finally by beam blocking (by plugging specific pores with the collimator helmet).
2. *Selectivity:* This implies precise targeting of the lesion with a rapid dose fall-off, thus avoiding radiation damage to adjacent normal tissue. This is influenced by the size of the collimator, the beam penumbra (distance between the 80% and 20% isodose lines), mechanical stability of the treating machine and the number of radiation fields. Multiple shots with small sized collimators is likely to improve the selectivity of a given radiation dose plan (Fig. 1).

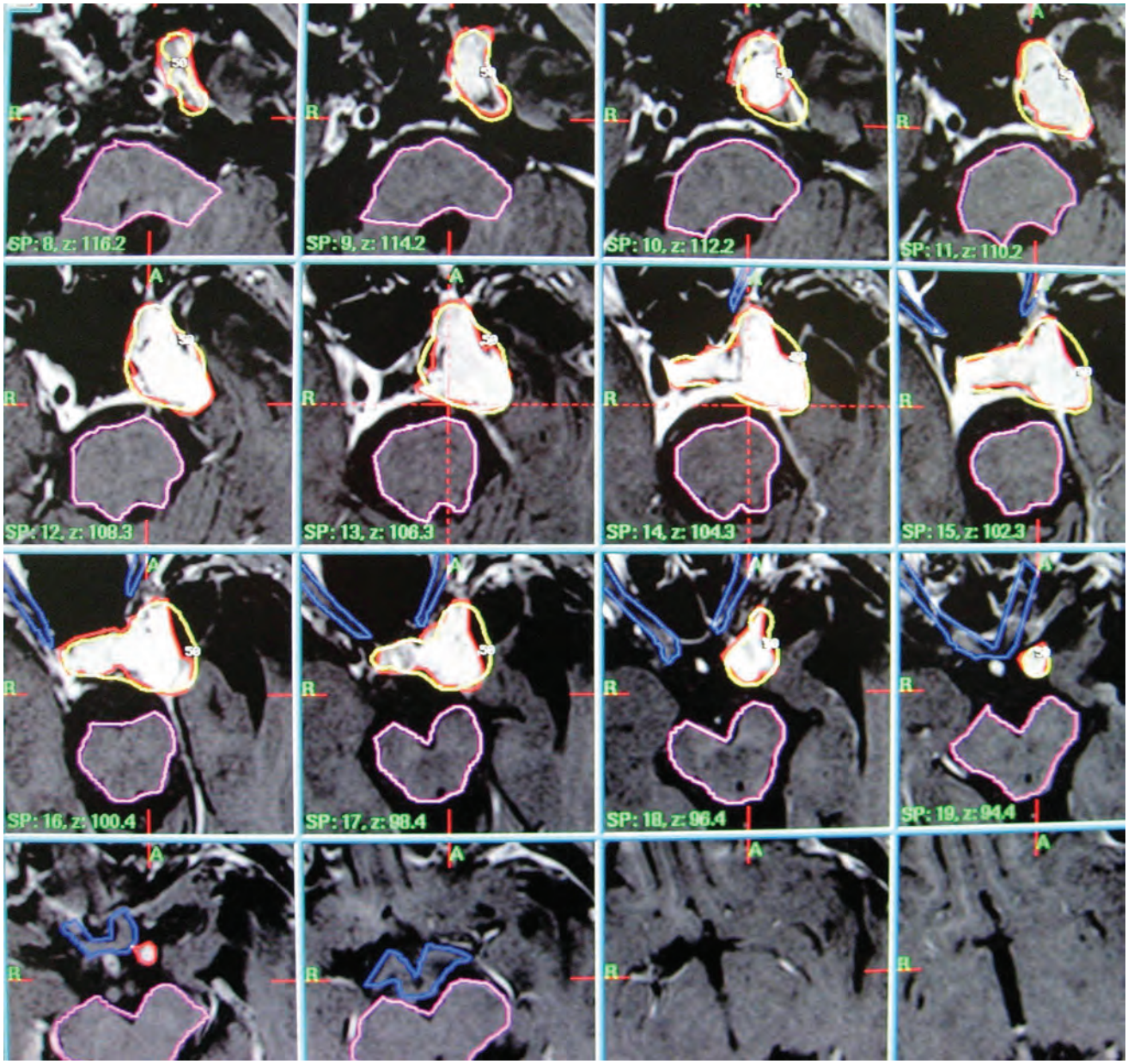


Fig. 1: Planning for a residual left cavernous sinus meningioma. The meningioma is depicted in red, the brainstem in pink and the optic pathways in blue. The radiation isodose seen in yellow is applied as closely as possible to the tumour margin to ensure conformity and selectivity

Dose-Volume Histogram

These measurements can be used to compare and contrast multiple dose plans by indicating the radiation doses received by a specific volume of target tissue at a particular isodose. Most users target 90–100% of the lesion at the 50% isodose line.

Conformity Indices

These are objective measures of the fitness of a particular plan. The simplest conformity index (CI) is related to the prescription isodose volume (PV) and the target volume (TV) by the following equation:

CI = PV/TV

Ideally CI should be 1. Practically, any value less than 2 is satisfactory. There is a fundamental flaw in this index, in that it does not measure the degree of overlap between the two volumes, the PV may actually completely miss the target and yet be 1. To overcome this lacuna, Paddick et al. proposed the following ratio: Conformity = PV/TV × % target coverage.

Thus, the plan is penalised for poor overlapping.[45]

RADIOBIOLOGY

GKS is better classified as a form of stereotactic radiosurgery (SRS), which has been defined as the precise destruction of a chosen target containing healthy and/or pathological cells, without significant concomitant or late radiation damage to adjacent tissues.[26,29] SRS involves the delivery of high dose single fractions of radiation, as opposed to multiple smaller doses (fractionation) in

stereotactic radiotherapy (SRT), which is used to treat larger volumes.

SRS is by necessity highly accurate and the system has an inherently steep dose fall-off (selectivity), which enables the precise and focused delivery of a single fraction of high dose radiation. This overcomes the so-called 'radiation resistance' of benign tumours which are late responders and in whom fractionation has no value.

GKS has been performed mostly for benign tumours. As these patients generally have normal survival and rarely require salvage surgery, little tissue is available to study its *in vivo* effects. Animal experiments using athymic nude mice with subrenal allografts of human vestibular schwannomas (VSs) and meningiomas, indicates that tumour size reduction may be due to neoplastic cell death and a decrease in vascularity.[27] Tsuzuki et al.[63] postulated that apoptosis my play a central role in controlling the growth of tumours after GKRS. Tumour volume was rapidly reduced in lymphomas and in some benign tumours, characterised by strong positive immunohistochemical staining for PCNA and Bcl-2. They hypothesised that targets with a large proportion of proliferating cells may undergo DNA damage, enter the cell cycle and then undergo apoptotic cell death without necrosis or inflammation.

GKS in AVMs seems to cause a proliferative vasculopathy and endothelial cell injury, leading to vessel wall thickening, hyalinisation and luminal closure.[51] Activated myofibroblasts too may add to the obliteration of AVMs.[59] In the standard recommended doses, GKS does not seem to affect normal brain vessels, not even tiny perforators. Perhaps it is only abnormal angiogenesis that may be selectively affected by high dose single fraction GKS.[27]

Gamma radiation changes may be characterised as:

1. *Acute:* This entails sharply demarcated parenchymal coagulative necrosis with apoptosis and an acute inflammatory reaction. Blood vessels show endothelial destruction and fibrinoid changes in the walls.
2. *Subacute:* In this stage, macrophages replace polymorphonuclear cells. Granulation tissue and reactive gliosis sets in as does proliferative vasculopathy with luminal narrowing.
3. *Chronic:* Necrosis is replaced by scar tissue, lymphocytic infiltrates, hyaline change and calcification. Subendothelial cell proliferation is seen in vessel walls with hyalinisation and subtotal/total luminal obliteration.[60]

DOSE SELECTION

This is the final phase of treatment planning. The dose to be administered depends on the actual or anticipated histopathology based on the imaging, the proximity and radiation safety tolerance limits of adjoining normal structures and the anticipated lifespan of the patient. It is useful to consult risk prediction curves, especially in AVMs, to balance the therapeutic advantage of dose escalation versus the risk of developing an adverse radiation reaction. Flickinger et al.[9] postulated an integrated logistic formula to estimate the risks of brain necrosis from radiosurgery, in order to limit the risk to less than 3%. Using a multivariate analysis, they found that radiation change correlated significantly with only one variable, the total volume of AVM plus normal tissue receiving greater than 12 Gy of radiation (the 12 Gy volume).

GKS uses marginal doses between 12 and 25 Gy for the most benign and malignant tumours prescribed at the 50% isodose. Maximum doses up to 90 Gy have been used to treat trigeminal neuralgia (TGN). Although Steiner et al.[8,57] reported that doses more than 180 Gy may be required for gammathalomotomy, 130–140 Gy may be adequate. Just to put this in perspective, a whole body exposure of 6–10 Gy of gamma radiation will produce a 100% fatality in untreated humans within 14 days (LD 100/14). GKRS enables the safe delivery of up to 15 times this dose because of its high specificity and conformity.

The following tables indicate standard prescription doses to the margin of the lesion and the radiation safety tolerance limit of crucial adjoining structures, as practiced in our centre (Tables 1 and 2).

Table 1: Commonly recommended dose prescriptions

Diagnosis	*Prescription dose (Gy) at the 50% isodose*
AVM	20–25 Gy
AVF	20–25 Gy
Ac. Neuroma	12–14 Gy
Meningioma	12–14 Gy
Pit. adenoma	12 Gy
Functional pituitary	25–35 Gy
Craniopharyngioma	12–14 Gy
Neurofibroma	12–14 Gy
Metastasis	20–25 Gy
Glomus jugulare	16–25 Gy
Malignant glioma	20–25 Gy
Haemangioblastoma	20–25 Gy
Trigeminal neuralgia	70–90 Gy
Cavernoma	14–20 Gy

Table 2: Radiation tolerance limits

Critical structure	*Radiation tolerance limit (Gy)*
Brainstem	12 Gy
Visual pathways	8–10 Gy
Cranial nerves	8–12 Gy
Eye lens	< 1.5 Gy

PROCEDURE

GKRS requires a close liaison between the radiation oncologist, the medical physicist, the neuroradiologist, the nursing staff, technicians and the neurosurgeon.

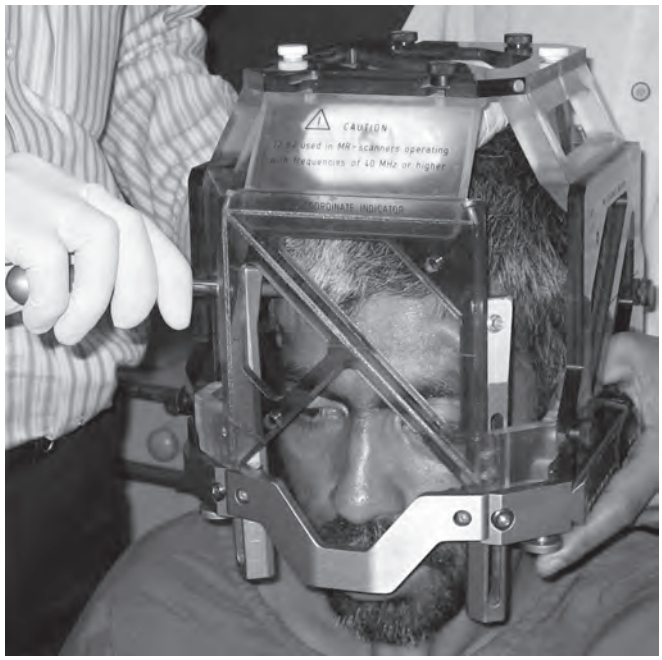


Fig. 2: Frame application under local anaesthesia. We place the MRI indicator box on the frame during fixation so as to avoid any subsequent collision with the skull

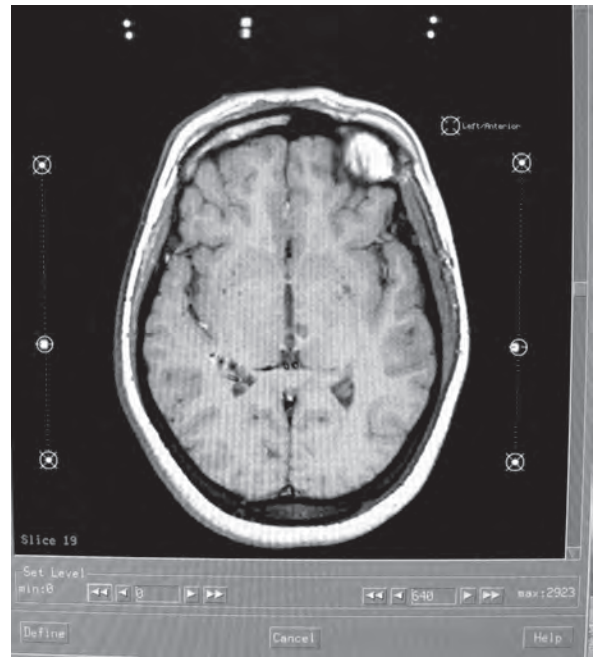


Fig. 3: Image definition. The fiducials are recognised by the software as is the orientation

Every centre has its own stylised protocol, right from frame fixation under general/local anaesthesia to imaging sequences to target delineation prior to radiation delivery and dose prescription. A brief description is provided below.

Basic Principles

Prior to beginning GKRS, the patient's head is immobilised in a frame which has posts and screws which provide secure skeletal fixation and rigid immobilisation. The frame also houses a marker box with columns for copper sulphate solution which can be picked up on axial MRI images as round fiducials in each cut (Fig. 2). These fiducials are used to define the images in proprietary software and transpose CT/MRI co-ordinates into Cartesian co-ordinates, based on the gradations present on the Leksell frame (Fig. 3). Thus, the principles of stereotaxy very much apply here and instead of delivering a needle into the required depth, the frame is used to guide stereotactic radiation beams with the isocentre of the arc being the centre of the tumour. The software also generates a 3D reconstruction of the skull which is used to calculate the distance of the lesion from the scalp. This helps determine attenuation of radiation with distance. Combined with the rate of radiation available for that day as per the half-life and days since installation of the Cobalt source, the software calculates the time duration for which radiation therapy will be given at each isocentre. The software also gives the isocentre (x, y and z) co-ordinates for each shot and the patient's head and frame are positioned in such a manner, as to place the tumour in the centre of a secondary collimator with a pore size varying between 4, 8, 14 and 18 mm, which further focuses the gamma rays onto the exact centre of the target for the particular shot (Fig. 4). As the individual beams carry less radiation, the remaining brain receives a low dose of radiation, which is below the safety tolerance threshold. Several shots are used to plan a compound conformal radiation isodose, which should ideally cover about 90% of the lesion at least. Dose-volume histograms (DVHs) are then calculated to determine whether the safety tolerance limits of vital structures, such as the brainstem, optic pathways and/or adjoining cranial nerves, are not exceeded. In eccentrically placed tumours, collisions are looked for between the skull and the frame and/or posts and screws, as determined by the software and the 3D skull reconstructions. After checking all these variables, a plan is selected

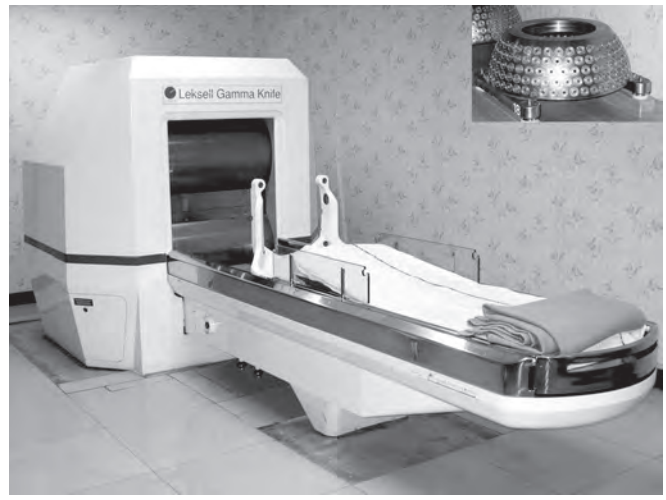


Fig. 4: The Leksell Gamma Knife Unit B. The collimators are seen in the inset

and the patient is then transferred to the GKS gantry for administering radiation.

Specific Steps

Frame Fixation

Care is taken to place the frame in such a manner as to position the tumour in its centre as far as feasible. For example, if the patient has a left parieto-occipital lesion, the frame is placed as far back and to the left as dictated by the size of the patient's head, which can prove to be a major limitation in well built patients with eccentrically placed lesions. Sometimes, the presence of collisions may make radiation delivery impossible and patients with the above characteristics must be warned beforehand that radiation delivery may need to be aborted and the frame removed because of technical limitations. The frame can be placed under local anaesthesia or under a general anaesthetic, especially in children less than 7 years of age. When anticipating a need for a general anaesthetic or heavy sedation, it is advisable to place the face plate of the frame in such a manner so as not to obstruct the airway or prevent possible endotracheal intubation.

Imaging

MRI with contrast is best used for evaluating brain tumours. Routine T1- and T2-weighted (T1WI and T2WI) sequences are run in thin 2 mm contiguous sections, either in the axial and/or coronal planes through the region of interest. Fat saturation may be added for base of skull lesions and in post-operative patients with pituitary adenomas with nasal packing performed at the time of surgery. Most centres now use 3D volume acquisition (MPGR or SPGR) sequences which are less time consuming and thus produce less motion artifacts. T2WI may be of superior benefit in treating patients with AVMs. Heavily T2-weighted images are of benefit (CISS) in visualising the trigeminal nerve in the treatment of neuralgic pain. Occasionally, CT and MRI fusion can be carried out for small intracanalicular acoustic neuromas, as CT scans can be acquired at 1 mm intervals and thus may halve the error of image acquisition. Positron emission tomography (PET) fusion is a capability of the 4C and Perfexion™ softwares which can help target the metabolically active part of residual tumours, especially those which have received prior radiation. Angiograms are performed with simultaneous vertebral and carotid injections (if need be) and images acquired in the anteroposterior and lateral projections in the capillary phase.

Cross-Registration

MRI and/or CT images are then defined by the software after feeding them into the computer by scanning, through a PACS/Ethernet system or via a CD/DVD. Fiducials are recognised as is orientation and images are accepted only after the error is within permissible limits. The software generates its own coronal and sagittal reconstructions based on the axial imaging. This helps planning. The shape of the skull is also generated based on manual depth readings, provided by a bubble placed on the patient's frame.

Planning

This is the most crucial part of the procedure. Images are viewed on a convenient workspace on the computer and the target is defined using a marker function. A matrix is then placed around the target to produce a snug fit. The matrix contains 136,789 arbitrary points which are used to calculate the radiation dose. Adjoining vital structures such as the optic pathway and the brainstem too are delineated (segmented). Multiple isocentres are then placed to encompass at least 90% of the tumour with minimal spillage onto normal structures (Fig. 1). The dose is finally prescribed in consultation with the radiation oncologist based on proximity to adjoining vital structures and the actual or anticipated histopathology. A final check is made to ensure that the software does not anticipate any collisions before transferring the patient into the radiation suite.

Manual/Automatic Positioning

The older GKS platforms use mandatory manual changing of secondary collimators and the patient's head position while partial and complete roboticisation is a feature of the 4C and Perfexion™ systems, respectively. This is as crucial as planning because the sub-millimetric accuracy of the software can easily be negated by a manual error in reading the Vernier caliper scale used to fix the frame in the x, y and z axes. The Perfexion™ system has 192 C0-60 sources and three inbuilt mobile collimators (4, 8 and 16 mm), which eliminates the need to manually change helmets. Thus, the operating time is reduced, as is the capacity for human error. The chances of collision too are reduced, as the distance between the frame and the inner collimator is also increased. Thus, it makes treatment of multiple targets, especially polar metastases, less time consuming, more accurate and feasible within a single sitting itself. After the treatment is over, the frame is removed and the patient can be discharged home.

ADVANTAGES OF GAMMA KNIFE RADIOSURGERY

Gamma Knife is superior to conventional surgery in that it has the accuracy of a knife, especially when conventional surgery may be risky or lesions may be considered inoperable (Fig. 5). It is extremely precise as it is guided by thin slice stereotactic MRI and CT scans. The mechanical precision of the unit has been estimated at between 0.25 mm and 0.3 mm. It is safe as the radiation falloff is steep and the exposure of normal brain is minimised. It has also been designed primarily as a neurosurgical tool to be used in consultation with the radiation oncologist and the medical physicist. This is advantageous in

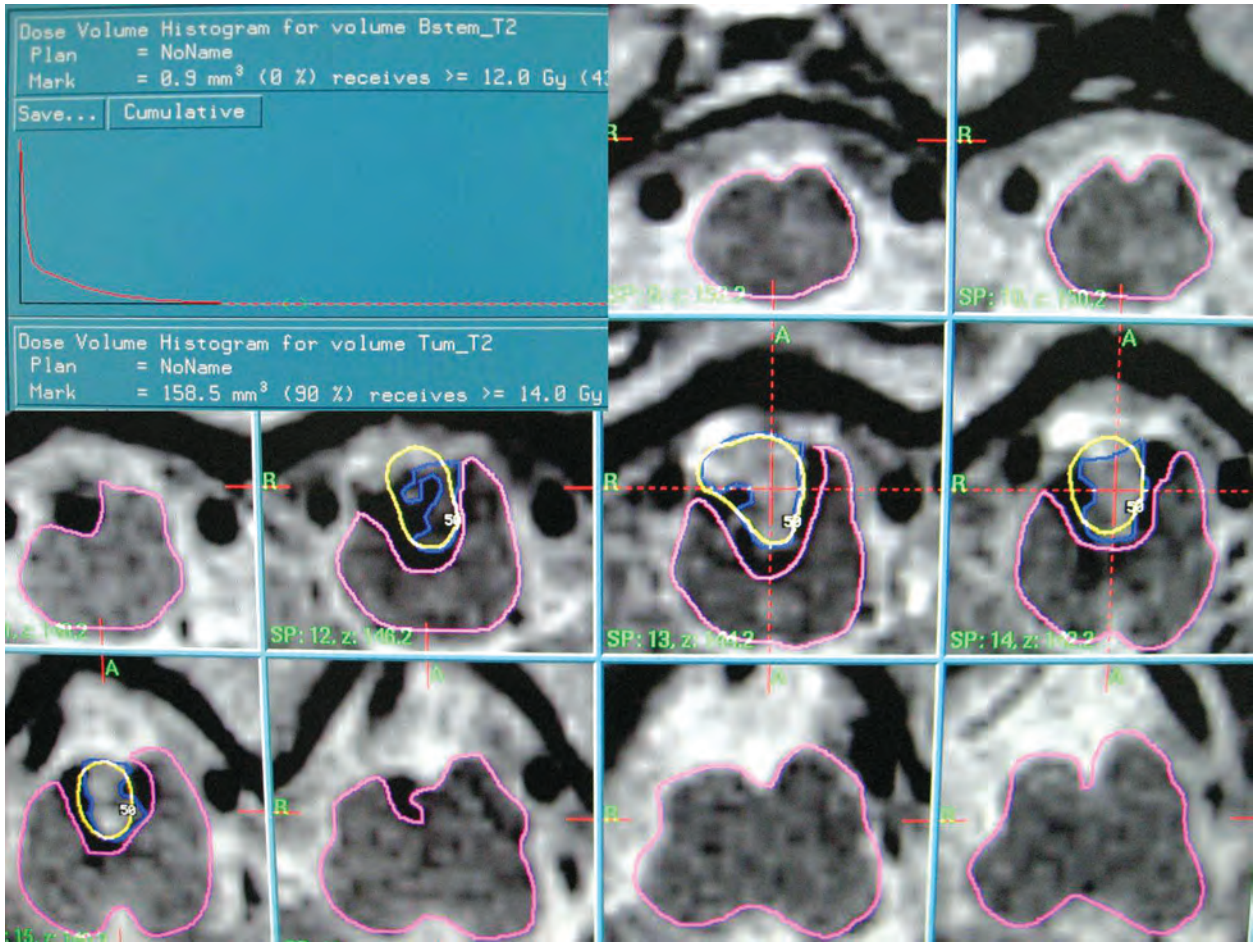


Fig. 5: Treatment planning for an intra-medullary cavernoma (T2-weighted MR axial images). Surgery was considered very high risk and consent was taken for GKS, as the patient had two previous bleeds (see text for rationale). The haemosiderin ring was excluded and the brainstem exposure was below 12 Gy (see Dose volume histogram in the inset). The brainstem is segmented in pink, the cavernoma in blue; the yellow line marks the 14 Gy 50% isodose line

that the neurosurgeon retains a primary and direct role in planning either primary or adjuvant therapy for a variety of benign, malignant and functional neurological disorders.

Current Uses

Although the GK platform was originally used in Stockholm for treating functional disorders of the brain, its scope has now drastically widened and evolved to include a variety of benign lesions such as pituitary adenomas, acoustic neuromas, meningiomas, schwannomas, haemangioblastomas, chordomas, chondrosarcomas, glomus jugulare (GJ),[52] posterior third ventricular tumours, pilocytic astrocytomas, gangliogliomas and craniopharyngiomas. Malignant lesions, such as haemangiopericytomas, malignant gliomas, endolymphatic sac tumours and metastases, may also benefit because of the excellent local control that may be provided by GKS.

AVM therapy has possibly been the most significantly revolutionised by the introduction of GKS. Three-year obliteration rates may approach 90% with minimal side effects (Figs 6A to D). This is all the more remarkable because most of these lesions are inaccessible to surgery and not amenable to embolisation.

A growing indication for GKRS is now multiple metastases—the most common indication in the West where detection and locoregional control rates are high. In our centre, AVMs remain the primary indication for GKS followed by VSs.

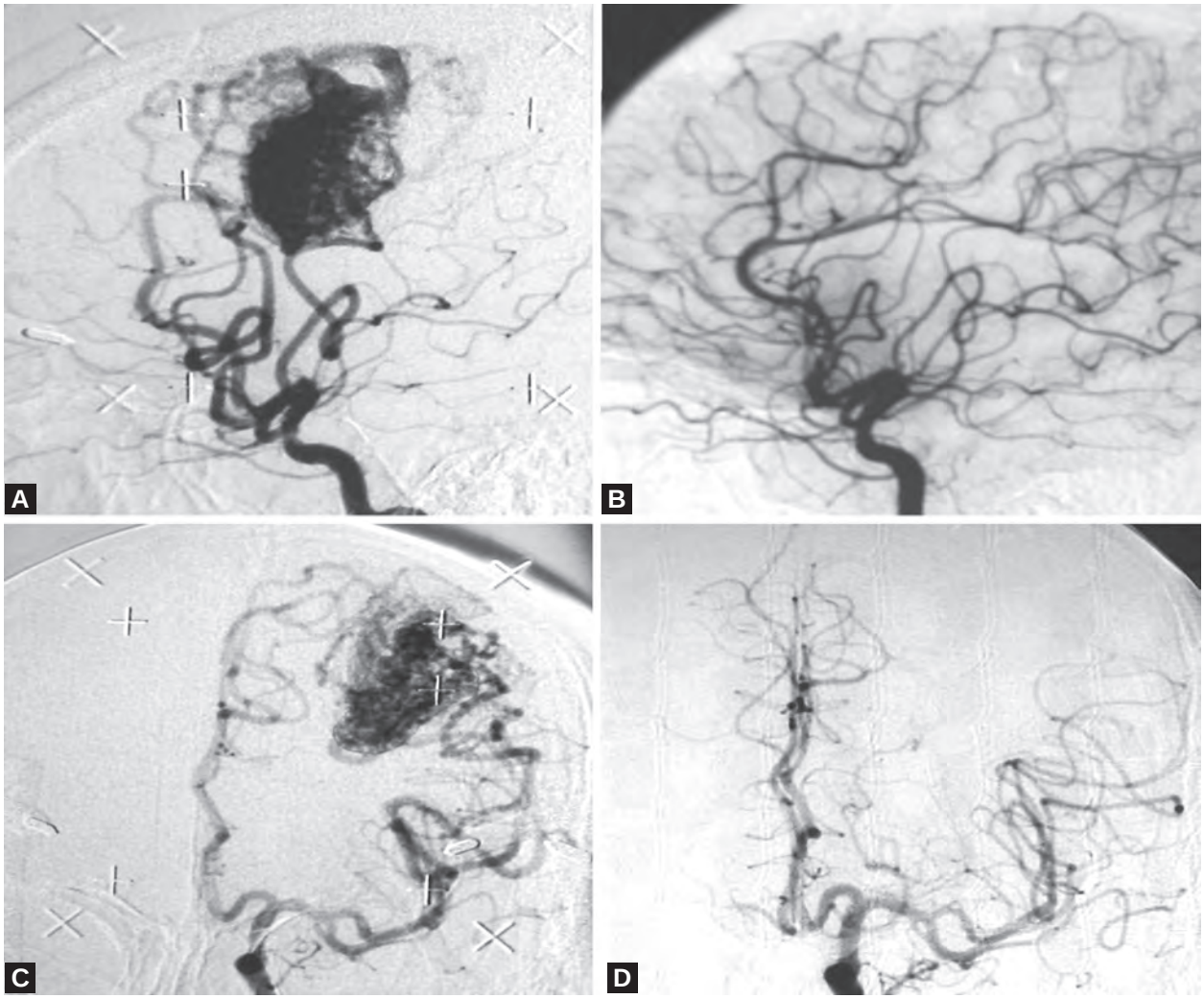
Standard limitations for administering GKS are:

- Tumour diameter exceeding 3 cm.
- Tumour volume greater than 19 cc.

These limits are only indicative and depend largely on the proximity of critical neural structures such as the optic pathways and the brainstem.

Review of Literature

Gamma knife has been used as a key word in 5,211 peer-reviewed articles indexed by Pubmed till date. As more and more follow-up MRI scans of patients accumulate from a greater number of centres around the world, the extent of both clinical and radiological follow-up has now begun to outstrip those available in surgical literature. The significant advantage of GKS remains its association with a demonstrable improvement in a



Figs 6A to D: Angiograms documenting AVM obliteration three years post-GKS. The images on the left are stereotactic, the fiducials can be seen on the plates

patient's quality of life.[6,41,42,46,47,48] Moreover, the same standardised machine is available throughout the world. Thus, results do no longer depend upon the skill and experience of the operating surgeon but on the available technology and the quality of imaging.

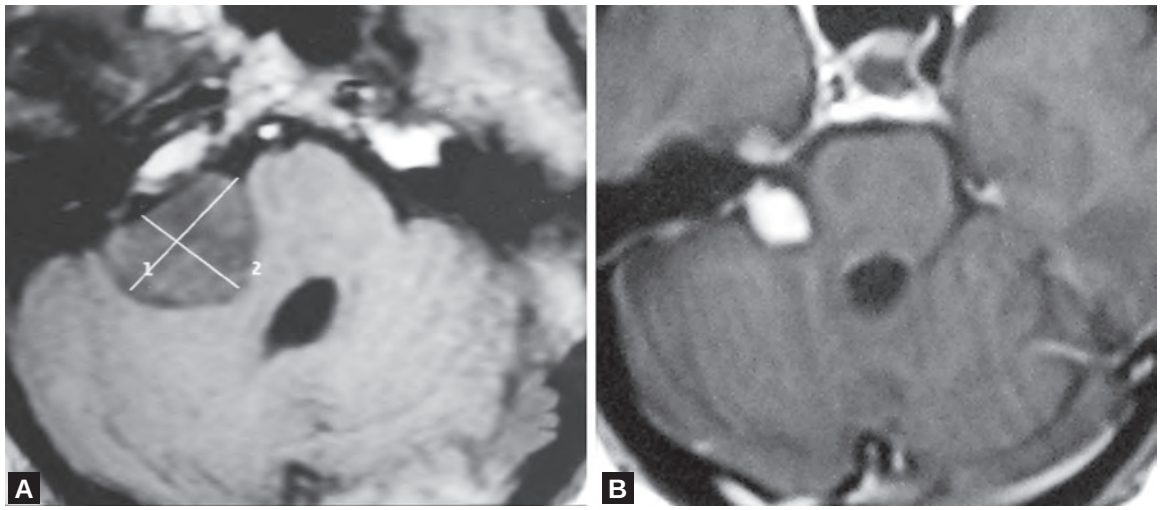
GUIDELINES AND SUCCESS RATES

We have attempted to compile the results of some of the largest available series of patients to date to provide an idea of the effectiveness and complication rates associated with GKS in the following conditions.

Vestibular Schwannomas

GKS has now become the standard of care in the treatment of VS, if it is less than 3 cm in size. Tumour control rates reported by the Pittsburgh group approached 97% at 10 years in their 15 year experience of 829 cases (mean tumour volume 2.5 cc). Hearing preservation was possible in up to 90% of intracanalicular tumours. Complications included a 3% risk of trigeminal neuropathy and a 1% risk of facial palsy. Pollock et al.[34] in a prospective study from the Mayo clinic reported 82 patients with unilateral, un-operated schwannomas less than 3 cm undergoing surgical resection (n = 36) or radiosurgery (n = 46). At a mean follow-up of 42 months, normal facial movement and serviceable hearing was more frequently seen in the radiosurgical group at 3 months ($p < 0.001$), one year ($p < 0.001$) and at the last follow-up examination ($p < 0.01$) compared with the surgical resection group. They concluded that pending an unacceptable rate of recurrence in later follow-up, radiosurgery should be considered the best management strategy for VS less than 3 cm in size.[46] Figures 7A and B depicts the reduction in size after 6 years of a large VS given 12 Gy of radiation.

In bilateral VS, GKS does appear to be safe, although results are not as favourable as for sporadic tumours. In the largest series so far, 74 VS (mean tumour volume 5.7 cc) were studied in 62 patients in whom ipsilateral serviceable hearing was present in 35%. The mean marginal dose was 14 Gy and the median follow-up was 53 months. Actuarial control rates were 85% and 81% at 5 and 15 years, respectively. The actuarial serviceable



Figs 7A and B: Reduction in size of a large VS demonstrated six years after GKS. It is to be noted that acoustic neuromas with a mass effect on the pons can also be successfully treated with GKS, although with a slightly lower control rate

hearing preservation rate was 73% at 1 year and 48% at 5 years after radiosurgery. The rates of facial and trigeminal neuropathy were recorded at 8% and 4%, respectively.[36]

Meningiomas

Kondziolka et al.[36] reported their 18 year experience in 972 patients with 1,045 intracranial meningiomas of whom 49% had undergone a previous resection. The overall control rate was 93% at 10 years follow-up. Delayed resection after radiosurgery was necessary in 51 patients (5%) at a mean of 35 months. The overall morbidity rate was 7.7%. Mindermann et al.[39] reported that tumour control rates approached 95%, 92% and 100% in patients with parasagittal or convexity meningiomas, skull base and posterior fossa meningiomas, respectively. They also observed that neurological deficits tend to resolve in deep tumours following GKS.

Pituitary Adenomas

Non-functioning Tumours

Liscak et al.[30] over a period of 10 years treated 140 patients with non-secreting pituitary adenomas (median volume 3.45 cc) of whom 85% had had previous surgery. The median marginal dose was 20 Gy (range; 12–35 Gy) while the median follow-up was 60 months. Tumour control rates were 100%; 89% of treated adenomas decreased in size showing a median volume reduction of 61%. There was no visual impairment or ocular motor paresis after radiosurgery. Pituitary hormone deficiency occurred in two patients. They also concluded that contact between a non-secreting pituitary adenoma and the optic pathway is not an absolute contraindication for GKS.

Cushing's Disease

Jagannathan et al.[22] studied 90 patients over 15 years with adrenocoticotropic pituitary adenomas (89 were previously operated upon) with a mean endocrine follow-up of 45 months (range 12–132 months). The mean marginal dose was 23 Gy (median 25 Gy). Normal 24-hour urinary free cortisol levels were achieved in 49 patients (54%) after an average of 13 months post-procedure (range 2–67 months). A decrease in tumour size occurred in 80%, while tumour growth was recorded in 6% of patients. Twenty per cent of patients experienced a relapse after initial remission at a mean interval of 27 months. Redo GKS was associated with a remission rate of 43%. New hormone deficiencies developed in 22% of all patients, while 5.6% of all patients developed new onset visual deficits or ocular motor paresis.

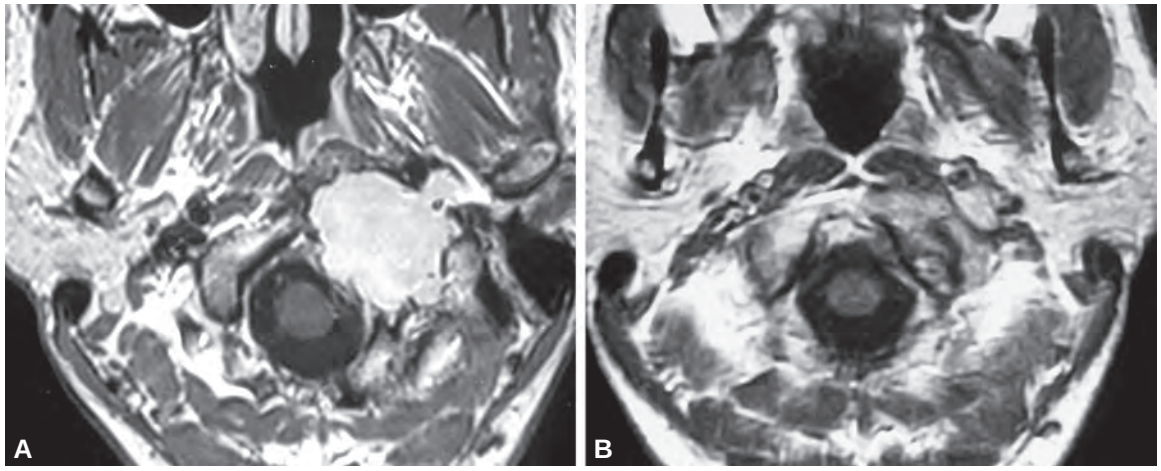
Acromegaly

Jezkova et al.[23] studied 96 acromegalic patients (median tumour size 1,350 mm^3) over a mean follow-up period of 53.7 months of whom 24 received primary GKS. Thirteen patients needed a second sitting; fifty per cent of the patients achieved mean GH less than 2.5 ug/l within 42 months, normalised their IGF-I within 54 months and achieved GH suppression in the oral glucose tolerance test with normal IGF-I within 66 months. The effectiveness of GKS depended on initial GH and IGF-I serum levels and not on the size of the adenoma. Hypopituitarism occurred only at doses exceeding 15 Gy. Patients with primary neurosurgery followed by GKS had better outcomes than those with GKS alone.

The choice of therapy for functioning pituitary adenomas still remains open surgery, as the prescription dose in GKS is limited by the proximity of the tumour to the optic pathways.

Chordomas and Chondrosarcomas

Hasegawa et al.[16] studied 37 patients; 27 chordomas, 7 chondrosarcomas and 3 radiologically diagnosed chordomas treated with GKS. The mean tumour volume was 20 cc, the mean marginal dose was 14 Gy and the mean



Figs 8A and B: Twenty-two months follow-up contrast MR axial images revealing significant reduction in the size of a glomus jugulare treated primarily with GKS at the level of the C1 lateral mass

follow-up period was 59 months post-procedure. The actuarial 5-year and 10-year local tumour control rates were 76 and 67%, respectively, and 100% for patients with low-grade chondrosarcomas. Tumour volumes less than 20 cc significantly affected tumour control. Only one patient developed facial numbness. They recommended treating patients with a generous margin with prescription doses exceeding 15 Gy to achieve best long-term tumour control.

Glomus Jugulare

GKS has revolutionised the treatment of this rare tumour with primary therapy being offered on presumptive radiology. In a study from our centre, 24 patients with GJ underwent 25 procedures, 15 patients received primary GKS. Mean tumour size was 8.7 cc (range 1.1–17.2 cc); 93.1% coverage was achieved using a mean prescription dose of 16.4 Gy (range 12–25 Gy) at a mean isodose of 49.5% (range 45–50%). At a median interval of 24 months follow-up, six patients had improved clinically while a single patient developed transient TGN. Tumour control was 100% with MRI scans recording a decrease in size in 70% of all patients. Our data indicated that 83% of patients who underwent primary GKS had tumour regression on MRI, as opposed to 50% of patients who underwent GKS after an open procedure. Eighty per cent of patients developed a Grade V/VI House and Brackman facial palsy after surgery and the average volume of residual tumour was 9.2 cc. For large tumours, we have now begun fractionating GKS by targeting the intradural and extradural tumour segments separately in different sittings. Figures 8A and B reveals dramatic tumour reduction 22 months after GKS at the level of the C1 lateral mass.

Haemangioblastomas

Matsunaga et al.[37] in a study of 22 patients with 67 tumours (mean volume 1.69 cc) who received a mean marginal dose of 14.0 Gy had a tumour control rate of 83.6% at a mean follow-up of 63 months. The only factor adversely affecting tumour control was the presence of a cystic component. Wang et al.[64] found that a prescription dose exceeding 18 Gy resulted in a total absence of tumour cells within 48 months. In their series of 35 patients followed-up for a mean of 66 months, tumour control rates were 71% at the end of 5 years (mean prescription dose was 17.2 Gy).

Gliomas

Pilocytic Astrocytomas

Hadjipanayis et al.[4] studied 37 patients with biopsy proven recurrent or unresectable pilocytic astrocytomas, of which 18 involved the brainstem. Tumour volumes varied from 0.42 to 25 cm^3. The median prescription dose was 15 Gy. Complete tumour resolution was demonstrated in 10 patients, reduced tumour volume in 8, stable tumour volume in 7, and delayed tumour progression in 12.[13] GKS may be the only modality available in such cases. In another study from Karolinska institute involving 16 patients in whom GKS was used to treat residual tumours with a prescription dose of 10–12 Gy, tumour control was achieved in all patients at a mean clinical follow-up time of 8.5 years and a mean radiological follow-up time of 5.9 years.

Low-Grade Gliomas

In a study of 12 histologically proven cases of recurrent or unresectable World Health Organization (WHO) grade II fibrillary astrocytomas, Hadjipanayis et al.[14] found that GKS using a median prescription dose of 16 Gy to volumes ranging 1.2–45.1 cc resulted in complete tumour resolution in one patient, reduced tumour volume in four patients, stable tumour volume in three patients and delayed tumour progression in four patients of whom three patients presented with an increase in cyst size alone. All patients were alive at a

median follow-up of 52 months after radiosurgery and 103 months after diagnosis.

Malignant Gliomas

GKS offers effective treatment as a salvage therapy for patients with small recurrent glioblastoma multiforme (GBM). In a study of 32 patients with 36 treated lesions, who had previously undergone neurosurgical resection and fractionated external beam radiotherapy (EBRT), it was found that the median overall survival after SRS was 10 months, with a progression-free survival of 7 months. The median interval between primary irradiation and re-irradiation was 10 months. The median prescription dose was 15 Gy delivered at the 80% isodose. No concomitant chemotherapy was given. No acute or long-term toxicity was observed.[5] Nwokedi et al.[44] studied 64 GBM patients treated with EBRT alone (Group 1) or those who received both EBRT plus a GKS boost (Group 2). GKS was administered to most patients within six weeks of the completion of EBRT. The median EBRT dose was 59.7 Gy and the median GKS boost was 17.1 Gy. The median survival was 13 months in Group 1 versus 25 months in Group 2. The addition of a GKS boost was a significant predictor of overall survival. Hsieh et al.[20] further concluded that adjuvant GKS performed at tumour progression seemed to increase median survival to 16.7 months compared with 10 months when performed after tumour resection.

Metastases

The magnitude of this problem can easily be assessed by the fact that cerebral metastases occur in 15–30% of cancer patients during their lifespan. Brain metastases can be dealt with surgery, GKS/SRS, whole brain irradiation (WBI) or combinations thereof.

Current Recommendations

Aoyama et al.[1] presented the first multi-institutional, prospective, randomised comparison of WBI plus SRS versus SRS alone for 1–4 cerebral metastases less than 3 cm in diameter and found that the median survival and the 1-year actuarial survival rate were 7.5 months and 38.5% in the WBI + SRS group and 8.0 months and 28.4% for SRS alone. The one year brain tumour recurrence rate was 46.8% in the WBI + SRS group and 76.4% for the SRS alone group. There were no significant differences in cognition between the two groups. Thus, WBI did not confer a survival advantage whereas its omission upfront increased the chances of intracranial relapse. Conversely, a trial comparing WBI + SRS versus WBI alone for 2–4 metastases less than 2.5 cm found that the rate of local failure at 1 year was 100% after WBI alone but only 8% in patients who had boost SRS. Patients who received WBI alone lived a median of 7.5 months, while those who received WBI + SRS lived 11 months. Survival was dependant on the extent of extracranial disease.[28] This lack of significant survival benefit but improved local control has also been supported by a Cochrane database meta-analysis.[62]

For single metastases, current recommendations suggest that surgery followed by WBI may improve functionally independent survival but not overall survival and may reduce the proportion of deaths due to neurological causes, without increasing the risk of an adverse outcome as compared to WBI alone.[15,40] Although there is no data to confirm or repudiate the effectiveness of SRS as a single modality of therapy or compare surgery with SRS as the initial modality of therapy, the addition of SRS to WBI confers a significant survival advantage.[31,56]

These do not apply to patients with metastatic lymphoma, small-cell lung cancer, germ-cell tumour, leukaemia or sarcoma.

Vascular

Arteriovenous Malformations

Steiner revolutionised AVM management by demonstrating AVM obliteration without open surgery in the 1970s.[58] Since then, historically, AVMs have formed the bulk of cases for whom GKS is done. In one of the largest published series, Liscak et al.[31] analysed 330 patients with AVMs with a median volume of 3.9 cc. Repeat radiosurgery was performed on 76 patients after angiography failed to demonstrate obliteration after 3 years. AVM obliteration was achieved in 74% of patients after the first round of radiosurgery and in 69% after the second, with the overall chance of cure being 92%. Smaller volume AVMs and the application of a higher radiation dose resulted in a higher chance of obliteration. The risk of re-bleeding was 2.1% annually until full obliteration. The risk of permanent morbidity was 3.4%. In a study from our centre, 103 children (mean age 13.9 years) with a mean follow-up of 26.4 months were studied (57 had Spetzler-Martin Grade I or II, and 46 had Grades III–V). The mean volume of the AVMs was 2.4 cc and the mean marginal dose was 24.4 Gy. Complete obliteration of the AVM was documented in 87% of patients with a 4 year angiographic follow-up. The three-year actuarial rate of nidus obliteration was 66%. Three patients (2.9%) experienced bleeding during the latency period and symptomatic radiation-induced oedema was noted in four patients (3.8%). A significantly higher incidence of radiation oedema was noted in patients with AVM volumes greater than 3 cc and in patients with Spetzler-Martin Grade IV and V AVMs.[24]

Cavernomas

There is a great deal of controversy regarding the role of GKS in cavernous malformations. This is because these lesions are angiographically occult and MR scans reveal persisting blood products; thus, it is very difficult to assess whether these have been obliterated post GKS. Hence, an analysis of bleeding rates may perhaps verify the efficacy of GKS in the same. Hasegawa

et al.[17] examined the long-term haemorrhage rate after radiosurgery for 82 patients with symptomatic cavernous malformations in the brainstem or diencephalon, in which surgery was deemed to be very high risk. They found that the annual haemorrhage rate was 12.3% per year for the first 2 years after radiosurgery, followed by 0.76% per year thereafter. When compared to the natural history of these lesions (annual bleed rate of 0.6% per annum in previously unruptured cases, 4.5% per annum in patients with a single previous bleed and a 30% per annum bleed rate in patients with greater than two bleeds), GKS may confer a greater than 30 fold reduction in the baseline risk of symptomatic bleeding.[25] Liscak et al.[32] also studied 112 patients with cavernous haemangiomas, treated with a median prescription dose of 16 Gy with GKS of which 107 patients were followed for a median of 48 months. They observed that the re-bleeding rate was 1.6% while it was 2% prior to radiosurgery. A transient morbidity rate of 20.5% and a permanent morbidity rate of 4.5% were also observed. Before radiosurgery, 39% of patients suffered from epilepsy and this improved in 45% of them. Re-bleeding was more frequent with a prescription dose below 13 Gy.

Functional

Trigeminal Neuralgia

TGN was one of the first indications for GKS. However, microvascular decompression provides more effective pain control over longer periods of time. GKS should be reserved for patients who are not optimal surgical candidates and have TGN refractory to medical treatment. Sheehan et al.[54] reported the results of GKS in 151 cases of TGN, wherein the trigeminal nerve was targeted 2–4 mm anterior to the pons with 50–90 Gy of radiation. Around 90%, 77% and 70% of patients experienced some improvement in pain at 1-, 2- and 3-year follow-up, respectively, with 27% of patients suffering a relapse and 9% developing new onset facial numbness. Although these results have been validated by a large number of series, our experience, though limited, suggests that only about 50% of patients have some improvement in pain relief after this procedure.[10,12] It is our experience that GKS is possibly a good second line treatment option for patients with typical TGN. It is the procedure of choice for patients with TGN secondary to multiple sclerosis.

Movement Disorders and Epilepsy Surgery

Although SRS is the only non-invasive form of treatment for functional disorders, these contribute only a small percentage of treated patients. The drawbacks in using GKS is that only anatomical targeting is possible, this is an ablative procedure and very high doses (up to 150 Gy) are utilised, making shielding of adjacent neural structures impossible. Radiosurgical treatment for epilepsy and certain psychiatric illnesses is performed in several centres as part of strict research protocols.[11] Radiosurgical pallidotomy or medial thalamotomy has been associated with a 50% risk of complications and is no longer recommended. However, radiosurgical ventrolateral thalamotomy for the treatment of tremor in patients with Parkinson's disease, multiple sclerosis and essential tremor may be indicated in patients with advanced age, at high risk for surgery or those on anticoagulation.[7] A promising new application of GKS is the delivery of a high-dose of 160 Gy to the pituitary stalk, using an 8 mm or two 4 mm collimators in patients with intractable pain related to bone metastasis. A prospective multicentre study proved the efficacy and the safety of this treatment in nine patients, all of whom reported pain resolution without significant complications. Pain relief was observed within several days and this effect was prolonged until the day that they died.[18]

COMPLICATIONS AND SIDE EFFECTS

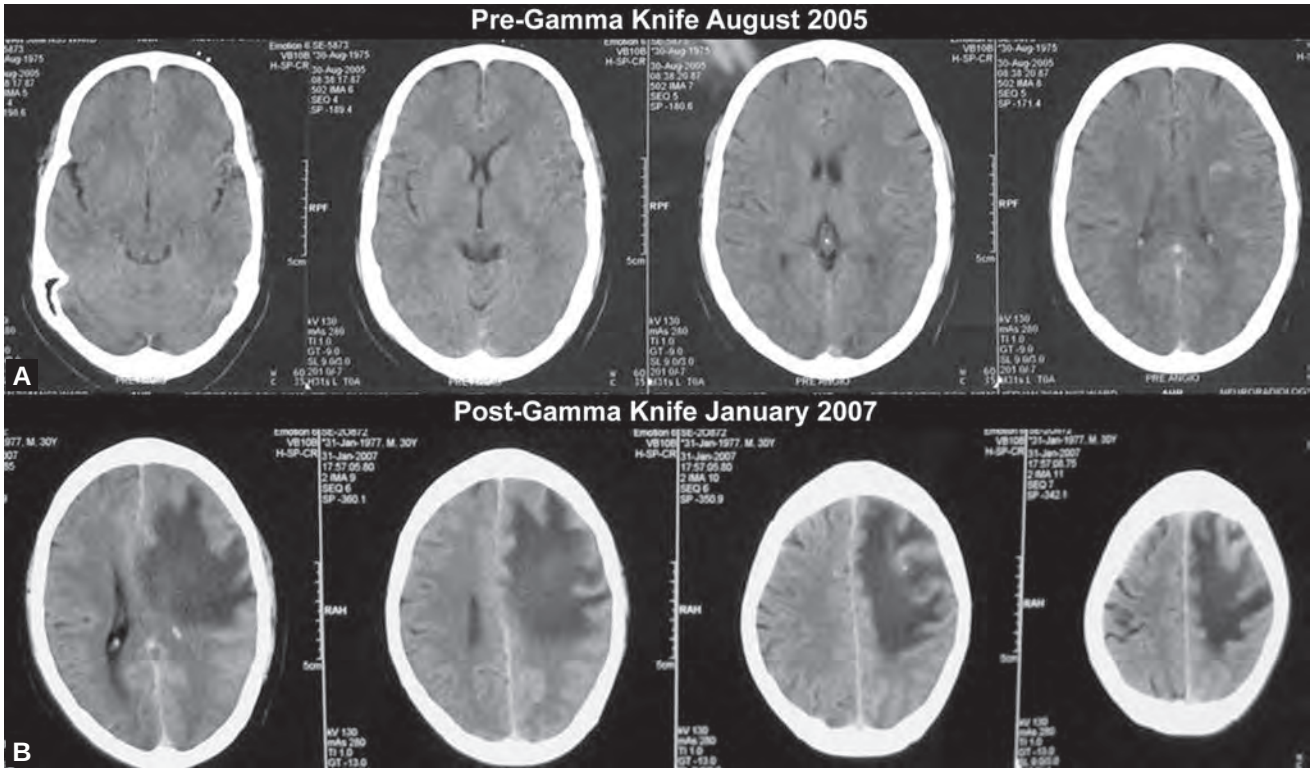
GKS has caught the imagination of the lay population and the neurosurgical community because of its ability to treat lesions with a very high conventional surgical risk of morbidity and mortality, with exact precision and a very low risk of complications. Principal among these are:

Acute Complications: Post Gamma Knife Headache a New Syndrome?

Although conventional wisdom dictates that the overall risk of adverse effects that a patient undergoing GKS has to contend with is about 2–4%, a study from our centre revealed that 12.7% of patients had immediate (less than 24 hours) complications, while 11.3% of all patients developed acute (24 hours–3 months) complications such as headache, nausea/vomiting, vertigo and seizures. None of these were severe. The incidence of perilesional oedema on follow-up radiology was 9.8% and correlated significantly with a maximum target diameter more than 25 mm and prescribed dose more than 20 Gy.[35] St George et al.[55] found that the incidence of headache following GKS was greater than 50% in a cohort of 47 patients followed-up for two weeks. Rozen et al.[49] have tried to identify a stereotypic "post-gamma knife (PGK) headache", but these complaints have never been severe nor are the mechanisms of induction clear. It has to be stressed that early complications are, with few exceptions, never severe.

Radiation Myelitis

Radiation changes can or do occur in the normal adjacent brain parenchyma due to a number of complex reasons which are not altogether understood. Flickinger et al.[57] used an integrated logistic formula to study the effect of dose and location on adverse radiation imaging effects (ARIE), after GKS for AVMs and found that the entire volume under the 12 Gy line correlated significantly with the same. Thus, the anticipated risk should be plotted against the estimated chances of AVM occlusion before prescribing the final dose. Care should be taken to avoid



Figs 9A and B: Serial axial CT scans revealing post-GKS radiation changes in the region of the left sensorimotor cortex of the patient whose angiograms confirmed AVM obliteration in Figure 6

exceeding the conventional tolerance doses of the optic pathways, cranial nerves and the brainstem. When MR changes do develop, these are often asymptomatic or else produce transient neurological deficits, which can be dealt with a prolonged course of steroids and free radical scavengers. Only rarely have patients required a decompressive craniectomy for the same. Figures 9A and B illustrates the ARIE which developed prior to the successful obliteration of the large motor strip AVM depicted in Figure 6. The patient had developed dysphasia and hemiparesis, which resolved over six months with steroids and decongestants.

ARIE may be most devastating in the compact cross-section of the brainstem. A collaborative study from our centre has shown that patients with benign intra-brainstem gliomas, cavernomas and AVMs run an 18.7% risk of developing an ARIE at a median prescription dose of 15 Gy delivered at the 50% isodose. Exposure of the brainstem at volumes as low as 0.1 cc to doses greater than 12 Gy resulted in ARIE. Four of these patients developed new neurological deficits which were all transient. The presence of an ARIE in this study was linked significantly to the development of new neurological deficits and age below 40 years. ARIE, thus, was actually a favourable prognostic marker to predict recovery from a new neurological deficit.[53]

Cyst Formation

Despite a favourable outcome after GKS, cysts may sometimes form at the target site which may produce a mass effect and require surgery, especially in AVMs and VS. Izawa et al.[21] studied 12 such patients with delayed cyst formation in the vicinity of the AVM after an average period of 6.7 years, following GKS which had shown complete angiographic obliteration. Eight of these patients subsequently required surgery. Cyst formation after GKS for VS may produce hydrocephalus and acute neurological deterioration warranting monitoring with serial MR scans.[19]

Hydrocephalus

Hydrocephalus has also been reported following GKS for VS, whether a causative relationship exists is highly debatable, as these may occur as a consequence of the natural history of the disease process.[61] Following fractionated SRT, however, Sawamura[50] reported an 11% incidence of hydrocephalus in a series of 101 patients who received 40–50 Gy administered in 20–25 fractions over a 5–6 week period. The mean size of tumours associated with this change was 25.5 mm and was significantly higher than the rest of the cohort.

Second Malignancy

Perhaps the most dreaded complication associated with the use of GKS, especially for benign lesions, is the risk of inducing a second malignancy. Twenty such cases have been reported thus far, 10 tumours developed *de novo* of which eight were malignant. Fourteen patients had VS of whom eight had neurofibromatosis-2.[3]

As nearly 400,000 patients have undergone GKS thus far, the incidence of brain cancer in this cohort is about 5 per 100,000. This should be compared with the overall age-adjusted incidence rates for brain cancer in the United States, which was reported to be 6.4 cases for every 100,000 persons in the year 2002.[65]

PLATFORMS DELIVERING STEREOTACTIC RADIOSURGERY

Leksell Gamma Knife™

The Leksell Gamma Knife™ (Elekta instruments AB, Stockholm, Sweden) has patented most of the widely used GKS platforms using either 201 (models B and C) or 180 (Perfexion) Co-60 radiation sources. Most available research in GKS emanates from this technology. These platforms remain some of the most expensive single pieces of medical equipment that a hospital could invest in.

Rotating Gamma System

A more recent entrant in this field is a Rotating gamma system (RGS) developed by OUR International Inc. Shenzen, China. This uses 30 Co-60 sources contained in a revolving hemispherical shell with six groups of five collimator holes, which provide varying radiation beams. The advantages lie in that helmets need not be changed manually and the chances of collisions are low.

LINAC Based Radiosurgery

Great interest has recently been focused on the Cyberknife® (Accuray Inc., Sunnyvale, California, USA) which utilises a 6 MeV Linear accelerator (LINAC) attached to a robotic manipulator which is mobile in six different axes. The robot guides the LINAC which aims the beam at the target. Unlike GKS, a rigid stereotactic frame is not used, target localisation is achieved by a mask or by fiducials. Two orthogonal X-ray cameras and an optical tracking system are used to track the patient's movements. An integrated X-ray image processing system then compares the actual real time images with those acquired previously and stored in a database to determine the shift. This information is then conveyed to the robot which makes the necessary corrections before radiation delivery. The accuracy of this system is 0.7 mm. CT is the primary modality of imaging. Treatment is often over multiple days and can be fractionated. The advantage lies in that this system can be used to target extracranial targets too.

Charged Particle Radiosurgery

Proton beam radiation using either the Bragg-peak to make these charged particles stop within the target or the plateau-beam to deposit particle energy remains, theoretically, the most attractive option of delivering intracranial radiation, as spillage is minimal due to a sharp dose fall-off as the charged particle rapidly loses energy. This facility, however, requires sufficient space to accommodate a cyclotron, significant maintenance overheads, continuous quality control and installation costs to the tune of Rs 160 crore. Only two facilities exist in the United States (Massachusetts General Hospital and Loma Linda University, California) and none in India.[43]

EVOLVING INDICATIONS AND FUTURE TRENDS

Despite the volume of clinical material documenting the efficacy of GKS in the host of benign, malignant and functional disorders detailed above, there is still a paucity of histopathological data to convincingly document the biological response of normal and/or pathological tissue to the effect of high dose single fraction delivery of stereotactic radiation. The development of an animal model will go a long way in our understanding of the radiosurgical dose response. The other areas of advancement are likely to be in the extension of the stereotactic space available for targeting polar lesions, advances in imaging and segmentation of target structures and normal tracts and in peri-operative pharmacological treatment, to protect normal tissue and sensitise target cells.

The Perfexion™ platform may significantly enhance our capability to treat lesions in the cervical spine, paranasal sinuses, the oral cavity and even the neck. Ophthalmic indications for using GKS now include uveal melanomas, haemangioblastomas, ocular metastases, macular degeneration and even glaucoma.[33]

Integration of Magneto-Encephalography (MEG) into planning may offer epilepsy surgery programs a truly non-invasive means of specifically targeting seizure foci, while minimising the risk of radiation myelitis. Integration of Positron-emission Technology (PET) too can help us treat malignant disease with greater specificity.

Future research needs to be directed towards the development of radiosensitisers, injected during the pre-GKS angiograms that would allow us to target larger AVMs with a lower prescription dose to increase obliteration rates, while reducing the risks of radiation damage to adjacent normal structures. Similarly, the use of hypothetical neuroprotective agents during GKS for malignant disease may help us escalate the prescription dose to enhance the tumour kill capability, without increasing the risk of adverse radiation effects.

GKS remains a most valuable tool for the neurosurgeon, both in the primary therapy of neurological disease and as an adjuvant to conventional surgery. Its scope and indications have crystallised over the last two decades and are likely to broaden with the further passage of time. This represents the next phase of modern neurosurgery and arguably ranks as its most important innovation since the introduction of the operating microscope.

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192 Psychosurgery

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The increase in our knowledge of the functions of the human brain, especially in the realm of cognition has now made it possible to make discrete lesions in selected areas of the brain and achieve amelioration in predominantly psychiatric illnesses. This field of surgery may be termed psychosurgery or functional neurosurgery. The WHO defines psychosurgery as; "the selective surgical removal or destruction of nerve pathways for the purpose of influencing behaviour".[11,47] Another definition of psychosurgery is as follows: "Any surgical procedure that attempts to alter, through manipulation of neural tissue a thought or thought process that is associated with a psychiatric disorder categorised in DSM-IV and that is not caused by any known structural lesion".[25] The WHO also mentions depression as the 4th largest group in the global burden of disease. Surgical procedures on the brain to control restless or aggressive behaviour have been included under the term *sedative neurosurgery*.[89,90]

HISTORY OF PSYCHOSURGERY

Observations on excavated skulls have shown well circumscribed defects, which suggest some form of a procedure on the skull of a living person, presumably an attempt at 'letting the devil out' of a 'mental' patient. After these early attempts, psychosurgery was abandoned due to ignorance regarding psychiatric diseases which were held to arise from various extraneous and non-human influences and due to many superstitions that clouded psychiatric illnesses and their management. Ancient India had specialised in the science of the mind and its control. Yoga and the universal acceptance of a tolerant attitude helped minimise psychological stresses. But in ancient Indian works on medicine, psychiatric illnesses were still attributed to extracorporeal influences. With increasing and better scientific study of psychiatrically ill patients, early 20th century saw a more rational approach to the problem of mental illnesses.

Franz Gall's phrenology tried to localise brain functions, based on external calvarial landmarks. Paul Broca ushered in the era of cerebral localisation. In 1891, Gottlieb Burckhardt, a Swiss psychiatrist, drilled holes in the heads of 6 severely agitated psychiatric patients and extracted parts of their frontal lobes. Three patients' outcomes were deemed "successful". Burckhardt's report gives us an insight into the desperation with regard to mental illnesses in those times. The concept of *primum non nocere (first do no harm) had given way to Melius anceps remedium quam nullum (better an unknown cure than no cure at all).* He was forced by his colleagues to abandon further such endeavours. In the late 1800s, Fredrich Goltz did temporal lobectomies in dogs and observed that the animals became more calm and tame than non-operated ones.[45,48]

The functional basis of psychosurgery was laid down by Fulton[28] who, in 1935, published his observations on frontal lobectomy in two chimpanzees. But Fulton also cautioned that, "….turning to questions involving perception, learning, memory and other higher intellectual functions, objective data are far more difficult to obtain in humans". Fulton and Carlyle Jacobson observed behavioural changes in chimpanzees after frontal lobe ablation and concluded that such procedures could decrease anxiety states in chimpanzees.[47] In 1936, Egaz Moniz and Almeda Lima published their experience with prefrontal lobotomy in humans. Moniz himself remarked, "We are certain that these experiments shall stir up keen discussions in the medical, psychiatric, psychological, philosophical, social and other fields. We expect that and hope at the same time that this discussion shall promote the progress of science and above all, the benefit of mental patients".[64]

That Moniz received the Nobel Prize for Medicine in 1949, is proof of the desperate situation prevailing in the field of therapy for mental illnesses.

Prior to psychosurgery there was no treatment for mental patients. Therapeutic nihilism was the philosophy of treatment, i.e. patients were allowed by default to languish according to the natural history of the disease. In the 1930s, somatic therapies, like ECT and others, were introduced. Walter Freeman, a neuropsychiatrist of the organicist school of psychiatry, popularised psychosurgery in the USA by publishing his work in the style of pulp-fiction thus abandoning scientific protocol. Moniz's procedure, the frontal leucotomy, was modified by Freeman and Watts as a prefrontal lobotomy. Freeman later devised the transorbital prefrontal lobotomy with an ice pick leukotome. Freeman with an ice pick severed psychosurgery's final ties with its roots, those of neurosurgery itself. His practice did not follow scientific principles and gradually a public campaign of misinformation was mounted against psychosurgery as

a form of mind control and this led to its near disappearance from the field of neurosurgery.[47] Govindaswamy and Rao[30] published, in 1944, the first series of leucotomies in India and Whitty et al.,[101] in 1952, in the United Kingdom. The results of prefrontal leucotomy were so remarkable that a large number of operations were performed. Although many patients benefited, in some instances the patients deteriorated and became dull and apathetic with alterations in personality and this led to dissatisfaction with the long-term results. The discovery of chlorpromazine in 1945 heralded the fall of psychosurgery. In 1947, Spiegel and Wycis started stereotatic dorsomedial thalamotomy and this formed the basis of subsequent stereotactic procedures in psychosurgery.[4,47] In 1949, Scoville[92] devised and modified leucotomies in the hope of diminishing the unsatisfactory side effects of the classical leucotomy. Ramamurthi, working in the United Kingdom, in 1949, had performed open orbital undercutting operations with satisfactory results.[41] In 1947, Fulton warned against the widespread use of leucotomy and hoped that neurosurgeons will not allow their zeal to outrun their knowledge of function. He also suggested that operations on the cingulate gyrus could be done as a *"limited" leucotomy.*

Hugh Cairns in London and Le Beau in Paris took up this suggestion and started removal of a portion of the anterior cingulate gyrus under direct vision. Reporting on 37 cases, Lewin[52] found that after cingulate resection, there were no ill effects on the personality of the patients and the complication rate was low. It may be mentioned here that Miller[63] in a ten year follow-up of patients who underwent leucotomy (lobotomy) for mental illness, between 1948 and 1952, found that 61% were working and rehabilitated in the community. In 1967, the Harvard Neurosurgeon H Thomas Ballantyne Jr ushered in the era of modern stereotactic psychosurgical procedures with air ventriculography for localisation and thermocoagulation for lesion making. He also deserves credit for making psychosurgery truly multidisciplinary with the involvement of psychiatrists and neurologists and also for the use of questionnaires for documentation of the outcome in patients undergoing various psychosurgical procedures.[40] *"It has all been done before"* remarked Holmes in the BMJ.[36] Readers of psychosurgery are requested to acquaint themselves with the achievements of the *Madras school of psychosurgery* pioneered by Profs. B. Ramamurthi, V. Balasubramaniam, S. Kalyanaraman, T. S. Kanaka, Jagannathan et al. through the 1960s and the 1970s. Several anatomical targets were selected and approached stereotactically, via various trajectories. Balasubramaniam and Ramamurthi reported on the largest clinical series of patients to date who were submitted to stereotactic amygdalotomy.[49] Prof. Lars Leksell pioneered the use of the gamma knife in lesion making in psychosurgery. The contributions of Norman Geschwind, Luria and Muriel Lezak, in the parallel fields of neuropsychology and cognitive neurology, also deserve mention in mankind's effort to unravel the mystery of the human brain. Early attempts at controlling aggressive behaviour disorders by ablation of the frontal or temporal lobe were not uniformly successful and also led to undesirable results. The understanding of the various behavioural mechanisms was hampered by the fact that the part of the brain which controlled behaviour was labelled the rhinencephalon or olfactory brain and was considered vestigeal in man. The breakthrough came when Bard[15] and Cannon[22] following Woodworth and Sherrington[104] established that the 'sham rage' phenomenon arose from the region of the hypothalamus.

LIMBIC SYSTEM ANATOMY—NEWER PERSPECTIVES

The functional anatomy of the limbic system has undergone a sea change with advances in neurobiology and neurosciences. The earliest concept of *networking* was provided by Prof. Niewenhuys in 1936[53] when he considered the LS to be comprised of five concentric C-shaped circuits which were as follows:

1. Stria medullaris thalami, habenular nuclei and habenulointerpeduncular tract.
2. Amygdalae and stria terminalis.
3. Fimbriae and fornix.
4. Hippocampus with extension over the corpus callosum and the septal nuclei.
5. Parahippocampal gyrus and cingulum.

Another classification is the division of the limbic system into limbic areas comprising the amygdala, parahippocampal gyrus, hippocampus, septum, hypothalamus, limbic thalamus, insula and paralimbic areas comprising the anterior temporal pole and the orbitofrontal cortex.

Papez suggested a circuit for human emotion in 1937 which was as follows: Cingulate gyrus → Hippocampus → Fornix → Mammillary bodies (Hypothalamus) → Anterior thalamic nuclei → Cingulate gyrus.

To this circuit, MacLean in 1952 added the septal area, nucleus accumbens, orbitofrontal cortex, anterior temporal cortex, DM thalamic nucleus and amygdala.[57]
Goldenberg in 1988[30] suggested three limbic sub-circuits:

1. *Medial limbic circuit:* This is the classical Papez circuit.
2. *Basolateral circuit:* Orbitofrontal cortex and anterior temporal cortex → amygdala → magnocellular DM nucleus of thalamus (fronto-thalamic fibres).
3. *Defence reaction circuit*: Comprising the hypothalamus, stria terminalis and amygdala.

It has been postulated that interruption of any of these pathways can block inputs to frontal lobes and relieve psychiatric symptoms by affecting one of the primary functions of the frontal lobes namely, cognition.[84]

Mega et al.[61] classified psychiatric disorders into three groups localised to specific anatomical structures and circuits. Limbic system disorders were classified based on the increased, decreased and distortional activity of the circuits.

Concept of Thalamocortical Dysrhythmias[97]

This brings the concept of mental disorders down to disturbances in single cell physiology using MEG. These are a group of disorders characterised by localised and protracted low frequency spontaneous recurrent activity of the thalamocortical system and this underlies certain chronic psychotic, affective and anxiety disorders, including obsessive compulsive disorders (OCD). The re-establishment of normal oscillation could be achieved with anteromedial pallidal and centrolateral thalamic lesions. These were based on the studies of Spiegel and Wycis who targeted the MD thalamic nucleus for psychosis.[79]

The features of thalamocortical dysrhythmias (TCD) are as follows:

- Hyperpolarisation through disfacilitation and/or over-inhibition of thalamic relay and/or reticular cells by the disease source. Psychosis is therefore attributed to corticothalamic disfacilitation and a striatal anomaly providing thalamic over-inhibition. Chronic dysfunction of the cognitive network triggers neurotic disorders.
- Hyperpolarised state is due to a source of calcium T channel de-inactivation, causing production of low threshold Ca^{2+} spike (LTS) bursts by thalamic or reticular neurons.[106]
- Neurons in such a state have a slow rhythmicity of thalamic cortical loops. They are locked up in theta rhythm low frequency domain by ionic currents. Recurrent divergent corticothalamic and reticulothalamic projections cause coherent diffusion of frequency to various cortical areas.
- The proposed existence of activation of higher frequencies, i.e. beta and gamma cortical domains due to asymmetrical corticocortical GABAergic collateral inhibitions. This is similar to the edge effect due to lateral inhibition in the retina.

The essential feature is that resonant oscillatory thalamocortical properties are required for the generation of normal hemispheric function.

The concept of thalamocortical slow burn, i.e. progressive cortical and thalamic atrophy, due to self-destruction by calcium triggered apoptosis, further reinforces the concept of TCD. The above concept is important, as it provides a neuroanatomical target for psychosis, which was previously considered as a contraindication to psychosurgery. The concept of thalamocortical dysrhythmia will be of importance in the near future, as psychiatrists are gradually understanding that schizophrenia, OCD, depression, etc. are different manifestations of dysfunction in the same or related anatomical circuits.

The targets selected by researchers of TCD are:

- *Centrolateral nucleus of the thalamus* which is located by the co-ordinates: 2 mm posterior to the posterior commissure, mediolaterally 6 mm lateral to the lateral border of the 3rd ventricle, dorsoventrally at the inter-commissural plane. It is reached by an anteroposterior angle of 60 degrees and mediolateral angle of 5–10 degrees. The size of the lesion must be 4 mm in diameter and 12–14 mm in length.
- *Anteromedial paralimbic thalamic nucleus* which is located by the co-ordinates: anteroposteriorly 4 mm posterior to the anterior commissure, mediolaterally 12 mm lateral to the lateral border of the lateral ventricle, dorsoventrally 2 mm ventral to the intercommissural plane. It is reached by an a-p angle of 55 degrees and a mediolateral angle of 20 degrees. The lesion size must be 4 mm in diameter and 6 mm in length.

The authors employed the above targets in patients with psychotic hallucinations/delusions, OCD, major depression, BPD, anxiety states and impulse control disorders (ICDs) and had good results. The sample size was however small, comprising 11 patients.

Note: *The targets are based on documented magnetoencephalography (MEG) data. They do not imply a reduction of functional thalamocortical loops and are based on regulation towards normalisation of the dysrhythmic thalamocortical oscillation.*

Figure 1 shows the schematic diagram of (highly simplified) connections of limbic system.

The amygdala was excluded in the concept of the behavioural brain initially. During the past two decades, however, it has become increasingly obvious that the amygdala plays a pivotal role in the production of behavioural patterns through its connections to the cortex, the limbic system, the hypothalamus[88] and thalamus. The circuit that Papez proposed is essentially on the medial side of the hemisphere aligned parallel to the sagittal plane. In 1937, Papez remarked that "the cingulate gyrus is the seat of dynamic vigilance by which emotional experiences are endowed with an emotional consciousness".[62] Livingston[55] proposed another limbic circuit at right angles to the plane of the Papez circuit and termed it the basolateral circuit, consisting of the orbito-insular-temporal connections. The median circuit of Papez connects to the anterior thalamic nucleus, while the basolateral circuit connects to the dorsomedian nucleus. The basolateral circuit reaches the thalamus without the interposition of a hypothalamic midbrain relay. Livingston[55] also suggested that normal behaviour may be the result of a balance between the basolateral and the median circuits.

The behavioural brain may be conceived as having a central core of executive structures with extensions and distant connections. The amygdala, the hypothalamus and the periaqueductal grey form the central core. The inferior orbital cortex is connected to the amygdala by the uncinate fasciculus and functions as a frontal extension of this system.[66]

The cingulum is connected to the limbic nuclei of the thalamus and is more concerned with emotional 'feeling' (a purely subjective phenomenon) than with emotional behaviour. The dorsomedian nucleus of the thalamus, by virtue of its connections with the cingulum

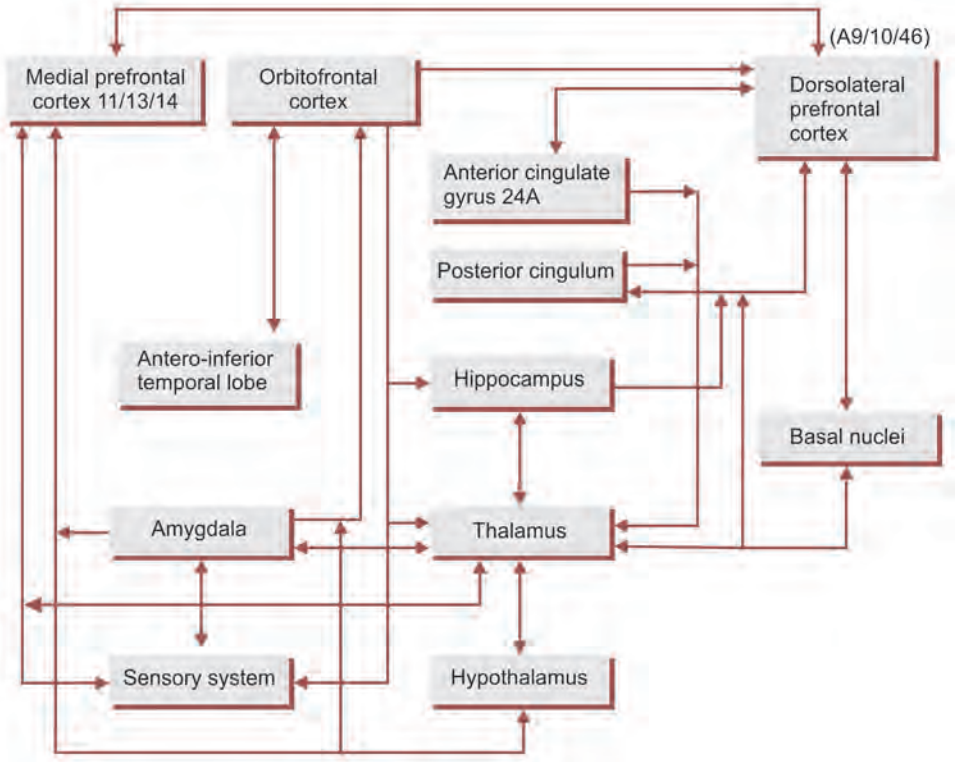

Fig. 1: Affect regulation circuit—cognition and emotion

and hypothalamus, forms an integral part of the behavioural brain on the 'affect' side. The anterior third of the internal medullary lamina of the thalamus connects to the hypothalamus and is involved in the modification of behaviour. Figure 2 shows connections of the cingulated gyrus.

The close proximity of the olfactory brain and the behavioural brain and their interconnections was not only an anatomical accident but also represents an important stage in functional evolution of humans from lower animals, in whom olfactory sensations were major determinants of behaviour. Thus, in man also, the olfactory and non-olfactory parts are closely interrelated at many levels, including the amygdala.

Amygdala

The amygdaloid nucleus has a dual origin. It develops partly from the primitive olfactostriatum and partly from the hypopallium. It has been identified in cyclostomes and tail less amphibians. As we go up the evolutionary scale, it undergoes an increase in size, until it reaches a maximum size of 1200 cumm in man. It becomes very complex in man and the terminology used to describe the amygdaloid nuclei is a little confusing because the same descriptive terms used for lower animals have been applied to man, without taking into consideration the changes in the position of the amygdaloid nuclei. The amygdaloid primordium lies on the floor of the temporal horn. As the temporal horn changes in form, the amygdala is carried medially and also rotates until, eventually (in man), it lies on the anterosuperior wall,

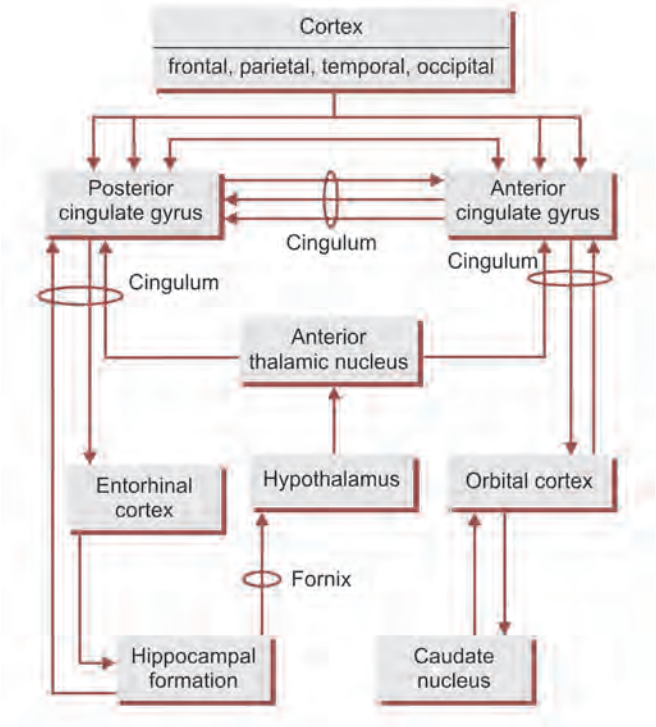

Fig. 2: Connections of the cingulate gyrus

exactly opposite the inferolateral bulge of the hippocampus. It is this shift that causes some confusion when terms, like corticomedial and basolateral, are used. The amygdaloid nucleus lies in close approximation to the superomedial wall of the temporal horn. The tail of the caudate nucleus, as it runs forwards, seems to end in the

amygdala. In sagittal sections, the centre of the amygdaloid nucleus is about 4.5 mm in front of the most anterior point of the temporal horn; its long axis lies along the roof of the temporal horn. In the coronal plane, it is related to the medial margin of the temporal horn.

Structure of the Amygdala

Broadly speaking, the amygdala can be divided into the *basolateral* (which is non-olfactory) and *corticomedial* (which is olfactory) parts. The basolateral part is further divided into a basal and a lateral nucleus; similarly the corticomedial is divided into a medial and a cortical part. The main sub-divisions have different afferent and efferent connections.

In addition to the study of cytoarchitecture by Nissl and Golgi stains, efforts at understanding the structural organisation of the amygdala include a consideration of its chemoarchitecture. On the basis of acetylcholinesterase stains, monoamine oxidase stains and dithizone and Timm stains, various divisions have been proposed. Most of these studies also confirm the broad division of the amygdala into a corticomedial and a basolateral part.

Connections of the Amygdala

The amygdala connects many nuclear groups and structures. For some of them, both electrophysiological and anatomical evidence is available. A few of these connections, however, still need anatomical verification, although there is abundant electrophysiological proof, e.g. the amygdalo-hippocampal pathway. The connections of the amygdala are to the temporal lobe, the hypothalamus, the thalamus and the frontal lobe. All these connections are predominantly unidirectional circuits. The important fasciculi of the amygdala are as follows:

A. Amygdalo-temporal connections: The amygdaloid nucleus connects to the temporal pole by the amygdalo-polar bundle. It is this bundle that is the main link between the amygdala and the inferior orbital cortex.[39]
B. The Amygdalo-hypothalamic pathways: The amygdalo-hypothalamic pathway is the most important link in this system. Originally, the amygdalo-hypothalamic pathway was probably a single entity, but subsequently it was separated into a dorsal and a ventral part, by the development of the basal ganglia and the internal capsule. The dorsal amygdalo-hypothalamic pathway is the older of the two and is referred to as the stria terminalis. It is a bi-directional pathway, although its main flow is to the amygdala. It runs along the roof of the temporal horn posteriorly and then turns superiorly to reach the anterior commissure. Here, it divides into two main components known as the precommissural and the postcommissural components.

The precommissural component ends mainly in the septal nuclei and also connects to the hypothalamus. The postcommissural component ends mainly in the hypothalamic nuclei. The ventral amygdalo-hypothalamic pathway is more important functionally. Arising mainly from the basolateral part of the amygdala, it runs medially and superiorly to reach the level of the anterior commissure where it splits into two. One division enters the hypothalamic nuclei particularly the posteroventral medial nuclear group. The other turns superiorly and ends in the subcallosal gyrus and the septal nuclei.

C. The Amygdalo-thalamic bundle: This is a distinct band that arises from the basolateral part and for a certain distance is part of the inferior thalamic peduncle. It eventually ends in the dorsomedian nucleus of the thalamus.
D. The uncinate fasciculus: This arises partly from the temporal pole and partly from the amygdala and ramifies after reaching the inferior orbital cortex, which is considered to be a frontal extension of the limbic system. The internal medullary lamina, which is the thalamic extension of the reticular system, contains in its anterior one-third nuclei which form part of the behavioural brain. Their connections with the amygdala have not been deciphered as yet. However, considerable electrophysiological evidence exists to show that the hippocampus projects to the amygdala, but anatomical studies have not been demonstrated.
E. The olfactory connections of the amygdala: They are practically confined to the corticomedial group of nuclei. The olfactory tract divides into three bands:
    i. The intermediate fibres end in the anterior perforated substance, which is encircled by the lateral and medial bands.
    ii. The medial tract passes deep to the cortex and ends in the region of the subcallosal gyrus.
    iii. The lateral goes to the corticomedial group.
F. The term extended amygdala includes the central and medial amygdaloid nuclei, various divisions of the bed nucleus of the stria terminalis, the interconnecting cell populations along the course of the stria terminalis dorsally and the caudal part of the ventral striatum and populations of neurons in the subpallidal region of the basal forebrain (previously called the substantia innominata). The extended amygdala has a high degree of internal associative connections. It has been considered to be a separate anatomical-functional unit. It must be emphasised that only the "non-cortical-like" central and medial nuclei of the amygdaloid complex and not the "cortical like" basal and lateral amygdaloid nuclei are included in the concept of the extended amygdala. This unit has rich afferent projections from the association cortex, basolateral amygdala and hippocampal formation and has efferents to the basal nuclei,[107] hypothalamus and various brainstem nuclei. Heimer et al. suggest that a functional derangement of the extended amygdala leads to a constellation of motor, affective, endocrine and autonomic symptoms.[62]

Figure 3 shows the connections of amygdala.

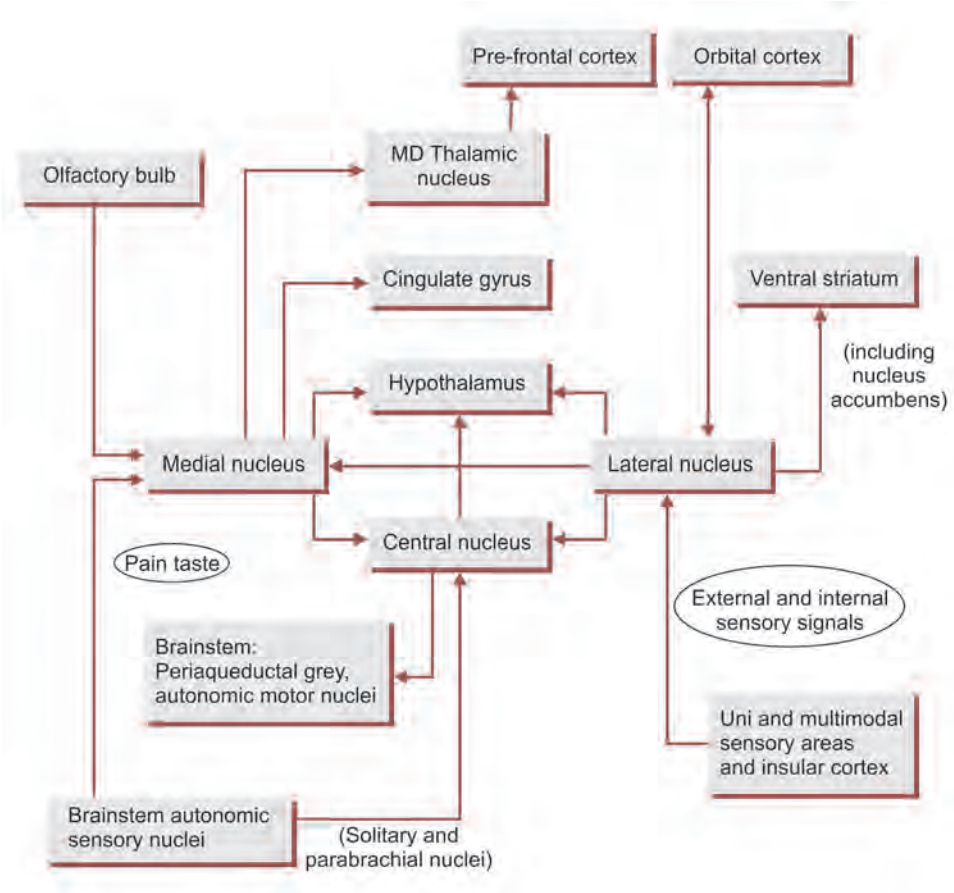

Fig. 3: Major connections of amygdala

Nucleus Accumbens

The nucleus accumbens is an enigma that has long been thought to be one of the main crossroads between the limbic (hippocampus and amygdala) and the motor systems, the focal point of an expression of motivational and emotional processes into motor behaviour. The shell of the nucleus accumbens is in reality a transition zone between the amygdala and the striatum. The ventral tegmental area (VTA) has a modulatory effect on this limbic-motor interface. Derangements of this meso-limbic dopamine system at the level of the nucleus accumbens has been implicated in specific aspects of drug addiction, schizophrenia and other affective disorders. The antipsychotic effects of neuroleptic drugs are mainly mediated through the shell of the nucleus accumbens.[62]

HYPOTHALAMUS

The hypothalamus was the first structure to be recognised as associated with behavioural mechanisms. Cannon,[22] in 1929, demonstrated that the hypothalamus was responsible for rage reactions, and Bard[15] localised the 'rage centre' in the hypothalamus. One of the nuclear groups in cats, which on stimulation gives rise to a rage reaction, is the periforniceal nucleus. The nucleus that corresponds in man to the feline periforniceal nucleus is the ventromedial nucleus. A few facts about the anatomy of the hypothalamus as pertaining only to the behavioural system are described here.

Two important fibre tracts course through the hypothalamus:

1. The median forebrain bundle connecting the various areas of the limbic system and the mesencephalon.
2. The fornix, an efferent pathway from the hippocampus to the mamillary body, consisting of many fibres to the hypothalamic nuclei.

The afferent connections of the hypothalamus are:

- The amygdala-hypothalamic pathways that have already been described,
- Fronto-hypothalamic fibres and
- Fibres from the ventral anterior nucleus of the thalamus to the hypothalamus.

The efferent connections are many, the more prominent one being the dorsal longitudinal fasciculus of Schultz. This runs from the medial hypothalamic zone up to beyond the mesencephalic tegmentum.

Physiology

Stimulation of the amygdala in cats is known to cause a rage reaction. By means of such stimulation studies, Ursin and Kaada[31] were able to show that certain parts of the amygdala controlled the fighting reaction and certain areas controlled the flight reaction. Removal of the amygdala has been shown to tame some naturally

ferocious animals, such as the Australian marsupial known as the Tasmanian devil. Electrical stimulation of the amygdala in humans does not produce rage or anger, although this has been reported in certain studies.[31,44,96]

For the purposes of behavioural physiology, the hypothalamus can be divided into two zones: the medial-ergotrophic and the lateral-trophotrophic zones, the former corresponding to the dynamogenic and the latter to the adynamogenic zones of Hess.[35] Most of the amygdaloid connections end in the medially situated ergotrophic zone. Stimulation of this zone (particularly near the periforniceal nucleus) produces sham rage. The psychovisceral phenomena of emotions are autonomic in nature, whether they are concerned with flight or fight and hence the hypothalamus can be presumed functionally to be the chief effector centre of the behavioural brain.

With the increasing telencephalic control of the diencephalon, the areas concerned with behaviour get represented in the amygdala and the limbic system (the behavioural brain).[34,99] If one compares the behavioural brain to the motor system, one can distinguish an upper level and a lower level. The upper level is represented by the amygdaloid nucleus and its connections with the limbic system and the thalamus. The amygdala acts as the higher centre by receiving inputs from various regions and levels, like the viscera, the endocrine organs and from the hippocampus. The lower level is represented by the hypothalamus and the periaqueductal grey, which are the common efferent pathways for all behavioural impulses akin to the final common pathway in the anterior horn cells for motor phenomena.

The internal medullary lamina helps to reinforce the amygdalo-hypothalamic influences and can be considered a reinforcing centre like the cerebellum in the motor system, if one might extend the analogy.

Early Psychosurgery

The procedures in vogue were: (1) operations on the frontal lobe; (2) cingulumotomy (cingulotomy) and (3) sedative neurosurgery.

The psychosurgery procedures that were used subsequently were further improvements of the above procedures.

Choice of Target

To understand the rationale behind target selection, one needs to understand the following concepts. Interoceptive and exteroceptive stimuli impinge on the frontal lobe wherein, by means of conceptual thought, the proper response is decided upon.[5] This response is 'driven by' two pathways: (a) directly to the hypothalamus from where the resultant action may come through and (b) more often through the cingulum, the amygdala and the thalamus and indirectly to the hypothalamus. At all stages this response is modified by the memory records coming in from the hippocampus. Thus, there is a reverberating circuit within the system which according to Papez can "add emotional colouring to the psychiatric process".

In cases where the thought processes are disturbed or chaotic, surgery has to be directed to the frontal lobe and hence a leucotomy is indicated. When the drive is strong and uninhibited, an interruption of the cingulum is indicated. But when the disturbances consist of wandering, aggressive or destructive behaviour, one has to target the amygdala or the hypothalamus.

In spite of nearly seven decades of work, there is no unanimity about the fibres that are to be divided in a leucotomy. In the earlier days it was perhaps correct to speak of quadrantic, bimedial or inferomedial cuts. Many of them were in alignment to the lesser wing of the sphenoid. With the increasing knowledge of the connections of the frontal lobe, one has to name the tracts involved, if scientific accuracy is to be achieved.

Freeman and Watts[27] claimed that in the most restricted leucotomy, the fronto-hypothalamic fibres were divided. In the bigger cuts, more of the fronto-thalamic connections were divided, which was why one observed a retrograde degeneration in the thalamus of certain patient groups. Knight[46] suggested that the usefulness of this procedure was due to the interruption of fibres of the orbital fasciculus, lying beneath the caudate nucleus (subcaudate tractotomy or basofrontal tractotomy). He believed that in basofrontal tractotomy, one divides the centripetal and centrifugal fibres of the amygdaloid nucleus, the fronto-hypothalamic connections, some connections of the median forebrain bundle and the diagonal band of Broca.[20]

CLASSIFICATION OF PSYCHIATRIC DISORDERS[3]—AN OUTLINE

Before proceeding to a full fledged discussion on the treatment of mental disorders, it would be appropriate to familiarise ourselves with the psychiatric classification of diseases.

The first psychiatric classification of mental disorders appeared in the international classification of diseases-6 (ICD-6) just after WWII. The American Psychiatric Association published the Diagnostic and statistical manual-I for classification of psychiatric diseases in 1952 which was based on ICD-6. Since then, there have been several revisions—the present one being ICD-10 and DSM-IV TR. The aim is to establish definite scientific criteria for diagnosis and research in psychiatry. It is strictly not to be used by unqualified personnel.

Most mental disorders are categorised into mild, moderate, severe, in partial remission, in full remission and as past history of mental illness. There are five axes in DSM-IV TR namely:

Axis I: That comprises clinical disorders and other conditions that may be a focus of clinical attention

Axis II: Personality disorders, mental retardation

Axis III: General medical conditions
Axis IV: Psychosocial and environmental problems
Axis V: Global assessment of function

Personality disorders are classified into three clusters: (*DSM-IV TR pp. 685-721).*

Cluster A: Which comprises paranoid, schizoid and schizotypal disorders.

Cluster B: Under which come antisocial, borderline, histrionic and narcissistic personality disorders.

Cluster C: Which includes avoidant, dependent, obsessive disorders and personality disorders not otherwise specified.

Each mental illness is diagnosed with definitive criteria and has multiple subsets. However, it must be remembered that: "The concept of mental disorders like many other concepts in medicine and science lack a consistent operating definition that covers all situations."

AN OVERVIEW OF THE COMMON PSYCHIATRIC MALADIES AMENABLE TO PSYCHOSURGERY (NEUROANATOMY AND CLINICAL FEATURES)[91]

Obsessive Compulsive Disorder (OCD)

It afflicts about 2–3% of the general population. It starts in childhood/adolescence and is characterised by recurrent thoughts, images, feelings or behaviours that persist after the patient's attempts to eliminate them and which are accompanied by marked and often overwhelming anxiety. The mainstay of treatment is selective serotonin re-uptake inhibitors (SSRIs) with clomipramine as a 2nd line drug.

The main side effects of these medications are weight gain, sexual dysfunction and sedation. Tardive dyskinesias and dystonias can also occur. Behavioural therapy is useful in 70–80% but has a poor compliance, as many feel the distress exposure which is a part of the therapy annoying. Ten per cent of all cases of OCD are refractory to all medical/behaviour therapies. It is in this subgroup of patients that psychosurgery has a role to play.

Neuropathologic Circuitry

In OCD, the circuitry involved is the *cortico-striato-thalamocortical circuitry (CSTC).*[1,2]

The orbitofrontal cortex, anterior cingulated cortex and the caudate nucleus are central to the pathogenesis of OCD. The relative imbalance favouring the direct versus the indirect paths within this circuitry, leads to overactivity, i.e. amplification within the orbitofrontal cortex and the anterior cingulated cortex including the caudate nucleus and thalamus resonant with failed striato-thalamic inhibition, i.e. filtration within this same circuitry. This model *(striatal topography)* can be extended to explain Tourette's syndrome and trichotillomania and body dysmorphic disorder as well.[46] In OCD there is a deficit at recruiting the striatum in the service of thalamic gating.[81] Therefore, in OCD, interruption of the reciprocal projections between the orbitofrontal cortex and the thalamus would theoretically decrease the reverberating (amplified) activity in the orbitofrontal cortex-caudate nucleus CSTC and thereby decrease OCD symptoms.

Intractable OCD[82] which comprises 10% of all OCD cases is defined as:

Failure of treatment despite:

- maximum doses of 5 or more than 5 SSRI for 10 weeks with augmented doses of buspirone hydrochloride and lithium carbonate
- Yale-Brown obsessive compulsive score more than 20
- Global assessment of function score (GAF) less than 50

"Both Parkinson's disease and obsessive compulsive disorder share the same cortico-basal ganglia-thalamic circuits and both should be considered as tremors. In PD, it is a motor tremor while in OCD, it is a limbic thought tremor."[40]

Depression

Major Depression (MD) is characterised by apathy, anhedonia, appetite and weight disturbances, sleep disruptions, psychomotor abnormalities, fatigue, guilt, suicidal ideas and behaviour, delirium, hallucinations and catatonia. It affects 2.6–5.5% of males and 6–11.8% of females.

The *circuitry* involved in major depression is as follows:

1. *Dorsal component*: Anterior, dorsal and lateral prefrontal cortex, dorsal anterior cingulated cortex, parietal cortex and pre-motor cortex (Cognitive circuit).
2. *Ventral component*: Paralimbic cortex, subgenual anterior cingulated cortex, orbitofrontal cortex, anterior insular cortex (Affective circuit).
3. The hypothalamic-pituitary-adrenal pathways are also associated with behaviour.

Major depression, therefore, is due to hypoactivity of the dorsal circuit and hyperactivity of the ventral circuit.[91]

Deactivation of the subgenual anterior cingulated cortex or disruption of interconnections among elements of the ventral component is a plausible mode of therapeutic action by anterior capsulotomy. The pregenual anterior cingulate cortex has the capacity to facilitate restoration of the dynamic equilibrium between compartments, via its inhibitory influence over dorsal and ventral elements. Thus amygdala hyperactivity and hippocampal insufficiency play an important role in the pathogenesis of depression major. Hyperactive amygdala innervation is seen in patients with major depression. The amygdala is assessed by the response to pictures of human faces with various emotional expressions. Right amygdala dysfunction results in failure to habituate to threat related stimuli in anxiety disorders.[80]

Sexual Disorders and Drug Addiction

Abnormal and compulsive sexual drives are very difficult to treat. Such drives may be directed against the opposite sex, the same sex or against children. Medical

therapy with oestrogen has been tried. Surgical therapy with castration has been suggested, but is not always useful and is also unethical. In such cases, stereotactic lesions in the region of the tuber cinereum seem to confer good benefit without any appreciable disturbance of other aspects of hypothalamic functions. Careful assessment of this type of surgery is necessary.

IMAGING IN PSYCHIATRY

Radiology, of late, has aided us tremendously in our understanding of mental illnesses. MRI, fMRI, SPECT and PET are the main modalities of imaging in neuropsychiatry. *Morphometric MRI* is able to detect subtle volumetric abnormalities in the striatum in OCD.[38,69] Decreased caudate nucleus volume is also reported in OCD.[85] Decreased putaminal and lenticular size is seen in trichotillomania and Tourette syndrome.[67] MRS showed a decrease in striatal NAA but normal NAA in the lenticulum in OCD.[16] fMRI in post-traumatic stress shows stimulation of the anterior cingulate cortex and other anterior paralimbic regions. In symptomatic OCD, there is recruitment of the caudate nucleus and the anterolateral orbitofrontal cortex. Pre-treatment neuroimaging is used to test the hypotheses regarding the prediction of response to treatment. Increased activity in the orbitofrontal cortex suggests a better treatment response to behaviour therapy versus pharmacotherapy (and also predicts the usefulness of SSRI therapy) in OCD.[21] Emotional state and presenting symptoms at the time of injection are important determinants in brain perfusion in SPECT but less critical in PET. SPECT study during symptom provocation is better than resting SPECT for studying the pathophysiological mechanism of OCD. Presurgical CMR (with PET) within the posterior cingulated gyrus predicts the outcome after cingulotomy.[78]

To summarise, the SPECT studies in OCD are as follows: there is increased perfusion in the anterior cingulate gyrus, left basal nuclei and orbitofrontal cortex. A decrease in rCBF in the above structures results in symptomatic improvement.[55]

MRI studies in depression are done by cortical parcellation methods. In depression, decreased volume of the subgenual cortex and the orbitofrontal cortex are noted.[18,19] This finding corresponds with the post-mortem brain studies done in patients who had depression major, wherein glial cell loss was seen in the subgenual cortex, dorsolateral prefrontal cortex and the orbitofrontal cortex.[72]

It has thus been concluded that the severity of major depression is inversely proportional to orbitofrontal cortex function.[77] Baseline pregenual anterior cingulated cortex level of activity predicts the response to antidepressants. The greater the activity, the better the response to therapy is.

Indications for Surgery

There are no universal guidelines for surgery. The indications are decided by the local hospital committees (e.g. The Cingulotomy Committee of the Massachusetts General Hospital). The criteria[82] are as follows:

- The patient must fulfil the DSM IV or WHO criteria for OCD/major affective criteria/anxiety.
- The duration of the illness must be 5 or more than 5 years duration and has been documented to be refractory to all therapy available.
- The disease must be shown to cause substantial suffering and significant impairment to the patient's psychosocial function.
- Prognosis without relief of symptoms is shown to be very poor.
- The patients and the family must be willing to participate in pre-operative evaluation and long-term post-operative rehabilitation.
- The referring physician must demonstrate a commitment to pre-operative and long-term post-operative care of the patient.
- The patient has a Y-BOCS score over 20 (for OCD), BDI over 30 (for depression major) and GAF under 50.

The contraindications are as follows:[23]

- Age less than 18 years or more than 65 years.
- Concurrent complicating DSM IV-Axis I disorders (organic brain syndromes/substance abuse).
- Complicating Axis II cluster A or B disorders (personality disorders).
- Complicating Axis III disorders (brain tumour, atrophy).
- Medical conditions which would increase the risk of surgical/imaging complications.

Indications for surgery described in another study,[37] had slight differences such as:

- Duration of disease should be more than 3 years.
- Substantial suffering as evidenced by various rating systems.
- Current and up to date treatment options have been tried systematically for 3 years without appreciable effect on symptoms or have to be discontinued because of intolerable side effects.

Contraindications to surgery were the same. But the patients were kept off medications for 4 weeks before obtaining a baseline SPECT image prior to surgery and also after surgery.

In both studies there were certain essential features, like all patients were thoroughly assessed pre-operatively with various psychiatric rating scales and were reviewed by an institutional board comprising two psychiatrists, one neurologist and one neurosurgeon. In all cases it had to be made clear that the surgery was only to relieve the patient's suffering and restore normal function. All patients who were undergoing psychosurgery must be able to give informed consent, which is usually possible in cases of OCD and depression where insight is retained. This was enforced by the Medical Ethics

Committee of North America to prevent the chaos of the Freeman era from recurring.

PROCEDURES USED IN MODERN PSYCHOSURGERY

Modern psychosurgery has seven standard procedures[29] in its armamentarium to help combat mental illness. (Deep brain stimulation has been approved by the FDA for obsessive compulsive disorder, depression major epilepsy and Parkinson's disease.) They are:

1. Cingulotomy
2. Subcaudate tractotomy
3. Anterior capsulotomy
4. Limbic leucotomy
5. Amygdalotomy
6. Hypothalamotomy
7. Thalamotomy

Cingulotomy

The goal of cingulotomy is to cut the anterior supracallosal fibres of the cingulate gyrus and interrupt a major component in the medial limbic circuit. The conceptual thought processes arising in the frontal region reach the hypothalamus through the cingulum, the amygdala and the thalamus. This results in the desired action being exhibited for the benefit of the subject. When this process gets exaggerated and out of control, thoughts revolve in the mind of the patient leading to an obsession, as well as to the performance of compulsive acts. In such cases, dividing the cingulum bundle breaks the vicious cycle.

The cingulum as a target was conceived by the experiments of Jacobsen in lower animals and Fulton in primates. In 1949–1951 Fulton proposed lesions in the anterior cingulate gyrus in the Papez circuit. Fulton suggested cingulotomy as a form of restricted leucotomy. Freeman and Watts, in 1942, noticed an overall decrease in the tension of patients who undergo cingulotomy. The first open cingulotomy was done by Scoville. Others attribute it to Cairns.[101] Whittey, in 1952, excised anterior supracallosal fibres of the cingulate gyrus, as treatment for depression. Foltz and White undertook stereotactic cingulotomy for intractable pain. Ballantine and Giriunas practiced modern stereotactic cingulotomy in patients with psychiatric illnesses.[25]

Indications for Cingulotomy:

- Unipolar disorder
- Depressive component of bipolar disorder
- OCD
- Generalised anxiety disorder
- Chronic pain syndrome
- Drug addiction

It has been advocated even for aggressive behaviour.[98] It was found that after cingulumotomy for painful conditions, it was possible to withdraw the pain killing drugs without serious side effects. There were no withdrawal symptoms. It was thus only logical to conclude the benefit of cingulumotomy for drug addiction. This procedure not only relieves the persistent preoccupation of the patient with the idea of consuming the drug, but also relieves him of the drug habit, without having to suffer the withdrawal symptoms. The abolition of these symptoms was demonstrated in animals by Foltz and White.[26] Cingulumotomy primarily for drug addiction has been practised and popularised by Balasubramaniam et al.,[5] Ballantine et al.[13] and Foltz and White.[26]

Anatomical Considerations

The cingulum bundle runs anteroposteriorly in the cingulate gyrus, forms an essential part of the Papez circuit and is a major integrating force in the limbic system. It contains fibres that run from the frontal lobes to the hippocampus and also has connections to the anterior and dorsomedial nuclei of the thalamus and the hypothalamus. As the hypothalamic connections are the pathways through which the autonomic disturbances are mediated, the lesion must be made at the point where these fibres join the cingulum (i.e. in the plane of the foramen of Monro).

Technique of Cingulotomy (As was Used by Profs. Balasubramaniam V and Ramamurthi B)

The anterior horns of the lateral ventricles are visualised in the lateral and AP views by pneumoencephalography. This technique continues to be useful even after the advent of MR guided stereotactic surgery. The usual level of the target is 9 mm above the upper margin of the anterior horn in the plane of the foramen of Monro. In the AP view, the lesion is made 9 mm from the midline. In the air studies, the subcallosal cistern gives an idea regarding the thickness of the corpus callosum. But in cases of doubt or when it is necessary to know the thickness of the corpus callosum, angiography may be done with the stereotactic frame in position.[5] The position of the anterior cerebral artery and its branches gives one an idea about the thickness of the corpus callosum and that of the cingulated gyrus.[5] Usually, such elaborate estimation is not necessary. With MR guided stereotactic techniques, the landmarks mentioned above can be identified and the lesion placed precisely at the desired target. In patients being operated upon under local analgesia, stimulation may produce either sudden relief or a feeling of tension. As soon as the lesion is made, the patient may experience a change for the better in his mental status. The lesion is made with diathermy coagulation, a cryogenic probe or oil wax. Thermal lesions are better avoided, because of the proximity of the anterior cerebral vessels.

Results

The results of cingulumotomy for OCD are good and the complications are few (Table 1). In 573 procedures performed on 400 patients, Ballantine[14] reported two hemiplegias and no death. Post-operative psychological assessment revealed no deterioration in personality or

Table 1: Various cingulumotomy studies

Author	*Target*	*Imaging and probe*	*Results*
1. Balasubramaniam V	9 mm above upper margin of anterior horn in the plane of the foramen of Monro AP: 9 mm from midline. The ACA was a guide.	Pneumoencephalogram diathermy coagulation	n = 154 17% well 50% improved
2. Cosgrove, Rauch	Three separate lesions encompassing the cingulum from the ventricle roof to cingulate sulcus. 2–2.5 cm in ant. CG (2–5 cm above lat ventricle roof). 7 mm from the midline, 20–25 mm Posterior to the tip of the frontal horn. The lesion size 15–20 mm in height and 10 mm in diameter.	MRI Thermocoagulation (Radionics) 85 deg for 90 seconds.	n = 18, > 35% imp

mental skills. Of 154 patients followed-up by Ballantine,[12] 17% were well and 58% had significantly improved. Our results of cingulumotomy on 37 patients with obsessive neurosis were similar.[74] Based on a 25 year follow-up of patients operated upon in Boston, Jenike et al.[37] concluded, in 1991, that cingulumotomy is a potentially effective treatment for patients with severe and disabling obsessive compulsive disorder.

For drug addiction the results depend on many factors. One of the most important is the personality type of the addict (psychopathic or non-psychopathic) and the nature of the drug abuse. In the case of alcohol, the results are uncertain because the alcohol habit up to a point is socially accepted in daily life. Cingulumotomy often helps established addiction, but it is not a safeguard against future addiction.

Long-term experience has shown that the effects of limited operations on the frontal lobe and those of cingulumotomy are similar. But in our experience, there seem to be preferential sites for different types of psychiatric illnesses like depression and obsessive neuroses. At times, the two procedures may have to be combined or repeated one after the other to obtain maximum benefit. Stereotaxic cingulumotomy does not produce any appreciable or demonstrable deficit. In the series of Ballantine,[13] Foltz and White[26] and Balasubramaniam et al.,[5] the subjects did not have post-surgical deficits.

An important feature of Cosgrove's study was that the lesioning was done in 2–3 stages. When the patient did not improve the next lesion was made, the time interval being as long as 1 year. It was subsequently noticed that creating one large lesion and following-up the patient revealed the same benefit as a staged procedure.

Transient complications of cingulumotomy were headache, nausea, urinary difficulties and seizures. It is, however, believed that cingulotomy causes fewer side effects and cognitive disturbances compared with other psychosurgical procedures and is therefore used more frequently on the American side of the Atlantic.

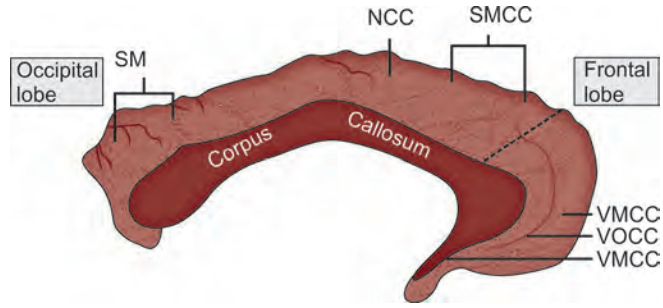

Fig. 4: Divisions of cingulated gyrus

Figure 4 shows the cingulum and its subdivisions.

Subcaudate Tractotomy

The aim of the procedure is to lesion the substantia innominata of Reichert in the area inferior to the caudate nucleus head, whereby white matter tracts between the orbitofrontal cortex and the subcortical structures (thalamus, hypothalamus, amygdala) are interrupted. This disrupts the basolateral circuit and cortico-striato-thalamic pathways. In this area, the diagonal band of Broca, anterior commissure and medial forebrain bundle traverse with cholinergic inputs from the entorhinal cortex, pyriform cortex and hypothalamus. Secondary degeneration of the dorsomedial nucleus of the thalamus occurs. The connections in this area generate endocrine, autonomic and somatomotor responses to emotional and motivational states, leading to increasing primary sensory stimuli. Scoville did the first open orbital undercutting. Knight (1964) did the first stereotactic tractotomy originally with Yttrium 90 radioactive beads.[25]

Indications

1. Major depression (most common indication).
2. Chronic pain.
3. OCD (2nd most common indication).
4. Anxiety.
5. Bipolar disorder.

It has been observed that in patients who have depression major with sudden midlife onset or in the peripartum period and, also have a positive family history of psychiatric disorder or if they have a history of having responded to ECT in the past, there is a very good response to SST.

Target

The earlier operations were done through a coronal burr hole and were open procedures. The stereotactic landmarks in the earlier era with pneumoencephalography for basofrontal-tractotomy were 0.5 cm in front of the plane of the tuberculum sellae, 1 cm above the orbital roof and 1 cm from the midline.[47] The lesions were made by radiofrequency current or oilwax. Knight[47] created localised lesions with Yttrium 90 seeds and found that the majority of patients improved.

The target co-ordinates for stereotactic tractotomy using an MRI based system[58] are as follows: three lesions are made of about 8 mm diameter each bilaterally in the same coronal plane, 15 mm anterior to the base of the anterior clinoid process.

1st lesion: 6 mm lateral to the midline and 10 mm superior to the floor of the anterior cranial fossa.

2nd lesion: 6 mm lateral to the midline and 15 mm superior to the floor of the anterior cranial fossa.

3rd lesion: 14 mm lateral to midline and 10 mm superior to the anterior fossa.

Results

The results of basofrontal tractotomy depend on: (a) the type of disease (schizo-affect, schizophrenia etc.); (b) the duration of the illness; (c) the type of operation and (d) the post-operative rehabilitation. When all these factors are taken into consideration and the results assessed, it is clear that basofrontal tractotomy has a distinct place in the management of selected psychiatric disorders. Bartlett et al.,[17] reported 68% recovery from depression, 63% from anxiety states and 53% recovery from obsession in cases who had basofrontal (subcaudate) tractotomy. In our series of 42 cases of basofrontal tractotomy for severe depression, 72% showed recovery. In some cases, the results are not immediately apparent, but progressive improvement occurs over a few weeks.[41] Response to medications which were previously ineffective is augmented after tractotomy,[56] while in others the benefits are transient. The latter cases may require a second procedure, depending on their predominant residual psychiatric complaint. The addition of a lesion in the cingulum often helps these patients. Poor results are seen in primary psychosis and substance abuse (Table 2).

Transient Complications Seen in Patients

These complications are: headache, confusion, transient disinhibition and somnolence for about a week. These patients had no decrease in general intelligence, speed, attention and frontal lobe cognitive tasks. They were assessed 1 week prior to surgery, and 2 weeks and 6 months after surgery and were found to have insignificant long-term side effects.[42] In a series of 42 cases, Balasubramaniam and Ramamurthi had no deaths and one case had post-operative epilepsy, with none having deterioration following basofrontal tractotomy.

Anterior Capsulotomy

Anterior capsulotomy as a procedure was discovered by serendipity. Post-mortem studies on patients having undergone frontal lobotomy revealed degeneration betwixt the mediodorsal thalamic nuclei through the anterior limb of the internal capsule. It was first devised as a technique by Talairach et al. in 1949. In 1950, Lars Leksell of the Karolinska Institute in Sweden invented the gamma knife and used it for anterior capsulotomy.

The rationale behind anterior capsulotomy is as follows: By lesioning the anterior limb of the internal capsule, anterior capsulotomy interrupts the connections between the orbitofrontal cortex and the midline thalamic nuclei, thus disrupting part of the basolateral limbic circuit and cortico-striato-thalamic pathways. Anatomical studies have confirmed that the anterior limb of the internal capsule has anterior thalamic radiations (fibres connecting the frontal lobe with the medial and anterior thalamic nuclei) and prefrontal

Table 2: Various studies in patients who have undergone SST[21]

Author and year	*Number of patients*	*Results*
1. Goktype (1975)	n = 208	68% became independent 62.5% of the above had anxiety disorder 50% in OCD.
2. Strom-Olsen-Carlisle (1971)	n = 150	55% became independent 36% had anxiety, 50% had OCD.
3. Lovett et al. (1989)	n = 15 (unipolar disorders)	10 patients had decrease in symptoms 5 patients had decrease in frequency of episodes
4. Bridges, Bartlett et al. (1994)	n = 1300	40–60% returned to normal lives Suicide rates dropped to 1% in the surgical group.

Table 3: Various clinical series in patients who have undergone anterior capsulotomy

Author and year	*Patients*	*Outcome*
1. Leksell et al. (1956)	n = 116 gamma knife	For various reasons therefore no comparison
2. Leksell (1961)	n = not specified	50% OCD pts improved, 48% major affective disorders improved. Poor results were seen in schizophrenics. Overall success in OCD 60%
3. Burgley (1971)	n = 35 OCD pts	71% improved at 35 months (20 pts returned to Society).

corticopontine fibres.[25] Electrical stimulation of the anterior limb of the internal capsule results in a generalised sense of well-being with decreased anxiety and tension. Extrapyramidal responses, like tremors in the contralateral limbs, also occur. Disruption of the pathological CSTC circuitry at the level of the orbitofrontal cortex-caudate nucleus/reciprocal orbitofrontal corticothalamic connections underlies the therapeutic effects of anterior capsulotomy. Anterior capsulotomy is more popular on the continental side of the Atlantic.

Target

The target co-ordinates for anterior capsulotomy are as follows: The target height is 20 mm that spans the anterior limb of the internal capsule bilaterally. Radiofrequency probes are used for lesioning at 80–85°C for 45 secs. The inferior target is 2–4 cm lateral to the anterior tip of the lateral ventricle and the superior target is 1 cm superior to the inferior target site. The target used by Lars Leksell for his capsulotomy was as follows: Anterior 1/3rd of the anterior limb of the internal capsule, 5 cm behind the frontal horn tip and 20 mm lateral to the midline at the intercommissural plane. The technique used routinely involved the use of thermocoagulation and was also called thermocapsulotomy, in contrast to Leksell's gamma knife capsulotomy (Table 3).

Kullbey found no difference in outcomes between capsulotomy and cingulumotomy.

Side Effects

Transient deterioration in mental status was seen more in the patients undergoing capsulotomy, compared with those who underwent cingulumotomy.[50] Other rare but longer lasting complications include haematomas, nocturnal incontinence, mild frontal syndrome, aggressiveness, memory deficits and weight gain. "Slovenliness" has been described after capsulotomy. Gamma knife capsulotomy results are as good as conventional stereotactic capsulotomy.

Limbic Leucotomy

The total isolation of the frontal lobe from the rest of the brain, as was practised by Moniz, is unnecessary and harmful. The fibres that are to be divided are included in the inferomedial quadrantic leucotomy. Cuts that run laterally involve the uncinate fasciculus and result in some of the undesirable effects of leucotomy. Freeman and Watts[27] also claimed that in transorbital leucotomy only the fronto-hypothalamic connections are divided.

This procedure combines anterior cingulumotomy and subcaudate tractotomy, although the lesions for subcaudate tractotomy are more anteriorly placed. Kelley (1973) introduced limbic leucotomy, so as to combine the benefits of two procedures. He had an 84% improvement rate. Brown introduced *multitarget limbic leucotomy* wherein the amygdala are bilaterally lesioned too. Richardson used brain stimulation techniques for target localisation in the substantia innominata during limbic leucotomy. The lesion was only done if ANS changes like apnoea/blood pressure changes were seen during stimulation.[83] Long-term side effects, although rare, are transient like headache, confusion, lethargy, sphincter disturbances and preseveration.

Limbic Leucotomy is the Procedure of Choice in the Treatment of Intractable OCD[26]

Cosgrove and Rauch, after comparison, find that although therapeutically all procedures are equally effective, cingulumotomy is the safest.[24] Recently, limbic leucotomy has also shown to be of benefit in self-mutilation disorders and Tourette's syndrome.

Comparing the surgical results in OCD and major depression, it was found that limbic leucotomy was most effective.

Effectiveness in OCD (Percentage of Improvement): 56% cingulumotomy, 50% tractotomy, 61% limbic leucotomy, 67% capsulotomy.

Effectiveness in major depression: 65% cingulumotomy, 68% subcaudate tractotomy, 78% limbic leucotomy, 55% capsulotomy.[24]

Dorsomedian Thalamotomy

The aim and effectiveness of leucotomy lies in the division of the fronto-thalamic and hypothalamic connections. These can also be achieved by eliminating the thalamic end station of these limbic relay systems, namely the dorsomedian nucleus, as was demonstrated by Speigel and Wycis in 1950.[93] The results are comparable with those of leucotomy.

Amygdalotomy

Aetiology of Behaviour Disturbance

A disturbance of the delicate balance between various neuronal circuits in the hypothalamo-limbic system

results in abnormal behaviour patterns. While such disturbances may occur temporarily from injury, drugs, toxins, etc. more lasting trouble results from epileptic disorders and encephalitis. Post-epileptic behavioural disorders may occur in a patient who has a long history of tonic-clonic seizures. The behavioural disorder often sets in some time after adequate control of the seizures by anticonvulsant medication. Such a combination is often seen in association with temporal lobe epilepsy. Post-encephalitic behavioural disorders may follow immediately or some months after an attack of encephalitis. The Japanese B virus is the most prevalent type in India. This type of behaviour disorder is often associated with varying degrees of mental subnormality, ranging from minimal cerebral dysfunction to severe mental retardation. The other aetiological factors include trauma, meningitis, vascular disorders and schizophrenia. In these cases the behaviour disorder occurs without epilepsy.

Selection of Cases

The subjects for whom sedative neurosurgery is recommended are carefully chosen. Surgery is indicated when adequate drug or psychiatric therapy have not helped, even after a prolonged trial. A change of environment may sometimes help to modify the behaviour and this can be advised when feasible. When all conservative measures have failed, surgery is advised. Once surgical therapy has been decided upon, it is better to do it early to give relief to the patients as well as to the long-suffering parents and relatives.

Selection of Targets

Amygdalotomy or hypothalamotomy is effective in aggressive, violent behaviour, in low rage threshold and self-mutilation. Restlessness or hyperkinesis sans violence is difficult to treat. In these cases thalamolaminotomy combined with amygdalotomy gives better results than either of these procedures alone. Amygdalotomy is preferred as the first step by some,[8,32,65] since it is the 'higher centre' and is strategically located. In amygdalotomy, the lesion usually involves the entire nucleus, although the part directly concerned with behaviour is the basolateral part.

Stereotactic hypothalamotomy was first performed by Spiegel and Wycis[87,94] in a schizophrenic patient. Sano et al., reported on a series of 22 cases, in 1966,[89] and 51 cases in 1970.[86] The lesion in the hypothalamus is placed in the medial or ergotrophic zone, after elicitation of sympathomimetic effects on stimulation. This area corresponds to the posterior part of the ventromedial nucleus. Modern stereotactic amygdalotomy was commenced by Lee (1998) with MRI.

EEG may be normal, may show generalised paroxysmal dysrhythmia, diffuse disturbance or evidence of unilateral or bilateral temporal lobe dysfunction.[95] EEG is not helpful in the selection of cases for surgery, as there are frequent discrepancies between EEG findings, the clinical picture and the response to surgery.

Unilateral or Bilateral Operations

Unilateral amygdalotomy or hypothalamotomy may be done if the behavioural disturbances are of moderate severity but most cases require bilateral amygdalotomy or hypothalamotomy. Operations for behavioural (or emotional) disorders have generally to be done on both sides, since there is no laterality demonstrable in emotion or behaviour. One condition in which a strictly unilateral procedure (either amygdalotomy or hypothalamotomy) gives good relief is the behaviour disorder associated with infantile hemiplegia. These patients, who were once candidates for hemispherectomy, are considerably benefited by unilateral sedative neurosurgery.

One-stage or Two-stages

Bilateral amygdalotomy may be done in two successive stages. Bilateral one-stage amygdalotomy can be done safely and is not accompanied by extra deficits attributable solely to the bilaterality of the procedure. Bilateral hypothalamotomy is done only in successive stages.[6]

Amygdala First or Hypothalamus First

Some surgeons prefer hypothalamotomy as the procedure of choice,[86,89,90] while others prefer amygdalotomy as the first step,[7,33,65] due to the following reasons:

- The amygdala is considered to be the 'higher' centre.
- Bilateral amygdalotomy is a one stage operation, whereas hypothalamotomy has to be done in two stages.
- Eliminating the amygdala is perhaps more logical, as in many cases of behaviour disorders there is likely to be a defect in the amygdala; full proof for this is however lacking.

In patients in whom bilateral amygdalotomy does not succeed, hypothalamotomy is performed. Hypothalamotomy done after amygdalotomy has been termed *secondary hypothalamotomy* and in such cases, unilateral lesions in the hypothalamus are usually effective.[7] In severely retarded violent children, it is preferable to perform hypothalamotomy as the first procedure *(primary hypothalamotomy).*

The following are the types of abnormal behaviour patterns amenable to amygdalotomy and hypothalamotomy:

- *Hyperkinesis (restlessness and wandering tendency)*: Hyperkinesis is the term used to describe a tendency to keep moving aimlessly. This may be within or outside the house. In severe cases, the patient may exhibit a tendency to wander away from the house for some hours or days.
- *Destructive and violent tendencies*: These may be continuous or intermittent and may arise with or without provocation. Articles and objects within reach are broken and destroyed. The patient, for no obvious

reason, may suddenly throw objects at people nearby or attack them with heavy objects. The basis for this type of behaviour disorder is not clear. It cannot be equated with predatory aggression or even agnostic behaviour. At times the aggression suddenly bursts out after a period of augmentation. It is only in these cases that the aggressive act may be considered as the culmination of 'anger'. Patients with a low threshold for rage explode into a catastrophic rage reaction over trivialities. This is similar to the aggressive acts of the paranoid schizophrenic.

- *Pyromania*: A few patients have an obsessive desire to set fire to objects inanimate or animate. They derive pleasure and immense self-satisfaction from these acts of arson.
- *Self-destruction*: Some of the patients exhibit a marked tendency to hurt themselves. Instead of destroying external objects these patients tend to mutilate themselves and one of the most common ways is biting. Callous ulcers may be produced on the forearms by the constant biting. These patients seem oblivious to the pain produced by the biting. Similarly, some patients exhibit persistent head banging which would alarm any onlooker. The patients who indulge in self-mutilation do not attack others. The self-mutilation of the lips seen in Rett's syndrome is a different entity and is not considered here.

Assessment

The history of the disorder and the account given by the relatives are important in the assessment of a patient with behavioural disorder. It is difficult to quantitate aggression, violence or self-destruction. Hyperkinesis and restlessness may be measured, but accurate rating scales have not been worked out since many variables are involved. Narabayashi[65] used a room divided into blocks; the number of blocks the patient traverses over a fixed time period gives an insight into the intensity of the restlessness. *Clinical examination* is often difficult but may be possible during quiescent periods. Usually there is no neurological deficit, but occasionally, infantile hemiplegia with asymmetry of the limbs may be seen. Mental deficiency may often be obvious as also are the signs of self-mutilation or epileptic injuries.

Surgical Technique for Amygdalotomy (As Used by Balasubramaniam and Ramamurthi)

1. *Determining the Co-ordinates*: Under general anaesthesia, with the patient supine, bilateral coronal burr holes are made. A temporal or a posterior route may also be chosen.[59] The tip of the temporal horns are visualised by installing water soluble contrast medium through the burr holes, after the Leksell's stereotactic frame is fixed. In this position the dye clearly visualises the temporal horn in the AP and lateral X-rays. Use of CT/MR makes this step dispensable. The co-ordinates are calculated from the tip of the temporal horn. The centre of the amygdala lies 4 mm in front of and 4 mm above the anterior most point of the temporal horn. In the coronal plane this is 3 mm medial to the medial margin of the temporal horn.
2. *Depth Recording*: Recording of the electrical activity of the amygdala is not essential for localisation of the target, but is useful to get an idea of the rhythm of the amygdala and to find out if there are any abnormal discharges. In some patients, the amygdala shows spindle activity of about 25 microvolts at 12–15 cis. Narabayashi[65] has described injury potentials, consisting of small amplitude waves of 40–50 cis for 10–30 seconds. In an abnormal amygdala, there may be spike discharges or a flat record.
3. *Verification of Electrode Placement*: When an electrode reaches the target, three types of electrical activity may be recorded:
   a. High voltage spikes of transient duration; these are injury potentials
   b. High voltage fast activity
   c. Low voltage longer lasting waves occurring in spindles, the amygdala spindle.[5]

These patterns may not be elicited in every case. In some cases, typical spikes suggestive of focal epilepsy may be recorded.

Depth EEG is not always a reliable method of verifying the correctness of electrode placement, as our knowledge of the electrical activity of the amygdala is incomplete. Elicitation of evoked potentials from the amygdala, when the patient inhales ether, is more reliable.[65]

Stimulation of the target serves as a good method of verification. The stimulation, with a current of 2–3 volts at 50–60 c/s for 2–5 seconds, usually results in apnoea. Sometimes, vasopressor effects, dilatation of the pupils and increase in gastric acid secretion are also observed.[73] In some cases, despite correct anatomical localisation, the stimulation effects are not obvious. The explanation proffered is that the amygdala is diseased and cannot, therefore, function normally.[5]

4. *Making the Lesion:* The lesion in the amygdala can be made by diathermy coagulation, myodil wax injection or by the loop. The results do not depend on the paraphernalia used for lesioning, but do depend on the volume of the lesion made. The lesion must be at least 1 cc in volume for effects to be discerned.
5. *Post-operative Complications:* Complications can occur even in the best of hands despite meticulous planning and technique. These are seen in 2–3% of the patients undergoing the procedure. Usually all these complications are transient and revert back to normal in 3–4 weeks.

They are as follows:

1. Injury to the neighbouring structures:
   a. When the electrode placement is too deep and medial, the crus may be injured causing hemiparesis. Delayed hemiparesis has been noted to

occur 2–3 days after surgery; the cause for this is not clear, but is probably due to delayed white matter oedema.
   b. The subcortical white matter fibres may be injured by too many insertions of the electrode thereby causing hemiparesis.
   c. Dysphasia may occur if the electrode tract passes through the superior temporal gyrus.
   d. Injury to the optic tract, which lies medial to the amygdala, may produce a homonymous hemianopia.
2. Post-operative haematemesis may rarely occur and is due to an acute stress phenomenon. This is because of the connections of the amygdala with the hypothalamus.
3. Pulmonary oedema, although rare, can occur.
4. Loss of memory may occur if the lesion placement is too far posterior bilaterally. The Kluver-Bucy syndrome (or its equivalent in humans as described by Terzian and Ore)[43] has not been seen.
5. Transient hyperphagia and hypersexuality have been noted (two cases out of 260).[6]
6. Face processing impairments occur after partial bilateral amygdalotomy, especially for new faces. The patient is unable to interpret social signals from the face.[105]

Results

In 1963, the first large series of patients treated by amygdalotomy was published by Narabayashi et al.[65] who reported improvement in 51 out of 60 patients. Heimburger[33] reported that 17 out of 25 cases improved after amygdalotomy. Balasubramaniam et al.[25] reported on 44 cases with good results in 59% of the patients. In a report on 205 cases by the same group in 1973, improvement was seen in 65% of cases. Kiloh et al.[43] found 50% of 18 patients operated upon to show improvement a year after operation; in seven out of these nine patients, the improvement was maintained for periods ranging from 2–6 years (Table 4).

Table 4: Tabulation of the results of various clinical series in amygdalotomy

Author and year	*Patients*	*Imaging*	*Target*	*Results*
1. Narabayashi (1963)[65] (for severe behaviour and hyperactivity)	n = 60	Pneumography	Lateral group nucleus. Depth electrode recording with olfactory stimuli	85% improved
2. Chitanondh (1966)[23] (for olfactory fits, schizophrenia with olfactory hallucination and post-trauma personality disorder with olfactory hallucinations).	n = 7	(LA) — contrast ventriculogram amygdalography (EEG) Mechanical block with beeswax.	Medial ½ of amygdala	100% on EEG
3. Heimburger (1966)[32]	n = 25	pneumoventriculogram	2 cm lateral to midline, 1 cm below intercom line 45% posterior to AC along i-c-line in ant-med angle	35% cured, 45% improved.
4. Balasubramaniam, Ramamurthi (1960–70) For aggressiveness	n = 603	Leksell stereo-iophendylate ventriculography, intra-operative EEG, depth elec stim.	481 bilateral amygdalotomy 122 unilateral amygdalotomy.[8-10, 76] 0.5–2 V at 50 cyc/sec for 1 min, Diathermy coagulation 200 cc lesion. Total lesion size 2800 cc more than amygdala volume.	39% good, 37% improved
5. Hitchcock and Cairns (1973) For hyperactive destructive rebellious disorder with history of epilepsy[35]	n = 18	Physiological localisation.	Bilateral stereo amygdalotomy transtemporal route. Safest anatomical target with physiological localisation 3 x 1.8 cm depth elec stim, 1–10 V, 50–100 Hz, Medial group of nuclei.	27.7% imp
6. Lee (1998)[51] For intractable aggressiveness	n = 2	MRI, mod Todd-Wells Schaltenbrand and Warren atlas	EMG of facial muscles and skin conduction RF lesion, 3 separate lesion 3 mm apart b/l the largest 10 mm	100%

Hypothalamotomy (Surgical Technique as Described by the Senior Author)

Determining the Co-ordinates

After fixing the stereotactic frame, with the patient in the sitting position, a lumbar air study is performed and AP and lateral X-rays of the skull are taken. The co-ordinates for the target are calculated with reference to the anterior and posterior commissures and the lateral wall of the third ventricle. Sano et al.[86] used a target which lies in the triangle formed by the anterior border of the mamillary body, the mid-commissural line and the rostral end of the *aqueduct (the ergotropic triangle).* The chosen point lies 3 mm inferior to and 1 mm anterior to the mid-commissural point and is also 3–6 mm from the lateral wall of the third ventricle. A more anterior target, 6.5 mm in front of the mid-commissural point, 5 mm below the CA-CP line and 3–6 mm from the lateral wall of the third ventricle, has been found by Balasubramaniam and Kanaka[7] to be more useful than the conventional targets.

Depth Recording

Depth recording from the hypothalamus is not essential for surgery, as it does not provide useful information for localisation. Microelectrode recording and eliciting evoked potentials by peripheral painful stimulation may yield fruitful results.

Verification of Electrode Placement

Stimulation of the target and eliciting the required sympathomimetic responses is an essential step. The parameters of stimulation are 1–3 volts at 50 c/s for 10–30 seconds. If the original point chosen does not give the required response, adjacent points are stimulated to select the ideal site for the lesion. The stimulation effects are sympathomimetic in nature. They consist of dilatation of the pupils, ocular movement, tachypnoea, tachycardia and rise of blood pressure.

Pupillary dilatation is obtained on stimulation from a wide area. The ipsilateral pupil usually dilates more than the contralateral one. In most cases, medial or medial and downwards eye movements are seen. At times there may be some nystagmoid jerks.

In the series of Sano,[86] tachypnoea has been the most common finding. Apnoea was first noted by Balasubramaniam.[6] Both the afore mentioned are sympathetic responses. When the electrode is moved laterally, bradypnoea may be elicited. Tachycardia is a common result of stimulation. Sometimes there are minor degrees of arrhythmias like extra systoles. There may be a rise of systolic blood pressure. Movement of the neck to the side of stimulation or to the opposite side may occur.[86] There is an increase in circulating ketosteroids because the stimulation is similar to acute stress. The eosinophil count also falls. Sano[86] has reported a rise in non-esterified fatty acids. Increased gastric acid secretion has also been reported.[73] Electrical stimulation of the ergotrophic area results in desynchronisation of the EEG with production of theta waves in the hippocampus or diffuse irregular delta waves of high voltage.[86]

Making the Lesion

The lesion is made by diathermy coagulation. When coagulation is done by diathermy, a non-magnetic pellet is introduced into the site of the lesion. Post-operative X-rays were taken for the purposes of mapping out the site of the lesion on a standard brain atlas.

Post-operative Complications

These are rare and include:

- Transient diabetes insipidus
- Haematemesis may occur if the lesion is too far anterior
- Haemorrhagic pulmonary oedema is a recognised complication following hypothalamic destruction in animals, but rare after human hypothalamotomy and
- Ballistic movements have been reported presumably due to injury to the body of Luys.

Thalamolaminotomy[71,90]

Since this part is also connected with the limbic system, stimulation may produce apnoea. The lesion can be made either with wax or diathermy. Both sides can be done at one sitting. There has been no noteworthy complication after this operation.

Results of Hypothalamotomy and Other Sedative Neurosurgical Procedures

The results of hypothalamotomy in a large number of cases have been reported by Sano,[86] where 95% of patients showed improvement. In the series of Balasubramaniam and Kanaka,[6] 68.5% of patients had improved. In most cases the improvement is seen within a few days after the operation and consists of a reduction or abolition of aggressiveness. The fearless and restless child becomes obedient and quiet. In some cases there is an absence of the rage reaction to frustrating situations. Some patients exhibit a welcome placidity while in the hospital, but relapse into violence at home. These patients require progressive rehabilitation in a special institution. Sano et al. (1962) reported a series of 43 patients who underwent posterior hypothalamotomy for violent, restless behaviour. He used a bipolar needle electrode 0.8 mm in diameter and 0.5 mm being the inter bipolar distance. The imaging technique was pneumoencephalography. The lesions are made in the posterior medial hypothalamus 1 mm to 2 mm posterior to the midpoint of the intercommissural line, 2–4 mm below the intercommissural line and 2 mm lateral to the lateral wall of the 3rd ventricle. Bilateral lesions were made and improvement was seen in 7 days. Around 30.2% of patients had excellent results while 65.1% were good. 1 patient died due to aspiration.[89,90]

In addition to the abolition of aggression, a positive gain may also be observed such as a co-operative attitude hitherto unnoticed and also the emergence of a sense of responsibility, especially when insight improves. Another disability which may regress after sedative neurosurgery is the tendency for generalised convulsions. Although, the primary aim of amygdalotomy or hypothalamotomy is the control of behavioural problems, it has been observed that in many cases seizures, when present, are decreased in intensity and frequency. Aggressive destructive behaviour presenting as a major component of schizophrenia is also benefited by amygdalotomy. Vaernet and Madsen[100] reported disappearance or marked reduction of aggressive episodes in 11 out of 12 patients, on whom bilateral amygdalotomy was done. In about 30% of cases of amygdalotomy, the improvement disappears after some time and the patient reverts to his pre-operative state. This may happen even though the lesions had been of adequate size and were accurately placed. Such patients need hypothalamotomy. The results often depend on the aetiology of the condition. If the original cerebral damage is not extensive, the results of sedative neurosurgery are better. Thus, behavioural disorders following epilepsy do much better than post-encephalitic cases where the brain damage may be widespread. Patients with primary mental retardation respond the least to surgery.

The experience so far shows that sedative neurosurgery is a useful procedure in alleviating aggressive behaviour disorders. Wise patient selection yields good results without damaging the patient's personality. An established useful procedure in surgery should not be abandoned due to irrelevant and unscientific reasons.

OUTCOME MEASUREMENTS IN PSYCHOSURGERY

Evaluation of psychosurgery patients has come a long way from Walter Freeman's 'experience' to modern scientific questionnaires and outcome scores. There are several disease specific scores such as Yale-Brown Obsessive Compulsive score (Y-BOCS) for OCD, Hamilton depression rating (HA-DRS) and the Beck depression inventory (BDI) for depression and the Hamilton Anxiety Rating Scale (HA-ARS) for anxiety. Other tests used in neuropsychological evaluation of the patient are—the Wechsler Adult Intelligence score and its Korean modification (WAIS and K-WAIS), Hopkin's Verbal Language Test (HVLT), Rry-Osterrieth complex figure test, Wisconsin Card Sorting Test, Stroop test, tests of verbal imaging, Mini Mental State Examination (Folstein's and the Korean versions), etc. These scores help to aid in the diagnosis and also in the quantification of disease severity.

The post-operative assessment which was used previously is as follows:

The pre-operative and post-operative assessment of behavioural disorders is based on clinical impression in most cases. The results may be graded under the following five categories:[25]

1. There is no need for drugs. The patient is able to mingle easily with others.
2. Very much docile and given only to occasional outbursts.
3. Manageable when given drugs, although not leading a useful life.
4. Transient improvement followed by relapse.
5. No change.

The assessment is arrived at by direct observation and by interrogation of the relatives, nurses and attending doctors. The same type of assessment is used for amygdalotomy, hypothalamotomy and the other procedures of sedative neurosurgery.

To assess the outcomes of psychosurgical procedures, the *Pippard post-operative rating* scale[70] is presently used which is as follows:

- Very much improved
- Much improved
- Slightly improved
- Unchanged
- Worse

The *clinical global improvement (CGI)* may also be used which is an improvised version of the above score:

- Very much improved
- Much improved
- Slightly improved
- Unchanged
- Slightly worse
- Much worse
- Very much worse

NEWER MODALITIES OF TREATMENT IN PSYCHOSURGERY

Vagal Nerve Stimulation

Cervical VNS as a treatment modality was approved by the FDA in 1997. The implant used has only one manufacturer (Cyberonics, Houston, Texas). The vagal nerve nucleus (nucleus of the tractus solitarius) projects to the limbic system, higher cortex, parabrachial nuclei and the locus coeruleus which in turn project to the thalamus, amygdala, hypothalamus, insula and orbitofrontal cortex. In 1938, Bailey and Bremner observed synchronous activity by VNS in cats. The response obtained is a slow wave response in the anterior rhinal sulcus and amygdala in awake cats through corticospinal pathways. Zabara realised the relationship between VNS and anticonvulsant effects.[108] In 1988, the first FDA trial for VNS was done for drug resistant epilepsy. The number of patients who developed hoarseness was 0.7%. VNS for epilepsy has been recommended to be as effective and safe (Class I evidence). VNS acts in two ways. It increases NTS GABA which in turn is responsible for the antiseizure activity. VNS also increases 5-HIAA, HVA and DA which is responsible for the mood stabilising action

of VNS. As VNS has only been recently commissioned as a treatment modality there have been few studies. The one of interest is the "D-01" study which compares the efficacy of VNS to ECT (the gold standard of treatment of depression). There were 60 patients in the study and 36.5% patients had a reversal of their clinical condition after 10 weeks of VNS. Of these, 15% of the patients had full remission of their disease. 1 mA or more current strengths bring about better responses. Another interesting feature is that VNS seems to be effective only in the long-term and this has been proven by blood oxygen level dependent MRI (BOLD-MRI). There have been several other applications for pulsed electrical signals awaiting approval by governments the world over. These include: movement disorders, eating disorders (obesity), anxiety, dementia, Alzheimer's disease, chronic pain, migraine, cardiac arrest, post-traumatic stress and bilateral diaphragmatic VNS for morbid obesity. The battery life of a VNS unit is about 8–10 years. Another very important feature of VNS is that whole body MRI is contradicted in patients with *VNS.*[54]

Transcranial Magnetic Stimulation (TMS)

Transcranial Magnetic Stimulation (TMS) is a non-invasive method of cortical stimulation by creating a powerful transient magnetic field. It is a research tool and is still not approved by the FDA for therapeutic purposes. The principle behind TMS involves the use of a powerful handheld magnet to create a time varying magnetic field, so that a localised pulsed magnetic field over the head surface depolarises underlying superficial neurons. High intensity current is rapidly turned on and off in an electromagnetic coil through discharge of capacitors. This generates brief but very powerful magnetic fields, which is different from the 'magnetic fields used in alternative therapy'. TMS acts solely through production of electric currents in the cortex. Repetitive and rhythmic TMS is called *rTMS.* If the frequency is more than 1 Hz, it is known as *fast rTMS* with current frequencies up to 25–30 Hz. Increasing the frequency in TMS increases the seizure risk. The frequency of TMS is slow, compared with that of DBS (where stimulation frequencies progress up to 150 Hz.). There is limited depth penetration and the amount of electricity needed to cause changes in the cortex varies from person-to-person. An important parameter to be defined in TMS is that of the motor threshold. *Motor threshold* is defined as the minimal amount of electricity needed to produce movement in the contralateral thumb, when the coil is placed optimally over the primary motor cortex. This can be determined either by an observer or by EMG. *Paired pulsed TMS* has immediate effect within seconds. It comprises of applying two TMS pulses to the same region with varying interpulse intervals and intensities. This can be used to assess the stimulatory and inhibitory systems of the brain at rest in individuals with different disorders. Speech arrest can easily be accomplished by TMS and is due to a "virtual lesion" in the speech centre. There are safety issues regarding the use of TMS. The TMS safety table is calculated using a surrogate end point—for seizure; it is the spread of TMS induced motor evoked potential (MEP) beyond the target area of stimulation. This is applicable only to the motor cortex. A past history of seizures puts one at an increased risk of seizures during TMS. There is, however, no decrease in cognitive performance in patients undergoing TMS when compared with patients receiving ECT, although rTMS is similar to ECT but functions at subconvulsant levels. The heating of metallic cochlear implants and pacemaker inactivation during TMS is another hurdle preventing its clinical use. TMS has been found to correlate with fMRI findings in the determination of eloquent cortex. TMS has been found to increase dopamine levels in the pre-frontal cortex. It provides insights into the methods of drug action, e.g. lamotrigine was found to augment the effects of TMS in the limbic region. TMS has been found to be beneficial in the treatment of drug resistant depression.[68] TMS has been found to be better than sham studies in meta-analyses.[60] It could be used in future to prevent relapse and also treat mania. An interesting observation is that TMS over the supplementary motor area worsens Parkinson's disease, although this finding has been greatly contested. TMS is being evaluated as a therapy for writer's cramp, Tourette's syndrome and OCD. Schizophrenia with hallucinations and anxiety disorders may also be amenable to TMS, although some reports suggest that prolonged TMS aggravates the auditory symptoms of schizophrenia.

There are several newer therapies which are emerging as neurobiology and other neuroscience fields grow at an astronomical pace. It would be wise to remember Sir William Osler who said: *"…..We, the doctors are so fallible, ever beset with the common and fatal facility of reaching conclusions from superficial observations, and constantly misled by the ease with which our minds fall into the rut of one or two experiences", while dealing with newer treatment modalities all of whom promise to be in the field of mental disorders.*[103]

ETHICS OF FUNCTIONAL NEUROSURGERY[75]

Psychosurgery has had its crescendo and decrescendo periods orchestrated by human emotions rather than by rational thought. The anti-psychosurgery campaigns by self-styled pundits resulted in misconceptions about the procedures used to this day. It was viewed as a form of 'mind control' and even spawned the popular science fiction of a whole generation. But to look at the brighter side of the argument, the smear campaigns forced practitioners of psychosurgical procedures to develop a high degree of accuracy where everything was based on reason and rational scientific thought with no room for abstract concepts. It has become necessary to state the case for functional neurosurgery, although in countries with a different background, this may appear to be stressing the obvious.

Efforts of the scientists and medical men to improve the lot of their fellow beings have always met with initial opposition from a society which has not yet adjusted itself to a new idea. The objection to neurosurgical procedures to improve those with severe mental illnesses, unfortunately, evokes a public resistance, the fires being ignited and stoked by those ignorant of scientific facts. Such a resistance which is expressed openly and sometimes violently in the developed countries has retarded or even stopped the progress of psychosurgery in these countries. The ingrained ancient concepts of the mind being separate from the body and of its inviolability and sanctity still seem to be a drag on an unbiased approach to the problem of the afflicted.

The medical profession has taken upon itself the task of alleviating many ills and afflictions of the body. Similarly, it is its duty to help, by all possible means at its disposal, the mentally afflicted, since mental diseases are also basically due to an underlying brain disorder, chemical or organic. Consequently, success in restoring the mental balance of a person and returning him to society is as much the aim of surgeons and physicians as their declared and accepted ambition to treat bodily ailments like hypertension, diabetes or cancer. The dichotomy of approach to a mental problem as opposed to a physical problem clouds judgement and thus prevents relief from being given to the mentally ill, who desperately require help to return to normal life, by whatever means available. To deny them this is to deny the role of medicine as a provider of relief and succour to the ill. Precise neurosurgical procedures in appropriate cases enable the patient to return to society without any alteration in his basic personality.[102]

The fact that the operations are on the brain, 'the seat of the mind' and the confusion between the soul and the mind in some aspects of Western thought, seem to have raised a furore over psychosurgical procedures. Luckily, in the Orient, such a mix-up is not seen, the mind being associated only with the physical body at a much lower level than the soul. Reports from centres in the world, where such procedures are practiced and also where there is good patient follow-up subsequently, have shown that with precise and well-planned procedures in properly selected patients, the results can be extremely encouraging with no deleterious effect on personality.

The field of psychosurgery has moved from ablation to neuromodulation and palliation. The lessons of history are to be learnt for the ethical conduct and regulation of neuropsychological research. It is a field, which, although is fascinating, must be tread upon with caution. The fears have to dispel as the benefits outweigh the risks. In conclusion, we must remember that: *"...to be afraid of our technology is to be afraid of ourselves. It is essential that we protect ourselves here, as everywhere, from arrogance and insensitivity. The answer is not to prohibit technology but to insist that it always be subservient to the transcending values of human worth and dignity".*[105]

APPENDIX 1: THE YALE-BROWN OBSESSIVE COMPULSIVE SCALE (Y-BOCS)

The Severity Rating Test

Obsession Rating Scale (Item Range of Severity)

1. Time spent on obsessions:
   0 hr/day
   1 0–1 hr/day
   2 1–3 hr/day
   3 3–8 hr/day
   4 more than 8 hr per day
2. Interference from obsessions:
   0 none
   1 mild
   2 definite but manageable
   3 substantial impairment
   4 incapacitating
3. Distress from obsessions score:
   0 none
   1 little
   2 moderate but manageable
   3 severe
   4 near, constant and disabling
4. Resistance from obsessions score:
   0 always resists
   1 much resistance
   2 some resistance
   3 often yields
   4 completely yields
5. Control over obsessions:
   Control
   Much control
   Some control
   Little control
   No control

Compulsion Rating Scale

1. Time spent on compulsions:
   0 hr/day
   1 0–1 hr/day
   2 1–3 hr/day
   3 3–8 hr/day
   4 more than 8 hr/day
2. Interference from compulsions:
   0 none
   1 mild
   2 definite but manageable
   3 substantial impairment
   4 incapacitating
3. Distress from compulsions:
   0 none
   1 little
   2 moderate but manageable
   3 severe
   4 near, constant and disabling

4. Resistance to compulsions:
   0 always resists
   1 much resistance
   2 some resistance
   3 often yields
   4 completely yields
5. Control over compulsions:
   0 complete control
   1 much control
   2 some control
   3 little control
   4 no control

   Total score = 0–7 Subclinical OCD
   8–15 mild OCD
   16–23 moderate
   24–31 severe
   32–40 extreme

APPENDIX 2: ITEM HAMILTON RATING SCALE FOR DEPRESSION

1. Depression mood (sadness, blues, weepy)
   Have you been down or depressed this past week? How often have you felt this way and for how long?
   0 absent
   1 indicated only on questioning
   2 spontaneously reported verbally
   3 communicated non-verbally (facial expressions, posture, voice, weeping tendency)
   4 patient reports virtually only these feeling states in spontaneous verbal and non-verbal communication

   Note the length of time if depressed mood is present. Do not enter it in the score.
2. Feelings of guilt: (self-criticism, self-reproach)
   In the past week, have you felt guilty about something you have done, or that you have let others down?
   0 absent
   1 self-reproach (letting people down)
   2 ideas of guilt or ruminating about past errors and sinful deeds
   3 present illness is a punishment. Delusions of guilt
   4 hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations
3. Interest, pleasure, level of activities (work and activities)
   Are you productive at work and at home as usual? Have you felt interested in doing the things that usually interest you?
   0 no difficulty
   1 fatigue, weakness or thoughts/feelings of incapacity (related to work, activities, hobbies)
   2 loss of interest (directly reported or indirectly through listlessness, indecision and vacillation)
   3 Decrease in actual time spent in activities or decrease in productivity
   4 Stopped working due to current illness
4. Tension, nervousness (psychological anxiety)
   Have you been feeling more tense or nervous than usual this past week? Have you been worrying a lot?
   0 no difficulty
   1 subjective tension and irritability
   2 worrying about minor matters
   3 apprehensive attitude apparent in speech or face
   4 stopped working due to current illness
5. Physical symptoms of anxiety:

In this past week, have you had any of these symptoms?
   GI—dry mouth, gas, indigestion, diarrhoea, cramps, belching
   CVS—palpitations, headaches
   RS—Hyperventilation, sighing
   Having to urinate frequently
   Seating
   Have much of these things been bothering you in the past week?
   Note: Don't rate, if these are clearly due to medication.
   0 absent
   1 mild
   2 moderate
   3 severe
   4 incapacitating
6. Energy level
   How has your energy level been this past week? Have you felt tired? Have you had any aches or pains or felt any heaviness in your limbs, back or head?
   0 none
   1 heaviness in limbs, back or head (backache, headache muscle aches: loss of energy and fatigability)
   2 any clear cut symptom rates two points.
7. Suicide (ideation, thoughts, plans, attempts)
   Have you thought that life is not worth living or you'd better be dead? Have you thought of hurting or killing yourself? Have you done anything to hurt yourself?
   0 absent
   1 feels life is not worth living
   2 wishes to be dead (or any thoughts of possible death to self)
   3 suicidal ideas or gestures
   4 attempts at suicide (any serious attempt rates 4 points)

Total score =……..

HAMD-7 score less than or equal to 3 indicates full remission.

HAMD-7 score greater than or equal to 4 indicates non/partial response.

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193 Neural Transplantation and Stem Cell

PN Tandon

The nearly absent ability of the neurons to regenerate or multiply has prompted neuroscientists to search for the means to replace the damaged or dead cells. The failed attempts using adult tissue initiated nearly a century ago ultimately brought a ray of hope, when developing foetal neurons were used for transplantation in the 1970s. The initial excitement was tempered by limited success and ethical issues, but these efforts unequivocally established the feasibility of successful neural transplantation, provided appropriate tissue was available. The ability to derive embryonic stem cells with their totipotent potentials by Thomson in 1998 rekindled the interest in their use for replacement therapy for damaged brain tissue. The present review surveys the current status of this promising field of stem cell research, especially in respect to their therapeutic potentials for purposes of neural transplantation. A brief account is provided of the ongoing Indian efforts in this direction.

HISTORICAL BACKGROUND

While attempts at neural transplantation for repair of damaged/diseased brain started a century ago,[84] the real enthusiasm was stimulated after the pioneering work of Das and Altman (1972),[20] Bjorklund and colleagues,[9–12] Olson (1970)[61] and Lund and Hauschka (1976).[51] These studies heralded an explosion of investigations, which established that use of foetal-neural tissue provides a reliable method of achieving a successful graft in an adult host. Investigators all over the world initiated experiments dealing with various aspects of neuronal grafting, as a strategy to replace damaged areas of the brain in the late 1970s. It has been unequivocally demonstrated that such grafts "take", grow, develop at least limited two-way connections with the host brain, produce appropriate neurotransmitters, and to a variable extent restore functional deficits, resulting from disease or damage to the host brain (Tandon 1992).[3] Furthermore, these grafts have been found to induce "trophic" effects on the host nervous system. These results in experimental animals were so tantalising that for once the neurosurgeons jumped straight from the "rat-to-man" without even waiting for the results of the studies in higher primates. The first neural transplants in humans were performed in Sweden by Backlund and his colleagues in 1982 and 1983.[3] In 1984-85, a multidisciplinary group was established at the All India Institute of Medical Sciences, New Delhi, India to study the neurobiological and behavioural consequences of the neural transplants in rats and in rhesus monkeys. Donor tissue was obtained from 16 days to 17 days old rat foetuses. This was transplanted as a "plug" and not as a dissociated cell suspension. Successful transplantation could be achieved in 80–85% of adult rats. Recognising the limitations of transferring information gathered from rat to man, it was decided to study the fate of foetal neural transplants in sub-human primates. Rhesus monkeys were utilised for this purpose. Following a number of trials, ultimately successful transplants were observed in the caudate nucleus in two monkeys.[52] These studies revealed that the foetal-neural transplant in rhesus monkey is successful in 20–30% cases only. At 3–4 months after transplantation most of the grafts had resorbed completely, leaving behind a necrotic cavity heavily infiltrated by lymphocytes and macrophages.

However, in the rodent model, the transplanted neurons matured, differentiated and developed phenotypic characteristics, comparable to the normal adult nigral neurons. Electron microscopy revealed characteristic sub-cellular organelles and synapses. Golgi stain clearly demonstrated the growth and branching of neuronal processes up to 1–3 mm. While initially the dendritic pattern closely resembled that of the age-matched control, with passage of time the processes were found to be wavy and with restricted centrifugal spread. Some of these neurons migrated into the surrounding brain. Neuronal processes could be demonstrated to cross the graft-host interface in either direction. Immunohistochemistry confirmed that these neurons and their processes were positive for tyrosine hydroxylase (TH), implying their capacity to produce the appropriate neurotransmitter: dopamine. This remained so for the first 3–4 months after the implant. Most investigators did not study the fate of these grafts beyond this period. The unique observations of our study were those related to morphological details in long-term surviving grafts. At varying intervals, we observed changes compatible with premature aging leading to neuronal loss. These changes were characterised by the appearance of clear spaces, membrane bound vacuoles, paucity of organelles, especially rough endoplasmic reticulum and increasing accumulation of lipofuscin granules in the cytoplasm. Such changes continued to increase in frequency and severity with further passage of time, so

that at the end of 18 months and 2 years, the majority of the surviving neurons were so affected. [33] While it is impossible to demonstrate the development of intricate circuitry between the graft and the host, a number of observations would indicate that such circuitry, at best, can only be very partial. Thus, the majority of neuronal processes were no longer than 1–3 mm. In a large structure like the striatum, these could probably develop contacts with the host neurons in the immediate vicinity only. In spite of the tremendous enthusiasm generated by the reports of the beneficial effect of adrenal medullary transplants in the head of the caudate nucleus of patients of Parkinson's disease by Backlund et al. (1985)[3] and Madrazo et al. (1987),[52] it was generally accepted that the neurobiological basis of the observed clinical effects was not clear. Peterson et al. (1989)[69] could not find any surviving cells at autopsy of a Parkinson's disease patient treated with adrenal to brain transplant. It is, therefore, obvious that in spite of claims to the contrary by Madrazo et al. (1991),[53] there is now a general consensus that there is hardly any place for the use of adrenal chromaffin cell transplant in cases of Parkinson's disease. The clinical trials so far conducted have provided enough evidence, that at least for patients of Parkinson's disease, there can be mild to moderate improvement in their motor function, although it may be temporary. Nevertheless, it is also obvious that translation of findings of animal experiments to human beings is not without its limitations and pitfalls. The legal and ethical issues, implicit in the use of human foetuses for therapy, need to be carefully assessed and deliberated upon. These considerations alone would necessitate search for alternate sources for transplantable cells, cultured, cryopreserved or genetically modified. There are already leads in this direction.[45]

Long before embryonic stem cells were demonstrated to give rise to all types of brain cells, an extensive experience had already accumulated in respect to the use of foetal neural tissue, obviously containing neural progenitor cells or even stem cells for repair or replacement of damaged brain.[3,9–12,45] Similarly, stable clones of neural stem cells (NSCs) isolated from human foetal telencephalon were shown to replace neurons and respond to development clues, when transplanted in new born mouse brain.[28] There has been rapid success in devising *in vitro* protocols for differentiating human ES cells to neuroepithelial cells. Progress has already been made to guide these neural precursors further to more specialised neural cells, such as spinal motor neurons or dopamine-producing neurons (or various types of glia). However, some of the *in vitro* produced neuronal types such as dopamine neurons do not possess all the phenotypes of their *in vivo* counterparts, which may contribute to the limited success of these cells in repairing the injured or diseased brain or spinal cord. Hence, efficient generation of neural subtypes with correct phenotypes remains a challenge, although major hurdles still lie ahead in applying the human ES cell-derived neural cells clinically.

In February 2001, only 15 months after the publication of two seminal papers by Thompson, and Snyder and McKay in Science on isolation of human embryonic stem cells (ESC), the author published a General Article—"Neural Stem cell research: A revolution in the making" in Current Science.[24] A decade after the Science papers, the prediction made in 2001, has been validated beyond imagination by the voluminous literature that has already accumulated, the number of specialised centres, departments, laboratories established globally, the scientific conferences held and the socio-political, ethical implications debated all over the world and even a large number of clinical trials initiated. Unlike research on the human genome, owing to the prompt initiatives taken by the Department of Biotechnology, research in the field was promoted early in the country. Several state-of-art facilities have been created, both for basic research and its translation into clinical practice.

At the same time, the conclusion arrived at in the 2001 paper[24] "… it could be safely stated that NSC research needs to be pursued with vigour for it to be of clinical use. While there is a lot of hope one should not be carried away by the hype and prematurely raise the expectations among those most in need of it" has continued to be echoed even today by a large number of distinguished researchers from all over the world. This has prompted a prestigious journal like Philosophical Transactions of the Royal Society to devote a complete issue in January 2008[54] on the subject of "Stem Cells and Brain Repair". I could do no better than to quote Magnus and colleagues from Stem Cell Section, Laboratory of Neurosciences, National Institute on Aging, NIH and Children's Research Centre, Michigan, "Stem Cells, although difficult to define, hold great promise as tools for understanding development and as therapeutic agents. However, as with any new field, uncritical enthusiasm can outstrip reality. We have listed nine common myths that we believe affect our approach to evaluating stem cells for therapy".[54]

Having followed the subject keenly during the past decade, having observed the interest it has generated among colleagues, both basic scientists and clinicians and concerned about the inadequate knowledge, often verging on gross misconceptions amongst some of them, has prompted this review of the existing knowledge on the subject primarily restricted to aspects of interest for neuroscientists.

Grafting cells for therapeutic purposes has been ongoing for a long time in the case of bone marrow or skin transplantation. But now we are faced with the exciting prospect that cells with large differentiation potential, that are maintained *in vitro* in normal proliferation state, could provide a variety of cell types for transplantation and therefore help cure disease for which there is as yet no other treatment.[45]

The first experimental demonstration that stem cells exist goes back to the early 1960s when the haematopoietic system was shown to harbour single cells responsible

for the renewal of the circulating blood.[85] Historically, it was EB Wilson who, in 1925, introduced the term stem cells in his description of the development of the *Ascaris* worm. Pioneering work of Weissman and his colleagues on the biology of haematopoietic stem and progenitor cells[24,58], the purification and characterisation of mouse haematopoietic cells,[78] clonal analysis of haematopoietic stem cell differentiation *in vivo*,[76] as also the isolation of a candidate human haematopoietic stem cell population[6] helped a great deal in understanding the basic biology of haematopoietic stem cells, which has important lessons for stem cell biology in general.[94]

EMBRYONIC STEM CELLS

The discovery of the embryonic stem cell constitutes one of the greatest achievements of modern biotechnologies. It was observed that at the blastocyst stage each embryonic cell is essentially as totipotent as the egg itself. Already, in 1980, Evans and Kaufman[23] established culture of pluripotent cells from mouse embryo. However, it was only in 1998 when Thompson et al. published that they had been able to derive embryonic stem cell lines (ES) from human embryo that the technology attracted global attention.[83] In the same year, it was shown that germ cells isolated from gonads of older human embryos can also give rise to permanent lines of embryonic stem cells endowed with properties that are very close to those of embryonic stem cells derived from the inner cell mass at the blastocyst stage. The stem cells that result from germ cell proliferation are designated EG cells in order to distinguish them from the classical ES cells.[75]

DEFINITIONS

Stem Cells

Cells able to reproduce themselves throughout the life span of the animal and are able to give rise to differentiated cells. They have the ability to divide for indefinite periods in culture and give rise to specialised cells.

Embryonal Stem Cells

Cells derived from embryo—pro-implantation or post-implantation—prior to their differentiation into specific cell types.

Totipotent Cells

Cells which have the potential to differentiate into derivatives of all three embryonic germ layers, i.e. ectoderm, mesoderm and endoderm. In addition, they can also specialise into extraembryonic membranes and tissues.

Pluripotent Cells

Cells which can give rise to different types of cells representing derivatives of two different germ layers, e.g. skin (ectoderm) and muscle (mesoderm).

Neural Stem Cells

Cells which can generate neural tissue, either both neuron and glia (astrocytes, oligodendrocytes) or one of them. The term is also used for stem cells derived from embryonic or adult nervous system, which normally differentiate into nervous tissue. These cells remain undifferentiated for long periods of time while retaining the potential to differentiate into nervous tissue.

Progenitor Cells

Cells with a more restricted potential than a stem cell and are generally destined to give rise to a specific cell type.

A vast amount of new information has accumulated on human stem cell biology. The generation of human embryonic, foetal and adult stem cell lines has been standardised. It is proposed that the cells obtained from these different sources could contribute different but, perhaps, equally important properties of therapeutic relevance. Three fundamentally different stem cell strategies could lead to a cure of neurodegenerative diseases. Stem cells could deliver bioactive proteins or peptides to modify or biomodulate the disease process. At the opposite end of the spectrum, stem cells could generate exact neuronal or glial cells lost in disease affected systems. Although fully restoring a degenerated neural network is a worthy, yet lofty goal, disease symptoms could be alleviated by introducing stem cell-derived neurons ectopically, to modulate an affected network.[63]

Stem cells from different sources have unique attributes that will differentially affect their suitability for use in therapeutic strategies.

SOURCES OF STEM CELLS

Human embryonic stem cells, derived from the blastocyst inner cell mass of excess embryos generated by *in vitro* fertilisation, can provide an unlimited source of cells for transplantation and can be directed into neural precursors which can generate neurons, oligodendrocytes and glia both in culture and *in vivo*.[41,81,99] Perrier et al. in 2004,[67] demonstrated *in vitro* and *in vivo* differentiation of human embryonic stem cells into dopamine neurons. It may be mentioned that, over the years, culture conditions that rely on the use of various cytokines and growth factors have made it possible to induce the differentiation of a high proportion of ES cells into selected cell types, such as neurons, pancreatic islet cells, cardiomyocytes, etc.[46]

The ease with which hESCs can be expanded in culture as normal diploid cells is a significant advantage over foetal and adult stem cells that require immortalisation via mutation or proto-oncogene introduction, to escape eventual senescence. Cultured hESC grow very efficiently and maintain pluripotency, but the potential risk of developing malignant transformation cannot be ruled out in the current stage of knowledge.

Foetal neural stem cells harvested from the postmortem human foetal brain maintain a normal karyotype for a significant number of passages in culture and can produce a large number of neurons and astrocytes.[80] These posses a relatively high proliferative capacity and yet do not generate tumour, following transplant. These are really mostly progenitor cells and not true ESCs. Seth at National Brain Research Centre, Manesar, Haryana, India has established a foetal brain derived cell culture system, to obtain CNS stem/progenitor cells. These could be selectively differentiated to astrocytes and neurons, by providing appropriate growth factors and defined media conditions. Development of such a cell culture system has to a great extent eliminated the need for a constant supply of foetal material which raises some ethical concerns.

Adult Neural Stem Cells

Contrary to the earlier belief, neural stem cells persist throughout life, not just in the two now well-known sites of adult neurogenesis, e.g. the subventricular zone and hippocampus but also at other sites.[29,30,40] It has been claimed that adult neural stem cells can be harvested from brain tissue, postmortem or through biopsy and expanded in culture both in rodents and humans. These cells exhibit genetic stability over many passages and differentiate into neurons, astrocytes and oligodendrocytes, under suitable culture conditions.[65,71] Lie et al. described the existence of progenitor cells with neurogenic potential in the adult substantia nigra.[49] Young and Black have provided a detailed review of adult stem cells. However, their proliferative capacity is somewhat limited.[98]

Non-Neural Adult Stem Cells

A number of recent studies have challenged the traditional view that stem cells present in somatic tissues are restricted to producing that tissue's cell types. The first such observation was in respect to bone-marrow derived stem cells (BHMSC), which could develop into liver cells,[68] muscle,[34,44] bone[27,60,64] and neural tissue.[14,32,55,92] Woodbury et al. claimed that adult rat and human bone marrow stromal cell differentiate into neurons.[72] Zhao et al. demonstrated neural differentiation and functional recovery after transplanting human bone marrow stem cells into the ischaemic brain of rats.[37] Sanchez et al. observed expression of neural markers in human umbilical cord blood.[73]

Recently there has been great excitement about the possibility of generating neural progenitor cells from such diverse sources as mesenchymal cells derived from skin,[38] bone-marrow[18] or adipose tissue.[42,87] It may be mentioned that a reproducible technique to convert them into authentic CNS cells has not yet been accomplished.

Recently, evidence has been presented that stem cells identified in organs other than the haematopoietic system (HSC) and skin thought to be responsible for the generation of mature differentiation cells of one organ, such as HSC, may have the ability to differentiate across lineage and contribute to tissues other than haematopoietic cells, including neuronal tissue.[37,39,72,73,85] Such apparent lineage switch has been termed stem cell plasticity. This had led to much sensationalism as evident from such titles of reports as, "Blood to bone" or "Bone to Brain", etc. However, many questions remain as to the validity of a number of these studies, in a large part owing to loose criteria, which have been used to describe 'neural differentiation'.[90]

Fernandez et al. have demonstrated that cultures of multipotent precursors can be grown from dermis of neonatal and adult mammalian skin.[25,26] The skin derived precursors (SKPs) display multi-lineage differentiation potential, producing both neural and mesodermal progeny *in vitro*. The presence of such cells in human skin obtained from the scalp had already been demonstrated by Toma et al.[86] More recent work using skin from other sites has now been verified to be identical to the findings in rodents.

According to Toma et al., analysis of expanded human SKPs demonstrated that they maintain their differentiative abilities for at least one year in culture. They have a potential similar to embryonic neural crest derived precursors.[87]

However, differentiation of SKPs under neurogenic conditions resulted in the production of cells that fulfill most, but not yet all criteria for neuronal differentiation.[48] They believed that SKP-derived neurons are probably peripheral in nature, since they express peripherin and proteins characteristic of a catacholaminergic phenotype and almost all of them are positive for p75 NTR, a hallmark of peripheral neurons.

One type of stem cell that definitely differentiates into mature terminally differentiated and functional neural cells *in vitro* is NSC.[66,74,77,97] Criteria used to define differentiation of NSCs to mature neural cells should be used as the gold standard to gauge whether somatic stem cells of non-neuronal origin, such as HSCs or mesenchymal stem cells (MSCs), can give rise to neural progeny. Authors describe a series of criteria like expression of these markers should occur in a temporal sequence consistent with development and that the differentiated cells should display function characteristics consistent with neurons and glia, such as voltage-gated sodium channels, depolarising response to neurotransmitters and release of neurotransmitters on depolarisation, as has been demonstrated for ES derived neurons *in vitro*.[48] Other caveats exist that need to be kept in mind when assessing the ability of non-neural stem cells to generate neurons or glial cells. However, more recent studies have demonstrated that at least MSC's generated neural progeny have functional characteristics consistent with neurons.[21,95] Pluchino et al. using syngeneic culture derived adult NSCs in an animal model of multiple sclerosis, demonstrated promotion of multifocal remyelination.[70]

It needs to be kept in mind that the functional benefit following transplantation of such cells may not be due to integration of donor neural cells but due to trophic effects elaborated by the donor cells that promote endogenous neural cells to repair the deficit.[16,50,97]

Induced Pluripotent Stem Cells

In November 2007, two groups headed by James Thompson at the University of Wisconsin – Madison and Shinya Yamanaka and his post-doctoral fellow Kazutoshu Takahasi at Kyoto University, Japan, described methods to re-program adult human cells from skin to a pluripotent state, using genetic engineering techniques. These cells, called induced pluripotent stem cells (iPS) were found to be similar to human embryonic stem (ES) cells in morphology, proliferation, surface antigens, gene expression, epigenetic status of pluripotent cell-specific genes and telomerase activity. Furthermore, these cells could differentiate into cell types of the three germ layers.[82] This technique could help generate patient and disease specific cells, which cannot be generated from ES cells. The problem related to the epigenetic transformation of the somatic cells has recently been elaborated.[56] In addition, excellent reviews on the subject are available.[36,96] Soon after, George Daley of Harvard Medical School in Boston confirmed these findings and also demonstrated that iPS cells could be generated from a wide variety of adult cells. Attempts are underway to improve the current 1% efficiency of transformation of somatic cells to embryonic stem cell-like state using the four genes—oct 4, sox2, klf4 and cmyc—by using some other combination of genes. Reprogramming protocols that exclude cancer-associated gene c-myc have been developed.[17] However, at the moment, iPS cells remain a research tool and not a potential therapeutic agent.[13] David Cyranoski quoting a number of other investigators in the field pointed out that the greatest challenge still exists: the generation of high-purity, clinically relevant cell populations.[19] It takes a couple of months to establish a cell line, several more to expand it, more still to differentiate the iPS colonies into cell types required, a few more to expand those and then a good half-year of testing to ensure that the cells do not form tumours. In addition, to produce and use custom-made cells "would take a ridiculous amount of money". Attempts are already on to establish a library of therapy-ready cell lines from donated placental and cord-blood tissue.

Zhang [100] has provided detailed accounts and comparison of methods for neuroepithelial differentiation from human ES cells. Ideally, the method should be simple, efficient, chemically defined, scalable and reproducible and the end product should be an enriched or purified homogeneous neural progenitor population.

Neuroepithelial cells produced from human ES cells using different methods may appear similar in morphology and expression of certain neural precursor markers. However, they, in fact, differ significantly from each other, depending upon the culture conditions. Carefully designed strategies will be needed, in order to direct ES cells to the vast array of neuronal subtypes that are harboured in the primate forebrain. In order for neuroepithelial cells to make a decision between a dopaminergic, serotonergic or GABAergic neuronal fate, the neuroepithelial cells have to be able to 'sense' the nuances within the set of morphogens (e.g. the amount, sequence, isoform, etc.) and/or additional signals.

In vitro, like during development, human ES cell-derived neuroepithelial cells produce neurons first followed by astrocytes and oligodendrocytes. There appears to be a significant progress in producing oligodendrocytes from hES cells.

The ability to differentiate into versatile neuronal subtypes in a neurogenic environment places human ES cell-derived neuroepithelial cells as a useful source of cells for neural replacement therapy in multiple neurological disorders. Recognising the therapeutic potentials of stem cells, a number of public and private organisations like International Stem Cell initiative, UK Stem Cell Bank, ES Cell International in Singapore, Cellartis in Sweden and Millipore in USA have developed ES cell lines to be made available to researchers.[13] However, due to their restricted migration and differentiation in the adult brain regions, it may require further specification of the neuroepithelial cells to a more restricted fate, in order to achieve targeted differentiation.

Despite significant progress in an efficient differentiation of neuroepithelial cells (70–90%) and a few neural subtypes, such as dopamine neurons (approximately 30%), spinal motor neurons (approximately 20%) and oligodendrocytes more than 90%, protocols for generating many neuronal subtypes have to be established.

Demonstration of functional integration of human (ES derived) neural cells in the brain is still awaited (our experience with foetal neural transplant-lessons learnt are probably valid for ES derived cells also).[22] While functional improvement occurs, it is obvious that intricate integration in host circuitry was not unequivocally observed. The functional improvement could be partially attributed to a protective role of the graft on endogenous neurons. Under most circumstances, neural transplant acts as a local chemical replacement, rather than due to integration in the host circuitry. As a consequence, the release of neurotransmitters is uncontrolled. This may be the reason for dyskinesia observed in patients who received foetal neural transplants, as reported by Olanow et al.[59]

NINE MYTHS ABOUT STEM CELLS

In a review, Magnus et al. have listed nine common myths that affect our approach to evaluating stem cells for therapy.[54]

Myth 1: Stem Cells are Immortal

This idea is based on reliable observations in the haematopoietic system. This has lead to the assumption of the

same ability for extensive self-renewal to other stem cells also. However, several reports challenge these assumptions. It has been suggested that NSCs cannot divide in culture more than 12 passages without undergoing dramatic changes.[15,57]

Mesenchymal stem cells appear to have a limited self-renewal potential and generally cannot be expanded indefinitely.[39] Even *in vivo* stem cells age and cannot be assumed to have a lifespan which is greater than that of an individual. Bailey et al. have reported that ageing leads to a substantial mutational load within the NSC compartment, a change that is likely to affect the function of these cells.[4] Taken together, these results argue that not all stem cells have a lifespan that is extensive and that not all stem cells maintain their karyotypic integrity over the prolonged time period required for expansion and differentiation.

Myth 2: Asymmetric Divisions are Required to Define Stem Cell

This does not appear to be strictly true on either theoretical or practical grounds. Several alternate models can be proposed. In many systems, particularly haematopoietic and neural systems, stem cells undergoing asymmetric division best fit the available data both *in vitro* and *in vivo*. However, even in these systems, it is unclear whether asymmetric divisions are obligatory.

Myth 3: Adult Stem Cells are like Foetal Cells, only Better

This is, however, not true. More detailed analysis of foetal and adult stem cell populations harvested from the same tissue has suggested that changes occur. Like somatic cells during normal process of ageing, adult stem cells show similar signs of ageing. These findings raise concerns about the potential for reactivating endogenous NSCs within the aged brain or the use of adult NSCs in transplantation.

Stem cells isolated at different stages of development display different properties. Overall, we note functional differences between foetal and adult stem cells, which preclude the assumption that stem cells from different ages will act alike. Indeed, decreased survival and migration of adult compared with newborn neural progenitors is seen, when they are transplanted into a chick embryo. In general, neural replacement in the adult system is mainly successful in areas of ongoing neurogenesis, like the hippocampus and the olfactory bulb.

Myth 4: Cells Similar to Embryonic Stem Cells Exist in Adult Tissue

ES cells are unique among all stem cell populations and have a well defined core-identity. According to the authors, none of the adult pluripotent cells (APCs) share the key features of ES cells. APCs do not appear to express ES cell markers, do not form teratomas and when injected into blastocysts do not develop reliable germ lines. These authors do not believe that available data allow any adult-derived stem cell population to be reasonably classified as "Es-like".

Myth 5: Stem Cells are more Plastic than Other Cells

It appears that bone marrow contains a population of pluripotent cells that can differentiate into a variety of cells lineage including astrocytes, oligodendrocytes and neurons.[1,43] In different injury model systems, these cells were found to be integrated into the brain parenchyma and, in part, were associated with a functional improvement.[35] On the other hand, it has been shown that both mouse and human NSCs transplanted into the bone marrow of irradiated mice will generate cells of the haematopoietic lineage.[62] Galli et al. demonstrated the skeletal myogenic potential of human and mouse neural stem cells.[31] However, the most convincing demonstration of trans-differentiation suggests that such events are rare.[91] For example, when several million cells were infused into the venous circulation, at best a few hundred trans-differentiated cells could be identified.[47]

It is not to argue that trans-differentiation does not occur or that it has not been convincingly demonstrated by numerous researchers. But it is a myth to assume that stem cells trans-differentiate in a robust and reliable fashion.

Myth 6: The most Primitive Stem Cell for a Tissue or Organ is the Best Stem Cell to Use

Authors believe that the available data do not support such a conclusion. In the nervous system, there is a limited role for stem cells in adults. In general, an intermediate or restricted blast or progenitor cell will often repair such tissue. Several ES cell biologists have suggested using (differentiated) dopaminergic cells derived from ES cells, rather than NSCs for therapy.

Myth 7: Stem Cells can Home and Migrate to Sites of Injury

This concept has largely been developed in the haematopoietic system. Reviewing the existing data, it is observed that the turnout and survival of transplanted stem cells is so low, even given the relatively large number of transplanted cells. The authors predict that, depending on the tissue, homing of stem cells will be difficult and survival will be limited.

Myth 8: Stem Cells do not Provoke an Immune Response

Numerous studies have challenged this view, by showing that a potent immune reaction can and does occur even in the CNS.[2] Rejection of neural allografts and xenografts were observed in several studies. However, there is evidence to indicate that MSCs do not elicit an immune

response. Today, it is difficult to say if histocompatibility in stem cells is as critical as it is in bone marrow or organ transplant or is an irrelevant issue. However, the lack of available relevant evidence highlights the importance of additional experiments to clarify the issue.

Myth 9: Therapy will be Straight-forward and will Mimic Strategies used in Bone Marrow Therapy

The oldest and arguably the best characterised stem cell is the HSC. It is also, thus far, the only clinically useful stem cell. Current strategies for cell replacement therapy appear to model this strategy. This belief has led to so much excitement that several clinical studies have been initiated utilising bone marrow derived 'stem cells' for a variety of clinical conditions, as diverse as congestive cardiac failure, cardiac infarct, stroke and spinal cord injury. It is hard to understand conceptually how stem cells in other systems could adopt the "HSC strategy" notwithstanding a report by Englund et al. [22] It is difficult to imagine that in a solid tissue like the brain or spinal cord how the issues of targeting, migration and connectivity will be overcome, which are not faced by HSCs in the bone marrow. Luskin, already in 1993, pointed out restricted proliferation and migration of post-natally generated neurons derived from the forebrain subventricular zone. In these systems, the most primitive stem cell may not be as appropriate to transplant as a more differentiated cell. Notwithstanding all the hopes generated in respect to therapeutic uses of stem cells, the above observations make it obvious that their routine clinical use has still a long way to go.

OTHER USES OF STEM CELLS

Human ES cell-generated neural cells provide a tool for screening pharmaceuticals that may have therapeutic values in neurological disorders, as also for toxicity screening and possibly drug discovery. The availability of human ES cells with natural diseases,[89] via somatic nuclear transfer or through genetic alterations in laboratories, will provide not only disease-specific neural cells for drug screening but also a tool to unveil some fundamental pathological processes underlying individual neurological disorders.

EXPANSION OF HAEMATOPOIETIC STEM CELLS

The number of HSC, that one can isolate from mobilised blood or from umbilical cord or from bone marrow limits the full application of HSC transplantation in man. Attempts to expand HSC with the known cytokines, stem cells factor, steel factor (SLF), thrombopoietic (TPO), interleukins 1, 3, 6, 11 plus or minus the myeloerythroid cytokines and erythropoietin have never resulted in a significant expansion of HSC. However, cytokines, such as GCSF and SLF can increase the number of HSC in the blood, especially if administered for several days following a cytoxan pulse.

Weissman reported that "We and others have attempted to reproduce the demonstration of production of critical neurons from marrow or haematopoietic stem cells precursors and have failed".[93] Nevertheless, these experiments have led to extensive clinical trials in humans[8,62,79] primarily for myocardial regeneration and more recently for patients with stroke. Unfortunately the claims made in this regard have not been universally accepted.[5,7] Using strict criteria, the author concluded "We do not believe there is sufficient evidence for any of the transplant claims of trans-differentiation. In fact, most, if not all, reports of donor markers in unexpected tissues are the result of cell fusions and the rarity of cell fusions makes it questionable that such events are regeneration rather than reflect the functions of post-injury phagocyte cells".

In addition to haematopoietic stem cells, the following stem cells have been prospectively isolated to homogeneity: Peripheral nervous system stem cells, central nervous system stem cells,[88] skin, as well as the mesenchymal stem cell.[37]

In the case of human CNS stem cells, extensive experiments of transplanting them into the lateral ventricle, into the brain or into the spinal cord of SCID mice have shown that they contributed in a robust way to engraftment of the neurogenerative cells. These robust regenerations stand in contrast to microglial contributions and the rare Purkinje cell fusion derived from bone marrow and haematopoietic stem cells.

STEM CELL RESEARCH IN INDIA

Soon after the publication of the paper in Current Science,[24] as Chairman of the Medical Biotechnology Task Force of DBT, a meeting was called to take stock of the interest in the field among biomedical scientists in the country and to prompt them to initiate studies in this emerging field, by providing research grants. This had progressively emerged as a major national effort primarily steered by DBT. The key components of the strategy are: Creation of centres of excellence (CoE), virtual network of centres, generation of adequate human embryonic stem cell (hESC) lines, human resources development through training, short and long-term overseas fellowships, study the biology of all types of adult stem cells and in parallel evaluate its safety and efficacy in animal models and clinical research on myocardial infraction and stroke for safety and efficacy. Over 30 institutions, hospitals and industry are involved in SCR in the country. The government has invested about 8.0 million US$ for SCR in the last 2 years. Draft guidelines for SCR in the country have been formulated and the same are currently being placed for public debate. The major ongoing programmes include among others: Establishment of hESC lines, use of limbal stem cells to repair damaged cornea, isolation, purification and characterisation of haematopoietic, mesenchymal and liver stem cells and differentiation of stem

cells into neural, cardiac β cell lineages. Studies have been supported to explore the potential applications of adult stem cells in stroke, cardiac, pancreatic, spinal cord injury, use of lectins for haematopoietic stem cell preservation, etc. Reliance Life Sciences, Mumbai has characterised several stem cell lines including two neuronal cell lines, dopamine producing neurons and neurons for patients of stroke. One cell line has been deposited in the National Centre for Cell Science (NCCS), Pune. Interaction between clinicians and basic scientists already exists in several centres in India, such as the Christian Medical College, Vellore; LV Prasad Eye Institute (LVPEI), Hyderabad, National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore and All India Institute of Medical Sciences (AIIMS), New Delhi. Limbal stem cells are being routinely used at LVPEI, Hyderabad and AIIMS to repair corneal surface disorders caused by limbal stem cell deficiency. At CMC, Vellore, a technology has been established for collection, isolation and purification of HSC for haploidentical haematopoietic stem cell transplantation. The first haploidentical haematopoietic transplantation was carried out at CMC, Vellore, in April 2003. A phase I multi-centric clinical trial and a pilot study using bone marrow mononuclear cells have been initiated in the country for myocardial infarction and stroke, respectively. A 'CMC-DBT Centre for Stem Cell Research' has been created at CMC, Vellore. Clean room facilities for SCR are being established at SGPGIMS, Lucknow: KEM Hospital, Mumbai and LVPEI, Hyderabad. Dedicated short-term and long-term overseas fellowship programmes have been initiated by the Government of India for providing training to 25 fellows every year in niche areas including stem cells. A stem cell bank may be a useful repository for all types of stem cells, i.e. cord blood. In India, some companies have started establishing the repositories of cord blood banking. Reliance Life Sciences, Mumbai has a repository of 3000 cord blood samples. These samples have been processed and tested for infectious disease and stored at -196°C. Life Cell is a Chennai-based company and has a licence agreement and knowledge-sharing tie-up with Cyro-Cell International, USA. They have a repository of 1000 cord blood samples and are offering to preserve stem cells for 30 years. There is no controversy in the research involving stem cells derived from adult tissues and umbilical cord blood. These have been summarised in Table 1. The crux of the debate centres around derivation of the embryonic stem cells which require the destruction of an embryo. Draft guidelines for SCRF in India have been formulated jointly by the Department of Biotechnology, Ministry of Science and Technology and Indian Council of Medical Research. The same is currently being placed for public debate (Sharma, A; Personal Communication). National Brain Research Centre, Manesar has actively pursued basic science investigations on both commercial ES cells and neural precursor cells derived from human abortuses.

Neural progenitor cells: Based on promises of initial transplantation experiments in experimental and clinical studies, stem cell therapy promises hope for patients and caregivers for several neurodegenerative diseases. However, the pre-requisite of a purified, continuous and sufficient population of well-characterised human neural precursor cells (hNPCs) with ability to differentiate into glial cells and neurons remains the biggest hurdle. Several investigators claim success in isolation of purified population of hNPCs, but the procedure is typically difficult with ill-defined protocols. A detailed description of protocols for isolation, expansion and differentiation of hNPCs as well as characterisation of glial and neuronal cells differentiated from hNPCs is largely unavailable. Seth and his team at National Brain Research Centre, Manesar have designed a standardised 3 week protocol that describes an ethically approved stepwise process for isolation, maintenance, expansion, differentiation and characterisation of undifferentiated as well as differentiated hNPCs from human foetal brain samples collected from abortus material. They have studied the kinetics of cell specific and physiologically relevant markers in differentiating cells (unpublished work). The neuronal cells differentiated from hNPCs cultures established by them express markers, like neuron specific markers, intermediary filament and immature neuronal cell marker Tuj-1 and microtubule associated protein-2 (MAP-2), and the mature neuronal cell marker, human specific enolase, neprilysin, polysialic acid neural cell adhesion molecule (PSA-NCAM) and N-methyl-D-aspartate receptor (NMDA-R). The astrocytes derived from hNPCs express the astrocytic marker, glial fibrillary acidic protein (GFAP) and another astrocytic marker S-100 beta, further confirming the identity of astrocytes. Several batches of astrocytes were found to express a functional astrocytic marker, Glutamate transporter-1 (Glut-1). Their work has yielded a unique resource in the country of human neural stem cells that can be used for various basic and transplantation studies.

Intrinsic factors that control the commitment to neuronal lineage and that play a role in neuronal differentiation and cell type specification are largely controlled by transcription factors that contain the basic helix-loop–helix (bHLH) motif. Proneural bHLH factors are involved in the commitment of a multipotent neuroepithelial progenitor cell to the neuronal lineage. These include the neurogenins and Mash. Terminal neuronal differentiation further involves a second class of bHLH factors, known as neuronal differentiation factors. This includes NeuroD, NDRF and Nex. Expression of neuronal differentiation factors results in cell cycle arrest and differentiation of neurons in culture. The pattern of expression of neural differentiation genes *in vivo* is overlapping but not identical. In fact, some of these genes are expressed in specific subsets of neurons and suggests an additional important function of these factors, that they may be involved in specifying neuronal cell type. Knock-out mice have been generated in order to

Table 1: Institutes, hospitals and industries which involved a stem cell research

Embryonic stem cell research	• National Institute for Research in Reproductive Health, Mumbai • National Centre for Biological Sciences, Bangaluru • National Centre for Cell Sciences, Pune • National Brain Research Centre, Manesar • Rajiv Gandhi Centre for Biotechnology, Thiruvananthapuram • Centre for Human Genetics, Bangaluru • Jawaharlal Nehru Centre for Advanced Scientific Research, Bangaluru
Haematopoietic stem cells and bone marrow mononuclear cells	• Christian Medical College, Vellore • Sanjay Gandhi Post Graduate Institute for Medical Sciences, Lucknow • Post Graduate Institute of Medical Education and Research, Chandigarh • Manipal Hospital, Bangaluru • All India Institute of Medical Sciences, New Delhi • National Centre for Cell Sciences, Pune • National Institute of Immunology, New Delhi • Indian Institute of Science, Bangaluru • Indian Institute of Technology, Delhi • Research and Referral Hospital, New Delhi
Limbal stem cells	• LV Prasad Eye Institute, Hyderabad • RP Centre, AIIMS, New Delhi • Regional Institute of Ophthalmology, Kolkata
Neural stem cells	• National Brain Research Centre, Manesar • National Institute of Mental Health and Neurosciences, Bangaluru • National Centre for Cell Sciences, Pune • University of Hyderabad, Hyderabad
Mesenchymal stem cells	• Christian Medical College, Vellore • Sanjay Gandhi Post Graduate Institute for Medical Sciences, Lucknow • Manipal Hospital, Bangaluru
Liver stem cells	• Centre for Liver Research and Diagnostics, Hyderabad • Centre for DNA Fingerprinting and Diagnostics, Hyderabad
Pancreatic progenitor cells	• National Institute of Nutrition, Hyderabad • National Centre for Cell Science, Pune
Cardiac stem cells	• Sree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvananthapuram
Muscle stem cells	• Centre for Cellular and Molecular Biology, Hyderabad
Cancer stem cells	• Indian Institute of Science, Bangaluru
CMC-DBT centre for stem cell research	• Christian Medical College, Vellore
Stem cell research facilities	• Postgraduate Institute of Medical Education and Research, Chandigarh
Clean room facilities for stem cell research	• Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow • KEM Hospital, Mumbai • LV Prasad Eye Institute, Hyderabad
Cord blood bank	• Reliance Life Sciences, Mumbai • Life Cell, Chennai

Source: (Information provided by Dr Alka Sharma, Joint Director, Department of Biotechnology, Government of India)

study whether these differentiation factors are involved in the specification of neuronal subtype. At NBRC, studies are underway to elucidate the function of proneural and neural differentiation bHLH genes using ES cells as a model system for studying neuronal differentiation.

The embryonic stem cell (ESC) is the 'mother' of all other cells. Adult stem cells may be derived from the bone marrow, peripheral blood, tissues, muscles, cardiac tissues, cartilage, brain tissues, etc. MSCs are present in many tissues of adult cells. MSCs may be isolated from various sources from normal healthy volunteer donors and manufactured under strict cGMP conditions. Stem cells may also be isolated from the umbilical cord blood. Much like the bone marrow, cord blood is one of the richest sources of stem cells. Any disease in which there is tissue degeneration may be a potential candidate for stem cell therapies, including conditions and disabilities as Parkinson's and Alzheimer's disease, spinal cord

injury, stroke, burns, heart disease, type 1 diabetes, osteoarthritis, rheumatoid arthritis, liver diseases, retinal degeneration, limb ischaemia, hair cell regeneration, etc. Extensive basic research is required for standardisation of methods for the isolation of embryonic and adult stem cells from various sources. Future prospects for embryonic stem cell research include the following: generation of therapeutic grade cell lines; identification of human embryonic stem cells (hESC) growth factors; controlled differentiation, i.e. generation of specific cell population; study of fundamental changes in cell cycle control that occurs during embryonic stem cells differentiation; maintenance of stem cell in undifferentiated stage; regulation of differentiation of ESC; pluripotency and differentiation of established cell lines; standardisation of animal free defined culture condition; developmental potential of human versus mouse ESC; standardisation in use of specific stem cells to specific organ systems, etc. (Sharma 2006; Personal communication).

Use of *ex-vivo* expanded stem cells has been identified as a new drug as per FDA, USA, i.e. investigational new drug (IND). This would require information about the source, number, purity, appropriate stage, optimum condition and criteria for harvesting stem cells; also standardisation of doses in terms of concentration and number of stem cells for each application and minimal manipulation of cells for clinical use. Good animal models are required to address the issues of safety and efficacy before attempting clinical applications of stem cells.

The basic requirements for clinical trial are: adequate infrastructure, i.e. Good Manufacturing Practices (GMP), clinical grade reagents, trained manpower, proper documentation, Standard Operating Procedures (SOPs), quality control, etc.

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SECTION

15

Pain

AK Singh

194 Pain: Anatomy and Physiology

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"Nothing begins and nothing ends,
That is not paid with a moan,
For we are born in others' pain,
And perish in our own."

Francis Thompson

INTRODUCTION

"Where life ranks highest, there it can suffer most. Human life has among its privileges that of a pre-eminence of pain." Sherrington (1940).[83]

Since time immemorial, the most important goal of medical science is the relief of pain in all its various manifestations. In modern times, neurosurgery has made substantial contributions towards achieving this easier said than done task. This has been made possible due to:

- A better understanding of the physiology and pharmacology of pain perception and conduction
- Advances in neurobiology and allied neurosciences in providing new insights into the functioning of the nervous system.
- Newer and safer neurosurgical techniques like stereotaxy, percutaneous, intraspinal and intracere bral stimulation and suppression techniques
- Development of newer technologies and devices proving true the quote; "Today's science fiction is tomorrow's scientific fact."

DEFINITIONS OF PAIN

The word pain is derived from the Latin word "paena" which is synonymous with "dolor" and not easily defined. The Oxford English Dictionary defines pain as 'suffering or distress of body or mind". The Greek philosopher Aristotle (303-322 BC) described pain as an agony of the soul of mind. Spinoza (1632–1677) defined pain as a form of focal sorrow. Tagore, through his various verses, expressed pain as a form of psychic agony.[42] Sherrington defined pain as, "the physical adjunct of an imperative protective reflex.'' Pain is defined as an "unpleasant sensory and emotional experience with actual or potential tissue damage or which can be described in terms of such damage" (International Subcommittee on Taxonomy 1979). This was re-stated in 1986 by Morsky and was accepted by the International Association for the Study of Pain. The definition runs thus; "Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or as described in terms of such degree". Wall in 1985 defined pain as: "a state akin to hunger and thirst in which action is imperative. Behaviour must be changed to prevent further damage including psychological damage".[26]

The sensation of pain is protective in nature and essential for the well-being of the organism. It urges the sufferer to seek measures for relief from the disturbing influence by suitable means. Diseases that have pain as an early symptom have a greater chance of attention than, for example, a malignant lesion which may progress to an advanced stage without any pain being apparent. The real problem arises when pain becomes persistent and demands continuous attention. In such cases, the phenomenon of pain seems to be purposeless and instead of being protective becomes a means of destroying the organism. Neurosurgical relief of pain is required mostly in such cases where there is persistent and purposeless pain.

In case of chronic persistent pain, the psychology of the individual gets deeply involved in the pain phenomenon and the problem of pain transcends the anatomical pathway of conduction and physiology and extends in to the higher realms of cerebral physiology and neuropsychology. It has been observed that even after complete destruction of the pain conducting pathways, a subject may still complain of pain, which is certainly of psychogenic origin. The description by people of the severity of pain varies according to their personal concept, intelligence, vocabulary and psychic background. Some persons are born without the sensation of pain. In such patients there may be an absence of the peripheral sensory receptors or a deficiency in the conducting mechanism. The patient may feel other sensations but may not appreciate pain. Such patients do not have the protective measures when the various parts of the body are subjected to the ordinary trauma of everyday life. A

greater intensity of ordinary stimuli such as heat, cold, touch and pressure can induce a subjective sensation of pain. As the intensity of any stimulus increases, one can differentiate two stages: metaesthesia which is just uncomfortable and algaesthesia which could indicate pain.[47]

Perception of pain is variable in different individuals and in the same individual at different times and thus, it is difficult to assess the severity of pain objectively. Physiologists have attempted to assess the degree of pain from polygraphic recordings of psychogalvanic reflexes like tachycardia, cutaneous pallor and hypotension. Methods have been devised to assess objectively or qualitatively the intensity of pain by a special mechanical pressure apparatus, like an algometer or by chemical means, e.g. the blister base being stimulated by chemical solutions of different strengths.[46] "Pain" itself cannot be measured, but the stimulus leading to the pain can serve as an analogue of the pain. Thus, the stimulus leading to an experimental pain equal to the intensity of a pathological pain can serve as an analogue of the intensity of the latter.[45] Pioneering work in the first decade of the 20th century by Foerster,[25] Spiller and Martin[87] and Schueller,[81] served to initiate the surgical science of amelioration of intractable pain.

ANATOMICAL AND PHYSIOLOGICAL CONSIDERATIONS

The human sensory nervous system carries information from the external and internal environment to the brain which is responsible for the ultimate perception and appreciation of pain. Particular areas are especially involved in different facets of sensation like appreciation, memories of sensations and their emotional significance.

Peripheral Receptors

There are a variety of sensory receptors, usually known after the names of those who initially described them, namely, Meissner, Ruffini, Merkel, Krause, Pacini, Golgi, Mazzoni, etc. The histological peculiarities and the specificity of these receptors are now known. It is now becoming increasingly clear that these receptors are much less specialised in function than previously assumed. Weddell[98] and his group proposed that the various cutaneous sensations do not arise from the selective activation of specific receptors, but from the selective activation between the various types of stimuli, the differentiation depending on the spatiotemporal pattern of excitation of non-specific sensory endings.[52] In large parts of the body surface specific end organs are altogether absent, except those in relation to hair follicles.[98] The cutaneous plexus of naked axoplasmic filaments have not only a large part to play in pain reception, but also seem to identify a wide variety of stimuli. The cornea has only fine small fibres and yet these fibres carry touch, as well as pain and temperature sensation.[6] Neurophysiological research work on mammals has shown the existence of pain receptors (nociceptors) of different types in different structures.[76] There is no doubt as to the presence of nerve endings which respond only to painful or tissue damaging stimuli and are therefore to be identified as pain receptors or nociceptors.

In the appreciation of sensation, the specificity of the receptors as well as spatiotemporal summation of stimuli plays an important role. This is further modified by the phenomenon of modulation in receptor activity. The receptor sensitivity is under the influence of environmental stimuli, the state of the tissue, as well as feedback information from other levels of the nervous system, all of which can alter the receptor response to stimuli. The receptors are divided into high threshold nociceptors,[38,41,74,75] mechanical nociceptors, polymodal nociceptors[9,32] and muscle[72] (Table 2) and visceral nociceptors.[41] These connect with the fine medullated or unmyelinated fibres in the peripheral nerves.

Lewis[53] described, in 1935, the occurrence of hyperalgia at the site of the noxious stimuli and the surrounding area and attributed it to the production of pain producing chemicals from the injured tissue. Tissue damage releases H+, K+, 5-HT, histamine, prostaglandins, bradykinin, and substance-P and these cause pain. Calcitonin gene related peptide (CGRP), vasoactive intestinal peptide (VIP) and somatostatin are also released by C-fibre stimulation.[70] Prostaglandins potentiate the role of inflammation and pain and enhance the effects of other inflammatory substances. Corticosteroids, by blocking the formation of arachidonic acid (precursor of prostaglandin) from membrane phospholipids, reduce pain and the inflammatory response. Aspirin and indomethacin relieve pain by inhibiting cyto-oxygenase, an essential enzyme in the cycle of production of prostaglandins. Substance P, present in the peripheral terminals of unmyelinated fibres, has a role in the initiation of pain. Capsaicin is used in the study of secondary hyperalgesia. It selectively activates nociceptors and causes a large zone of hyperalgesia when topically applied. Capsaicin hyperalgesia closely resembles thermal injury/laceration.[84]

There are four peripheral mechanisms of pain generation and transmission:[85]

- Tissue receptors
- Generated potentials (voltage and ligand gated channels)
- Membrane receptors (NMDA, AMPA, GABA, etc.)
- Signal modulators (NMDA agonists, etc.).

Sensory Nerve Fibres

The Bell-Magendie law segregated motor and sensory functions in a nerve. We, however, know that is not exactly true. Some sensory fibres also pass through the ventral root. Thirty per cent of ANS fibres in the ventral root are unmyelinated. These ventral root fibres take two pathways: they either turn back and enter via the dorsal root (DR) and the dorsal root ganglion (DRG) or they continue through the ventral root and traverse the grey matter and terminate in the superficial layers of the dorsal horn.[70]

The sensory nerve fibres travel proximally in the peripheral nerves towards the spinal cord, form the first relay in the bipolar cells of the dorsal root ganglia and they enter the spinal cord in the posterior roots. The cells in the dorsal root ganglia are of two types: large A cells and small B cells. The A cells give rise to large myelinated axons and the B cells to small (A delta) myelinated axons and non-myelinated axons (C fibres) (Table 1). The pain impulses travel in the small myelinated fibres (A delta) and in non-myelinated fibres (C fibres). This has been confirmed by single fibre recordings in animals[16] and by percutaneous microneurography.[94] Conduction in A delta and C fibres is blocked early during the injection of local anaesthetics, whereas the bigger fibres get blocked early in ischaemia. The conduction along A delta fibres leads to discrete localisation of the pain, whereas C fibre stimulation leads to a diffuse and longer lasting uncomfortable sensation resembling pain. It has been proposed that this differential conduction of pain may be the cause of the double pain, e.g. when the skin is pricked there is an immediate pricking sensation (first pain) followed after a short interval by an unpleasant sensation (the second pain).

Phylogenetically the C fibres belong to a primitive afferent system relatively complete in itself with a large spectrum of sensibilities. C fibres are polymodal nocipceptors which respond to various noxious stimuli, including thermal, mechanical and chemical stimuli.[32] This has been overlaid during development by an independent system of fast fibres (A) connecting to the newer parts of the brain.[11]

Table 1: Erlanger and Gasser classification of nerve fibres

Cutaneous sensory fibres	*Description*	*Diameter (μm)*	*Mean conduction velocity (MCV)/ms*
A-beta	Mechanoreceptor (low threshold)	8 (5-15)	50 (40-70)
A-delta	Mechanothermal nociceptor (Type I). Hair mechano-receptor (low threshold). A-fibre mechano-, heat- and nociceptor (AMH). Chemosensitive AMH (type II)	<3 (1-4)	15 (2-40)
B	Pre-ganglionic sympathetic	3 (1-3)	7 (3-15)
C	Mechano-, heat-, chemical nociceptive	1 (0.5-1.5)	1 (0.5-2)
C	Post-ganglionic sympathetic	1 (0.5-1.5)	1 (0.5-2)

Table 2: Lloyd Hunt classification of muscle sensory endings

Type	*Description*	*Diameter*	*Mean conduction velocity (MCV)/ms*
Ia	Primary muscle spindle	15 (12-14)	100 (70-120)
Ib	Golgi tendon apparatus		
II	Secondary muscle spindle, Spray (Ruffini) endings, Lamellated (Paciniform) endings	9 (4-12)	55 (25-70)
III	Mechanoreceptor	3 (1-4)	11 (10-25)
IV	Mechano-, chemical nociception, thermoreceptors	1 (0.5-1.5)	1 (0.5-2)

Sensory perception on the skin surface is not compartmental. There are overlapping areas supplied by adjacent sensory nerves. After surgical section of a single posterior root, the analgesic effects are negligible. To produce loss of sensation of pain in a predetermined part of the body, it is essential to cut several posterior roots above and below the appropriate segmental level. The possibility of the existence of some sensory fibres in the anterior spinal root (motor) has been suggested by physiologists. Obviously, these sensory fibres cannot be divided without jeopardising motor function.

Nociceptors

Pain sensitive fibres are called nociceptors. There are two types of pain receptors namely, unimodal nociceptor subserving only one sensation and polymodal nociceptor subserving chemical, mechanical and thermal nociception.[2] A delta and C fibres comprise the various nociceptors.

C Polymodal Nociceptor[70]

These are very important in nociception. Ninety five per cent of sensory C-fibres in the human skin are constituted by C Polymodal Nociceptors (CPNs). They respond to intense mechanical stimulation (more than 1g), thermal stimulation (threshold 38 degree C) and chemical stimuli. CPN activation thresholds are similar to high threshold mechanoreceptors (HTM), although CPNs demonstrate a graded sensitivity to thermal stimuli from 38–49 degree C (45–51 degree C is the maximum sensitivity range). They are further characterised by prolonged discharge with slow adaptation. They are associated with release of histamine, KCl, etc.

A-delta fibres: These are lightly myelinated. They respond to intense noxious mechanical stimuli and are not activated by noxious thermal/chemical stimuli, although intense cold

or repeated chemical stimuli sensitise them. They have multiple discrete receptor fields (less than 1 sq. mm) over the body and face. The active threshold is 5–1000 times more than the low threshold mechanoreceptors (LTM). The high threshold mechanoreceptors (HTMs) are initially quiet, but with repetitive stimulation are characterised by a slow background firing pattern.

Myelinated mechanothermal nociceptors (MMTN) are basically A-delta fibres. They have a thermal stimulation range of 40–46 degree C (45–53 degree C maximum sensitivity). They also are stimulated by mechanical stimuli and are involved in the genesis of first/fast pain.

Cold nociceptors: These respond to intense cold and noxi ous stimuli (A-delta or C fibres). They are insensitive to mechanical stimuli.

Visceral Pain

Pain sensation from the viscera is generally more diffuse. This is due to the high proportion of small C fibres in the visceral nerves and the existence of extensive ramifications between the nerves. In addition, afferent impulses from a given visceral area enter the central nervous system via many DRs. The visceral afferent fibres run in the autonomic nerves but are not a part of the autonomic nervous system. This explains the value of sympathectomy in some types of visceral pain and pain of vascular origin. The *convergence theory* wherein somatic and visceral afferents converge on the same spinothalamic neurons and the *facilitation theory* wherein collateral connections for visceral afferents to dorsal horn neurons receiving pain impulses from somatic stimulation facilitate pain have both been used to explain referred pain which occurs in visceral pain.[28]

ORGANISATION OF THE SPINAL CORD

The spinal grey matter has been organised into 10 laminae. These were initially studied in the cat by Rexed. That human beings too possess a similar laminar arrangement was proved by the work of Truex and Taylor[4,59,93] (Fig. 1).

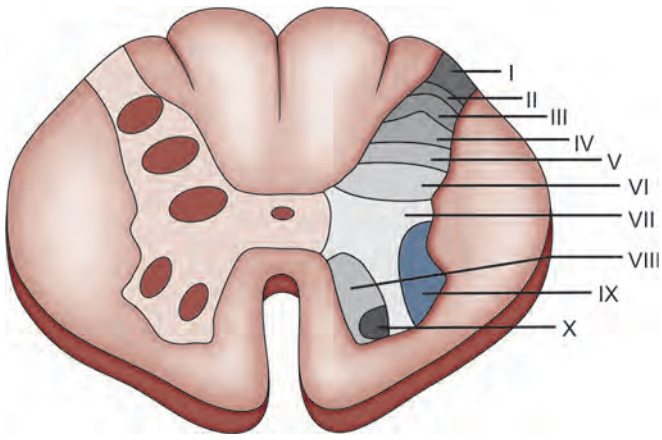


Fig. 1: Cross-section of the spinal cord showing laminar arrangement of spinal grey matter

Lamina I

The grey matter is situated at the margin of the dorsal horn. There is a marginal plexus which constitutes a hori zontal group of fibres. Larger elements of this lamina constitute the *marginal cells of Waldeyer* which respond to mechanical or thermal nociceptive information released secondary to tissue destruction and contributes elements to the contralateral spinothalamic tract.

Lamina II (Substantia Gelatinosa of Rolando)

This exists throughout the spinal cord with a narrow outer zone and a broader inner zone. Afferents to the SGR come from the tract of Lissauer, posterior column and adjacent parts of the lateral funiculus of the spinal cord. Nociceptive special neuronal soma is in lamina I and in the outer Lamina II. Innocuous mechanical stimuli occur in the inner zone of lamina II. Lamina II is a closed system with no axonal contributions to the other relay systems. The SGR neurons project to Lissauer's tract and fasciculus proprius. Lamina II primarily serves to influence the neurons in the deeper laminae and has a modulatory function.

Laminae I and II have a high concentration of substance P which is synthesised in the DRG and then transported into the terminals of the DR fibres. Substance P stimulates nociceptive impulse transmission. Both these regions have high concentration of opiate receptors. After dorsal root rhizotomy, there is a significant decrease in the number of opiate receptors in the deafferenated spinal segments.

In the substantia gelatinosa of Rolando (Lamina II) and in Lamina I, there are a group of neurons which are interposed between the first order and second order afferent neurons. These interneurons play an important role in regulating the afferent impulses, resulting in segmental control of input and output. The output pattern of the cells is modified not only by the peripheral input, but also by the facilitatory or inhibitory action of central tonically active descending systems.[76] A barrage of impulses via the large myelinated fibres produces inhibition of small cells and C fibres.[24] Counter irritation to modify pain and therapeutic transcutaneous nerve stimulation (TENS) reduce the firing of dorsal horn cells, inhibiting segmental as well as descending control. Descending control of dorsal horn cells is well known. Stimulation of the periaqueductal grey or the nucleus raphe magnus results in prolonged analgesia.[103]

Laminae III-V

These are vertically oriented with larger neurons and dendrites which arborise dorsally into laminae I and II. Afferent input consists of myelinated axons. The laminae are mostly comprised of interneurons and receive low threshold mechanoreceptor input. There are 2 types of projection neurons here namely, dorsal columns and spinocerebellar tract. Lamina IV has the thickest layer of large neurons external to lamina II. The grey matter

of laminae III and IV comprise the principal sensory nucleus/nucleus proprius. Large diameter primary afferents terminate here. Lamina V is a broad zone across the neck of the dorsal horn. The output depends on the degree of convergence of large and small fibre input—low threshold, wide dynamic range (WDR) or nociceptive specialised neurons. Hyperalgesia is primarily due to unmasking of low threshold inputs to nociceptive neurons.

Laminae VI and VII

Lamina VI is across the base of the dorsal horn and in the cervical and lumbar region. It has group I muscle afferents to the medial lamina VI terminating in the lateral zone. Lamina VII (zona intermedia) is situated between the anterior and posterior horns. The size and the boundaries of the laminae vary according to the level of the spinal cord. They have well defined cell groups, including the dorsal nucleus of Clarke (nucleus thoracicus). Lamina VII also serves as the origin for the uncrossed dorsal spinocerebellar tract and intermedio lateral and intermediomedial nuclei and tract.

Laminae VIII-X

These occupy the ventral horn of the grey matter. They also contribute to the gamma efferents to the muscle spindle. Lamina X is around the central canal and processes nociceptive input from visceral afferents and spinothalamic projection neurons.

A brief synopsis of the above is as follows:

Lamina I-VI: Dorsal grey, Lamina II-SGR, III and IV-nucleus proprius, V-formatio reticularis, VI-limb enlargements (brachial and lumbar), VII-nucleus thoracicus, intermedio-medial and intermedio-lateral columns which include the inhibitory interneurons of Renshaw, VIII-base of ventral column, IX-somata of motor neurons (alpha and gamma), VIII-X: Dorsal grey, X-spinal grey commissures.

PAIN PATHWAYS IN THE SPINAL CORD

The following tracts (Figs 2A and B) have been studied in great detail by horseradish peroxidase labelling and antibodies:[101]

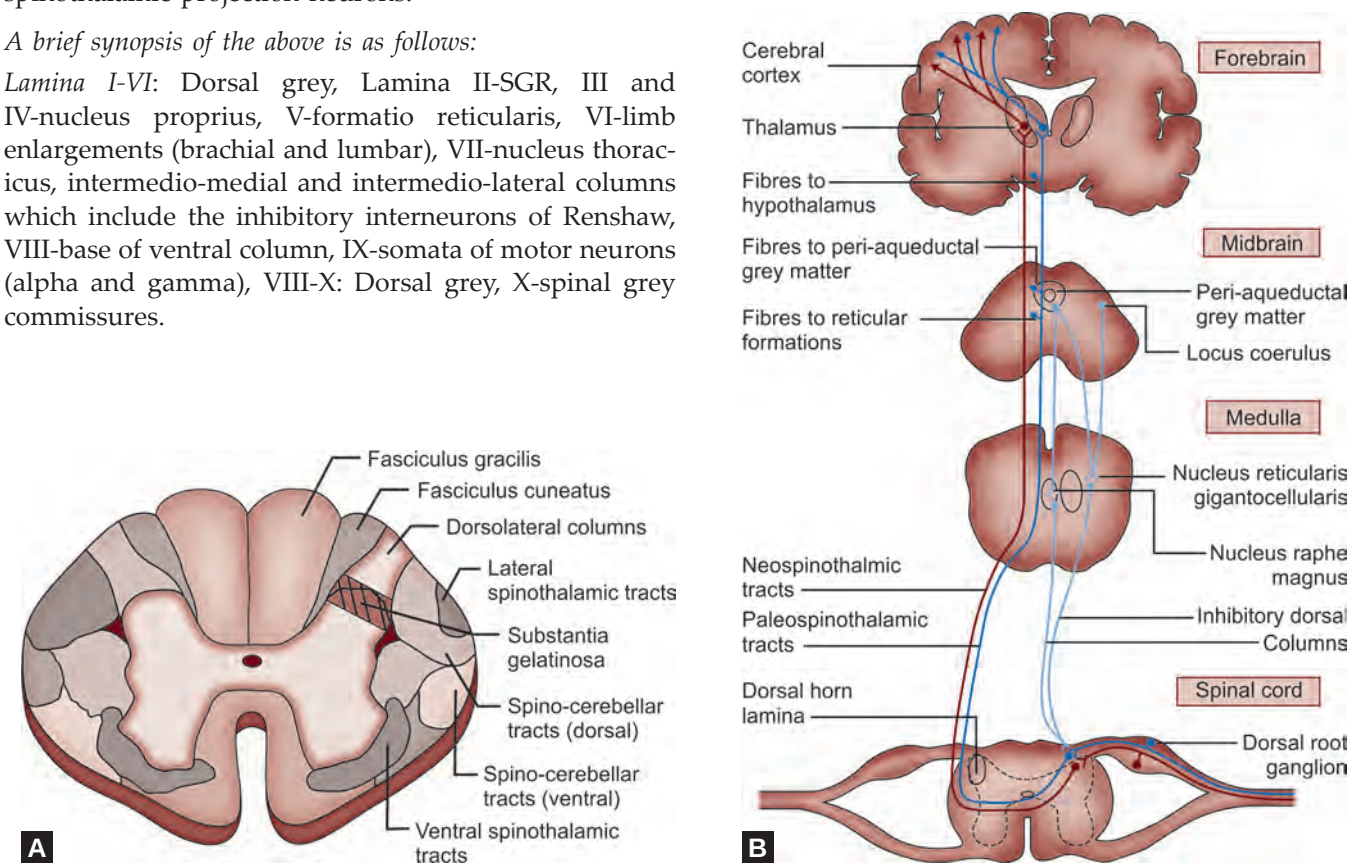
Dorsolateral Tract of Lissauer

This tract is situated laterally and caps the dorsal horn. It has A-delta and C-fibres and is concerned with nociception. Fibres from the lateral division of the dorsal root bifurcate into ascending and descending branches that give off a number of collaterals. These terminate in the SGR with interneuronal synapses.

The tract of Lissauer (TL) is situated dorsolateral to the dorsal horn and consists of:

Medial part: Here the small afferents enter and bifurcate to reach the dorsal horn, either directly or through ascending/descending pathways. This part transmits excitatory effects of each DR to the adjacent segments. The medial division contains large medullated fibres which carry proprioceptive stimuli from the muscles.

Lateral part: Through this part, a large number of long endogenous propriospinal fibres interconnect at different levels of the SGR. These convey the inhibitory influence of the SGR into the neighbouring metameres. The small medullated fibres and the fine unmyelinated fibres conveying pain sensibility pass through the lateral division and end in the area of the substantia gelatinosa of Rolando (SGR) encasing the posterior horn.



Figs 2A and B: Pain pathways. (A) Cross-section showing spinal tracts. (B) Spinal supraspinal pathways of pain

Spinothalamic Tract

The spinothalamic tract (STT), spinoreticular tract (SRT) and spinomesencephalic tract (SMT) together constitute the spinal lemniscus and may be considered to be a single path. The origin is from laminae I and V-X. The fibres from laminae I-V go to the ventralis posterior nucleus of the thalamus and those from laminae VI-IX project to the ventralis posteromedial nucleus. In the brainstem, as it is nearing the thalamus, the spinothalamic tract divides into:

A large lateral neospinothalamic tract, which terminates in the ventroposterior lateral nucleus along with the quintothalamic tract (trigeminothalamic) fibres and

A small medial portion which terminates in the most rostral part of the ascending reticular activating system (ARAS) and in the central nuclei of the thalamus (the so-called non-specific thalamus).

The Vpm and Vpl nuclei then project to the somatosensory cortex and these fibres are called the neospinothalamic tract (neo-STT). Second order fibres from the deeper laminae project to the reticular formation, pons, mesencephalon, periaqueductal grey and hypothalamus and thence to the medial and intralaminar thalamic nuclei. These constitute the paleospinothalamic tract (paleo-STT) of Mehler[61] and project to the limbic forebrain. The paleospinothalamic tract in lower vertebrates represents the only true connection to the thalamus. The neo-STT is highly organised somatotopically, while the medial paleo-STT is not. The fibres in the STT are arranged from lateral to medial (sacral, lumbar, thoracic, cervical).[3,49] Bishop[11] and Mehler[61] proposed that the neospinothalamic tract becomes more prominent and the paleospinothalamic tract less prominent in higher mammals. Anterolateral cordotomy interrupts the SRT and SMT together with the STT.

In the cervical cord, the disposition of the tract is as follows: sacral, lumbar, thoracic, cervical from outside inwards. At different levels of the spinal cord, the depth of the incision required to interrupt the spinothalamic fibres during an anterolateral cordotomy must vary to obtain optimal effect. Hyndman and Van Epps[40] regarded the lamination of the spinothalamic fibres as having a postero anterior distribution, rather than an onion peel arrangement. Hitchcock[36] supported this view as he observed that a 3 mm incision often produces as complete and lasting analgesia as the 4–5 mm incision. This fact is of importance, as too deep an incision would inevitably injure the visceral fibres.[35] There are 3 types of spinothalamic neurons namely, low threshold neurons which are mechanoreceptors in lamina VI and VII, high threshold neurons which are nociceptors in lamina I and wide dynamic range neurons from lamina IV and V, involved in mechanoreception and nociception.[2]

Magoun[57] described the two systems of central pain pathways as lemniscal and extra lemniscal systems. It may also be noted that the afferent responses evoked in the thalamus through the lemniscal system are somatotopic, i.e. spatially organised, whereas those in the extra lemniscal system are also capable of evoking various reflex effects both in the somatic and the autonomic systems, e.g. the peripheral results of arousal and alarm reactions.

Spinoreticular Tract

This is triggered by arousal and is influenced by emotional and affective aspects of pain and somatic autonomic reflexes.[13] The fibres originate from lamina VII and VIII and are in the anterolateral quadrant of the cord. It projects ipsilaterally and contralaterally but mostly to the contralateral side in the lumbar region. It terminates bilaterally in the medullary reticular formation, the nucleus subceruleus and the raphe magnus nucleus. From here, fibres proceed to the medial thalamic nuclei.

Spinomesencephalic Tract

It is similar to the spinoreticular tract. The fibres originate from laminae I and V. These fibres are 1–5 μm in thickness and conduct at 7m/s. Sixty per cent to 75% project to the contralateral brainstem, where these fibres diverge from those of the STT and SRT and turn dorsomedially into the midbrain. Most of the fibres terminate in the mesencephalic reticular formation (RF), periaqueductal grey and rostrally in the medial and ventrobasal thalamus. These fibres serve a discriminative function and also a role in autonomic reflexes. Ascending impulses activate supraspinal descending inhibitory pathways.

Spino-Cervical Tract

This originates in laminae III and V and subserves non-noxious tactile stimuli.[13] It lies in the ipsilateral dorsal funiculus and extends up to the lateral cervical nucleus; a small group of cells in the upper cervical cord lying lateral to the dorsal horn. Fibres from the spino-cervical tract (SCT) project to the contralateral thalamus. It is an inconsistent pathway in humans and has a yet unclear role in nociception.

Dorsolateral Posterior Synaptic Pathway

Laminae III and IV of the dorsal horn give rise to dorsolateral posterior synaptic pathway (DLPSP). This carries noxious and non-noxious stimuli. Less than 10% respond to noxious input. Somatotopic arrangement exists in this pathway. This tract plays a role in pain modulation.

Propriospinal Multisynaptic Ascending System

Propriospinal Multisynaptic Ascending System (PMAS) originates in the deep dorsal column in lamina X, with input from nociceptors and midline structures. It projects to the brainstem reticular formation and medial and intralaminar thalamic nuclei. Selective ablation of this path is considered to be effective in the treatment of bilateral visceral pain, without the potential problems associated with commissural (extralemniscal) myelotomy.[33]

Dorsal Root Entry Zone[86]

The dorsal root entry zone (DREZ) is an entity including the 1 mm central part of the dorsal rootlet, the posterior medial part of the tract of Lissauer and the most dorsal layers (I-V) of the dorsal root where afferents synapse with cells of the spino-reticulo-thalamic pathway. Each DR divides into 4–10 rootlets according to metameres and is 0.25–1.5 cm in diameter, according to the cord level. Each rootlet is a functional entity, i.e. a miniature root. In each dorsal rootlet and in its corresponding DREZ, there is a spatial segregation of afferent fibres according to their size and destination. The fine fibres re-group in the lateral region of the DREZ.

The tract of Lissauer (TL) is situated dorsolateral to the dorsal horn and consists of two parts as described above.

Most fine nociceptive afferents enter the dorsal horn through the medial part and then through the dorsal aspect of the SG. Ramon y Cajal's recurrent collateral vessels of large lemniscal fibres enter the dorsal horn through the ventromedial aspect of the SG. Because dendrites of the spino-reticulo-thalamic tract (SRT) cells make synaptic connections with primary afferent fibres inside the SG layers, it is assumed that the SG has a segmental modulatory effect on nociception. When large lemniscal afferents in the peripheral nerve/dorsal root are stimulated, there is a decrease in the inhibitory control of the dorsal horn which can cause excessive firing of the dorsal horn neurons. This is the origin of de-afferenation pain. Micro-DREZotomy (MDT) involves preferential destruction of the nociceptive fibres in the lateral bundle of the dorsal rootlets, as well as the excitatory medial part of the LT. Descending control of dorsal horn cells is well known. Stimulation of the periaqueductal grey or the nucleus raphe magnus results in prolonged analgesia.[103]

Trigeminal Nerve and its Nuclei

A special reference is made here to the trigeminal system as it subserves the pain of the face and as tic doloureux is so commonly seen in clinical practice (Table 3).[34]

There are two patterns of trigeminal somatotopic organisation within the descending trigeminal tract and the nucleus caudalis. The first is that of concentric rings with the middle part of the face being subserved by the trigeminal nucleus in the rostral medulla. The caudal end of the face is subserved by the spinal nucleus at the caudal end of the medulla. The second pattern is that arranged along the three divisions of the trigeminal nerve V1,V2,V3.[31]

The Thalamus (Table 4)

The spinothalamic tract enters the posterior part of the ventral lateral nucleus (VpL). The pain fibres from the face travel as a separate bundle called the quintothalamic tract and terminate in the posteroventromedial (VpM) nucleus of the thalamus. According to Glees,[30] the termination of the medial fillet lies between those of the spinothalamic and quintothalamic tracts. Other fibres carrying pain sensation enter the interlaminar nucleus and many of them terminate in the centromedian and parafascicular nucleus, which comprise the nucleus parafascicularis (the paleosensory system). The dorsomedian nucleus of the thalamus, through its connections with the VA nucleus and the limbic system, plays a part in the emotional reaction to pain.

The thalamus has been divided into:[13]

- *Medial paleothalamus* which comprises the medial and intralaminar nuclei. It has no somatotopy. The role of these nuclei in pain processing is primarily related to the emotional and motor reaction associated with aversive behaviour, rather than discriminative sensory function.

Table 3: Nuclei of trigeminal nerve

No	*Nucleus*	*Location*	*Distribution*	*Function*
1.	Nucleus motoricus trigeminus	Midpons (lateral reticular formation)	Special visceral efferents (SVA), branchial muscles of mastication from branchial arch I.	Motor supply to masseter, temporalis, pterygoids, tensor tympani, tensor palatine, mylohyoid and the anterior belly of digastrics.
2.	Nucleus mesencephalicus trigeminus	Rostrally from the primary nucleus to the superior colliculus of the mesencephalon	General sensory afferents (GSA), proprioception from organs of mastication.	Force of bite controlled.
3.	Nucleus sensiblis principlis trigemini	From the tegmentum of the midpons at the trigeminal root entry zone.	General somatic afferents (GSA), exteroceptive	Tactile facial sensation.
4.	Nucleus tractus spinalis trigeminus	From the midpons at the level of the trigeminal root entry zone caudally to C2.	Exteroceptive	Pain and temperature sensation of the face.

- *Neothalamus* which receives fibres from laminae VI-VIII of the dorsal horn through multiple ascending systems and the brainstem RF. The neothalamus comprises the VpL and VpM nuclei and has a high degree of somatotopic organisation. VpL receives the neoSTT via the medial lemniscus and the VpM receives the spinal-trigeminal system via the ventral tegmental tract (VTT).

Summary of the Neurophysiology of the Thalamus[89]

The thalamic lesion sites for pain relief have been classified as follows:[90]

- Thalamic nuclei of the limbic system and their radiation
- Hypothalamus
- Thalamic nuclei of the frontal association system and their radiation
- Spino-thalamic relay nuclei for the medial lemniscus and the spino-quintothalamic tract and their radiations
- Intralaminar nuclei.

NEUROPHARMACOLOGY OF PAIN

An understanding of the neurochemical mechanisms involved in sensory conduction and pain helps to understand the basis of pharmacological therapy.

Substance P is an important neurotransmitter concerned with transmission of nociceptive stimuli. Substance P also contributes to the inflammatory response and nerve sensitisation. Recent studies have shown calcitonin gene related polypeptide (CGRP) to exist with substance P in the primary afferent neurons.[37] Its role may be neuromodulation rather than neurotransmission. Other substances are serotonin and norepinephrine which mainly act as neurotransmitters of the descending pathways from the nucleus raphe magnus and locus ceruleus, respectively. The other important modulators are endogenous opiates which are present in the substantia gelatinosa, lamina V, nucleus raphe magnus and periaqueductal grey (PAG).

Peptides like substance P, VIP, somatostatin, chole cystokinin and angiotensin are present in the dorsal horn.[32] Substance P is present in 20% of the cells of the dorsal root ganglion (DRG), mainly in the small cells. Noxious peripheral stimuli result in the production of substance P, which probably acts more as a neuromodulator than a neurotransmitter.[51]

Opiate receptors are found in laminae I and II of the dorsal horn, the medial raphe nucleus, the periaqueductal grey, the locus ceruleus and the hypothalamus. Endorphins are found near these receptors. Seven different endorphins have been identified with varying receptor specificity.[50] The descending control of dorsal horn activity is an opiate dependent mechanism. The periaqueductal grey projects to the raphe nucleus which projects to the dorsal horn.[7] The neurotransmitters involved in these projections are serotonin and norepinephrine.

Table 4: Nuclei of the thalamus

No.	*Nucleus*	*Stimulation*	*Miscellaneous recording*	*Applications*
1.	Ventrocaudal (Vc)	Paraesthesia	Tactile neuron	Lesion and chronic stimulation for pain relief
2.	Parvocellular ventrocaudal (Vcpc/VMpc)	Warm, cool, painful effects and paraesthesiae	Nociception, thermoception	Pain relief lesions
3.	Anterior ventral oral (Voa)	None recognised	Voluntary cells	Dyskinesia
4.	Posterior ventral oral (Vop)	Motor "on" effects	Voluntary cells	Functional dyskinesias
5.	Ventralis intermediate (Vim)	Paraesthesiae, vestibular, sensorimotor effects.	Kinesthetic and deep sensory nuclei	Lesioning and chronic stimulation for tremor and dyskinesia control
6.	Anterior nucleus (A)	None-recognised	None-recognised	Lesions for relief of psychiatric disease
7.	Parafascicular (Pf)	None	Nociception	Pain relief
8.	Periventricular grey (PVG) medial parafascicular	Acute pain relief, satiety centre.	None	Chronic stimulation for pain relief
9.	Interlaminar (IL)	None/pain/burning sensations.	Nociception	Pain relief
10.	Pulvinar (Pu)	None-recognised	Vision	Pain and spasticity relief
11.	Dorsomedian nucleus (DM)	None-recognised	Firing cells	Psychiatric disease treatment
12.	Centromedian nucleus (CM)	None, pain	None-recognised	Lesion for pain relief and also for treatment of movement disorders

Substance P is also present in this projection to the dorsal horn. The opiates have mu 1 and 2, delta 1 and 2 and kappa 1, 2 and 3 as receptors.[97] When cloning of opiate receptors was attempted, an orphan opioid like receptor (ORL) was deciphered. The agonist of this receptor was nociceptin and the antagonist was nocistatin. These are under investigation.[28]

The endogenous analgesic system:[60] This consists of the peri aqueductal grey (PAG), nucleus raphe magnus (NRM), parabrachial region, midbrain medullary RF, dorsal raphe nucleus, cuneiform nucleus, medial reticular formation, nucleus of trigeminal spinal tract and SGR; the first four being the most important. The pathway on receiving painful stimuli stimulates the release of endorphins which serve as pain modulators. Low intensity electric stimulation of the raphe nuclei cause analgesia mediated by norepinephrine and serotonin (5-HT). Analgesic action of the system of endogenous opioids is blocked by the depletion of 5-HT levels and NE.[23,29]

Towards the Understanding of Pain—Pain Models

The Biophysical Model of Pain

This states that pain behaviour is only the outermost manifestation of nociceptive inputs filled through each individual patient's pain perception and suffering.[55]

The Gate Control Theory of Pain

One of the functions attributed to the interneurons is that of a gate control system modulating the afferent input (Gate control theory of Melzack and Wall).[62] The theory was first stated in 1965 by Wall and Melzack and was then re-stated by Wall in 1978 and 1983 to embrace the criticism about the role of the SGR, extent of pre-synaptic inhibition in nociceptive afferents in the dorsal horn and the known fact of stimulus specificity of nerve fibres. Simply stated the theory runs thus—information about the presence of injury is transmitted to the CNS by peripheral nerves. Cutaneous small diameter fibres (A delta and C fibres) respond only to injury, while others with lower thresholds increase their discharge frequency if stimuli reach noxious thresholds. Cells in the spinal cord/trigeminal nucleus which are excited by these injury signals are also facilitated or inhibited by other nerve fibres which carry information about innocuous events. A descending control system originating in the brain modulates the excitability of cells which transmit information about the injury. The brain receives by way of the gate control system, injury signals, descending signals and other types of afferents.

The gate control theory was based on certain observations from experimental physiology. It was noted that, in cats, when the spinal cord was transected, neurons in lamina V responded to noxious stimuli which led one to speculate about a tonic inhibition of nociceptive responses in the spinal cord by a descending pathway.[96] Stimulation produced analgesia associated with (in animals) inhibition of nociceptive reflexes like the tail flick reflex (by intra-spinal neurons). Stimulation of analgesia producing brainstem loci selectively inhibits nociceptive response cells in the dorsal horn of the SC.[27] Monoamine receptor antagonists could antagonise this inhibition by bulbospinous monoaminergic pathways. Discrete lesions in the dorsolateral funiculus (DLPS) also inhibit the effects of SPA on behavioural response to pain.[5] The gate control theory has also been refuted by many who have questioned the overstated role of the SGR cells.[66,92]

This theory of gating, although modified later, is generally still applicable to many levels of the nervous system. The interneurons have an inhibitory effect on the afferent fibre terminals. This inhibition is increased by activity in the large diameter fibres and decreased by activity in the small diameter fibres. The balance of activity between the two sets of fibres influences the interneurons, to control the afferent input into the central nervous system. The descending pathways from the cortex and the brainstem also exert an inhibitory influence on the gate control system. Thus, the role of the interneurons is to help in the convergence, interaction and control of afferent influences. It is probable that such neural switches or gates exist all along the sensory system.[76] But for such control, the bombardment of the central nervous system by innumerable sensory stimuli will be intolerable.

"The busy line effect" wherein antidromic conduction interferes with the impulse propagation of noxious stimuli has also been implicated in the gate theory.[39]

The technical details of the gate control theory are as follows (Fig. 3):

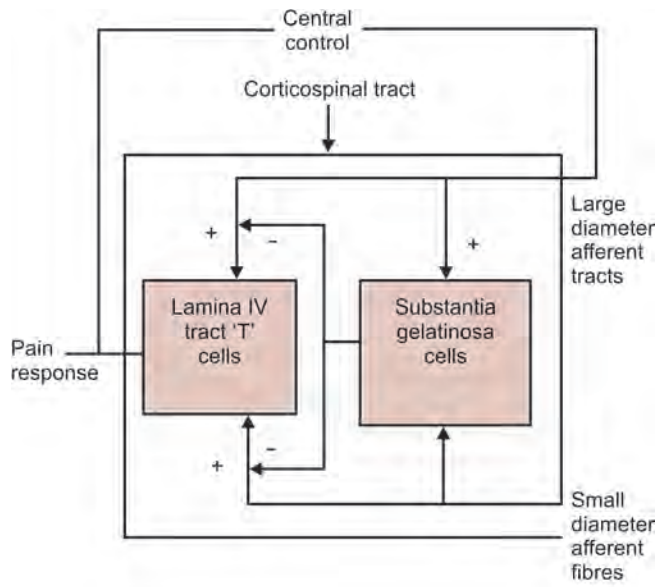


Fig. 3: Sensory gate control circuit (Melzack and Wall)

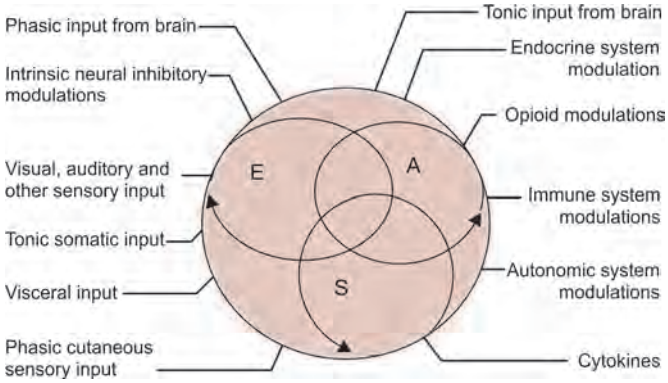


Fig. 4: The neuromatrix theory of pain

- Ongoing activity preceding a state is caused by tonic, slowly adapting fibres that tend to keep the gate open.
- Peripheral stimulation activates both small and large fibres. Discharge of large fibres will initially cause the tract cells (T cells) to fire by the direct route and then partly close the gate in Lamina II. This facilitates pre-synaptic inhibition.
- Balance between large and small fibre activation will determine the state of the gate. If the stimulus is prolonged, large fibres will adapt which will result in a relative increase in small fibre activity and cause the gate to open. The gate functions and there is an increase in T cell activity. However, if large fibre activity is increased by a proper stimulus (vibration) the gate will then close and the T cell activity will decrease.

Neuromatrix Theory of Pain[63]

Neuromatrix theory of pain (Fig. 4) states that the body-self neuromatrix comprises a widely distributed neural network that includes somatosensory, limbic and thalamic cortical components. There are 3 parallel networks which account for the dimensions of pain experience namely, S-sensory discriminative, A-affective motivational and E-evaluative-cognitive.

The synaptic architecture of the neuromatrix is determined by genetic and sensory influences. The neurosignatory output of the neuromatrix results in a pattern of nerve impulses of varying temporal and spatial dimensions and is produced by neural programs genetically built into the neuromatrix and which determines the quality and other properties of pain experience and behaviour. Multiple inputs that act on the neuromatrix programs and contribute to output neurosystems include:

- Sensory inputs from the somatic receptors
- Visual and other sensory inputs that influence cognitive interpretation of the situation
- Phasic and tonic cognitive and emotional inputs from other brain areas
- Intrinsic neural inhibitory modulation inherent in all brain function
- Activity of the body's stress regulation systems including cytological as well as endocrine, autonomic, immunologic and opioid systems.

CHRONIC PAIN SYNDROMES

While generally pain is beneficial as a warning to the organism, continuous and chronic pain with all its variations seems to serve no biological purpose. The onset and continuance of chronic pain appears to arise from the intrinsic complexity of the peripheral sensory and pain conducting systems, the peripheral nerves, the dorsal root ganglion, the dorsal horn, the ascending tracts and the higher brain centres. In chronic pain syndromes (CPS), the complaints are usually stated in affected terms like—excruciating, throbbing, stabbing, etc. and have no dermatomal pattern.

Pain in Peripheral Nerve Lesions

In peripheral nerve injuries, long-lasting discharges occur in the small sensory fibres and not in the large sensory or motor fibres.[1] It was suggested that cross connections between sensory and motor fibres in an injured nerve (ephaptic transmission) leads to perpetuation of pain as seen in causalgia. Further work has not confirmed the presence of such connections either by light or electron microscopy.[65,88] The persisting pain has been attributed to the possible formation of small injury neuromas inside the nerve,[79] where the axonal sprouts are sensitive to physical and chemical stimulation. Spontaneous and evoked afferent activity has been noted from the affected area. Adrenergic receptors have been shown to develop on the axonal sprouts at the site of the injury. While catecholamines increase the afferent activity, local anaesthetics abolish these. Even in minor localised injuries, it has been suggested that focal demyelination may lead to spontaneous impulse generation and mechanical sensitivity.[17] This abnormal physiology gets reflected also in DRG cells. Microneurography studies in humans have confirmed that mechanical sensiti vity and ectopic discharges occur at the sites of nerve damage.[69] Neurotrophins, Protein Kinase-C, 5-HT and NO are involved in neuropathic pain.

During regeneration after nerve injury, recovery is only partial even after carefully performed surgery. The patients often suffer from paraesthesiae in the affected part, and also spontaneous pain, allodynia and hyperpathia. These abnormal sensory phenomena arise from many factors. The possibilities are: 1) conduction in sensitive fibres that have not yet made a receptor connection in the periphery, 2) death of DRG cells affecting the larger cells more than the smaller cells and increasing small fibre input into the cord, 3) functional connection between fibres serving high threshold and low threshold receptors and 4) impaired inhibition in the spinal cord.[20,54,62,79]

Root pain: Root pains are referred to discrete areas, can be intense and usually there is no sensory loss. Pressure

on the posterior nerve roots often causes changes in the DRG, because of its close proximity to the affected area and cell death can occur in the DRG. Prolonged pressure causes demyelination in the nerve roots leading to ectopic discharges and mechanosensibility. In long standing cases, the radiating pain may disappear leaving an area of sensory loss with hyperaesthesia or hyperalgesia.

Post-herpetic neuralgia is a painful syndrome characterised by anaesthesia, paraesthesia, hyperpathia and allodynia in the affected area. The virus of herpes zoster causes damage to the peripheral nerve, the DRG, the dorsal root and the dorsal columns.[22]

Cerebral Areas for Pain Perception

Cerebral discrimination and assessment of all varieties of sensations including pain is essential for highly deve loped organisms, especially man, so that the response may be adequate and appropriate. This is a function shared by many areas of the cortex. Cephalad to the thalamus, the impression of pain sensation is carried by multiple pathways to the sensorimotor cortex, the parietal lobe, the limbic system and the temporal and frontal lobes. These areas are concerned with the appreciation and assessment of pain, including the memory of pain, its significance and the reaction to the pain. Ablation of these areas does not produce objective impairment of pain or of touch sensation. The parts of the cerebral hemispheres concerned with the sensation of pain have been mapped out by various physiologists. Foerster,[25] in 1927, was one of the earliest to study the effects of electrical stimulation of the sensory areas of the cerebral cortex. Penfield and Boldrey,[73] found that on stimulation of the cortex, the subjects felt paraesthesia instead of pain. The cortical areas concerned have been studied by eliciting evoked potentials. These studies show that there is basically a fixed pattern of cortical representation but this often becomes labile during stimulation, reflecting the great plasticity of sensory representation at the cortical level.

Fibres from the posteroventral nucleus of the thalamus proceed to the sensorimotor cortex. Although the majority ends in the post-Rolandic sensory area, many of them can be traced to the motor strip also. The sensory cortex is concerned with the primary appreciation of sensation. Lesions in this area which include the parietal lobe may cause spontaneous hemibody pain and dysaesthesia which may be indistinguishable from thalamic pain except for its paroxysmal nature, resembling an epileptic discharge. Its pathogenesis is dependent on complex paleothalamic interrelationships.[78]

In addition to the direct thalamocortical sensory fibres, many fibres concerned with sensation travel to the parietal operculum to end in the second sensory area. The second somatic sensory area[10,74] situated near the parietal operculum is the most primitive area for appreciation of pain from the phylogenetic point of view. It is to this area that the unmyelinated fibres ultimately project. The other complex routes for pain assessment are to the limbic system, to the temporal lobes (for memory storage and comparison) and to the frontal lobes (for final assessment and judgement) and back to the limbic system, viz. the claustrum, the amygdala and the orbital cortex (for emotional colouring). The connections to the limbic system are important as they are involved in the motivational and affective determinants of pain.[19]

Mechanisms of Central Pain[4,70]

- Selective destruction of neo-STT
- Irritation of the sensory pathways
- Irritation of sympathetic pathways
- Hypothalamic disturbances
- Loss of nociceptive inhibitory influences
- Activation of secondary pathways
- Activation of non-specific pathways related to the paleospinothalamic system
- Abnormal findings of de-afferenation
- Hyperactivity in de-afferenated reticulo-thalamic pathway.

Thalamic Pain Syndromes (Dejerine and Roussy)

The following are the various types of thalamic pain syndromes which have been described in Table 5.[2]

Congenital Indifference to Pain (Pain Asymbolia)

This condition is a good model for study of the mechanism of pain appreciation. The disorder, a definite clinical entity, differs from insensitivity to pain resulting from drugs, surgical pain relieving procedures or hysteria. The patient perceives the painful stimulus, but this is not accompanied by discomfort or suffering. Careful anatomical studies of the nervous system of such individuals have not shown any specific abnormality. Magee[56] reported a decrease in the number of

Table 5: Thalamic pain syndromes

Type	*Central pain*	*Vibration, touch and joint sensations*	*Pain and temperature sensations*	*Somatosensory evoked potentials (SSEP)*
I (analgetic)	Absent	Lost	Lost	Absent
II	Present	Lost	Present	Absent
III	Present	Present	Present	Decreased
IV (pure algetic type)	Present	Present	Present	Normal

myelinated fibres, whether this finding has any direct significance to the problem of congenital indifference to pain is uncertain. The demonstration of a localised anatomical lesion in such cases will prove to be a great advance in the surgery of pain, as it may then be possible to place a small stereotaxic lesion in the concerned area which will relieve the patient of the unpleasantness of pain without altering his personality. Osuntokun et al.[71] reported the occurrence of congenital indifference to pain associated with auditory imperception in two siblings. They support the suggestion made by Boyd and Nie,[14] that there may not be any specific underlying defect in pain asymbolia which may be dependent upon lack of established cerebral dominance.

Congenital analgesia may occur as a developmental defect and may be associated with anhydrosis, vasomotor instability and hyporeflexia. A defect in neural crest differentiation has been suggested as the underlying embryonic abnormality.[15]

Summary of Physiological Principles

The physiological principles on which surgical procedures for pain relief are based are:

- Pain is a sensory modality
- It has definite pathways of conduction in the spinal cord and the brain with definite neurochemical basis
- The mechanisms of pain conduction and perception are different from pain appreciation, the latter being confined to the higher brain levels.

Physiology of pain has come a long way from the "doctrine of specific nerve energies" of Muller in the 1830s to the law of specific projection. The Weber-Fechner law states that the magnitude of any sensation felt is proportional to the log of the stimulus intensity. There are also two types of pain; an initial fast/mild pain mediated by A delta fibres through glutamate and a slow secondary pain mediated by substance P through C fibre endings.[28]

Knowledge accumulated from recent neurophysiological studies in animals and in man tends to suggest that the above orthodox concepts are too simple. The current efforts in research on pain have highlighted the following facts which need careful consideration:

Definition and assessment: The idea of "pain" itself requires better definition and better classification with a more objective assessment. This sensation of pain, "discomfort", "ache" and so on needs to be differentiated into various subgroups with properly assessed significance, e.g. metaesthesia, algaesthesia, paraesthesia and anaesthesia.

The Periphery: a) The specific end organs do not need necessarily to have special functions, b) it is not always possible to relate specific fibres to certain modalities of sensation. No particular fibre type is exclusively related to any particular class of stimulus, c) the unmyelinated fibre network in the skin may carry sensations other than pain, d) being a network, a single stimulus in this system will activate a number of fibres.

In the spinal cord: The spinothalamic tract is not a bundle of fibres which arises from one group of nerve cells and ends in another distant group. Although admittedly there are large numbers of long fibres in the spinothalamic tract, the majority of them is short fibres with multiple synapses and forms a multisynaptic afferent system.[68] This system has an inbuilt capacity for temporal and spatial summation as well as for inhibition. This arrangement of the fibre system would also imply that even a well planned section of the spinothalamic tract does not necessarily cut off permanently all the pathways of pain in the spinal cord.

In the brain: All fibres of the spinothalamic tract do not reach the thalamus, but the majority of them proceed bilaterally to various cell groups in the medulla and the brainstem and communicate with the reticular system. Stimuli conducted both by the large and small fibre systems come into the mesencephalic tegmentum and stimuli intense enough to be noxious are summated into a prolonged central response. In the thalamus, there is more than one area concerned with pain, with the neospinothalamic tract going to the posterior regions, while the old fibre system reaches the interlaminar nuclei, including the centrum median nucleus and the nucleus parafascicularis.

The response of the central nervous system to any noxious stimulus is modified by numerous central and peripheral influences on the neuronal pool of which the spinothalamic tract forms a part. The perception of pain is associated with reverberations and feedback among these cell groups.

Inhibition: Neurons have been seen to receive myelinated as well as unmyelinated fibres at the secondary sensory neuronal level. Stimulation of one group of fibres might selectively inhibit the passage of impulses along another pathway. This is seen when stimulation of one area of the brain selectively inhibits impulses in other pathways and this may also be a possible explanation for yogic control of pain and acupuncture analgesia.

Experimental stimulation of some areas of the brain (the caudate nucleus, septal, preoptic region or medial geniculate) raises the threshold of pain, while stimulation of other areas may reduce the threshold (central tegmental tract, ventral posteromedial nuclear group in the thalamus or the periaqueductal grey).[80] These studies confirm the already well-known experience of pain being suppressed in some extreme situations of pleasure or excitement only to become evident a little later.

These facts help to explain the successes and failures of neurosurgery for pain. By and large, the surgical procedures based on the presently accepted "orthodox" knowledge do give benefit and have proved their usefulness in the large majority of cases.

The above physiological considerations suggest the following mechanisms of chronic pain:[48]

Physiological Classification of Pain[91]

- Stimulation of peripheral nociceptors (e.g. Carcinomatous deposits in the long bones)
- Direct stimulation of nerve trunks, plexi and roots (e.g. Carcinoma in the L-S plexus)
- Impulses related to neural injury (neuropathic pain/sciatica)
- Central re-organisation pain (allodynia, hyperpathia, peripheral neuropathy, sympathetically mediated pain).

A special type of pain is "mirror pain" seen post-cordotomy, occasionally due to unmasking of cord pathways subserving pain.

Mechanisms of Chronic Pain

1. Nociceptive
   a. Somatic
   b. Visceral
2. Neuropathic
   a. Deafferentation
   b. Peripheral
3. Sympathetic
4. Psychogenic
   a. Without a coexisting organic lesion
   b. With an organic lesion.

CHRONIC REGIONAL PAIN SYNDROME

Chronic regional pain syndrome (CRPS) was first described by Paget in 1862. The syndrome was re-defined in 1995.

There are three types (*Stanton Hues, 'International Association for the study of Pain –IASP 1995*):

Chronic regional pain syndrome (Type I) (Reflex sympathetic dystrophy):

The features are as follows:

- The syndrome develops after an initial noxious event
- Spontaneous pain/allodynia/hyperalgesia not limited to the territory of a single peripheral nerve and is disproportionate to the exciting event
- There is evidence of oedema/shiny skin and abnormal blood flow with abnormal sudomotor activity in the region of the inciting event
- Exclusion of any condition that would account for the above dysfunction.

Chronic regional pain syndrome type II (Causalgia)

- This develops after a nerve injury
- Spontaneous pain/allodynia/hyperalgesia occurs and is not necessarily limited to the territory of the injured nerve
- There is evidence of oedema/shiny skin and abnormal blood flow with abnormal sudomotor activity in the region of the inciting event
- Exclusion of any condition that would account for the above dysfunction.

There are three stages in causalgia:

- Pain/oedema and wasting
- Cold skin with trophic changes
- Atrophy.

Chronic regional pain syndrome type III: Not Otherwise Specified

Pathophysiology of Chronic Regional Pain Syndrome

There are several theories of CRPS:

- Vicious circle of Leriche (1939) and Livingstone in 1943.
- Walker and Nielsen (1948) attributed the pain due to action of the sympathetic nervous system. Patients undergoing pregnancy sympathectomy had electrodes placed along the sympathetic chain. Activation of the sympathetic ganglia post-operatively blocked the pain. This was confirmed by White and Sweet in 1969.
- Pain in CRPS is relieved by local anaesthetic sympathetic blockade/sympatholytic procedure like the regional application of guanethidine/IV phentolamine.
- Pain may re-initiate/exacerbate by the application of an alpha adrenoceptor agonist, either iontophoretically or by injection of a limb with pain and hyperalgesia.
- Guanethidine elicits pain when injected IV in the affected extremities. Represents a response to NE released from the post-ganglionic tissue.

Coupling of sympathetic afferents and efferents results in abnormal afferent impulses generated by the sympathetic nervous system. This explains why RSD is abolished by sympathetic block.

The following explains the mechanism of this coupling:

- Direct chemical coupling between NE terminals and primary afferents through an alpha 2 receptor that produces excitation/sensitisation of afferent fibres
- Coupling occurs in traumatised neurons (no experimental proof exists)
- Coupling in DRG to large diameter afferent fibres and possibly unmyelinated fibres
- Indirect coupling in microvascular beds/non-neural cells proximate to afferent receptors (hypothetical)
- Indirect coupling with post-ganglionic NE axon terminals serving as mediators in the sensitivity of nociceptive afferents (involving NE and others like prostaglandins)
- Ephaptic coupling between sympathetic and afferent fibres.[43]

Diagnostic Criteria for Chronic Regional Pain Syndrome

Clinical Signs and Symptoms

- Burning pain
- Hyperpathia/allodynia
- Temperature or colour changes
- Oedema
- Hair changes/nail changes.

Lab Results

- Thermometry/thermography
- Bone radiography
- Three phase bone scan
- Quantitative sweat test
- Response to sympathetic blockade.

Interpretation

- More than 6 points present—probable RSD
- 3–5 points present—Possible RSD
- Less than 3 points present—Unlikely to be RSD.

Table 6: RSD probability scoring system

Parameter	*Definitive RSD*	*Probable RSD*	*Possible RSD*	*Not RSD SMP*
A. Allodynia • Touch (a) • Pressure (b) • Movement (c)	3/3	2/3	1/3	0/3
B. Vasomotor • History • Examination Swelling: • History (a) • Examination (b)	4/4	Greater than or equal to 2/4	Less than or equal to 1/4	0/4

Scores

- 7–definitive RSD
- 4–6-probable RSD
- 2–3-possible RSD
- 0-not RSD.

Clinical Correlates in Pain

The symptomatology of pain is easily remembered by the mnemonic "PQRST" wherein P, Q, R, S and T stand for palliative/provocative factors, quality of pain (burning, shooting or stabbing), radiation of pain, spatial distribution and temporal aspect, respectively.

The definitions of certain terms used in pain are as follows:[18]

- *Allodynia*: Increased sensibility to pain, pain in response to a stimulus which is not normally painful.
- *Alloaesthesia*: Perception of a sensory stimulus at a site other than where it was delivered. Kinetic alloaesthesia is feeling something other than at the site of stimulation.
- *Analgesia (alganaesthesia)*: Abnormal sensitivity to pain.
- *Anaesthesia*: Absence of all sensations.
- *Dysaesthesia*: Unpleasant/painfully abnormal perverted sensation—spontaneously or caused by normally non-painful stimuli, e.g.: burning response to touch, other accompanying paraesthesiae.
- *Hypalgesia*: Decrease in pain sensibility.
- *Hyperalgesia*: Increase in pain sensibility or pain in response to a stimulus not normally painful.
- *Paraesthesiae*: Abnormal spontaneous sensations experienced in the absence of specific stimulation (feelings of hot, cold, numbness, burning, itching, etc.).

Hyperalgesia

There are two types of hyperalgesia. Primary at the site of injury and is due to mechanical and thermal stimuli. The injured area and the test stimulation area must coincide. Secondary hyperalgesia occurs in the areas surrounding the injury site and therefore, does not coincide with the site of stimulus.[64,102] Primary hyperalgesia results from sensitisation of peripheral nociceptors (leftward shift of stimulus response function) and is characterised by decreased threshold, augmented responses to suprathreshold stimuli and ongoing spontaneous activity. Primary hyperalgesia can be further divided into mechanical and thermal hyperalgesia: mechanical hyperalgesia comprises stroking hyperalgesia (allodynia) and punctuate hyperalgesia (tested with von Frey's probes). Hyperalgesia also occurs due to loss of central inhibition. NGF is involved in inflammatory hyperalgesia and BDNF is involved in alleviated hyperalgesia.[2]

Secondary hyperalgesia: This occurs in the area surrounding the primary zone. Enhanced pain response occurs only in response to mechanical stimulation. Spreading sensitivity occurs with secondary hyperalgesia, predominantly by the release of substance P. Secondary hyperalgesia differs from flare, in that it is larger than the zone of flare and does not cross the anatomical midline. Flare can occur without induction of hyperalgesia. Peripheral sensitisation does not occur with secondary hyperalgesia.

Grading of Pain

There is an old Portuguese proverb which runs thus; "*The wearer knows best where the shoe hurts*." In no other field of medicine other than pain is this true. The results have to be quantified and the outcomes scored only on the basis of the patient's assessment of his condition. To quantify pain, several scales have been developed which are enumerated below:

Unidimensional scales (Verbal rating scale): This rates pain as none, mild, moderate, severe.

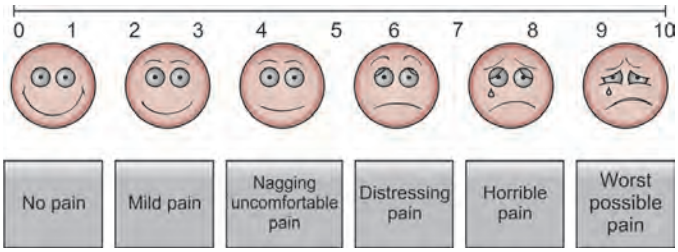


Fig. 5: Visual analogue scale for pain

Visual analogue scale (VAS): Continuous/intermittent pain. This is a 10 cm unmarked line where the pain is graded from:—no pain to worst pain (Fig. 5).

Colour red analogue: This includes a pictographic representation of the patient's emotional state of mind in relation to the pain.

Berman, Tagg et al. (1996) put forth a system of pain grading to standardise quantification of pain:[8]

Severe: Continuous disturbance of daily life or of work or study/sleep. (Visual analogue scale 9–10).

Significant: The patient is able to sleep but he cannot work/study/engage in hobbies due to pain (VAS 7–8).

Moderate: The patient is able to work; sometimes severe pain which results in the patient taking time off (VAS 4–7).

Mild: Patient aware of pain but can pursue a normal life (VAS 0–3).

Psychological Issues in Pain Management

"Each person carries his own doctor inside him. They come to us not knowing the Truth. We are our best when we give the doctor who resides within each patient a chance to go to work."

Dr Albert Schweitzer

Nowhere in medicine do the afore-quoted words ring more true than in the management of pain. Pain is intricately connected with the limbic system and is influenced by the mental state of the patient. Understanding the patient's personality and mental make-up will go a long way in helping us treat our patients.

Several personality disorders have been noticed in patients with chronic pain.[82] These are:

- Narcissistic and histrionic personality disorders
- Depressive personality disorder
- Compulsive personality disorder
- Borderline personality disorder.

The following are the indications for a psychological consultation in clinical practice, while treating a patient with chronic pain.[21] These are:

- Diagnosis and clinical signs do not fit with each other
- Three or more Waddell signs (vide infra)
- Markedly unusual reaction with or without medicine or treatment
- Emotional instability
- Personality crisis
- Suspicion of poor/inadequate/inappropriate coping, fears, beliefs, distress, expectation and/or attitude.

Waddell, et al.[95] in 1980 described five categories of signs to define the non-organic component of pain:

- *Tenderness tests*: Superficial and diffuse tenderness and/or non-anatomic tenderness
- *Simulation tests*: These are based on movements which produce pain, without actually causing that movement, such as axial loading and pain on simulated rotation
- *Distraction tests*: Positive tests are rechecked when the patient's attention is distracted, such as a straight leg raise test
- *Regional disturbances*: Regional weakness or sensory changes which deviate from accepted neuroanatomy
- *Overreaction*: Subjective signs regarding the patient's demeanor and reaction to testing.

Three or more of the above signs are positively correlated with non-organic pain.

Psychological tests and questionnaires in the assessment of chronic pain:

Function	*Examples*
1. Pain (qualitative)	McGill pain questionnaire, Numerical rating scale, Visual analogue scale, Verbal rating scale, Pain diaries, North American Spinal Society questionnaire.
2. Mood and personality overall function	Minnesota multiphasic Personality inventory 2 (MMPI 2), Beck depression inventory, Illinois behavioural questionnaire (IBQ), Personality assessment inventory (PAI).
3. Pain beliefs and coping	Multidimensional pain inventory: Coping strategy questionnaire, pain relief efficacy ruestionnaire, Pain self-efficacy questionnaire, Survey of pain attributes; Sickness impact profile (SIP).
4. Level of function/ Perception of disability	Multidimensional pain inventory, Oswestry disability questionnaire, Sickness impact profile, Short Form Health Survey (SF-36), Pain disability index, Roland-Morris disability scale.
5. Cognitive function	MMSE, Microcognitive neuropsychological tests

Risk factors for poor surgical outcome identification in presurgical psychological screening interviews:[12]

Risk factor	*Risk of treatment failure*
• Pending legal action related to injury	high risk

- Worker's compensation — high risk
- Job dissatisfaction (Moderate/extensive) — moderate/high risk
- Heavy job demands (frequent lifting of > 50 pounds) — high risk
- Substance abuse:
  - Pre-injury — moderate risk
  - Current/untreated — high risk
- Reinforcement of disability by family — moderate to high risk
- Marital dissatisfaction — moderate risk
- Physical/sexual abuse
  - Pre-injury — moderate risk
  - Current — high risk
- Pre-injury psychological problems
  - Out patient department — moderate risk
  - In-patient — high risk

Predictors of poor outcome in the management of chronic pain:[67]

These were initially listed as contradictions to spinal stimulation but can be used in a wider perspective. They are:

- Active psychosis
- Active suicidality
- Active homicidality
- Untreated depression major
- Somatisation disorder
- Alcohol/drug dependency
- Compensation resolution
- Lack of social support
- Cognitive deficits.

Cognitive behavioural therapy may produce benefits by decreasing peripheral nociceptive activity, enhancing descending inhibition of pain transmission or directly altering pain transmission in the CNS.

Alternative and Complementary Treatment in Pain

> *"For all the happiness mankind can gain,*
> *Is not in pleasure, but in rest from pain."*
>
> ***Dryden***

To achieve pain relief, man has turned to all sources for a remedy. Western science in the early days scoffed at the traditional wisdom of the orient. The approach to health in the orient is holistic. The dawn of the 21st century has seen a renewed interest in these traditional systems. Many of these concepts are now being tested with the solid scientific and reasoning methods which modern science has to offer and have proved their worth. Now, every textbook in the field of modern medicine has a separate section dedicated to these alternative therapies. The American Academy of Neurologists also recommends some of these as treatment options in chronic pain.

"To believe with certainty, we must begin by doubting" remarked King Stanlislos I of Poland and nowhere has this been proved to be more true than in the treatment of pain in medicine.

The following is a brief synopsis of these alternative treatments. The reader is advised to refer to standard books on the subject for further reading:

Acupuncture:[99] Acupuncture is based primarily on traditional Chinese medicine which is derived from the Taoist philosophy that the human body is in a state of dynamic interaction with nature—the environment/universe which in turn is in a state of continuous change. Changes arise from an inherent dynamism of cyclical patterns and are constant. "Huang Di Nei Ying" or the "Yellow emperor's inner classic" is the Bible of Chinese medicine. There are 12 major and two collateral meridians with intermediate nomenclatures. Classic acupuncture points usually are situated at points of low resistance to electricity. They are found near major nerve bundles. There are different types of needles in acupuncture, each stimulating a particular opioid receptor type. Studies have shown acupuncture is akin to PAG stimulation and causes release of endorphins.[44,58]

There are other types of acupuncture such as, auricular acupuncture developed by Dr Paul Nogin of France and the *Koryo hand therapy* wherein the pressure points are applied to describe points on the pinna and the palm, respectively, each having its own homunculus.

QiGong

Qi in traditional Chinese medicine is described as the vital energy that protects and nourishes organs. QiGong is the science that ensures the normal flow of Qi. Studies have shown that QiGong for intervertebral discs stimulate the autonomic nervous system and cause pain relief.

Tai-Chi

It is a set of slow, free flowing exercises useful in pain prevention. It was founded by Bodhidharma.

Traditional Indian Systems of Medicine[100]

Ayurveda is holistic medicine and aims at prevention. The system of Yoga teaches about *Nadis* which are akin to nerve plexi. The pranayama (breath control) of yoga aids in stress relief. The concepts of energy flow from the tail through the spine (*Sushumma*), together with coiled and intertwined energy channels (*Ida* and *Pingala*) are described in great detail. The points of intersection of these energy channels are called *chakras*. Pingala stimulates the sympathetic nervous system and Ida stimulates the parasympathetic nervous system. The concept of the spinal gate mechanism was known and was extensively used.

Biostimulation

Laser biostimulation is based on the fact that light stimulates pain at low frequency and inhibits pain at high frequencies.

Magnetic biostimulation is based on the principle that a magnetic field through ions would generate

heat (Hall effect) and this heat would then generate an action potential (Lorentz force). The WHO has recently approved the use of 2 Tesla magnets for this purpose.

Other forms of treatment such as *chiropractice* (mobilisation and manipulation) of painful joints and *aroma therapy* have also been used in the treatment of chronic pain.

Multidisciplinary Approach to the Management of Chronic Pain

As seen above, when dealing with a subject as complex as pain, it would be wise to use all available treatment modalities based on proven scientific principles, rather than be prejudiced against any of them. The complexity of the issue has led doctors to coin the term "multidisciplinary approach to pain management". The organisation of such a team approach has been outlined by Rawl:[77]

Truly, the subject of pain which has been perceived with awe and dread by humans since time immemorial is still an enigma to us. It is intricately connected with behaviour and represents one of the last frontiers which neuroscience has to conquer.

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195 Surgery for Intractable Pain

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TREATMENT

Intractable pain of multiple aetiologies remains a substantial problem for many patients presenting in the clinical setting. Recent years have seen the introduction of powerful pain relieving drugs and their use has been extended to chronic pain syndromes where the cause of the pain cannot be eliminated. Treatment of chronic intractable pain needs a multidisciplinary approach. With the advent of newer analgesic and antidepressant drugs, the first line of treatment is medical. If the pain is not ameliorated with these drugs, anaesthetic procedures to block the pain pathways or neuroaugmentative or neuroabalative procedures can be offered.

DRUGS

At present there are no drugs which effectively ameliorate the chronic pain of non-cancerous origin. Improved pain relief can be achieved and adverse effects minimised by multimodal analgesic combinations. Substantial evidence supports combining analgesics for the management of pain and, in some instances, they have a heterogeneous pharmacologic sparing effect. Fixed-dose combination analgesics with demonstrated efficacy and safety are useful for pain management. One also has to take care of anxiety and depression which are common in these patients.

Non-Narcotic Analgesic Drugs

Acetaminophen (Official Generic Name: Paracetamol)

It is an antipyretic analgesic with no effect on the platelet function or inflammatory cascade. It acts centrally, inhibiting prostaglandin function.[11] Due to its lack of significant inhibition of peripheral cyclo-oxygenase (COX), it does not promote bleeding, thus making it safe to use in the peri-operative period. Taken within the prescribed dose range, it is safe. The main safety concern is dose-related hepatic toxicity. Overdose is treated with N-acetylcystine.[87]

Salicylates

Aspirin is an antipyretic, anti-inflammatory, analgesic agent. It is quite effective and its action may be central, blocking prostaglandin synthesis. It is the prototypical non-steroidal anti-inflammatory drug (NSAID), being a non-selective COX inhibitor at usual analgesic doses, although it may somewhat selectively inhibit COX-1 at doses typically used to reduce platelet aggregation therapeutically.[130] It is used in a dosage of 500–1000 mg/q 4–6 hourly, with a maximum daily dose of less than 4,000 mg. Gastrointestinal side effects are common. It predisposes to haemorrhage even in low doses; while gastrointestinal bleed is common, intracranial haemorrhage is well documented.

Non-Steroidal Anti-inflammatory Drugs

These types of non-opioid analgesics are frequently used as first-line analgesics. They lack significant abuse potential and do not induce the development of analgesic tolerance. These drugs act by inhibiting the biosynthesis of prostaglandins at various stages, through inhibition of the COX enzymes, thus reducing the inflammatory process. There are two similar, but distinct, isoforms of COX identified: (1) COX-1 and (2) COX-2. Several drugs are now available that selectively, more accurately and preferentially inhibit COX-2, which is responsible for inflammatory processes and pain relief. They too have side effects on the gastrointestinal system.[55] The commonly used drugs are indomethacin (25–50 mg/q 8 hrs), diclofenac (50 mg/q 6 hrs), ibuprofen (200–400 mg/q 4–6 hrs) and naproxen (250 mg/q 6 hrs). Their use depends on their being tolerated by the patient. The COX-2 selective non-steroidal anti-inflammatory drugs are etodolac, meloxicam, celecoxib, rofecoxib, etoricoxib, valdecoxib and lumiracoxib.

Phenothiazines

Phenothiazines block dopamine and epinephrine postsynaptically and have a strong atropine like action. Commonly used phenothiazines are chlorpromazine 50 mg/q 8 hourly, thioridazine 50 mg/q 8 hourly and fluphenazine 2 mg/q 12 hourly. Combinations of tricyclic drugs, which are mood elevators, with phenothiazines have been found to be useful in the management of postherpetic neuralgia and intractable cancer pain.[55]

Phenytoin

Phenytoin has a direct effect on both axonal conduction and synaptic transmission.[44,150,169-171] It is found useful in many pain syndromes such as trigeminal neuralgia,

post-herpetic neuralgia,[51] glossopharyngeal neuralgia[123] and diabetic neuropathy.[29]

Carbamazepine

It may act at the level of central synapses.[38] It is found effective in treating patients with trigeminal neuralgia and some forms of neuropathic pain.[139] It is effective at serum levels between 8 μmg/ml and 12 μmg/ml. The dosages of these drugs have to be individualised for effective response.

Oxcarbazepine

Oxcarbazepine is the 10-keto analogue of carbamazepine, but has a distinct pharmacokinetic profile. In contrast to the oxidative metabolism of carbamazepine, oxcarbazepine is rapidly reduced to its active metabolite, 10,11-dihydro-10-hydroxy-carbamazepine. Direct comparison of oxcarbazepine and carbamazepine has shown no difference in efficacy between these two agents in terms of reducing seizure frequency in patients with partial epilepsy with or without secondary generalisation, or with tonic-clonic seizures. Limited data indicate that oxcarbazepine may be a useful alternative to carbamazepine in the management of trigeminal neuralgia.[46] Zakrzewska et al. found an overall serum therapeutic concentration range of 50–110 mumol/l of 10-OH-carbazepine corresponding to a daily effective dose range of 1200–2400 mg (14.6–35.6 mg/kg body weight) oxcarbazepine. Onset of the effect was observed within 24 hours in all cases.[177]

Gabapentin

Gabapentin resembles gamma-aminobutyric acid (GABA), and was initially marketed as an adjunctive anticonvulsant. However, it was found to be an effective analgesic for conditions where neuropathic pain was a significant contributor, such as post-herpetic neuralgia.[119] Its advantages are that it is not metabolised, so there is no concern regarding accumulation of active metabolites. Gabapentin is not a GABA agonist, nor is it metabolised into GABA. It is cleared renally, and needs to be used cautiously in the presence of renal dysfunction. Gabapentin absorption is mediated by a saturable transporter system located in the upper gastrointestinal tract, indicating a short window of absorption. It has a dose dependent oral bioavailability. A dose of 400 mg is approximately 25% less bioavailable than of a dose of 100 mg. Above 800 mg per dose, there is little additional absorption of gabapentin. The recommended maximum daily dose is approximately 3,600 mg.

Benzodiazepines

They increase both pre- and post-synaptic inhibition. The effect appears to be caused by facilitation of the inhibitory neurotransmitter GABA.[85] Clonazepam is effective in the management of chronic neuropathic pain and in patients with nerve or plexus injury.[110,151] The commonly used benzodiazepines are diazepam, alprazolam, chlordiazepoxide and flurazepam.

Tricyclic Antidepressants

They probably act by facilitation of monoamine transmission by inhibition of serotonin and norepinephrine reuptake at the synapse. They may also potentiate the descending analgesic pathways. They are effective in neuropathic pain, especially post-herpetic neuralgia and diabetic neuropathy.[154,159] They also inhibit the encephalin hydrolyzing activity, thus increasing the level of encephalin in the CNS.[63] The commonly used tricyclic antidepressants are amitriptyline (75–300 mg/day), imipramine (150–300 mg/day) and doxepin (150–300 mg/day).

Pregabalin

Pregabalin is a potent ligand for the alpha-2-delta subunit of voltage-gated calcium channels in the central nervous system that exhibits potent anticonvulsant, analgesic and anxiolytic activity in a range of animal models. Pregabalin has been advocated for the treatment of neuropathic pain associated with diabetic peripheral neuropathy and post-herpetic neuralgia. Most patients with chronic lumbosacral radiculopathy have also been found to respond well to pregabalin therapy. Pregabalin is rapidly absorbed following oral administration, with peak plasma concentrations occurring between 0.7 hour and 1.3 hours. Pregabalin oral bioavailability is approximately 90% and is independent of dose and frequency of administration. Food reduces the rate of pregabalin absorption, resulting in lower and delayed maximum plasma concentrations. However, the extent of drug absorption is unaffected, suggesting that pregabalin may be administered without regard to meals. Pregabalin elimination half-life is approximately 6 hours and steady state is achieved within 1–2 days of repeated administration. Corrected for oral bioavailability, pregabalin plasma clearance is essentially equivalent to renal clearance, indicating it undergoes negligible non-renal elimination. Pregabalin is eliminated renally; thereby renal function affects its pharmacokinetics. It is not subject to hepatic metabolism and does not induce or inhibit liver enzymes such as the cytochrome P450 system. An effective starting dose of 150 mg/day is advocated in clinical practice.[16]

Narcotics

Narcotics should be reserved only for the management of chronic pain due to cancer.[68,160,161] Patients usually develop tolerance and may require increasingly higher doses. If a narcotic is used for non-malignant pain it should be for short periods only. Morphine, codeine and thebaine are naturally occurring opioids isolated from opium poppy. Fentanyl, meperidine and methadone are synthetic opioids. Oxycodone, hydromorphone and hydrocodone are semisynthetic opioids made by chemically modifying thebaine.

Opioids in Cancer Pain

About 70% of patients with advanced cancer experience moderate to severe pain, necessitating the use of opioid medication for pain relief. According to the WHO in 1986, the worldwide daily cancer pain prevalence is a staggering 4 million patients and the yearly worldwide prevalanec is 19 million patients. Effective analgesia can be achieved in 70–80% of these patients with opioid adjuvant medications. Opioids are the main stay in the treatment of moderate to severe cancer pain of all causes. The WHO advocates the following three step approaches:

Step 1 for mild pain involves 24 hour coverage with acetaminophen or NSAID medication. When these medications fail to provide adequate analgesia or when pain is moderate at onset, a "weak" opioid, such as codeine or oxycodone, is appropriate (step 2). A strong opioid (step 3) is indicated for the patient in whom relief of pain is inadequate with step 1 or 2 or when the pain is severe at onset. Some of the common drugs used in step 3 are morphine, hydromorphine, levorphanol tartarate, methadone hydrochloride and fentanyl.

To begin with, the oral route is preferred because of the ease of administration and good oral bioavailability of most opioids. Orally administrated morphine sulfate immediate release (MSIR) is generally considered the first-line drug in severe cancer pain. Treatment generally begins with a low dose. Mean starting doses of MSIR are 10–30 mgm 4 hourly throughout the day and night. "As needed" dosing is inappropriate and should be avoided and a constant plasma level required for good analgesia is achieved by 'round the clock' administration. There is no "standard" opioid dose and therapy should be highly individualised and dose titrated until analgesia is achieved or side effects are unmanageable.

Adverse effects of opioids include sedation, nausea, constipation, respiratory depression or myoclonus. Generally no narcotic is universally better or worse with respect to others. Most opioid side effects are manageable. Constipation, to which tolerance rarely develops, is avoided by the use of stool softeners or bowel stimulation.

Tolerance to respiratory depression develops rapidly. Severe respiratory depression may necessitate mechanical ventilation and the use of the opioid antagonist naloxone hydrochloride. Tolerance also develops to opioid induced sedation but, if it is incomplete, a trial of a stimulant like methylphenidate hydrochloride or dextroamphitamine 5 gm. bd may be used.

Nausea during opioid administration may be produced by different mechanisms. Nausea due to direct stimulation of the chemoreceptor trigger zone of the medulla occurs constantly is unrelated to food intake and is best relieved by a phenothiazine. Nausea which is worse after eating is due to reduced gastric motility and decreased gastric secretions and this responds to metaclopromide. Nausea due to sensitisation of the vestibular apparatus occurs with changes in the position of the head, and responds to treatment with scopolamine or meclizine. Myoclonus, especially common with meperidine occurs during sleep and responds to clonazepam or change of opioid. Thus, most opioid side effects are manageable either by waiting for tolerance to develop or by symptomatic treatment.

Approximately 5–10% of patients with cancer related pain will have inadequate control of pain with oral medication and at sometime during the course of their illness these patients require other interventional techniques for relief of pain. Parenteral administration of opioids by intravenous or subcutaneous administration has the advantage of rapid pain relief, ease of adjustment of dosage, constant plasma levels and fewer side effects and is also useful in patients with gastrointestinal dysfunction.

Continuous infusion by long-term central venous catheter or by portable ambulatory infusion pumps which are presently available is suitable for some patients. Patient controlled analgesia has also proved to be useful in selected patients with cancer related pain. This is especially suitable for patients with fluctuating pain or incident pain (as pain precipitated by movement) and allows for rapid adjustment of analgesic level to the degree of pain.

Spinal Delivery of Opioids

Injection of morphine or fentanyl in the spinal epidural or subarachnoid space, when parenteral administration fails, provides intense analgesia with lesser side effects. The injection can be as a bolus or continuous infusion with a pump system. For long-term spinal analgesia access to the epidural or intrathecal space by an indwelling catheter system is possible, but appropriate test doses of an opioid should be administered to ensure that the patient's pain will respond to spinal analgesia without excessive or intolerable side effects.

Intraspinal narcotic therapy has the advantage of delivery of low doses near the site of action in the spinal cord. Yaksh[172,173] demonstrated the long lasting efficacy of intrathecally administered opioid alkaloids and peptides. Their action is antagonised in a dose dependent fashion by systemic or intrathecal naloxone. The onset of analgesic activity is dependent on lipid solubility; agonists, such as mepiridine, being highly lipid soluble, have a rapid onset of action, and agents, such as morphine, have a slower rate of onset, but longer lasting effect. An intraspinal implanted morphine infusion pump can be used to deliver continuous low dose morphine to effectively control intractable pain due to malignancy.[107] The dose of morphine can be significantly reduced and with 0.5–1 mg of lumbar intrathecal morphine, analgesia may be achieved for 8–30 hours. In spite of these advances, relief from intractable chronic pain may continue to elude therapy. There are many conditions of chronic or recurrent pain in patients with long or normal life expectation, where medical therapy is ineffective because of inadequacy of the drugs, reactions to the drug or fear of addiction. In these cases neurosurgical relief of pain is indicated.

Anaesthetic Measures

The use of reversible nerve blocks or lysis of neural tissue by appropriate agents is efficacious both in the diagnosis and management of certain painful states. Reversible nerve blocks result in temporary interruption of nociceptive transmission and can be achieved by percutaneous injection of a local anaesthetic, which results in temporary abolition of pain. More permanent nerve blocks can be achieved by destruction of neural tissue, by the use of chemicals such as alcohol or phenol or by physical methods such as heat or cold. Chemical neurolysis can also be achieved by intraspinal delivery of the agent (epidural, subdural or subarachnoid).

Peripheral Nerve Block

This can be achieved by using phenol or alcohol. The nerve to be blocked has to be confirmed first by using a local anaesthetic agent. An RF lesion can also be used to destroy the nerve. This is commonly used for intercostal block and trigeminal neuralgia.

Autonomic nerve blocks are also used to relieve pain. The commonly used targets are the paravertebral sympathetic chain, the coeliac plexus and the stellate ganglion. The relief of pain following sympathetic blockade may be because of 'cross talk' between sympathetic efferents and unmyelinated afferents, the sympathetic efferents interacting with cutaneous afferents to produce contacts between sensory efferents and tiny cutaneous afferents within the skin, or excessive sympathetic outflow resulting in change in vascular permeability and an elevation in extracellular substances that produce pain.

Spinal Neurolysis (Subarachnoid, Subdural and Epidural)

Subarachnoid neurolysis is one of the most common methods used. The duration of pain relief is directly related to the amount of nerve fibre destruction. The major drawback of this procedure is the risk of destruction of other structures coming in contact with the neurolytic agent. There is gradual regeneration of pain fibres following chemical neurolysis. Hence the pain will recur after varying periods.

The agents commonly used are phenol (5–8%) in glycerine (0.5–1 ml), absolute alcohol (1–2 ml) and chlorocresol (parachlorometacresol (1 in 50) in glycerine (0.5–1 ml). The drugs should be given slowly. Phenol and chlorocresol are gradually released from glycerine, limiting their spread. Phenol and chlorocresol in glycerine are hyperbaric solutions while absolute alcohol is hypobaric. This should be kept in mind while positioning the patient for injection.

Injection of cold or hypertonic saline into the subarachnoid space[56] helps to relieve pain in many cases. The effect on the roots is more due to the ions than to the low temperature of the fluid. After repeated perfusion of cold saline in the lumbosacral region Tsubokawa[158] showed that conduction is blocked in the A delta and C fibres and that afferent depolarisation in the dorsal column is altered. As mentioned earlier, adoption of these techniques is still prevalent in many countries.

The main complication with these procedures is the risk of injury to other nerves resulting in motor weakness and sphincter disturbances. Epidural neurolysis has the advantage of less risk of spread intracranially and less chance of motor and sphincter disturbances. Subdural neurolysis is not an easy procedure and is used in intractable neck and shoulder pain.

SURGICAL PROCEDURES

The management of chronic pain by neurosurgical techniques is not new. The surgical manoeuvres described are directed at various sites in the pain pathway ranging from the most proximal to the most central components of the central nervous system, i.e. from the peripheral nerves to the cerebral cortex and subcortical areas. On the basis of the sites of operative intervention, they can be classified as:

1. The peripheral and cranial nerves: peripheral neurectomy
2. The posterior roots:
   a. Section (Rhizotomy) in:
      i. the spinal canal
      ii. the middle cranial fossa
      iii. the posterior cranial fossa
   b. Intrathecal injections for blocking the posterior roots, chemical rhizotomy using phenol, alcohol, glycerol or cold saline
3. The sympathetic chain: sympathectomy
4. The spinal cord:
   a. dorsal root entry zone (DREZ) lesions
   b. spinothalamic tractotomy, open or percutaneous
   c. commissural myelotomy
5. The medulla:
   a. medullary spinothalamic tractotomy
   b. trigeminal tractotomy
6. The mesencephalon: mesencephalic spinothalamic tractotomy
7. The thalamus:
   Stereotaxic thalamotomy (chemical, thermal, cryogenic or gamma rays): posteroventrolateral nucleus, centrum median, dorsomedian, pulvinar
8. The hypothalamus: posterior median hypothalamotomy
9. The sensory cortex: ablation of the sensory cortex
10. The frontal lobes:
    a. prefrontal leucotomy or lobotomy
    b. cingulumotomy
    c. basofrontal tractotomy
    d. fornix section
11. Pituitary ablation
12. Non-destructive procedures:
    a. transcutaneous nerve stimulation
    b. acupuncture
    c. dorsal column stimulation (DCS)
    d. periaqueductal grey stimulation
    e. thalamic stimulation
    f. spinal and intraventricular morphine.

Peripheral Neurectomy

Peripheral neurectomy is one the oldest surgical procedures decribed for the relief of pain, and is performed on the cranial or peripheral nerves. Severe forms of pain may sometimes be well localised in the area of distribution of a peripheral nerve, permitting local sensory denervation by section or avulsion of the nerve. In the case of purely sensory nerves such a procedure is simple, but in mixed nerves careful consideration is necessary before deciding on a nerve section; although, in pain due to malignant neoplastic diseases with a short life expectancy, one may perhaps ignore the resulting motor disability.

The common indications for peripheral neurectomy are supraorbital or infraorbital neuralgias, inferior alveolar neuralgia, and painful stump neuromas. The other indications are meralgia paraesthetica, malignant invasion of the chest wall, selected cases of post-herpetic neuralgia, causalgia, painful arthtritis and phantom limb. Radiofrequency or cryogenic techniques can be used to make lesions. The procedure is also useful in some cases of peripheral vascular disease of the lower limbs with incapacitating rest pain, where the cutaneous nerves can be divided with benefit. As the peripheral nerves tend to regenerate after simple division, a section of the nerve is removed during surgery. Although neurectomy is useful in many instances, there is always a risk of development of neuropathic pain. As some peripheral nerves contain both motor and sensory fibres, division can cause sensory loss, weakness and atrophy.

Cerovic et al. analysed the remission period after repetitive neuroexeresis of the same neural branch, to calculate "predicted" remission, and to evaluate the benefits of repetitive neuroexeresis. They found the remission time after repetitive neurectomy decreases, and there is no point in repeating the surgery on the same neural branch more than three times.[23]

Posterior Root

Section (Rhizotomy)

In 1898, Sherrington[138] demonstrated that in monkeys each part of the distal extremities was supplied by three overlapping sensory spinal roots and, in 1889, Abbe[1] and Bennett[17] independently performed spinal rhizotomy. Posterior root section or posterior rhizotomy implies section of the posterior root of a peripheral or cranial nerve for relief of pain. In the spinal canal, the section is made between the cord and the posterior root ganglion. It is a useful operation which can be selectively done to cover a number of dermatomes without any involvement of the motor fibres. Considering sensory overlapping in continuous dermatomes it is necessary to cut at least two posterior roots above and below the area of pain. The results of rhizotomy may not be long lasting in many cases. The sensory supply of muscles and bones (myotomes and sclerotomes) does not conform to the overlying cutaneous sensory arrangement in all parts of the body. Hence, in disease involving bones and muscles, rhizotomy, to be useful, must include the concerned roots, also in addition to those supplying the dermatome.

In cases of thoracic pain due to tumour infiltration of the chest wall or pleura or other causes, posterior rhizotomy is helpful. In some cases of post-herpetic neuralgia, as also thoracic radiculopathy, pain may be relieved by such an operation.[67] Sensory rhizotomy is also useful in patients with chronic pain in the lower extremity resulting from repeated disc surgery. The posterior roots can be sectioned intradurally after laminectomy. In the thoracic region an interlaminar approach may be adopted. Extradural spinal sensory rhizotomy has been advocated by Scoville[128] as a useful and simple procedure where the dorsal root in its dural sleeve is exposed by "one bite with the rongeur" in the lower edge of the lamina just caudal to the transverse process. Trans-spinal ganglionectomy (removal of the posterior root ganglion) has been advocated by Smith[143] for relief of intercostal pain. In cases of malignant disease of the head and neck, pain can be relieved by section of the upper cervical and lower cranial nerve roots. Rhizotomy is also useful in occipital neuralgia and in coccydynia where bilateral sacrococcygeal root section helps.[4]

The drawback of rhizotomy is the possible development of deafferentation pain syndrome in some cases. Rhizotomy is also not useful for benign peripheral neuropathic pain.[126,153]

Selective Rhizotomy (Rhiziditomy)

Sindou et al.[141] proposed selective destruction of rootlets which carry the small afferent fibres. These are grouped on the ventrolateral part of the posterior root before they re-enter the cord. The technique has been found useful in the treatment of malignant lesions involving the brachial and pelvic plexuses.

Percutaneous Radiofrequency Rhizotomy

Interruption of nerve root function by the percutaneous route using radiofrequency current is now preferred over the previous techniques mentioned; this has proved to be effective and safe and has been performed for relief of pain as well as of flexor spasms.

Dorsal Root Entry Zone Lesions

Nashold[100] advocated lesions in the spinal cord at the zone of entry of the dorsal roots in the substantia gelatinosa, either by thermocoagulation or by laser. The procedure is based on the concept that deafferentiation in the root or peripheral nerve lesions leads to loss of control and inhibition in the neurons of the dorsal horn and a DREZ lesion helps to restore the balance. The lesion probably involves Lissauer's tract and the deeper layers of the dorsal horn.[126] Ramer et al. studied the ability of intrathecal neurotrophin-3 (NT3) to promote axonal regeneration across the DREZ and functional recovery

in adult rats. Quantitative electron microscopy showed good penetration of CNS tissue by regenerating sensory axons treated with NT3 at 1 and 2 weeks post-rhizotomy. Light and electron microscopical anterograde tracing experiments showed that these axons re-entered appropriate and ectopic laminae of the dorsal horn, where they formed vesicle-filled synaptic buttons.[114]

They found recovery depended on NT3-mediated sensory regeneration: preventing regeneration by root excision prevented recovery, and concluded NT3 treatment allows sensory axons to overcome inhibition present at the DREZ and may thus serve to promote functional recovery following dorsal root avulsions in humans.[114] DREZ lesions have been found useful in brachial plexus avulsions, phantom pain,[22] painful paraplegia and some cases of post-herpetic neuralgia.[18]

Chemical Rhizotomy

It is done using phenol, alcohol, glycerol or cold saline. Percutaneous transovale trigeminal rhizotomy by injecting glycerol into the retrogasserian cistern of Meckel's cave is a useful treatment modality for tic douloureux. The major advantage of glycerol rhizotomy is significant reduction in post-operative facial deafferentation and its sequelae when compared to differential thermal rhizotomy performed by graded radio-frequency-induced lesions.

Sympathectomy for Visceral Pain

The fibres carrying pain sensation from the viscera and blood vessels travel along the sympathetic system and interruption of the system at the appropriate level gives relief from specific types of visceral pain. Paravertebral injection of procaine may relieve intractable visceral pain for short periods; this may be followed by surgical section of the sympathetic chain for more lasting effects. Resection of the upper four thoracic ganglia relieves precordial pain of cardiac origin. Alcohol block of the coeliac plexus helps to control pancreatic pain. Resection of the splanchnic nerves and the lower thoracic sympathetic ganglia relieves upper abdominal visceral pain and if, along with these, the lumbar sympathetic ganglia are also resected, pain from the kidneys is abolished. Presacral neurectomy has been found to be of benefit in severe dysmenorrhoea, as well as in pain due to lesions of the urinary bladder and other pelvic viscera. Sympathetic denervation of limbs relieves vascular pain[74] and the pain of phantom limb in some cases. Sympathectomy is the treatment of choice for cases of causalgia. Unilateral thoracoscopic sympathectomy induces adequate and lasting relief of pain caused by benign as well as malignant diseases originating from the pancreatic region, chronic pain from upper gastrointestinal tract diseases and portal vein thrombosis. The sympathetic chain and splanchnic branches are divided from level IV to X-XI, with all patients reporting substantial relief of pain post-operatively.[83]

Operations on the Spinal Cord

Cordotomy is one of the treatment choices in pain caused by malignancies localised unilaterally to the extremities as well as the thorax and the abdomen.

Spinothalamic Tractotomy-Anterolateral Cordotomy

Section of the lateral spinothalamic tract in the spinal cord was first suggested, in 1910, by Schueller, who coined the term 'Chordotomie', in 1911. The next year, Spiller also suggested the same procedure and it was first performed in the USA by Martin.[147]

Schueller[127] developed the idea of cordotomy for the relief of intractable pain after extensive animal experiments and suggested that anterolateral cordotomy could lead to immense relief from intractable pain due to malignant disease of the lower half of the body.

In anterolateral cordotomy the pain carrying fibres in the anterolateral quadrant of the cord are divided. The level of choice for this operation is the upper thoracic (the 2nd thoracic level) and the upper cervical region (between the first and the second cervical segments). Open cordotomy is seldom performed nowadays although it was a popular procedure four decades ago.

Percutaneous Cervical Cordotomy

Percutaneous cervical cordotomy (PCC) was described, in 1963, by Mullan et al.,[96] who introduced a strontium needle into the cord and destroyed the anterolateral region by irradiation. In later operations, the destruction was made by radiofrequency current instead of by irradiation.[98,121] An anterior approach to the lower cervical cord has been described for percutaneous cordotomy.[40,42,80] It is claimed that this approach is safer, as it leads one directly to the anterolateral part of the cord and the incidence of respiratory complications are minimal. Hardy et al.[50] emphasised the benign postoperative course with the use of the operating microscope via the anterior route.

Crul et al. determined whether there is still a place for PCC in actual clinical practice with its wide spectrum of pain therapies. All their patients had severe unilateral pain due to cancer, resistant to opioids and co-analgesics. Following PCC, mean pain intensity was reduced from numeric rating scale (NRS) 7.2 to 1.1. Initially, following PCC, a good result (NRS < 3) was obtained in 95% of patients. At the end of life, a good result was still present in 69% of patients. Complications were minimal and subsided within 3–4 days. Thereby, PCC remains a valuable treatment option in patients with treatment-resistant cancer pain and still deserves a place in the treatment of terminal cancer patients with severe unilateral neuropathic or incidence pain.[26] CT-guided percutaneous cordotomy is an option in specially selected cases with malignancy with intractable pain. The target of computed tomography (CT)-guided percutaneous cordotomy is the lateral spinothalamic tract located in

the anterolateral region of the spinal cord at the C1-C2 level. Kanpolat et al. performed CT-guided percutaneous cordotomies in 207 patients mostly suffering from intractable pain related to malignancy. The patients' pain scores and Karnofsky Performance Scale scores were evaluated pre- and post-operatively. The initial success rate of CT-guided percutaneous cordotomy was 92.5%, and was higher in the malignancy group. Bilateral selective percutaneous cordotomy was successfully performed in 12 cases.[69] CT-guided bilateral high-level percutaneous cordotomy can be used in the treatment of intractable upper trunk pain in patients with cancer without pulmonary dysfunction.[15]

Autopsy examination of cervical cords occasionally show lesions in areas away from the spinothalamic tract even after carefully performed percutaneous cordotomies.[93] Hitchcock[56,57] introduced stereotactic spinal surgery for greater precision. Hitchcock[57] mentions that Clarke of Horsely-Clarke fame had developed a spinal stereotactic apparatus in 1921, in addition to the well-known cranial apparatus. With his apparatus Hitchcock was able to stimulate and record from the tracts in the spinal cord and was able to site his lesions accurately. By the stereotactic technique the complications can be lessened and the benefits extended to more seriously ill patients.[152]

Despite the drawbacks of the level of analgesia lowering after a few weeks and of the possibility of limb, bladder or respiratory weakness, the procedure of cordotomy (thoracic or cervical) continues to be a useful procedure, giving benefit to the majority of patients operated upon, specially to those suffering from pain due to malignancy. Cordotomy is not effective in deafferentation syndrome.

Complications: While unilateral cordotomy spares bladder function, bilateral cordotomy most often results in its impairment. However, the bladder function returns to normal in most patients after varying intervals. There may also be post-operative weakness of muscles of the lower extremities. After a thorough study of 106 cases patients who underwent open cordotomy with full follow-up including autopsy, McKissock[88] concluded that cordotomy offers complete relief of pain in half the patients, and a good result in a further quarter. Lipton[81] reviewing 300 cordotomies found complete relief in 76% and partial relief in 8%. In the immediate post-operative period 40% of patients had lower limb weakness. There is a 20% risk of serious weakness of the arm or leg and permanent disturbance of sphincter control after successful bilateral operations. To minimise such complications, bilateral cordotomy is performed at different levels, e.g. either at the upper and lower limits of the same exposure or at the first thoracic and the first cervical level in two separate sittings.

Impairment of respiratory function may occur after bilateral cervical cordotomy due to interference with the motor fibres to the diaphragm that lies between the anterior horn and the cervical fibres of the spinothalamic tract. There is reduction in tidal volume. This respiratory difficulty is seen chiefly when the patient falls asleep and so to say 'forgets to breathe'. This is usually transitory.[97] It is not possible to predict which case will develop this complication, even by extensive pre-operative pulmonary function tests.[122] Krieger and Rosomoff[73] suggest that this respiratory dysfunction is due to damage to the ascending reticular fibres in the ventrolateral segment of the spinal cord, in view of the fact that the apnoea occurs only during sleep, it is reversible by arousal and there is no evidence of motor changes. Respiratory paralysis was the cause of death in seven out of nine patients who died in a series of 400 patients treated by percutaneous cordotomy.[54] Severe hyponatraemia and hypochloraemia have been reported following bilateral cervical cordotomy.[82] This has been ascribed to extensive vasoparesis, increased vascular and cellular permeability and consequent dilution of the extracellular space. In the series of Lahuerta et al.,[75] pain relief was reported by 64% of patients, with a mortality of 6% due to respiratory problems.

Commissural Myelotomy

Commissural myelotomy (CM) was introduced to overcome some of the limitations of bilateral cordotomies in the treatment of bilateral pain syndromes. CM disrupts pain-conducting fibres as well as a polysynaptic pain pathway that runs through the centre of the spinal cord. The thin fibres which enter the spinal cord through the zone of Rolando and cross over to the opposite side may be severed at the site of crossing by splitting the cord in the midline. This results in bilateral relief of pain at the segmental level corresponding to the site of incision. The idea formulated first by Greenfield, in 1926, was implemented by Armour,[5] in 1927, and later by Putnam,[111] in 1934. The operation has been used for relief of pain in the upper abdomen and pelvis and also for pain in the upper limbs, chest and neck. The most common side effect is transient diffuse dysaesthesia which improves over days or weeks.[21] The procedure may also produce sphincter or motor dysfunction. It is a common observation that pain relief is not limited to areas rendered analgesic to pin pricks. Sourek[144] suggested that the myelotomy destroys the slow conducting anterolateral system and a fast conducting mediodorsal system. In the modern operation of CM, the cord is divided in the posterior midline with an additional lateral extension of the incisions.[76]

Stereotactic CM avoids major surgical exposure unsuited for ill patients. Hitchcock[58] found more extensive areas of analgesia after cervicomedullary stereotactic myelotomy. In this method, after visualising the cord by myelography, steel, gold or tungsten wires are placed inside the cord stereotactically and electrolytic lesions are made to destroy the commissure. Tasker[153] in a review found the analgesia to be transient.

Medullary and Mesencephalic Tractotomy

Patients complaining of severe pain in the head, face, neck and shoulders due to malignancy cannot be helped

even by high cervical cordotomy. In such cases the spinothalamic tract may be divided in the medulla or the midbrain. Mesencephalic tractotomy is most effective for nociceptive cancer pain, and the aim is to interrupt the lateral spinothalamic and spinoreticular tracts at the level of the superior or inferior colliculus while preserving the medial lemniscus.[20]

For the treatment of trigeminal neuralgia Sjoquist[142] described, in 1938, the method of cutting the spinal tract of the trigeminal nerve in the medulla. Walker, in 1942, devised a method of severing the spinothalamic tract in the midbrain (mesencephalic tractotomy). This resulted in analgesia and thermoanaesthesia of the opposite half of the body, but often the relief was incomplete and short lasting and sequelae like ataxia and dysaesthesia frequently incapacitated the patient.[164]

Stereotaxic coagulation of the dorsolateral tegmentum of the mesencephalon at the level of the posterior commissure was developed, in 1948, by Spiegel and Wycis.[145] A number of publications report significant relief of pain by this method, especially in central dysaesthesia and phantom pain,[104,117,146] but undesirable ocular and motor deficits may occur.[157]

Gioia et al.[43] believe that the creation of minute bilateral lesions stereotactically in the reticular activating system would modify the reception of peripheral sensory stimuli and relieve pain. With that intent, they produced thermal lesions stereotactically at the midcommissural level, 5 mm lateral to the posterior part of the third ventricle and obtained good results in ten patients.

Nashold et al.[101] improved the results by adopting stimulation techniques and by combining mesencephalotomy with a lesion in the thalamus. Stimulation causes pain referred to the limbs, to the trunk or head and neck area, thus helping in better siting of the lesions. In Nashold's series, patients with deafferentation pain due to a brachial plexus lesion benefited the most. The mortality was about 3%. Tasker[153] found better relief with nociceptive pain than deafferentation pain. Scadding[126] concludes that nowadays this operation is rarely a procedure of first choice.

Thalamus: Stereotaxic Thalamotomy

Currently, ablative stereotactic procedures for relief of chronic pain have limited application except in a few patients, because of the low rate of success achieved, relatively short duration of pain relief and associated complications. The advent of newer non-destructive techniques such as electrical stimulation of deep brain structures, chronic intraspinal and intra-ventricular administration of opiates with lower chances of complications and the reversible nature of the effect have further reduced the need for ablative stereotactic procedures.

Lesions can be made in the thalamus for the relief of intractable pain, but the results may not always be good or constant. Heat, cold (cryo) or chemical lesions may be produced stereotactically at predetermined foci. Gamma rays have also been used for this purpose.[148] In 1949, Hacaen et al.[48] made a lesion in the post-eromedial nucleus of the thalamus with resulting abolition of pain and loss of temperature sensation on the opposite side of the body. Spiegel and Wycis[146] reported a number of cases of pain treated by mesencephalic lesions and by lesions in the post-eroventrolateral nucleus and in the dorsomedian nucleus. Lesions made in the PVL nucleus of the thalamus have not been uniformly successful. A dissociated sensory loss may result and the pain recurred in about 50% of cases.[118] Ramamurthi and Kalayanaraman[113] reported success with lesions in the post-eroventromedial nucleus of the thalamus for intractable pain in facial and pharyngeal malignancies. The area of maximum pain response is determined by stimulation studies using a bipolar probe of 1 mm diameter. Pain relief was reported with no demonstrable sensory deficit. The lesions were made in the termination of the quintothalamic tract which is most medially situated. The operation seems to work in pain due to malignancies and not in other types of facial pain.

On the contrary, lesions made in the termination of the palaeospinoreticular tract in the internal medullary lamina including the centrum medianum nucleus seem to offer more lasting pain relief.[49] Mitchell and Kaelber[92] and Sano et al.[124,125] demonstrated in cats the effectiveness of destruction of the centrum-medianum-parafascicularis-subparafascicularis complex in the abolition of reaction to painful stimuli. The extent of destruction necessary varied with the intensity of pain stimulus. If the pain is well localised and lateralised, lesions in the contralateral thalamus would suffice. However, if the pain is diffuse or bilateral, a bilateral lesion would be required.[162] Askensay et al.[6] recommended combining mesencephalic reticulotomy with a centrum median lesion, as the benefits from the latter are often short lived. Tasker[153] reviewing the results of many authors found pain relief for nociceptive pain in up to 57%, but with a recurrence rate of 50%.

Lesions in the dorsomedian nucleus interfere with pain appreciation and not with pain perception and act more like a selective leucotomy. If there is a psychological inadequacy, a lesion in the dorsomedian nucleus is useful.[117] Lesions have also been made in the medial and lateral pulvinar nuclei for intractable pain. Siegfried[140] found only 25% of patients having relief for four weeks. Medial thalamotomy is one of the first stereotactic operations to have been used for neurogenic pain, and has a low complication rate with no risk of the development of iatrogenic neurogenic pain. It represents selective local relief for all types of pain, without causing somatosensorial deficit. Balas et al. performed 39 post-eromedial thalamotomies in patients with persistent intractable pain due to various disorders. Half of their patients operated on had relief of pain after thalamotomy. In 84% of their cases this relief occurred on the second day. They found post-eromedial stereotactic thalamotomy under MR guidance can provide safe, effective treatment for

persistent, intractable pain.[7] Young et al. treated 20 patients who suffered persistent intractable pain from a variety of disorders by medial thalamotomy with the Leksell Gamma Knife. The lesions were directed at the intralaminar nuclei, the lateral portion of the medial dorsal nucleus, the centromedian and the parafascicular nuclei. Lesions were made with radiation doses from 140 Gy to 180 Gy using a 4-mm beam collimator helmet and either a single isocentre (1 patient), two isocentres (17 patients) or three isocentres (2 patients). Two-thirds of the patients experienced either excellent or good pain relief in a follow-up period between 1 month and 22 months. One patient died due to radiation necrosis following a bilateral thalamotomy. Medial thalamotomy with the Gamma Knife produces thalamic lesions which are reliable in size, shape and location with a low complication rate and offers a minimally invasive, cost effective treatment for certain selected patients with chronic intractable pain.[174-176]

Hypothalamotomy

This was suggested by Sano[125] Nashold[103] suggested implantation of chronic electrodes in various parts of the brain in intractable pain. Stimulation studies are conducted later on to determine the best site for the lesion which is by thermocoagulation.

Sensory Cortex Ablation

It has been observed during stimulation experiments on the human sensory cortex that pain occurring in a 'phantom limb' could be explained by a cortical sensory projection from the missing limb. In this type of painful condition, the sensory cortex is subpially ablated under local anaesthesia. The precise area of ablation is determined by electrical stimulation during surgery. It is disappointing that after initial success from such operations the end results are temporary.

Frontal Lobes

Frontal lobotomy or prefrontal leucotomy can be performed to give relief to patients suffering from intractable pain when other measures have failed. The frontal lobe fibres which are severed in such an operation have no relation to pain pathways; still the operation proves effective on many occasions, as the patient is relieved from the psychic apprehension of pain. Fibres project from the dorsomedian nucleus of the thalamus to areas 9, 10, 11 and 12 of the anterior portion of the frontal cortex as well as to areas 13 and 14 of the supraorbital cortex, while fibres from the anterior nucleus run to area 24 in the cingulate gyrus. Interruption of these fibres or the corresponding cortical areas suppresses awareness of suffering and the reactive expression of pain. These operations do not raise the sensory threshold for pain.[167]

Operations on the frontal lobe have been performed for relief of pain chiefly on patients in the terminal stages of malignancy. These operations carried with them definite risks of psychological disturbance and were performed only on those patients with a short life expectancy. Scarff[129] advocated, in 1948, a unilateral frontal leucotomy and found that while the patient had good relief from suffering, personality change was absent or minimal. Gutterman and Shenkin[47] have reported on the usefulness of saline injections into the frontal lobe for relief of intractable pain. Specific and limited operations on the frontal lobe can now be performed by dividing only the fibres in the inferior quadrant of the frontal lobe, those arising from the orbital cortex (subcaudate tractotomy). This may be done either as an open operation or by the stereotactic technique. Personality disturbances are minimal after these operations. Operations on the frontal lobe should be performed only when other methods have not given relief and when the life expectancy is very short.[32,57,167]

Cingulumotomy

Stereotactic coagulation of the rostral part of the cingulum bundle gives relief from chronic pain. The results are often short-lived (for a few months) and are similar to an open operation. Foltz and White,[36] Ballantine et al.,[10] Paillace et al.[109] and Balasubramaniam et al.[8] found cingulumotomy useful for pain relief. The operation is based on the knowledge that the cingulum consists of multisynaptic pathways connecting the medial frontal cortex, the anterior thalamic nuclei and the rostral midline and intralaminar nuclei with the hippocampal formation. In painful conditions, this system becomes overactive and hypersensitive so that the emotional status of the patient becomes dominant in his reaction to an evaluation of the pain. In such cases, where the emotional factors are marked, transection of the cingulum gives benefit by a volumetric reduction effect that interferes with the involved feedback mechanisms.[37] The operation is simple and does not leave behind an apathetic person or any obvious psychological defect.[8] Paillace et al.[109] reported some impairment of cognitive function (non-verbal) after cingulumotomy, but the overriding significance of verbal behaviour in man masks these minor deficits. Patient selection for cingulumotomy must be based on assessment of the cause of pain and the overall personality of the patient.

Hypophysectomy

Hypophysectomy has been efficacious in reliably relieving pain due to secondaries from carcinoma of the breast and the prostate. Endocrine manipulative measures, such as oopherectomy and adrenalectomy were found to have a beneficial effect in advanced carcinoma of the breast with metastasis, by tumour regression and pain relief. The addition of hypophysectomy to the armamentarium of the surgeon dealing with advanced carcinoma of the breast and prostate was possible, following the popularisation of the trans-sphenoidal microsurgical

approach which reduced the morbidity and mortality of the transcranial approach.

Hypophysectomy can be performed by various means such as stereotactic radiofrequency or cryogenic destruction, chemical destruction by use of absolute alcohol through the transnasal trans-sphenoidal route or the trans-sphenoidal microsurgical approach. The most reliable complete destruction of the pituitary gland is achieved by direct surgical exposure (trans-sphenoidal), but involves slightly more morbidity than the percutaneous stereotactic methods. In patients with metastases from carcinoma of the breast or prostrate, significant relief of pain is noticed.[94] Pain relief with equal efficacy has also been reported in other malignancies not related to endocrine function.[156] The mechanism of pain relief is not clear and an endocrine effect (endorphin) and a neurogenic mechanism have been postulated. There is still no agreement as to the relationship of the extent of pituitary destruction, hypopituitarism and the extent and duration of pain relief.

In general, pain relief occurs in 80% of patients with pain due to disseminated malignancies, usually lasts for 3–6 months, although in some it may last for 1 year or more. Currently, hypophysectomy is considered a useful procedure for relieving terminal disseminated cancer pain when other less invasive measures have failed. Hypophysectomy by stereo radiosurgery, radiofrequency coagulation or by chemical agents carries the least risk.

Intracranial Neurostimulation for Pain Control

First employed in 1954, intracranial neurostimulation represents one of the earliest uses of neurostimulation for the treatment of chronic pain refractory to medical therapy. Currently, there are two kinds of intracranial neurostimulation which are commonly used to control pain: (1) motor cortex stimulation (MCS) and (2) deep brain stimulation (DBS), which have proven effective for treating a number of neuropathic and nociceptive pain states not responsive to other therapies. Intracranial neurostimulation for pain relief is most frequently delivered by stimulating the motor cortex, the sensory thalamus (ST), or the periaqueductal and periventricular grey matter. The increasing use of intracranial neurostimulation for the treatment of chronic pain, especially for pain not responsive to other neuromodulation techniques, reflects the efficacy and relative safety of these intracranial procedures.

Motor Cortex Stimulation for Neuropathic Pain Syndromes

The unique lack of stimulation-induced perceptual experience with MCS makes it uniquely suited for double blind studies of its effectiveness. MCS has emerged as a promising technique for the management of pain in patients with difficult neuropathic and central pain conditions. Although MCS has proven most successful for patients with trigeminal neuropathic/deafferentation pain and central post-stroke pain, other conditions are now emerging as potential targets for this therapy. Based on previous as well as ongoing work, it would appear that the future of MCS is indeed bright. With the ongoing work in this area, investigators will be able to develop a better understanding of the mechanisms underlying this modality and be able to further refine the technique of MCS. It is also possible that with the use of non-invasive tools, such as transcranial magnetic stimulation, practitioners will be able to predict with accuracy which patients are likely to respond favourably to MCS.[108] Lefaucheur et al. reported their results of the first randomised controlled trial using chronic MCS. Sixteen patients were included with pain origin as follows: trigeminal neuralgia (n = 4), brachial plexus lesion (n = 4), neurofibromatosis type-1 (n = 3), upper limb amputation (n = 2), herpes zoster ophthalmicus (n = 1), atypical orofacial pain secondary to dental extraction (n = 1) and traumatic nerve trunk transection in a lower limb (n = 1). A quadripolar lead was implanted, under radiological and electrophysiological guidance, for epidural cortical stimulation. Clinical assessment was performed up to 1 year after implantation and was based on the following evaluations: visual analogue scale (VAS), brief pain inventory, McGill Pain questionnaire, sickness impact profile and medication quantification scale. At final examination, the mean rate of pain relief on VAS scores was 48% (individual results ranging from 0% to 95%) and MCS efficacy was considered as good or satisfactory in 60% of the patients. Their results suggest that the indications for MCS might be extended to various types of refractory, chronic peripheral pain beyond trigeminal neuropathic pain.[77]

Deep Brain Stimulation

Prospective randomised clinical trials to confirm the efficacy of these intracranial therapies have not been published. DBS may be employed for a number of nociceptive and neuropathic pain states, including cluster headaches, chronic low back pain, failed back surgery syndrome, peripheral neuropathic pain, facial deafferentation pain and pain secondary to brachial plexus avulsion.[78]

To better understand its efficacy, Bittar et al. performed a meta-analysis of DBS for pain relief. Databases were searched using key words DBS, ST, periventricular grey and pain. Stimulation sites included the periventricular/periaqueductal grey matter (PVG/PAG), internal capsule (IC) and ST. The long-term pain alleviation rate was highest with DBS of the PVG/PAG (79%), or the PVG/PAG plus ST/IC (87%). Stimulation of the ST alone was less effective (58% long-term success). DBS was more effective for nociceptive than deafferentation pain (63% vs 47% long-term success; $p < 0.01$). Long-term success was attained in over 80% of patients with intractable low back pain (failed back surgery) following successful trial stimulation. They found higher success rates were

seen with phantom limb pain and neuropathies. They conclude that DBS is frequently effective when used in well-selected patients.[19,115]

Afferent Stimulation for Abolition of Pain

The skin and peripheral nerves could be electrically stimulated to obtain relief of pain [transcutaneous electrical nerve stimulation (TENS)].[84,91,131] The principle on which it is based is the fact that when the larger diameter myelinated afferent cutaneous fibres or their extensions into the dorsal column are stimulated, there is a diminution in the activity in the dorsal horns induced by stimulation of the smaller or unmyelinated fibres. This is based on the gate control theory of pain proposed by Melzack and Wall.[89]

Acupuncture techniques are generally based on the above principle. The stimulation is of high frequency and low intensity just sufficient to cause tingling. Endorphin levels in the CSF show an increase during TENS. The indications for TENS are many and include a wide variety of nociceptive, deafferentation and neuropathic pains.[169]

TENS has been useful in both acute and chronic painful states. It has been used in acute painful states of postoperative pain or pain due to musculoskeletal injury. In chronic pain of various causes as the failed back, sympathetic dystrophies and post-herpetic neuralgia, it has been found useful in relieving pain. It has no use in the treatment of central pain as in the deafferent state.This procedure has the advantage of being non-invasive and can be used for long-term stimulation at home by the patient. The efficacy of TENS tends to decrease over time and many patients show a decline in response after 1 year of use. There is no significant morbidity due to the procedure. Pigmentation and skin hypervascularity may occur in areas of chronic stimulation.

Dorsal Column Stimulation

Chronic intractable pain can also be relieved by intermittent stimulation of the dorsal column. Surface electrodes were applied to the dorsal columns by Shealy et al.[132,133] and Sweet and Wepsic[149,150] for the treatment of intractable pain and encouraging results were obtained. Stimulation of the dorsal column may also be done by direct implantation of electrodes into the dorsal column with subsequent electrical self-stimulation to relieve the pain.[102] About 50% of patients get good relief. The results are expected to be better, if well defined objective criteria for patient selection could be established. Direct implantation carries with it the risk of morbidity like transient paresis of the leg, CSF leak, root pains and delayed intraspinal haemorrhage. There is also the problem of long-term tolerance of the tissues to the implant. The best results have been obtained using multipolar electrodes, with epidural placement above the level of the pain segments. When the pain is localised and stimulation induced paraesthesias completely overlap the pain segments, the results are better.The main indications for DCS are pain due to the failed back syndrome, post-amputation pain, incomplete plexus lesions, peripheral nerve lesions, sympathetic reflex dystrophy and rest pain in peripheral vascular disease. It is contraindicated in pain due to complete transverse lesions of the cord, cancer pain, deafferentation pain due to spinal root avulsion and post-herpetic neuralgia.

In carefully selected patients, pain relief is seen in 60% of patients early and over a long-term 40% of patients have pain relief. A positive stimulation test predicts a 70% chance of benefit from implantation while a negative result reduces the chance to 25%. Hence, it is essential to perform trial stimulation at exactly the same level as the final implantation for optimal results.

Focal Brain Stimulation

Relief of chronic pain may also be achieved by precise focal electrical stimulation of brain centres.[2,52,45,116] Stimulation of the IC was utilised for the successful suppression of chronic pain by Adams et al.,[3] who suggested that the pain suppression was due to the stimulation of parietal corticofugal inhibitory fibres.

Stimulation of the periaqueductal grey has been reported with 50% good results by Richardson and Akil[116] and Hosobuchi et al.[62] The procedure is more useful in nociceptive pain and not in deafferenation pain. Meyerson[91] recommends the procedure for patients with malignancy with a life expectancy of 6 months. Thalamic stimulation of the ventrobasal nuclei has also been tried and found effective in deafferentation pain and anaesthesia dolorosa.[61] Levy et al.[79] found that 48% of 628 patients obtained relief from ventrobasal thalamic stimulation. The mechanism of pain relief by stimulation of VPM and VPL is not clear, and it is thought to be due to activation of an inhibitory system independent of the endogeneous opioid system.

The surgical procedure involves placement of platinum flexible electrodes into the appropriate target area using CT/MR guided stereotaxy or positive contrast ventriculography. Physiological parameters, especially the response to electrical stimulation help in accurate placement of the electrodes. The lead wires are brought out of the scalp and temporary electrical stimulation is done for about a week to determine the efficacy of stimulation. If pain relief is good, then the electrodes are internalised for permanent placement and are connected to a programmable battery powered pulse generator.

Extensive clinical experience has shown that the procedure is efficacious in pain relief in around 60% of the patients.[174] Relief of nociceptive pain is higher at 80%, while deafferentation/central pain relief is about 50%.

As with any surgical procedure for pain relief, efficacy diminishes with time and long-term success rates are lesser. The most common complications of the procedure are technical malfunction of the apparatus and infection (5-20%). The risk of permanent neurological morbidity and haemorrhage is around 5%. The drawbacks of the

procedure are the expense involved and the required technical expertise being limited to a few centres.

Chemodes, which are fine tubes through which a defined chemical agent may be delivered into the brain, may also be used for this purpose. Mark et al.[86] used a silastic brain chemode to transport an anaesthetic gas into the human thalamus to obtain pain relief. Morphine can also be injected into the III ventricle and produces very good analgesia with few side effects.

Hypnosis

Rosen[120] reported the usefulness of analgesia induced during a hypnotic trance in patients with intractable pain, especially in phantom limb pain. Hypnotic suggestion has been tried to cure chronic pain unrelieved by previous cordotomy. It is obvious that the relationship between damaged tissues, conscious awareness of pain and the reaction to pain is little understood.

From the large variety of procedures used in different parts of the nervous system, it is clear that patients with intractable pain present a variety of anatomical, physiological and psychological problems. 'They are often difficult to mange, but generally are grateful for even unsuccessful efforts to relieve them. Success, especially when not entirely expected, continues to inspire us and failure, especially when unexplained, to challenge us'.[163]

Outcome Assessment

Quality of life (QOL) is probably the most useful and important measure of outcome that is generally collected. The standard QOL measure has been the SF-36. A 36-item short-form (SF-36) was constructed by Ware et al. to survey health status in the Medical Outcomes Study. The SF-36 was designed for use in clinical practice and research, health policy evaluations and general population surveys. The SF-36 includes one multi-item scale that assesses eight health concepts: (1) limitations in physical activities because of health problems; (2) limitations in social activities because of physical or emotional problems; (3) limitations in usual role activities because of physical health problems; (4) bodily pain; (5) general mental health (psychological distress and well-being); (6) limitations in usual role activities because of emotional problems; (7) vitality (energy and fatigue) and (8) general health perceptions. The survey was constructed for self-administration by persons 14 years of age and older, and for administration by a trained interviewer in person or by telephone.[165]

In 1993, Ware and Sherbourne published a new short-form health survey, the MOS 36-Item Short-Form Health Survey (SF-36), consisting of 36 items included in long-form measures developed for the Medical Outcomes Study. The SF-36 items and scoring rules are distributed by MOS Trust, Inc. Strict adherence to item wording and scoring recommendations is required in order to use the SF-36 trademark. The RAND 36-Item Health Survey 1.0 (distributed by RAND) includes the same items as those in the SF-36, but the recommended scoring algorithm is somewhat different from that of the SF-36. Scoring differences and new T-scores are presented for the 8 multi-item scales and two-factor analytically derived physical and mental health composite scores.[52]

CHRONIC PAIN SYNDROMES

Deafferentation Pain Syndromes

Pain is commonly due to tissue injury, but can also result from damage to peripheral or central somatosensory pathways. Neuropathic pain which follows damage to peripheral or central somatosensory pathways is termed deafferentation pain.[178] This chronic pain may then be referred to the deafferented regions of the body surface. Neuropathic pain is defined as the pain which arises as a result of damage to the somatosensory pathways that transmit pain.[85] Neuropathic pain after trauma tends to be delayed in onset, severe in intensity and resistant to treatment.

Pain following brachial plexus avulsion, phantom limb pain, amputation stump pain and pain occurring after neurosurgical ablative procedures are examples of deafferentation pain and may be due to changes in central somatosensory pathways, as in the dorsal horn.

Clinical Syndromes of Deafferentation Pain

The clinical syndromes of pain following deafferentation include pain associated with both peripheral and CNS damage.

Peripheral Nerve and Root

Some common examples of painful peripheral neuropathy include those due to diabetes, chronic alcoholism, amyloidosis and neurotoxins. Pain is due to deafferentation of the dorsal horn. Herpes zoster afflicts the roots to cause neuropathic pain with deafferentation of the cord segments. Trigeminal and other cephalic neuralgias and arachnoiditis are other examples of deafferentation pain due to root involvement.

Spinal Cord

Traumatic cord injury interrupts the central connections of nociceptive neurons in the spinal cord. Demyelination, necrotizing myelitis, spinal cord injury, syringomyelia, spinal cord AVMs and tumours are other causes of deafferentation pain due to cord involvement.

Brainstem

Common examples of pain due to deafferentation of the brainstem are those due to vascular occlusions, surgical procedures or demyelination.

Thalamus

The thalamic syndrome of Dejerine and Roussy is usually due to vascular injury (ischaemia or haemorrhage) to the ventroposterolateral (VPL) and ventroposteromedial

(VPM) nuclei of the thalamus and it is characterised by persistent, spontaneous burning pain.

Cortex

Large subcortical parietal lesions interrupting the thalamocortical sensory pathways may produce pain similar to thalamic pain.[35]

Treatment

The treatment of deafferentation pain is difficult, and the pain is intractable. Anticonvulsants, like phenytoin, carbamazepine, clonazepam and valproic acid, have been reported to be effective in relieving pain due to diabetic neuropathy, post-herpetic neuralgia, phantom limb pain and trigeminal neuralgia. Anticonvulsants may inhibit abnormal spontaneous activity of other damaged neurons. Steroids and NSAIDs may be useful, especially as adjunctive drugs.[14] Opiates are of limited efficacy in the management of deafferentation pain. TENS may be useful in some patients with brachial plexus avulsions, post-herpetic neuralgia (PHC), phantom limb pain and spinal cord injury. Generally, ablative neurosurgical procedures do not result in lasting relief in deafferentation pain. However, DREZ lesions have been shown to be effective in pain relief in conditions like brachial plexus avulsion, phantom limb pain, post-herpetic neuralgia (PHN), etc.[99]

Phantom Limb and Stump Pain

Stump pain is the pain in the residual limb after amputation, and phantom limb pain is a referred pain in the absent amputated limb. Long-term control of these pain syndromes is difficult and up to 80% of amputees are known to experience significant stump or phantom limb pain.[137] The underlying mechanisms of pain are poorly understood, and the most commonly used treatment regimens are ineffective at one year follow-up.

Acute Pain Following Amputation

Most patients undergoing amputation experience acute stump pain as a result of surgery and nearly all amputees experience phantom limb feelings after amputation. Such patients are frequently distraught if they have not been prepared about phantom limb sensation or pain. Stump pain is usually severe immediately after amputation and subsides with healing. Persistent post-operative pain or worsening pain may indicate an inadequate blood supply interfering with proper healing or may be due to post-operative infection.[135] The optimal treatment of acute post-ampuptation phantom pain includes patience, stress control and relaxation training.

Mechanisms of Pain in Chronic Stump and Phantom Limb Pain

Phantom limb pain has previously been ascribed to psychological mechanisms, peripheral nerve and CNS transmission mechanisms or centrally generated reverberating circuits. Evidence suggests that each major variation of phantom limb and stump pain may have different mechanisms and that stump and phantom limb pain having similar descriptions may have similar mechanisms.[134]

The following are some of the mechanisms underlying specific pain patterns seen in phantom limb pain.

Blood Flow

Decreased blood flow in the stump has been described to be associated with persistent burning, throbbing and tingling phantom limb and stump pain. An increase in peripheral blood flow to the stump can result in decreased pain. A further proof of a vascular related mechanism for burning phantom limb pain is the short-term effectiveness of sympathetic blocks and sympathectomy that increases blood flow to the limb.

Voluntary Muscle Spasm

In some amputees, cramp like pain is present when the residual limb muscles are in spasm and is relieved when they are relaxed. Such pain may respond to biofeedback training to reduce muscle tension.[136]

Psychological Factors

Current evidence[137] does not establish a relationship between the occurrence of phantom limb pain and psychological factors, but intensity may be affected by stress and exhaustion.

Treatment

The following are some of the guidelines for treatment. Complete evaluation of an amputee involves a team approach.[72] Evaluation includes correlation of pain with diet, weather, physical/mental stress and the use of prostheses. Residual limb pain is to be treated before tackling phantom limb pain. The prosthesis should be evaluated for its fitness and its effect on gait. If trigger points are present and pain is reproduced by them local blockade may be of use. When phantom limb pain is of a burning quality and related to decrease in stump temperature, it is probably due to decreased blood flow in the residual limb and may respond to biofeedback, peripheral vasodilators or sympathetic blocks. A cramping type of pain associated with spasm would be optimally treatment by muscle tension biofeedback and muscle relaxants. When pain is neither burning nor cramp like it is more difficult to treat, but short-term treatment may be effective with TENS, active motion exercises, ultrasound at the stump, steroids and sedatives/hypnotics. Neurosurgical ablative procedures with the exception of DREZ lesions may not result in long-term effective pain relief.

POST-HERPETIC NEURALGIA

Post-herpetic neuralgia (PHN) is a common cause of severe intractable neuropathic pain. PHN is a consequence of herpes zoster which is caused by reactivation of varicella zoster virus contracted in childhood.

The virus initially causes varicella and remains dormant for many years in the trigeminal, the geniculate or the dorsal root ganglia and re-erupts in the elderly or in immunocompromised states. The resulting segmental haemorrhagic inflammatory reaction of the skin and mucous membrane is very painful before, during or after the appearance of the rash. This pain subsides with healing, but if it persists for more than 1 month it is said to be PHN.

Natural History and Epidemiology

PHN occurs in 9–14.3% of patients with herpes zoster.[60,112] Of these, a third continue to have pain at 3 months and in another third it lasts for more than one year. Both the severity and incidence of PHN are directly related to the age of the patient. Demoragas[27] found that 50% of patients with herpes zoster who were over 60 years old and 75% over 70 years of age developed PHN 1 month after the rash. The sex incidence is equal and PHN has a predilection for the thoracic dermatomes, especially T5 and T6, and the ophthalmic division of the trigeminal nerve. Pain in PHN may be both steady and paroxysmal[106] and is described by patients as burning or gnawing for the constant pain and sharp or shooting for the paroxysmal component. The pathologic changes are characterised by haemorrhagic inflammation involving the dorsal root ganglion, peripheral nerve, roots, leptomeninges and the spinal cord.[53] Both central and peripheral mechanisms may be involved in PHN; innocuous sensory stimuli from the periphery may cause hyperaesthesia, dysaesthesia and allodynia and the failure of peripheral deafferentation surgery and the limited success of DREZ lesions point to a central mechanism.

Prevention of Post-Herpetic Neuralgia

Several studies[28,30,70] have found steroid administration in the acute phase of herpes zoster to be beneficial in reducing the incidence of PHN. The bulk of evidence supports the use of moderate doses of steroids, such as prednisolone 60 mg/day at the onset of HZ, in non-immunosuppressed patients with tapering of the dose over two weeks. Some of the other measures reported successful in reducing the incidence of PHN are sympathetic blockade,[24] amantadine,[41] levodopa and benserazide[128] and intramuscular alpha-interferon.[90] Significantly, acyclovir does not reduce the incidence or severity of PHN in immuno-competent or in immuno-compromised patients.[9,12,13,33,110]

Treatment

The past 60 years have witnessed a bewildering array of medical and surgical approaches for the treatment of PHN, the sheer number of which demonstrates the difficulties in managing this disorder.

Medical Treatment

Antidepressants and neuroleptics: Woodforde et al.[168] used amitryptiline to treat depression in patients with PHN and found that all patients had good pain relief at doses of 40 mg/day initially and stepped up to 100 mg/day. Watson[166] found that pain relief with amitryptiline occurred in patients who had no depression and at doses lower than those used for treating depression.

Anticonvulsants: Carbamazepine, phenytoin and valproic acid have been shown to be of limited use in PHN.[71]

Tropical capsaicin: Capsaicin (8-methyl N-vanilyl 1-6 nonenamide) selectively stimulates and then blocks unmyelinated sensory afferents from the skin and mucous membranes.[64-66] Capsaicin is thought to act by depleting substance P. It should be used 4–5 times a day for at least 4 weeks. Burning after application may be a significant problem, but may respond to lidocaine ointment and analgesics.

Other therapies: Repeated nerve blocks, ethyl chloride spray,[155] sympathetic blocks,[25] chlorprothixene[34] and epidural injection of methyl prednisolone[39] have all been claimed to be effective. Nathan[105] found TENS useful when used for a prolonged period of time.

Surgical Treatment

Stereotactic trigeminal tractotomy[59] in ophthalmic PHN was found to be effective. Nashold[99] found DREZ lesions to give good long-term results.

PAIN IN MULTIPLE SCLEROSIS

Pain is a common feature in established multiple sclerosis (MS) and is reported to occur in up to 55% of patients.[95] It may manifest as acute, subacute and chronic pain syndromes. Acute pain syndromes are exemplified by trigeminal neuralgia, Lhermitte's phenomenon, tic like extremity pain and painful tonic seizures.

Subacute pain syndromes are seen days or weeks after the onset of MS and typical examples are retrobulbar neuritis and painful peroneal and unlar nerve palsies. Treatment of MS with steroids or immunosupressants can itself lead to subacute pain syndromes due to vertebral compression fractures, haemorrhagic cystitis, etc. Relief of pain assumes a high priority in treatment of an incurable disease like MS. It is important to realise and characterise the type of pain syndrome for effective treatment.

In patients with a mean duration of illness of more than 10 years, chronic pain is common and is almost always associated with myelopathy. Three major pain patterns are dysaesthetic extremity pain, back pain and painful leg spasms. Dysaesthetic extremity pain has been treated with tricyclic antidepressants, DCS and DBS with varying degrees of success. Chronic back pain due to spastic weakness and abnormal stresses on the paravertebral muscles may accelerate degeneration of the intervertebral disc, resulting in herniation or

degeneration of the facet joints and mechanical pain. Treatment consists of NSAIDs, physical therapy and disc removal. Painful leg spasms may respond to muscle relaxants such as baclofen, dantrolene and diazepam, or a short course of high dose steroids. A novel approach in the management of severe pain and spasticity is spinal opiate administration[31] which is effective at lower doses when compared to parenteral administration and has the advantage of being non-destructive.[173] Neurolytic procedures like dorsal rhizotomy and intrathecal phenol have been found useful, but may worsen the neurological deficit.

PAIN SYNDROMES WITH CANCER

Pain is a common presenting symptom of neurologic involvement in cancer patients. Pain syndromes due to cancer can be due to various causes and can be broadly considered in three major categories.

The first and the most important category is pain associated with direct tumour infiltration of the dura, cranial nerves, spinal cord and peripheral nerves or compression of these structures by tumour in contiguous tissues, e.g. epidural spinal cord compression and brachial plexopathy.

The second category includes pain syndromes associated with cancer therapy including surgery, chemotherapy and radiation pain. Post-chemotherapy pain syndromes include peripheral neuropathy, steroid pseudorheumatism, aseptic necrosis of bone, headache and mononeuropathy. Post-surgical pain syndrome may be due to post-mastectomy pain, post-radical neck dissection pain, post-thoractomy pain and phantom limb and stump pain. Post-radiation pain may be due to radiation fibrosis of the brachial or lumbosacral plexus, radiation myelopathy or acute herpetic and post-herpetic neuralgia.

The third category of pain syndromes in cancer are not related to either cancer or its therapy (e.g. lumbar disc disease, epidural abscess, osteoporosis). It is, therefore, important to categorise the cause of pain in cancer patients for their optimal management.

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196 Trigeminal Neuralgia

Ramakrishna Easwaran

The Serpent comes
Fork tongued and unctuous
It slithers down the ganglion,
Fang flickering, nerve licking
Where and when to strike?

('Tic douloureux', a poem written by Roger Levy, a sufferer of trigeminal neuralgia)[97]

Trigeminal neuralgia is rated by patients as the worst of all pains that afflict mankind. Although tremendous progress has been made in the last three decades in alleviating the suffering caused by trigeminal neuralgia, its basic pathogenesis remains mysterious.

HISTORY

John Locke provided the first physician's description of trigeminal neuralgia when he treated the Countess of Northumberland in 1667.[66] In 1756, Nicholas André described two patients and gave the name 'tic douloureux'. The clinical description of the trigeminal neuralgic pain by John Fothergill, in 1773, can hardly be improved upon. The initial surgical procedures were essentially ablative. The first effective non-ablative surgical therapy was the introduction of microvascular decompression (MVD) by Jannetta[20] (Table 1).

Table 1: Landmarks in the treatment of trigeminal neuralgia

	Ablative		*Non-ablative*
1891:	Horsley, Taylor, Coleman—Intradural preganglionic root section	1932:	Dandy—Observation of vascular compression (proposed as cause but continued to perform root section)
1892:	Hartley, Krause—Extradural subtemporal Gasserian ganglionectomy	1952:	Taarnhoj—Surgical decompression of Gasserian ganglion (? minimal ablation) early success, high recurrence
1901:	Frazier, Spiller—Modification of Hartley-Krause operation to spare corneal sensation	1962:	Blom—Carbamazepine therapy Gardner-Vascular compression
1910:	Harris—Percutaneous alcohol ablation		
1925:	Dandy—Posterior fossa sensory root section	1967:	Jannetta—Early vascular decompression reports
1928:	Stookey—Differential middle fossa root section, dividing only the fibres of affected division	1975:	Jannetta—Microvascular decompression for trigeminal neuralgia, hemifacial spasms
1937:	Sjöqvist—trigeminal tractotomy		
1955:	Shelden—Trigeminal ganglion compression procedure	1984:	Fromm—Baclofen therapy Baker—Synergism of carbamazepine and baclofen
1971:	Leksell—Stereotactic radiation to produce Gasserian ganglion lesion	1989:	Zakrzewska—oxcarbazepine therapy[99]
1974:	Sweet, Wepsic—Radiofrequency rhizolysis, temperature monitoring, localisation by stimulation	1998:	Khan—Gabapentin, for trigeminal neuralgia in multiple sclerosis[51]
1981:	Håkanson—(Serendipitous discovery) retrogasserian glycerol injection	2007:	Obermann—Pregabalin therapy[70]
1983:	Mullan, Lichtor—percutaneous balloon compression		
1991:	Rand—Gamma knife radiosurgery		

INCIDENCE

The crude incidence rate of trigeminal neuralgia was reported to be 4.3 per 100,000 in the Rochester population based study.[50] The right side is more often involved than the left, in the ratio of 3:2. The disease is rarely bilateral (about 5% of cases), but the incidence of bilateral neuralgia in patients with multiple sclerosis is 18%.[65] Women have been reported to be more affected in most series from the West, while in Indian series men are more affected.[47,94] The maxillary (V2) division is the most common single division to be involved and nearly a third of patients have the pain in the maxillary (V2) and mandibular (V3) divisions, simultaneously (Fig. 1). There is over-representation of ophthalmic (V1) division and holotrigeminal neuralgia in the MVD series, due to selection bias. The mandibular (V3) division is similarly over-represented in many series of percutaneous ablative procedures.

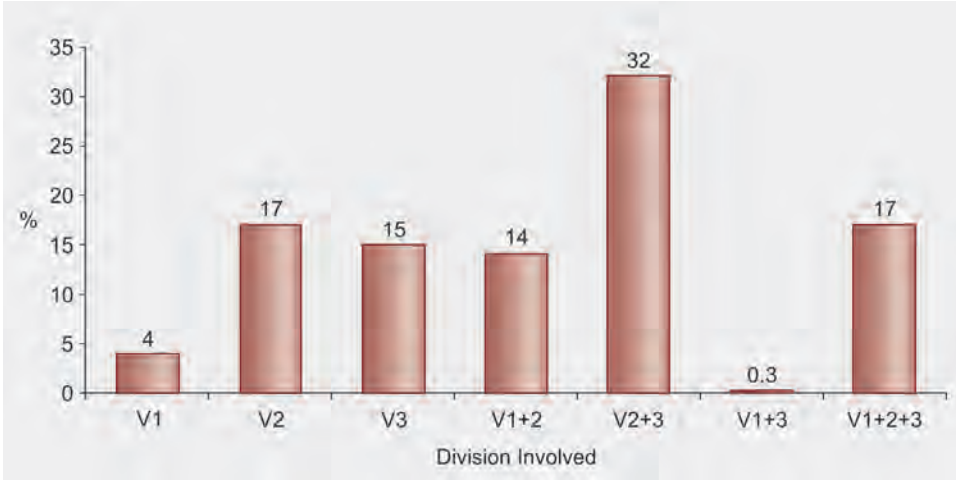


Fig. 1: Divisions involved in trigeminal neuralgia (based on data from 16 series of 8,124 cases)[94]

The age at onset is generally in the sixth decade (Fig. 2). Idiopathic trigeminal neuralgia and vascular cross compression are very rare in children.[18] The occurrence of trigeminal neuralgic pain in children should prompt a thorough search for another cause such as abscess or tumour.

CLINICAL FEATURES

Tic douloureux is diagnosed solely on the patient's history. The characteristic feature is the sudden stabbing (described as lancinating or lightening or electric shock like) pain in the distribution of one or more divisions (or branches thereof) of the trigeminal nerve, generally on one side. Each pain episode is stereotyped and it occurs as a brief spell lasting a few seconds or a minute. The onset of each spell is sudden and the intensity severe. Many such pangs of pain may be felt repeatedly in a short span of time and this leads the patient to describe the attack as going on for hours or days. Some patients describe a burning pain. The pain can occur spontaneously or may be triggered by light touch over the nasolabial fold, upper lip or tooth ('trigger zones'). Talking, smiling, eating (chewing or swallowing), contact with cold breeze or water on the face, brushing the teeth or shaving are common daily events that precipitate pain and become impossible tasks. Often the patient can give the history only by writing. The unshaved, halitotic and cachectic appearance signals unremitting prolonged spells of pain. The pain commonly starts in the teeth or gums and patients have usually had several teeth extracted before coming to the neurosurgeon. Some patients rub the face vigorously during the attack while most others guard their face from the slightest of contact. Patients learn to avoid cold drinks and fear the winter. There might be a sudden wince of the facial muscles in response to the pain and this characteristic gives the name tic douloureux. True hemifacial spasms are also seen along with trigeminal neuralgic pain and this is described as tic convulsive.[22] A single dolichoectatic vessel may be found compressing both the trigeminal and facial root entry zone in such cases. The pain may be confined to one branch of a division. The supraorbital/nasociliary (from V1), infraorbital/zygomaticotemporal (from V2) and inferior alveolar/auriculotemporal (from V3) branches may be exclusively involved.

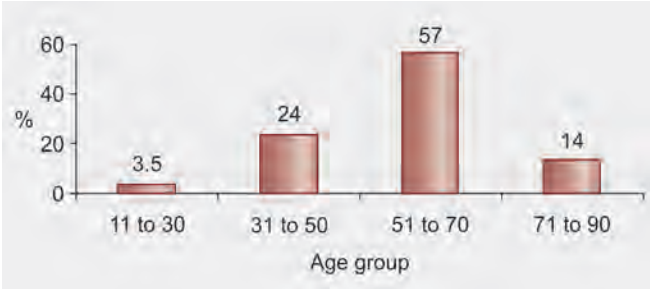


Fig. 2: Age at onset of trigeminal neuralgia (based on data from 16 series of 8,124 cases)[94]

The pain episodes are well known to spontaneously remit and patients may even be able to stop medication. The pain may cease for several months only to return with renewed vigour, increasing in severity and frequency with each episode. In due course, the attacks might cease and then start in a different division and rarely on the opposite side. Recently an attempt has been made to separate the above described 'classical' trigeminal neuralgia (TN 1) from the 'atypical' trigeminal neuralgia (TN 2). In the latter syndrome the pain is aching, throbbing or burning for more than 50% of the time and there is constant background pain but strictly confined to the anatomical distribution of the trigeminal divisions. TN 2 might represent progression of idiopathic TN 1 or it might indicate a secondary cause, such as tumour.[26] This entity of 'atypical' trigeminal neuralgia is not to be confused with atypical facial pain syndrome. 'Atypical' trigeminal neuralgia has also been treated with MVD and multiple vascular conflicts are the rule.[38] Familial trigeminal neuralgia is infrequent but well reported.[36]

Clinical examination is remarkable for the absence of physical signs. A slight sensory loss over the area of

pain may be disclosed by careful examination during the attack and is in itself not against the diagnosis of primary or idiopathic trigeminal neuralgia. Absent corneal reflex behoves a search for a cerebellopontine angle mass in a patient presenting with trigeminal neuralgia. Profound sensory loss may be due to a past ablative procedure but must lead one to suspect a secondary cause. Arterial hypertension, especially systolic hypertension, is seen more often than in age-matched controls. Good control of blood pressure alone may reduce the severity and frequency of trigeminal neuralgia. This author has had patients in whom the blood pressure was impossible to control, until the pain was relieved by MVD of the trigeminal root entry zone. Antihypertensive medication was no longer needed in some after surgery for trigeminal neuralgia. Hypertension caused by vascular cross compression on the vagal root entry zone or the ventrolateral medulla (neurogenic hypertension), its coexistence with trigeminal neuralgia or hemifacial spasm and its response to MVD of the vagus and medulla are a different issue altogether.[8]

PATHOLOGY

Trigeminal neuralgia has been classified into primary (idiopathic) and secondary varieties. The primary variety is far more common. In the secondary variety, there is a tumour, vascular malformation or cyst causing compression, stretch or distortion of the trigeminal nerve. Such cases account for 6% of all patients with trigeminal neuralgia.[60] The distinction between primary and secondary varieties was sacrosanct in the CT and pre-CT era but with the advent of MR imaging, the distinction is not as straightforward as it might seem. This is because a good degree of nerve compression by a vascular loop may be demonstrable with MR in the so-called 'idiopathic' cases. On the other hand, even in patients who have trigeminal neuralgia due to a mass lesion, the neuralgia has been reported to be due to concomitant vascular cross compression.[10] The pain gets relieved in such patients not merely with the removal of the mass but with MVD performed at the same time.[78] Epidermoid tumour in the cerebellopontine angle must be suspected in young patients and vestibular schwannoma in adults. The occurrence of trigeminal neuralgia on the contralateral side of the mass has been reported.[37,77] This is believed to be due to distortion of the brainstem, arachnoiditis or a contralateral vascular cross compression of the opposite trigeminal nerve. Unlike ipsilateral neuralgia, contralateral neuralgia generally resolves with the excision of the mass. If it does not do so, exploration of the affected nerve, MVD and partial sensory rhizotomy (PSR) might be needed.[35] Trigeminal neuralgia can be a false localising sign of raised intracranial pressure.[52] The list of lesions causing secondary trigeminal neuralgia is summarised in Table 2.

Table 2: Causes of secondary trigeminal neuralgia

Lesions causing secondary trigeminal neuralgia:
• Vestibular schwannoma[81]
• Epidermoid tumour[22,63]
• Meningioma[10]
• Petrous osteoma[79]
• Abscess[12]
• Tuberculoma[9]
• Cysticercosis[78]
• Chiari malformation[32]
• Cavernoma of V nerve[23]
• Aneurysm[91]
• Arteriovenous malformation[6]

The pathology in the idiopathic variety was not detectable before surgery until the advent of modern MR imaging in the last decade. After the widespread use of MVD, an extensive body of literature has been built up about the vascular compression on the trigeminal root. It is proposed that with age, the arteries become tortuous, elongated and rigid. This, coupled with the sagging of the brain, tends to bring the trigeminal nerve in to position of contact or compression by the vessels. The reported incidence of vascular cross compression has been as high as 96%.[42] Some, who are more rigid in their concept of what constitutes vascular cross compression, have found lower rates of such vessels during the course of posterior fossa exploration for sensory rhizotomy (11% of 57 patients).[1] Table 3 summarises the vessels implicated in the genesis of trigeminal neuralgia from an Indian study, which found compression in 98% of 58 cases.[86] These figures conform to a personal series of 98 cases of MVD.

Jannetta reported that the compression is on the rostral and anterior portion of the nerve when the pain is in the V2 or V2-3 distribution. The vascular conflict is on the caudal aspect of the root entry zone in V1 neuralgia.[43] This correlates well with the known anatomical fact of the inverted distribution of the fibres in the trigeminal root entry zone (caudal ones representing the V1 division). The degree of compression may be variable. While some vessels make only a contact, others distort and

Table 3: Vessels implicated in the genesis of trigeminal neuralgia

Findings from an Indian study of microvascular decompression[86]
• Arteries 84%
• Superior cerebellar artery or its branch 77%
• Anterior inferior cerebellar artery 2%
• Combinations of both 5%
• Veins 5%
• Combined artery and vein 9%
• No vascular compression 2%
Other reports:
• Dolichoectatic basilar/vertebral artery[85]
• Persistent trigeminal artery[17]
• Transverse pontine vein[61]

groove the nerve, even to the point of atrophy. In fact the nerve atrophy can be demonstrated in MR imaging.[27] The compression may be between two straight vessels running at an acute angle, rather than be caused by an elongated tortuous loop. The compression might be anywhere from the pontine attachment of the root up to the Meckel's cave. This was believed to be because of the variable length of the Obersteiner-Redlich zone, i.e. the junction of the central (oligodendroglial) and peripheral (Schwann cell) myelin in the trigeminal root.[41] A recent microanatomical study dispels this view and shows that the transition zone extends only one-fourth the length of the trigeminal root from the pons to the Meckel's cave.[72] Hence, some mechanism other than demyelination of the central myelin needs to be invoked to explain the trigeminal neuralgia due to more distal vascular conflicts. Additional findings such as arachnoiditis may also be seen. With modern MR imaging, it has become rare to find a small tumour as a surprise finding at surgery. Platybasia has been found to be more common in patients with tic douloureux than in controls.[49] This might alter vascular relations to favour cross compression. Reduced volume of the pontomesencephalic cistern by 13% has been reported on the symptomatic side by MR volumetry.[76] This might also contribute to crowding and promote vascular compression.

Enthusiastic espousal of the vascular compression theory must be tempered by the fact that vascular contact and compression may be seen in those who do not have trigeminal neuralgia. This has been shown in 26 out of 50 cadaver nerves.[39] It has also been shown in a recent 3 Tesla MR study of 110 persons, without trigeminal neuralgia, that 49% of the nerves made a contact with a vessel and contact with mild deviation of the nerve occurred in 15%. However, moderate or severe deviation of the nerve by the vessel was never seen in the asymptomatic person.[45]

In an ultrastructural study of trigeminal root entry zone biopsies obtained during MVD, axonopathy and axonal loss, demyelination, dysmyelination, residual myelin debris and the presence of excess collagen, including condensed collagen masses, were found.[24] Within zones of demyelination, groups of axons were often closely apposed without an intervening glial process. Pathological characteristics of nerve fibres were clearly graded with the degrees of root compression noted at operation. Remyelination has been noted and one wonders if this explains the spontaneous remission in pain.[59]

PATHOGENESIS

Gardner postulated that 'short-circuiting' between the demyelinated axons in the trigeminal root results in 'cross talk' (ephaptic transmission) leading to the paroxysms of pain.[30] The abnormal peripheral discharge has been shown by microneurographic recording during the course of radiofrequency gangliolysis.[15] Since remyelination cannot explain the immediate recovery after MVD, reversal of a conduction block caused by the compression has been invoked.[55,58] Impaired trigeminal nociceptive processing has been described in patients of trigeminal neuralgia, who have concomitant chronic facial pain. This has been proved by nociceptive blink reflex (nBR) testing and by recording pain related evoked potentials (PREP).[69] Prolonged latency and threshold elevation have been demonstrated during trigeminal evoked potential (TEP) studies in patients with the classical form of trigeminal neuralgia.[13] TEPs are altered in patients with trigeminal neuralgia secondary to tumours.[88] Arguing by the same token, an MR demonstrable vascular compression can be held as the cause of trigeminal neuralgia, if similar TEP abnormalities are seen. Trigeminal reflex elicited by electrophysiological study also helps distinguish the idiopathic and symptomatic varieties of trigeminal neuralgia.[21] Central mechanisms in the pontine nuclei or tracts may also play a part in the genesis of trigeminal neuralgia. Multiple sclerosis is the best example.

IMAGING

Trigeminal neuralgia remains a clinical diagnosis. CT scans are routinely done prior to definitive therapy for trigeminal neuralgia to exclude a secondary cause such as tumour. The mass lesion might be on the contralateral side.[37,77] CT might show dolichoectasia of the vertebrobasilar arteries and this can be confirmed by CT angiography.[85] Although dolichoectatic vertebrobasilar arteries may be present, the compression on the root may often be due to a superior cerebellar artery loop, rather than the dolichoectatic vessel. Figure 3 shows an example. MR imaging can demonstrate the neurovascular conflict and help select patients for and to plan the surgery (Fig. 4). Several MR techniques are available for imaging the artery and the nerve simultaneously. These include 3-D constructive interference in steady state (3-D CISS) and 3-D fast inflow with steady-state precession (3-D-FISP).[2] MR angiography with multiplanar reconstruction helps detail the anatomy of the arterial compression, while the veins are shown in 3-D CISS

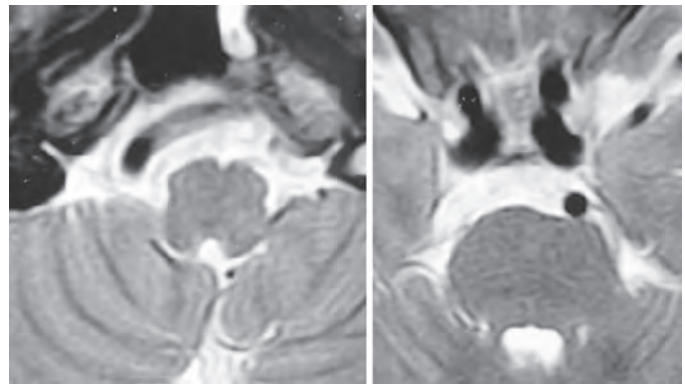


Fig. 3: Axial T2-weighted MR images of a patient with left trigeminal (V2) neuralgia although he has dolichoectasia of the carotid and vertebrobasilar arteries, the compression was on the ventral aspect of the nerve by a loop of the left superior cerebellar artery

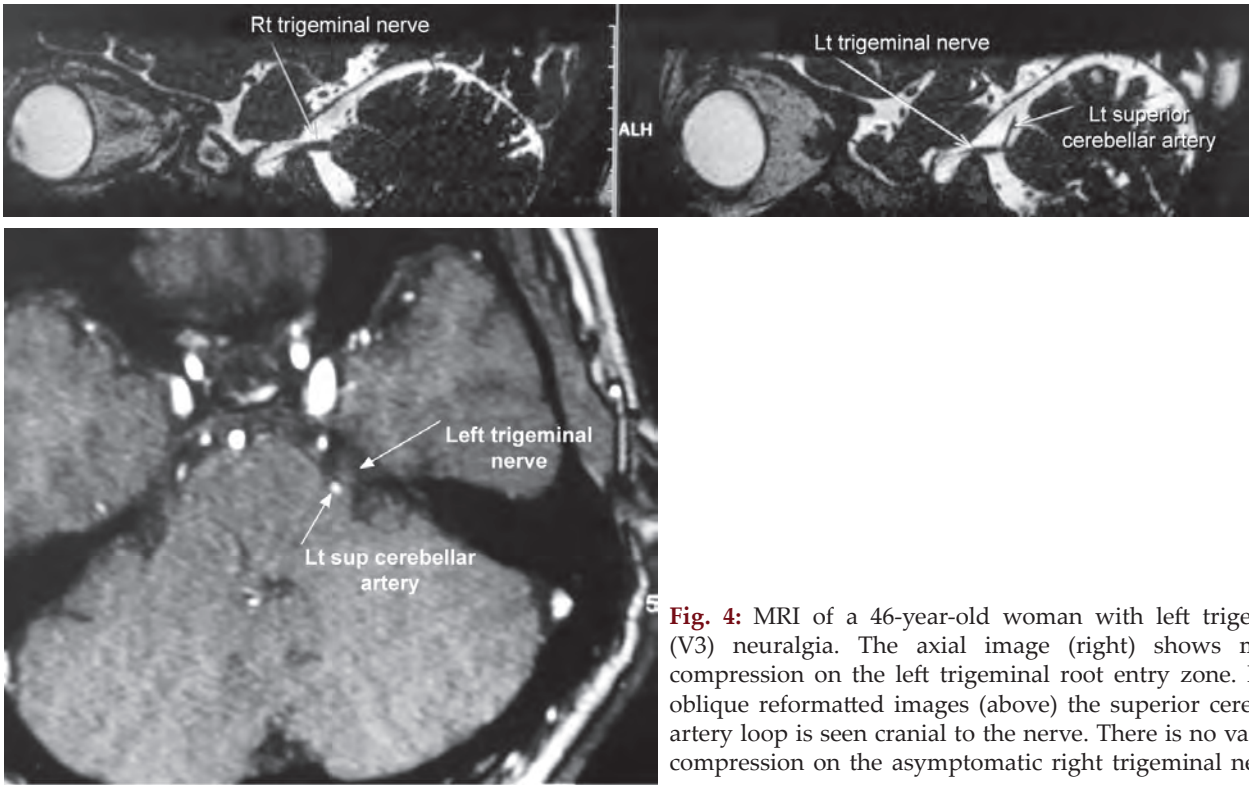


Fig. 4: MRI of a 46-year-old woman with left trigeminal (V3) neuralgia. The axial image (right) shows medial compression on the left trigeminal root entry zone. In the oblique reformatted images (above) the superior cerebellar artery loop is seen cranial to the nerve. There is no vascular compression on the asymptomatic right trigeminal nerve

imaging only. The pre-operative prediction of the site of compression and the exact vessel responsible was found correct in all 15 operated cases in one report.[96] On correlating with the surgical findings, the sensitivity of contrast enhanced MRA was 90.5% and the specificity 100% in a prospective, single blinded study.[71] Recently balanced fast-field echo (BFFE) imaging with 3-D TOF MRA and gadolinium enhanced 3-D SPGR imaging have been combined to accurately predict the neurovascular conflict.[64]

TREATMENT

Emergency Room Management

Traditional analgesics, including narcotics, make hardly any impact on the severe pain of trigeminal neuralgia. We have found a loading dose of phenytoin (15 mg/kg IV by infusion) to be of help in tiding over the crisis. Lignocaine can be used similarly.

Medical Therapy

Carbamazepine is the sheet anchor drug in managing trigeminal neuralgia.[93] The efficacy of carbamazepine has been proved in at least six placebo-controlled randomised trials.[19] The response is specific enough to use it as a 'therapeutic diagnostic test'. The dose that gives relief may be as little as 100 mg bid in some patients, while others get relief only with 1600 mg per day. The controlled release preparations used for epilepsy are not ideal for management of pain. It is ideal to keep the dose strength at a low level (200–300 mg) and increase the frequency (say 4–5 times a day). This gives sustained pain relief and helps minimise the peak dose ataxia, drowsiness and visual blurring. The patient must be told to take the drug before eating, washing, brushing or shaving. Skin rash and depression of blood counts are the most frequent reasons to switch over to another agent. The drug of choice to those intolerant of carbamazepine should be oxcarbazepine.[67] The pain generally escapes control with carbamazepine over some months or years. Drug additions at this stage improve the pain. The additional drug could be lamotrigine or baclofen.[44] Gabapentin has been used alone or in combination with trigger point block with a local anaesthetic.[57] Topiramate was found ineffective in a placebo-controlled crossover trial but only 3 patients were studied.[31] Although several non-antiepileptic drugs, like tizanidine, clomipramine, tocainide and pimozide have been tested in randomised trials, there is no conclusive evidence supporting any of them.[40] One study suggests that sumatriptan administered subcutaneously controls intractable trigeminal neuralgia.[48] Recently, injection of botulinum toxin in the face has been advocated for intractable trigeminal neuralgia, but this drug has been claimed to work for migraine, tension, headache and post-herpetic neuralgia too.[92]

Surgical Procedures

The ideal surgical procedure for trigeminal neuralgia should have a 100% initial success rate with no recurrence of pain on long-term follow-up. It should not leave the face numb and there should be no dysaesthesia or anaesthesia dolorosa. It should not be associated with

Table 4: Practical goals for procedures used to treat trigeminal neuralgia

Initial success	> 95%
Long-term recurrence	< 10%
V sensory dysfunction	
Ablative procedure	< 50%
Non-ablative procedure	< 2%
Minor complication	< 5%
Major complication/death	< 0.5%

mortality or morbidity to the neighbouring cranial nerves, brainstem and cerebellum. It should be suitable for all ages and should come at an affordable cost. The skill must not be difficult to master. It should also address the aetiology as is known now. Needless to say that such a utopian procedure does not exist. What we do have is a plethora of procedures, which are all good in parts, like a curate's egg. The problem is compounded by the master surgeons stridently championing one procedure over the other. It is too simplistic to assume that every neurosurgeon dabbling in trigeminal neuralgia surgery now and then would be able to get the same results as the experts with large operation volumes. Hence, we are forced to lower the bar and set reasonable and practical goals of treatment for trigeminal neuralgia (Table 4). Results from the literature are mere guideposts and milestones. Each surgeon must chart his/her own course, tempered by the knowledge of what he/she is good at.

Peripheral Procedures

The peripheral procedures, which were widely used earlier, have not found favour with modern neurosurgeons. These consist of trigeminal branch blocks with local anaesthetic, followed by alcohol injection or branch avulsion. Sensory loss is invariable. The pain invariably comes back within a few months in case of alcohol/glycerol block and within a year or two in case of branch avulsion.[28,29] The recurrence is due to quicker regeneration in the more peripheral sites of the trigeminal nerve, as compared to lesions made in the retrogasserian roots. Such peripheral procedures may need to be considered only in the very old and infirm patient with neuralgia restricted to one branch of a trigeminal division.

Percutaneous Retrogasserian Glycerol Rhizolysis

Glycerol, which can be harmlessly ingested by humans, is neurotoxic when injected into the nerve or around it. Percutaneous retrogasserian glycerol rhizolysis (PRGR) offers a low-cost, low-risk method of treating trigeminal neuralgia that can be easily repeated in case of recurrence.

Technique of Percutaneous Retrogasserian Glycerol Rhizolysis

The procedure can be done entirely under local anaesthesia, but it is ideal to have an anaesthetist for administering fentanyl-midazolam sedation or short intravenous propofol anaesthesia and for monitoring the patient. The Härtel technique for percutaneous needle placement through the foramen ovale is followed. The puncture is made on the skin of the cheek 2.5 cm lateral to the corner of the mouth. The needle is directed in the sagittal plane towards the pupil and in the coronal plane to a point 2.5 cm in front of the tragus on the zygomatic arch. Radiographical confirmation with anteroposterior and lateral views on C-arm image intensifier screening is essential to prevent accidental entry into the optic canal, superior orbital fissure or the carotid artery. CSF flow is seen when the needle is in the trigeminal cistern but this does not exclude subtemporal placement. Radiographical confirmation with iohexol trigeminal cisternography is desirable as it helps to visualise the retrogasserian fibres in the lateral view but it is not mandatory. More importantly it shows inappropriate positioning into the posterior fossa, middle fossa or cavernous sinus. The volume of the cistern is judged with iohexol and generally it is around 0.3 ml. About 0.15–0.3 ml of sterile 99.9% anhydrous glycerol is then injected. This viscous liquid is easier to push through a 19G spinal needle. The injection is done in the head up position. Mixing radio-opaque tantalum powder with glycerol helps in marking the trigeminal cistern permanently.[53]

Results of Percutaneous Retrogasserian Glycerol Rhizolysis

The initial complications include headache, transient cardiac dysrhythmia, hypertension, seizure, temporal lobe haematoma, other cranial nerve palsies due to spread of glycerol, oral herpes and aseptic/bacterial meningitis. The procedure fails in about 10% due to technical reasons. About 70% of patients, in whom the procedure can be completed, note a hypalgesia in the face but hypoaesthesia occurs in about 30% only. Dysaesthesia and corneal sensory loss occur in less than 2%. Anaesthesia dolorosa is not seen. The initial relief evaporates as the patient is followed-up for longer periods. The recurrence rate is about 20% at 1 year and by 4 years it might be as high as 70%.[89] The factors, which predict success of PRGR, are patients without any constant facial pain, patients with immediate facial pain during glycerol injection and patients with new trigeminal deficits after PRGR.[73]

Percutaneous Radiofrequency Thermocoagulation (PRFTC)

This procedure depends on the differential sensitivity of nerve fibres to heat damage. The myelinated touch fibres are more heat resistant than the unmyelinated pain fibres. Therefore, controlled heating using radiofrequency energy ablates the pain carrying fibres, while theoretically leaving the other sensations largely intact. The technique enables proper localisation in the 'stimulation mode' and temperature monitoring in the 'lesion mode'.

Technique of Percutaneous Radiofrequency Thermocoagulation

The anaesthetic technique is similar to that for PRGR, but PRFTC is potentially more painful than PRGR and there are greater changes in the blood pressure and pulse. The crux of the anaesthetic technique is to keep the patient pain relieved, while keeping the sensorium intact for getting patient feedback during stimulation. The needle placement technique is the same. The 20G needle is directed at the vertex of the angle between the shadows of the clivus and the petrous ridge in the lateral view of the C-arm image intensifier screening. The 7.5 mm straight electrode is the standard one passed through the needle. In the AP view, the target is 9 mm medial to the lateral border of the internal auditory meatus. The electrode tip is placed just proximal to the clivus for V3, at the clivus for V2 and projecting just beyond the clivus for V1 access, as seen in the lateral projection. Impedance monitoring is not routinely done. When the electrode is properly placed, the impedance should be 150–350 Ω. The impedance is higher if the electrode is in non-neural tissue.

Next, stimulation of the retrogasserian root is done with 100 mV square wave current at 50 Hz and 1 msec duration. This should produce a tingling paraesthesia in the distribution of the desired root. The stimulation current strength and frequency are increased in steps until the patient reports the paraesthesiae. If more than 0.5 V is needed or if there is a motor response, the electrode tip must be repositioned. Having confirmed the proper placement radiographically and by stimulation testing, the lesion is made under short anaesthesia. The size of the coagulum in the roots depends on both the current strength (in milliampere) and the duration. The lesion generator machine generally automatically selects the current strength and voltage when the operator sets the desired temperature. The usual limit is 60°C for 60–90 seconds. If the threshold for stimulation is high, a higher temperature setting is needed for lesioning. The end point is hypoalgesia (tested with a pin on the face) and not hypoaesthesia. This can of course be tested only when the patient awakens enough from the anaesthesia. If adequate numbing has not been achieved, additional lesions can be made in 5°C increments up to 80°C. If the smaller cordotomy type electrode is used, anaesthesia may not be needed and this ensures sensory testing as the lesioning proceeds. However, the cordotomy electrodes do not generally permit temperature monitoring. Corneal sensation can be protected by repeatedly testing the blink repose to light touch over the eyelid or eyelashes. Tew electrodes are smaller than the standard ones and are curved. The incidence of motor palsy, corneal anaesthesia and dysaesthesia are lower with the Tew electrode.[65]

Results of Percutaneous Radiofrequency Thermocoagulation

About 93% of patients undergoing PRFTC report immediate and excellent or good pain relief. Around 15% have recurrence of pain within 5 years and by 15 years an additional 10% have had recurrence of pain. There is an inverse relation between the degree of hypalgesia achieved during the procedure and subsequent recurrence. The sensory loss might not trouble most patients in the mandibular or maxillary division but corneal anaesthesia with neurogenic keratitis occurs in about 9% of patients. Painful dysaesthesia (20%) and anaesthesia dolorosa (1%) are other undesirable effects.[65] Masticatory weakness due to motor root involvement is seen in about 20% but it generally resolves fully in 3–6 months. The rare complications are carotid-cavernous fistula, monocular blindness and 6th nerve palsy.[25]

Percutaneous Trigeminal Balloon Compression (PTBC)

This procedure may be looked upon as a closed version of the original Shelden procedure of open trigeminal ganglion compression, reported in 1955.

Technique of Percutaneous Trigeminal Balloon Compression

In the procedure described by Mullan and Lichtor, a 14G needle is passed percutaneously up to the foramen ovale but not into it. A balloon catheter is pushed for 1 cm beyond the needle tip and is inflated to 0.5 cc for about 1–10 minutes.[68] The balloon inflates to a pear shape and this can be seen under image intensifier screening, as the inflation is done with iohexol. The shorter balloon inflation time is associated with lower rates of initial pain relief, lesser facial dysaesthesia and a higher recurrence risk. Higher inflation pressures are associated with greater incidence of transient bradycardia, severe hypertension or hypotension during the procedure. The incidence of trigeminal motor weakness is the highest with PTBC as compared to PRGR or PRFTC.

Results of Percutaneous Trigeminal Balloon Compression

In one 20-year follow-up study, all except one of 522 completed procedures had initial improvement in their pain. Recurrence rate was 19% at 5 years and 32% over 20 years. Painful dysaesthesia occurred in 4% but there was no neurogenic keratitis or anaesthesia dolorosa.[87]

Comparison of the Three Percutaneous Ablative Techniques

There are several studies of each of the percutaneous techniques but there has been no randomised study comparing the three methods so far. Morgan and Tew have analysed the results of studies since 1989 reporting 100 patients or more for each of the techniques. Table 5 is derived from their exhaustive analysis. The references to the individual studies are given in their analysis.[65] The largest reported experience is with PRFTC and this has also had the longest follow-up reports. Dense sensory loss is associated with higher rates of pain relief, less

Table 5: Comparison of the three percutaneous ablative techniques for treating trigeminal neuralgia[65]

	PRGR	*PRFTC*	*PTBC*
No. of studies	12	14	9
No. of patients	2,273	8,246	1,737
Follow-up (years)	5	7	4.3
Long-term pain relief	57%	71%	76%
Troublesome dysaesthesia	4.5%	5.5%	6%
Corneal anaesthesia	4.3%	5%	0.4%
Trigeminal motor weakness	1.1%	11%	8.4%
Cranial nerve palsy	0%	0.6%	0.6%
Minor morbidity	0.6%	0.3%	0.3%
Major morbidity/mortality	0.2%	0.1%	0.1%

recurrence rate, longer time to recur and higher rate of troublesome dysaesthesia.

Microvascular Decompression

MVD surgery has been dealt with extensively in another chapter of this textbook. Hence, only some pertinent issues and findings from recent literature are addressed here.

Table 6 summarises the indications and contraindications for MVD. Fitness rather than the age should be the determinant.[5] None of these are absolute and there is every need to tailor-make the decision to the patient.

Microvascular decompression surgery can be accomplished in a minimally invasive manner. Over the years, the size of the incision and the bony opening has diminished. Self-retaining cerebellar retractors can often be dismissed, especially when an endoscope is also used. Personal preference is not to use self-retaining retractors as far as possible, as we feel that the retraction distorts the vascular relations to the nerve. Retraction has been associated with hearing impairment and with accidental tear of the petrosal vein.[84] A contrary opinion, favouring the use of self-retaining retractor is expressed in a recent

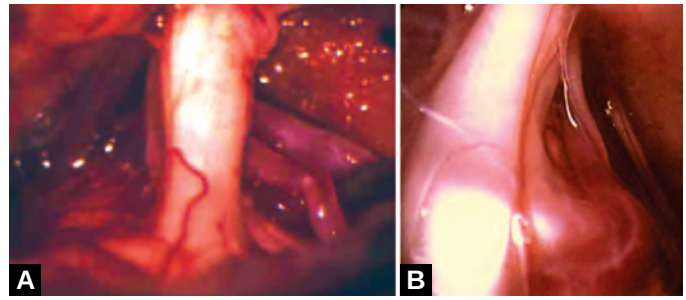
Table 6: Indications and contraindications for MVD

Indications for MVD

- Failure of medical therapy
  - Lack of initial response
  - Escape of control with medication over time
  - Unacceptable side effects of medication
- Patient fit for anaesthesia
- V1 division pain (singly or in combination)
- MR demonstrable compression/distortion by vessel
- As a primary procedure for fit patients, especially the young
- As a secondary procedure when pain recurs after a previous ablative procedure
- Tic convulsif-associated need for facial MVD
- Patient choice (those who are averse to facial sensory loss)

Contraindications for MVD

- High anaesthetic risk, medical risk
- Anaesthesia dolorosa from a previous ablative procedure
- Pain on the side of the only good hearing ear
- Very elderly patient



Figs 5A and B: Comparison of the views obtained of the left trigeminal root entry zone and the superior cerebellar artery vascular compression from microscopic. (A) and endoscopic. (B) perspectives in two different patients

article.[33] A bulge from the petrous bone (endostosis) may cover the view of the trigeminal nerve in about 4% of cases. It can be drilled away or endoscopic assistance can be used to avoid drilling.[83]

While some prefer to do the vascular mobilisation under the endoscope, others (including me) prefer to use the endoscope as a visualising tool (see Figures 5A and B for comparing the microscopic and endoscopic view of the trigeminal root entry zone and the vascular conflict). This is especially so for compression on the ventral portion of the root. In one study, of 113 endoscopically assisted MVD procedures, in 38 patients (33%), endoscopy revealed arteries that were poorly seen (25%) or not seen at all (8%) with the microscope.[90] Dolichoectatic vessels are no longer a contraindication for MVD. On exploration, a non-dolichoectatic vessel or vein may be found to be the cause of the trigeminal root entry zone compression, rather than the dolichoectatic vessel *per se*. Even if the dolichoectatic vessel were found directly distorting the root, it can be effectively encircled.[95] Use of fenestrated aneurysm clip and sling to draw a vessel away from the nerve is a recently described technique, for long and ectatic arteries that repeatedly fall back into a position of compression, despite adequate arachnoid dissection.[7] The distance between the acousticofacial bundle and the trigeminal nerve is small when the tentorial angle is steep (< 50°) and this limits the space for vascular manipulation.[80]

Every series of MVD has shown a fall in the complication rate, as experience builds up and as technical modifications are adopted.[62] The recurrence rate was higher when muscle was used as the interposing substance. Muscle was replaced by polytetrafluoroethylene (PTFE-Teflon®) pledgets. These pledgets must be fluffy and cut to the required shape and size. The pledget must be placed in contact with the vessel, rather than in close contact to the nerve. Persistent headache due to aseptic meningitis and Teflon® induced granuloma have been reported.[14,16] Transient brainstem signal intensity change on MRI after MVD has been noted.[3] The mortality for trigeminal MVD is mainly due to cerebellar injury and brainstem infarction. The petrosal vein has been coagulated and divided with no consequences in many patients, while there are reports of death due to venous infarction of

the brainstem after petrosal vein tear or intentional coagulation.[62,84] The complications of trigeminal MVD, their frequency in the author's personal series and the techniques of avoidance are listed in Table 7.

Table 7: Complications and avoidance of complications of MVD (figures from personal series)

Complications and avoidance—Trigeminal MVD	*Frequency N = 98*	*Avoidance*
New facial numbness	3%	Avoid coagulation on V nerve, irrigation during small vein coagulation, keep Teflon away from nerve
Hearing impairment	4%	Avoid excess retraction, avoid tailed cottonoids on VII-VIII nerves, BAER monitoring[75]
Vestibular syndrome	4%	Same as above, wax mastoid air cells on the way in and out
Facial paresis	3%	Same as for VIII nerve. Occurred in a delayed fashion in two patients due to? Teflon reaction, responded to steroids in 2–3 weeks
Trochlear palsy	0%	Reported in literature Avoid dissecting on tent undersurface, ensure that Teflon is not pushed too high
Abducent paresis	2%	Use low pressure suction, take care when mobilising dolichoectatic vessel
CSF leak	5%	May be from wound, ear or through nose (paradoxical rhinorrhoea). Meticulous dural closure, if needed with pericranial graft, is essential. Waxing mastoid air cells
Pseudomeningocoele	1%	Dural closure, bone replacement. May need lumbar drainage
Meningitis	2%	Peri-operative antibiotics, avoid CSF leak
Chronic operation site pain	10%	Avoid cutting greater occipital nerve during exposure, replace bone at craniectomy site
Brainstem infarct	1%	Petrosal and pontomesencephalic vein coagulation to be avoided
Cerebellar infarction or haematoma	1%	Adequate CSF drainage before retraction, intermittent release of retractor, avoid a retractor that juts out of the field too much which may be bumped accidentally
Supratentorial haematoma	1%	Avoid excessive CSF suctioning, avoid mannitol, take care when applying the pins of the head frame

The early long-term results of MVD have been well documented.[11] The best results come from centres and surgeons with a high volume of work.[46] The results are always better in those who have not undergone a previous ablative procedure. While failures may be due to missed vessels, recurrences might be due to recanalisation of veins.[56] The results from a personal series of 98 cases of trigeminal MVD are presented in Table 8. This is in keeping with the much larger series of cases.

To summarise, the advantages of MVD over the ablative procedures are the near-absence of facial sensory loss, least long-term recurrence and the best patient satisfaction in the successful cases. These must be balanced against higher cost, a slightly higher risk of neighbourhood neurological dysfunction and mortality. At the present time MVD seems to be closest to the ideal goals set in Table 4.

Partial Sensory Rhizotomy

The middle fossa rhizotomy procedures are now history. The posterior fossa procedure is done during the course of MVD operation, if no vascular compression is seen. The facial numbness is lasting and the inferior part of the nerve is spared for preserving corneal sensation. Naturally, the patients undergoing PSR are less satisfied with the outcome than those getting relieved with MVD.[98]

Radiosurgery

The latest (and the most expensive) method of treating trigeminal neuralgia is to ablate the retrogasserian cisternal part of the trigeminal nerve with gamma knife radiosurgery. Linear accelerator based radiosurgery seems to be nearly as effective.[34] The lower radiation dose (70 Gy) with a single 4 mm isocentre results in less sensory dysaesthesia. Two isocentres and an initial higher dose (90 Gy) appear to relieve pain better and faster—even this takes about 3 weeks.[4] Targeting with MRI is superior to targeting with CT.[100] Generally, some relief is reported in around 80% of patients. Troublesome sensory loss is seen in 10%.[54] A recent study reports relief in 44% and improvement in 70% at 3 years.[82] Radiosurgery has been used in patients with multiple sclerosis but they fare poorer than the idiopathic variety. In a retrospective comparison (of prospectively maintained data), it was found that posterior fossa exploration (MVD and PSR) gave better outcome than radiosurgery.[74]

CONCLUSION

From purging prescribed by Locke to gamma knife radiosurgery, we have come a long way in treating trigeminal neuralgia. It is sobering that till date no randomised controlled trial is available to compare the results of the various procedures used to treat trigeminal neuralgia (and none is in the offing). Therefore, the surgeon has to base his decisions on level 3 evidence at best and blend it with the surgeon's personal experience. It is essential

Table 8: Early and follow-up results of trigeminal MVD (personal series)

	Results of Trigeminal MVD			
	All cases	*Primary MVD*	*MVD after ablative procedure*	*Comments*
Early results	N = 98	N = 77	N = 21	
Total relief	91%	96%	77%	4 patients took a week to get relief
Partial relief, reduced medication	4%	1.3%	14%	
No relief	2%	1.3%	4.5%	1 had no compression, rhizotomy not done. 1 had vein that could not be mobilised
Disabled/death	2%	1.3%	4.5%	1 disabled from cerebellar haemorrhagic infarction, 1 petrosal vein coagulation led to brainstem infarction
Follow-up results (minimum 5 years, longest 12 years)	N = 47	N = 38	N = 9	
No recurrence	81%	84%	67%	
Recurrence, controlled with medication	13%	11%	22%	
Recurrence, not controlled with medication, needing another procedure	6%	5%	11%	

to inform the patient of the choices available, results and unwanted side effects, so as to make the patient a partner in choosing the treatment. A surgeon who is a one-trick pony should guard against the tendency to fit all his/her patients into a Procrustean bed. It is hoped that the future will allow us to raise the bar further towards the utopian ideal method of treatment alluded to earlier.

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197 Glossopharyngeal and Other Cranial Neuralgia

Ravi Ramamurthi, Goutham Cugati

INTRODUCTION

Weisenberg, in 1910, was the first to describe severe pain in the distribution of the glossopharyngeal nerve.[60] The word glossopharyngeal neuralgia was coined by Harris in 1926.[17] It has a striking similarity to trigeminal neuralgia with a few exceptions.

CLINICAL FEATURES

Glossopharyngeal neuralgia is described as a paroxysmal painful condition confined to the somatosensory distribution of the IX nerve (ear, tonsillar region, larynx, posterior 1/3rd of tongue and nasopharynx) and triggered off by swallowing, coughing, laughing, speaking and yawning. The pain is described classically as lancinating and may last from a few seconds to several minutes. It can also cause an unpleasant sensation in these areas, palatal myoclonus, syncope and cardiac arrest. As is usual with paroxysmal painful syndromes, it is characterised by periods of exacerbation and remission. The period of remissions may vary from a few months to several years. The longest known remission is 20 years.[44,58] A very small percentage of patients with glossopharyngeal neuralgia occasionally become hypotensive, bradycardic, lose consciousness and have seizures associated with a paraoxysm of pain.[37] This syndrome, called vagoglossopharyngeal syncope, is due to enhanced vagal outflow. The association between glossopharyngeal neuralgia and syncope was initially described by Riley et al. in 1942.[42] The cause of seizures is thought to be due to cerebral infarction secondary to episodes of asystole.[41]

CAUSES

Glossopharyngeal neuralgia is thought to be caused by irritation of the IX cranial nerve and most of the time the source of irritation is never found. Some of the known causes producing this type of pain are:

- Vascular loop pressing over the cisternal portion of the IX nerve
- Benign and malignant lesions of the skull base
- Local infections and tumours in the throat and mouth
- Eagle's syndrome
- Infarction (Lateral medullary)
- Multiple sclerosis.

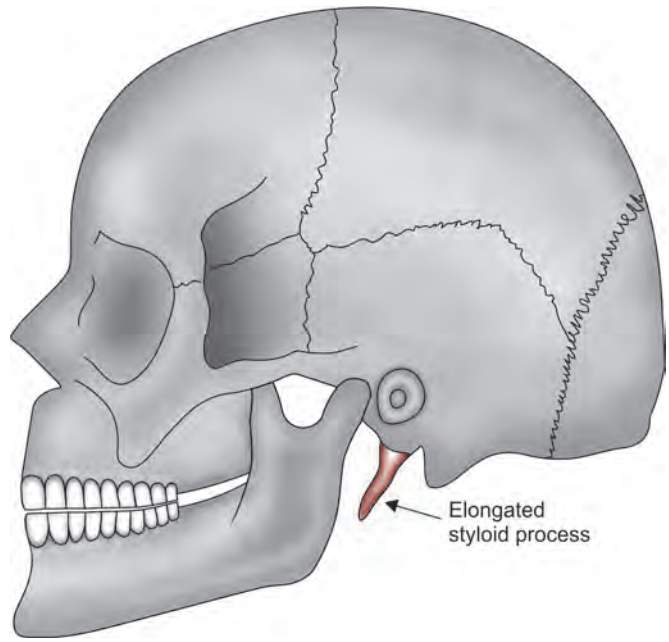

Fig. 1: Diagram of the skull showing elongated styloid process

In Eagle's syndrome, an elongated styloid process (Fig. 1) or an ossified stylohyoid ligament results in the compression of the glossopharyngeal nerve.[50] This has been described mostly as an acquired condition after trauma or a surgical procedure in the throat like tonsillectomy.[27] Chiari type I malformation presenting as glossopharyngeal neuralgia has been reported by Kanpolat et al.[25]

Although there has not been so strong an association of glossopharyngeal neuralgia and multiple sclerosis as seen with trigeminal neuralgia, there have been reports of glossopharyngeal neuralgia being seen in patients with multiple sclerosis.[24,44]

EPIDEMIOLOGY

A comparison of epidemiological and clinical features of trigeminal neuralgia and glossopharyngeal neuralgia in Rochester revealed that the overall age and sex adjusted annual incidence rates were significantly higher for trigeminal neuralgia than for glossopharyngeal neuralgia (4.7 vs 0.8 per 100,000 population).[26] The ratio of incidence of trigeminal neuralgia to glossopharyngeal neuralgia as described by Spruling and Grantham[53] is

70:1, by Brzustowicz[10] 88:1 and by Böhm and Strang[7] 100:1. Glossopharyngeal neuralgia is milder than trigeminal neuralgia, as indicated by the number of episodes, treatment and characterisation of pain. The right side is affected more often and bilateral involvement is less common in trigeminal neuralgia, as compared to glossopharyngeal neuralgia.[26]

EXAMINATION

The patient suffering from glossopharyngeal neuralgia may not have any neurological deficits. If a lesion in the skull base is the cause for the neuralgia, there may be multiple cranial nerve deficits, depending on the extent of the lesion. An enlarged styloid process may be palpable in the tonsillar fossa as in Eagle's syndrome. Digital palpation of the styloid process often reproduces pain or a foreign-body sensation.[27] A thorough ENT evaluation is required if local pathology is suspected.

DIAGNOSIS

Previously, cocaine test was used to confirm glossopharyngeal neuralgia. This was first used at the Mayo Clinic in 1925. The application of 10% cocaine solution to the throat gives relief of pain in a classical patient with glossopharyngeal neuralgia and also predicts a better outcome from surgery.[44] X-ray lateral views of the skull base and cervical spine may show an enlarged styloid process ipsilateral to the side of pain which helps to diagnose Eagle's syndrome.[27] ECG is mandatory for all patients and especially those having syncopal attacks. ECG monitoring, done during swallowing induced syncope (loop monitoring), shows cardiac asystole which is characteristic of glossopharyngeal neuralgia.[30]

MRI is an important investigation to rule out a tumour, one of the common causes of symptomatic glossopharyngeal neuralgia. Gadolinium enhanced images will pick up even small lesions and, in larger lesions, it clearly delineates the extent of the tumour. Schmitz et al.[48] and Huang et al.[21] proposed that 3D constructive interference in steady state (CISS) and 3D fast imaging with steady-state free precession (FISP) MR angiography, may be useful for evaluating neurovascular contact of the nerve root exit zone of the glossopharyngeal nerve, which is located in the supraolivary fossette. The posterior inferior cerebellar artery (PICA) is the most common offender followed by the vertebral artery, the anterior inferior cerebellar artery (AICA) and other vessels or combinations of vessels.[20,25,38,39,46] Brihaye et al.[8] and Kondo[29] have observed a tortuous and atheromatous vertebral artery as the offender in glossopharyngeal neuralgia. The AICA divides into cranial and caudal branches of which the caudal trunk is supposed to be in proximity to the nerve root entry zone. The diameter of the offending artery was also found to be greater as compared to the opposite side.[20]

Balloon occlusion test using double microcatheter technique helps to identify the vessel responsible for glossopharyngeal neuralgia. Once the microcatheter is in the desired vessel, the balloon is inflated to block the vessel which will make the pain disappear, while deflation of the balloon reproduces the pain. This test is repeated several times and the same pattern seen consistently confirms vascular compression as the aetiology. This way, patient selection for MVD can be done. This procedure may lead to complications like thromboembolism, balloon migration, premature deflation and others.[18]

TREATMENT

Medical Management

The medical management of this condition is similar to that of trigeminal neuralgia and the medications used include carbamazepine, oxcarbazepine, gabapentin, pregabalin, phenytoin and several other newer antiepileptics.[34] Antidepressants like amytriptyline have also been used in treating this condition. Neuropathic pain is generally not controlled by opioids. However, Kouzaki et al.[32] have described the usefulness of opioids in glossopharyngeal neuralgia and enumerated the possible mechanisms. Opioids control neuropathic pain by their effects on cortical brain regions and the thalamus, the descending antinociceptive pathway (via actions on the periaqueductal grey matter) and by modulating pain transmission in the spinal dorsal horn.

Surgical Management

Surgery should be advised when medical management fails to control the pain. This can be microvascular decompression in the posterior fossa or section of the glossopharyngeal roots in the neck or in the posterior fossa.[2,14,35] The supraolivary fossette, which is the most medial portion of the cerebello-ponto-medullary angle, is close to the root entry zone of the glossopharyngeal nerve and is the vulnerable location for neurovascular decompression surgery.[46] In patients with cardiac syncope, peri-operative placement of a temporary pacemaker is advocated.[15]

Microvascular Decompression

(Refer to Chapter 199 on microvascular decompression.) Glossopharyngeal nerve root section in the posterior fossa gives good results. Before surgery, if the patient is weak from malnutrition, as a result of difficulty in swallowing due to severe pain, application of a local anaesthetic to the throat before each meal would help the patient pick up strength. The glossopharyngeal nerve emerges out of the skull along with the vagus nerve roots through the jugular foramen. The glossopharyngeal roots are rostral and are identified from the vagal roots by a dural partition, which separates the fibres at their exit from the skull. This makes it easy to pick up and divide the glossopharyngeal roots. Gentle handling is necessary while isolating the nerve roots, to avoid

cardiac abnormalities and sudden changes in blood pressure. Sometimes, division of the glossopharyngeal root may give rise to an increase in blood pressure due to its connection with the carotid sinus. As the posterior auricular branch of the vagus nerve is at times involved in the pain, a few rostral fibres of the vagus nerve should also be divided.[11,14,48,55] The results of glossopharyngeal section are most gratifying. Transcranial endoscopic approach for glossopharyngeal neurotomy has also been tried with good outcome.[5]

Ferroli et al. in their series of 31 patients found vascular compression of the IX cranial nerve in all the patients.[16] It is found that the offending vessels are usually the branches of the posterior inferior cerebellar artery, vertebral and rarely AICA. There is a possibility of a hypertensive crisis, while handling the glossopharyngeal roots at the root entry zone near the brainstem.

Resurgery (MVD) in patients with recurrent glossopharyngeal neuralgia has been performed with good results. Patients who had evidence of vascular compression in their initial surgery, followed by drug resistant recurrence of pain are the ideal candidates for resurgery.[16] Recently, there has been a report of keyhole microsurgery with good outcome.[36] Gamma knife radiosurgery has been used for intractable pain with the target being the distal part of the nerve and the maximum dosage being 75 Gy. More studies are awaited to determine the optimal radiation dose and target of GKS for achieving long-term pain relief.[61]

Resection of the elongated styloid process or the ossified stylohyoid ligament will provide relief of pain in Eagle's syndrome. A lateral transcutaneous approach and resection is required.[50]

Other Ablative Procedures

Percutaneous rhizotomy of the glossopharyngeal nerve in the jugular foramen should be undertaken only by surgeons trained in this technique. The surgeon and patient have to be aware of the unavoidable sensorimotor deficits of the IX and X nerves.[51] Tractonucleotomies at the medullary level should be reserved essentially for pain of malignant origin.[51] Microwave ablation of the glossopharyngeal nerve has been tried.[57]

Complications

Post-operative complications of surgical treatment of glossopharyngeal neuralgia have been described in many series:

- Sensory and motor deficits of IX and X nerves
- Vocal cord paralysis[36]
- Cerebellar or/and brainstem infarction
- Hypertensive crisis
- CSF leak and pseudomeningocoele
- Intra-operative mortality.[57]

GENICULATE NEURALGIA

Geniculate neuralgia, also known as nervus intermedius neuralgia, is characterised by pain deep in the ear radiating to the pinna. The pain is lancinating and, unlike other typical neuralgic pains, may last for an hour or so. It is due to abnormalities of the somatosensory branch of the VII cranial nerve (nervus intermedius of Wrisburg) and the geniculate ganglion. Patients have also complained of having salivation, bitter taste, tinnitus and vertigo during the pain attacks which might reflect the central connections of the nervus intermedius.[23]

The pathology in this condition is presumed to be similar to any other neurovascular compression, where a vascular loop is causing compression over the root exit zone of the nervus intermedius.[23] Jannetta has described microvascular decompression for such patients with favourable results. Geniculate neuralgia can also be seen in Ramsay Hunt syndrome which is caused by varicella zoster virus. Rash with facial paralysis are the additional features seen in patients with Ramsay Hunt syndrome.[56]

Geniculate neuralgia may respond to carbamezapine. Operative treatment consists of MVD or section of the nervus intermedius or the geniculate ganglion. This was first done by Clark and Taylor in 1909. Rupa et al.[43] recommend a combined posterior fossa-middle fossa approach for adequate exploration and/or section of the V, IX and X cranial nerves, as well as the geniculate ganglion and nervus intermedius. Sachs[45] recommended surgery under local anaesthesia, so that the nerve may be stimulated and the patients' pain confirmed. Gamma knife is an alternative, but studies on the outcome are awaited.[23]

PERSISTENT IDIOPATHIC FACIAL PAIN

Persistent idiopathic facial pain (PIFP) refers to pain along the trigeminal nerve distribution that does not fit into the classical description of other cranial neuralgias. Previously termed as atypical facial pain, in 1924, by Frazier and Russel, there is no obvious cause and the pathophysiology is unknown.[13,54]

The International Headache Society defines PIFP as follows:[19,54]

- Pain in the face
- Pain confined at onset to a limited area on one side of the face, which is poorly localised
- Pain present throughout or for most of the day and daily
- No sensory loss or other physical signs
- No abnormalities in laboratory or imaging studies.

This entity predominantly affects adults with no sex predilection. Neurological examination is essentially normal. PIFP is a diagnosis of exclusion. Hence, the more common causes of facial pain need to be excluded with all available facilities before coming to the diagnosis of PIFP. Contrast MRI is the investigation of choice.

Treating this condition is difficult and is less effective than in other facial pain syndromes. Medications used include anticonvulsants, antidepressants, topical anaesthetic agents and narcotics. Kuhner[33] stresses that destructive trigeminal surgery has no role in the

treatment of this condition and quotes figures of more than 58% deteriorating after surgery. Multimodality approach with involvement of a psychiatrist and pain therapist is appropriate.[13,54]

TOLOSA-HUNT SYNDROME (PAINFUL OPHTHALMOPLEGIA)

This syndrome is a non-specific inflammatory process in the region of the cavernous sinus/superior orbital fissure. It is characterised by periorbital or hemicranial pain, ipsilateral ocular nerve palsies, oculosympathetic paralysis and sensory impairment in the trigeminal nerve distribution (mainly ophthalmic and occasionally maxillary division). Occasionally, there may be additional cranial nerves palsies (II, V2, VII) ipsilateral to the ophthalmoplegia. Having a relapsing and remitting course, they respond promptly to systemic corticosteroid therapy.[28]

In 1954, Tolosa[59] first reported a patient with left orbital pain, ipsilateral progressive visual loss, total left ophthalmoplegia and reduced sensation over the first division of the trigeminal nerve. Per-operatively no abnormality was found and the patient died in 3 days. Granulomatous inflammation of the carotid artery and cavernous sinus was found at post-mortem. In 1961, Hunt et al.[22] described a clinical entity similar to that of Tolosa. In 1966, Smith and Taxdal[52] named it "Tolosa-Hunt syndrome".

This syndrome affects patients of any age group and there is no sex predilection. There have been reports of bilateral involvement.[9] Orbital pain usually lasts for 2 weeks. All the three nerves supplying the external ocular muscles can be involved in various combinations. There have been reports of involvement of the optic nerve which might favour pathology around the orbital apex.[3,63] There have been reports of involvement of cranial nerves away from the orbital apex or cavernous sinus, like the mandibular or maxillary divisions of the trigeminal nerve and the facial nerve.[1,28,47]

The differential diagnosis of this condition is trauma, neoplasm or aneurysm in the region of the cavernous sinus/superior orbital fissure.[28] Contrast enhanced MRI is the investigation of choice. Coronal views may show abnormal soft tissue with contrast enhancement in the region of the cavernous sinus, the intensity of which is similar to an inflammatory process. High resolution CT can demonstrate the same, but is less sensitive. The findings on the MRI may be confused for a cavernous sinus meningioma, lymphoma or sarcoidosis. Hence, post-steroid therapy MRI showing decrease in the size of the lesion is considered diagnostic.[31,49,62] Cerebral angiogram has showed segmental narrowing of the intracavernous carotid artery, which also resolves with corticosteroid administration. Biopsy of the lesion is done as a last resort.

Corticosteroids have been used effectively for treating this condition. They dramatically decrease the periorbital pain and also shorten the natural course of the disease.[28,49] Tolosa Hunt syndrome is a diagnosis of exclusion where all the probable causes of a parasellar lesion causing painful ophthalmoplegia are ruled out.

OCCIPITAL NEURALGIA

Occipital neuralgia is caused by irritation of the greater occipital nerve, the causes being entrapment of the nerve in the trapezius muscle due to post-operative scarring or injury to the nerve. Patients may have unilateral or bilateral throbbing pain over the occipital region. Since the greater occipital nerve receives branches from the superior cervical sympathetic ganglion, the trigeminal ganglion, acoustic and vestibular nerves, it may produce additional symptoms of vomiting, nausea, vertigo and photophobia.[6,12,40] Pressure on the greater occipital nerve will produce a positive Tinnel's sign.[40]

Potentially dangerous conditions, like craniovertebral junction pathologies which may produce similar symptoms, have to be ruled out before coming to the conclusion of occipital neuralgia.[40] Nerve block will often relieve the patient of the neuralgic pain. In patients with persistent pain, nerve decompression or sectioning of the nerve stem, which causes loss of feeling in the occipital region, may be required.[4]

COSTEN'S SYNDROME

Costen's syndrome is temporomandibular joint dysfunction characterised by aching pain felt in front of the ear which is aggravated by chewing. It is due to mal-alignment of the TM joint or rarely to rheumatoid arthritis.

READER'S SYNDROME

Reader's syndrome also called the paratrigeminal syndrome is characterised by pain around the eye associated with a sympathetic paresis (ptosis and small pupil) and is usually associated with granulomatous lesions or nasopharyngeal carcinoma involving the middle fossa.

Other different varieties of pain syndromes may be encountered in practice. Some patients have a combination of the features of trigeminal neuralgia and ciliary neuralgia. The pain occurs in paroxysms and is accompanied by redness and watering of the eyes. Simultaneously, there are trigger zones in the forehead and around the eye that initiate the paroxysm. A combination of carbamezapine and ergot therapy has been found effective.

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198 Microvascular Decompression

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For long, the treatment of conditions, like trigeminal neuralgia (TN), glossopharyngeal neuralgia and hemifacial spasm (HFS), was based on disruption of the conductivity of central and peripheral nerve pathways through various techniques. These procedures led to relief in most of the cases, but at the cost of sensory or motor loss or the possibility of recurrence. The real pathophysiology was not clear till several observers beginning with Dandy, Gardner, Rand and Jannetta showed compression of nerve elements by neighbouring vascular structures and produced good relief by eliminating such compression of the nerves by the blood vessel. Now microvascular decompression (MVD) has become an established procedure for the relief of several syndromes.

The proximity of the blood vessels to the nerves in the cerebellopontine angle makes the cranial nerves vulnerable to compression by the blood vessels. This compression is a major cause of trigeminal neuralgia (V), hemifacial spasm (VII) and glossopharyngeal neuralgia (IX). It may also cause vertigo (VIII), tinnitus (VIII), hypertension (X) and spasmodic torticollis (XI).

HISTORY

Dandy,[19,20,21] reporting on a series of 215 patients with TN, found an artery compressing the nerve in 66 cases and a vein in 30 cases. Gardner,[34] using the posterior fossa approach to treat patients with recurrence of pain following the middle cranial fossa approach, found vascular compression of the trigeminal nerve in one-third. Gardner and Miklos[32] interposed a piece of Gelfoam® between the offending artery and the trigeminal sensory root. Rand and Jannetta[47] introduced and popularised vascular decompression using microsurgical techniques. The first report from India was by Virani and Palande,[111] in 1985.

Campbell and Keedy[12] found vascular compression of the facial nerve in HFS. Dandy,[20] in 1932, treated Meniere's disease with vascular decompression of the vestibular nerve. Lille and McCraig[65] reported on improvement in hearing after decompressing the auditory nerve. Laha and Jannetta[61] reported on MVD in glossopharyngeal neuralgia. Jannetta and Gendell[45] decompressed the left lateral medulla for hypertension as did Fien and Frishman.[28] Freckmann et al.[31] and Pagni et al.[72,78] reported on successful treatment of spasmodic torticollis by MVD.

PATHOPHYSIOLOGY

It has been proposed that a number of cranial nerve dysfunction syndromes are caused by vascular cross compression of the root entry zone (REZ) of the appropriate cranial nerve. This may be a direct reflection of the ageing process[13,29,46,47,59,110] which leads to: (a) arteriosclerotic degeneration of the arteries resulting in their elongation and (b) in hind brain sag (descent) which causes abnormal contacts between the blood vessels and the lower cranial nerves.

The arteries in the posterior fossa arise anteriorly and travel posterolaterally around the brainstem and have a relatively long course. Elongation of these arteries by sagging of the brainstem may cause abnormal neurovascular contacts. The relation between the neural structures and the veins, both intrinsic and bridging veins, may also be altered. The abnormal neurovascular contact may cause hyper or hypoactivity, depending on the site of contact and the rapidity with which this contact occurs. In general, hyperactivity results when there is a gradually progressive compression at the point on the nerve where peripheral myelin (Schwann cell) changes to central myelin (oligodendroglia). This area is at the root entry zone (REZ) of the V and VII nerves and in the VIII nerve is located peripherally, near the internal auditory meatus. It had been assumed that vascular contact at the REZ was solely responsible for the dysfunction. De Ridder[22] et al. have divided the nerves into a central nervous system (CNS) segment and a peripheral nervous system (PNS) segment, separated by the REZ. They have proposed that compression on the CNS segment alone causes symptoms. The PNS part is quite resistant to compression. Sindou et al.[99] in their anatomical observations during surgery for TN, found in addition to vascular compression, that alterations were seen in the whole trigeminal nerve. In 42%, there was significant global atrophy, in 18.2% local thickening of the arachnoid adherent to the nerve, in 12.6% the nerve was severely angulated while crossing the petrous ridge and in 3.9% the nerve was compressed between the pons and the petrous bone due to the small size of the posterior fossa.

The chronic compression causes transaxonal short circuiting of the action potential in the nerve.[32,34] Segmental demyelination of A alpha and beta fibres

occurs in the region of transition and results in artificial synapses with ephaptic transmission between fibres carrying different sensations.[10,25,56] Spontaneous discharges may occur at the site of compression[33,114] and pathophysiological changes occur in the nucleus due to the chronic compression. Bannett and Jannetta[5] presented data on evoked potentials studied in patients with TN. There was increased latency and threshold consistent with V nerve compression. Patients with atypical facial pain did not have similar findings. The presence of pre-operative evoked potential abnormalities was associated with post-operative pain relief.

TRIGEMINAL NEURALGIA

Selection of Patients

The indications for MVD are failed medical therapy using carbamazepine, phenytoin or both, or when the patient has adverse reactions to medication. Fitness for anaesthesia and major surgery is vital in older patients and the usually accepted cut off point is 65–70 years of age. Older patients may also be operated upon, if found fit. Elderly patients have been operated upon and good results have been reported.[16,77]

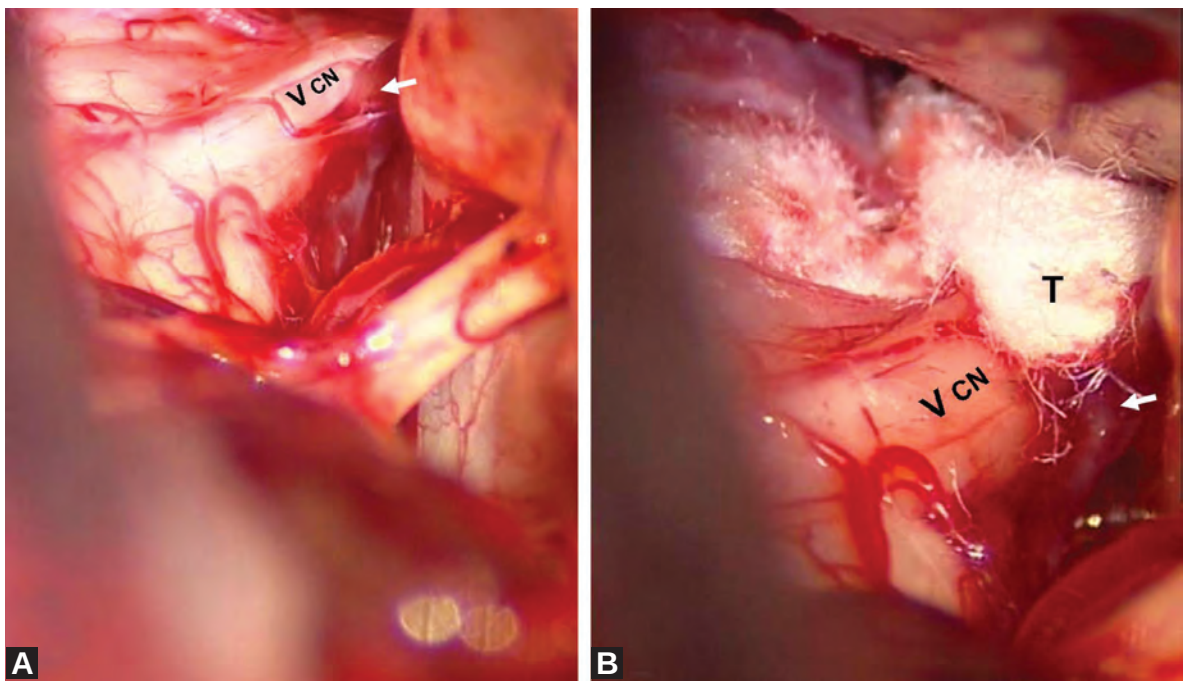
Investigations

Plain skull X-rays are done to see the configuration of the skull, especially the posterior fossa and are useful in planning the craniectomy. The size and aeration of the mastoid air cells are noted, as also of the auditory meatus and the petrous temporal bone.

CT scans and MRI are done to rule out extra-axial tumours, plaques of multiple sclerosis, ecstatic arteries and possible arteriovenous malformations. Three-dimensional time-of-flight magnetic resonance angiography (3D-TOF MRA) is useful in demonstrating cranial nerve compression, as well as in excluding other aetiologies.[14,60,94,104] A boundary imaging of fusion three dimensional (3D) magnetic resonance (MR) cisternogram/angiogram has been used for virtual assessment of the spatial relationship of the neurovascular compression at the REZ.[95] Pre-operative imaging of the neurovascular structures can be performed using constructive interference in the steady state magnetic resonance (CISS MR) imaging, which consists of 2D images. The 3D visualisation is generated after segmentation of the CISS MR imaging in combination with direct volume rendering (DVR) in the operating room.[104] Electrophysiological tests are useful in pre-operative assessment and in post-operative follow-up and include otovestibular testing, BAER and trigeminal evoked potentials.

Anatomy of the Trigeminal Nerve in the Cerebellopontine Angle

The root entry zone (REZ) of the trigeminal nerve is the first one centimetre of the nerve after it has emerged from the pons.[38] In its intradural course, the nerve emerges from the lateral part of the pons just inferomedial to the ala of the cerebellum and runs obliquely upwards, towards the petrous apex and enters Meckel's cave, leaving the posterior fossa beneath the tentorial attachment.[39] The angle of entry of the trigeminal nerve into the pons is acute and in some cases the portion near the pons may be parallel to the pons (Figs 1A and B).



Figs 1A and B: (A) Intra-operative picture of a patient with trigeminal neuralgia showing a vascular loop (white arrow) around the trigeminal nerve (V CN) in the right CP angle. (B) Teflon (T) placed between the trigeminal nerve (V CN) and the vascular loop

The number of fascicles is variable, as is the diameter of the nerve. About a hundred fascicles, which form the dorsal root and emerge from Meckel's cave, coalesce about half to one centimetre from the pons into a gelatinous mass and this mass is surrounded by pia-mater and is called the portio major. This is the "fibrous cone" described by Dandy.[18]

About 20% of the sensory fascicles do not enter the "fibrous cone" and are separate from the portio major. They enter the pons between the portio major and the motor fibres. These fibres carry a considerable part of light touch and proprioception and, therefore, complete section of the portio major gives good results without much of touch and proprioception loss.

The motor part arises as a large number of fascicles, which join together 2 or 3 mm from the pons to form two distinct structures surrounded by pia mater. The motor part courses medial to the sensory root, crosses under the Gasserion ganglion and exits through the foramen ovale.

Surgical Procedure

The positioning of the patient depends on the surgeon and the best position to use is the one with which the surgeon and the anaesthetist are more comfortable and familiar. The positions that may be used are lateral, park bench, supine with head rotated, and sitting. Janetta et al.[42] have described the steps of surgery in detail.

A vertical retromastoid incision is made about half to one centimetre medial to the mastoid notch. The incision is 5–7 cm long and one-third of this should be superior to the nuchal line. The incision is carried down to the bone and craniectomy (2.5 cm x 2.5 cm) is done, exposing the transverse sinus superiorly and the sigmoid sinus laterally. It is essential to expose the junction of the transverse and the sigmoid sinuses. The dura may be opened in any convenient fashion, but it is essential to expose the junction between the superior and the lateral surfaces of the cerebellum.

The superior petrosal vein is identified and, if absolutely necessary, it is coagulated and divided, if it prevents access to the entire length of the trigeminal nerve. The ala of the cerebellum is retracted and the trigeminal nerve comes into view. The arachnoid over the nerve is dissected using sharp dissection and the whole nerve is exposed. The IV nerve lies above and parallel to the V nerve. In lower division TN, the offending vessel is usually the superior cerebellar artery compressing the nerve superiorly or anteriorly and in upper division TN, the anterior inferior cerebellar artery is often the offending artery. The whole complex of arterial loops is gently elevated from the nerve. Various substances, like Gelfoam®, muscle or plastic prosthesis-like Ivalon and shredded Teflon felt, have been interposed between the offending vessels and the nerve (Figs 1A and B). It is preferable to use non-absorbable materials, as the others may get absorbed before the vessel is permanently repositioned. In complicated cases such as re-operations and transpositions of long ectatic arteries, fenestrated aneurysm clips can be used to maintain transposition of the culprit vessels.[3,113]

When a vein is compressing the nerve and it cannot be separated from the nerve, it should be coagulated and divided. Care should be taken to see that too many veins are not sacrificed during the procedure. If adequate decompression of the nerve is not possible, then sectioning of the portio major gives good results.

The cross compression may be due to an arterial loop, a vein or a combination of both. Other causes are tumours, AVM and aneurysm. In a few patients there may be a negative exploration. The various causes of nerve compression are given in Table 1.

Results

In about 20–40% of the patients, some pain may persist in the immediate post-operative period. If the nerve had been manipulated during surgery, the post-operative pain is absent, but if it is not manipulated the pain may persist for a period of up to 2 months. This is not a true recurrence and this pain promptly responds to phenytoin therapy. True recurrence is seen when the pain occurs with the same intensity as pre-operatively and also if the pain subsides initially to recur with the same intensity 3–4 days post-operatively. In these patients it is better to re-operate within 2 weeks. Barker

Table 1: The various causes of nerve compression

Author	*Number of cases*	*Artery %*	*Veins %*	*Artery and veins %*	*Tumours %*	*AVM aneurysm %*	*Negative %*	*Arachnoiditis %*
Apfelbaum[1] (1992)	500	79	15	--	3	--	3	--
Jannetta[43] (1985)	411	59	13	24	3.25	0.5	0.25	--
Virani[112] (1993)	100	76	6	6	8	--	--	4
Kolluri and Heros[59] (1984)	72	65	10	22	1.5	--	1.5	--
Chandy[13] (1988)	65	69	11	--	7.5	--	5	--
Klun[58] (1992)	178	79	7	7	7	--	--	--

et al.[7] reported 70% excellent results and 4% good results on long-term follow-up of 1,185 patients. The overall long-term results in various series have been reported to be excellent in about 70% and good in an additional 4–7%.[1,15,49,50,100,112] The results in atypical TN have been excellent in 35% and good in 16%.[109] The results are worse when there is purely venous compression without an arterial component.[62] When there is late recurrence that is not controllable medically, repeat MVD or other procedures may be needed for pain relief. None of the patient related factors, like sex, age of the patient at surgery, hypertension, duration of pain or previous surgery, were found to have an influence on the outcome.[100] More severe the degree of compression, the better is the outcome. Patients with neuralgia involving the ophthalmic division of the trigeminal nerve had better long-term results than those without V1 involvement. When the neuralgia involved all three nerves, the outcome was worse. Older patients had a better outcome than the younger age group.[100] The relief from MVD after a prior destructive procedure has been reported to be not as good as when a previous procedure has not been done.[6,10,11,68,81,102,103] Later reports claim that this is not so.[44,100,105,108]

The mortality and morbidity are low. Four out of 1,000 in Jannetta's series[44] and three out of 500 patients in Apfelbaum's series 1 had a fatal outcome. Klun[58] has reported a mortality of 3/220 and Bederson et al.[8] no mortality. The cranial nerves IV (2–3%), VI (1%), VII (2%) or the VIII (3%) may be affected.[1,44,58] In later series, the complication rates have come down. This is attributable to improved techniques and increasing operator experience.[67]

The cranial nerve dysfunction that may occur is usually temporary, except in the case of the VIII nerve where there is usually permanent hearing loss. Cerebellar dysfunction due to infarction or haemorrhage may occur in a small percentage of patients. Rare complications, like polytetrafluoroethylene-induced granuloma, brainstem cyst and brainstem infarction, have been reported in literature.[101,102,107]

Various imaging changes, which occur in TN in the nerve and in the pons before and after TN, have been studied by Jawahar et al.[52] The brainstem was found to be normal in all patients before surgery. Eighty-eight patients had undergone one or more MVD procedures. In 34% the nerves were normal, 30.8% demonstrated perineural scarring, 28.4% a distortion of the course of the nerve, 23.8% had a brainstem infarction and 17% a persistent vascular compression.

HEMIFACIAL SPASM

HFS is more common in women than in men and more on the left side than the right side. Two types of HFS have to be differentiated, typical and atypical. Typical HFS, seen in 90% of patients, begins in the orbicularis oculi muscle and spreads caudally to involve the rest of the face. Atypical HFS, affecting 10% of patients, starts in the buccal muscles and spreads upwards. This differentiation is of surgical importance as, in typical HFS, the offending vessel is on the anterior caudal side of the nerve or on the pons over the intrapontine part of the facial nerve. In atypical HFS the vessel compresses the rostral posterior aspect of the nerve and may be located between the facial and the auditory nerves or above the auditory nerve.

Selection of Patients

MVD for HFS is a cosmetic operation and should be undertaken only if it seriously affects the patient's social or professional life. Patients who are fit for surgery are selected, age being no bar.

Anatomy of the Facial Nerve in the Cerebellopontine Angle

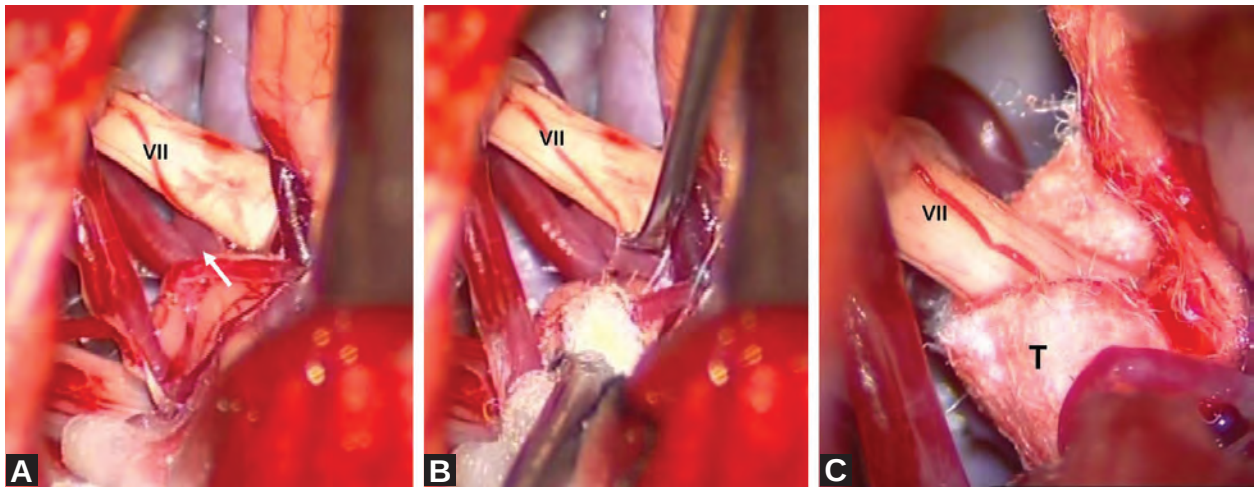
The facial nerve may be compressed either in its intrapontine or extrapontine course in the cerebellopontine angle. The junction zone between central and peripheral myelin is close to the exit of the nerve from the pons. The nerve runs superficially in the pons in a caudorostral direction starting at the pontomedullary junction. On exiting from the pons, it runs laterally in the cerebellopontine angle to enter the internal auditory meatus along with the VIII nerve and the nervous intermedius.

Surgical Technique

The anaesthesia and positioning are the same as for TN. The craniectomy is made more caudally and extends up to the sigmoid sinus laterally and the floor of the posterior cranial fossa inferiorly.

After opening the dura, the cerebellum is elevated from the floor of the posterior cranial fossa. It should not be retracted in a lateral to medial direction, to avoid injuring the VIII nerve and producing hearing loss. The IX and X cranial nerves are identified and the arachnoid over them is dissected with a sharp hook. The caudal cranial nerves are followed medially, till the flocculus is seen. The pons is then visualised as well as the choroid plexus at the lateral exit foramen of the IV ventricle. The VII nerve is thus approached from a caudal direction in typical HFS. The view of the VII nerve may be obstructed by the offending vessel, either single or multiple arteries or a vein. The dissection must be carried out all around the nerve to make sure that a second compressing vessel is not missed (Figs 2A to C). The technique and the materials used are the same as in TN. A whole range encircling method has been described by Qi which is claimed to be a safe approach, associated with high cure rate and minimises of the rate of recurrence and complications.[82]

BAER and direct monitoring of VIII nerve function during this operation have been found useful in preventing injury to the VIII nerve.[37,41,69,70,71,76] Facial muscle EMG is also useful to make sure that the compression has been relieved.[70] The lateral spread response (LSR)



Figs 2A to C: (A) Intra-operative picture of a patient with hemifacial spasm showing a vascular loop (white arrow) around the facial nerve (VII) in the left CP angle. (B) Gentle dissection being carried between the facial nerve and the vessel. (C) Teflon (T) placed around the facial nerve (VII) to prevent contact with the vascular loop

was studied in a series of 300 patients undergoing MVD for HFS by Doo-Sik Kong et al.[24] In 263 (87.7%), LSR was observed during surgery. In 230 (87.4%) of these 263, the LSR disappeared after decompression. The one year outcome was worse in patients in whom the LSR persisted following decompression.

Results

In the majority of patients the compression is by an artery. The offending arteries may be the AICA, PICA, vertebral or an ecstatic basilar artery. The anterior inferior cerebellar artery (42.6%) was found to be the main offending vessel by Yuan.[115] In 62% of patients there is a single artery, in 26% multiple arteries, 9% are compressed by an artery and a vein and it is purely venous in 2%. The remaining 1% may be due to tumour, AVM or aneurysm.[48]

In Japan, Kato et al.[55] summarised the results of long-term follow-up of 4,865 HFS patients who had undergone MVD in 23 hospitals. They found 83.7% of the patients were symptom free, there was some relief in 12.2% and the surgery failed in 4.1%. Other authors have also reported similar results.[90,115] Results of re-operation are quite good and in patients who have no response, re-operation must be considered.[27] It would be best to wait for a month before re-operation is decided upon. Nagahiro et al.[73] analysed the patterns of vascular compression in unsuccessfully treated patients. Good results are obtained with caudal compression by the AICA or PICA; however, the results were not as good in patients with compression by the vertebral artery or when the offending vessel was between the VII and VIII nerves.

The mortality is low 1/750.[48] The most common and permanent damage is ipsilateral hearing loss (3%). Transient facial weakness (5%) may also occur and in a few patients this may be permanent (2.4%).[93,115] Delayed facial palsy on an average time of occurrence of 12 days was reported to be seen in 5.4%.[84] The VI nerve may be involved temporarily.

ESSENTIAL HYPERTENSION

Experimentally, hypertension may be produced by electrical stimulation of the cortex, bilateral lesions of the anterior hypothalamus and bilateral lesions of the nucleus tractus solitarius (NTS). The cell mass, the pars commisuralis, probably forms the primary medullary centre for the baroreceptor reflex. The rostral ventrolateral medulla (RVL) is a critical area for auto-regulation and control of arterial blood pressure. At the rostral end of the inferior olivary nucleus and within the RVL, adrenergic neurons are present which contain the adrenaline synthesising enzyme phenylethanolamine N-methyl transferace (PNMT).[2,35,40,86,89] These neurons are innervated by projections from the nucleus tractus solitarius.[17,87,88] The NTS receives input from arterial baroreceptors, chemoreceptors and other cardiovascular afferent fibres.[54] Cardiovascular baroreceptor impulses from the carotid sinus travel in the X nerve and those from the aortic arch in the IX nerve. The left X nerve also carries afferent signals from mechanoreceptors in the wall of the left atrium. The RVL projects to the intermediolateral and intermediate columns of the spinal cord via fibres travelling through the principal tegmental tract. This tract is the source of tonic and reflex drive to preganglionic neurons of the intermediolateral columns of the spinal cord.[30,85,88] Lesioning the RVL leads to reduction in blood pressure and stimulation to an increase, indicating that RVL medulla carries sympathetic fibres.[17,36,86] Experimentally, in cats and baboons, pulsatile mechanical pressure using a balloon was applied to the left RVL. This pressure is similar to what happens when there is a vascular compression and led to hypertension in all the animals. They became normotensive when the compression was released. There was no hypertension in the control group.[43,97,98] In a cadaver study in 1992, Naraghi[74] found that all patients with essential hypertension had a vascular compression of the left lateral medulla. In a study of a family with autosomal dominant hypertension and brachydactyly

mapped to chromosome 12, Naraghi[75] found on MRI and MRA that all 15 affected members had vascular compression of the left medulla. None of the 12 non-affected members had a vascular compression.

A major portion of the afferent impulses from the myocardial receptors of the left ventricle and atrium are conducted by cardiac c-fibres of the left vagus nerve to the NTS.[106] Mechanical damage to these nerve fibres by vascular compression may partially block conduction in these fibres resulting in partial deafferentation of the NTS. Doba and Reiss have demonstrated in animal experiments that deafferentation or destruction of the NTS results in fulminant hypertension.[23] It has been shown that NVC of the rostral ventrolateral medulla in patients with essential hypertension is accompanied by increased central sympathetic outflow.[96]

In 1979, Janetta published his first report of MVD for hypertension.[45] The offending vessel is usually the vertebral artery or the PICA.[63] MVD is indicated for essential hypertension in a select group of patients. It is reserved for those with intractable, poorly controlled essential hypertension, while on at least three different antihypertensive medications or who have three failed attempts with different medical regimens.[63] Out of 53 patients operated upon by Janetta[63], 51 had microvascular compression of the left RVL medulla. In 42, MVD was done. On follow-up, 31 patients were normotensive, 13 of whom were on no medication, 12 on diuretics and 6 on combination medical therapy. Similar results have been reported in smaller series.[30,64] The selection of patients who will benefit from MVD for hypertension is still a difficult problem. Further studies will be required.

GLOSSOPHARYNGEAL NEURALGIA

Glossopharyngeal neuralgia is uncommon. It is characterised by intermittent lancinating pain in the posterior part of the tongue and the pharynx. Often it radiates to the inner part of the ear. Medically refractory neuralgia has to be treated by surgery. Classically, the IX nerve and the upper rootlets of the X nerve are cut in the posterior fossa through a retromastoid approach. In 1977, Laha and Janetta[61] reported on four cases where MVD was done. The largest reported series of 217 patients is by Patel et al.[79] The immediate relief is in the range of 90–98%.[79,83] On long-term follow-up 70–76% of patients were relieved of pain. The complications are permanent hoarseness of voice and mild dysphagia (11%) and, rarely, facial palsy.[79,91] When there is associated hypertension, the MVD results in reduction in blood pressure. MVD is a safe and effective procedure in the management of glossopharyngeal neuralgia.

ENDOSCOPE IN MICROVASCULAR DECOMPRESSION

Recently, endoscopes have been used for treating neurovascular compression. Supplementing an endoscope to the microscopic procedure has demonstrated improved localisation of neurovascular conflicts and has improved the efficacy of surgery. The endoscope has superior visualisation and also minimises the risks of brain retraction.[26,51,57] Initially, the endoscope was being used to supplement the microscope. Later on, many have reported fully endoscopic vascular decompression surgeries. Of the total of 255 patients who underwent fully endoscopic vascular decompression of the trigeminal nerve, 95% had complete relief by the end of the initial 3 months, as reported by Kabil.[53] In 1994, Magnan introduced a combined microscopic and endoscopic approach to vascular decompression of the facial nerve for HFS.[66] Recent studies have reported a success rate of 92.5%.[4]

RADIOSURGERY VERSUS MICROVASCULAR DECOMPRESSION

Gamma knife radiosurgery has been used to treat neurovascular compression but the results are delayed and are not satisfactory, with complete pain relief in less than half.[9] Radiosurgery is more likely to be the final treatment for recurrent TN regardless of the initial treatment.[80,92]

MVD is an operation that has come to stay and is recognised as the surgery of choice in TN, HFS, glossopharyngeal neuralgia and in some selected cases of vertigo, tinnitus, hypertension and spasmodic torticollis. The mortality and morbidity of this procedure is low and decreases further with increasing experience of the surgeon.

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SECTION

16

Epilepsy

Ravi Ramamurthi

199 Epilepsy: Overview

Dinesh Nayak S, Radhakrishnan K

INTRODUCTION

Epilepsy is one of the most common neurological disorders worldwide and yet not very well understood by physicians and the general public alike. The word epilepsy comes from the Greek verb '*epilamvenien*', which means "*to be seized*", "*to be taken hold of*", or "*to be attacked*". Excellent descriptions of epileptic attacks or apasmara can be found in the treatise *Caraka Samhita*, written by one of ancient India's immortal physicians Caraka, who probably lived in the 2nd century BC.[78] He postulated the cause of epilepsy to be a perturbation of the three doshas, and recommended a variety of treatment protocols based on Ayurvedic principles. Although Hippocrates, as early as in 400 BC, correctly postulated epilepsy as a disease originating in the brain, which needs to be treated by drugs and diet and not by religious incantations,[36] superstitions and myths abound to this day, especially in the developing countries.

DEFINITIONS

Epilepsy is defined as a group of neurological conditions characterised by recurrent unprovoked epileptic seizures. Epilepsy is not a specific disease or even a single syndrome, but is a broad category of symptom complexes arising from a number of disordered brain functions that may themselves be secondary to a variety of pathological processes. A *syndrome* is defined as a clustering of symptoms and signs consistently occurring together and not fortuitously. *Active epilepsy* is defined as having had at least one seizure in the previous 2 years. *Chronic epilepsy* is defined as epilepsy being active 5 years after onset. *Terminal remission* means a seizure-free period of 5 years or more, lasting to the time of most recent follow-up.[35,37,65]

Modern concepts of epilepsy are largely based on Hughlings Jackson's work.[38] His definition of a seizure in the late 19th century as "sudden, rapid, excessive synchronous discharges from a group of neurons" has not been bettered, and it sums up the mechanism and the paroxysmal nature of the condition.

MAGNITUDE OF THE PROBLEM

The prevalence rate of active epilepsy from the developed world is around 5 per 1,000 population (0.5%).[65] To this number, new patients will be added every year at a rate of about 50 per 100,000, which gives an incidence rate of 0.05%. Although prevalence rates in the developing countries are reported to be 2–25 times that of the developed world, this may be related to misdiagnosis, inclusion of single seizures, acute symptomatic seizures, febrile seizures and inactive epilepsy.[22] Recent community-based surveys from India have shown prevalence rates comparable to those from developed countries.[22,55] In one of the largest community based studies from India, conducted by Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum (Thiruvananthapuram), comprising 50,000 households and a population of 200,000 in central Kerala, the prevalence of active epilepsy was found to be 4.9 per 100,000.[55,58] In a meta-analysis of the prevalence data obtained from 20 community-based studies from India, the overall prevalence rate per 100,000 was found to be 5.3.[74] These figures are comparable with prevalence rates from the developed world. Increased prevalence rates in some parts of the developing countries may be attributable to regional factors like higher prevalence of infections, such as cerebral cysticercosis and hot water epilepsy.[45,66] The only incidence data on epilepsy from India, found it to be 49.3 per 100,000 population per year.[42]

Around 20–30% of patients with epilepsy continue to suffer recurrent seizures, despite optimal antiepileptic drug (AED) therapy.[57] This has an adverse impact on education, marriage, employment and quality of life. The ICMR monograph [Epilepsy in India edited by PN Tandon (1989)] provides detailed information on this aspect. The last two decades have witnessed remarkable advances in the management of such patients. Patients with medically refractory epilepsy need to be identified early in the course of the disease and referred to a comprehensive epilepsy care program for detailed diagnostic evaluation, to determine candidacy for surgical or other modes of treatment, before their quality of life is irreparably adversely affected.

BASIC MECHANISMS OF EPILEPTOGENESIS

Epileptogenesis is the result of abnormal firing of a group of neurons sufficient to produce epileptiform activity that can be recorded as electroencephalographic

(EEG) seizure activity with or without clinical findings. Such activity may be restricted to a small population of neurons, as in focal epilepsies or may involve large areas of the brain simultaneously as in generalised epilepsies. There is alteration in the balance between excitatory and inhibitory mechanisms. Epileptogenesis may either be due to increased excitation or reduced inhibition or a combination of both.[53] The three main elements in the expression of epileptogenesis are: (1) the capability of membranes of pacemaker cells to develop intrinsic burst discharges; (2) reduction of gamma aminobutyric acid (GABA) inhibition and (3) enhancement of synaptic excitation. Synchronisation of cellular activity and its spread to involve a significant number of neurons is required to produce EEG and clinical seizure activity, as well as in the generation of cellular paroxysmal depolarisation shifts.

Neurons get depolarised by entry of extracellular sodium (Na^+) into the cell to set-up the action potential, called the *sodium action potential*. Similarly, calcium (Ca^{2+}) influx also produces the *calcium action potential*. Repolarisation takes place when potassium re-enters the cell. Any factor that affects the balance of depolarisation or repolarisation can affect cellular excitability. Therefore, agents that block potassium channels (tetraethyl ammonium and barium) prolong the action potential and therefore are proepileptogenic. Blockers of Na^+ and Ca^{2+} (e.g. phenytoin, valproic acid, ethosuximide and lamotrigine) inhibit action potentials and are used in the pharmacotherapy of epilepsy.[46]

A number of neurotransmitters and their receptors mediate excitation and inhibition in the central nervous system. The amino acid glutamate is an excitatory neurotransmitter and mediates synaptic excitation. The post-synaptic excitation induced by glutamate largely depends on stimulation of receptors. Based on their physiological and pharmacological properties, glutamate receptors are organised into two classes: ionotropic and metabotropic. The ionotropic receptors are further sub-divided into two classes: those that respond to α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionic acid (AMPA) or kainic acid (KA) and those that respond to N-methyl-D-aspartate (NMDA).[80] The metabotropic glutamate receptors (mGluRs) are second messenger-coupled receptors and play a role in neuronal plasticity and epilepsy.

The inhibitory system is mainly based on the neurotransmitter Gama aminobutyric acid (GABA). The GABA receptors are divided into two subtypes: $GABA_A$ and $GABA_B$.[50] Activation of $GABA_A$ receptors open a chloride channel and results in hyperpolarisation and, therefore, inhibition. $GABA_B$ receptor is a G protein-coupled receptor that can open potassium channels or close calcium channels. This results in prolonged hyperpolarisation and therefore leads to post-synaptic inhibition. Other receptors that have been implicated in epileptogenesis are acetylcholine receptors and adenosine receptors.

One of the most important prerequisites in the development of an epileptic seizure is the manner in which excitatory neuronal populations synchronise. Usually, recurrent synaptic excitation is balanced by recurrent inhibition. Blockade of inhibition results in paroxysmal depolarisation shifts. When recurrent inhibition is affected in various pathological conditions, there is multi-synaptic excitatory-induced synchronisation of neurons leading to the generation of after discharges. The glial network is protective in nature and glial cells take up glutamate. Failure of these mechanisms can result in secondary generalisation of a focal seizure.[40]

CLASSIFICATION OF SEIZURES AND EPILEPSIES

Seizures are broadly classified into partial and generalised seizures.[15] Partial seizures indicate initial activation of a group of neurons limited to one part of the cerebral hemisphere, as evident clinically and electrographically. Depending on whether consciousness is preserved or not, partial seizures are further classified into simple partial (consciousness preserved) and complex partial (consciousness impaired). A simple partial seizure may evolve into complex partial and then secondarily generalised seizures. The manifestations of simple and complex partial seizures may be motor, sensory, autonomic and psychic. Generalised seizures are those in which the first clinical changes indicate initial involvement of both hemispheres. Consciousness may be impaired and this may be the initial manifestation. Motor manifestations are bilateral, and the ictal EEG changes are bilateral. The generalised seizures include absences, myoclonic, tonic, atonic, clonic and tonic-clonic.

Epilepsy syndrome classification is a more useful concept for the prognosis and treatment than seizure classification, because it includes elements other than seizure symptomatology and EEG. The 1989 International League Against Epilepsy (ILAE) classification[16] is based primarily on the definition of electroclinical syndromes (Table 1). They are broadly divided into localisation-related epilepsies (in which seizure semiology or findings at investigation disclose a localised origin of the seizures) and generalised epilepsies (seizures in which the first clinical changes indicate initial involvement of both hemispheres and initial ictal EEG changes are bilateral).

Table 1: Classification and coding of epilepsies and epileptic syndromes (Modified from ILAE, 1989)[16]

1. Localisation-related epilepsies and syndromes
1.1. Idiopathic localisation-related (with age-related onset) epilepsies
1.1.1. Benign childhood epilepsy with centrotemporal spikes (BECT)
1.1.2. BECT in brain-damaged children
1.1.3. Childhood epilepsy with occipital paroxysms

(Contd ....)

1.1.4. Benign frontal epilepsy of childhood
1.1.5. Benign psychomotor epilepsy of childhood
1.2. Symptomatic localisation-related epilepsies
1.2.1 Temporal lobe epilepsies
1.2.2. Frontal lobe epilepsies
1.2.3. Parietal lobe epilepsies
1.2.4. Occipital lobe epilepsies
1.2.5. Chronic progressive epilepsia partialis continua of childhood (Rasmussen's syndrome)
1.3 Cryptogenic localisation-related epilepsies
1.3.1. Temporal lobe epilepsies
1.3.2. Frontal lobe epilepsies
1.3.3. Parietal lobe epilepsies
1.3.4. Occipital lobe epilepsies
2. Generalised epilepsies and syndromes
2.1 Idiopathic generalised (with age-related onset) listed in order of age
2.1.1. Benign neonatal familial convulsions
2.1.2. Benign neonatal convulsions
2.1.3. Benign myoclonic epilepsy of infancy
2.1.4. Childhood absence epilepsy
2.1.5. Juvenile absence epilepsy
2.1.6. Juvenile myoclonic epilepsy
2.1.7. Epilepsy with generalised tonic-clonic seizures (GTCS) on awakening
2.1.8. Other generalised idiopathic epilepsies not defined above
2.1.9. Epilepsies with specific modes of seizure precipitation
2.2 Cryptogenic or symptomatic generalised epilepsies (in order of age)
2.2.1. West syndrome
2.2.2. Lennox-Gastaut syndrome
2.2.3. Epilepsy with myoclonic-astatic seizures
2.2.4. Epilepsy with myoclonic absences
2.3 Symptomatic generalised epilepsies
2.3.1. Non-specific aetiology
Early myoclonic encephalopathy
Early infantile epileptic encephalopathy with suppression burst
Other symptomatic generalised epilepsies not defined above
2.3.2. Specific syndromes
Disease in which seizures are a presenting or predominant feature
3. Epilepsies undetermined whether focal or generalised
3.1 With both generalised and focal seizures
3.1.1. Neonatal seizures
3.1.2. Severe myoclonic epilepsy in infancy
3.1.3. Epilepsy with continuous spike-waves during slow wave sleep
3.1.4 Acquired epileptic aphasia (Landau-Kleffner syndrome)
3.1.5. Other undetermined epilepsies not defined above
3.2. Without unequivocal generalised or focal features

(Contd ....)

4. Special syndromes
4.1. Situation-related seizures
4.1.1. Febrile convulsions
4.1.2. Isolated seizures or isolated status epilepticus
4.1.3. Seizures associated with acute metabolic or toxic events, such as alcohol, drugs, eclampsia, non-ketotic hyperglycaemia, and hepatic and uraemic encephalopathies
5. Differentiation between epileptic and non-epileptic events uncertain.

Localisation-related and generalised epilepsies are further divided into idiopathic, symptomatic and cryptogenic. *Idiopathic* means "arising spontaneously from" and imply normal intelligence and neurological examination. Many of the idiopathic syndromes may be genetic disorders. *Symptomatic* means there is an obvious underlying cause for the epileptic syndrome. The term cryptogenic presumes an underlying symptomatic cause but this has not been detected in these patients.

In 2001, the Classification Task Force of the ILAE proposed to use the term focal instead of partial.[27] This Task Force also proposed a diagnostic scheme for detailed characterisation of each seizure disorder. The scheme involves assessment along five axes: (1) symptoms and signs; (2) seizure types; (3) syndromes; (4) aetiology and (5) impairment. This scheme is still under development. Many times, the syndromic diagnosis can be made only retrospectively, or on long-term follow-up. The outcome of epilepsy depends on the syndromic diagnosis. Thus, four different groups can be made depending on the prognosis.[65] Syndromes with excellent prognosis consist of the benign epilepsy syndromes of childhood such as benign Rolandic epilepsy and benign occipital lobe epilepsy. Almost all these children remit as they grow older and many of them may not require AED therapy. Although childhood absence epilepsy (CAE) and juvenile myoclonic epilepsy (JME) are two forms of primary idiopathic epilepsy, they vary in the prognosis. Both are easily controlled with appropriate AED therapy. CAE enter remission during adolescence, while JME rarely remits even after several decades. There is evidence to suggest that the recurrence of seizures itself does not influence the outcome of epilepsy. Rather, it is the underlying syndrome that determines the prognosis. Although AED therapy is effective in controlling seizures, they probably do not prevent the development of chronic epilepsy. Contrary to the concept held in the early 20th century, seizures do not beget seizures in humans, and epilepsy is a self-limiting disorder in most.

GENETICS OF EPILEPSIES

There has been an explosion in the knowledge of the molecular basis of epilepsy in the last 15 years or so. Although the heritability of epilepsy was known from the time of Hippocrates, it is only in the last two decades that the biological mechanisms are beginning to be

understood.[67] The first step is to obtain a detailed family history. This is not easy, since there is considerable social stigma attached to epilepsy and history may not be forthcoming even when there is a positive family history. On the other hand, spontaneous gene mutations are well known to occur and in such cases no positive family history will be present. A single genetic defect may result in several phenotypes, while a single phenotype can be a result of several genetic mutations.

Patterns of inheritance follow two broad groups: (1) Simple Mendelian [autosomal dominant (AD), autosomal recessive (AR) and X-linked] and (2) complex (non-Mendelian). Mendelian disorders are relatively rare, cluster in families and have a high rate of penetrance (expression), so that if one carries the gene, the disorder is likely to manifest. This makes it easier to trace the abnormal gene.

Complex disorders may have several genes (multiple genotypes) involved and not everyone who carries the gene will get seizures. In clinical practice, complex modes of inheritance are more common than Mendelian disorders. Approximately 10 genes have been identified for the idiopathic generalised epilepsies within the last 15 years, all of them simple Mendelian disorders with AD transmission (Table 2). These genes involve either an ion channel (sodium and potassium) or a neurotransmitter receptor (acetylcholine and GABA). Autosomal recessive disorders are associated with multiple cerebral abnormalities as well.

Table 2: Inheritance patterns and gene localisation of some epilepsy syndromes

	Inheritance	*Identified gene*
Simple (Mendelian) inheritance idiopathic generalised epilepsies		
Benign familial neonatal convulsions	AD	Potassium channels
Benign infantile convulsions	AD	19q
Generalised epilepsy febrile seizure (GEFS) plus	AD	Sodium channels, GABA receptors
Partial		
Nocturnal frontal lobe epilepsy	AD	α4 nicotinic acetylcholine receptors
Partial epilepsy with auditory features	AD	LG 1 (leucine rich repeats)
Complex (non-Mendelian) idiopathic epilepsy syndromes		
Childhood absence epilepsy	UCL	
Juvenile absence epilepsy	UCL	
Juvenile myoclonic epilepsy	UCL	
Idiopathic generalised epilepsy	UCL	
Partial		
Benign rolandic epilepsy	UCL	
Febrile seizures	UCL	

(AD = autosomal dominant; UCL = unconfirmed chromosome localisation)

NATURAL HISTORY OF EPILEPSIES

The factors that determine the development of epilepsy, following an initial unprovoked seizure and its refractoriness to AED treatment, are largely unknown. Recent epidemiological studies have thrown light on some of these questions. Around 15% of patients will go on to develop refractory epilepsy after a first unprovoked seizure.

Initial Unprovoked Seizure

The risk of developing a second seizure after a first unprovoked seizure varies between 27 and 80%.[1,34,65] This wide variation is mainly because of selection bias in the patient population. A population-based prospective study in the United Kingdom involving 564 unselected patients with non-febrile seizures showed that 67% had recurrence within 12 months of the initial seizure and 78% had recurrence in 36 months.[34] The risk of recurrence is greatest in the first 6 months and diminishes over time. In another population-based study from Rochester, Minnesota, Annegers et al.[1] observed the risk of recurrence after an initial unprovoked seizure among a cohort of 424 residents to be 36% in one year, 48% in 2 years and 56% by 5 years. Based on these studies, it can be concluded that around 60% of persons go on to develop epilepsy after a first unprovoked seizure.

Natural History of Treated Epilepsies

The British National General Practice Study of Epilepsy investigated the remission rate of 1,091 newly diagnosed patients with epilepsy.[14] The remission rate was 87% at the end of 3 years and 71% at the end of 5 years. The majority of those who remitted did so within the first 2 years of onset of epilepsy. In a more recent prospective, long-term population-based study from Finland,[70] 144 patients with childhood onset of epilepsy were followed-up for an average of 37 years. Terminal remission was achieved in 67%. Three patterns of terminal remission were noted: early (within 1 year of seizure onset, in 31%), late (after a mean delay of 9 years, in 50%) and remitting-relapsing in 19% (terminal remission following a relapse after early or late remission). Drug resistance was observed in 19% of patients and another 14% relapsed after early or late remission and never achieved terminal remission. Thus, 70–80% of persons with newly diagnosed epilepsy will eventually achieve remission. Most of those who remit will be able to discontinue AED therapy and remain seizure-free. This goes against the common perception that epilepsy is a chronic disease and needs life-long therapy in the majority of patients.

Natural History of Untreated Epilepsies

In the developing countries, it is common to encounter *treatment gap*, which is defined as the percentage of persons with active epilepsy who have never received AED treatment. Population-based studies in the developing regions have shown the treatment gap amounts to

70–90%.[2,41,42,56] Epidemiological studies from rural areas in Karnataka,[42] West Bengal[20] and Kashmir[41] found treatment gap in 78%, 74% and 75%, respectively. The treatment gap was as high as 36% even in Kerala,[55] the most literate state in India. The treatment gap was, however, only 6% in the literate and affluent Parsi community of Mumbai.[7] This is unlike in the developed world where most patients with epilepsy would be investigated and receive AED therapy. The reasons are both medical and social, and include lack of medical services, lack of diagnosis of epilepsy, reluctance to accept the diagnosis and take "English" medicines, lack of knowledge about diagnosis and treatment and non-availability or non-affordability of medication.

In a population-based study from Equador, only 29% of epilepsy patients ever received treatment.[52] Interestingly, 46% of the untreated patients were in long-term remission. The duration of untreated epilepsy and number of seizures do not appear to influence the chances of remission. In a study from Kenya, half the patients had epilepsy for more than 5 years and 38% already had more than 100 generalised tonic-clonic seizures (GTCS) at the time of therapeutic trial.[29] Neither the duration nor the number of GTCS correlated with response to therapy. These results clearly belie the popularly held notion that chronic epilepsy will develop unless treatment is initiated early.

Chronic Epilepsy

Although the majority of patients with epilepsy do go into remission with or without treatment as discussed above, around 20–30% of patients will continue to get seizures despite appropriate treatment (pharmacoresistant epilepsy).[57] This works out to around 1 million patients in India. Fortunately, around 30% of these patients are candidates for epilepsy surgery.

Determinants of Natural History of Epilepsies

There are certain well established predictive factors for the development of pharmacoresistant epilepsy. These include onset of epilepsy in infancy, organic brain damage (mental retardation and neurological signs), seizure type (tonic, atonic and myoclonic seizures), multiple seizures, high seizure frequency, long duration of uncontrolled seizures, failure of past AED treatments and an abnormal EEG.[75] Most of these factors are especially relevant to prognosticate the outcome of epilepsy in children.

Refractory Epilepsies

Despite the fact that the majority of patients with epilepsy remit, about 20–30% of patients continue to suffer recurrent seizures despite appropriate AED therapy.[57] These unfortunate patients are a challenge to the treating team. Fortunately, about 25% of these patients are candidates for epilepsy surgery. When selected appropriately, surgical treatment results in a cure in the majority of patients.

The definition of refractory epilepsy is essentially an individual one. A rough rule would be a patient who suffers two or more disabling seizures per month and who has failed trials of two appropriate AED monotherapy trials and one polytherapy trial over a period of 2 years. Patient's expectation, degree of disability, AED toxicity, employment and education, and obtaining driving license are some of the factors that ultimately influence the decision for surgery. The natural history studies have shown that most patients who are destined to achieve seizure control will do so within the first 2 years of onset of epilepsy.

Mechanisms of Pharmacoresistance

Resistance to AEDs can be explained by two putative neurobiological mechanisms:[68] (1) removal of AEDs from the epileptogenic tissue through excessive expression of multidrug transporters and (2) reduced drug-target sensitivity in epileptogenic brain tissue. Overexpression of certain genes, like MDR 1 and MDR associated protein 1 (MRP1) in the epileptogenic tissue, can result in pharmacoresistance.[71] Therefore, pharmacoresistance may develop even before the first seizure or may develop many years after the onset of epilepsy. Pharmacoresistance may reverse in some patients.

Comprehensive Epilepsy programme

Patients with refractory epilepsy are best managed by a team of specialists within a comprehensive epilepsy programme. There are many problems encountered by patients with refractory epilepsy. Some of them include incorrect or imprecise diagnosis, inappropriate AED therapy, inadequate polypharmacy, frequent adverse effects of AED therapy, physical injuries related to seizures, psychosocial problems, educational and occupational problems, disturbed family life, economic problems and poor quality of life.[77] The team should include a neurologist with special expertise in epilepsy (epileptologist), a neurosurgeon with expertise in epilepsy surgery, a neurophysiologist, a neuroradiologist with special interest in epilepsy, a psychiatrist, a psychologist, a medical social worker and on occupational therapist. The team is usually led by the epileptologist. Although seizure control is the most important aspect in the treatment of epilepsy, it is not the sole factor and other issues, like education, employment, marriage and quality of life, are equally important in the management.

Nearly one-third to one half of patients with refractory epilepsies are potential surgical candidates. In carefully selected patients, epilepsy surgery offers the best chance of cure of epilepsy.

DIFFERENTIAL DIAGNOSIS OF EPILEPSIES

Epileptic seizures are paroxysmal in nature, with varying manifestations ranging from brief absences to the most bizarre motor phenomena as seen in some patients

with frontal lobe epilepsy. A variety of paroxysmal phenomena, which are non-epileptic, can mimic epileptic seizures. These can be sub-divided into physiologic and psychogenic non-epileptic events.

Physiological non-epileptic events include syncope, paroxysmal movement disorders, transient ischaemic cerebrovascular phenomena, non-epileptic myoclonus and sleep disorders. Psychogenic non-epileptic events include somatoform disorders, dissociative disorders, anxiety disorders and malingering. A very careful history and appropriate investigations will usually help in differentiating between true epilepsy and non-epileptic events, although in some instances, the distinction can be extremely difficult. It is not uncommon for patients with non-epileptic seizures to be treated as intractable epilepsy with multiple AEDs for years. It is important to recognise that around 20% of patients with chronic epilepsy referred to a video-EEG unit proved to be non-epileptic attacks.[8] Meticulous history and judicious use of investigations will help clarify the existence of the two seizure types.

INVESTIGATION OF EPILEPSIES

Electroencephalography

"On the paper of the electroencephalogram the brain writes out its own record in the language of electrical potentials, but it does not make its own diagnosis and in some cases it is strongly silent" (Jasper H 1954) (In Electroencephalography in Epilepsy and Functional Anatomy of the Brain. Penfield WP and Jasper HH (Eds). Boston: Little Brown & Co; 1954).

The first electroencephalogram in humans was performed by Hans Berger in 1928.[6] Since that time, EEG has played a central role in the diagnosis and management of epilepsy. The generators of the EEG signals on the scalp are not precisely known. The EEG represents summated synchronised post-synaptic potentials, which may be excitatory or inhibitory. These excitatory and inhibitory post-synaptic potentials (EPSP and IPSP) are generated from apical dendrites of neurons in the superficial cortex. The electrical fields generated from deep sources do not normally get recorded over the scalp, unless the more superficial cortical neurons get activated.

The EEG is the only test that provides information about epileptogenesis. It is important to recognise that epilepsy is essentially a clinical diagnosis. The role of the EEG in epilepsy is mainly to support the clinical diagnosis of epilepsy and to aid in the syndromic classification of epilepsy (Figs 1 and 2A to C).

The diagnostic sensitivity of a single awake EEG with photic stimulation and hyperventilation is about 50% in adults with epilepsy.[9] After four EEGs, the sensitivity increases to 92%.[64] Recording EEG during sleep increases the sensitivity considerably; a single awake plus sleep record will be positive in about 80%.[26,81]
The diagnostic specificity of the EEG depends on the proper interpretation of the EEG. Misinterpretation

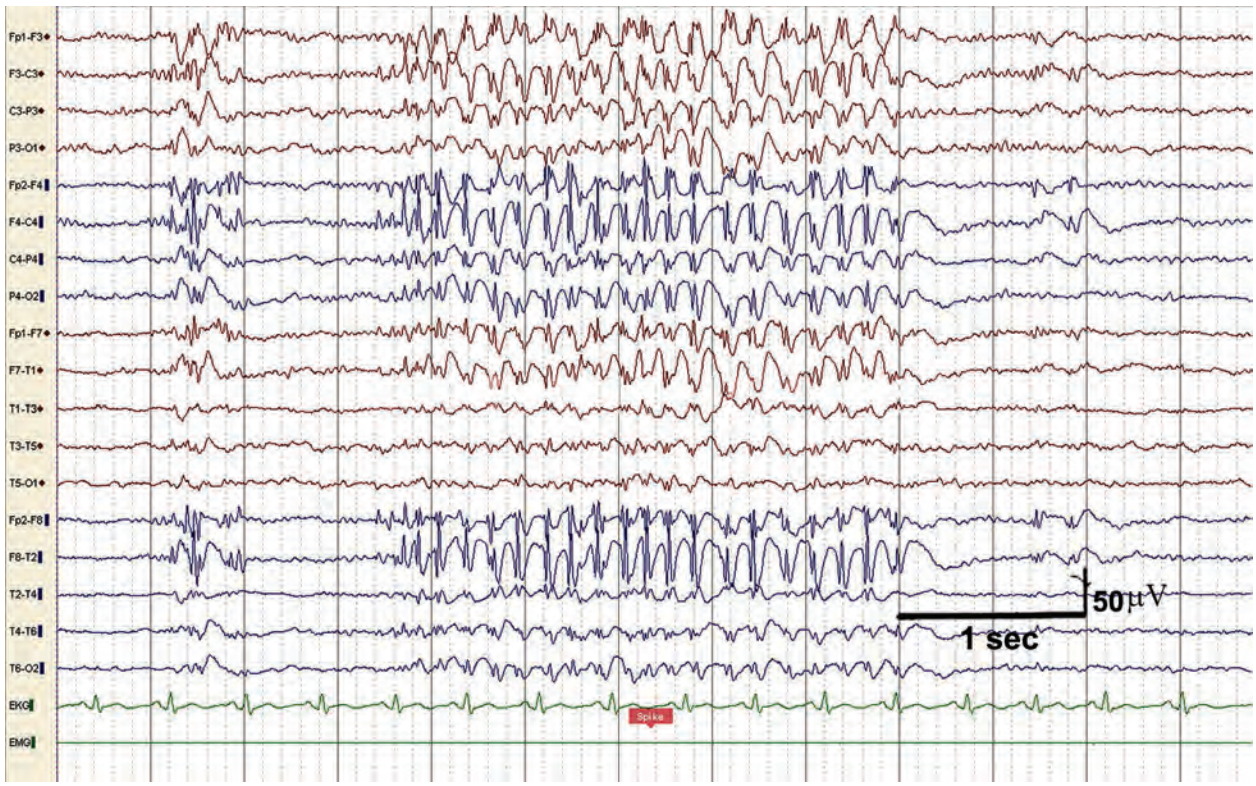
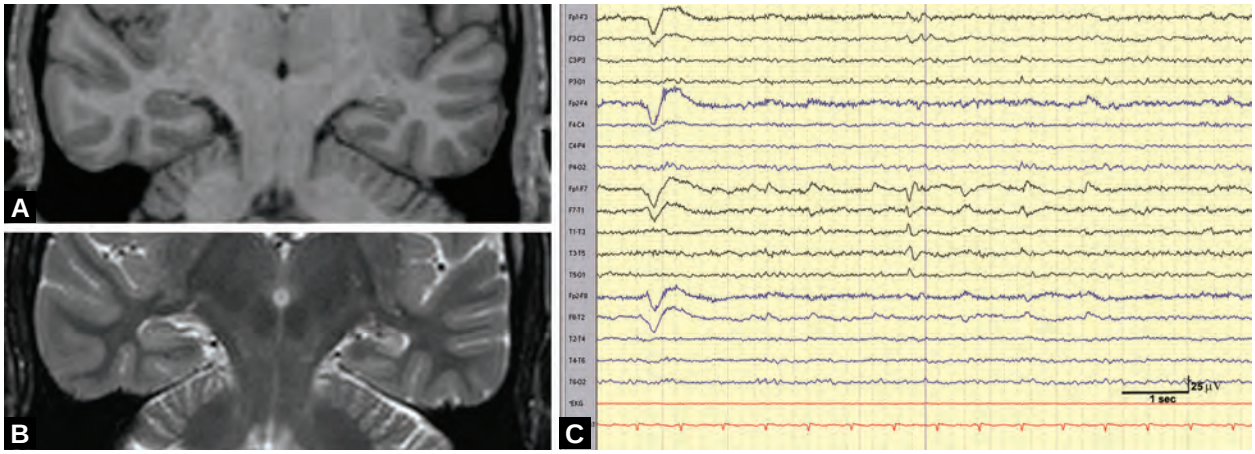


Fig. 1: EEG of a patient with juvenile myoclonic epilepsy (prototype of idiopathic generalised epilepsy syndrome), showing generalised atypical spike and wave discharges



Figs 2A to C: MRI-EEG correlation in a patient with medically refractory mesial temporal lobe epilepsy, prototype of symptomatic focal epilepsy syndrome, shows. (A) Small left hippocampus on T1-weighted coronal MRI sequence. (B) Increased signal intensity on T2-weighted coronal MRI sequence. (C) Left anterior temporal spike discharges

of normal variants and artefacts can lead to a wrong diagnosis of epilepsy and unnecessary AED therapy. It is also important to understand that a normal EEG does not exclude epilepsy. As discussed above, the EEG may remain normal despite repeated EEG recordings in 5–10% of patients. Such patients usually have only simple partial seizures or mesial frontal or parietal lobe epilepsy.[43]

Most of the EEG laboratories in India now have digital EEG machines. They have several advantages over the conventional analogue paper machines[18] Digital EEG machines are paperless and have automatic event detection systems. Recording parameters can be changed *post hoc* and the EEG can be displayed in a variety of montages. Brain mapping is the topographic display of digitally quantified EEG information on a stylised head model. These tools are used extensively but do not offer any advantage over conventional reading of the EEG. In fact, they can mislead the clinician. Interpretation of the EEG must always be done in the clinical context. There must be a dialogue between the referring physician and the person doing the EEG, regarding the clinical problem and the questions the EEG is expected to answer. Specific interictal EEG abnormalities can be found in a small number of epilepsy syndromes. These include hypsarrhythmia in West syndrome, centrotemporal spikes in Benign Rolandic Epilepsy of childhood and slow spikes in Lennox-Gastaut Syndrome.[25]

Video-EEG Telemetry

Video-telemetry or video-EEG is the simultaneous and synchronous recording of clinical events on video, along with EEG. It has several advantages over the routine EEG recording.[12] Prolonged Video-EEG monitoring provides the opportunity to study interictal and ictal paroxysmal electrographic and clinical events synchronously, thereby permitting electroclinical correlation. The routine scalp EEG allows recording for a limited period of time, thereby making it less sensitive and specific than a long-term video-EEG recording. The occurrence of interictal epileptiform abnormalities in a patient with epilepsy is variable and is usually maximal during drowsiness and light sleep. During wakefulness, epileptiform discharges can be absent for several hours, hence a routine awake EEG may be normal, whereas the scope of recording these discharges is much greater during video-EEG monitoring.

Video-EEG is used to confirm seizure disorder, classify seizure type(s), distinguish epileptic seizure from non-epileptic seizure, assess seizure frequency, study precipitating factors and most importantly, to localise the ictal onset zone in patients who are evaluated for focal resective epilepsy surgery.

Interictal epileptiform abnormalities in the form of spike-waves and sharp waves can be focal, multi-focal or generalised. The distribution of these discharges helps in localising the lobe of origin. In mesial temporal lobe epilepsy (MTLE), which is the most common surgically remediable epilepsy syndrome, the epileptiform discharges are maximal at the anterior temporal electrodes, whereas in neocortical temporal lobe epilepsy, the spikes are maximal at the mid-and/or posterior temporal locations. In unilateral MTLE, the incidence of bilateral independent temporal epileptiform abnormalities is around 30% during routine scalp EEG recording, whereas it increases to around 70% during prolonged video-EEG monitoring.[28] The spikes in mesial frontal epilepsy are usually seen over the midline vertex region. Generalised spike discharges can also occur and indicate secondary bilateral synchrony.

One of most important aspects of video-EEG monitoring is the recording of clinical seizures. The semiology of seizures would help classify seizure types into generalised, complex partial seizures of temporal or extratemporal (frontal, parietal and occipital) type or simple partial seizures.

Ictal electrographic rhythms differ from interictal discharges and consist of low voltage beta activity,

rhythmic medium amplitude theta or alpha activity, rhythmic delta activity and runs of spikes or sharp waves. Electrodecremental response, either focal or diffuse in distribution can also occur, but is less specific. The rhythmic activity evolves into different frequencies and morphologies and propagates to regions remote from the origin. Ictal onset can be focal or diffuse. In temporal lobe seizures, the rhythm is typically a focal rhythmic 5–7 Hz theta activity over the temporal region, which remains lateralised for several seconds before spreading to other regions.[24] The electrographic changes usually precede the clinical onset, but may be delayed. In some, the electrographic onset is diffuse, but thereafter lateralises to one side, a phenomenon called late lateralisation pattern.[10] In some instances, the electrographic change is initially on one side, but later switches to the opposite side (switch of lateralisation).[69] This may indicate bitemporal epileptogenecity.

Frontal lobe seizures are typically hypermotor and the ictal rhythm may be obscured by myogenic and movement artefacts. In such instances, interictal abnormalities and the ictal clinical semiology may be more informative than ictal electrographic changes.[63]

Post-ictal changes can be in the form of slowing or attenuation of the background activity and can be focal, hemispheric or generalised. Focal post-ictal change is of lateralising value. The video-EEG is expensive, labour-intensive and time consuming to analyse. If used judiciously, the test is cost-effective and can result in a change in management of the patient. In a study of 324 patients who underwent long-term video-EEG monitoring at the R Madhavan Nair Centre for Comprehensive Epilepsy Care, around 30% had a change in the diagnosis and thereby a change in treatment.[13] Nearly one-third of patients could be recruited for epilepsy surgery. It must, however, be emphasised that notwithstanding the utility of video EEG, the majority of patients requiring surgery for their epilepsy can be selected on the basis of conventional EEG and clinical evaluation.

Neuroimaging

Rapid advances in neuroimaging in the last couple of decades have made available a wide array of imaging modalities to the treating team. These modalities include computed tomography (CT scan), magnetic resonance imaging (MRI), positron emission tomography (PET), interictal and ictal single photon emission computed tomography (SPECT), MR spectroscopy (MRS), T2 relaxometry and functional MRI (fMRI). The main goals of neuroimaging in persons with epilepsy, as laid out by the Commission on Neuroimaging of the ILAE,[17] are: (1) delineation of structural and functional abnormalities in the suspected epileptic zone; (2) prediction of the nature of structural pathology; (3) detection of abnormalities distant from the putative epileptogenic region (diffuse or dual pathology) and (4) identification of eloquent brain regions, such as language, memory and sensorimotor areas, and the relation of these regions to the epileptogenic lesion.

The most common imaging modalities used in epilepsy are the CT scan and MRI. The CT scan detects only gross structural lesions and a negative CT scan does not exclude subtle epileptogenic lesions. The current role of CT in epilepsy is mainly in an emergency situation and in a patient presenting with recent seizures in an area known to be endemic for cysticercosis.[32,60] The MRI is currently the best investigation to define both normal and abnormal brain structures.[24] The most common structural pathology detected on MRI in patients with focal epilepsy is mesial temporal sclerosis (MTS). Other lesions include malformation of cortical development, vascular lesions and low-grade neoplasms, and focal atrophic lesions (Figs 3A to D).

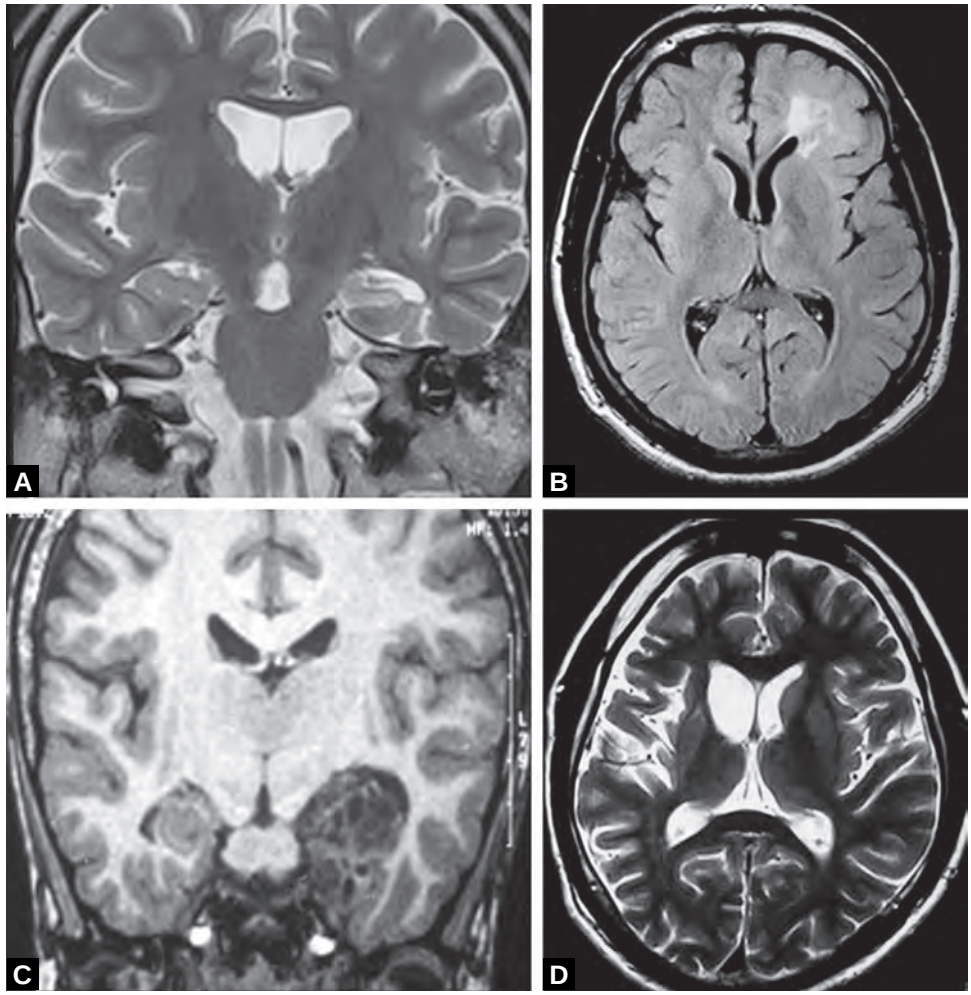
Not all patients with epilepsy need neuroimaging. Patients with primary generalised epileptic syndromes, such as childhood and juvenile absence epilepsies, juvenile myoclonic epilepsy and idiopathic benign localisation related childhood epileptic syndromes do not need neuroimaging. On the other hand, patients with refractory focal epilepsy must be investigated with MRI. It is also important to emphasise that the imaging must be done with a strict protocol laid out for epilepsy imaging.

Special imaging modalities, like PET, SPECT and fMRI, are available in selected centres in India. The PET scan is usually done in the interictal state and measures the metabolic rate of the tissue.[79] Epileptogenic tissue will usually be seen as hypometabolic.[62] The SPECT is usually done by injecting a radiotracer within a few seconds of a seizure onset. The seizure focus will show hyperperfusion, whereas interictal SPECT will show reduced perfusion.[72] By co-registration of interictal and ictal SPECT on the MRI (SISCOM), the seizure focus can be mapped with great accuracy.[49]

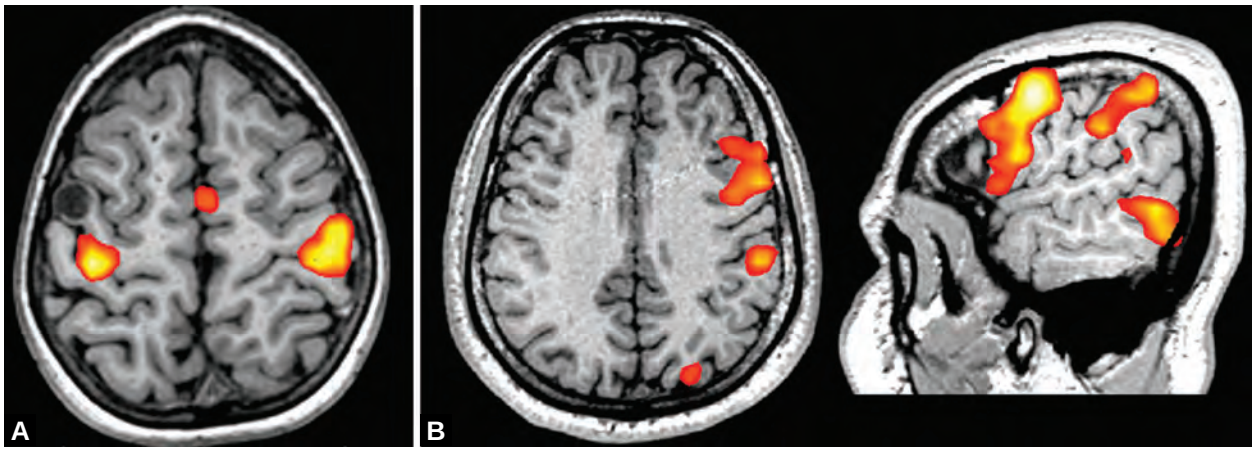
The fMRI is used to map out eloquent cortical regions using the blood oxygenation level dependent (BOLD) technique. Changes in oxyhaemoglobin levels during activation of the cortex results in a change in MRI signal. Language, sensorimotor and visual areas can be mapped out (Figs 4A and B). This technique is now being routinely used in the evaluation of patients with intractable extratemporal epilepsy with epileptogenic zones close to eloquent areas.[39]

Invasive Video-EEG Monitoring

When there is discordance between various non-invasive tests, like scalp EEG, video-EEG, MRI and functional imaging findings or in cases of focal cortical dysplasia where the epileptogenic focus is usually more widespread than the MRI abnormality, invasive monitoring is required to exactly delineate the epileptogenic focus.[83] This is achieved by means of implanting multicontact



Figs 3A to D: The MRI appearances in some surgically remediable focal epilepsy syndromes. (A) Coronal T2-weighted sequence shows increased signal intensity in the left hippocampus in a patient with mesial temporal sclerosis. (B) Axial FLAIR sequence shows left frontal lesion with thickened cortex and hyperintense signal suggestive of focal cortical dysplasia. (C) Coronal T1-weighted sequence shows hypointense mass lesion in the left hippocampus in a patient with pathologically verified ganglioglioma. (D) Axial T2-weighted sequence shows left perisylvian atrophy with increased signal and severe caudate nuclear atrophy characteristic of Rasmussen's encephalitis



Figs 4A and B: Functional MRI (fMRI) for language and motor activation. (A) Inline BOLD fMRI shows activation of both hand motor areas and supplementary motor area with bilateral finger tapping task. The lesion is just anterior to the motor hand area on the right side. (B) Inline BOLD fMRI language area mapping with verbal fluency task shows a strongly left lateralised language function

subdural grid or strip electrodes or stereotactically implanted intracerebral depth electrodes. It is very important to generate a hypothesis regarding the probable epileptogenic focus/foci, before deciding on the type of electrodes and the extent of coverage. This will avoid the danger of inadequate or inappropriate sampling of the brain, resulting in a false negative study.

Invasive monitoring carries a risk of infection, haemorrhage, weakness or even death. Around 3.5% patients will have transient morbidity, while the risk of permanent morbidity is about 0.7%.[4] Moreover, invasive monitoring is very expensive and this is a significant constraint in developing countries like India. Furthermore, the very need for invasive monitoring for localisation of seizure focus is indicative of a less favourable post-surgical outcome, when compared to those who could be selected utilising a non-invasive protocol.

NEUROPATHOLOGY OF EPILEPSIES

The six common neuropathological substrates of chronic epilepsies in adults are: (1) hippocampal sclerosis; (2) malformations of cortical development; (3) traumatic lesions and changes secondary to chronic epilepsy; (4) tumours and hamartomas; (5) infective (tuberculosis, cysticercosis, encephalitis) disorders and inflammatory lesions (Rasmussen's encephalitis) and (6) Sturge Weber syndrome and angiomas.

Hippocampal sclerosis is the most common pathologically confirmed lesion in chronic temporal lobe epilepsy (Figs 5A to D). In the last decade, advances in MRI techniques have made it possible to accurately diagnose MTS pre-operatively. Typically, there is marked loss of pyramidal neurons in the CA1 region, followed by less severe loss in the CA3 and CA4 sectors, followed by hilar and granule cells, whereas the neurons in the CA2 region are typically resistant to damage.[44]

Malformations of cortical development have long been recognised as an underlying cause of epilepsy in a proportion of adults with early or late onset disease, as well as in the paediatric age group.[76] The basic problem is a disturbance in the migration of neurons from the periventricular germinal mantle to the cortical mantle along the radially oriented glial fibres. The type of insult, its severity and time of occurrence, influence the extent, location and type of malformation, which in turn affects the degree of clinical disability. Malformations can be divided into focal and diffuse abnormalities; focal malformations include focal cortical dysplasia (Fig. 5), cerebral microdysgenesis, grey matter heterotopia, polymicrogyria, pachygyria or agyria and schizencephaly. Diffuse malformations include hemimegalencephaly, microdysgenesis, grey matter heterotopia and lissencephaly.

The two most common tumours which cause chronic epilepsy are dysembryoplastic neuroepithelial tumour (DNET)[21] and gangliogliomа[82] (Fig. 5). Other tumours include low-grade astrocytomas, oligodendroglioma, pleomorphic xanthoastrocytoma and subependymal giant cell astrocytoma.

Rasmussen's encephalitis is a rare disorder that presents in childhood or adulthood as epilepsia partialis continua and progressive hemiparesis. The disease progresses through various stages. The neuropathology is one of chronic polio-encephalitis, which is typically unilateral and characterised by neuronophagia and perivascular cuffs of lymphocytes.[51]

TREATMENT OF EPILEPSIES

The mainstay in the treatment of epilepsy is AEDs. The medical and surgical management of epilepsy will be dealt with in detail in subsequent chapters.

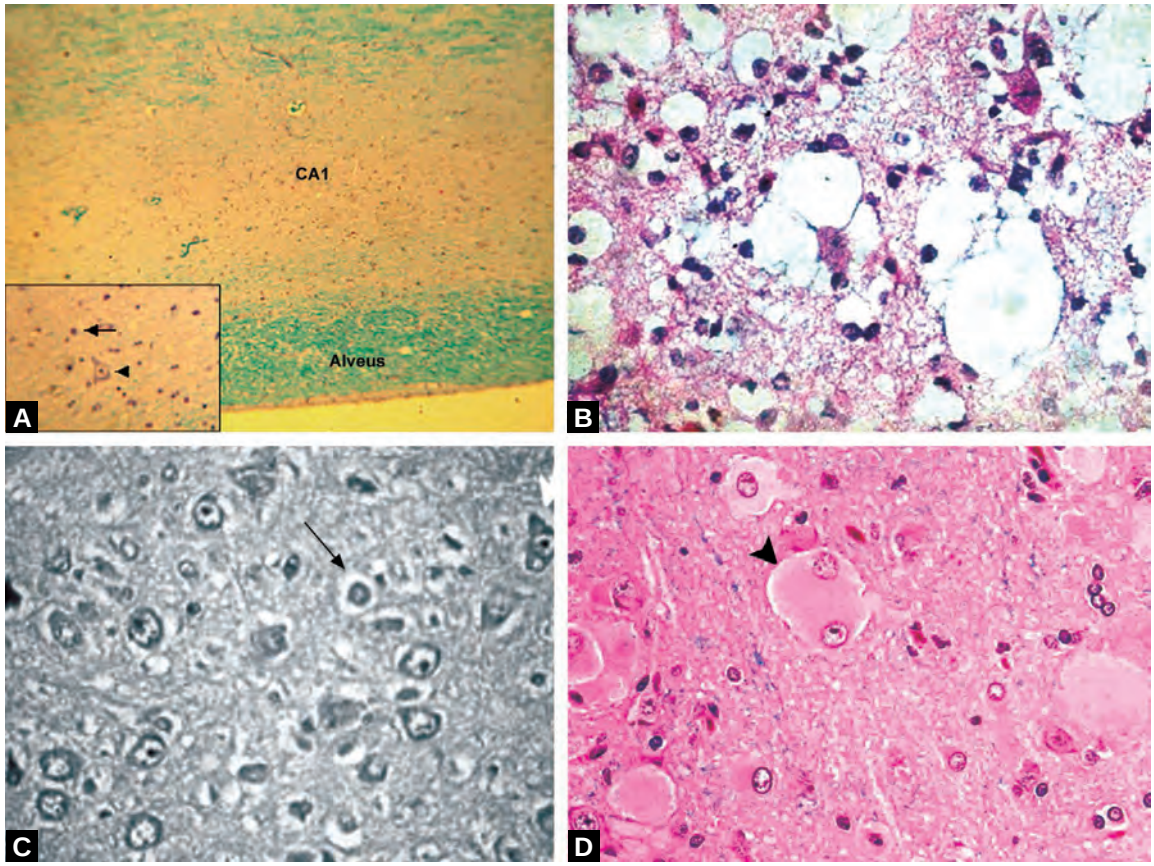
Emerging and Alternative Treatment for Epilepsy

Treatment options are limited for patients with pharmacoresistant epilepsies who are not candidates for resective surgery. In the recent years, however, two well studied options have emerged: (1) vagus nerve stimulation and (2) ketogenic diet.

Vagus Nerve Stimulation

More than 30,000 patients have been implanted with vagus nerve stimulation (VNS) since 1997, when the USFDA approved its use for adult patients with refractory epilepsy. Clinical trials have shown reduction in seizures and improvement in quality of life measures.[19,33] The device consists of a battery-powered pulse generator (Cyberonics™) which is implanted subcutaneously in the anterior chest wall below the clavicle, lead wires which are attached to the vagus nerve (the left vagus nerve is used for stimulation since the right vagus has strong cardiac innervation) and a hand-held magnetic wand which can activate or deactivate the pulse generator. The stimulation parameters are programmed by means of a personal computer or laptop. The stimulation is carried out intermittently once every 2–5 minutes (off time) for a period of 30 seconds (on time) at a current intensity of 0.25 mA, which is gradually ramped up to a maximum of 3.5 mA. Meticulous follow-up is required to adjust the duty cycle and to ensure proper functioning of the device. Optimal stimulation parameters are achieved usually within 3–4 months. The hand held magnet can be used to abort a seizure, either by the patient when he/she experiences an aura or by a family member/caretaker as soon as a seizure develops.

The mechanism of action of VNS is still not clear. The vagus nerve has extensive afferent connections in the brainstem, forebrain and hypothalamus. Animal studies have demonstrated that an intact locus ceruleus in the brainstem is essential for the efficacy of VNS. The adverse effects of VNS consist of hoarseness of voice, cough and breathlessness. Over time, these symptoms tend to subside. The battery life of newer devices is approximately 7 years.



Figs 5A to D: Histopathology of common lesions associated with refractory focal epilepsies. (A) Shows neuronal loss in the CA1 sector of the hippocampus in hippocampal sclerosis. Inset shows a neuron (arrowhead) and reactive gliosis (arrow); Luxol-fast blue-PAS stain X 150, with magnified inset. (B) DNET: photomicrograph showing characteristic microcystic spaces containing pale staining material. Some of these microcystic spaces contain well-formed neuronal cells-floating neurons. In between these, sheets of glial cells are also seen [haematoxylin and eosin (H&E stain X 200)]. (C) Photomicrograph shows admixture of neoplastic ganglion cells (white arrow) and astrocytes (dark arrow) characteristic of ganglioglioma (H&E X 200). (D) Focal cortical dysplasia: photomicrograph shows classical balloon cells (arrowhead) (H&E stain X 150)

Ketogenic Diet

The ketogenic diet has a long history and antedates the use of AEDs. With the advent of phenytoin, ketogenic diet fell out of favour. It resurfaced in the 1990s and has been found to be effective in patients who have failed multiple AEDs.[48] While on the diet, lower doses of AEDs are required, thereby reducing the potential for AED-related side effects. The diet is very high in fat and low in carbohydrate and protein at a ratio of 3:1. South Indian and North Indian versions of the ketogenic diet are available. A brief period of hospitalisation is required during the initiation of the diet. The diet is monitored by measuring urinary ketones, which must be 4+ to ensure that the diet is sufficiently ketogenic.

The exact mechanism of action is not known. It appears that the effects on the brain are multiple, with overall changes in brain phosphorylation state and altered gene expression. Many studies have shown that ketogenic diet is effective in medically refractory epilepsy in children. Adverse effects include acidosis, anorexia, dehydration, diarrhoea and symptomatic hypoglycaemia, renal stones, etc.

Yoga

The ancient Indian practice of Yoga has been shown to reduce stress and create relaxation. Studies have shown reduction in seizure frequency and a feeling of well-being.[59,61] In a recent prospective, non-randomised, open-label, add-on trial of yoga meditation protocol study, there was significant reduction of seizure frequency at 3, 6 and 12 months in 20 patients with drug-resistant chronic epilepsy.[59]

COMMUNITY AWARENESS AND ATTITUDE TOWARDS EPILEPSY

Even to this day, people with epilepsy are discriminated against because of misunderstanding and lack of knowledge and awareness throughout the world. Many studies from both the developed and the developing countries have investigated public awareness and attitudes towards epilepsy.[43] Only in recent years has the public perception about epilepsy begun to change for the good in the developed countries, whereas considerable stigma continues to be attached to epilepsy in the developing countries. In a study conducted in central Kerala,[21] 27%

respondents considered epilepsy as a mental disease, 11% would object to their children playing with a child with epilepsy, 44% would not employ a patient with epilepsy, compared with 3%, 6% and 9% in the United States.[11] These negative attitudes even in the highly literate population of Kerala towards epilepsy are not much different from less literate North Indian and Pakistani populations.[3,31] Detailed information on this subject is available in the multicentric ICMR publication "Epilepsy in India".

PROBLEMS ASSOCIATED WITH LONG-STANDING EPILEPSY

Sudden Unexplained Death in Epilepsy

People with epilepsy are 2–3 times more likely to die prematurely than those without.[5] The many causes of death among patients with epilepsy include accidents, status epilepticus, sudden unexplained death in epilepsy (SUDEP), ischaemic heart disease and various malignancies.

The SUDEP is defined as "sudden, unexpected, witnessed or unwitnessed, non-traumatic or non-drowning death in patients with epilepsy, with or without evidence of a seizure and excluding status epilepticus, in which postmortem does not reveal a toxicological or anatomical cause for death".[47] The aetiology is poorly understood but a higher incidence has been noted in patients with intractable epilepsy, thereby indicating that seizure frequency and severity are risk factors. Polytherapy may also be a risk factor but evidence is conflicting. Risk of SUDEP in someone with epilepsy in the community is 24 times higher than for someone without epilepsy.[30]

Psychiatric Disorders

Depression, anxiety and other psychosis can develop in patients with medically refractory epilepsy. Major depression can occur in around 30% of patients,[80] while the risk of developing interictal schizophrenia-like psychosis is significantly higher than in the general population.[54] Psychiatric disorders are not absolute contraindications to epilepsy surgery, but it is important to identify and stabilise the symptoms pre-operatively.

Quality of Life Outcome

There are several measures of quality of life (QOL) that assesses various domains of social, physical, psychological, vocational and economic well-being.[73] It has been shown that patients with chronic epilepsy have lower QOL scores than those without epilepsy.[23]

SUMMARY

The epilepsies are a group of disorders with diverse aetiologies and variable prognoses, with recurrent unprovoked seizures being the common feature. Syndromic diagnosis is important for choosing the appropriate treatment as well as for determining the prognosis. While nearly 80% of patients with epilepsy achieve remission with or without medication, the remaining 20% will be refractory to medical therapy, with considerable psychosocial morbidity. Around 50% of these unfortunate patients are potential candidates for epilepsy surgery, while the remaining may benefit with newer antiepileptic drugs and novel therapies, like vagal nerve stimulation and the ketogenic diet. These patients need to be evaluated in a comprehensive epilepsy centre and there are only a handful of them in India. The need of the hour is to set up such centres in various parts of the country, in order to reduce the huge medical and surgical treatment gap.

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200 Epilepsy: Medical Management

Ashalatha, Radhakrishnan K

INTRODUCTION

Epilepsy affects every sphere of an individual's life, cutting across age, gender and social differences. Major areas of education, employment, marriage and social functioning are affected and the overall quality of life is hampered due to the nature of the illness and its consequences. Therefore, management of a patient with epilepsy involves much more than treatment with antiepileptic drugs (AEDs). The steps in the management of a patient with epilepsy are summarised in Table 1.

The medical treatment of seizure disorders is a complex process requiring extensive interaction and co-operation between the physician and the patient. The physician is required to have an accurate knowledge of the type of seizures and epileptic syndromes, pharmacology of AEDs and experience with their therapeutic applications. It is important that patients or a responsible member of the family in case of children and mentally challenged individuals should be informed about the nature of the disorder, fully involved in the therapeutic decision making and should be active participants in the treatment process. In addition, it is important to emphasise the vital necessity to strictly follow the instructions regarding the dose, the frequency and regularity of treatment.

An enquiry conducted between 1979 and 1983 by the Commission on AEDs of the International League Against Epilepsy (ILAE) on the availability of AEDs in 35 developing countries, including India, concluded that "older and less efficacious compounds (such as phenobarbitone) are the only AEDs available to most patients, whereas newer and more compounds are either not available or restricted to a very limited number of cases".[29] According to WHO, 3 out of 4 persons with epilepsy in the world do not receive treatment at all. The approach to pharmacological treatment of epileptic disorders has changed substantially over the last 25 years due to several factors: (a) improved knowledge of the efficacy and tolerability of AEDs;[11,16] (b) acquisition of new information through observational studies and clinical trials, which led to more rational therapeutic decisions;[1] (c) introduction of new AEDs[15,30] and (d) availability of alternate treatment options such as surgery for refractory partial epilepsy.[7,26] Recent worldwide trends in the management of patients with epilepsy emphasise the use of a single AED (monotherapy) over the previous approach of using multiple AEDs simultaneously (polytherapy).[17,25]

Health care delivery in developing regions is largely governed by the three As: availability, acceptability and affordability. The introduction of seven new AEDs (e.g. clobazam, gabapentin, lamotrigine, topiramate, oxcarbazepine, levetiracetam and zonisamide) in India over the last 10 years, in addition to better availability of already existing standard AEDs (Table 2), have provided physicians and their patients with new treatment options, but has in several ways complicated the management of epilepsy. New AEDs are expensive and are beyond the reach of the majority of the patients with epilepsy in developing countries. Despite their promise, only very few patients, who have not responded to standard AEDs, became seizure free while they were initiated on treatment with new AEDs.[10] Primary and secondary care physicians, without special training and expertise in the disorder, treat a majority of patients with epilepsy in India and other developing countries,[14] which often results in indiscriminate usage of the available AEDs.[22] In a recent study, which inquired about the user profile of AEDs in Kerala, the following pertinent observations were made: (a) polytherapy, especially with sub-optimal dosages of AEDs, is quite prevalent;

Table 1: Steps in epilepsy management

Correct diagnosis
Epilepsy education
Treatment with appropriate AEDs
Psychosocial support
Early detection of medical refractoriness

Table 2: Commonly used AEDs currently available in India

Standard AEDs	*New AEDs*
Phenobarbitone	Clobazam
Phenytoin	Gabapentin
Carbamazepine	Lamotrigine
Sodium valproate	Topiramate
Clonazepam	Oxcarbazepine
	Levetiracetam
	Pregabalin
	Zonisamide

(b) the use of relatively expensive AEDs, often in combinations, has escalated the cost of AED treatment and (c) better availability of AEDs has not been supplanted adequately by education of the treating physicians.[22]

This review provides a framework for the choice of AEDs in five clinical situations: (1) newly diagnosed epilepsy; (2) seizure recurrence on initial monotherapy; (3) seizures controlled on polytherapy; (4) seizures poorly controlled on polytherapy and (5) special clinical situations. The role of serum AED monitoring will critically be appraised. Many AEDs are available currently as extended release preparations; their therapeutic implications will be briefly discussed. A practical guide to AED withdrawal in seizure-free patients is provided. A detailed account on the management of status epilepticus, epilepsy in pregnancy and paediatric seizure disorders is beyond the scope of this review.

NEWLY DIAGNOSED EPILEPSY

It is now generally accepted that 65–70% of newly diagnosed patients with epilepsy can successfully be treated with the available AEDs.

The goal of AED therapy is to make the patient completely seizure-free without causing undesirable side effects and thereby achieve improved quality of life. Most epileptologists now agree that monotherapy is the appropriate choice in newly diagnosed epilepsy. The advantages of monotherapy are listed in Table 3.

Nearly 75% of patients with newly diagnosed epilepsy achieve one-year seizure freedom with a single appropriate AED.[17,24]

Various factors, such as seizure type, the epilepsy syndrome, age and gender of the patient, side effect profile of the AED and economic factors, influence the choice of AED for a newly diagnosed patient with epilepsy. Although, the seizure type is the principal consideration in the selection of AEDs, over the last few years, emphasis has shifted from treating the seizure type to treating the epilepsy syndrome. However, in a significant proportion of patients, the syndromic diagnosis of epilepsy may not be possible initially or may not be evident despite long-term follow-up. The choice of drug based on seizure type is given in Table 4.

It is advisable to choose the AED to 'fit the fit and fit the patient'. Valproate is the drug of choice in patients with absence epilepsy and juvenile myoclonic epilepsy. Carbamazepine is contraindicated in these groups of patients. If the patient can afford it, valproate is preferred in patients with all types of primary generalised epilepsies, although phenobarbitone, phenytoin and carbamazepine are also effective and can safely be used in some of them. Lamotrigine either alone or, if necessary, in combination with valproate is a good choice in these groups of patients. In partial epilepsies, since there is little difference in the efficacy of different AEDs, availability and affordability govern the choice.

Phenytoin and carbamazepine may worsen absence and myoclonic seizures.[19] Drug-induced drowsiness caused by clonazepam and clobazam can exacerbate absence seizures. Sedative drugs, like barbiturates and benzodiazepines, are better avoided in children as they can produce subtle cognitive and behavioural disturbances and in adults with occupations involving driving and operating dangerous machines. Phenytoin can cause coarsening of the face and hirsutism, which may be unacceptable to women. Coexistent medical problems, like porphyria, hepatic or renal diseases, will also influence the selection of AEDs. Teratogenic effects of AEDs is an important consideration in women of child bearing age and supplementation of 5 mg of folic acid is routinely recommended with all AED prescriptions for this group of patients.

The cost of the AED is an important factor, which the physicians often forget to give due consideration (Table 5). Newer AEDs escalate the cost of therapy

Table 3: Potential advantages of AED monotherapy

Fewer adverse effects
Improved compliance
No drug interaction
Improved seizure control
Less expensive
Less risk of teratogenicity

Table 4: Efficacy of AEDs according to seizure types

Seizure type	*First line drugs*	*Second line drugs*
Primary and secondarily generalised seizures,	DPH, PB, CBZ, VPA	PRM, CZP, CLB, TPM, LTG, LEV, SPS, CPS
Generalised absence seizures	VPA, ESM	LTG, CLB, CZP, LEV
Atypical absence, tonic and clonic seizures, myoclonic seizures	VPA	CZP, CLB, LTG, PB, PRM, LEV, PIR

Table 5: Cost of AED treatment

Drug	*Average daily dose (mg)*	*Daily cost (Rs)*
Phenobarbitone	90	2.08
Phenytoin	300	3.24
Carbamazepine	800	6.26
Sodium valproate	1200	11.27
Primidone	750	8.67
Clonazepam	4	8.25
Clobazam	20	12.20
Gabapentin	1600	50.33
Lamotrigine	200	24.60
Topiramate	200	33.71
Oxcarbazepine	1200	19.08
Levetiracetam	2000	50.0
Zonisamide	500	45.0

several fold, without offering a significant advantage in seizure control over the established drugs. Hence, their indiscriminate use is unrealistic in a developing country set-up. Even among first line AEDs, cost of treatment with carbamazepine and valproate is 3–4 times more than that with phenytoin or phenobarbitone.

Notwithstanding these concerns, especially regarding the routine use of such affordable drugs, like phenobarbitone, hydantoins or carbamazepine, there should be no hesitation in their use for the large number of economically disadvantaged individuals. A large multicentric study in India involving more than 3,000 patients revealed these drugs provided satisfactory therapeutic control of seizures in nearly 70% of cases without any serious adverse effect.

SEIZURE RECURRENCE ON MONOTHERAPY

What to do when the first AED fails? The first step to be taken is to review the diagnosis and treatment. Common diagnostic errors are failure to consider non-epileptic events and missing the history of myoclonic jerks in syndromes like juvenile myoclonic epilepsy. One of the most important reasons for failure of AED therapy is poor patient compliance.[13] Over one-third to one-half of persons with epilepsy are non-compliant to the extent of interfering with their optimal treatment.[15] A significant factor that may lead to non-compliance is insufficient education regarding medication regimen, treatment with multiple drugs, multiple dosing and apprehension about adverse effects of AED. Patients' education has been shown to be highly effective in improving compliance and thereby seizure control.[10]

Some patients may not achieve seizure control until their serum drug levels are higher than the conventional therapeutic range. It may be advisable to increase the dose of the AED up to maximum tolerated doses in such patients, rather than adhering to serum AED levels.

Patients who do not improve with appropriate monotherapy should be switched on to an alternate AED. A second drug is added slowly and, after reaching the optimal dosage, the first drug is gradually withdrawn. Reducing the dose of the first drug while titrating the second AED may result in an increase in seizures making the physician and the patient to prematurely conclude that the second drug is ineffective.

In patients who have failed two or more monotherapy trials, adding a second AED (duotherapy) may improve seizure control in 20–25% of patients, but is likely to result in complete seizure freedom in only 5–10% of patients.[17] If seizures are completely controlled with duotherapy, consideration should be given to withdrawing the first AED in order to minimise the adverse effects and cost of therapy. For example, over 40% of patients whose seizures were completely controlled when lamotrigine was added to valproate, phenytoin or carbamazepine, remained seizure-free when treated with lamotrigine alone.[3] In a study from South India involving 972 patients with epilepsy, with change over from polytherapy to monotherapy, frequency of side-effects decreased from 29% to 20%, seizure control increased from 29% to 45% and resulted in net saving of Rs. 750 per patient per year.[22]

CONTROLLED ON POLYTHERAPY

The advent of several new AEDs has widened the scope of AED treatment. Given the lower side effect profile of the newer AEDs, there may be a role of polytherapy in certain clinical instances, particularly when a patient develops refractory epilepsy. The term 'rational polytherapy' refers to combining AEDs with different, presumably synergistic mechanisms of action.[8] Several combinations of AEDs appear to fit the model of rational polytherapy. An example would be combining a sodium channel-blocking agent (such as phenytoin, carbamazepine or topiramate) with a GABA enhancing agent (benzodiazepines, valproate or tiagabine). For the treatment of partial epilepsies, the addition of newer AEDs to standard drugs has led to a significant decrease in seizure frequency. Use of ethosuximide and valproate or valproate and lamotrigine in patients with refractory absences or idiopathic generalised tonic-clonic seizures, respectively, are well-accepted forms of rational polytherapy.[1] However, many irrational AED combinations are used as is frequently observed during clinical practice.

Patients, whose seizures are controlled on polytherapy, should be re-evaluated periodically to determine the need for multiple AEDs. Although polytherapy may be responsible for the seizure control, it is also possible that one of the AEDs alone might be effective. Withdrawing AEDs in patients on polytherapy can result in complex drug interactions. For example, discontinuing enzyme-inducing AEDs, such as phenytoin or phenobarbitone, may increase the plasma levels of other AEDs. Conversely, stopping valproate in a patient on therapy with valproate and lamotrigine could result in sub-optimal lamotrigine levels. An increase in seizures in such a situation could be managed by increasing the dose of lamotrigine rather than by re-introducing valproate.

POORLY CONTROLLED ON POLYTHERAPY

Patients whose seizures are not controlled on multiple AEDs should have their diagnosis and treatment critically evaluated in a comprehensive epilepsy care centre. A proportion of patients with medically refractory epilepsy can be cured by surgical treatment and others might benefit from vagus nerve stimulation or ketogenic diet.[23] Surgical treatment of epilepsy should not be considered as the last resort after all combinations of AEDs have been tried. With 10 commonly used AEDs (phenobarbitone, primidone, phenytoin, carbamazepine, valproate, clonazepam, clobazam, gabapentin, lamotrigine and topiramate), there are 45 two-drug and 36 three-drug combinations to which a patient with chronic epilepsy may be exposed to; the trials with all of them will require the whole life-time of the patient to complete. In

general, patients who continue to exhibit one or more disabling seizures per month for a period of two or more years, despite supervised medical trials (6 months each), twice with monotherapy and once with polytherapy, are candidates for presurgical evaluation in a comprehensive epilepsy program.[23]

SPECIAL CLINICAL SITUATIONS

A significant change in the patient's general medical condition should prompt a re-evaluation of the AED treatment. Carbamazepine is a well-documented pro-arrhythmic drug and should be avoided in patients with cardiac disease.[12] Valproate is generally contraindicated in the setting of hepatic failure because of direct hepatotoxicity and risks of fulminant hepatic failure.[4] An increased incidence of valproate-induced pancreatitis has been described in patients with renal failure.[21] Carbamazepine and oxcarbazepine have the least potential for toxicity in renal failure. Gabapentin is the drug of choice for seizure control in patients with porphyria.[27] Patients who are contemplating pregnancy should have their AED treatment reviewed and simplified, if possible. The risk of foetal malformations increases with high dose of valproate and with polytherapy.[18]

The pharmacokinetics of many AEDs change in old age. Also the associated co-morbid conditions will affect AED clearance, leading to potential toxicities and interactions between AEDs and non-AEDs.[31] There is no drug of choice for the treatment of epilepsy in the elderly. AED therapy has to be tailored to the individual patient, weighing potential adverse effects against the benefits. Monotherapy in a low dosage is to be initiated and titration should be graded until the desired benefit is attained. The patient should be seen on a regular basis to screen for potential adverse effects.

LONG-ACTING ANTIEPILEPTIC DRUG FORMULATIONS

Successful treatment of epilepsy requires good patient compliance. It has been reported that adherence to AED treatment falls as the number of daily doses of the drug increases.[5] Maximum compliance is achieved with once-daily dosing regimens.[5] A number of extended release formulations of AEDs have been developed with the goal of providing patients with effective and well-tolerated seizure control through less frequent daily doses. The major advantages of extended release AED preparations are: (a) more stable serum levels with fewer fluctuations, thereby minimising the chance of peak dose related side effects and breakthrough seizures related to low serum AED levels and (b) improved compliance resulting in better seizure control. Several long-acting formulations of carbamazepine and valproate, which can be administered in once or twice daily doses, are currently available. To achieve equivalent serum level, 20–30% increase in the dosage will be required, while converting from conventional to extended release formulations.[6] The bio-availability of most of the locally available long-acting carbamazepine and valproate preparations are unknown.

ROLE OF SERUM ANTIEPILEPTIC DRUG LEVEL MONITORING

Since the goal of pharmacotherapy of epilepsy is to make the patient seizure-free without side effects, measuring the serum level of AEDs has a sound basis in clinical practice. If utilised selectively to address patient and drug-specific issues, serum AED monitoring helps to maximise seizure control and minimise side effects (Table 6).[9] However, plasma AED concentrations are often measured unnecessarily and interpreted incorrectly.

Because of its long half-life, saturation kinetics of its metabolism and narrow therapeutic index, phenytoin makes the soundest case for therapeutic drug level monitoring. The serum level monitoring is less dependable for carbamazepine, since its serum level shows considerable variation between patients and is markedly influenced by the presence of other enzyme-inducing AEDs. Sodium valproate has a wide therapeutic range of serum levels and has very little clinical application. The therapeutic serum levels of new AEDs have not been defined.

Timing of blood sampling for AED assay is influenced by the time taken to achieve a steady blood level, phenomenon of autoinduction and half-life of individual AEDs.[20] A reliable steady blood level of phenytoin can be obtained only after 3 weeks of its constant dose. Carbamazepine markedly induces its own metabolism (autoinduction), which is usually completed within 20–30 days of its initiation. Therefore, for both phenytoin and carbamazepine, serum AED assay should wait for at least one month of being on a constant dosage of these drugs. Once the steady state is achieved, due to the long half-life, for phenytoin, a morning sample will give the steady state serum level. With carbamazepine and sodium valproate, blood samples taken 6 hours and 4 hours after drug intake, respectively, is recommended.[20] If AED assay is being undertaken to verify a toxic side

Table 6: Indications for serum AED level monitoring

Poor response despite adequate dose: to identify unusual pharmacokinetic patterns or poor compliance
Physiological or pathological conditions known to be associated with altered pharmocokinetics (hepatic disease, renal disease, pregnancy, elderly)
Establishing drug toxicity
Minimising the problems caused by non-linear kinetics with phenytoin
Detect and minimise the problems caused by drug interactions
Detect altered bioavailability caused by changes in drug formulations

effect, blood drawn at the time of maximum symptoms will be the most relevant. Failure to educate the patient about the timing of the blood sample is a common mistake made in clinical practice.

A PRACTICAL GUIDE FOR ANTIEPILEPTIC DRUG WITHDRAWAL

Nearly two-thirds of patients with epilepsy will become seizure-free on AEDs within a few years of diagnosis and more than 60% of seizure-free patients on AED will remain seizure-free when the medication is withdrawn.[17,24] In a recent meta-analysis of over 5,000 patients, 29% had a recurrence of seizures within 2 years after initiating AED withdrawal.[2] In most patients, the relapse occurred within the first 6 months after withdrawal. A few readily available patients' attributes help in the clinical decision making for or against AED withdrawal (Table 7). Those with the lowest rate of relapse rate have no seizures for over 2 years after start of AED, a normal IQ, neurological examination and EEG and do not have JME.

The decision to withdraw or continue the AED centres on the risk or relapse and the consequence of seizure recurrence. The social consequences of relapse are smaller in children and women, as driving privileges and employment are not a concern, while adverse influence of AEDs on cognitive performance and pregnancy, respectively, are concerns. The physician's duty is to provide full information about risk of relapse and the consequences to the patient and care givers and leave the final decision to them.

Although no data is available on the optimal rate of AED withdrawal, a slow withdrawal extending not less than 2 months is recommended. A recent randomised trial, which compared a 6-week versus a 9-month withdrawal in 1333 seizure-free children showed a similar relapse rate.[28] In patients taking more than one AED, withdrawal will have to be done of one drug after the other. Sedative medications, such as phenobarbitone, primidone, clobazam and clonazepam are usually withdrawn more slowly.

CONCLUSION

The pharmacotherapy of epilepsy is more complicated now than the years past, due to better availability of already existing standard AEDs and the introduction of new AEDs. A majority of patients with recent onset epilepsy can be successfully treated with one of the standard AEDs (monotherapy). Although several factors influence AED selection, in a developing country, the cost and the seizure type are the principal ones. Long-acting AED formulations, through less frequent daily doses, improve compliance and thereby seizure control. In patients who have failed to benefit from appropriate monotherapy trials, adding a second drug results in seizure control only in a minority of patients. Patients whose seizures are not controlled on polytherapy should be re-evaluated periodically to determine the need for multiple AEDs. Patients whose seizures are not controlled on multiple AEDs should have their diagnosis and treatment critically evaluated in a comprehensive epilepsy care centre. Surgical treatment should not be considered as a last resort after all combinations of AEDs have been tried; a diagnosis of medically refractory epilepsy can be made within 2 years of supervised AED treatment. In patients who are seizure-free for 2 years or more, AED withdrawal should be considered. Those with lowest rate of relapse following AED withdrawal rate have normal IQ, neurological examination and EEG, and do not have juvenile myoclonic epilepsy. If utilised selectively to address patient and drug-specific issues, serum AED monitoring helps to maximise seizure control and minimise side effects.

Table 7: Profile of patients with high likelihood of remaining seizure-free following AED withdrawal

Normal neurological examination and normal IQ
Normal EEG prior to AED withdrawal
Epilepsy with a single seizure type
Seizure-free for > 2 years prior to AED withdrawal
No juvenile myoclonic epilepsy

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201 Surgery for Epilepsy: General Principles

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INTRODUCTION

Definitions

An epileptic seizure is a transient occurrence of signs and/or symptoms, due to an abnormal and excessive or synchronous neuronal activity in the brain. Epilepsy is a chronic condition of the brain characterised by an enduring propensity to generate recurrent unprovoked seizures and by the neurobiological, cognitive, psychological and social consequences of this condition. Epileptogenesis is the sequence of events that turns a normal neuronal network into a hyperexcitable network.[59] Epilepsy surgery is the resection or functional manipulation of part of the brain with the aim of alleviating seizures, improving the cognitive function and the quality of life.[22]

Magnitude of the Problem

Epilepsy constitutes a major public health problem in both developing and developed countries.[83,89] At any time and in any place, at least 5 out of 1,000 population have active epilepsy and to this burden, new patients will be added every year at a rate of about 5 per 10,000.[99] A majority of these people with newly diagnosed epilepsy will eventually achieve remission. However, 20–30% of patients continue to exhibit chronic recurrent seizures, despite optimal treatment with antiepileptic drugs.[82] Among these medically refractory patients, there are identifiable subgroups with surgically remediable lesional syndromes.[9] The seizures in patients with these lesional syndromes are resistant to treatment with antiepileptic drugs but have a high rate of cure following surgery.[20,88] A number of centres have reported that epilepsy surgery is not only possible in countries with limited resources, but can also be undertaken in a cost-effective way.[109] In this chapter, we elaborate on the pathological substrate, principles of pre-surgical evaluation, selection of ideal candidates, surgical treatment and post-operative outcome of patients with medically refractory epilepsy.

HISTORICAL PERSPECTIVE

The history of modern epilepsy surgery began in the late 1880s. Victor Horsley performed the first surgery for epilepsy by excising the visible frontal cortical scars in 1886.[29] Based upon autopsy studies, Hughlings Jackson reported in 1888 that a chronic seizure disorder could be the initial and only symptom of a foreign-tissue lesion such as a tumour, vascular malformation or cicatrix in the brain.[32] However, between 1900 and 1930, a number of operations were carried out in vain to control epilepsy (Table 1). Following Hans Berger's invention of the human electroencephalograph (EEG) in 1929, EEG was adopted to identify and better localise epileptiform abnormalities, particularly in the temporal lobe.[58] Wilder Penfield and his colleagues made pioneering contributions in promoting surgery for epilepsy at the Montreal Neurological Institute, Canada.

Epilepsy surgery had an early beginning in India. A sizeable number of patients with refractory epilepsy were operated upon at the Christian Medical College, Vellore, Tamil Nadu, India[1,15,18,45] and at the Institute of Neurology, Chennai, Tamil Nadu, India[66,67] in the 1950s, 1960s and the first half of the 1970s. In the mid seventies, like elsewhere in the world, epilepsy surgery took a dramatic downwards trend in India as well. There was resurgence of interest in the early 1990s. This was due to better understanding of the surgically remediable lesional epilepsy syndromes, the advent of computerised EEG and video-EEG telemetry, magnetic resonance (MR) imaging of the brain as well as application of microneurosurgical techniques for

Table 1: Epilepsy surgery procedures carried out in the period from 1900–1930

• Trepanation
• Trephination
• Carotid artery occlusion
• Bilateral vertebral artery occlusion
• Cervical sympathectomy
• Castration
• Circumcision
• Hysterectomy/Oopherectomy
• Adrenalectomy
• Dural splitting
• Colectomy and other bowel resections
• Arterialisation of internal jugular vein

Source: www.ilae-epilepsy.org

epilepsy surgery. Incorporating these recent technological advances, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum, Kerala, India.[61,65] All India Institute of Medical Sciences, New Delhi[8,14] and a number of other institutions in India have successfully developed epilepsy surgery programs.

PHYSIOLOGY

The brain consists of neurons and neuroglia. Neurons are inherently excitable cells and are continuously electrically active. Seizures are a result of an excessive synchronised discharge of abnormal neurons. Seizures start when a small group of abnormal neurons undergo prolonged depolarisation associated with the rapid firing of repeated and synchronised action potentials. These abnormally discharging epileptic neurons recruit adjacent neurons or neurons with which they are connected into the process. Seizures may then spread to involve adjacent areas of the brain or through established anatomic pathways to other distant areas.

Cellular Mechanisms

The intracellular phenomenon that represents abnormal neuronal excitation is the "paroxysmal depolarisation shift (PDS)" in the intraneuronal electrical recording. This is a sustained depolarisation of the neuron that results in a series of action potentials within the neuron and in turn generates a series of "excitatory post-synaptic potentials" at the apical dendrite. The PDS is followed by sustained hyperpolarisation of the cell when it is relatively inexcitable. The excitatory electrical activity spreads via synaptic mechanisms in neuronal networks, to activate more and more cortical neurons and thereby generate interictal epileptiform discharges. That such abnormal discharges do not occur in the normal brain is because of highly efficient and ubiquitous inhibitory systems. An unstable relationship between excitatory and inhibitory mechanisms in the brain results in the generation and propagation of seizures. In addition to the inhibitory and excitatory synaptic mechanisms that involve gamma-aminobutyric acid (GABA) and glutamate, respectively, other non-synaptic neuronal interactions also contribute to the spread of electrical activity in neuronal networks. These include gap junctions, fluctuating extracellular ionic concentrations, especially potassium and field effects. Recently, evidence has been accumulating to establish the role played by astrocytes in this process.

Seizure Generation

Although several hypotheses have been proposed, the simplest of these is the concept of a discrete seizure focus with spreading epileptic activity and is probably best applied in lesional partial epilepsies. This hypothesis is fundamental to the feasibility of surgery as a therapeutic option for epilepsy. The second theory of distributed networks proposes the presence of multiple, spatially distinct neuronal groups that act as seizure generators that may be phase-linked through a neuronal network. The latter hypothesis explains the mechanism of primary generalised seizures to involve both cortical and sub-cortical generators. Networks represent functionally and anatomically "connected" cortical and sub-cortical brain structures and regions bilaterally. Activity in one part of the network affects activity in others, i.e. vulnerability to seizure in one part of the network is influenced by activity elsewhere in the network. The network as a whole produces clinical and electrical phenomena associated with seizures. This model could also predict the success of epilepsy surgery by hypothesising that successful epilepsy surgery requires removal of all epileptic generators.

Current theories try to explain the mechanism(s) for the abnormally increased propensity of the brain to develop excessive discharges of cerebral neurons. The early theory, according to which disruption of the normal balance between excitation and inhibition in the brain results in seizure generation, may have been an oversimplification. Cortical networks that generate oscillations, on which inhibitory neurons, neuronal communication (e.g. synaptic transmission) and intrinsic neuronal properties (e.g. ability of a neuron to maintain burst firing) are dependent, are thought to be crucial elements of seizure generation. The occurrence of epileptic activity may be an emergent property of such oscillatory networks. Transition from normal behaviour to a seizure behaviour may be caused by a number of factors, including greater spread and neuronal recruitment secondary to a combination of enhanced connectivity, enhanced excitatory transmission, a failure of inhibitory mechanisms and changes in intrinsic neuronal properties.

Seizure Classification

Epileptic seizures are broadly classified according to their site of origin and pattern of spread. In 1981, the International League Against Epilepsy (ILAE) developed an international classification of epileptic seizures that divides seizures into two major classes: (1) Partial-onset seizures and (2) Generalised-onset seizures. Partial-onset seizures begin in a focal area of the cerebral cortex, whereas generalised-onset seizures have an onset recorded simultaneously in both cerebral hemispheres. Some seizures are difficult to fit into a single class and they are considered unclassified seizures. Focal or partial seizures arise from a localised region of the cortex and have clinical manifestations that reflect the area of brain involved. Focal discharges can remain localised or they can spread to nearby cortical areas, to sub-cortical structures and/or transmit through commissural pathways, to involve the whole cortex. The latter sequence describes the secondary generalisation of focal seizures. As an example, a seizure arising from the left motor cortex may cause jerking movements of the right upper extremity.

If epileptiform discharges spread to adjacent areas and then the entire brain, a secondary generalised tonic-clonic seizure ensues. Primary generalised seizures begin with abnormal electrical discharges in both hemispheres, simultaneously. Generalised seizures involve reciprocal connections between the thalamus and the neocortex. The manifestations of such widespread epileptiform activity can range from brief impairment of consciousness (e.g. absence seizure) to generalised motor activity accompanied by loss of consciousness (e.g. generalised tonic-clonic seizure).

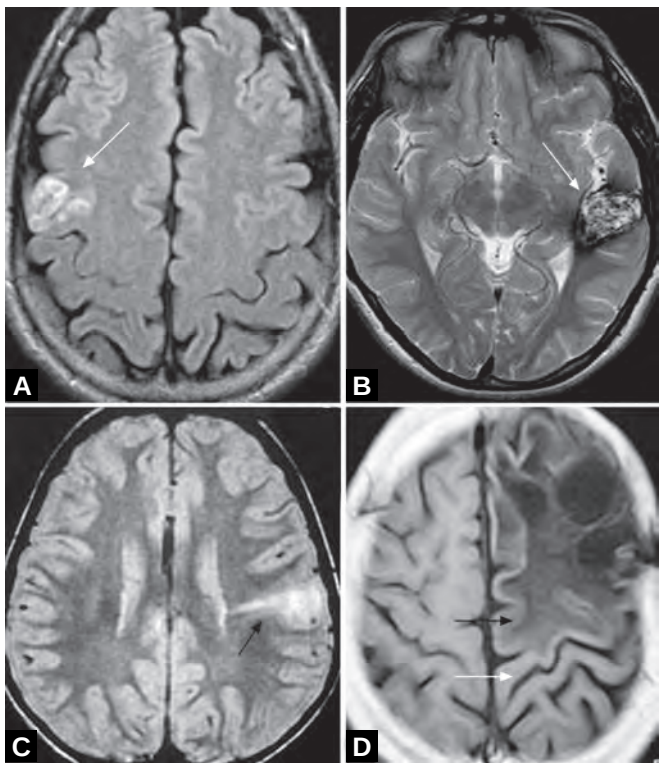
PATHOLOGY

Mesial Temporal Lobe Epilepsy

(Refer to chapter 203 on "Surgical Treatment of Temporal Lobe Epilepsy")

Neocortical Epilepsy

Whereas most temporal lobe epilepsy (TLE) is characterised by hippocampal pathology, neocortical epilepsy lacks a common pathological substrate.[7,62] A wide range of structural anomalies have been associated with chronic partial neocortical epilepsy (Figs 1A to D). These anomalies can be classified into five categories: (1) Malformative; (2) tumoural; (3) ischaemic; (4) traumatic and (5) infectious.



Figs 1A to D: Spectrum of neocortical lesions in people with epilepsy: (A) DNET involving the face motor cortex. (B) Cavernoma involving the posterior temporal neocortex. (C) Focal cortical dysplasia adjacent to the central sulcus. (D) Frontal gliosis in an operated case of tuberculoma

In a small number of patients, the non-specific substrate of gliosis is found. Most of these lesions are not believed to be epileptogenic per se; rather, the epileptogenicity is due to excitability of the surrounding cortex. Numerous mechanisms have been implicated in the epileptogenicity.[76] These include neurochemical changes, pressure effect, ischaemia and intrinsic epileptogenicity in the congenital malformative diseases.[55]

Developmental Lesions

Developmental lesions associated with chronic seizures are mainly malformations of cortical development. These abnormalities are often diffuse and, therefore, less amenable to surgery.[74] Such widespread abnormalities include pachygyria, lissencephaly, band heterotopia and subependymal heterotopia. Focal abnormalities include focal cortical dysplasia, polymicrogyria, schizencephaly, focal subcortical heterotopia and tuberous sclerosis. When a focal ictal onset zone is identified and completely resected, an excellent outcome can be achieved otherwise the overall surgical outcome in this group is sub-optimal.[54,56,102] In gelastic epilepsy and hypothalamic hamartoma, seizure remission has been achieved by hamartoma resection,[77] suggesting possible seizure origin in the hypothalamic lesion. Surgical treatment has recently been advocated for patients with intractable infantile spasms. Patients who fail treatment with antiepileptic drugs and corticosteroids and who demonstrate predominantly unilateral abnormalities on EEG, PET and MRI may be suitable for lobar or multilobar cortical resection.[16]

Developmental Tumours

The natural history of the lesions associated with intractable seizures is variable.[93] The main concern with tumours in this patient population is the possibility of tumour progression or transformation.[37] As a general rule, the glial tumours associated with intractable seizures have a rather indolent course[10,25] Given their developmental nature, gangliogliomas and dysembryoplastic neuroepitheliomas are frequently associated with cortical dysplasia.[19] This could explain the persistent seizures following some lesionectomies. In dealing with this pathology, wide resection of the gyrus involved is recommended, rather than a pure lesionectomy. If seizures persist, an invasive electrode study is indicated.

Vascular Malformations

Vascular malformations, like cavernous angiomas and arteriovenous malformations (AVMs), are increasingly being detected in patients with localisation-related epilepsy.[35]

Although the pathophysiological mechanism appears to be very focal in cavernous angiomas, several series have recorded suboptimal seizure outcome following lesionectomies. This could be due to incomplete

resection of the haemosiderin-impregnated area or the existence of dual pathology, specifically when located in the mesial temporal lobe. Arteriovenous malformations are characterised by a steal phenomenon resulting in ischaemic damage and haemorrhage in the surrounding cortex. The surgical management of AVMs with respect to seizure outcome is also controversial. Good seizure outcome has been reported following resection of AVMs and additional epileptogenic cortex identified by interictal electrocorticography.[115] On the other hand, good seizure outcome has been reported following radiosurgery for AVMs.[27] Sixty per cent of patients presenting with seizures became seizure free, following stereotactic proton beam radiation. This suggests that the epileptogenic zone is in the immediate vicinity of the vascular malformation rather than at a distance from it.

Brain Trauma

Penetrating injuries to the brain are frequently complicated by seizures.[12,101] Focal and diffuse pathological changes are noted.[108] The focal damage results in the classically described meningocerebral scar. Seizure outcome following cortical resection is excellent if the pathological changes are focal and correlate well with the semiology and electrophysiology of the seizures. A variety of pathological changes have been noted following blunt or non-penetrating injury to the brain.[34] These are axonal damage, intracerebral haematomas, ischaemic parenchymal changes and contusions, frequently involving the orbitofrontal cortex and the basal and anterior temporal lobes. The incidence of seizures following blunt injury is variable.[33] Due to the diffuse nature of closed head injury, localisation of the epileptogenic cortex is frequently difficult. Patients are considered for surgery when there is a good correlation between the electroclinical syndrome and pathological changes on MR. Wide cortical resections are recommended to ensure a good surgical outcome.

SURGICALLY REMEDIABLE LESIONAL EPILEPSY SYNDROMES

Surgically remediable syndromes (Table 2) are epileptic disorders for which: (a) the pathophysiology is understood; (b) the natural history is reasonably well known to be medically refractory or even progressive, once the major first-line antiepileptic drugs fail; (c) pre-surgical evaluation can be accomplished and (d) surgery offers an excellent chance that disabling seizures will completely be eliminated or markedly reduced.[9] The presence of a lesion in a patient with refractory partial epilepsy does not invariably indicate that the lesion is responsible for the seizures. There is a consensus at present that a comprehensive epilepsy pre-surgical evaluation should be performed in patients with a lesional epilepsy syndrome associated with pharmacoresistant seizures, to establish a relationship between the MRI-identified lesion and the site of the epileptic brain tissue.[21]

PRE-SURGICAL EVALUATION

The principle of epilepsy surgery is to identify and resect or disconnect a single identifiable epileptogenic focus without risk of neurological deficit. The rate of success of epilepsy surgery depends upon the accurate localisation of the epileptogenic zone, which is defined as the area necessary and sufficient for initiating seizures and whose removal or disconnection is necessary for abolition of seizures.[40] Since the epileptogenic zone cannot always be reliably defined pre-operatively, selection of ideal candidates for epilepsy surgery requires a multimodal evaluative approach, by careful correlation between clinical, electroencephalographical, radiological and neuropsychological data.[21] This constitutes the pre-surgical evaluation. Concordance of multimodality data for a single epileptogenic focus which can safely be removed is crucial for good surgical outcomes. The relationship between a lesion and the area generating epileptic seizures is also a concern when the lesion is poorly circumscribed and more diffuse, as in focal encephalomalacia or neuronal migration disorders.

Objectives of Pre-surgical Evaluation

It aims to accomplish the following: (a) establish the epileptic nature of the paroxysmal events; (b) identify a discrete structural abnormality, either directly with neuroimaging techniques or inferentially because of an associated functional deficit; (c) provide evidence of localised abnormal neuronal excitability of that actual or presumed structural lesion and (d) establish lack of vital function (e.g. speech and movement) in the suspect region.

Candidates for Pre-surgical Evaluation

Natural history studies have shown that most of the patients with epilepsy, who are destined to achieve satisfactory seizure control with antiepileptic drugs, will do so within two years of the onset of epilepsy.[36,82] Continuing frequent seizures during childhood and

Table 2: Surgically remediable lesional epilepsy syndromes

• Mesial temporal lobe epilepsy:
(Temporal lobe epilepsy associated with hippocampal atrophy/sclerosis)
• Benign neoplasms:
Ganglioglioma
Dysembryoplastic neuroepithelial tumour
Low-grade astrocytoma
Oligodendroglioma
• Disorders of cortical development:
Glioneuronal hamartoma
Focal cortical dysplasias
• Other focal lesions:
Vascular malformations
Atrophic scars
Rasmussen's encephalitis

early adult life can produce devastating psychosocial, educational and occupational consequences. Recurrent seizures are known to result in pathological changes locally, which enhance the tendency for refractoriness. In addition, these may produce a secondary epileptogenic focus, for example, the "mirror focus" on the opposite side. More emphasis is therefore now being placed on early referral for epilepsy surgery. As a general rule, patients with refractory epilepsy continuing to exhibit one or more disabling seizures per month for a period of two years or more, despite supervised therapeutic trials (six months each) twice with a single antiepileptic drug and once with a combination of two antiepileptic drugs, are candidates for detailed evaluation in a comprehensive epilepsy care program[62] (Table 3). Many epilepsy syndromes are well characterised and have defined prognoses, simplifying the selection process; thus, idiopathic partial and generalised epilepsies are not amenable for surgery, whereas surgery might be considered the treatment of choice for some specific surgically remediable syndromes discussed above.

Absolute contraindications to epilepsy surgery include primary generalised seizures, underlying degenerative or metabolic disorders or supervening medical illness and psychogenic seizures. Psychogenic non-epileptic seizures are frequently seen at epilepsy centres, where they represent approximately 20% of patients referred for medically refractory seizures. Relative contraindications to surgery include medication noncompliance, interictal psychosis, mental retardation and severely dysfunctional family dynamics. Establishment of refractoriness of epilepsy in an individual patient requires a complete clinical re-evaluation with a detailed medical history. All efforts should be made to establish that seizures are truly epileptic and determine the electroclinical syndrome. Unresponsiveness to antiepileptic drugs should not be due to inappropriate AED choice or wrong AED combinations, poor drug compliance, social or psychological factors.

Table 3: Indications for pre-surgical evaluation

- Persistent seizures despite appropriate pharmacological treatment (usually at least two drugs as monotherapy and one combination as polytherapy appropriate to seizure type, at adequate doses, with adequate compliance)
- Impairment of quality of life due to ongoing seizures
- Memory deficit, attention deficit, injuries, accidents due to ongoing seizures
- Severe adverse reactions of antiepileptic medications

Contraindications for epilepsy surgery

- Minor seizures that do not impair quality of life
- Primary generalised epilepsies
- Non-epileptic seizures
- Progressive medical or neurological disorder
- Active interictal psychosis or behavioural problems

Pre-surgical Evaluation

The standard pre-surgical evaluation includes non-invasive tests consisting of high resolution brain MR imaging, scalp video-EEG telemetry and neuropsychological assessment. Concordance of data obtained from these tests may be adequate to perform surgery with good results, as in the classical mesial temporal epilepsy syndrome. For patients with epileptogenic lesions located at or near the primary motor, sensory, or language cortex, several non-invasive tools of functional mapping have been developed. These include magnetoencephalography (MEG), positron emission tomography (PET), and, more recently, functional MRI.[17]

NEUROIMAGING

MRI has revolutionised the evaluation of medically intractable epileptic patients who are being considered for surgery. Now the pathologic substrates can be identified pre-operatively, which has led to a renewed interest in the surgery for neocortical epilepsy. MRI can detect almost 100% of structural lesions that are associated with epilepsy (Figs 1A to D) and can almost always detect the mesial temporal sclerosis associated with mesial TLE. The advent of high resolution MR imaging and multiplanar analysis have significantly improved the ability to visualise malformations of cortical development in patients with epilepsy.[5] Abnormalities of the gyral and sulcal pattern have been studied with various techniques, including curvilinear reformatting and volumetric analysis in patients with focal cortical dysplasia.[91] Ictal SPECT is particularly useful in non-lesional extratemporal epilepsies, often revealing discrete neocortical regions of activation, not appreciated by video-EEG monitoring or MRI.[38,92] Interictal metabolic PET imaging has been extensively utilised in pre-surgical evaluation of refractory seizures to correlate with ictal electrophysiologic and structural magnetic resonance findings.[16] Regardless of the presence of structural abnormalities, functional imaging by PET or SPECT provides complementary information. Ideally, these techniques should be used and interpreted together to improve the localisation and understanding of the epileptic brain.[95]

Non-invasive Electroencephalography

The purpose of video, EEG telemetry is to record habitual seizures, identify the seizure type and syndrome and obtain information about the electrical localisation of the seizure onset. It is also useful to rule out the rare possibility of non-epileptic events. While video-telemetry is a very useful addition to the diagnostic armamentarium for pre-surgical evaluation, a large majority of patients can still be satisfactorily evaluated for surgery without[103] this facility. Hence, this should not be considered

an absolute requirement, although no doubt a desirable one for difficult cases. The duration of recording is individualised and varies from 24 hours to 7 days, based on the number of seizures to be captured and the baseline seizure frequency in the patient. Uncomplicated cases with a single seizure type may require only one seizure to be recorded, patients with multiple seizure types or multiple interictal foci may require prolonged recording to capture all types of seizures. The semiology of the clinical seizures provides evidence for the symptomatogenic zone, while the localisation of the scalp ictal-EEG represents the ictal onset zone. In the classical lesional mesial temporal epilepsy syndromes, the ictal scalp-EEG patterns are usually typical and adequate for surgical decision making. Not uncommonly however, ictal scalp EEG may show widespread changes even in focal lesions and especially in extratemporal epilepsy. Sphenoid electrodes may help to localise the spiking and ictal onset zones in mesial TLE.[44] The interictal EEG represents the irritative zone and provides equally valuable and often localising information about the epileptogenic zone during scalp video telemetry.

Neuropsychological Assessment

Neuropsychological assessment is included as a part of the standard pre-surgical evaluation. Neuropsychological assessment is the best single means of quantifying the cognitive abilities and psychosocial status of a person.[28] The pattern of cognitive strengths and weaknesses provide evidence for the area of cerebral dysfunction, also referred to as the functional deficit zone, which may overlap with the epileptogenic zone. In addition, the neuropsychological evaluation also plays a unique role in assessing the potential risk to cognitive function after surgery. In the context of temporal lobe surgery, this involves quantification of verbal and visual memory scores prior to surgery. Frontal lobe epilepsy patients perform worse on measures of speed/attention, motor sequencing and concept formation.

Intracarotid Amobarbital (Wada) Test

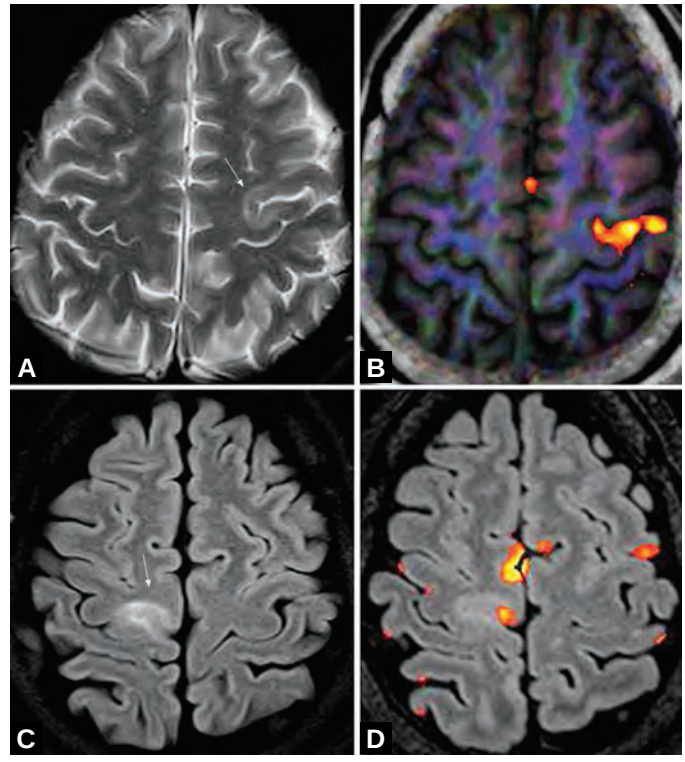
The intracarotid amobarbital (Wada) test is used to temporarily anaesthetise each hemisphere in turn by intracarotid injection of amobarbital or methohexital, in order to determine the language and memory abilities supported by the non-anaesthetised hemisphere.[107] While language assessment during the Wada test is simple and straight forward, interpretation of memory deficit is complex and requires a carefully designed protocol.[104] Recently, a non-invasive method, like the functional MRI, is gradually replacing the Wada test for the lateralisation of language and memory, due to ease of use and reproducibility.

Functional Magnetic Resonance Imaging

Functional magnetic resonance imaging (fMRI) is an exciting new technique that provides maps of human cortical function[17] (Figs 2A to D). Motor cortex and vision can adequately be displayed using this methodology.[31] The value of fMRI in language and memory localisation is being assessed, but requires excellent patient co-operation. Both functional MRI and magnetoencephalography (MEG) can now be used preoperatively to create functional brain maps that can be linked to several of the available frameless stereotaxy workstations.

Invasive Electroencephalography

Intracranial EEG is indicated in the setting of uncontrolled epilepsy considered for resective surgical treatment when: (a) there is likely to be a single region of seizure onset; (b) localisation of this region is insufficiently precise or impossible, based on the combination of non-invasive EEG and tests of focal functional deficit and structural abnormalities and (c) the available information from non-invasive evaluation in an individual patient allows a hypothesis about the suspected region of seizure onset to be further investigated.[40] To further define the ictal onset area, several classes of invasive electrodes have been introduced. These consist of electrodes of intermediate invasiveness, such as epidural pegs, electrodes introduced through the foramen ovale and more invasive electrodes, such as depth, subdural grid, and strip electrodes. Foramen ovale electrodes provide a definite advantage over both scalp EEG and sphenoidal electrodes. In patients with suspected TLE,



Figs 2A to D: (A and B) Focal cortical dysplasia involving the hand motor cortex with functional activation in the same area. (C and D) Leg motor cortex with functional activation in the same area, as well as in the supplementary motor cortex

foramen ovale electrodes like depth electrodes reliably pick up epileptiform activity generated in or involving the hippocampal formation. However, these have definite limitations also. Depth electrodes are inserted with stereotactic MR or CT guidance, such that the trajectory, termination point and location of each contact can be accurately predetermined. Cortical grids may be useful to stimulate and localise certain essential cortical regions, such as language and sensorimotor areas, when awake craniotomies are not possible such as in children.[46] Grids are particularly useful when both seizure onset zone and cortical function have to be mapped. With intracranial EEG, the decision to offer surgery rests primarily on the ictal EEG, a measure of the brain's excitability. If seizure onset is well localised, surgery is recommended. If it is poorly localised, or multifocal seizure onsets are detected, then resective surgery is not advised.[98]

Cortical Stimulation Mapping

In 1909, Victor Horsley reported on the function of the motor cortex based upon stimulation of the cortex in front of the central sulcus with a bipolar electrode. Fedor Krause reported[96] patients operated upon for focal epilepsy after performing brain mapping by electrical stimulation in 1912. Penfield and Jasper, in 1954, provided the most extensive maps of cortical localisation, based on a very large series of carefully recorded observations, following electrical stimulation of the cortex during surgery for epilepsy on conscious, co-operative patients.[58] When the lesion or the epileptogenic zone involves or is adjacent to eloquent cortex, functional mapping should be performed to delineate eloquent cortex and thereby permit a safe and complete resection. Mapping is usually performed when resection is contemplated in or near eloquent cortex that includes the central area (motor and sensory cortices), dominant inferior frontal cortex, dominant temporal lobe posterior to the precentral sulcus (language cortex) and the dominant parietal lobe and occipital lobe (visual and association cortex). Mapping may be done pre-operatively during invasive video-EEG telemetry and by other methods mentioned above. Stimulation mapping may also be done intra-operatively in selected cases with good patient co-operation. Direct cortical stimulation with bipolar electrode stimulators under propofol anaesthesia can be used to readily identify the motor cortex during surgery. Monopolar cortical stimulators are also used with EMG recording electrodes placed in advance in the major muscle groups. Intra-operative mapping of the language cortex is more elaborate and requires patient co-operation with awake craniotomy. Somatosensory evoked potentials (SSEPs) are utilised to demarcate the central sulcus, by the identification of phase reversals.[114] Standard anatomical landmarks will aid in the identification of the central sulcus, as well as eloquent cortex prior to neurophysiological mapping (Fig. 3).

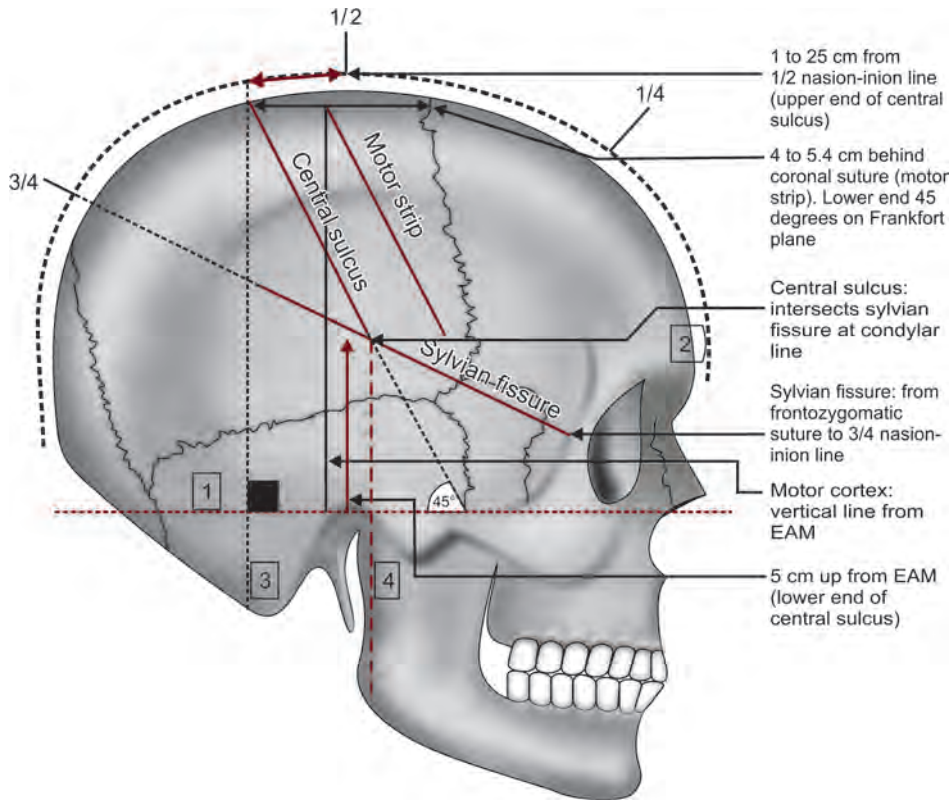


Fig. 3: Outline of the skull with anatomical landmarks to identify the central sulcus (*Reproduced with permission from Dr Sabbagh and the Pan Arab Journal of Neurosurgery*)

Awake Craniotomy

Wilder Penfield and his colleagues standardised the original technique of awake craniotomy at the Montreal Neurological Institute, Montreal, Canada. This technique has been facilitated with the introduction of propofol anaesthesia.[2] Patient co-operation and an anaesthesiologist familiar with the technique are essential. This technique provides continuous feedback, while the patient is maintained awake during resections adjacent to language, primary motor and sensory areas. An awake craniotomy is difficult to perform in children who, therefore, may require an implanted grid and extra-operative mapping of the eloquent areas.

Electrocorticography

Foerster and Altenburger introduced electrocorticography (ECoG) in 1934. It refers to intra-operative recording of EEG directly from the cortical surface. It has been used to identify the epileptogenic area and guide the extent of resection. The resection is extended to include all of the cortical areas showing active interictal spikes (so-called "spike chasing"). In addition, information regarding the presence of spikes in the rim of the resection or at a more distant location has been used for prognosticating seizure outcome after surgery.[87] It is mostly performed for extratemporal epilepsies. The major disadvantage of ECoG is its duration, limited to brief intra-operative periods and often complicated by anaesthetic effects.[42] Therefore, intra-operative ECoG is restricted to the definition of the irritative zone and thus, it has limitations for sufficiently delineating the epileptogenic zone or eloquent cortices. Residual spikes in the resection margins do not reliably predict residual epileptogenicity, nor does their absence guarantee post-operative seizure control. It is performed routinely at some centres, but the extent of resection was rarely dictated by ECoG, which depended on anatomical constraints and the feasibility of complete removal of a lesion.[3] Experience of routine ECoG is required to recognise anomalous findings. ECoG is useful particularly in intrinsically epileptogenic lesions like focal cortical dysplasia, as frequent continuous ictal-like electrographic activity can be identified in 65% of patients.[55]

Neuronavigation

One of the most significant advances in lesional epilepsy surgery has been neuronavigation.[46] Evidence suggests that seizure outcome correlates with the extent of lesion resection. In this regard, the ability of neuronavigation to optimise the surgical approach and confirm the extent of resection has been invaluable. It is particularly useful during the surgical planning and resection of hypothalamic hamartomas associated with gelastic seizures. Neuronavigation can be used to select the optimum side for the parasagittal craniotomy for corpus callosotomy, as well as to assess the completeness of callosotomy from rostrum to splenium.

SURGICAL PROCEDURES

Surgical procedures (Table 4) for epilepsy may be classified as resective procedures with an aim to stop seizures or palliative procedures that disconnect various regions of the brain to prevent seizure spread[47] (Fig. 4). While the former is employed if the pre-surgical evaluation identifies a single safely removable epileptogenic zone, the latter are employed when seizures are multiregional or overlap eloquent cortex.[60] Temporal lobe resections make up approximately two-thirds of all procedures currently performed at epilepsy surgery centres, reflecting the predominance of adult patients with intractable TLE. In paediatric epilepsy surgery centres, a greater proportion of patients undergo extratemporal, multilobar and hemispheric resections or disconnections.

Lesionectomy

Lesionectomy for epilepsy is a surgical procedure that is directed at the structural lesion, believed to be the aetiology of the seizure disorder. Complete resection of the lesion appears crucial for freedom from seizures in lesional epilepsy surgery.[19] The operative strategy may include: (1) lesionectomy, i.e. complete lesion excision, as determined by MRI, without attempting to resect the epileptogenic zone; (2) extended lesionectomy, i.e. resection of the lesion with “margins”; (3) resection of the lesion and the epileptogenic zone, as determined by ECoG; (4) resection of the epileptogenic zone alone. The most common resection strategy involves excision of the lesion with a “margin” around the lesion.[3,63] The extent of the resection may be determined by different criteria: (1) intra-operative visualisation of the tissue; (2) radiological margins determined by MRI signal abnormalities; (3) histologic margins based on intra-operative frozen section evaluation of the tissue and electrocorticographic margins based on intra-operative ECoG or a combination of these techniques. Incomplete resection can be due to poor differentiation of lesion from the normal brain. It is probable that systems that provide "image-guided surgical capabilities" or intra-operative imaging will help to solve this problem. The second cause of incomplete resection is the extension of the

Table 4: Surgical procedures to treat epilepsy

• Lesionectomy
• Corticectomy
• Lobectomy
• Multilobar resection
• Hemispheric resection and disconnection
• Multiple subpial transections
• Corpus callosotomy
• Radiosurgery
• Vagal nerve stimulation
• Deep brain stimulation

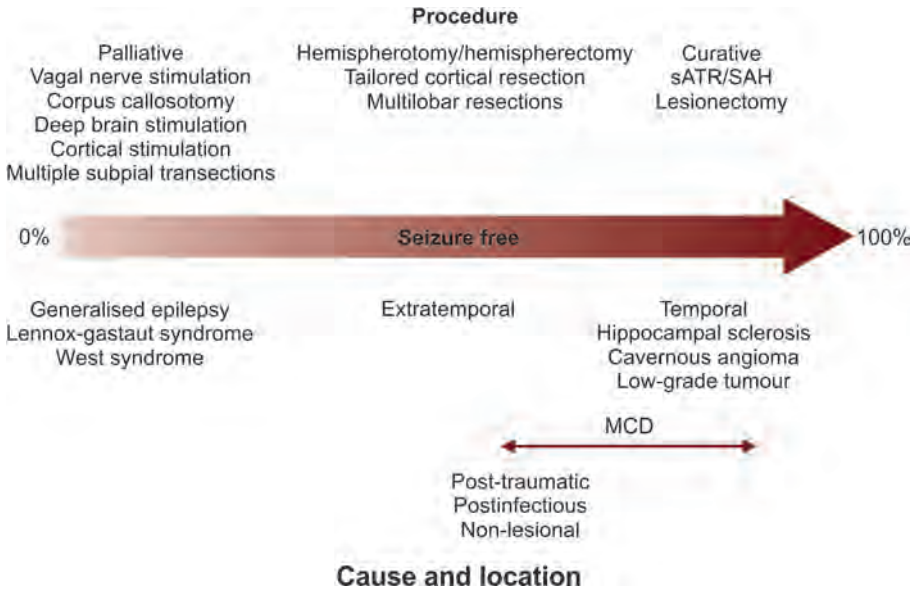


Fig. 4: Epilepsy surgery: indications, approaches and results (modified from McKhann et al.[47])

structural abnormalities to a functional area; multiple subpial transections have reportedly been successful in alleviating this problem.[48]

Lobar/Cortical Resections

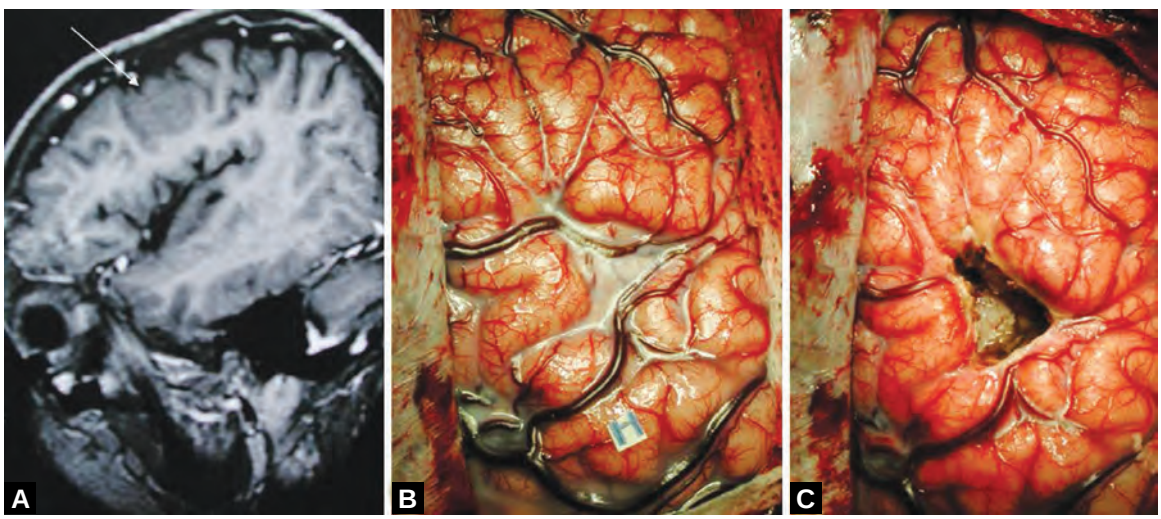
(Temporal Lobe Resections are discussed in detail in the Chapter 203)

Frontal Lobe Resections

In frontal lobe epilepsy the localisation of an ictal onset area is difficult and is facilitated when a lesion is present on imaging[69,71,72] (Figs 5A to C). When the epileptogenic zone is diffuse, a complete frontal lobectomy anterior to the precentral sulcus can be performed under general anaesthesia. The location of the central sulcus is determined using SSEPs or cortical stimulation.[52] In the dominant hemisphere, Broca's area should be identified and preserved. This is best performed under local anaesthesia or with the use of a subdural grid. Resection of the supplementary motor area leads to transient contralateral weakness and apraxia. On the non-dominant side, extensive resection of the orbitofrontal cortex can be performed. The intersection of the optic nerve and olfactory nerve is used as the posterior limit of the resection.

Central Resections

In central type epilepsy, resective surgery is performed, preferably under local anaesthesia with monitoring of motor function. A focal resection is performed if the ictal onset area is circumscribed and involves the primary face motor or sensory cortex or trunk or leg area.[39] Resection of the primary face area does not cause any significant deficit (Figs 6A to C). Resection of the hand area leads to severe disturbance in hand function. Resection of the



Figs 5A to C: (A) MR image showing focal cortical dysplasia in the premotor cortex (arrow). (B) Located with the identification of prominent overlying sulcus. (C) Resected with the aid of intraoperative monitoring and post-resection cavity

hand sensory cortex results in impaired position sense and stereognosis. Resection of the motor leg area leads to a footdrop; this usually improves and most patients can walk independently. The vascular supply of the primary motor area should not be disturbed and the geometry of the white matter tract is respected.[53]

Parietal and Occipital Resections

Seizures originating in the parietal and occipital lobes are rare.[70,110,111] Somatosensory aura, pain, vertiginous sensations, aphasia or disturbance of body image are suggestive of parietal origin of the seizures.[80] The ictal manifestations are varied and reflect the quick spread to the frontal lobe in superior parietal epilepsies and to the temporal lobe in inferior parietal cases. Interictal and ictal scalp EEG recordings are not reliable markers for parietal lobe epilepsy. In patients with occipital lobe epilepsy having hemianopsia, resective surgery carries little risk.[79] In the case of dominant hemisphere epilepsy, the speech-related cortex should be identified and spared. When a circumscribed lesion is found, lesionectomy can yield satisfactory results. In non-lesional cases, the ictal onset area should be precisely localised using invasive electrodes. These are used in addition to mapping of the calcarine cortex and speech-related cortex. With this strategy, visual deficits can be minimised.

Multilobar Resections

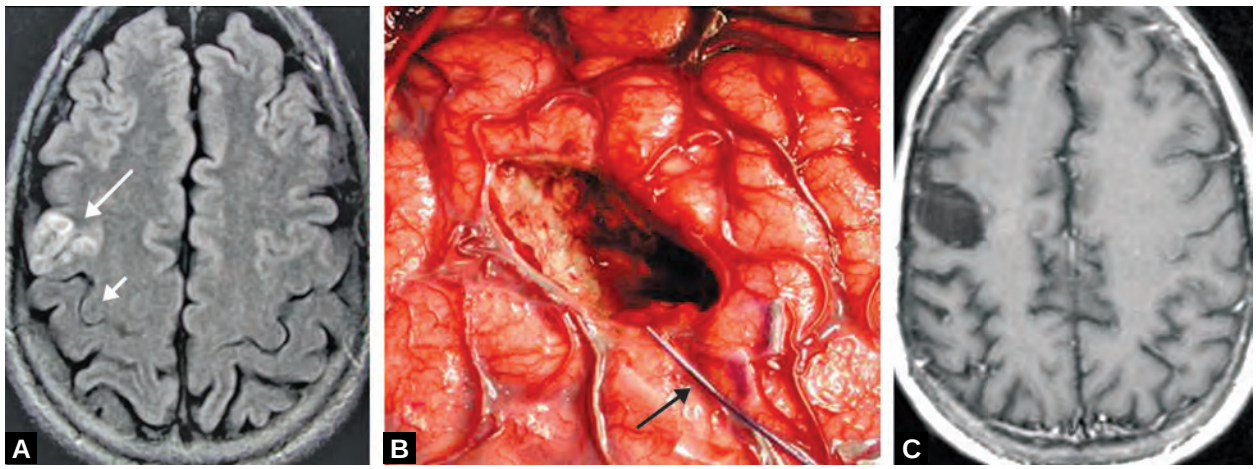
Multilobar resections are indicated for the control of pharmacologically refractory seizures, in the presence of widespread epileptogenicity involving more than one lobe in patients with preserved neurologic function. These patients have various types of lesions, including cerebral gliosis, atrophy (porencephaly), dysplasia (heterotopia, cortical dysplasia and hemimegalencephaly), Sturge-Weber syndrome or Rasmussen encephalitis. Patients with non-progressive disorders (e.g. atrophy, gliosis, dysplasia), with presence of fine-finger movements and foot-tapping are potential candidates for multilobar resections, as hemispherectomy is contraindicated in these patients.

Hemispherectomy

Hemispherectomy is generally indicated in patients with widespread unilateral EEG abnormalities, diffuse unilateral structural abnormality and clinical evidence of hemiparesis and hemianopia.[14] Three aspects of the aetiology may have an impact on the decision for and results of surgery: whether the condition is congenital or acquired, strictly unilateral or possibly bilateral, progressive or static. Congenital pathologies, such as large porencephaly resulting from in utero or perinatal insult or the Sturge-Weber syndrome, which are usually strictly unilateral, have a better prognosis with surgery than a congenital lesion, such as hemimegalencephaly, which may be associated with some degree of contralateral involvement.[112] Acquired unilateral pathology, such as Rasmussen's chronic encephalitis, has a better prognosis than infectious processes, which usually have bilateral involvement.[68] Various surgical techniques are employed to treat hemispheric epilepsy syndromes and include anatomic hemispherectomy, functional hemispherectomy, hemispherotomy and hemidecortication. Hemispherotomy may be more suitable for patients with perinatal stroke and Rasmussen syndrome, whereas a modified functional or anatomic technique may be better suited to patients with hemimegalencephaly and cortical dysplasia. The choice of technique depends in part on the patient's age, type of lesion, size of the hemisphere and lateral ventricle and the surgeon's expertise.

Corpus Callosotomy

In patients with symptomatic or cryptogenic generalised epilepsies, such as the Lennox-Gastaut syndrome, bilateral cerebral dysfunction and bilateral seizure onset, focal cortical resection is of no use. Atonic, tonic and tonic-clonic seizures may, in some patients, respond to



Figs 6A to C: (A) MR image showing DNET involving the face motor cortex (long arrow). (B) Adjacent hand area (small arrow), post-resection surgical cavity. (C) Post-operative MR image showing lesionectomy

corpus callosotomy, the rationale being interruption of the rapid secondary bilateral synchrony that underlies these seizures types.[13] The indications for corpus callosotomy are not standardised, but patients with drop attacks usually respond best. Recurrent episodes of convulsive status epilepticus are also eliminated in most cases.[43,51] A complete callosotomy is performed in those children who are developmentally retarded and who have no or very limited speech.[96] A partial callosotomy can be reserved for those children with partial speech preservation.[50]

A number of methods have been employed to assure accomplishment of the desired length of section.[4] These include physical measurement of the exposed callosum to be sectioned, identification of structural features (such as the thinning of commissure generally seen in the posterior body or the appearance of the fornices), intraoperative radiographs and, most recently, the image guidance of frameless stereotactic navigational systems. Radiosurgical corpus callosotomy may be a promising alternative treatment to open callosotomy.[57] A complete callosotomy is preferable to a partial callosotomy, in terms of long-term seizure control. However, the former may lead to debilitating functional impairments. The goal of surgery with callosal section is different from that of other epilepsy surgeries, in that it is usually palliative, rather than curative.[73]

Multiple Subpial Transections

The surgical technique of multiple subpial transections (MST) was first described by Morrell in 1969, as a means to eliminate seizure propogation in eloquent brain regions.[48] It was based on experimental studies by Kristian Kristiansen of Oslo, Norway. The technique takes into consideration the organisational anatomy of the cerebral cortex. It has been known for some time that neuronal function passes through vertical columns of the cortex, while the horizontal columns are thought to be important for the propagation of seizure activity. Multiple subpial transections disrupt the horizontal fibres that propagate seizure activity but maintain functional vertical columns.[30] The Landau-Kleffner syndrome of acquired epileptic aphasia is a rare disorder characterised by regression of language in early childhood, prominent EEG abnormalities that involve the language cortex and often, seizures.[84] In some children with impaired language who fail to respond to medical treatment, multiple subpial transection of perisylvian cortex on one side may be of benefit.[49]

Radiosurgery

Radiosurgery delivers focused radiation using stereotactic guidance to targets within the brain. Seizure reduction was documented when vascular malformations and hypothalamic hamartomas have been treated with radiotherapy.[86] For patients who are not suitable or not willing to undergo surgery, radiosurgery is an effective alternative. Stereotactic radiosurgery improves seizure outcome in the majority of patients and more than half of the patients with medically intractable partial epilepsy had an excellent seizure outcome after radiosurgery. The safety and efficacy of Gamma knife surgery in mesial TLE has been documented in a prospective study.[75] At 2 years, 65% of the patients (13 of 20) were seizure free with neither permanent neurological deficit nor neuropsychological deterioration.

Neurostimulation

Electrical stimulation to treat seizures in patients who are not suitable for resective surgery is a novel idea. Electrical stimulation is reversible. If it does not work, it can be discontinued and the electrodes can be removed. Neuronal tissue need not be destroyed or resected, except for the tissue directly along the tract of the stimulating electrodes. Stimulation can occur within seconds, enabling patients to turn the stimulator on at the beginning of a seizure. Despite these theoretical advantages, electrical stimulation is still far from being an established and effective therapeutic technique. Earlier experience with superior cerebellar stimulation utilising implanted electrodes failed the test of time.

Vagal Nerve Stimulation

Vagal nerve stimulation (VNS) is a technique that is used in patients with epilepsy that cannot be lateralised or localised. Several reports suggest that VNS can be used in both adults and children with intractable epilepsy, with varying degrees of success.[41,85] Vagus nerve stimulation is an accepted method of treatment with low morbidity and mortality, which improves seizure control in at least 30% of patients, together with concomitant improvements in QOL.

Deep Brain Stimulation

Electrical stimulation of relay nuclei may influence electrical activity in widespread regions of the brain and is useful for multifocal seizure types. Stimulation of deep brain targets in the cerebellum, caudate nucleus, diencephalon, anterior and centromedian nuclei of the thalamus, the subthalamus and mesial temporal structures, is practical.[24,105] There are indications that deep brain stimulation (DBS) improves seizure control in a group of patients previously not suitable for resective surgery and this methodology has enormous potential. Questions regarding the best target sites, best candidates for stimulation as well as the efficacy and safety of the stimulation have not yet been answered.

Stereotactic Surgery

Stereotactic lesionectomy and radiofrequency lesioning have been reported with variable safety and success rates in controlling refractory seizures.[66,67] Stereotactic

craniotomy is used for the excision of small lesions causing epilepsy and for lesions which are close to eloquent regions of the brain.[64] A major advantage of the stereotactic technique is the capability of resecting deep-seated intracranial lesions involving the functional or eloquent cortex, with a low surgical morbidity. A well-defined lesion can be resected stereotactically with much less morbidity than the conventional approach. In a series of 23 patients who underwent stereotactic lesionectomy for refractory partial seizures at the Mayo Clinic, USA, 74% had a significant seizure reduction and 56% were almost seizure free.[11] Stereotactic amygdalotomy for TLE was carried out by Ramamurthi et al. but long-term results were not encouraging.[66]

COMPLICATIONS

The general complications of any neurosurgical procedure include acute post-operative haemorrhage, retraction injury, wound infection and the usual peri-operative sequel, such as anaesthetic and medication intolerance, deep vein thrombosis and infections of the bladder, lung or intravascular lines. Whenever surgery for epilepsy is contemplated, the risks and benefits must be carefully weighed.[78] The risks of epilepsy surgery are acceptably low in the modern era, with overall mortality being less than 0.5% and morbidity less than 5%. Surgical complications include cerebral infarction, intracranial haemorrhage, intracranial infection, and direct cranial nerve or cerebral injury, possibly resulting in temporary or permanent neurologic deficits. Morbidity and mortality vary according to the patient's age and type of surgery; risks appear to be slightly higher in children compared with adults and in hemispherectomy and corpus callosotomy, compared with anterior temporal lobectomy and extratemporal resections.[6]

OUTCOME ASSESSMENT

Until recently, the outcome of epilepsy surgery was reported in terms of seizure frequency alone. Psychosocial, educational and occupational consequences of epilepsy and their treatment were rarely considered, when reporting the outcome of epilepsy surgery. Currently, a comprehensive outcome measure, emphasising the overall quality of life is practiced by a majority of the epilepsy surgery centres.[97]

Seizure Outcome

Surgery is widely accepted as an effective therapy for selected individuals with medically refractory epilepsy.[106] Numerous studies in the past 20 years have reported seizure freedom for at least 1 year in 53–84% of patients after anteromesial temporal lobe resections for mesial temporal lobe sclerosis, in 66–100% of patients with dual pathology, in 36–76% of patients with localised neocortical epilepsy and in 43–79% of patients after hemispherectomies. Careful patient selection even with non-invasive investigations can aid in obtaining a good outcome in patients with extratemporal epilepsy.[90]

A four-part classification system, called the Engel classification, categorising post-operative seizure outcome to Class I (free of disabling seizures), Class II (rare disabling seizures), Class III (worthwhile improvement) and Class IV (no worthwhile improvement) is still in widespread use today.[23] Engel has compiled seizure outcome data on more than 5,000 patients. Temporal lobe resections and lesional non-temporal lobe resections have a very high probability of success. Seizure freedom with anterior temporal lobectomy and lesionectomy are 67.9 and 66.6%, respectively. Hemispherectomies have a comparably high success rate with 67.4% seizure freedom. The seizure freedom is only 45% with neocortical and multilobar resections. Seizures completely stop in fewer than 10% of patients who undergo callosotomy. However, it can completely eliminate atonic seizures in approximately 70% of patients.[26] It is now a well-established fact that a prolonged longitudinal follow-up is essential for accurate assessment of seizure outcome, since initially seizure free patients may relapse and some patients with early post-operative seizures may become seizure-free subsequently (running-down phenomenon).[94] Reported rates for non-resective surgery have been less impressive in terms of seizure freedom; however, the benefit is more apparent when reported in terms of significant seizure reductions.

Resurgery

Seizures persist or recur in 20–60% of patients after resective surgery for intractable partial epilepsy. Re-operation is the performance of a further surgical procedure intended to relieve drug-resistant epilepsy, when a previous procedure for the same purpose has failed.[81] Overall, the outcome from resective re-operation is around 44% seizure-free and 25% not affected. However, when there is a structural lesion that has been missed or incompletely removed, the seizure-free proportion rises to 80–90%. Recurrent seizures after extratemporal resections were more likely to become persistent and intractable than seizures recurring after temporal resections.[113]

CONCLUSION

In recent decades, there has been increasing interest in the surgical treatment of patients with intractable seizures. Identification of patients with surgically remediable syndromes became easier with the application of relatively inexpensive non-invasive EEG and MRI approaches.[100] It is possible to identify ideal surgical candidates with the correlation of clinical semiology, neuroimaging and video EEG telemetry. It is essential to clearly delineate the underlying pathological substrate and resect completely to cure or control epilepsy. However, if such a resective procedure is not possible, then functional surgery should be considered. New centres can successfully

establish epilepsy surgery programs, by initially performing relatively simple and standard surgical procedures like anterior temporal lobectomy and lesionectomy. Subsequently, the programmes can be expanded to include patients with bitemporal and extratemporal epilepsy, as well as non-lesional epilepsy.

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202 Surgery for Temporal Epilepsy

Bhaskara Rao Malla, Jayanti Mani

INTRODUCTION

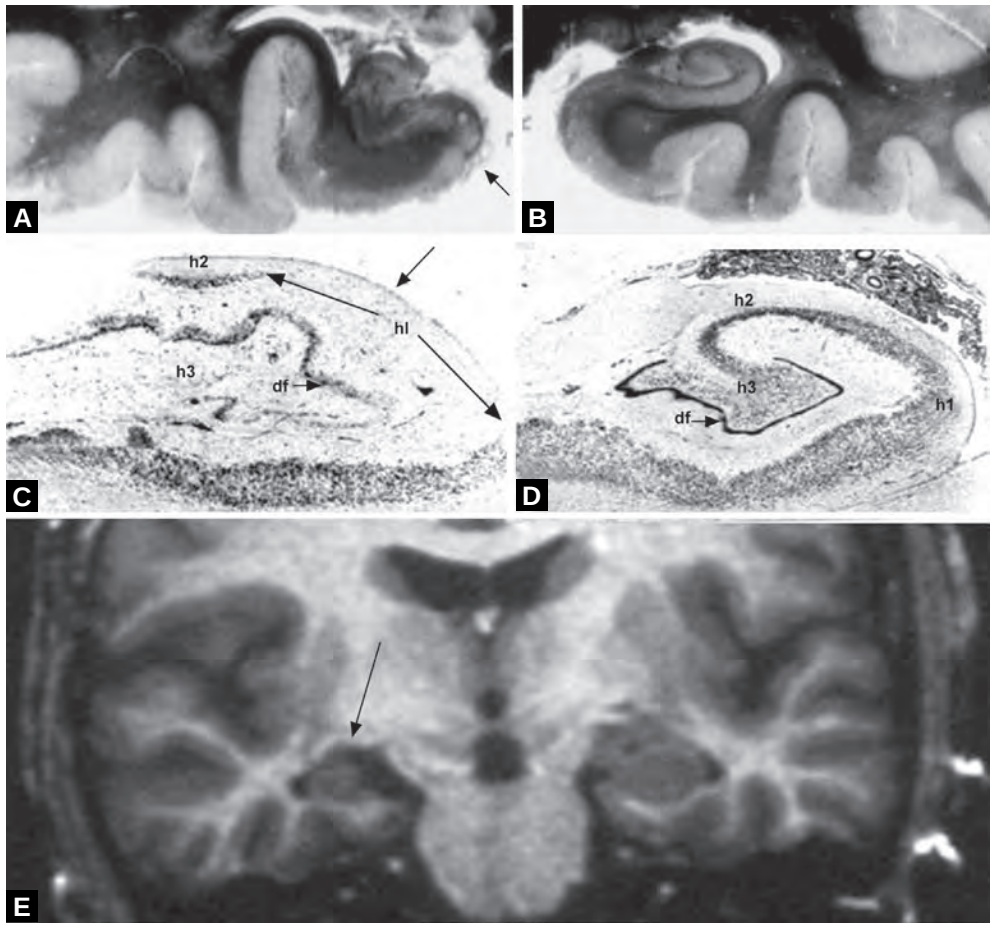
Temporal lobe epilepsy (TLE), especially mesial TLE (MTLE) is the most common form of human epilepsy. In the ICMR multicentric study involving 3,439 cases, TLE, with or without generalisation, accounted for 27.5%.[93] The pathological substrate of MTLE is usually hippocampal sclerosis, the most common epileptogenic lesion encountered in patients with medically refractory epilepsy.[23,24] The disabling seizures associated with MTLE are typically resistant to antiepileptic drugs but can be abolished in most patients by surgical treatment.[20] Anteromesial temporal resection, therefore, is the most common surgical procedure performed to treat epilepsy.[20] The benefits of surgery for TLE have been well demonstrated in terms of seizure control, cognitive function and quality of life (QOL).[85] In this chapter, we elaborate on the pre-surgical evaluation, selection of ideal candidates, surgical treatment and post-operative outcome of patients with medically refractory TLE.

HISTORICAL PERSPECTIVE

In 1825, Bouchet and Cazauvieilh[8] first described the association between epilepsy and a sclerotic hippocampus, based on gross pathological examination of brains from patients with mental alienation seizures. In the latter part of the 19th century, however, Hughlings Jackson[36] recognised the role of the temporal lobe in epilepsy, by associating the auras of taste, smell and epigastric sensations with temporal lobe lesions. With the advent of EEG Gibbs et al.[31] reported an ictal discharge pattern which they believed was characteristic of psychomotor seizures. It was Jasper and colleagues[37,38] who pointed out that inter-ictal and ictal epileptiform EEG abnormalities in psychomotor dreamy states and other phenomena now known to be limbic seizures, originated in mesial temporal structures. The first temporal neocortical resection for epilepsy was performed by Penfield in 1929[27] Bailey and Gibbs[4] were the first to perform anterior temporal lobectomy (ATL) on the basis of EEG evidence alone. Penfield and his colleagues[55–57] in a series of studies established the aetiology, pathology, clinical manifestations and treatment of this distinct entity. They elaborated the role of undue molding of the head during childbirth, resulting in mesial temporal herniation and ischaemia leading to incisural sclerosis.[17] In 1954, Penfield and Jasper[58] reported a better outcome with more complete resection of the mesial temporal structures and described the atrophic changes in the hippocampus, in the majority of the patients with epilepsy who underwent temporal lobectomy. Falconer[23] described the detailed pathology in the 'en bloc' temporal lobe resections. The term 'mesial temporal sclerosis (MTS)' was coined to include the entire spectrum of changes involving the medial temporal structures.[24] Falconer and Serafetinides[25] also highlighted the incidence of other pathologies like hamartomas as a frequent cause of TLE in these patients, in the absence of MTS.[23] In 1958, Niemeyer[51] developed a transcortical transventricular amygdalectomy and a 3 cm hippocampectomy, which was performed through a 2 cm middle temporal gyrus incision. Rasmussen and Jasper,[71] Falconer et al.[25,26] and later on Feindel and Rasmussen[28,71] and Engel and colleagues[18,21,22] made noteworthy contributions in the field. In India, both open and stereotactic procedures were performed for patients with intractable TLE at the Christian Medical College, Vellore[2,48] and at the Institute of Neurology, Madras [5,66,67] in the 1950s and 1960s. The current status of epilepsy surgery in India has been summarised in a recent publication in the Neurology India.[61]

PATHOLOGY

The most common pathology observed in nearly two-thirds of resected temporal lobes was MTS[90] (Figs 1A to E). In MTS, the hippocampal neurons were lost in the CA1 and CA3 regions and the dentate hilus.[43,60,65,105] Sommer[84] was the first to describe the neuropathological changes in Ammon's horn (*cornu ammonis, CA*) of patients with chronic epilepsy, predominantly characterised by a loss of pyramidal cells in the CA1 sector (often called the Sommer sector). Margerison and Corsellis,[47] in their study of TLE, observed two types of hippocampal sclerosis: (1) classical Ammon's horn sclerosis (with neuronal loss and gliosis in the CA1 sector and the dentate gyrus) and (2) end folium sclerosis involving the CA_3 and CA_4 sectors. Low-grade neoplasms such as ganglioglioma and dysembryoplastic neuroepithelial tumour, focal cortical dysplasia and vascular malformations comprised the rest.[63,105] In endemic areas for cysticercosis, calcified cysticercous granulomas as a cause for refractory partial epilepsy are not uncommon.[50] The spectrum of pathology in the paediatric population of



Figs 1A to E: (A and B) Gross specimen. (C and D) Photomicrographs. (E) MRI of the temporal lobes with arrows pointing towards atrophic hippocampus, suggestive of mesial temporal sclerosis (MTS)

TLE is different to adults. In a multinational report on paediatric epilepsy surgery, the most common pathology in the resected specimens was a tumour followed by cortical dysplasia and then hippocampal sclerosis. Thus, at an earlier age, developmental lesions are much common than hippocampal sclerosis.

MEDICAL REFRACTORINESS

Over 50% of patients with MTLE fail to respond to optimal medical treatment. A recent evidence-based report on the effectiveness of anteromeial temporal lobe resection has recommended that patients with disabling complex partial seizures with or without secondarily generalised seizures, who have failed appropriate trials of first-line antiepileptic drugs, should be considered for referral to an epilepsy surgery centre. Patients referred to an epilepsy surgery centre for the reasons stated above, who meet established criteria for an anteromeial temporal lobe resection and who accept the risks and benefits of this procedure over continued pharmacotherapy should be offered surgical treatment.[22]

PRE-SURGICAL EVALUATION

A non-invasive protocol for evaluation of patients with medically refractory TLE is provided in Table 1. Today, a majority of patients with TLE can be selected for surgery, based on the results of non-invasive methods such as scalp EEG, video-EEG, MRI and neuropsychological findings.[39,62,89,91,94] Concordance of MRI and scalp EEG abnormalities correlates with an excellent post-operative seizure outcome.[64] A sub-group of patients

Table 1: A non-invasive protocol for the evaluation of patients with medically refractory temporal lobe epilepsy

Review the history, past AED treatments, seizure frequency and EEGs
Medical and neurological examinations
16-channel awake and sleep scalp EEG recordings
Neuropsychological évaluation
Psycho-social evaluation
Psychiatric evaluation
Visual field testing
MRI with protocol for hippocampal volume loss and sclerosis
Long-term video-scalp EEG monitoring
Wada test in selected patients

AED—antiepileptic drug; EEG—electroencephalogram; MRI—magnetic resonance imaging

with MRI-negative TLE can also be evaluated and selected for surgery, by using clinical history and scalp-recorded inter-ictal and ictal EEG data. The attributes of these patients are antecedent history of febrile seizures, strictly unilateral anterior inter-ictal epileptiform discharges and concordant type 1 ictal EEG pattern.[92]

Non-invasive Evaluation

Seizure Semiology, Lateralisation and Localisation

Detailed study of the seizure semiology, as part of the video EEG evaluation, provides confirmation of the epileptic nature of the seizures and also provides valuable lateralising and localising information regarding seizure onset (Fig. 2). This procedure involves continuous recording of synchronous scalp EEG and video over a period of 24 hours to 7 days, with the aim of recording inter-ictal EEG and clinical seizures with corresponding ictal EEG. Medications are gradually withdrawn with the aim of recording habitual seizures.

The seizures associated with TLE consist of simple partial seizures without loss of awareness and complex partial seizures with loss of awareness. The partial seizures may secondarily generalise. In TLE, auras are reported in about 20–67% of seizures. They occur either as isolated events or as the first event that evolves into more elaborate seizures. Auras are more frequent in TLE. The epigastric or abdominal auras are considered to be typical of MTLE, although extratemporal origin of epigastric auras has also been noted. Psychic auras of fear and dèjà vu are related to the amygdala. Gustatory and olfactory auras are quite characteristic of TLE. Motionless stare with a behavioural arrest is the first evidence of the onset of seizures in a large number of patients. Oro-alimentary automatisms consisting of lip smacking, chewing and swallowing are common in TLE. Hand automatisms may be bimanual and when unilateral, they are often ipsilateral to the side of seizure onset. Contralateral arm dystonic posturing and forced contralateral version of the head and eyes are strongly lateralising features in TLE with specificity more than 90%. The latter is particularly useful when it occurs just prior to secondary generalisation of the seizures. Typically, the seizure lasts between 30 seconds and 2 minutes. Secondarily generalised tonic clonic seizures are rare in MTLE. Post-ictal phenomena, like nose wiping, spitting, coughing and vomiting, have been shown to occur in seizures from the non-dominant hemisphere, whereas post-ictal aphasia lateralises the seizure to the language dominant hemisphere. Auditory auras are seen in seizures from the lateral temporal neocortex. Early secondary generalisation and clonic phenomena involving the face and hands are also more frequent with lateral temporal epilepsy.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is the neuroimaging modality of choice for patients with TLE. All patients with newly diagnosed TLE should have a high-resolution imaging with at least a 1.5-Tesla MR

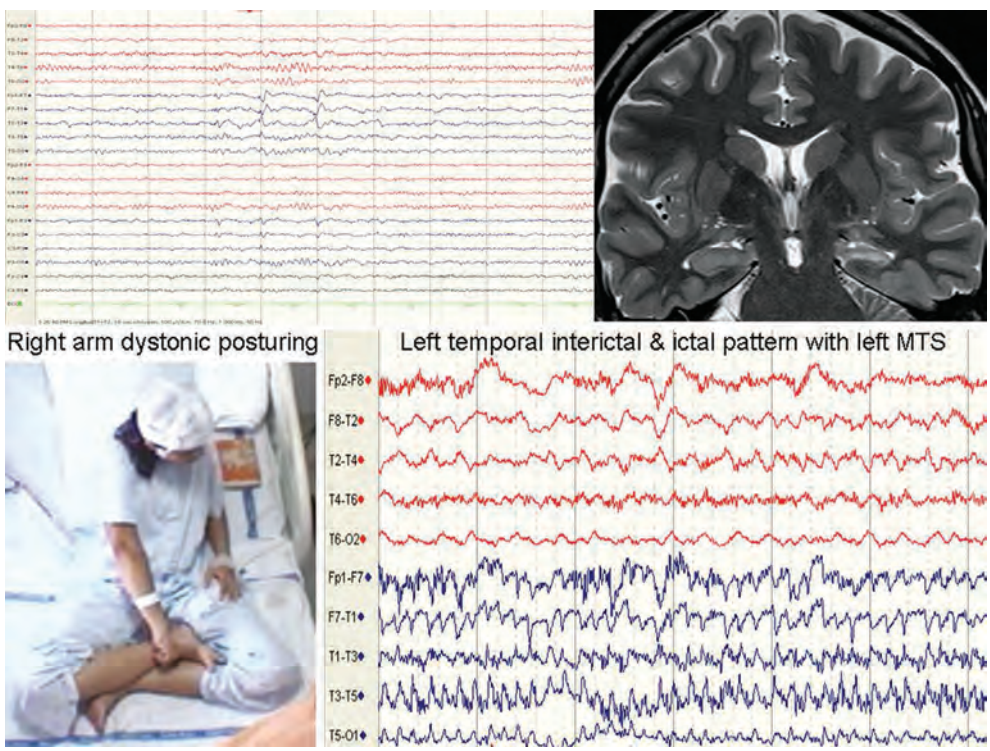


Fig. 2: Clinical, MRI and EEG correlation in a patient with medically refractory left temporal lobe epilepsy shows right arm dystonic posturing, small left hippocampus on T2-weighted coronal MRI sequence with left anterior temporal spike discharges and left temporal rhythmic theta EEG activity during a complex partial seizure

scanner, although the availability of a stronger magnet will increase the resolution. Thin coronal oblique slices through the temporal lobe, of 1.5–2 mm thickness with no gap using spoiled gradient recall images (SPGR) are recommended. Most brain MR scans do not include coronal images but, for TLE, this sequence is more informative than the axial and sagittal cuts. On MRI, decreased hippocampal size on T1-weighted images increased signal on T2-weighted and on fluid-attenuated inversion recovery (FLAIR) images characterise hippocampal sclerosis.[6,16] High-resolution MRI shows hippocampal atrophy in many patients with TLE by visual analysis alone. Hippocampal atrophy is bilateral in 10–15% of cases. Volumetry is used by some investigators to demonstrate asymmetry, although controversy exists as to the need for this quantitative technique.[10]

Neuropsychological Evaluation

The information obtained through neuropsychological testing helps in counselling patients about the potential risk of post-operative memory impairment and is also valuable in assessing progress in the follow-up period.[78] The Wada test is undertaken prior to temporal lobectomy to lateralise the distribution of language and memory function between the two hemispheres and to thereby predict the post-operative language and memory outcome.[95] While language assessment during the Wada test is simple and straight-forward, interpretation of memory deficit is complex and requires a carefully designed protocol. Inadequate memory support during the Wada test is not an absolute contraindication to ATL and should be considered within the context of the patient's basal neuropsychological functioning and the impact of the expected post-operative deterioration on one's QOL. Restricting the Wada test to patients with suspected bilateral temporal dysfunction, as evidenced by neuropsychological testing or MRI findings, may be a cost-effective approach in developing countries. In the near future, non-invasive evaluation with fMRI and PET may obviate the need of the Wada test.

Currently, the risk of severe post-operative memory decline, following unilateral ATL, can be predicted with reasonable accuracy.[32] The risk is higher when the following factors are present: (1) ATL on the language dominant side; (2) no hippocampal atrophy or sclerosis on the side of proposed resection; (3) a higher pre-operative memory performance; (4) evidence of bilateral hippocampal atrophy on pre-operative imaging; (5) seizure onset at an older age; (6) surgery performed at an older age; (7) functional assessments (e.g. Wada test) that suggest greater residual pre-operative function of the left temporal lobe and (8) left handed or ambidextrous patients. Thus, the risk would be highest for patients undergoing left temporal lobectomy with left cerebral language dominance, absence of left hippocampal atrophy/sclerosis, high baseline verbal memory, absence of unilateral left temporal lobe hypo-metabolism in the PET and the presence of high memory performance with right intracarotid amobarbitol injection, but low memory performance with left injection.

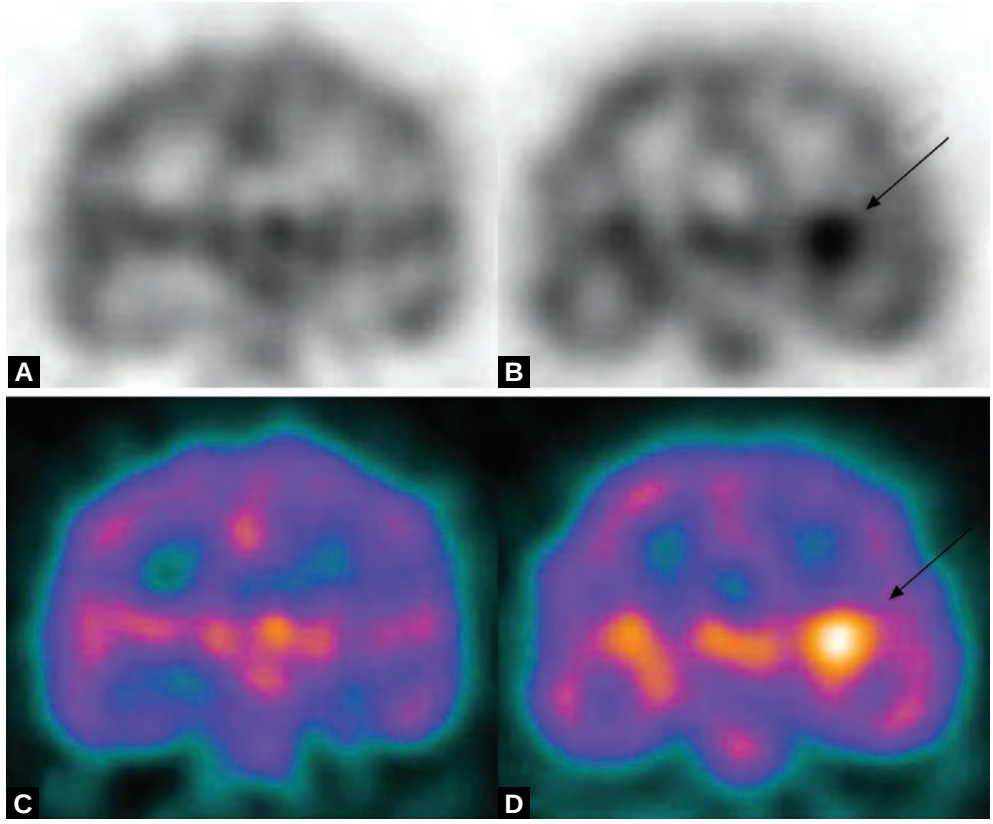
Functional Imaging in Temporal Lobe Epilepsy

Non-invasive mapping procedures, such as single photon emission computed tomography (SPECT), positron emission tomography (PET), functional MRI (fMRI), magnetic resonance spectroscopy and magneto-encephalography, may provide information complementary to that provided by EEG, video-EEG and MRI.[19] Peri-ictal SPECT studies are obtained by injecting a radiotracer during (ictal) or soon after the seizure activity (post-ictal), which necessitates electro-clinical correlation utilising continuous video-EEG monitoring.[82] Hyperperfusion of the epileptic temporal lobe occurs during the ictus and persists for up to one minute into the immediate post-ictal period. Ictal SPECT studies of temporal lobe seizures yield over 90% correct lateralisation of the epileptogenic focus[42] (Figs 3A to D). Post-ictal SPECT studies are lateralising in about 70% of temporal lobe seizures, whereas inter-ictal SPECT studies have a low yield of true positivity and an unacceptably high false positive rate.[42]

The findings of complex partial seizures of temporal lobe semiology, anterior temporal inter-ictal sharp waves arising in the mesial temporal structures, without evidence of extratemporal epileptiform activity on EEG and unilateral MTS on MR imaging without extratemporal lesions, together yield the diagnosis of MTLE (Fig. 2). Vascular lesions, such as cavernous angiomas and arteriovenous malformations, focal developmental abnormalities, hamartomas and low-grade neoplasms, may involve the medial or lateral parts of the temporal lobe (Fig. 4).[63] Due to the considerable overlap in the seizure semiology and inter-ictal and ictal EEG data between mesial and lateral TLE syndromes, the location of a lesion on MRI is the only reliable finding that helps to distinguish between these two epileptic syndromes.[99] Selecting patients with TLE for the appropriate operation begins by first using MRI to classify them into the three anatomical substrate categories noted above: (1) hippocampal atrophy (MTLE with presumed MTS); (2) lesions (LTLE) or (3) normal anatomy (CTLE). The presence of a lesion in a patient with refractory partial epilepsy does not invariably indicate that the lesion is responsible for the seizures. Patients with long standing lesions (e.g. developmental, atrophic or benign neoplastic lesions) may develop hippocampal atrophy (dual pathology) (Figs 5A to C).[12] The primary lesion, the secondary hippocampal sclerosis or both, may be responsible for the seizures.

Invasive Evaluation

Patients with TLE may require invasive monitoring, when the results of non-invasive methods such as scalp EEG, video-EEG and MRI are conflicting. In selected patients with presumed MTLE with sparse inter-ictal



Figs 3A to D: Inter-ictal and ictal SPECT images of the same patient shows hyperperfusion in the left mesial temporal region

epileptiform discharges or poorly defined ictal EEG activity, long-term monitoring utilising sphenoidal electrodes may help to localise the spiking and ictal onset zones.[3,46] Several types of intracranial recording electrodes, such as subdural strip and grid electrodes, epidural electrodes, intracerebral depth electrodes or their combination, may have to be utilised to define the site of seizure origin.[88] Exclusive use of either intracerebral or subdural electrodes may occasionally result in erroneous localisation because of insufficient sampling.[34] Patients with suspected MTLE, with bilateral temporal inter-ictal and ictal abnormalities and/or bilateral MTS, often will require bilateral depth electrode placement to the mesial temporal structures. Patients with TLE with normal MRI and equivocal SPECT and PET findings will require invasive monitoring with subdural and depth

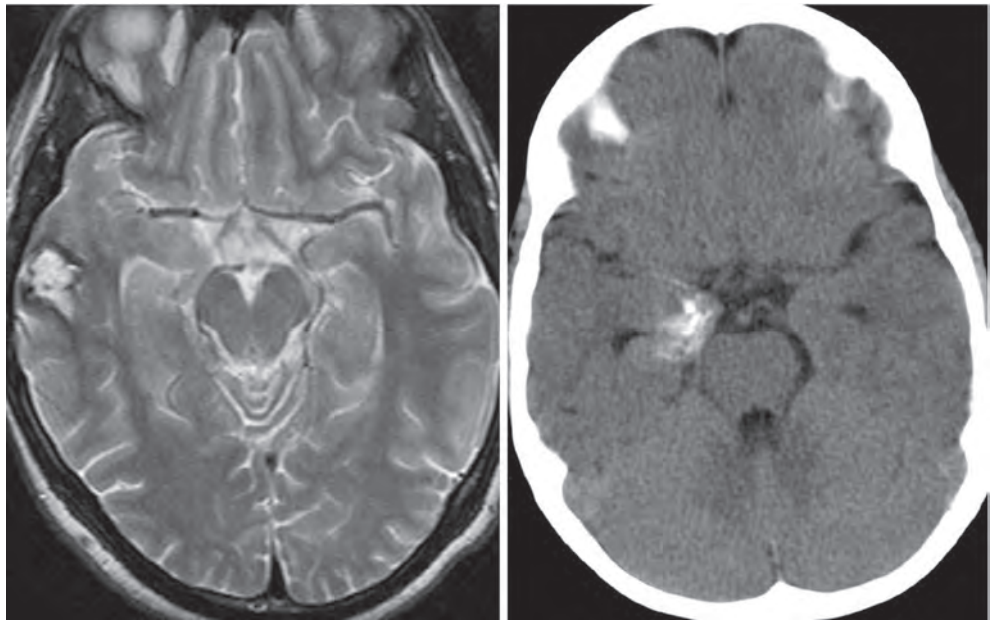
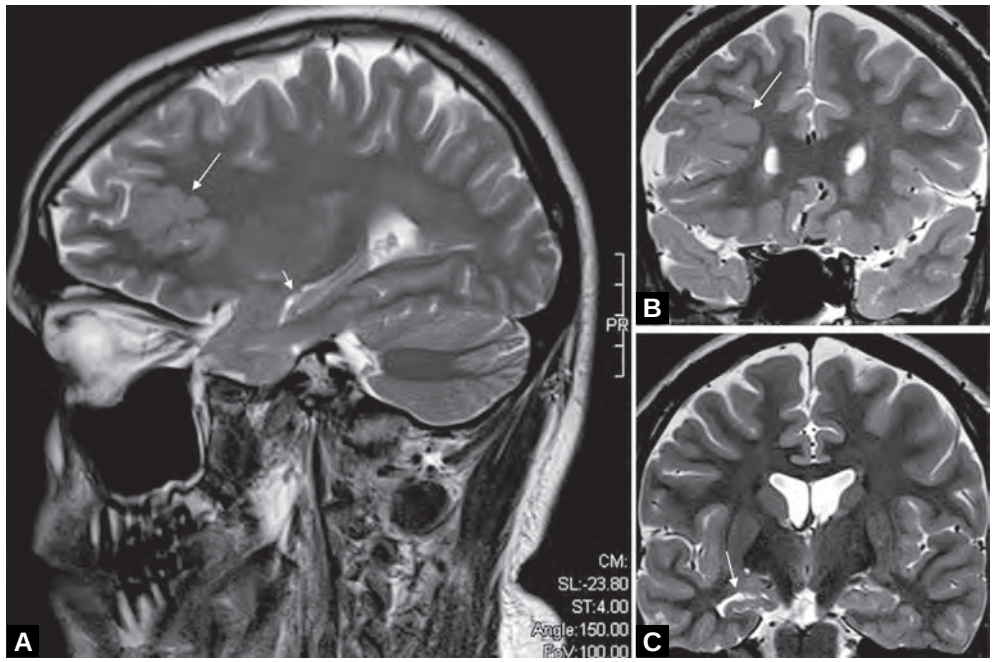


Fig. 4: MRI and CT scan of the brain show lateral neocortical and mesial temporal lesions



Figs 5A to C: MR images showing (A and B) frontal focal cortical dysplasia and (C) Hippocampal sclerosis suggestive of dual pathology (arrows)

electrodes to localise the zone of ictal onset.[88] Depth electrode recordings, using the Talairach's Stereo electroencephalographic (SEEG) method, may identify patients who can benefit from surgery, in spite of equivocal concordant pre-surgical investigation criteria, as well as to exclude from the selection process patients with multilobar or bilateral foci.[88] When neurosurgical procedures encroaching the neocortical sensory, motor and speech areas are planned, functional mapping using fMRI or during surgery with the patient awake or extra-operatively after placing intracranial electrodes is performed to circumscribe the area of resection, in order to avoid post-operative neurological deficits.[52]

SURGICAL TREATMENT

Surgical Approaches

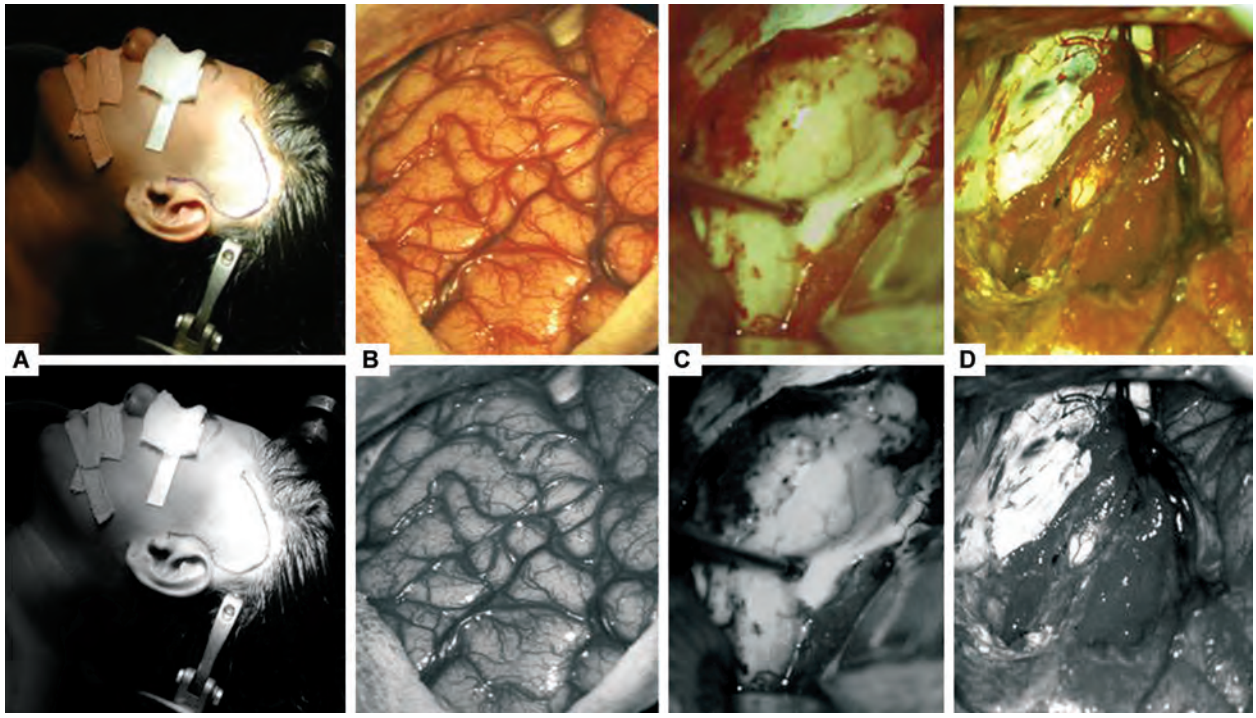
A diversity of operations has been undertaken for the management of refractory TLE (Table 2). ATL is the most common surgical procedure undertaken.[20] For patients with unilateral or predominantly unilateral seizures, most centres perform a standard ATL in which the anterior temporal neocortex, anterior hippocampus and lateral amygdala are resected.[13,28] Intra-operative electrocorticography (ECoG) and cortical stimulation are used at some centres to tailor the lateral temporal resection, according to the extent of EEG abnormality and the location of the language cortex.[52,89] Selective amygdalohippocampectomy (SAH), sparing the lateral temporal neocortex, is performed at some centres.[102] Other centres perform only lateral neocortical resections, sparing the amygdala and hippocampus. The aim of modified temporal resections is to reduce post-operative cognitive deficits.[32]

Anterior Temporal Lobectomy

Anterior temporal lobectomy is also known as standard or tailored ATL and anteromedial temporal lobectomy.[20] The procedure, as it is undertaken today, is a modification of the en bloc temporal lobectomy popularised by Falconer and Taylor.[26] Based on invasive electrophysiology and pathology, Spencer et al.[87] modified the standard resection for those patients with medial temporal ictal onset, such that all of the medial structures (amygdala, hippocampus and parahippocampal gyrus) were removed via a limited temporal pole resection. In the majority of epilepsy surgery centres, ATL (Figs 6A to D) is performed under general anaesthesia (Fig. 6A).

Table 2: Surgical techniques for the treatment of medically refractory temporal lobe epilepsy

Anterior temporal lobectomy with amygdalohippocampectomy
Standard
Tailored
Selective amygdalohippocampectomy
Transcortical-transventricular approaches
Through superior temporal gyrus
Through middle temporal gyrus
Through inferior temporal gyrus
Trans-Sylvian approach
Subtemporal approach
Selective lateral temporal (neocortical) resection
Lesionectomy
Multiple subpial transections



Figs 6A to D: Operative photographs showing: (A) Left temporal craniotomy. (B) Anterior temporal lobe.(C) Left hippocampus. (D) Anterior temporal lobectomy cavity

At a few centres, local anaesthesia is used as originally advocated by Penfield.

Anterior temporal lobectomy includes resection of the neocortex, extending up to 3.5–4.0 cm on the dominant side and 4.0–4.5 cm on the non-dominant side along the Sylvian fissure (Figs 6B and D). Lateral neocortical resection, especially the superior temporal gyrus, may have to be limited in certain cases, depending upon cerebral dominance and when large cortical branches of the middle cerebral artery or a prominent vein of Labbe are placed anteriorly. The vein of Labbe is inconstant and, when present, only indicates a posterior drainage of the Sylvian venous system. Opening the temporal horn of the lateral ventricle exposes the pes hippocampus (Fig. 6C). The amygdala and the hippocampus are always removed by a transventricular approach. En bloc resection is limited to the anterior two-thirds of the hippocampus and lateral two-thirds of the amygdala, along with the uncus and the parahippocampal gyrus by subpial dissection, using the operating microscope (Fig. 7). The medial part of the amygdala is not removed, as it abuts the striatum, anterior commissure and tail of the caudate nucleus. The hippocampal sulcus contains the artery of Ammon's horn, which is the fundamental landmark for a subependymal, subpial resection of the hippocampus. Both the hippocampal formation and the amygdala can be removed subpially. This approach minimises the coagulation, division and manipulation of the anterior choroidal artery and the branches arising from the posterior cerebral artery.

The role of ECoG during TLE surgery is uncertain. It is performed routinely at some centres, but the extent of resection was rarely dictated by ECoG, which depended on anatomical constraints and the feasibility of complete

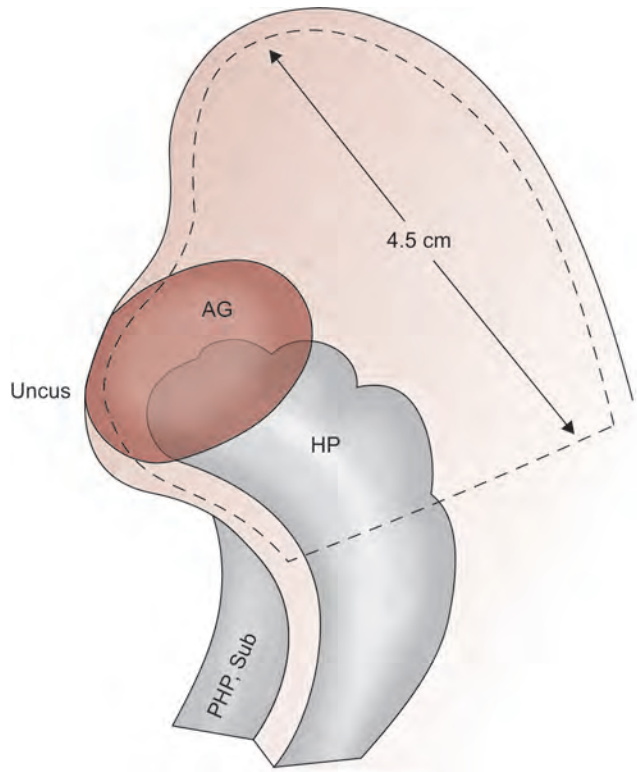


Fig. 7: Diagram illustrates the extent of resection in anterior temporal lobectomy with amygdalohippocampectomy consisting of 4 cm of anterior temporal neocortex, anterior two-thirds of the hippocampus (3 cm) and parahippocampal gyrus along with the lateral two-thirds of the amygdala and uncus (AG—amygdala, HP—hippocampus, PHG—parahippocampal gyrus)

removal of a lesion.[33] ECoG may help to tailor the extent of temporal lobe resection. However, the distributions of spikes in the pre-resection electrocorticogram (ECG) and quantity of residual spikes in the post-resection ECG, have not consistently correlated with the post-operative seizure outcome.[80]

Selective Amygdalohippocampectomy

Amygdalohippocampectomy is a selective resection of the amygdala, uncus and hippocampus posteriorly to the level of the superior colliculus. Amygdalohippocampectomy can be performed via different approaches. With this approach, the lateral temporal cortex is not resected. Since the introduction of SAH by Niemeyer,[51] several modifications of this technique have been proposed.[53,96] Wieser and Yasargil[101,102] suggested the trans-Sylvian approach. After dissection of the Sylvian fissure, the temporal ventricular horn is entered through the temporal stem in the inferior semicircular sulcus, followed by the resection of mesiotemporal structures. The dissection of the Sylvian fissure may be challenging, but a good overview of the hippocampus including the possibility of far dorsal hippocampal resection is provided. Damage or vasospasm of Sylvian veins, branches of the middle cerebral artery, anterior choroidal artery and branches of the posterior cerebral artery may result in hemiparesis or hemianopia. Olivier, at the MNI, modified and popularised the transcortical transventricular approach, which was initially done through the anterior part of the superior temporal gyrus and later through the superior temporal sulcus.[53] With the aid of neuronavigation, the ventricle is entered via the middle temporal gyrus, followed by a resection of the anterior parts of the hippocampus, then amygdala, uncus and parahippocampus. A smaller craniotomy is an advantage with neuronavigation, but the disadvantage is a more limited overview on the mesiotemporal structures. Spencer et al. described a combined approach to gain access to the posterior mesial temporal structures.[87] Other suggestions comprised the sub-temporal, zygomatic, subtemporal trans-parahippocampal, trans-Sylvian-transcisternal and even retrolabyrinthine-presigmoid approach, etc. However, all of them are being practiced by only a few, compared to the trans-Sylvian and trans-cortical approach. The sub-temporal approach is also technically complex because it entails zygomatic process removal for exposure of the floor of the middle fossa. For rare cases of tumour or cavernoma in the dominant hemisphere, this may be considered, but alternative approaches, notably awake temporal lobectomy with functional mapping, is usually preferred.[52]

In spite of technical advances, unilateral SAH has a limited place and in its present form it is probably applicable to 15–20% of patients in a centre offering a comprehensive range of surgical procedures. The indications for SAH are as follows: (1) a lesion confined to the medial temporal structures; (2) evidence of ipsilateral medial temporal onset of partial complex seizures; (3) indications that some of the patient's memory function was subserved by the operated temporal lobe, possibly more so in the dominant temporal lobe. The contraindications for SAH are as follows: (1) a lesion outside of the medial temporal structures; (2) a lesion confined to the medial temporal structures, but too large or too posterior; (3) a patient in whom neurophysiological evidence indicates a regional seizure onset within the temporal lobe; (4) a patient in whom the contralateral temporal lobe carries all or most of the recent memory function. In the last two circumstances, a temporal lobectomy would be preferred. Patients, in whom most of the memory function is carried in the temporal lobe to be operated upon and there is no evidence of a structural lesion in that temporal lobe also, are likely to have a poor result with regard to both seizure control and cognitive outcome.

The advantage of SAH over ATL lies in the fact that the former causes a smaller disruption of potentially functional temporal neocortex, while attaining the same post-operative seizure control as the latter. Different strategies for surgical approaches for TLE result in equally good outcomes. Seizure outcome is mainly dependent on the correct diagnosis and clinical factors, whereas the neuropsychological results are better after resections limited to an epileptogenic lesion and the focus.[1] A number of mechanisms may be involved in the control of seizures, including the removal of structural disease, disruption of neuronal connections and pathways and reduction in the mass of epileptogenic neurons available to participate in the seizure. The disconnection of afferent and efferent networks also helps to explain how the various temporal lobectomy approaches across the spectrum from standardised to tailored resections, may have similar outcome efficacy. There is no consensus regarding either the minimum necessary volume of resection or which structures must be resected for freedom from seizures, following TLE surgery. However, it is generally agreed that in patients with MTLE with MTS, the anterior two-thirds of the hippocampus and the lateral two-thirds of the amygdala along with the parahippocampal gyrus and uncus need to be removed to achieve seizure cure or control.

Lesional Temporal Lobe Epilepsy

In patients with various types of developmental, neoplastic or vascular lesions responsible for epilepsy, three surgical solutions are possible. First, only the lesion may be removed; second, the lesion and some portion of the medial structures may be removed to assure a margin of resection; and, finally, a formal antero-mesial temporal resection may be performed in addition to removal of the lesion.[9,63]

Stereotactic Procedures

Stereotactic procedures have been used for the surgical management of intractable epilepsy since the 1960s.[5] Stereotactic amygdalotomy was performed upon a

sizable number of patients with marked improvement in control of seizures, as well as behaviour disorder.[41,66,67] Currently, these techniques are widely used to implant electrodes in the temporal lobe, to determine the laterality and extent of the epileptogenic zone in patients with intractable TLE. Placement of depth electrodes can be performed using the orthogonal approach or an occipital approach. Both frame-based and frame-less stereotactic systems can be used for depth electrode placement. Frameless stereotaxy can be used for SAH. However, strict lesion resection guided by neuroimaging may be less efficacious in controlling seizures in the temporal lobe than in other cortical regions.[11]

Alternate Surgical Procedures

For lesions located in close proximity to eloquent areas, such as motor and speech areas, multiple subpial transection is a safe option to reduce the seizure frequency without causing morbidity.[49] Although multiple subpial transections alone seldom result in complete seizure control, transections surrounding a lesionectomy may minimise the excised volume without compromising seizure control.[35] Children with Landau-Kleffener syndrome may show substantial recovery of speech, following multiple subpial transections.[77]

The initial experience has shown safety and short-term efficacy of gamma knife surgery for MTLE,[73] but needs further confirmation of long-term efficacy. The role of deep brain stimulation to treat epilepsy is being investigated. For refractory epilepsy patients in whom resective surgical treatment is not an ideal option, neurostimulation therapies hold the promise of improving seizure control, without the adverse effects of multiple antiepileptic medications. Vagus nerve stimulation is currently an approved method of treatment for medically refractory epilepsy in adults[79] and children[45] who are not candidates for resective surgery.

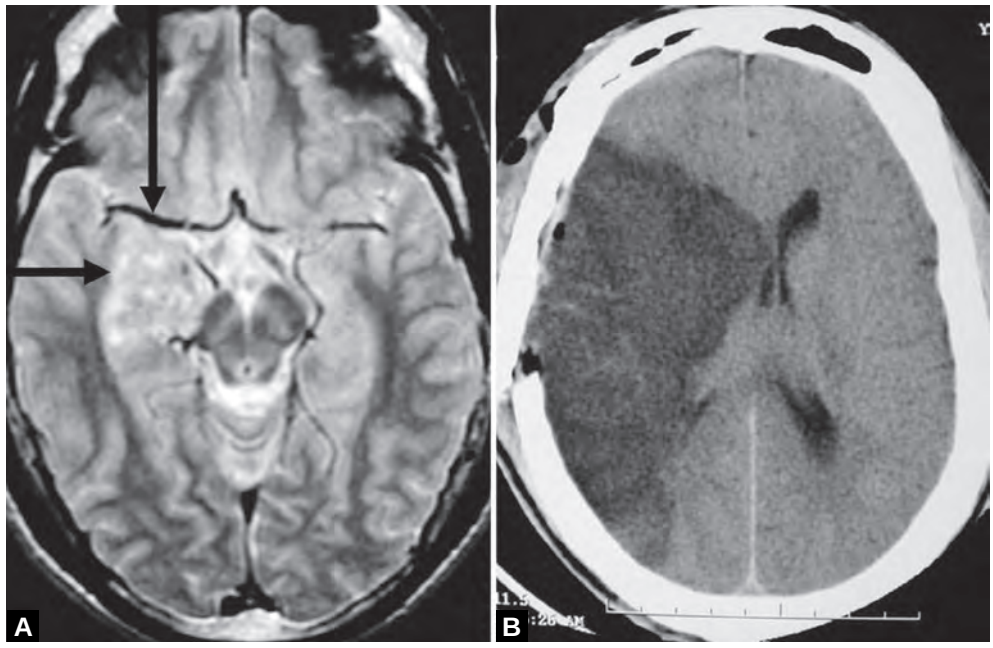
Complications

Specific complications of ATL include homonymous superior quadrantanopsia, due to involvement of either the optic tract or radiation and language deficits and manipulation hemiplegia (Figs 8A and B), due to vascular injury or spasm involving the Sylvian vessels, anterior choroidal artery branches supplying the cerebral peduncle or the perforators supplying the internal capsule.[59,74] These complications may be minimised if care is taken to avoid damage to the branches of the anterior choroidal artery and the branches of the P2 segment of the posterior cerebral artery. Disabling visual field defects are more likely to result from damage to or spasm of the vessels that supply the optic tract, than from direct injury to Meyer's loop. In the Mayo Clinic study,[68] the frequency of acute post-operative seizures was 21%. Only recurrence of habitual seizures predicted an unfavourable post-operative seizure outcome. Expanding cyst following temporal lobectomy has been reported as an unusual complication.[70]

OUTCOME ASSESSMENT

Seizure Outcome

Analysis of the pooled data from epilepsy surgery centres around the world revealed that over 70% of the patients become seizure free after temporal lobe surgery.[21] The exact type of temporal lobe resection (standard vs selective amygdalohippocampectomy) did not influence the



Figs 8A and B: MR images showing: (A) Ganglioglioma involving the anterior hippocampus (black arrows pointing the lesion and adherence of the lesion to the blood vessel). (B) Large middle cerebral artery infarct

seizure outcome.[21] The better seizure outcome in recent years compared to the past appear to be related to the advent of techniques, like digital EEG-Video monitoring and MRI, which have improved the localisation of the epileptogenic zone and thereby, the selection of ideal surgical candidates.[85]

Wiebe et al.[100] recently compared the seizure outcome in 40 patients with TLE randomly assigned to surgery, with that in 40 patients on treatment with antiepileptic drugs alone. At 1 year, the cumulative proportion of patients who were free of consciousness impairing seizures was 58% in the surgical group and 8% in the medical group; the difference was highly statistically significant ($p < 0.001$). This first randomised controlled trial conclusively established that, in refractory TLE patients, surgery is far superior to prolonged medical therapy.

In the initial series at SCTIMS,T[69] 107 patients (50.2%) were completely seizure free (including free of aura) and 166 patients (77.9%) had an Engel Class I outcome (no disabling post-operative seizures). Among the patients who had post-operative seizure recurrence, a majority had a reduction in seizure frequency. Only 6% exhibited a lack of improvement or a worsening in seizure frequency following surgery.[69] These results are similar to those reported from other major epilepsy surgery centres around the world.[7,20,64,81] It may be worth emphasising that during this period the SCTIMST protocol utilised a non-invasive pre-surgical evaluation protocol, to decide the indication for ATL and did not undertake intra-operative ECoG.

Paediatric populations coming to epilepsy surgery centres have shown similar seizure free rates as compared to the adult population. The seizure free range varied from 60 to 78% in different series and the spectrum of population. Various epilepsy centres are reporting cases with dual pathology; for instance, children with MTS and other pathology like cortical dysplasia of the temporal lobe. Surgical results in this group of patients are similar to adults with typical TLE, provided there is complete resection of the mesial temporal structures and the second pathology.

Surgical Failures

Reasons for surgical failures are not completely understood and include bitemporal, pseudo temporal, extratemporal and so-called temporal plus epilepsies, as well as insufficient resection of the mesial temporal structures.[30] It is now a well-established fact that a prolonged longitudinal follow-up is essential for accurate assessment of seizure outcome, since initially seizure free patients may relapse and some patients with early post-operative seizures may become seizure-free subsequently (running-down phenomenon).[75] In the majority of patients who exhibit seizures following ATL, seizures recur within the 1st year after surgery, often as early as in the first few weeks and months after surgery.[29,44,104] Incidence of seizure recurrence increases progressively with the length of follow-up; however, being seizure-free for 1 year after surgery is an excellent predictor of continued seizure-free outcome.[64] There are several reasons for failure of surgery.[29,30] A new area of epileptogenesis may develop at the resection edge or at another site such as the opposite medial temporal area. An error in localising the epileptogenic area during the pre-operative evaluation will result in the persistence of the focus. However, the most important reason for surgical failure is insufficient excision of the epileptogenic zone. In patients with ATL, retained mesial structures or diffuse epileptogenicity in the residual temporal lobe has been recognised as the reason for surgical failure.[30,54]

In 20 patients in whom the first surgery failed due to inadequate resection of the hippocampal formation, Olivier et al. performed a second surgery and removed the residual mesial temporal structures.[54] After the second surgery, 30% of the patients became seizure-free, 15% had a marked seizure reduction, 35% appreciated worthwhile improvement and 20% failed to achieve any significant seizure reduction.[54] Wieser and Yasargil reoperated on patients who had an initial amygdalohippocampectomy.[101] Using a standard ATL, they achieved a 50% seizure-free outcome. Sub-optimal post-operative seizure control following SAH has been found in patients in whom there is evidence of significant bitemporal or extratemporal seizure onset; patients requiring depth electrode investigation to clarify seizure lateralisation or localisation; bilaterally normal hippocampal volumes on MR imaging; pseudo temporal epilepsy and patients in whom the resection of mesial structures has been inadequate.[1] Wyler[106] reported a prospective randomised study of patients undergoing surgery for MTLE, the ictal onset being verified in each case by subdural recordings. The anteromesial temporal resection (AMTR) was compared to a more limited medial resection in this group. Complete seizure control was seen in 69% of the AMTR patients and in only 38% of the patients with a partial hippocampectomy.[106] QOL improves early after epilepsy surgery; the improvements are both statistically and clinically significant. Surgical morbidity with clinically significant permanent sequelae is 2%. In addition, successful TLE surgery appears likely to reduce the risk of seizure-related death. However, surgery remains largely under-used and overly delayed, partly because of the fear of possible surgical complications, such as verbal memory deficits and failure to control seizures.

Determinants of Post-Operative Seizure Outcome

The attributes of ideal surgical candidates for ATL with amygdalohippocampectomy are listed in Table 3. Nearly 90% of patients with unequivocal unilateral MTLE (TLE associated with MTS) achieve excellent seizure outcome, following this procedure.[15,20,40,64,69,103] By using the Seizure Frequency Scoring System, it has been demonstrated that seizure outcome remains stable after

Table 3: Ideal candidates for anterior temporal lobectomy or selective amygdalohippocampectomy

Prolonged febrile seizures during childhood
Normal neurological examination and IQ
Stereotyped semiology of the complex partial seizures
Unilateral temporal spikes in scalp EEG
MRI showing hippocampal atrophy/sclerosis
Site of seizure origin same as scalp EEG and MRI abnormalities

EEG—electroencephalogram; IQ—intelligence quotient; MRI—magnetic resonance imaging

ATL.[83] The pre-operative and post-operative predictors of seizure outcome following TLE surgery are cited in Table 4. While an MRI or histopathologically verified lesion is a strong predictor of a favourable seizure outcome, a normal MRI and absence of pathology in the resected specimen are often associated with post-operative seizure recurrence.[20,64] The seizure remission is better in those patients with a complete lesion removal, when compared to those with post-operative residual lesions.[40] A number of factors predictive for good seizure control have been reported as follows: (1) clear abnormality on MR imaging; (2) absence of status epilepticus; (3) MR imaging confirmed ganglioglioma or DNT; (4) concordant lateralising memory deficit and (5) absence of dysplasia on MR imaging.[1,13,76] A syndrome of paradoxical or pseudo-TLE (PTLE) has been described, in which the seizures may be the manifestation of a complex epileptic system composed of extrahippocampal components, secondarily involving the hippocampus. This PTLE substrate does not respond as favourably to anteromedial temporal lobe resection, because the epileptogenic pathology may have been left behind.[14]

Table 4: Predictors of seizure outcome following temporal lobe epilepsy surgery

Favourable outcome
Pre-surgical factors
• MRI detected lesion
• EEG abnormalities concordant with the lesion
Post-surgical factors
• Demonstrable pathology in the surgical specimen
• Complete seizure freedom during 1st year
Unfavourable outcome
Pre-surgical factors
• Normal MRI
• Bilateral temporal EEG abnormalities
Post-surgical factors
• Absence of a detectable pathology
• Recurrence of disabling seizures during the 1st year

EEG—electroencephalogram; MRI—magnetic resonance imaging

Quality of Life Outcome

Health-related QOL describes an overall state of health that includes domains of physical, social, psychological, vocational and economic well being.[86,97] QOL scores improve after temporal lobectomy. Post-operative neuropsychological testing revealed better memory function after AH and lesionectomy compared with standard ATL.[13,32] Patients who are completely seizure free (including aura free) after surgery usually achieve an excellent QOL.[76] Work outcome was favourably influenced by pre-surgical work experience, successful post-surgical seizure control and ability to obtain further vocational skills after surgery.[72]

Economics

The mean direct recurring cost of a patient with refractory TLE continued on medical treatment at a governmental medical organisation was reported to be Rs. 6,000 per year.[69] Even with new anti-epileptic drugs, complete freedom from seizures for 1 year is not more than 10% for patients with refractory TLE.[98] A major part of the recurring direct costs of epilepsy is the cost of anti-epileptic drugs. The out-of-pocket payment for pre-surgical evaluation and TLE surgery at most of the governmental medical facilities would be about Rs. 50,000, but is likely to be double this amount in a non-governmental medical organisation. Although this amount is substantial, there is a 70% chance that the patient will be seizure-free after ATL with amygdalohippocampectomy and a 30% chance that the patient will be completely off the antiepileptic drugs within 2 years after surgery.[69] A seizure-free person could be better employed, has less psychosocial problems and more often achieves an improved QOL[72,76] Therefore surgical treatment of medically refractory TLE is a better cost-effective option than continued medical treatment.

CONCLUSION

The last two decades have witnessed remarkable advances in the evaluation and treatment of patients with refractory TLE. The improvement in the localisation of the epileptogenic zone through the advances in technology, such as digital EEG, structural and functional neuroimaging and stereotactic placement of invasive electrodes, have facilitated the selection of ideal surgical candidates and, thereby, have improved post-operative outcome. Today, surgical treatment is certainly a cost-effective option in carefully selected patients with medically refractory TLE. Developing countries should concentrate on selectively utilising the recent advances to evolve cost-effective epilepsy surgery programmes, by selecting ideal surgical candidates by utilising locally available technology and expertise, without compromising patient safety. Surgical treatment could play a major role in reducing the population of people disabled by epilepsy in the developing world.

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SECTION

17

Cerebral Palsy

AK Purohit

203 Stereotaxy for Cerebral Palsy

Kanaka TS, Balasubramaniam V, Sampathkumar M

Cerebral palsy is a complex neurological syndrome involving intellectual, locomotor and postural functions. When intellectual retardation is prominent, the only method of treatment available is education at special institutions, but when the intellect is preserved and the motor aspects of the disease, like hypertonus and involuntary movements predominate, stereotaxic surgery may be helpful in relieving these features. Encouraging results with such surgery have been reported by Balasubramaniam et al.,[5,6,7] Heimburger,[24,26] Kanaka,[32,35] Krayenbuhl and Siegfried,[41] Laitinen,[42,43] Narabayashi et al.,[46,48,52] Siegfried[65] and Zervas.[74,75]

HISTORICAL ASPECTS

Ever since the description of cerebral palsy by Little in 1861, the management of this disease complex has been mainly along orthopaedic lines. However, sporadic attempts at neurosurgical treatment have been made from time to time.

Horsley[29] excised the precentral cortex, Walker[71] advocated pedunculotomy and Putnam[57] anterolateral cordotomy, in order to combat involuntary movements. These operations were done by these pioneers amidst their busy neurosurgical schedule and there was no concentrated or multidisciplinary approach towards the total problem of cerebral palsy. Narabayashi[47] was the first to approach this problem systematically.

DEFINITION

MacKeith and Polani[44] defined cerebral palsy as 'a persisting qualitative motor disorder appearing before the age of 3 years due to a non-progressive damage of the brain'. In 1964, the Little Club (a society devoted to the study of Little's Disease, in London) modified the definition as 'a permanent but not unchanging disorder of movement and posture due to a non-progressive defect or lesion in the brain in early life'. This definition does not impose an age limit. Moreover, the term 'disorder of movement and posture' is preferable to 'motor disorder'.

The World Commission[45] on cerebral palsy of the International Society for Rehabilitation of the Disabled approved of the following definition in 1969: Cerebral palsy is a persistent, but not unchanging disorder of posture and movement due to dysfunction of the brain (excluding dysfunction due to progressive disease) present before the growth and development of the brain are complete. Many other clinical features may also be present.

AETIOLOGY

The disease complex known as cerebral palsy is due to many aetiological factors the most common being trauma during birth. The birth trauma may occur due to excessive moulding of the head during delivery, resulting in multiple haemorrhages due to venous obstruction and brain distortion. Hypoxic damage can also result from placenta praevia, delayed second stage of labour, cord round the neck, neonatal aspiration or neonatal convulsions. However, cerebral palsy has often been noted in children whose delivery was uncomplicated and non-cyanotic. Towbin[70] provided evidence that in such cases the hypoxic damage occurs prior to labour and the lesion is localised in the depth of the cerebrum. Soon after birth, kernicterus can give rise to damage to the basal ganglia and result in dystonia and hypertonus. Kernicterus may also result from Rh incompatibility.

In the first few years of infancy and childhood, many diseases can damage the brain, the most common being encephalitis or 'hypertoxic state' as it is called now. The child suffers from a sudden rise of temperature and perhaps exhibits generalised seizures for 1 or 2 days. This may be followed by neurological deficits, like spasticity and mental retardation with behaviour problems. In most of these cases, special virological studies prove inconclusive.

In another group of cases, the patient develops high temperature with focal seizures. On recovery there is usually hemiplegia. In those cases, it is quite likely that the major insult is to the arteries (a form of obliterative arteritis) or to the veins (as thrombophlebitis). In some cases, a global damage also results. Investigations like angiography done months or years later are not helpful in revealing the aetiology, except in a few cases. Head injury during the first few years of life may also lead to cerebral palsy.

CLINICAL FEATURES

This condition is essentially a non-progressive one but, in an occasional case, it may be apparently progressive when a hypotonic patient becomes hypertonic or when a

hypertonic patient develops contractures or disuse atrophy of muscles due to lack of physiotherapy.

The clinical features of cerebral palsy could be classified into those due to:

1. Disorders of tone
2. Disorders of movement.

These are often in addition to varying degrees of other deficits like speech disorders, disorders of vision, cranial nerve palsies and disorders of hearing.[66] Associated seizures, mental retardation or frank behavioural abnormality may be seen in some cases. Arrest of cerebral development, early in life, results in the persistence of primitive reflexes like Moro's reflex. The tonic neck reflexes may often be elicited.

Disorders of Tone

These are of two types, viz., a. hypotonic, b. hypertonic. The hypotonic variety is seen in the classical 'floppy infant'. There is generalised absence of tone in the axial as well as in the apendicular system. In some cases, the tone returns as the child grows and the child may have hypertonicity. All these children have mental retardation.

Hypertonic cases may have spasticity, rigidity or a combination of both. This may involve one or more limbs and, often, the neck and the trunk. During passive movement of the limb, uniform hypertonus indicates rigidity and a sudden reduction of the hypertonus on continuing passive movement points to spasticity. It is not always possible to decide the type of hypertonus by clinical examination alone; surface EMG is useful in differentiation. The degree of hypertonus may vary from time to time and different observers may differ in their assessment if the examination is done at different times.

Abnormal Movements

Involuntary movements may co-exist with hypertonus and/or mental retardation. The common varieties are choreoathetosis, athetosis, torsion dystonia and intention tremor.

Athetosis refers to slow writhing movements particularly affecting the distal portions of the limbs, involving alternately the agonists and antagonists. There is always an element of hypertonus in these movements. Choreic movement is characterised by frequent jerky, quasi purposive movements predominantly of the distal parts of the limbs. The term 'choreoathetosis' is applied when the movements cannot be classified as choreic or athetotic and when there is a combination of both elements. Ballistic movements are more rapid, forceful, projectile and involve mainly the proximal parts of the limbs, rotating the limb in a wide arc. Intention tremors may also be seen in some patients.

Some children exhibit involuntary movements that are made worse by sensory stimuli like touch, noise, light or questioning. The movements may also be induced on attempts at voluntary acts. Left alone, the child is quiet and relaxed, but when the examiner asks the child to do something like putting out the tongue, the entire body goes into a severe dystonic posture.

Dystonia implies an abnormal fixity of posture due to sustained muscular contraction. When the posture continues to change, the abnormal fixity involves fresh sets of muscles, resulting in dystonic movements.

TREATMENT

Stereotaxic surgery does not replace physiotherapy. Physiotherapy, occupational therapy, education of the child and speech therapy (wherever needed) are ancillary treatments carried out pre-operatively and post-operatively.

Surgery for cerebral palsy was, earlier, confined to orthopaedic operations on muscles, tendons and selected neurectomies of peripheral nerves. Division of selected nerve roots may help in relieving localised severe muscular hypertonus.[27,56] However, all these operations give only partial relief and do not alter the central mechanisms responsible for the hypertonus.

Criteria for Selection of Cases for Stereotaxic Surgery

Patients with hypertonus and/or involuntary movements may be considered for stereotaxic surgery straight away if they are not grossly mentally retarded. For mild hypertonus, physiotherapy and orthopaedic corrective procedures may suffice. If after such a course of treatment, the hypertonus still interferes with function, stereotaxic surgery is considered. Patients with severe mental retardation, incontinence of urine and faeces, pseudobulbar signs or fixed contractures are not suitable for surgery. Patients with severe hypertonus and gross mental retardation are at times given the benefit of stereotaxic surgery mainly to ease the nursing care.

Pre-operative Assessment

In the pre-operative motor assessment, the Johnson's motor-age test and the severity index suggested by Beals[8] are of value to provide the base line to judge the degree of improvement during treatment.

Electromyographic Studies

To choose appropriate targets for making the surgical lesion it is necessary to have an accurate idea of the degree and variety of hypertonus. This information is objectively provided by surface EMG. As mentioned above, hypertonus can be of the following types: rigidity, rigidospasticity, spasticity[64] and spastorigidity.[37] Although clinically it may be easy to distinguish extremes of hypertonicity like spasticity or rigidity, surface electromyography is necessary for recognition of rigidospastic states and to have an objective assessment of the other types. EMG studies are also useful to determine the amount of hypertonicity present in cases with involuntary movements

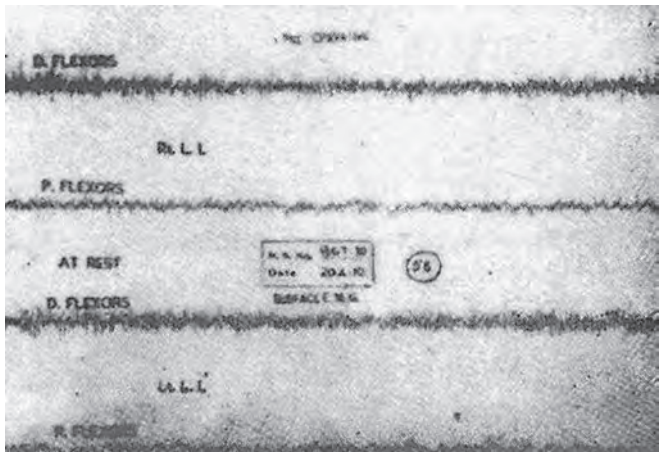

Fig. 1: Surface EMG (pre-operative) showing the continuous discharges from the muscles even during rest

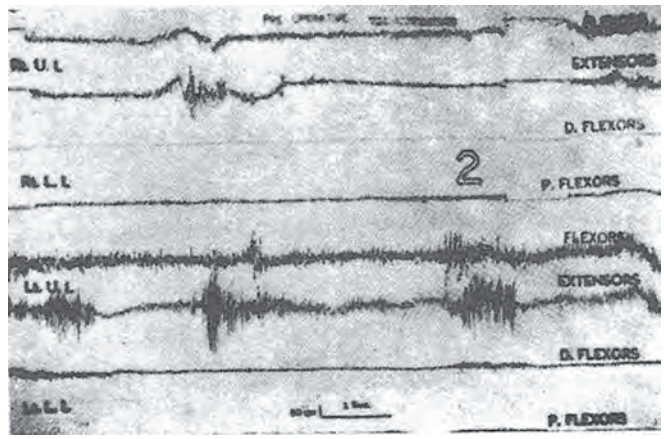

Fig. 3: Pre-operative surface EMG showing simultaneous contraction of flexors and extensors on active movement, indicating lack of reciprocation

Fig. 2: Surface EMG 1½ years after operation showing restoration of normality in the EMG

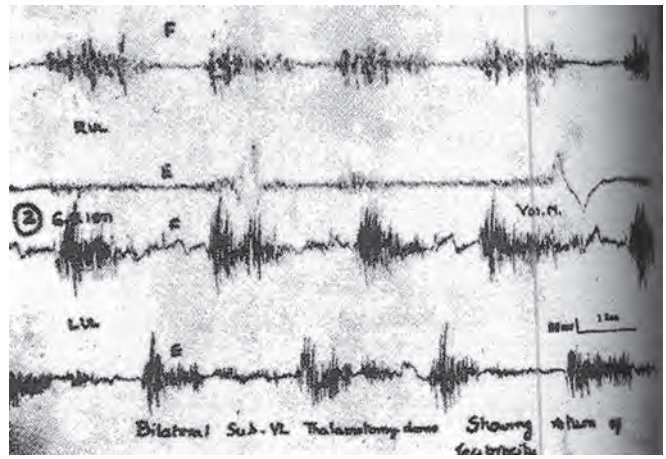

Fig. 4: Surface EMG after bilateral sub-VL thalamotomy, showing return of reciprocity

and to have comparable quantitative graphic records of the hypertonus before and after the operation (Figs 1 to 4).

Psychometric Assessment

The result of treatment of cerebral palsy depends to a large extent on the co-operation of the patient and, hence, the child should be sufficiently intelligent to follow the instructions during physiotherapy and occupational therapy. Psychometric assessment helps in decisions regarding surgery and prognosis.

The difficulties and limitation of intelligence tests in these children have been highlighted by many workers.[9,12,20,23,62,72] A definite relationship has been found between motor handicap and intelligence.[14,21,30] Tests advocated by Holt and Reynell,[28] which vary for different age-groups and degree of motor disability are more useful as they give a picture of the mental age of the patient, rather than relying totally on the psychologists' reports, based on tests meant for normal children. A much better assessment of these children can be obtained by taking into consideration the basic intelligence capacity for learning ability and willingness to co-operate with the physiotherapist, home environment and the severity of the physical handicap. This has been borne out well by the experience of the Madras Group in a large series of such patients.[36]

Timing of the Operation

Some workers prefer to postpone surgery till the child is 5 or 6 years old, treating the child in the meantime with intensive physiotherapy, but, generally, once neurosurgical treatment is considered useful, it is better to do it as early as possible even in children less than 5 years old.[36]

Early relief from hypertonicity and dyskinesias is conducive to better physiological growth of the limbs and an earlier commencement of the overall training programme of the child. Further, as many of these children may require multiple-staged operations, much time is lost if the surgical treatment is started late. The timing of surgery

is also guided by the intensity of the disability. In severe cases, stereotaxic surgery has to precede other measures.

In patients who need bilateral surgery on the thalamus, it is desirable to have an interval of at least 6 months between the two operations. This time-interval is not essential when a cerebellar lesion is to be combined with a thalamic lesion.

Pathophysiology and Choice of the Target

The disturbance of neural mechanisms in the brain of a patient with cerebral palsy is widespread and varies in each individual patient, although the resulting overall picture is one of movement and postural disturbance mixed with mental retardation. Such disturbances in the central mechanisms interfere with finely co-ordinated influences that act on the spinal motor neuron, upsetting its balanced precision, but the exact mechanisms are still controversial. Hypertonus has been ascribed by some to gamma motor neuron hyperactivity[59,60,64] and by others to hypoactivity.[22,67] The hypertonus may also be explained by central activation of the large motor neurons, through the alpha route and by gamma activation independent of muscle stretch.[3] We hypothesise that imbalance between the dynamic and static activity is responsible for various types of hypertonus seen in cerebral palsy. The choice of the target depends on the type of hypertonus of the muscle and the presence and nature of involuntary movements.

Rigidity

Rigidity is relieved by a lesion in the ventrolateral (VL) nucleus of the thalamus (Voa and Vop of Hassler). The extent and location of the lesion varies with different workers. Cooper[15] placed the lesion more posteriorly in the Vop nucleus of Hassler. Narabayashi[48,50,51] selected the VL and the area immediately below the VL nucleus abutting on the zona incerta (sub-VL thalamotomy) as, according to him, all the necessary fibres are included in a lesion at this site. We place the lesions in both the Voa and Vop and the sub VL areas and VIM.

Rigidospasticity and Spasticity

In cases with rigidospasticity and spasticity, thalamotomy alone fails to help, neither does pallidotomy influence significantly the cases with a spastic pattern.[64] In such cases, the addition of a lesion in the dentate nucleus of the cerebellum gives adequate relief. Following the work of Schneider and Crosby[61] and Heimburger,[26] we tried dentatectomy and found it useful in cases with spasticity. Nashold et al,[54] Zervas,[74,75] Krayenbuhl and Siegfried,[41] Siegfried[65] and Kanaka[35] have published favourable results with dentate lesions.

The cerebellum, as the only structure that receives the afferent influx from the annulospiral endings of the muscle spindle and from Golgi tendon organs, is of great importance in both the static and dynamic phases of muscle activity. This is seen clinically by the relief of rigidity, as well as spasticity after dentatectomy. It is of historical interest that the first successful open dentatectomy was performed for Parkinsonism by Delmas-Marsalet and Von Bogaert in 1935[19] and in 1958 by Toth.[69]

Sensory-induced Dystonia

In cases where the dystonic movements are aggravated by sensory stimuli (like a noise, flash of light or a question), a lesion in the centrum medianum (CM) nucleus in addition to the one in the VL-sub-VL area gives relief. The suggestion that the CM nucleus of the thalamus may have a critical role in movement disorders was first made by Schulman.[63] Many fibre systems converge on the CM nucleus. It receives collaterals from all sensory pathways indirectly through the connections with the reticular formation. Some fibres of the spinothalamic tract also terminate in this nucleus. Its efferents pass to the caudate and putamen, through which it probably influences the motor cortex.

Although still poorly understood, the physiologic role of the CM nucleus appears to be the integration and modulation of heterogeneous sensory and cerebellar impulses. The aggravation of the dystonia by sensory input is due to a lowering of the 'threshold for transmission from sensory to motor system'.[51] A lesion in the CM nucleus interrupts various converging fibre systems and destroys the cells of origin of the efferent neurons to the putamen, both of which may be critical in the genesis of movement disorders.[1]

In the patient with sensory-induced dystonia, it is felt that there may be an abnormality, either in the threshold or in efferent motor reaction mediated at the thalamic level to any sensory stimulus. This results in an abnormal motor response (non-purposive and uncoordinated) to a sensory stimulus. Although much of this hypothesis is still to be verified, there is no doubt about the relief obtained from CM lesions in cases of cerebral palsy with sensory-induced dystonia.[33-35,58]

Dyskinesias

In cases with various dyskinesias, a lesion in the VIM (Ventralis intermedius externus of Hassler) nucleus is helpful when combined with VL and CM lesions. These lesions were termed as "comma" lesion by Cooper.[15] On the contrary, Narabayashi[53] makes a pure VIM lesion to treat cases with involuntary movements (Figs 5 and 6).

The VIM nucleus is recognised as a distinct entity only by some workers. The nucleus receives fibres from and the impulses project to area 3-a. Hassler[22] suggested that the nucleus receives vestibular afferents. The exact function of this nucleus is not known. That it is a part of the tremerogenic zone is certain, as tremors are facilitated or produced on stimulation of this area. VIM externus lesions have been found to be of value in normotonic tremors.[34]

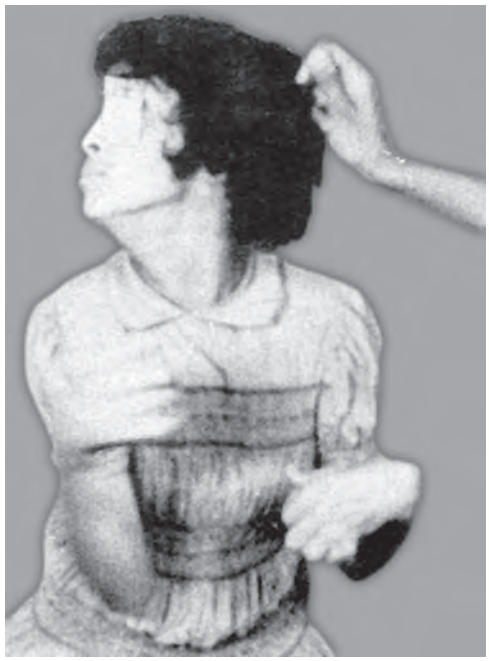

Fig. 5

Fig. 6

Figs 5 and 6: Pre-operative and post-operative pictures showing marked improvement in the upper limbs and the neck in a patient with severe dystonia after VL, CM and VIM lesions

Infantile Hemiplegia with Athetosis

Among the conditions, which prove recalcitrant to treatment, infantile hemiplegia with athetosis is one. In the hands of most workers, neither thalamotomy nor dentatectomy alone has given consistently good results. A combination of dentate and VIM lesions, 'dentatothalamotomy' has been found to give satisfactory results.[6,38] This suggests the existence of a servo-mechanism for correcting the position of the limbs in the dentate–VIM connections. Spinocerebellar fibres and afferents from the cerebellum probably play a role in this mechanism. Cooper et al.[15] have done pulvinotomy in such cases. Our immediate results with pulvinar lesions in selected cases are encouraging[37] (Figs 7 and 8).

To summarise: for rigidity the best results are obtained with VL and sub-VL lesions. Rigidospastic patients need thalamotomy and/or dentatectomy, depending on whether rigidity or spasticity predominates. Spasticity is relieved by dentatectomy. Sensory induced involuntary movements need CM thalamotomy for their relief. Normotonic involuntary movements are relieved by VIM lesions. Infantile hemiplegics with spasticity and

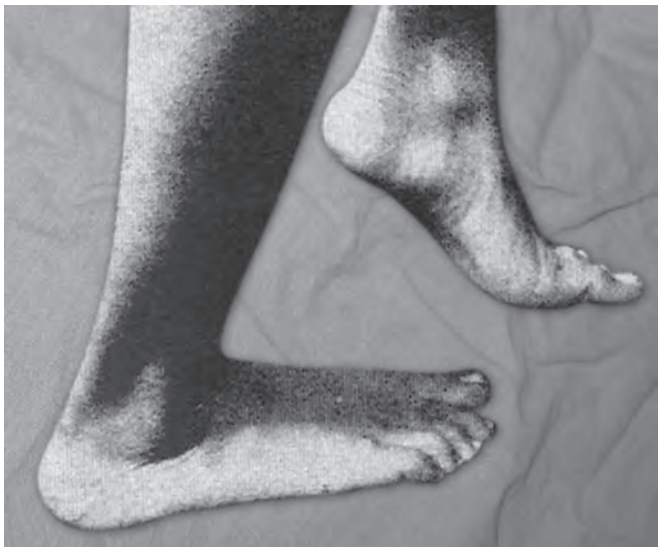

Fig. 7

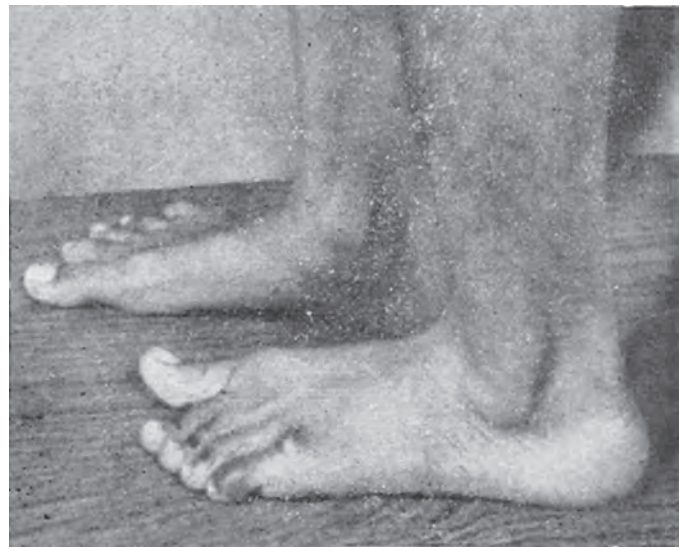

Fig. 8

Figs 7 and 8: Pre-operative and post-operative pictures, showing improvement in the posture of the left foot, in a patient with infantile hemiplegia (after pulvinotomy)

Fig. 9

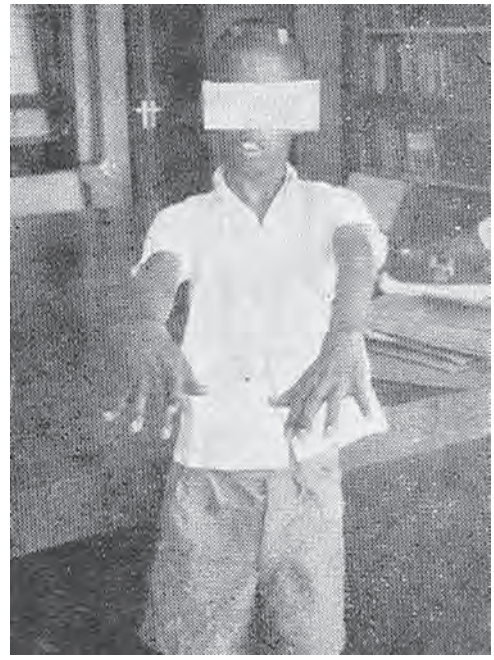

Fig. 10

Figs 9 and 10: Pre-operative and post-operative pictures showing marked improvement in both the upper limbs, in a patient with normotonic tremors (bilateral relief following Lt VIM lesion)

athetosis do very well with a combination of ipsilateral dentatectomy and contralateral VIM thalamotomy.

Ipsilateral Relief

About 35% of the cases show ipsilateral relief in addition to the expected results on the contralateral side.[36] This is probably due to the involvement of the uncrossed ascending fibres of the brachium conjunctivum in the lesion (Figs 9 to 12).

Location of the Target during Surgery

Since most of these operations are performed under general anaesthesia, the exact localisation of the target during surgery becomes important and at the same time

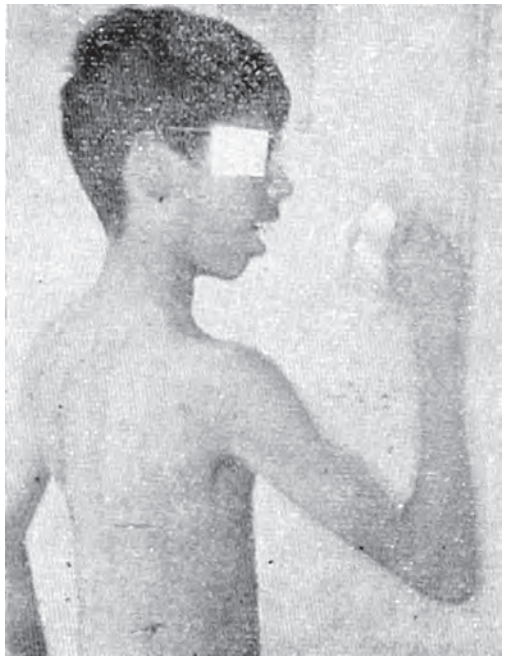

Fig. 11

Fig. 12

Figs 11 and 12: Pre-operative and post-operative pictures showing improvement in the right upper limb in the same patient

more difficult. Depth EEG may be useful in differentiating the thalamus from the white matter but it is not so informative in the recognition of individual nuclear groups. Some workers have tried to identify particular patterns of activity within specific nuclear groups.[2] However, this has not been sufficiently worked out in detail to be reliable during human surgery.

Recording of the evoked potentials from the cortex or from the concerned nucleus is a useful method. Yoshida et al.[73] used it to determine the site and size of the VL nucleus. The CM nucleus can be identified by evoked potentials on stimulation of a peripheral nerve like the ulnar nerve.[49] Balasubramaniam has suggested the "capsular delineation" method. Taking advantage of the fact that the VIM nucleus forms the medial border of the internal capsule, the position of the corticospinal tract is first determined by stimulation and noting the motor response; then the electrode is moved medially in steps of 2 mm at a time, until there is no motor response. Such a technique becomes easier with flexible electrodes that can be made to reach the desired area by necessary manipulation after the initial insertion of the probe. This method has been found useful and free from adverse effects, as most of the cases need stimulation at only two or three sites to determine the target. It is particularly useful in cases of infantile hemiplegia where there is a marked shift of the third ventricle to the atrophic side.

For localising the dentate nucleus, Heimburger[25] and the Madras group rely on calculations only. Nashold et al.[54] and Slaughter et al.[68] rely on depth electrographic analysis and stimulation responses. The calculations are made with reference to the roof of the fourth ventricle. The lesion is made 9, 13 and 17 mm from the midline.

Method of Making the Lesion

The method of making the lesion does not seem to matter as long as the lesion is big enough and is permanent. Both diathermy and oil wax lesions have given good results.

Post-operative Assessment

Post-operative assessment of cerebral palsy is limited by the fact that methods of quantification of disability are not standardised. It is better to evaluate results by comparing them with pre-operative function and in so far as is possible to determine if the improvement obtained justified the surgery having been done.[4]

Since the main purpose of surgery is to improve function of the limbs, a functional assessment would be of greater value than any other method. In this respect, the motor age test of Johnson et al.[31] has been found useful. The child is asked to perform small tasks and scores are given. The test is useful both for hypertonus as well as for involuntary movements.

A proforma has been devised taking into consideration the assessment of various specialists like the neurologist, orthopaedic surgeon and physiotherapist. Numerical estimation of improvement given by them, the patient and the parents and the objective assessment by surface EMG and motor-age determination are added together and the percentage of relief calculated.

Pre-operative and post-operative states of the patients are illustrated in the Figures 5 to 12.

To conclude, stereotaxic surgery for cerebral palsy is only one aspect of the overall management of the disabled children. Physiotherapy, education and some minimal orthopaedic procedures continue to be essential. In this context, it may be pointed out that physiotherapy in cerebral palsy is not rehabilitation, unlike in Parkinsonism where treatment results in relearning of an old skill. In cerebral palsy, new skills have to be achieved. The aim of stereotaxic surgery is only to reduce the tone and to abolish involuntary movements and, thereby, cut short the period of training and rehabilitation.

Later Additions to the Management of Cerebral Palsy

Electrical stimulation has been used for medical purposes since many centuries, but electrical stimulation of the brain gained importance in 1953 when Prof Wendel Kreig suggested the term "Neuro-prosthesis" for a device which can be implanted in the brain of a blind/deaf/motor paralysed person. His idea was implemented by Brindly and Lewin[11] who reported about the implantation of visual prosthesis in a blind nurse's visual receptor cortex. Cooper et al.[16,17] reported on the efficacy and safety of chronic stimulation of the cerebellum. Further, Delgado[18] reported that electrical stimulation of the brain by implanted electrodes can inhibit speech, movement and varieties of behaviour responses.

Chronic electrical stimulation of the brain was not used extensively as the equipment required was expensive. It has gained importance on account of its efficacy and safety.[10,13,55]

Our Experience

The electrodes consisted of platinum set in silicon. One of them was placed on the superior surface of the cerebellum, after performing an occipital craniectomy and the distal end of the electrode tunnelled to the infraclavicular region. The receiver is implanted subcutaneously in the infraclavicular region. The ends of the receiver and electrodes are coupled. Stimulation is carried out transcutaneously, using external antenna and an external stimulator (Figs 13 to 16).

At present many commercial totally implantable sets are available at huge cost. However, it was tried in an improvised way at the Institute of Neurology, Madras[39,40] (Figs 17 and 18).

Simple copper electrodes were used. Nine electrodes were introduced stereotactically into the dentate nucleus of the cerebellum. The distal ends of the electrodes are exteriorised and stimulated using Grass stimulator. The

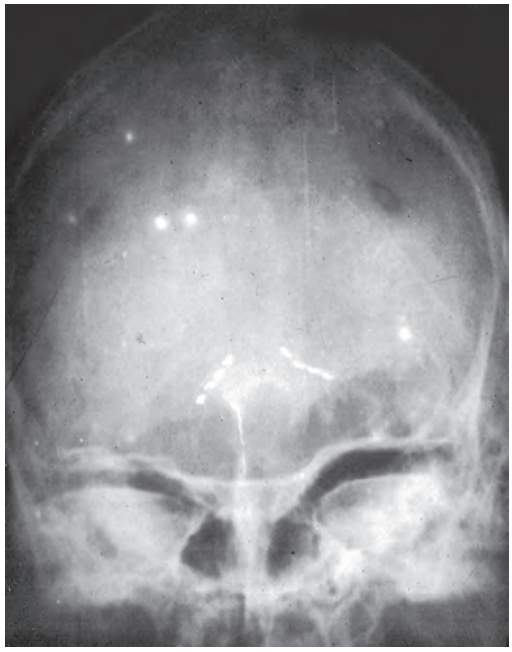

Fig. 13

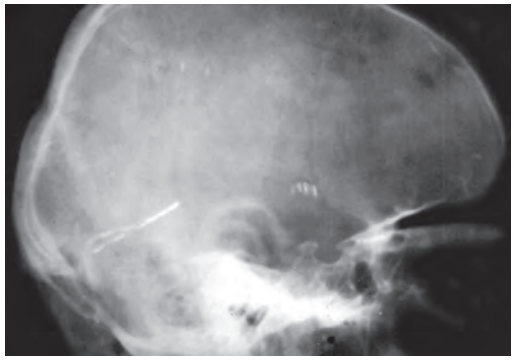

Fig. 14

Figs 13 and 14: X-rays shows the platinum electrodes placed on the superior surface of cerebellum

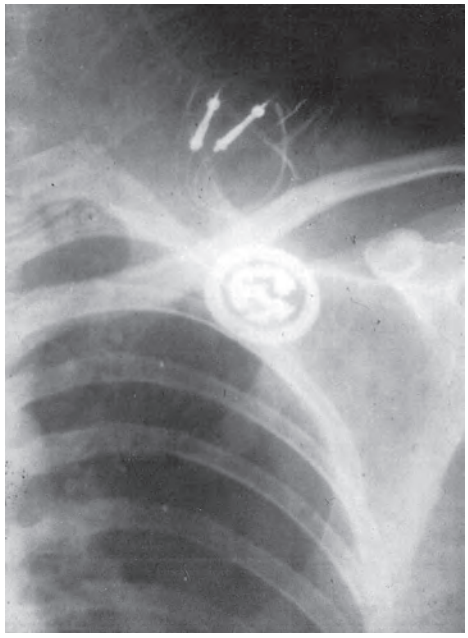

Fig. 15: This picture shows the receiver in the subcutaneous plane

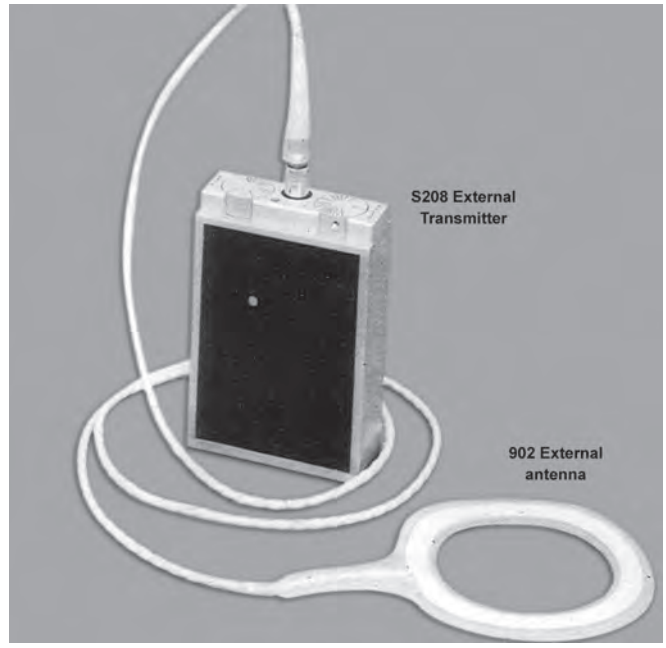

Fig. 16: Shows the external stimulating kit

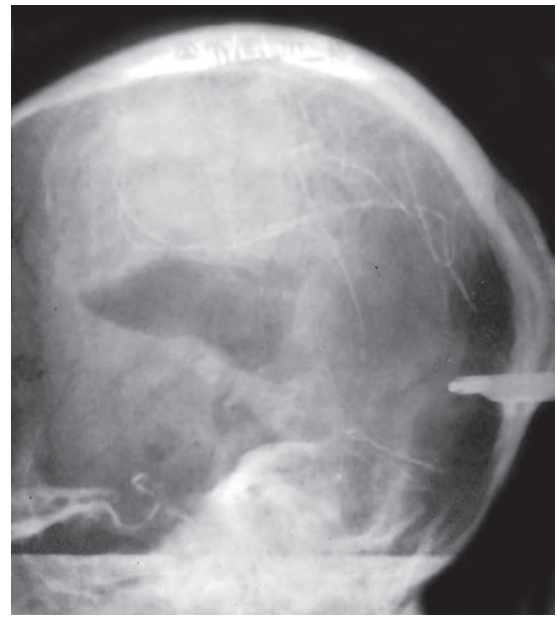

Fig. 17: X-ray showing the electrodes in the dentate nuclei

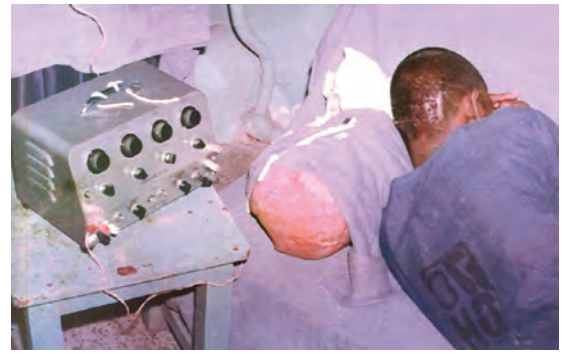

Fig. 18: Stimulation is carried out by connecting the exteriorised distal end of the electrode to the Grass stimulator

frequency, amplitude and current used are modified depending on the patient's response to stimulation and stimulation is done for 6–8 hours a day, and at the end of 3 months a kindling effect is produced. When the interstimulation period shows beneficial effects, stimulation can be stopped.

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INTRODUCTION

The motor pathways in the CNS may get affected directly or indirectly by various aetiological factors that may result in development of spasticity. However, these people may also have other associated motor and non-motor neurological and musculoskeletal impairments that can make the clinical picture highly complicated. This kind of picture is present, often, in cerebral palsy.

The task to relieve spasticity alone is not difficult. However, the task becomes difficult when neurological functions also have to be developed. This is the reason that there are many methods to deal with this problem, more so because ideal methods are not available for clinical use. Therefore, the team members are expected to have experience in all the available methods, so that they do not get favourably restricted and prejudiced to the only method they know of.

The selection of methods based purely on medical grounds has to be from least invasive (physical methods) through less invasive (chemicals–botulinum toxin, baclofen pump) to more invasive (ablative–rhizotomy, neurotomy) procedures. However, in practice, it is not easy to choose the methods like this. Say, physical methods that take a lot of time may not be feasible with the families having time constraint¸ whereas, the use of chemicals may not be possible where there are financial constraints (most families in the world). Therefore, the experience of the team with various methods is mandatory and, then, discussion with the family would lead to the most suitable method for that family. However, the team has to keep in mind, while deciding on the plan, that these methods are complimentary to each other and physical methods play an important role in improving neurological functional outcome.

This chapter would deal with various neuro-interventional methods to produce useful tone in people having spasticity. However, keeping in mind the patient as a whole, non-surgical and surgical management protocols will also be suggested.

MECHANISM OF GENERATION OF SPASTICITY AND BASIS OF ACTION OF VARIOUS PROCEDURES[10]

The exact mechanism of generation of spasticity and difference in spasticity generated due to brain and spinal cord pathologies is still not known.

The following are the two levels of control of muscle tone.

Suprasegmental Control

The reticular system of the brainstem plays a central role in the maintenance of normal tone. It consists of both an excitatory and an inhibitory centre. The excitatory centre is located in a diffuse area extending from the basal diencephalon, central gray and tegmentum of the midbrain and the pons and the lateral bulbar reticular formation outside the inhibitory field. The spinal projections of this system involve the ventral half of the cord and descend as the medial reticulospinal tract. This centre is supposed to be autonomous and is not under any cortical control.

The inhibitory centre is located in the caudal brainstem and is under the control of the motor cortex and to a lesser extent is also influenced by the cerebellar cortex and fastigial nucleus. The spinal projections of this system involve the dorsal half of the lateral funiculus and are conducted by the dorsal reticulospinal tract.

Normal tone consists of a balance between inhibitory effects on stretch reflexes, mediated by the dorsal reticulospinal tract and facilitatory effects on extensor tone, mediated by the medial reticulospinal tract and, to a lesser extent, by the vestibulospinal tract.

In cortical and capsular lesions, some of the drive on the inhibitory centre in the caudal brainstem is lost, resulting in spasticity. In partial spinal lesions like demyelinating disorders, there is involvement of both the pyramidal tracts and dorsal reticulospinal tracts, giving rise to severe spasticity due to the unopposed action of the medial reticulospinal and vestibulospinal tracts. In severe or complete cord lesions, there is loss of all supraspinal influences on the cord. During the period of spinal shock, the muscles remain flaccid, toneless and areflexic. After this period, there will be gradual development of hypertonia and hyper-reflexia due to the plasticity within the spinal cord, namely receptor hypersensitivity and sprouting of the axon terminals. This hypertonicity is different from the velocity dependent spasticity seen in partial cord lesions that results in virtually continuous flexor spasms.

Segmental Control

All these tracts normally inhibit the spinal myotatic monosynaptic circuit, through their influence on gamma

motor neurons that are found amongst various anterior horn cells. The gamma motor neurons, by nature, continuously discharge impulses (autogenicity) that travel through the anterior roots and peripheral nerves to reach muscle spindles located parallel to striated muscle fibres (extrafusal muscle fibres). The spindles by nature can sense the length of the muscle fibres and send the message via fibres that are located in the peripheral nerves and posterior roots. The message reaches alpha motor neurons that are found in the anterior horn cells. They in turn send the message via anterior roots to the extrafusal muscle fibres. The circuit is facilitatory in nature.

The tone in the muscles is the product of a balance between suprasegmental and segmental control mechanisms. In people with spasticity, the suprasegmental control gets altered and this results in generation of spasticity, whereas, the segmental control remains intact. However, it becomes overactive because of loss of suprasegmental inhibition. Therefore, the ideal treatment of spasticity is regeneration or implantation of damaged neural tissue that constitutes suprasegmental control. This development is yet to take place. However, the neuro-stimulation procedures performed presently on the brain or spinal cord, indeed, act by restoring suprasegmental control to some extent.[14]

Short of the ideal treatment and the limitations of neuro-stimulation procedures, scientists have worked on the overactive spinal circuit. They have been successful in reducing the electrical impulse transmission in this circuit.

TREATMENT PROTOCOL

People having spasticity due to various non-progressive causes are examined in detail. A management plan is prepared to rehabilitate the person, taking all the adverse factors into consideration. The methods are applied in the sequence of least invasive to more invasive methods. The socioeconomic and geographical constraints are also considered while planning the management. Usually, the following protocol is considered for such cases:

Physical Methods

- Physiotherapy, occupational therapy—to improve control, balance, functions and muscle tone
- Orthotic device application
- Special education
- Psychological assessment and treatment
- Speech therapy
- Ophthalmologist's consultation
- Control of seizures and other neurological problems

Management of resistant spasticity: Resistant spasticity is managed by various methods that will be discussed now in this chapter.

Selection of Cases

One of the most important steps in the success of spasticity relieving surgery is correct selection of cases. It is important to remember that the people with spasticity can have many other neurological deficits and/or musculoskeletal complications that may influence the results. The assessment of true muscle power in the presence of spasticity is also difficult. The clinician must also keep in mind that, sometimes, the spasticity can be helpful in performing some of the motor activities. The best example of helpful spasticity is paraplegia in extension. Such factors make the selection of cases for neuro-intervention a difficult task. If proper selection is not done, the surgical exercise may prove futile or even harmful.

Therefore, it is mandatory for all the members of the team to participate in the complete and careful evaluation of a case, before deciding on the necessity for neuro-intervention. During clinical examination, the following features should be noted:[60,61]

I. Non-progression of neurological deficits
II. Harmful spasticity
    1. Disabling spasticity
    2. Complications of spasticity and disfigurement
    3. Discomfort, pain and high energy consumption
III. Resistant spasticity
IV. Safety and usefulness of the procedure
V. Goals

Detection of Non-progression of Neurological Deficits

Preferably, persons having spasticity caused by non-progressive disorders are selected. There are various non-progressive disorders like cerebral palsy and injury to the central nervous system (CNS). Also, there are some diseases such as infections, vascular insult, neoplasm and lathyrism that, after treatment, may leave a person with some non-progressive neurological deficits like spasticity. Careful clinical and investigative procedures are advised to detect and differentiate these from partially treated progressive disease or incurable degenerative, metabolic and hereditary diseases. Surgical procedures are mostly indicated only for non-progressive disorders. However, if the disorder is very slowly worsening and producing harmful spasticity, certain selected procedures can be considered.

Detection of Harmful Spasticity

1. *Disabling spasticity:* Mostly, motor performance of the person is adversely affected by the presence of spasticity. However, spasticity may act as a natural inbuilt calliper and help the person to perform certain motor activities. For example, a person with spastic paraplegia in extension may be able to maintain an upright standing posture. He may be able to walk with the help of the spasticity, in spite of poor control in the lower limbs. Similarly, spastic elbow flexion is helpful in performing most of the activities of daily living. In general, in the presence of disabling spasticity, persons are unable to attain or maintain various postures or have difficulty in performing certain voluntary movements. Inadequate control in the limbs and trunk may also adversely affect motor activities.

It is a professional challenge to the team to detect that out of the two factors, spasticity and control, which one is mainly responsible for poor motor activities. For example, clinical tests like squat to stand and stand to squat can reveal the true degree of control. People who are able to perform such tests several times, by repeatedly interrupting the movements, are considered to have good control, while those who are unable to even initiate the movement are said to have poor control. Tests of similar nature can be applied to detect control of the trunk and upper limbs.

2. *Development of complications of spasticity:* Long standing spasticity can produce musculoskeletal complications like organic shortening of muscles, dislocations, etc. They may adversely affect motor activities and, therefore, the results of neuro-intervention. Such complications can also affect the appearance of the affected part.
3. *Discomfort, pain and high energy consumption:* Severe spasticity can cause discomfort and pain. Persons may get tired easily due to high-energy consumption. These factors adversely affect motor functions and performance during physiotherapy. In such cases, relief can be obtained following neuro-interventional methods, by improving functions.

Detection of Resistant Spasticity

Initially, most of the people with spasticity are advised to undergo proper physiotherapy. If necessary, anti-spasticity pharmacotherapy is also added. The patient is evaluated and treated for any nociceptive stimuli in the body like a spastic bladder, urinary tract infection, urolithiasis, chronic constipation, fissure in ano, perianal infection and bedsores. Sometimes, serial plaster of Paris cast application, temporary neural blocks, ice application and botulinum toxin injections, can also be tried to relieve spasticity. If residual spasticity persists despite all these measures for a sufficient period of time (usually 6 months), a person is said to have resistant spasticity. These measures may, in fact, either reduce the number and extent of surgical interventions or improve the person with spasticity to such an extent that surgery is not required.

Detection of Probable Safety and Usefulness of the Procedure

Surgical exposure should be safe. Therefore, in the presence of kyphoscoliosis, spondylolisthesis and poor trunk control, a laminectomy for intraspinal procedures is contraindicated. Relief of spasticity is also contraindicated in the presence of severe ataxia, dystonia and athetosis, because these neurological deficits may become more apparent after reduction in tone. Non-motivated people with spasticity may not be trainable by physiotherapy and, therefore, motor function improvement may not be possible. The presence of major and/or multiple musculoskeletal complications hamper motor performance, despite optimisation of the spastic tone. In some cases, however, improvement in motor performance may not be possible, but surgery can help in relieving pain, discomfort and improving nursing care.

Detection and Discussion of Goals

The goals of neuro-interventional methods vary from person to person and depend on the various factors mentioned above. Therefore, the expected improvement, duration of treatment and the nature of the recommended surgical procedure should be discussed with each patient and the relatives in simple words. Facility for post-operative physiotherapy and other rehabilitative therapy should also be confirmed. The whole discussion is written down when the consent is obtained.

In short, neuro-intervention for optimisation of the spastic tone is indicated only in those people who have non-progressive, harmful, resistant spasticity. The team should ascertain the safety and usefulness of the procedure and clearly discuss the goals with the person with spasticity and his relatives.

Ideal case: A well-motivated person having non-progressive, harmful, resistant spasticity with good control in the affected part and who has no musculoskeletal complications is considered as an ideal candidate for optimisation of the spastic tone by neuro-intervention, especially by ablative methods.

Neuro-interventional Procedures

Ideal Method

The ideal method to treat non-progressive harmful spasticity is regeneration or transplantation of the damaged neural tissue, prior to development of irreversible histochemical and structural changes in the neural structures and the musculoskeletal system. Some success with this procedure in movement disorders has been published, but there are no reports on spastic disorders.[3,5]

Short of regeneration or transplantation, other surgical methods can be considered; ideally, this surgical method should produce a calculated, reversible reduction in spasticity. In other words, it should produce optimum tone that is beneficial to the person, with least possible invasion and without adversely affecting the normal and potentially normal functions of the nervous system. The procedure should be safe, not too time consuming or expensive, and technically easy to perform. It should not cause geographical or any other dependency. There are various procedures in practice (Table 1) but none of them satisfy all the above mentioned criteria. However, presently, they are of tremendous help to people with spasticity.

CLASSIFICATION

The neuro-interventional procedures are classified according to the site and the nature of the neuro-intervention (Table 1).

Table 1: Classification of neuro-interventional procedures for optimisation of spastic tone

	Site	*Non-ablative*	*Ablative*
I. *Segmental* (Spinal Circuit)			
A. PNS			
1. Extra-craniospinal	Myoneural junction Peripheral nerves	— Temp. neural block Peripheral nerve stimulation	Botulinum Toxin Perm. Neural block Fasciculotomy (Neurotomy)
2. Intra-spinal	Spinal root	—	Rhizotomy
B. CNS			
Intra-spinal	Spinal cord	Intrathecal baclofen	Drezotomy Myelotomy
II. Supra-segmental			
A. CNS			
1. Intraspinal	Spinal cord	Spinal cord stimulation	—
2. Intracranial	Brain	Thalamic stimulation Cerebellar stimulation	Thalamotomy Pulvinarotomy Dentatectomy Fastigii lesions

** PNS – Peripheral nervous system, peripheral procedure, CNS – Central nervous system, central procedure, Temp.- temporary, Perm.- Permanent*

Anatomical Classification

Control Pathways

- *Suprasegmental:* The procedures that act on suprasegmental control of tone are called suprasegmental procedures. These are performed on the central nervous system (e.g. spinal cord stimulation).
- *Segmental:* The procedures that interrupt the spinal circuit responsible for the maintenance of tone are called segmental procedures. These are performed on the peripheral (e.g. fasciculotomy) or central nervous system (e.g. myelotomy).

Location

- *Central*: When surgery is performed on the brain or spinal cord.
- *Peripheral*: When surgery is performed on cranial nerves, spinal roots or peripheral nerves.

Physiological Classification

The procedures are classified into two types, depending on their effect on the nervous system.

- *Non-Ablative:* A reversible neural response is obtained without creating a lesion with the help of neurostimulation or chemical substances (e.g. spinal cord stimulation).
- *Ablative:* An irreversible lesion is created in the neural tissue (e.g. rhizotomy, fasciculotomy, etc.).

Non-ablative Segmental (Spinal Circuit) Procedures

Peripheral Procedures

Temporary peripheral (nerve) blocks: Chemical substances like bupivacaine are used on the peripheral neural structures to relieve spasticity, by reducing excessive gamma fusimotor drive. In the closed method, easily accessible nerves like the obturator, tibial, peroneal, musculocutaneous, ulnar and median nerves can be blocked by infiltration of chemical substances around the nerve. In the open method, inaccessible nerves are exposed surgically and a catheter that is connected with a reservoir for repeated injections is introduced, so as to obtain the effect of the drug for a long time. For example, a catheter can be introduced into the axilla to relieve spasticity of the upper limb. Both these procedures can also be used prior to any contemplated definitive neuro-interventional methods, so as to determine the amount of relief that can be expected and the possible motor function improvement or deterioration.

Central Procedures

Intrathecal baclofen (ITB):[4,11,30,31,40,42–47,64] Birkmayer et al. (1967) introduced oral baclofen for reduction in spasticity.[8] Penn and Kroin[53] used it intrathecally due to the poor penetration of the drug across the blood brain barrier. Baclofen is a GABA-B agonist drug that gets bound to the receptors on the superficial layers of the posterior horn. This inhibits presynaptic transmitter release, by depolarising the action potential induced calcium conductance.

Various kinds of pumps have been devised, to provide a smooth and sustained release of the drug. Under general or local anaesthesia, an intrathecal tube is passed from the back through the lumbar intervertebral space and left in the subarachnoid space. It is brought out at a convenient site on the abdomen through a subcutaneous tunnel and is connected to a reservoir that is implanted into the abdominal wall. Good and sustained reduction

in spasticity of spinal origin has been demonstrated with the use of intrathecal baclofen (ITB) in a number of studies conducted in the recent past. Spasticity of cerebral origin is also reduced, but the effect is less than in spasticity of spinal origin. Higher doses of baclofen can reduce spasticity further, but it causes weakness in the lower limbs and leads to other adverse events.[40,42]

An important positive aspect of ITB is that it is a non-ablative, reversible method and the reduction in spasticity can be titrated. ITB improves motor performance in the activities of daily living and in existing functions. However, the results do not vary much as far as lower limb functions are concerned, in comparison with much cheaper methods like selective posterior rhizotomy. The results in the spastic upper limbs are not good.

Unconsciousness to the extent of coma and respiratory failure, infection, disconnection of the tubes, geographical dependency and high expenses are the limiting factors for the use of this procedure. However, the use of better designs of the pump has lead to fewer complications. Recent reviews have shown that, even with the use of better pumps, adverse effects are common; however, they are manageable. Common adverse effects were worsening of seizures, somnolence, nausea and vomiting.[41–47]

Non-ablative Supra-segmental Procedures—Central Procedures

Neural-stimulation

Neural-stimulation for therapeutic purposes was first introduced in 1962 and, since then, has been used for pain relief and in movement disorders.[48] Later on, it was found useful for spasticity also.

1. *Spinal cord (dorsal column, posterior column) stimulation:* Cook and Weinstein[13] observed reduction in spasticity in a patient with multiple sclerosis who was being treated by spinal cord stimulation to relieve pain. The mechanism of relief of spasticity, resulting from spinal cord stimulation, is not yet clear. Stimulation of descending inhibitory pathways, blockade of nociceptive afferent influences on long loop reflexes and influence on the ascending and descending reticular systems, have been proposed.
   Electrodes are implanted in the midline posteriorly at the cervical, thoracic or lumbar epidural space by an open surgical procedure or by a closed method under fluoroscopy. The electrodes are connected to a receiver that is implanted subcutaneously in the subclavicular or sub-costal region. The frequency of stimulation is adjusted through an external spinal cord stimulator system called transmitter, which is a four electrode system using Lithium rechargeable Nickel-Cadmium batteries. Waltz[72] has reported moderate to marked overall improvement in the neurological condition of 75% of patients with cerebral palsy, head injury and spinal cord injury. Similar results have not been reproduced by other scientists. Therefore, its use has been recommended only in highly selected cases. Leakage of current, displacement of electrodes, infection, CSF leak, pain at the stimulation site, geographical dependency and high expenses, are the possible problems related to the use of this system.
2. *Thalamic stimulation:* Stimulation of the sensory relay nuclei of the thalamus has been tried for relief of spasticity.
3. *Chronic cerebellar stimulation:* This includes:
   a. Stimulation of the cerebellar cortex:[16,17,27,37,54,65] Electrodes are implanted on the posterior lobe of the cerebellum, under general anaesthesia through small bilateral craniotomies and are connected to a receiver pacemaker implanted subcutaneously in the sub-clavicular region. While some reports indicate improvement in spasticity by this technique[16,54], others did not observe any improvement. Neurotoxic effects of the stimulation have also been observed.[17,65]
   b. Dentate nuclei stimulation:[28,66,73] Schwarts et al. have reported that this procedure is effective in relieving spasticity in cerebral palsy. Spinal cord stimulation and ablative procedures are producing encouraging results and, therefore, the central neuro-stimulation procedures have not received wide acceptance. Besides the equivocal results, these implantable devices are very expensive and have not stood the test of time.

   Editors Comment: Most of these methods which are more than two decades old have not gained significant popularity suggesting their inherent limitations.

Ablative Segmental (Spinal Circuit) Procedures

Peripheral Proceduress

1. *Peripheral nerve blocks:* [12,21,35,71]Ablative peripheral neural blocks can be done on the peripheral nerves. The procedure is similar to the non-ablative technique described earlier. However, the chemicals used for this purpose are different and the effects are irreversible. They are phenol in glycerin[35,71] and alcohol.[21] The results obtained were sub-optimal and a high rate of recurrence of spasticity was noticed.
   Myoneural junction blocks:[2,15,26,70] In 1897, Von Ermengem related botulism to a toxin produced by clostridium botulinum and in 1949 Burgen showed that the toxin blocks neuromuscular transmission. In 1973, Alan Slot used botulinum toxin for the treatment of strabismus in non-human primates. In 1981, he used it for treating strabismus in humans. Tsui and Eisen used the toxin for treating cervical dystonia. Jancovic, used it for treating focal dystonias. Koman et al. first reported in 1994, the use of this toxin for patients with cerebral palsy. Bohlega studied its role in spastic paraplegics, following spinal cord injury. It was also used for treatment of spasticity in patients with multiple sclerosis and stroke.

Botulinum toxin blocks the release of acetylcholine (ACh) at the myoneural junction and, thereby, reduces spasticity. It is effective in dystonia, affecting the small muscles of the face and neck. It reduces spasticity of limb muscles also, but high doses are needed. It can be helpful in selected young children with cerebral palsy who have only focal spasticity, but quadriplegic patients having severe diffuse spasticity are not the right candidates. The drug is of no use in the presence of contractures. It can be complimentary to physical methods of treatment.

The toxin is injected at the myoneural junction. Sometimes, especially for small muscles, ENMG is required to localise the exact site of drug administration. There are no major side effects when injected into the limb muscles. However, recurrence is seen quite often. Therefore, repeated injections are required. In such cases, sometimes, antibodies against the drug can develop and then it becomes ineffective. Presently, the drug is very expensive. Recent papers and reviews have reported on the use of botulinum toxin for focal spasticity and for diffuse spasticity in young people having cerebral palsy. There is a reduction in spasticity for a short duration. However, the patients' responses were not predictable and there is no strong evidence to support or refute its use.[2] The results of long term use and functional outcome are still awaited. The functional outcome in a series of 758 children who had spasticity and received 1594 injections of botulinum toxin was studied. The functional goals were achieved fully in only 3% but, in 44% there was moderate improvement and, in 50% there was improvement.[6] Therefore, the results were compared with plaster casts. Interestingly GMFM (Gross Motor Function Measures) revealed no significant difference between the groups. It is inferred from these studies that further research on the use of the toxin to diminish spasticity and improve function is needed.[2,26]

2. *Neurotomy (neurectomy, fasciculotomy):*[18,19,20,29,32,38,62,63,69] In 1887, Lorenz first performed obturator neurotomy for relief of spastic hip adduction.[48] Intra-operative electrical stimulation of nerves was done by Gros et al. in 1977.[32] Only a few reports were available in world literature on neurotomy till 1998.[29,69] However, recently, there is an increase in the use of this procedure and many scientific papers have been published. The senior author coined the term selective motor fasciculotomy (SMF) (Fig. 1) in 1998 to give a precise picture of the procedure.[63]

Classification: This includes the following:

a. *Closed procedures*: Radiofrequency (RF) lesion[38]

b. *Open procedures*: This procedure has been classified into the following types:

i. Non-functional
   - Total neurotomy
   - Partial neurotomy

ii. Functional
   - Functional neurotomy (Selective neurotomy, Selective motor fasciculotomy)

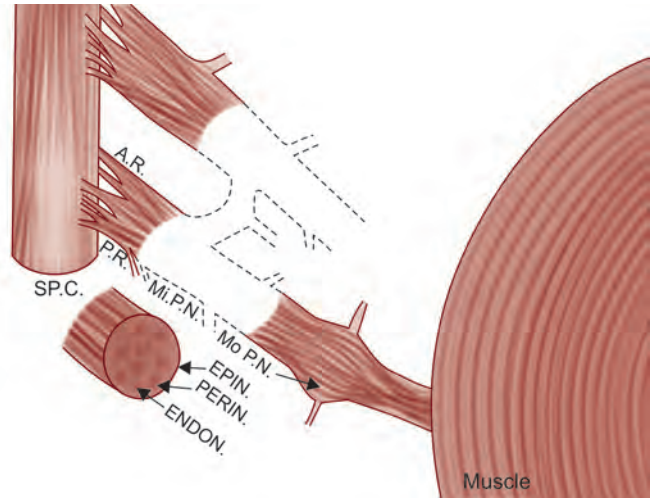

Fig. 1: Selective motor fasciculotomy: the motor peripheral nerve (MoPN) is dissected into its component fascicles. The fascicles are stimulated during selective motor fasciculotomy SpC—Spinal cord; AR—Anterior root, PR—Posterior root; MiPN—Mixed peripheral nerve; EPIN—Epineurium around a nerve fibre

In this procedure, the function of different nerve fascicles is determined by intra-operative stimulation[32] and the appropriate fascicles are divided.

Specific indications, selection criteria and goals: In general, this procedure is indicated for optimisation of focal spastic tone. However, the procedure can be performed on multiple nerves even in people with diffuse spasticity of the lower limbs when rhizotomy is contraindicated. For example, in children with diffuse spasticity of the upper limbs, this procedure is preferred to cervicothoracic rhizotomy, because a laminectomy to expose the cervicothoracic rootlets can cause cervical spinal deformity.

People with good control in the affected muscles are operated for improvement and gain in motor functions. People having only fair or poor control, may or may not improve in motor functions. However, they may get secondary benefits, like prevention of contracture, relief of discomfort and pain, improvement in the appearance of the limb and less fatigability. Fasciculotomy (SMF) of various nerves and corresponding spastic muscles has been shown in Table 2.

Procedure

In selective motor fasciculotomy procedures, the chosen nerve is exposed close to its entry into the spastic muscle say the median nerve in the cubital fossa. The component fascicles are dissected and stimulated with bipolar current, to ascertain that they are supplying the spastic muscle. The intensity of the response to the threshold current and the train stimulus is recorded. The fascicles that show hyperactive response are considered for ablation. Depending on these responses, the clinical picture

Table 2: Spastic muscles and selection of nerves for SMF

Nerves for SMF	*Spastic posture and movement*	*Spastic muscles*	*No of SMF in authors series*
Musculocutaneous	Elbow flexion	Biceps Brachii Brachialis	125
Median	Forearm pronation	Pronator teres Pronator quadrants	350
Ulnar	Wrist flexion Ulnar wrist flexion	Flexor carpi radialis Flexor carpi ulnaris	55
Obturator	Hip adduction	Adductor longus Adductor bravis Adductor magnus	130
Sciatic	Knee flexion	Hamstring muscles	40
Tibial	Ankle plantar Flexion, Toe flexion, Inversion	Gastrocnemeus, Soleus, Toe flexors	240

and the goals, the extent of ablation is determined. The fascicles are ablated by cutting them and cauterising the proximal stump by bipolar current. The number of fasciculotomies performed by the senior author has been shown in Table 2. If orthopaedic complications are present, then SMF and orthopaedic surgeries can be combined in patients having good control in the affected muscles.

Results

Following SMF, the spastic tone gets optimised right on the operation table. It is better appreciated once the operative pain subsides. The reduction in tone improves the range of movement across the joint. These movements become painless and more comfortable. However, if contracture is also present, the complete range of movement does not develop till soft tissue release surgery is also performed.

Functional improvement occurs, depending on pre-operative voluntary muscle control and motivation of the child. The presence of orthopaedic complications and previous orthopaedic surgery adversely affect the outcome. SMF improves the posture of the limb and the body. Improvement in pre-operative voluntary motor functions is observed very often following SMF. SMF of the lower limb nerves gives rise to improvement in sitting, crawling, standing and walking. Similarly, SMF of the upper limb nerves gives rise to improvement in upper limb functions related to activities of daily living and prehensile activities.

Usually, the maximum improvement is seen in the first six months. The long-term follow-up shows that spasticity does not recur and the improvement is maintained. Functional improvement is seen more often in people having spasticity in the lower limbs compared to the upper limbs. The procedure is quite useful in children who have diffuse spasticity in the upper limbs, wherein cervicothoracic rhizotomy cannot be done due to the risk of developing swan neck deformity. The procedure is quite cost effective because hardly any disposables are used and just a nerve stimulator is enough, as a special instrument that is also not an expensive tool.

Positive side effects: The procedure is found quite safe, simple and cost effective. In the upper limbs, interestingly, improvement in prehensile and shoulder movements is observed, following SMF of elbow flexors, pronators and wrist flexors. Improvement in a person's cooperation, behaviour and psychological functions also occur.

Negative side effects and complications: Paraesthesia, limb oedema, deep vein thrombosis, hypotonia, injury to vascular structures, wound gaping and infection are the possible rare complications. The senior author in his series of ten years has not faced any major problem.

3. *Rhizotomy:*[22,23,24,25,49,51,56,57,58,59,60,67] Rhizotomy means ablation of a spinal root. Depending on whether the posterior (dorsal, sensory) or the anterior (motor) root is ablated, the procedure is named accordingly. In selective rhizotomy, especially when the posterior root is selected for ablation to relieve spasticity, it is split into its component rootlets and each one is stimulated with bipolar current. The intensity of the response to the threshold current and the train stimulus is recorded. The rootlet that shows hyperactive response is considered for ablation. Depending on these responses, the clinical picture and the goals, the extent of ablation is performed. If the goals are to improve motor functions, usually under correction is preferred, because one can always reduce the spasticity further by either physical methods or extraspinal peripheral procedures like SMF, but over correction cannot be undone. Usually for this purpose 25–40% of the rootlets are ablated. Ablation is performed by sectioning the rootlet through and through. Cauterisation of the stump(s) is not required.

   In an open method, laminectomy is performed to expose the spinal roots.

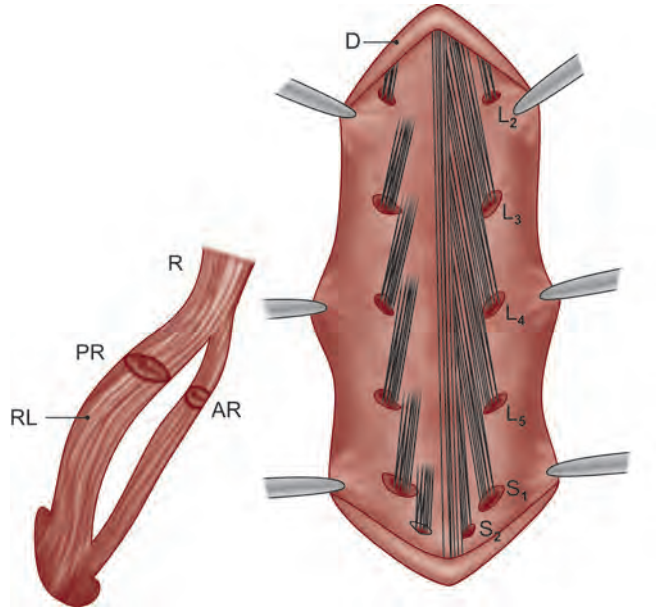

Fig. 2: Selective posterior rhizotomy: diagram on right side shows the cauda equina that has been exposed from L2 down to S2. The diagram on the left side shows dissected anterior (AR) and posterior roots (PR). Each root is composed of rootlets (RL). The posterior rootlets are dissected away from each other for stimulation during SPR R—Root

History: In an animal (cat) model of decerebrate rigidity, Sherrington, in 1888, observed relief in hypertonia, after sectioning of the posterior spinal roots.[67] Abbe[1], who first performed division of the posterior roots for relief of pain, suggested the possible use of this procedure for relief of spasticity. Otfrid Foerster first performed posterior rhizotomy in human beings for relief of spasticity.[24] Results in terms of reduction in spasticity were good, but there was widespread sensory impairment. In 1945, Munro[49] performed anterior rhizotomy in patients with spinal cord injury. This resulted in flaccid paralysis. Gros et al.[33], in 1967, introduced partial posterior root sectioning during lumbosacral rhizotomy. Based on a protocol of pre-operative mapping of spasticity and muscle functions, the rootlets responsible for function in useful muscles were spared by Privat in 1976 (Sectorial Posterior Rhizotomy).[56] In the recent past, many reports on lumbosacral rhizotomy have been published with minor modifications. In India, for the first time in 1988, WJ Peacock demonstrated selective posterior rhizotomy (Fig. 2) on cerebral palsy people at NIMS in Hyderabad. The senior author perfected and popularised the procedure and also extended the indications. He also performed for the first time, cervico-thoracic posterior rhizotomy for relief of upper limb spasticity, by using electro-stimulation technique.[59]

Indications and Specific Selection Criteria and Goals

People having diffuse spasticity in the lower or upper limbs are considered for lumbosacral or cervico-thoracic rhizotomy, respectively. In children, cervical laminectomy is preferably avoided because they are likely to develop spinal deformity.

Classification: Rhizotomies can be classified into the following types:

a. Open surgical method

i. Lumbosacral

This is done to relieve diffuse spasticity of the lower limbs. A limited T12 and L1 (Fasano's technique)[22,23] or L2 to L5 (Peacock's technique)[51,52] laminectomy and bilateral L2 to S2 SPR are performed. Improvement in motor functions has been observed in a significant number of cases. The senior author has performed Peacock's procedure on more than 225 people having cerebral palsy[58,60] and 20 others having spastic paraplegia[57] with good success.[57,60]

ii. Cervicothoracic[7,34,59]

This is done to relieve diffuse spasticity involving both the upper limbs. C5 to T1 laminectomy and bilateral C5 to T1 SPR are performed. The authors have observed improvement in motor functions including prehensility in middle-aged people having traumatic quadriparesis. The procedure was also performed in non-traumatic cases.[59]

iii. Sacral

This is indicated for spastic bladder. L5 laminectomy and partial removal of the sacrum are performed. All the sacral roots are stimulated and detrussor contractions are observed through cystometry or through some indirect methods. The goals vary from voluntary voiding to self-evacuation during socially acceptable timings.

b. Closed surgical method

Percutaneous radio frequency posterior rhizotomy[36]

Thermocoagulation of the posterior roots perhaps blocks the conduction of 'A' delta and 'C' fibres and reduces pain and spasticity. The procedure is performed under general anaesthesia in the lateral position. A skin incision, 6 cm lateral to the midline and at the level just below the site of passage of the posterior roots, responsible for carrying impulses to generate spasticity, is made. It can be considered in high-risk people with focal spasticity. A high rate of recurrence has limited its use.

c. Non-surgical method

i. Chemical rhizotomy

Intrathecal alcohol was first used by Dogliotti[21] in 1931, to relieve intractable pain. Maher used phenol in place of alcohol. Guttman used the same procedure to relieve hypertonia. Five percent phenol in glycerine, added to a water-soluble contrast medium, was also advised for this purpose. Chemical rhizotomy is indicated only in people with spasticity who are suffering from severe intractable painful spasms in the lower limbs, having no useful lumbosacral neural functions like bladder and bowel control and who have a short life expectancy, along with inability to withstand major surgery.

Results[22,23,51,52,57,58,59]

Spasticity and Spasms

Optimum reduction in hypertonicity can be achieved following SPR. However, considerable expertise is required in making a decision for ablation of a particular rootlet, as discussed earlier. The reduction in spasticity occurs immediately; however, it is well appreciated only after 3–4 days of surgery, i.e. after reduction in pain of surgical trauma. At this time, hypotonia may be present, due to electrical shock of the nerve roots that were stimulated during the surgery. SPR weakens the monosynaptic myotatic spinal reflex arc and produces quite an effective reduction in hypertonia, whereas, it produces no significant reduction in spasms, spastic patterns and mass reflexes, because they are mediated through multisynaptic pathways. Long-term follow-up reveals that no recurrence in spasticity occurs.

Motor Functions

Pre-surgical motor functions show considerable improvement within 3–9 months following SPR. New motor functions may also develop in ideal cases. The improvement is noticed in posture, balance, duration and ease of doing the activities. The awkward look also improves. Long-term follow-up reveals that the improved clinical picture is maintained.

Rhizotomy is contraindicated in the presence of significant ataxia, dystonia and athetosis. It is relatively contraindicated in the presence of multiple severe contractures, severe mental retardation, poor control in the lower limb, trunk and neck, and diseases of the spine, where laminectomy has to be performed. Relief in helpful spasticity can cause deterioration in the person's condition.

Side Effects

1. *Useful (positive) side effects*: There are many beneficial side effects, which have been observed following SPR:
   a. Improvement in upper limb function to the extent of picking of hair and threading the needle, bowel habits, swallowing and squint
   b. Clarity of speech
   c. Smooth flow and easy initiation of urination
   d. Decrease in seizures
   e. Improvement in respiratory functions and decrease in chest complications
   f. Improvement in social skills.
2. *Harmful (negative) side effects*: In a few cases troublesome post-operative numbness and paraesthesia have been observed. Usually they subside within a few days. Sometimes, mostly in adults, it may last for a few weeks to months and may require medications like carbamazepine or amitryptyline. Hypotonia can occur if an excess number of rootlets are sectioned. Rarely, touch, pain or kinaesthetic sensory impairment can occur. In the author's series of 225 cases, one child developed trophic ulcer in the foot, who walked bare footed and two others developed mild touch and kinaesthetic sensory impairment. In one case, cerebellar ataxia got worsened and in three cases neck holding worsened. All these complications were noticed in only the initial cases.
3. *Microsurgical drezotomy (MDT)—(Selective posterior rhizotomy in DREZ):* Lesions in the dorsal root entry zone (DREZ) (Fig. 3) were first used for the relief of pain. Sindou et al.[68] performed this procedure for relief of spasticity. At DREZ, the fine myelinated and unmyelinated nociceptive fibres and large 'A' alpha myotatic fibres are rearranged more centrally and laterally. During Drezotomy, these fibres are sectioned. A lesion at 45 degree into the DREZ spares the lemniscal fibres, responsible for carrying touch and kinaesthetic sensations. Although Drezotomy is being described here under the central procedures, please note it is a technique in which peripheral neural fibres are sectioned inside the cord.

   Under general anaesthesia, with only initial use of short acting muscle relaxants, the person is positioned prone. A hemi- or complete laminectomy, opposite the selected segments of the spinal cord, is performed.

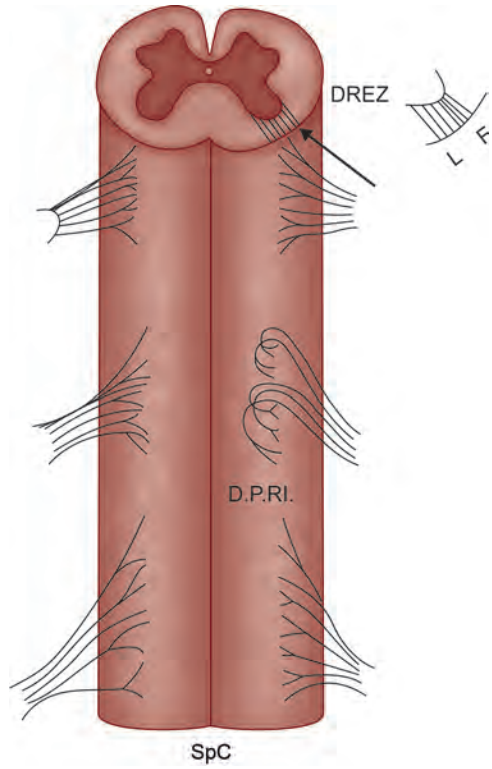

Fig. 3: Drezotomy: posterior surface of the spinal cord showing origin of posterior rootlets. One of the posterior roots rootlets have been dissected and lifted posteromedially (DPR—dissected posterior rootlets), so as to see dorsal root entry zone (Drez) clearly. The arrow is directed at 45 degrees angle into the Drez. This is the site and direction in which a lesion of the pain carrying fibres and myotatic fibres is created. The procedure spares the touch and kinaesthetic fibres

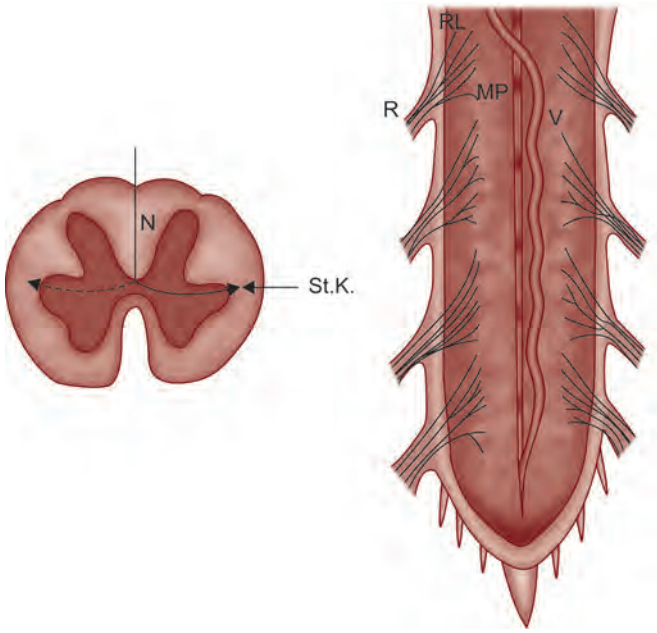

Fig. 4: Stereotactic myelotomy: longitudinal picture of posterior surface of spinal cord showing multiple black markings in the midline. These are the myelotomy puncture (MP) sites. RL—rootlets

The dura is opened and the correct site of the selected segments is confirmed by electro-stimulation of the roots/rootlets. Under magnification, the selected posterior rootlets are retracted dorsomedially from the dorsolateral sulcus, so as to reach the ventrolateral region of the DREZ. The vessels are dissected away from this site. A two mm deep incision is made at a 45 degree angle into the DREZ, with the help of a sharp knife. The area is coagulated with low intensity short duration bipolar cautery.

The procedure is indicated for adult people with spasticity, who have severe painful intractable diffuse spasticity involving one or both lower or upper limbs. The results are significantly better in people having spasticity due to pathology other than cerebral lesions. A highly significant reduction in spasticity and even painful spasms has been reported along with appreciable improvement in motor functions. Side effects like CSF leak, impairment of sensations and related complications, respiratory deterioration, urinary problems and weakness of the limbs have been observed.

4. *Longitudinal Myelotomy*: Wilhelm Bischof[9] first performed longitudinal myelotomy in 1951 and successfully relieved severe spasticity of the lower limbs. He passed the knife anterior to the attachment of the dentate ligaments on both the sides and divided the cord into anterior and posterior halves from L1 to S1 segments. The results were good in people suffering from severe frequent spasms and intractable spasticity in the lower limbs. Bischof also performed unilateral cervical myelotomy. In his technique there was a potential risk of damage to the pyramidal tracts.

Pourpre[55] modified Bischof`s technique. He opened the dorsal fissure of the spinal cord and passed a stylet knife in lateral directions. This disconnected the dorsal and ventral horns, thereby avoiding the complete interruption of corticospinal fibres.

Laitinen[39] introduced stereotactic[50] myelotomy, a more accurate and finer technique of disconnecting the ventral and dorsal horns, saving not only the corticospinal fibres but also the commissural region that transmits nociceptive and thermal fibres (Fig. 4). The incidence of spasms and of haematomyelia was less with the stereotactic procedure. The results were reported as gratifying.

Central Procedure

Refer chapter on stereotactic surgery for cerebral palsy.

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SECTION

18

Miscellaneous

Sanjay Behari

205 Anaesthesia for Neurosurgery

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Anaesthetic management of neurosurgical patients is based upon an understanding of the physiology of the central nervous system (CNS) and the effects of anaesthetic agents on it. The critical homeostasis of the pathological brain may be easily disturbed by variations in cerebral blood flow (CBF), cerebral metabolic rate (CMR), cerebral perfusion pressure (CPP), CO_2 reactivity and auto-regulation due to the effects of anaesthetic drugs and techniques.

In the present chapter, a brief review of the cerebral physiology, cerebrovascular effects of the anaesthetic agents and the criteria for selecting various anaesthetic interventions, according to differing neurosurgical situations, will be addressed.

CEREBRAL PHYSIOLOGY

The brain is a converter and consumer of energy. It converts substrates supplied as metabolic fuel into usable forms of energy, which support and regulate synaptic connections, voltage dependant ion channels and synthesis, transport and packaging of neurotransmitters. The CNS receives about 15% of the resting cardiac output (750 ml/min) and consumes about 20% (170 μmol/100 g of brain/min) of oxygen required by the body at rest, whereas the weight of the brain is only 2–3% of the total body weight. The brain consumes one quarter (i.e. 31 μmol/100 g of brain/min) of the total glucose consumed by the body. Lack of substrate storage in the brain and a high metabolic rate makes the brain relatively sensitive to the effects of ischaemia. Brain metabolism can be split into two parts: the portion that drives the work of the brain, that is synaptic transmission (activation metabolism) and, the portion necessary for cellular integrity (basal metabolism), in approximately 60% and 40% of total energy consumption, respectively. The larger portion of basal metabolism is devoted to the maintenance of transmembrane ionic gradient (i.e. Na^+-K^+ pump).

CEREBRAL BLOOD FLOW AND ITS REGULATION

Average Cerebral Blood Flow (CBF) in an adult is approximately 50 ml/100 gm of brain/min. Regional blood flow varies from 20 ml/100 gm to 80 ml/100 gm of brain/min. There is approximately fourfold difference in $CMRO_2$ and CBF between cortical grey and white matter (80 ml/100g/min and 20 ml/100g/min, respectively). A rapid and precise regulatory system has evolved in the CNS, whereby instantaneous increase in the metabolic demand can be rapidly met by a local increase in CBF and substrate delivery.

METABOLIC CONTROL

Under physiological conditions, fluctuations in cerebral glucose utilisation and oxygen consumption are based upon regional electrical activity differences, matched by changes in CBF. This is known as $CMRO_2$-CBF coupling. Roy and Sherrington[41] were the first to hypothesise that the principal determinant of CBF was cerebral metabolic activity and suggested that the brain possessed an intrinsic mechanism, by which its vascular supply could vary based on local variations in functional activity. $CMRO_2$ is influenced by several factors in the neurosurgical environment, including the functional state of the nervous system, anaesthetic drugs and temperature. When the cerebral function is depressed (as in a comatose patient or during hypothermia), both CBF and substrate delivery are less than in the fully conscious state. In contrast, during a seizure, the demand for glucose and oxygen increase dramatically and must be met by an increase in CBF. In the latter situation, CBF and $CMRO_2$ change in the same direction but increase in CBF is much higher than the change in metabolic rate.

This coupling can be modified by pathophysiological processes and drugs. Clinical assessment of uncoupling may be made by measuring the arterio-jugular venous difference in oxygen content (CaO_2-$CjvO_2$). If coupling is intact, the arterio-jugular venous difference in oxygen content remains in the normal range. If CBF is inadequate to meet the CMR demand, an increased extraction of oxygen will lead to a decrease in the arterio-jugular venous difference in oxygen content. In many pathophysiological processes, the CBF-CMR coupling may be deranged selectively in focal areas, such as the area around the tumour, in subarachnoid haemorrhage (SAH) and in the region around the epileptogenic focus. Adenosine and nitric oxide are the proposed mediators of flow-metabolic coupling.[26] Adenosine increases cyclic AMP production that causes cerebral vasodilatation, whereas nitric oxide (an intercellular messenger in the peripheral circulation and in CNS) causes smooth muscle relaxation and inhibition of platelet aggregation.

AUTO-REGULATION

In the normal brain, auto-regulation refers to the ability to maintain a relatively constant CBF over a range of perfusion pressure (independent of the CBF-CMR coupling). Thus CBF is constant between an MAP of 50–150 mm of Hg (under auto-regulatory range). Above and below this range, CBF is pressure dependant (pressure passive) and varies linearly with CPP. Auto-regulation maintains the internal milieu of the CNS. It appears that change in the CPP involves a myogenic response of the vascular smooth muscles (Bayliss effect).[37] This myogenic response may consist of two separate mechanisms: one responding to the MAP changes and the other being sensitive to pulse pressure.[52]

Pathological states of the brain, pharmacological agents and physiological alterations may impair auto-regulation. Chronic hypertension shifts the auto-regulatory curve to a higher range. Intracranial tumour, head injury, brain lactic acidosis, hypercapnia and cerebral vasodilators impair auto-regulation. More recent work has shown that following trauma, auto-regulation may still be functioning.[6] In this situation, if CPP falls below the critical value of 70 mmHg, the patient will have inadequate cerebral perfusion. Auto-regulation will cause cerebral vasodilatation, leading to a rise in brain volume. This, in turn, will lead to a further rise in ICP and induce the vicious cycle described by the vasodilatation cascade, which results in cerebral ischaemia. Raising the CPP by elevating MAP can break this process, inducing the vasoconstriction cascade. Thus, maintenance of arterial blood pressure at adequate level by careful monitoring and rapid correction is of paramount importance.

CARBON DIOXIDE

Carbon dioxide is a powerful modulator of cerebral venous resistance. At normotension, there is nearly a linear response of CBF at a $PaCO_2$ between 20 mmHg and 80 mmHg (CBF changes about 2–4% for each mm Hg change in $PaCO_2$). Vasodilation by CO_2 is probably mediated by nitric oxide and cGMP pathways in adults and by prostaglandins and cAMP in neonates.[7]

Hypocapnia reduces CBF and, hence, CBV and ICP, although the CO_2 induced cerebral vasoconstriction wanes over a period of 6–10 hours.[38] Hypocapnia, however, may adversely affect cellular metabolism and shifts the oxy-haemoglobin dissociation curve to the left.[44] While hypocapnia is maintained, there is a gradual increase in CBF towards control values, which will lead to cerebral hyperaemia (over-perfusion) if the $PaCO_2$ is returned rapidly to normal levels.[36] When long-term ventilation is required, only mild hypocapnia (34–38 mmHg; 4.5–5.1 kPa) should be induced. Response of CBF towards CO_2 is attenuated below a $PaCO_2$ of 25 mm of Hg. CBF cannot be further reduced, as the ischaemic vasodilatation effect counteracts the hypocapnia induced vasoconstrictor response. Therefore, there is no advantage in inducing further hypocapnia.

OXYGEN

Low arterial oxygen tension also has profound effects on CBF. When the former falls below 50 mmHg (6.7 kPa), there is a rapid increase in CBF and cerebral blood volume.

NEUROGENIC CONTROL

Autonomic factors do not appear to control CBF, but they may modify other regulatory responses. Perivascular innervation of the cerebral resistance vessels and the specific neurotransmitters contained within the perivascular nerve fibres, also modulate vascular responses to changes in the blood pressure. The innervation of the cerebral vasculature is extensive and involves serotonergic, adrenergic and cholinergic systems of both intracranial and extracranial systems. Although acetylcholine is the most abundant perivascular neurotransmitter, other mediators in this neural response include norepinephrine, neuropeptide Y, cholecystokinin, acetylcholine, vasoactive intestinal peptide and calcitonin gene related peptide.[29] Sympathetic stimulation can shift the auto-regulatory curve to the right, thus protecting the brain against severe elevations of MAP. Stimulation of parasympathetic fibres promotes a vasodilatory reaction to ischaemia. The protective response against ischaemia however, is overshadowed by hyperaemia mediated by the same fibres.

CEREBRAL PERFUSION PRESSURE

The brain and its blood vessels are encased in the rigid cranium and subjected to surrounding pressure, i.e. ICP. Therefore, net cerebral perfusion pressure (CPP) is defined as the difference between MAP and ICP. CPP represents the blood pressure gradient across the brain's vascular bed and thus determines blood flow through the brain. MAP determines the "head of pressure" perfusing the brain.

CPP = MAP - ICP

Normal CPP is 80 mmHg, but when reduced to less than 50 mmHg, there is metabolic evidence of ischaemia and reduced electrical activity. Inadequate CPP (less than 70 mmHg) has been shown to be a major factor in poor outcome of patients with raised ICP. Assessment of CPP is vital and possible, either by measurement of both ICP and MAP or by measuring MAP and making a reasonable estimate of ICP. During anaesthesia, therefore, if ICP is raised, a fall in blood pressure must be avoided or treated quickly by volume replacement or catecholamines (whichever is relevant).

A number of studies on patients with severe head injuries have shown an increase in mortality and poor outcome when CPP falls to less than 70 mmHg for a sustained period.[28,40] Two different approaches in the management of CPP attempt to maintain adequate cerebral perfusion to meet the cerebral metabolic demand, depending upon intact auto-regulation and integrity of the blood brain barrier (BBB).

Rosner Concept or Edinburgh Concept

During head injury, when CPP is maintained within the range of 75–95 mm of Hg, auto-regulatory vasoconstriction is induced, which decreases ICP, provided cerebrovascular auto-regulation is intact.[40] Patients with a shift of the auto-regulatory curve towards the right (i.e. those in whom a higher mean arterial pressure is required to maintain the perfusion to the brain) are the most benefited by this concept (as elevation in CPP returns the pressure flow relationship into the auto-regulatory range).

Lund Concept

A group of head injured patients with defective BBB and cerebrovascular auto-regulation is benefited from a reduction in precapillary hydrostatic pressure, as well as cerebral venous constriction. This reduces CBV and thus decreases brain oedema. This concept aims at stabilisation of CPP within the range of 65–70 mm of Hg by means of proper sedation, administration of osmotic diuretics and vasopressors, and maintenance of normovolaemia.[3,4]

Continuous monitoring of jugular venous bulb oxygen saturation ($SjVO_2$) monitors the adequacy of cerebral perfusion. As CBF and the delivery of oxygen is reduced below a critical value, the brain, in order to maintain its oxygen supply, extracts more oxygen from the blood. This leads to a fall in venous oxygen saturation. More specifically, when CPP is inadequate, the $SjVO_2$ (normal range 65–75%) falls because of increased oxygen extraction. Chan[8], in a study of head-injured patients, showed that when the CPP was below 70 mmHg, there was a rapid decrease in $SjVO_2$.

INTRACRANIAL PRESSURE

The principle constituents within the skull are brain (80%), blood (12%) and CSF (8%). Normal intracranial pressure is less than 15 mm of Hg and is considered as being abnormally high when a sustained elevation greater than 20 mm of Hg occurs. Abrupt and marked increase in the ICP leads to systemic hypertension and baroreceptor mediated bradycardia (called Cushing reflex). Although this reflex is designed to increase perfusion, it eventually aggravates intracranial hypertension.

PHARMACOLOGY OF ANAESTHETIC DRUGS

Inhalational Agents

Volatile anaesthetic agents like halothane, enflurane, isoflurane, sevoflurane and desflurane cause cerebral vasodilatation with an increase in CBF. They also produce some uncoupling of the normal relationship between metabolism and blood flow. When $CMRO_2$ decreases, local blood flow falls, as there is a reduced requirement for oxygen delivery and carbon dioxide removal. The latter is the indirect effect of these agents. Volatile agents uncouple or disconnect this relationship in a dose dependent way. The overall effect on cerebrovascular tone therefore, is the sum of both the direct vasodilatory effect and any indirect residual vasoconstrictor effect. Hence, at low doses, CBF is not elevated but, at higher doses, there is an increase of CBF. An important consequence of this is that any dilatation in turn raises cerebral arterial volume and increases brain volume. A stiffer noncompliant brain raises ICP.[15]

The normal auto-regulatory mechanism is gradually abolished, as the concentration of the volatile agent is increased and CBF becomes blood pressure dependent. Thus, as MAP rises, CBF increases and cerebral vasodilation occurs. In contrast, when blood pressure falls, there is no mechanism to sustain flow by a reduction in the cerebrovascular resistance. The volatile agents also affect the CO_2-CBF relationship, causing the curve to be shifted to the left. Hypocapnia is still able to reduce CBF and, therefore, to oppose the vasodilation. However, if CO_2 is allowed to rise, there is a much more rapid increase in CBF.

Halothane

It is a moderately insoluble agent (blood gas solubility being 2.5 and the MAC, i.e. the minimal alveolar concentration at which reflex to skin incision abolishes, of 0.75%). Halothane is a potent cerebral vasodilator and in the presence of cerebral swelling, it produces a large rise in ICP. Fortunately, hyperventilating the patient for 10 min before the introduction of halothane can prevent this rise in ICP.[1] Cerebral auto-regulation is reduced at 1% inspired concentration of halothane and abolished by 2% concentration.[30] It is reasonably safe to use halothane in a hyperventilated patient up to a concentration of 0.5% in conjunction with nitrous oxide. It should be avoided, if possible, by using alternative techniques; before the duramater is opened in patients who have a raised ICP.[57] Halothane sensitises the myocardium to catecholamines making the patient more prone to developing arrhythmia, especially when adrenaline is used for local infiltration.

Enflurane

It has similar effects as halothane, but appears to be a less potent cerebral vasodilator and a more potent depressant of CMR, but it does cause cerebral seizure activity, particularly when the patient is hypocapnic.[47] Epileptic activity is harmful as it induces a massive increase in CMR, which in turn increases CBF and hence cerebral swelling. Enflurane increases ICP by increasing the rate of production of CSF and also decreasing its reabsorption.

Isoflurane (Blood Gas Solubility 1.4 and MAC 1.2%)

It is the least potent cerebral vasodilator and the most potent metabolic suppressant. It causes both respiratory and cardiovascular depression, the latter occurring

predominantly due to a fall in systemic vascular resistance.[12]

CBF and CBV are not affected by concentrations of 0.6–1.1 MAC isoflurane, but a 1.6 MAC doubles CBF. In higher concentrations, it also causes an increase in ICP. There is less impairment of auto-regulation and CO_2 reactivity when compared to halothane. There is evidence of uncoupling between the direct vasodilator effect and indirect vasoconstriction effect of isoflurane on the cerebral vasculature. Therefore, up to 1.6 MAC, the vasoconstriction effect predominantly prevents CBF from rising. As the inspired concentration rises, the direct vasodilatory effect overrides the indirect vasoconstrictor effect. However, in a damaged or pathological brain, the indirect vasoconstriction due to the depression in CMR does not occur. Therefore, small concentrations of isoflurane will cause some cerebral vasodilation. Unlike halothane, isoflurane in the concentration of 1.1% significantly increases ICP despite hyperventilation in patients with intracranial tumours, with decreased intracranial compliance.[19] Because of favourable properties and fewer side-effects, isoflurane has been recommended as the preferred drug for neuroanaesthesia.

Sevoflurane (MAC 1.7–2% and a Low Blood Gas Solubility 0.6)

It has similar properties to isoflurane on the brain, CBF, CBV and ICP.[9,43] Response to $PaCO_2$ and auto-regulation appear intact up to 1MAC. Low blood gas solubility may have an advantage for rapid awakening even after many hours of surgery. Sevoflurane is also metabolised (5%), increasing blood fluoride concentration. So far no renal complications have been reported. When sevoflurane is used with soda-lime (used for absorption of expired CO_2 in the anaesthesia machine) in a circle system, a toxic compound is produced. However, no problems have been noted due to this effect. Sevoflurane is the volatile agent of choice for induction of anaesthesia, because of its faster onset of action and non-irritant nature.

Desflurane (MAC 5–10% and Blood Gas Solubility, 0.4%)

It is also similar to isoflurane in many respects.[9] Like sevoflurane, its main advantage is in providing rapid recovery from anaesthesia. It is expensive like sevoflurane and is only economically viable if used in a sophisticated low-flow system. However, in contrast to sevoflurane, it is more irritant to the tracheobronchial tree and requires a special vapouriser, but it is not metabolised or affected by soda-lime.

Nitrous Oxide

It was believed to have minimal effect on CBF. However, in a study with human volunteers, nitrous oxide has been shown to cause a significant increase in CBF, acting synergistically with the volatile agents.[42] Nitrous oxide alters cerebral auto-regulation, the effect depending on the other anaesthetic agents it is used with. Its stand alone action impairs auto-regulation but not when added to sevoflurane 1.5 MAC.[5] Cerebral auto-regulation improves when nitrous oxide is added during propofol anaesthesia.[20] Carbon dioxide reactivity is preserved when nitrous oxide is used in combination with volatile anaesthetic agents[9,49] and also with propofol,[22] which allows manipulation of CBF during anaesthesia. This property permits the safe use of nitrous oxide in clinical practice, as the increase in blood flow resulting from its use may be nullified by hypocapnia. Recently, the effects of 50% N_2O on the frequency and extent of spike activities was investigated on electrocorticogram in eleven epileptic patients under 1.5 MAC sevoflurane, with a small dose of fentanyl. It showed that the introduction of nitrous oxide in the combination significantly decreased the spike activity, although it did not affect the extent of areas with spikes. This suggested that nitrous oxide may be carefully used during electrocorticography monitoring in epilepsy surgery.[32] Despite the fact that N_2O increases ICP in patients with intracranial tumours, it may be safely used in most neurosurgical patients, as it causes minimal cerebral swelling. N_2O allows a reduction in the concentration of potent inhalational agents, although the effect of an equipotent combination of N_2O and isoflurane on ICP and CBF may actually be worse than that of isoflurane alone.

Hypnotics

Hypnotics are agents that induce sleep. They are used for induction as well as for maintenance of anaesthesia. In general, intravenous anaesthetics decrease CBF and CMR. These agents are not cerebral vasoconstrictors. The decrease in CBF is due to decrease in CMR consequent to cerebral functional depression.

Barbiturates

They reduce CBF by direct cerebral vasoconstriction and by a reduction in metabolism. They cause dose dependent reduction in CMR and which ultimately leads to a reduction in CBV.[34] Burst suppression dose of thiopentone decreases both CBF and $CMRO_2$ to about 40% (near maximum reduction) of the awake value in humans. There is a fall in ICP, possibly because of this change in CBF and CBV. Thiopentone has multiple uses. It is used for anaesthesia, to treat raised ICP in head injured patients, as an anticonvulsant and for neuroprotection in areas of focal ischaemia.[21] Large doses of barbiturates must be used with caution in patients with raised ICP as they also cause a marked fall in blood pressure, which will lead to a fall in CPP and may delay recovery from anaesthesia. Barbiturates may also decrease production of CSF and resistance to CSF flow.

Etomidate

It resembles thiopentone in its effects on CBF and CMR. It has less cardiovascular side effects than thiopentone. The maximum reduction of CBF is more rapid than the

maximum reduction of CMR, suggesting that it has an intrinsic vasoconstrictive property. Its adverse effects include adrenocortical suppression and involuntary muscle activity. Etomidate in low concentration appears to activate seizure foci in epileptic patients and should be used cautiously in these patients.

Propofol

It is an alkylphenol, which has hypnotic properties and has a potency 1.8 times that of thiopentone. It has been prepared in intralipid and causes both respiratory and cardiovascular depression. Propofol reduces CBF, CBV, ICP and CMR in a dose related manner. The drug is rapidly metabolised in the liver and a little amount is cleared by the kidneys. Anaesthesia, when maintained by propofol infusion is followed by rapid recovery when the drug is not used for more than 3–4 hours. Prolonged use of propofol may cause systemic acidosis, progressive cardiac failure and even death in children. It should therefore be used cautiously in children.[33,48]

Propofol is a very useful agent for maintenance of anaesthesia in neurosurgical patients, particularly when nitrous oxide is to be avoided. Propofol infusions are expensive and require sophisticated infusion pumps. More recently, the concept of target controlled infusions (TCI) has been introduced, where a specially designed syringe pump using a pre-programmed algorithm injects the drug at a rate necessary to achieve the blood level set by the clinician.

Ketamine

It is a derivative of phencyclidine that induces dissociative anaesthesia. It stimulates the cardiovascular system with minimal respiratory depression. It increases $CMRO_2$, CBF and ICP in patients with intracranial decompensation. It is a non-competitive antagonist at NMDA receptors and may therefore offer protection from the adverse effects of cerebral ischaemia. Ketamine should be avoided in neurosurgical patients especially in those with raised ICP and decreased intracranial compliance.

Narcotics

Narcotics are used for their analgesic actions. Their effect over CBF, CMR and ICP are variable and depend on the background anaesthetics. In spontaneously breathing patients, narcotics will depress respiration, indirectly increasing CBF and ICP by raising $PaCO_2$; however, if ventilation is supported, then the direct effect of narcotics on CBF is minimal. With controlled ventilation and in the presence of cerebral vasodilators (like halothane), opioids produce a decrease in CBF and CMR. When given along with cerebral vasoconstrictors or when given alone, opioids have either no effect or they increase CBF and CMR. An ideal narcotic has a predictable, short lasting effect. Most of the newer opioids cause skeletal muscle rigidity when given in large doses. Seizures have been reported in some circumstances with opioid agents.

Fentanyl

It has a peak effect that starts 4 min after injection and lasts for more than 15 min. Suppression of the cardiovascular response to painful stimuli can be achieved using 1.5–2.5 mcg/kg. There is usually no change in CBF or ICP, but if a large bolus is given, a small decrease in arterial pressure can lead to a similar change in CPP. Fentanyl may accumulate in the body when used for prolonged periods and the duration of action may be up to 60 min or more. Chest rigidity may result with induction doses of fentanyl. When used in combination with droperidol, it induces neuroleptanaesthesia (Neuroleptanaesthesia is characterised by trance like immobility in an outwardly tranquil patient who is dissociated to the surroundings).

Pethidine

It is a synthetic opioid with properties similar to other narcotics, with additional atropine like effects. It can cause marked hypotension (when given rapidly), an important consideration in a patient with high ICP. The duration of action is intermediate, i.e. 2 hours with a plasma half-life of 3–4 hours. Therefore, pethidine is not an ideal agent and is not in common use in neuroanaesthesia. The usual intravenous dose is 0.5 mg/kg.

Alfentanil

It is a more recently introduced opioid, which is less potent than fentanyl, but has a very rapid onset and shorter duration. The latter is due to its rapid excretion. Alfentanil is not widely distributed in the body. As the amount of drug required to produce an adequate effective concentration is less, it is rapidly excreted. The effect on CBF and CMR are comparable with fentanyl, but when given rapidly it decreases MAP, especially in elderly patients or in patients with compromised circulation. This is especially important when ICP is also increased since the decrease of MAP decreases the CPP.

Sufentanil

It causes 29% reduction in CBF and 22% reduction in CMR. Sufentanil causes an increase in ICP, when rapidly administered.[46]

Remifentanil

It is an ultra-short acting opioid.[54] It produces rapid analgesia, and has potency similar to fentanyl. It has typical opioid effects of respiratory depression, bradycardia and skeletal muscle hypertonus. It is rapidly broken down by circulating and tissue non-specific esterases. Thus, the half-life is 10–20 min with a plasma clearance of 3–4 l/min. The recovery is rapid, and is unaffected by the dose or the length of time the drug has been given. A

bolus administered over 1 min does not cause a significant rise in ICP (2–3 mmHg), but may decrease MAP, which may lead to fall in CPP. One of the problems with remifentanil is that residual analgesia does not occur. Therefore, post-operative pain relief needs careful consideration.

The use of infusion techniques of newer narcotics (Remifentanil, etc.) with propofol, are becoming increasingly popular. With the help of ultra-short acting drugs, anaesthesia is better controlled as the rate of infusion peaks at maximum stimulation and wears off when no longer required.

Neuromuscular Blocking Drugs

Suxamethonium

It is the only depolarising muscle relaxant useful in clinical practice. It has a rapid onset of action and is the relaxant of choice for rapid intubation. It has been reported to raise ICP.[55] Therefore, it is avoided in neuroanaesthesia, until absolutely indicated (full stomach, emergency case, safe and rapid control of airway). However, some recent reports have failed to register a rise in ICP in head injured patients following suxamethonium administration.[24]

Pancuronium

It does not affect $CMRO_2$, CBF or ICP during induction of anaesthesia. It may cause arterial hypertension and tachycardia, which may make intracranial conditions difficult during surgery (but may be advantageous for circulatory support in hypotensive patients).

Vecuronium

It is an intermediate acting non-depolarising neuromuscular blocking drug. Its principal advantage is that it has negligible effects on the cardiovascular system and does not induce histamine release. A preliminary report in neurosurgical patients has confirmed that there was no observed effect on ICP or CPP.[39] Following an induction dose of 0.15 mg/kg, the time of onset for neuromuscular blockade is approximately 140 seconds, which is adequate for elective procedures. Thus, vecuronium appears to have useful properties for inducing neuromuscular blockade prior to intubation in elective cases.

Atracurium

It is an intermediate acting neuromuscular blocking drug, which has the unique property of spontaneous degradation (Hoffmann degradation) in the blood and so is preferred in patients with renal or hepatic dysfunction. Its rapid administration causes histamine release. Laudanosine, its metabolite, is potentially epileptogenic.

Mivacurium

It has a brief duration of action (10–15 min). Infusion provides stable relaxation without the risk of accumulation. It appears suitable for use in neuroanaesthesia. It causes histamine related hypotension on rapid injection.

Rocuronium

It is a steroid and serves as a relaxant with a rapid onset time, but of low potency.

Choice of Anaesthetic

The basic principles of neuroanaesthesia management include: (a) clear airway; (b) full oxygenation without hypercarbia; (c) smooth induction with no coughing or bucking; (d) careful monitoring of the patient; (e) steady well controlled maintenance of anaesthesia and (f) well controlled emergence and recovery. Based on the effects of volatile agents on the normal brain either isoflurane, sevoflurane or desflurane appear to be a better choice than halothane for patients with intracranial pathology. None of these drugs have adverse effects when mild hypocapnoea is present. Sevoflurane and desflurane have an added advantage in intracranial neurosurgery, because of faster awakening. Ketamine is probably not appropriate as a sole drug in intracranial neurosurgery. The issue of the significance of the transient rise in ICP with succinylcholine remains unaddressed. Studies in acute head-injured patients suggest that the advantages of rapid intubation, offered by succinylcholine, may offset its potential disadvantage of ICP rise. Barbiturates lower $CMRO_2$, thus offering protection during focal ischaemia. Hypothermia also protects against ischaemia. There is a growing thought that the reduction in metabolic rate, produced by barbiturates, may not be as protective as once thought.

GENERAL ANAESTHESIA: AN OVERVIEW

Pre-operative Evaluation

The American Society of Anaesthesiologist's (ASA) classification of physical status stratifies the patient's pre-existing health[58] (Table 1).

History and Physical Examination

Assessment should evaluate the history of previous surgery (problems with airway management, post-operative nausea and vomiting, coagulopathy), recent medical treatment, present medication, the presence of allergies and the family history.

Table 1: ASA Classification of physical status

1.	No organic, physiologic, biochemical or psychiatric disturbance
2.	Mild to moderate systemic disturbance
3.	Severe systemic disturbance
4.	Severe systemic disturbance that is a constant threat to life
5.	Moribund patient, likely to die with or without surgery
6.	Brain dead organ donor

The detailed neurological examination will provide the baseline status for comparison with the post-operative status. A patient with a pre-operative decreased level of consciousness may have a slow or delayed emergence from anaesthesia and may require post-operative ventilation. Patients with brainstem lesions and/or lower cranial nerve dysfunction are at increased risk of aspiration pneumonitis. Patients who have had previous motor dysfunction may develop exacerbation of focal neurological signs after sedative doses of benzodiazepines or narcotics. A patient with damaged IX-Xth nerve may present with a hoarse voice secondary to vocal cord paralysis and may be at increased risk of airway obstruction and aspiration. Finally, patients with pre-existing motor deficits may develop life-threatening arrhythmia from hyperkalaemia, secondary to succinylcholine administration.

The degree of difficulty during intubation may be predicted by the Mallampati scoring system[27] (Table 2), thyromental distances and the restriction of neck movement.

The examination is done with the patient in the sitting position with a fully open mouth.

Smoking is an important predisposing factor leading to both cardiovascular and pulmonary disease and is associated with a threefold increase in peri-operative morbidity. Cessation of smoking for 6–8 weeks is recommended for reactivation of mucociliary clearance. Even cessation of smoking for 24 hours may reduce the carboxyhaemoglobin levels and improve oxygenation.[10] The presence of reactive airway disease indicates an increased risk of bronchospasm, during airway manipulation, tracheal extubation and emergence from anaesthesia. Effect of a recent upper respiratory tract infection, in the last 2–4 weeks, places the patient at risk of peri-operative respiratory morbidity. Obesity is an important risk factor for peri-operative pulmonary complications, because it may often cause post-operative atelectasis and pneumonia.

In chronically hypertensive patients, the risk of end-organ damage must be evaluated. Patients with poorly controlled blood pressure are more susceptible to the systemic hypotensive effects of anaesthetic agents at the time of induction of anaesthesia because of constricted plasma volume. A pre-operative and intra-operative intravenous fluid loading may obviate this risk. Untreated patients may have excessive hypertension, leading to left ventricular strain and ischaemia.

A thorough cardiac workup is required in cases having coronary artery disease. An echocardiography and stress testing may be indicated in patients with symptomatic ventricular dysfunction. Electrolyte imbalance may occur because of the use of diuretics, excessive vomiting and dehydration. Concomitant drug therapy required for the treatment of raised ICP may exaggerate the cardiac related complications.

Renal disorders may lead to increased total body water, but with coexisting depleted blood volume. They are often accompanied by hypertension, electrolyte disturbances and anaemia. The volume status is often difficult to assess in renal failure and may necessitate invasive monitoring, including placement of intra-arterial and central venous pressure catheters.

Patients on anti-platelet agents, such as aspirin and clopidogrel, should have their medications stopped for a week before intracranial surgery, whereas oral anticoagulant should be switched over to heparin. Clotting factors and platelets should be made available at the time of surgery.

Patients with pan-hypopituitarism may require replacement hormone therapy. Cushing's disease may be associated with hypertension, fluid retention and diabetes mellitus. Acromegaly may present with airway problems that may need special attention at the time of intubation.

Table 2: Sampson and Young's modification of Mallampati grade

Grade I:	Soft palate, uvula, tonsillar pillar and fauces seen
Grade II:	Soft palate, uvula and fauces seen
Grade III:	Soft palate and base of uvula seen
Grade IV:	Only hard palate seen

Premedication

Neurosurgical patients with intradural pathology may require steroids prior to surgery. H_2 receptor blockers should continue on the morning of surgery to prevent stress and drug induced gastritis. All antihypertensive and cardiac medications (except ACE inhibitors) should be continued on the day of surgery. A mild sedation in the form of benzodiazepines/opioids may be given to conscious patients who do not have significantly raised ICP. None of these sedatives should be given to patients with impaired consciousness or with raised ICP, because these drugs may cause hypercapnia, hypoxia and airway obstruction. On the other hand, non-premedicated, anxious patients may have systemic hypertension, leading to increase in CBF. Therefore, it is advisable that such patients be given intravenous sedative premedication.

General Anaesthesia for Neurosurgical Procedures

Comprehensive monitoring during anaesthesia is needed for adequate assessment of a neurosurgical patient. It includes haemodynamic monitoring in the form of electrocardiogram (to see the heart rate and detect arrhythmias), arterial blood pressure (invasive or non-invasive) and central venous pressure monitoring.

The CVP catheter placement is considered to be useful when there is a risk of venous air embolism (VAE), coexisting cardiovascular disease, anticipation of substantial blood loss or with the use of ionotropic drugs. The tip of the catheter is positioned near the superior vena cava-right atrial junction and provides measurement of the intravascular volume status. Pulse oximetry measures oxygen saturation and end tidal CO_2

monitoring (capnography) measures CO_2 concentration in the expired air. The latter may be useful in detecting air embolism, as well as in assessing partial pressure of CO_2 in arterial blood and its effect on CBF. A precordial Doppler ultrasound, pulmonary artery catheter and transoesophageal echocardiography (TEE) are useful in cases with coexisting cardiac disease, as well as in cases with the risk of air embolism and operation in the sitting position.

BIS monitoring (Bispectral assay) may also be used to measure the level of hypnosis or sedation. Varieties of EEG signals are analysed and interpretation is done in the form of numerical values, called the BIS index. These numbers, derived from EEG analysis, are helpful in assessing the depth of anaesthesia. Its use has been demonstrated in reducing the doses of anaesthetic agents and in reducing the recovery time.[17] ICP and neurophysiological monitoring are an important part of the monitoring armamentarium.

The primary goals during induction are: (a) control of $PaCO_2$; (b) control of blood pressure (adequate depth of anaesthesia); (c) prevention of outflow obstruction of jugular venous blood; (d) adequate oxygenation and hyperventilation and (e) prevention of awareness. The typical scheme for smooth induction include intravenous administration of thiopentone (4–7 mg/kg), propofol (2–2.5 mg/kg) or etomidate (0.3 mg/kg) to produce hypnosis and, an opioid (fentanyl 1–2 μg/kg, sufentanil or ramifentanil), to produce analgesia to maintain strict haemodynamic control during intubation. Before giving a muscle relaxant, mask ventilation of the patient is ensured, to reduce the risk of hypoxia if intubation fails following the administration of muscle paralysing agents. For muscle relaxation, vecuronium bromide or atracurium bysilate is preferred because of minimal cerebral haemodynamic alterations. The use of succinylcholine should be reserved for patients in whom intubation difficulties are anticipated or when rapid sequence induction is absolutely unavoidable.

To achieve the morning sniffing positioning (ideal intubation position) for the intubation, a small pillow should usually be placed under the occipit to flex the neck and extend the atlanto-occipital joint. This straightens the path of vision from the upper incisor to the larynx. The curved blade is inserted toward the right side of the patient's mouth to prevent the tongue from restricting the view of the larynx. The blade tip is advanced along the tongue in front of the epiglottis to the vallecula. Then the laryngoscope is used to lift the base of the epiglottis forward to reveal the cords. Intubation is done with an appropriate sized endotracheal tube, which may be of PVC or may be armoured. Confirmation of correct placement of the endotracheal tube is made as follows: (a) the anaesthetist watches the tube pass through the cords to a position in front of the arytenoids; (b) air entry into the trachea causing bilateral, symmetrical inflation of lungs may be ascertained by auscultation; (c) the end tidal CO_2 from the expired gas during ventilation through the endotracheal tube may be assessed (it is detected continuously when the tube is in the trachea, but disappears after a few breaths when the tube is in the oesophagus) and (d) the tracheal rings may be visualised by introducing a fibreoptic bronchoscope through the endotracheal tube.

Direct laryngoscopy and intubation cause an increase in heart rate, arterial pressure and in many cases, arrhythmias. The response may be minimised by deepening of anaesthesia by an additional dose of propofol or thiopentone,[56] fentanyl 2 μg/kg, lignocaine 1–1.5 mg/kg, β blocker esmolol 150 mg or vasodilators, like sodium nitroprusside or nitroglycerine.[45]

Application of head pins during patient positioning is a painful stimulus. This can be abolished by deepening the anaesthesia (e.g. Thiopentone 1 mg/kg or Propofol 0.5 mg/kg) or by administering an analgesic (bolus of Fentanyl 1–3 mg/kg, alfentanyl 10–20 μg/kg or remifentanil 0.25–1 μg/kg) in conjunction with local anaesthetic infiltration of the pin site, to prevent undesirable CNS arousal and haemodynamic activation.

Tight Brain during Surgery

Adequate brain relaxation facilitates neurosurgery and reduces the need for excessive brain retraction. A swollen brain is prone to develop ischaemic injury. In addition, brain swelling interferes with surgery and, on occasion, may prevent the closure of the duramater. The following manoeuvres may be instituted to treat this urgent problem:

- Check ventilation. Moderate hypocapnia (target $PaCO_2$ 25–30 mmHg) will produce cerebral vasoconstriction and consequently reduce brain swelling.
- Ensure normal oxygenation.
- Control blood pressure. The target is normotension (within 10% of baseline blood pressure).
- Ensure adequate venous drainage from the brain. Neck torsion or the placement of endotracheal tube ties around the neck can impede venous drainage from the brain.
- Head elevation (30° optimum).
- Check intrathoracic pressure. Rule out pneumothorax (especially if a central line has been placed).
- Maintain adequate neuromuscular relaxation.
- Administer intravenous mannitol.
- Make sure that the concentration of the volatile anaesthetic agent is less than 0.5 MAC.
- Discontinue the administration of N_2O.
- Switch to an intravenous anaesthetic technique. A combination of propofol and opioid infusion is ideal.
- If the brain swelling does not abate, then the probability of intracranial hypertension in the post-operative period is high. Barbiturates (pentobarbital) may be administered until either the swelling is reduced or burst suppression of the EEG is attained. On rare occasions, the surgeon may elect to amputate noneloquent brain or to close the scalp without closing the dura or replacing the bone flap.

The goal of fluid therapy during neurosurgical procedures is to maintain normotension and normovolaemia. Neurosurgical patients often receive diuretics (e.g. mannitol and/or furosemide) to reduce intracranial hypertension or oedema pre-operatively. Large amounts of intravenous fluid are required to correct pre-operative dehydration and to maintain intra-operative and post-operative haemodynamics. Hyperglycaemia may increase neurological damage during cerebral ischaemia and may worsen outcome from both focal and global ischaemia.[31]

Crystalloid solutions do not contain any high molecular weight compound and have an oncotic pressure of zero. Non-glucose containing iso-osmolar 0.9% normal saline is the solution of choice for intracranial surgeries. Colloids have an oncotic pressure similar to that of plasma and both contain large molecules that are relatively impermeable to the capillary membranes. Dextran and hetastarch (hydroxyethylstarch) are dissolved in normal saline, so the osmolarity of the solution is approximately 290–310 mOsm/L. It, therefore, is suitable for use as a plasma expander.

Emergence from Anaesthesia

The emergence of the neurosurgical patient from anaesthesia may be affected by depression of the central respiratory drive, decrease in the tone of airway muscles, rise in ICP by hypoxia or hypercarbia and sympathetic stimulation, leading to systemic hypertension and further increase in ICP. The emergence should be aimed at having minimal effects on the MAP, CBF, ICP, $PaCO_2$ and temperature. Neostigmine (an anticholinesterase drug) is given to reverse neuromuscular block and anticholinergic drugs (like atropine or glycopyrrolate) are added to counteract its cardiac side effects. The extubation is facilitated by a small top-up dose of intravenous anaesthetics or analgesics and a short burst of volatile agents, to prevent coughing or bucking on the endotracheal tube, during its removal.

If the patient is not responding even after 20–30 min of cessation of all the anaesthetic agents and opioids (delayed emergence), a CT scan or MRI scan may be done to rule out intracranial bleeding, cerebral oedema, pneumocephalus or cerebral infarction. A seizure or any other metabolic disorder should also be ruled out.

ANAESTHETIC CONSIDERATIONS FOR DIFFERENT TYPES OF NEUROSURGICAL SITUATIONS

Intracranial Tumours where ICP is a Concern

Traditionally, anaesthetic agents that increase CMR or CBF result in increased CBV and ICP. However, the relationship between these agents and ICP is complex and adjuvant techniques (e.g., hyperventilation) and medications (mannitol) often mitigate the possible adverse effects.

Among the volatile agents, isoflurane, sevoflurane or desflurane would be considered as a better choice than halothane for patients with intracranial pathology. However, none of the drugs appear to have adverse effects when hypocapnia is present. Sevoflurane and desflurane appear to have advantages for intracranial neurosurgery, because of the possibility of faster awakening. The situation with nitrous oxide is probably different. A growing appreciation of the propensity of nitrous oxide to increase CBF and ICP and the fact that hypocapnia does not reduce this effect, has suggested that it may be a poor choice in patients with high ICP. Nitrous oxide is also a poor choice when closed air-filled cavities are present (e.g. pneumothorax, air embolism and pneumocephalus) because nitrous oxide diffuses into these cavities, thereby increasing the mass effect. The role of ketamine also remains controversial because of its property of increasing CBF and ICP.

The disadvantage of the transient rise in ICP brought about by succinylcholine administration in acute head-injured patients and other emergency situations is counterbalanced by its rapid action that facilitates emergency intubation.

Posterior Fossa Surgery

Additional monitoring would include end tidal CO_2, precordial Doppler and trans-oesophageal echocardiography (TEE), especially when the patient is at risk of venous air embolism (VAE), during posterior fossa surgery. Mid right atrial placement of central venous catheter is required for aspiration of air in case VAE occurs during surgery. The common positions for posterior fossa surgery are prone, park bench or sitting. Neurophysiological monitoring of brain stem auditory evoked response may be done for the assessment of VIII nerve function, during cerebellopontine angle surgery; somatosensory evoked potential monitoring for the assessment of brainstem function and, electromyography for the function of trigeminal, facial and lower cranial nerves. The neurophysiological monitoring requires adjustment of the anaesthetic technique. The depth of anaesthesia should be adjusted to an optimal level, to obtain adequate recordings. In case an EMG is being performed, then the effect of the muscle relaxant should be minimal.

While placing the patient in the sitting position, hypotension may occur, unless the patient has been adequately hydrated prior to anaesthesia. The pontomedullary area of the brain stem has the cardio-respiratory control centre. The patient may develop dysrhythmia or haemodynamic changes during dissection of the tumour. At the end of the surgery, the endotracheal tube should not be removed until the patient shows signs of reversal and evidence of airway reflex activity. Post-operative intubation and ventilation may be required in case the surgical time has been prolonged, there have been profound intra-operative haemodynamic perturbations, the patient was in altered sensorium prior to being

anaesthetised, and/or handling of the region around the respiratory centre and lower cranial nerves (IX, X, XI and XII) has been done.

Aneurysmal Subarachnoid Haemorrhage

ICP may be higher (approximately > 30 mm of Hg) in poor grade (modified Hunt and Hess grade III-IV) patients after aneurysmal SAH; on the other hand, it may be normal in grade 0-II. Following SAH, there is a reduction in CBF to 30–40% of the normal values. Global reduction in CBF is proportional to the severity of the clinical grade.[23] Auto-regulation is also impaired in proportion to the clinical grade.[53] CO_2 reactivity of the vessels is preserved, unless there is severe physiological compromise.[11] Electrolyte imbalances are a frequent occurrence. Treatment should be aimed at correcting the electrolyte abnormality, while maintaining a normal intravascular volume. In addition, hyperglycaemia often develops in patients with SAH and is associated with a poorer prognosis.[25]

ECG changes primarily involve ST segment changes or T wave inversion and occur in 40–60% of patients having SAH.[2] These ECG changes usually do not affect outcome.[59] Ventricular dysfunction occurs in 10–20% of the patients and may be more severe in poor grade patients.[35]

The anaesthetic goals of the management, during clipping of the aneurysm, are maintaining adequate CPP, preventing rebleeding and cerebral ischaemia, providing cerebral protection, and maintaining good brain relaxation. The MAP should be meticulously maintained in the higher range, especially in patients in poor Hunt and Hess grade.

Suzuki[50] advocated a combination of mannitol (500 ml of a 20% solution or 100 g), vitamin E (500 mg) and dexamethasone (50 mg), popularly called Sendai cocktail for prevention of the effects of ischaemia during temporary arterial occlusion. In addition, pharmacological metabolic suppression with thiopentone 5–6 mg/kg or etomidate 0.4–0.5 mg/kg administered before temporary occlusion, decreases CMR of the tissue distal to occlusion and increases the tolerance to ischaemia. The complications of aneurysm surgery include premature aneurysmal rupture (as high as 17.5%), delayed recovery, seizure, pneumocephalus, hypernatraemia, hyponatraemia, delayed neurological deficit and infection.[16]

Spinal Surgery

Cervical spinal pathology may be associated with restricted neck movements and may require awake fibreoptic intubation. During spinal surgery, emphasis must be placed on preventing instability and minimising blood loss and, occasionally, venous air embolism. In the prone position, proper care should be taken to facilitate ventilation and avoid venous engorgement, by avoiding excessive intra-abdominal pressure. The trans-thoracic approach may require separation of two lungs by the placement of a double lumen tube and one lung ventilation. There is a need for replacing the double lumen tube with a single lumen endotracheal tube at the end of surgery.

Paediatric Neuroanaesthesia

In children, the physiological and pharmacological response of the CNS during anaesthesia is different from that in adult patients. Newborn children have a CBF of 40–42 ml/100 gm of brain/min, which increases to 90 ml/100gm of brain/min at 6–40 months, 100 ml/100 gm of brain/min at 3–12 years of age and 50 ml/100 gm of brain/min thereafter. The metabolic rate for oxygen consumption in children is 5 ml/100 gm of brain per minute as compared to 3–3.5 ml/100 gm of brain per minute in adults. CBF is coupled to the metabolic demand and both increase immediately after birth. Auto-regulation in children occurs at a lower absolute value of MAP when compared with adults. The response of CBF to arterial CO_2 tension is similar to that in adults. Open fontanelles and cranial sutures make the intracranial space more compliant. This will lead to the masking of increase in the ICP (by tumour or haemorrhage). Therefore, due to this masking of the clinical signs and symptoms of raised ICP in children, tumours may not be detected until they are in a fairly advanced stage.

Infants less than 6 months do not show separation anxiety from parents and may not require any premedication. Children between 6 months to 6 years do not tolerate separation and are difficult to handle. The latter group of children may be premedicated with oral midazolam 0.5–0.75 mg/kg, oral fentanyl citrate 20 μg/kg and oral promethazine 0.5 mg/kg.[14]

General anaesthesia may be established by inhalation of a mixture of sevoflurane, nitrous oxide and oxygen. Alternatively, if the patient has an intravenous access, anaesthesia may be rapidly induced with sedative/hypnotic drugs, such as thiopental (5–8 mg/kg). Patients with a full stomach and difficult airway should have a rapid-sequence induction of anaesthesia with thiopental or propofol, following which muscle relaxants like succinylcholine or rocuronium should be added.

The infant's larynx is funnel shaped and narrowest at the level of the cricoid cartilage. Thus, an infant is at risk of developing subglotic obstruction, secondary to mucosal swelling after prolonged endotracheal (ET) intubation with a tight-fitting ET tube. The trachea of infants is relatively short; an ET tube can migrate into the bronchus if their head is flexed during positioning. Therefore, both lungs should be auscultated to rule out an inadvertent intubation of a main bronchus, after the final positioning of the patient. The ET tube may also kink at the base of the tongue when the head is flexed. Nasotracheal tubes are best suited for situations when the patient is to be placed prone and when post-operative mechanical ventilation is anticipated.

Normovolaemia should be maintained throughout the procedure as fluid restriction, blood loss during surgery and diuretic therapy for brain relaxation may lead to haemodynamic instability. Normal saline is commonly used as the maintenance fluid during neurosurgery, because it is mildly hyperosmolar (308 mOsml/kg).

Hydrocephalus is the most common neurosurgical problem in the paediatric population. Shunt procedures are usually not associated with significant blood loss, but exposure of a large surface area of the body during surgery may cause hypothermia.

Hydrocephalus is frequently present in patients with meningomyelocoele and they require a CSF diversion procedure before the correction of the meningomyelocoele. Congenital heart defects occur in 37% of patients with meningomyelocoele. Other associated problems include split cord malformation, abdominal wall defects, malignant hyperthermia and latex allergy.[51] Intubation in the supine position may only be possible with the meningomyelocoele sac protected in a doughnut mattress. In cases with a very large defect, intubation may be done in the lateral position. Fibre-optic intubation may help.

Craniosynostosis surgery may be associated with risk of VAE or intra-operative blood loss, requiring appropriate management.[13]

Post-operative and Intensive Care

Mechanical Ventilation

The use of mechanical ventilation in a neurosurgical patient needs to be considered carefully and should be a joint decision of the surgeon and anaesthetist. The aim of mechanical ventilation should be decided and may include either support for airway protection, ventilation (CO_2 elimination) or oxygenation. Ventilation may be inadequate due to coexisting primary lung diseases, depression of ventilatory drive or residual effect of anaesthetic drugs. Ventilatory assistance may be provided with the following modes: (a) controlled mode of ventilation (CMV, to be used in patients with no spontaneous breaths); (b) assisted/controlled mode of ventilation (AMV, in patients who initiate spontaneous breaths but cannot maintain adequate minute ventilation without support); (c) synchronised intermittent mandatory ventilation (SIMV, when ventilator breaths are delivered synchronised with the patient's breaths); (d) pressure support ventilation (PSV, that augments spontaneous breaths by pressurising the ventilator circuit to a preset value until the inspiration is terminated) and (e) pressure controlled ventilation (PCV, that delivers a pressure-limited, time cycled breath which helps in limiting lung injury). Oxygenation can be improved by applying PEEP (positive end expiratory pressure, that keeps the alveoli open at the end of expiration) or by inverse ratio ventilation (that increases the proportional time of inspiration when compared with expiration). This will lead to improved functional residual lung capacity and reduced ventilation perfusion mismatch.

During mechanical ventilation, it is mandatory to use pulse oximetry to monitor oxygen saturation, capnography to assess the end tidal CO_2 level and serial arterial blood gas monitoring to assess arterial oxygen and CO_2 concentration, pH and electrolytes.

Sedation and Analgesia

In an intensive care setting, many sedative and analgesic drugs have been administered by continuous infusion. Midazolam, a water soluble, non-analgesic benzodiazepine with a rapid onset of action, induces sleep, reduces anxiety and decreases muscle tone. The loading dose is approximately 0.1–0.2 mg/kg followed by continuous infusion of 0.05 mg/kg/hr. Propofol in a dose of 2– 4 mg/kg/hr produces satisfactory sedation without any harmful effects on CPP.

In the narcotic group, morphine in the form of intermittent boluses (2–4 mg IV) or continuous infusion (2–3 mg/hr) may be given. Synthetic opioids like fentanyl (1 mcg/kg/hr) and alfentanyl (24 mcg/kg/hr) have a limited duration of action, due to a short elimination half-life and a small volume of distribution. Haemodynamic effects are minimal and recovery from respiratory depression is rapid. Intermittent supplementation with midazolam (0.1 mg/kg) can also be used for sedation along with these agents.

Haemodynamic Management

Hypertension: It may occur following reversal with the risk of precipitating cerebral haemorrhage and myocardial ischaemia. An antihypertensive agent may be selected from amongst short acting vasodilators like sodium nitroprusside (SNP) and nitroglycerine (NTG), ganglionic receptor antagonist like trimethaphan, rapidly acting beta adrenergic blocker like esmolol or metoprolol, a longer acting vasodilator like hydralazine (10–20 mg 4–6 hourly) or calcium channel blockers. SNP infusion is started in a dose of 0.5–10 μg/kg/min. Infusion of SNP and NTG lead to rebound hypertension when the infusion is terminated. ICP and level of consciousness should be carefully monitored during SNP infusion, as rapid infusion may lead to raised ICP when intracranial compliance is reduced. Both the drugs may cause increased ICP, because cerebral capacitance vessels dilate and increase CBV. Trimethaphan has a short half-life (1–2 min.) and it seldom increases ICP in patients with reduced intracranial compliance, because ganglionic blockade spares the cerebral circulation. Esmolol in the dose of 500 μg/kg bolus and 50–200 μg/kg infusion has been used successfully in controlling hypertension after craniotomy. It can be safely used in patients with hepatic and renal disease. Its action dissipates quickly in the post-operative period. Metoprolol caused no change in ICP, CBF and $CMRO_2$, when administered to patients with increased ICP after head injury.[4]

Nefidipine, nicardipine and hydralazine are difficult to titrate and may lead to intracranial hypertension.

During hypotension, the first step is to assess the patient for hypovolaemia. Clinical assessment and invasive monitoring are used to measure the intravascular volume. Volume replacement is done with crystalloids, preferably normal saline (0.9%) and colloids. Fluid therapy is guided with CVP monitoring and pulmonary artery pressure monitoring in patients with LV dysfunction.

If there is no response to fluid therapy, ionotropic drugs are infused. If left ventricular (LV) function is good and there is peripheral vasodilatation, phenylephrine in the dose of 2–10 μg/kg/min is given. Dopamine infusion (2–20 μg/kg) is a good choice if LV contractility is not good. Noradrenaline can be added if peripheral vasodilatation exists.

Management of Disorders of Sodium Concentration

Sodium is an osmotically active, primary cation in the extracellular compartment. It contributes 90–95% of extracellular osmotic activity. Clinical disorders of sodium concentration, i.e. hypernatraemia and hyponatraemia, usually reflect alterations of body water content and not the state of sodium balance. Regulation of sodium concentration is achieved by plasma volume receptors (atrial natriuretic peptide), endocrine and renal mechanisms (ADH and aldosterone).

Hyponatraemia ($Na^+ \leq 135$)

Symptoms and signs depend on both the rate and severity of decrease in serum sodium level. Levels less then 120 mEq/L usually result in CNS symptoms like disorientation, lethargy, and coma. Acute hyponatraemia may result in brain oedema. Hyponatraemia with a normal or high osmolarity results from the presence of non-sodium solutes like glucose, mannitol, urea or toxins. The treatment requires reduction of elevated concentration of the responsible solute.

Hyponatraemia with hypo-osmolarity is associated with high total sodium like in congestive cardiac failure and renal failure. It is treated with sodium and water restriction, increase in cardiac output and increase in renal blood flow. Hyponatraemia with low total body sodium is associated with non-renal or renal loss of sodium (e.g. adrenal insufficiency). This condition is treated by restoration of blood volume, eliminating excessive sodium losses and by treatment of the adrenal insufficiency.

Euvolemic hyponatraemia is associated with a relatively normal total body sodium and extracellular volume. The syndrome of SIADH is associated with excessive release of ADH. It is treated using water restriction, loop diuretics and haemodialysis.

Neurological symptoms due to severe hyponatraemia ($Na^+ < 115$ mEq/L) and water intoxication may require aggressive therapy with hypertonic (3%) saline and intravenous furosemide. Saline, administered at the rate of 1–2ml/kg/hr increases plasma sodium by 1–2 mEq/L/hr. CNS signs and symptoms usually improve within 24–72 hours. Excessively rapid correction of hyponatraemia may result in cerebral haemorrhage, congestive heart failure and a permanent neurological condition called central pontine myelinosis or the osmotic demyelination syndrome.

Hypernatraemia

Hypernatraemia ($Na^+ > 150$ mEq/L) indicates an absolute or relative water deficit, loss of water or gain of sodium in excess of water and is always associated with hypertonicity. The clinical consequences are most serious at extremes of age[18] and in cases when there is a rapid fall in sodium level. Brain tissue dehydration produces mental lethargy and seizures. Hypernatraemia can be associated with hypervolaemia, euvolaemia or hypovolaemia and is treated accordingly. Hypernatraemia is corrected slowly due to the risk of cerebral oedema and seizures and sodium levels are reduced by not more than 1–2 mEq/hr.

After pituitary surgery, patients have high chances of developing transient or permanent diabetes insipidus (DI). Hypernatraemia secondary to diabetes insipidus is managed, depending on whether it is due to a central or nephrogenic cause. Central diabetes insipidus may require exogenous replacement of ADH with either desmopressin (DDAVP in doses of 1–4 μg every 12–24 hours subcutaneously or intranasal in five times higher dose or aqueous vasopressin 5–10 μg subcutaneously 4–6 hourly). Total body water deficit can be estimated from plasma Na by the following equation (TBW = 0.6 × body weight in Kg) – (140 ÷ actual Na^+) × 0.6 × body weight in Kg. Replacement of half the deficit should be started and further deficits should be evaluated on an hourly basis. The fluid therapy is guided by serum and urine osmolality, Na^+, K^+ and glucose levels.

Every neurosurgical procedure causes alterations in myriad dynamic physiological processes of the CNS. An active and involved anaesthesiologist achieves a favourable outcome by using an anaesthetic technique which is most appropriate for the occasion and with which he is most familiar. The choice of the anaesthetic agent and the method used can directly influence the surgical procedure and may have a significant impact on the patient's outcome.

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206 Positioning in Neurosurgery

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POSITIONING FOR NEUROSURGERY

Positioning for neurosurgical procedures is of paramount importance to the outcome of surgery. Unlike in other surgical fields, a lot of importance is given for proper positioning of the patient during surgery. A good amount of time is spent following induction of anaesthesia in positioning the patient. Every neurosurgeon takes special care to be sure that the patient's position on the operating table is ergonomical and most appropriate for the surgery that is planned. Each neurosurgeon has his own specifications, as regards the way he wants the patient to be on the operating table. Also, each patient is unique and the final position should be tailor-made for that particular patient. This may mean modification from the standard position for that surgery. It may thus vary from the recommended standard textbook description.

Proper positioning in neurosurgical procedures is:

- To provide an adequate exposure of the operative site without excessive retraction of the brain.
- To make surgery ergonomical and less tiring for the surgeon. The more comfortable the surgeon is the better are the surgical results.
- To ensure patient safety and comfort, so as to reduce the post-operative discomfort of the patient.
- To permit free access to the anaesthetist for maintaining safe anaesthesia and ability to continuously monitor the patient.
- To permit extension of the operative field if required.
- To ensure adequate venous drainage from the brain in case of cranial surgery.
- To avoid undue pressure on vital tissues, especially during spinal surgery.

A good operating table is a pre-requisite for proper positioning. It can be selected according to the preference of the surgeon and financial resources. It should keep the patient secure and should be manoeuvrable, so that minor changes while performing surgery can be undertaken easily without much delay or difficulty.

The first step in the learning of neurosurgery is to know the appropriate exposure for the surgery and the position in which this can be accessed optimally.[3] Every neurosurgeon in his initial training has been careful to ask his chief operating surgeon the minor details for positioning the patient.

The principles/steps to be followed during positioning of the patients are:

- The operative site should be easily accessible.
- The operative field should be least dependant. This makes operating on the area of interest comfortable and less stressful. The area should also have a direct line of sight. This avoids undue retraction of the brain.
- Making use of gravity to help in retracting the brain. This reduces retraction induced injury to the brain and the morbidity associated with it.
- The patient should be comfortable throughout the procedure. The pressure points, such as the malleoli and the axilla should be properly padded and protected. Any undue pressure or traction of any of the limbs should be avoided. Special care regarding the position of the upper and lower limbs should be taken. This avoids undue pain and discomfort of the patient post-operatively, as also pressure palsies of nerves. Some surgeons use appliances as G suit, to prevent venous thrombosis in the lower limbs during prolonged surgeries.
- The operative field should be at a higher position than the heart. This helps reduce venous congestion and oozing, thus providing a bloodless field. There should be no pressure on the neck vein during cranial surgery and no compression of the abdomen while the patient is in the prone position.[4]
- Proper space should be available for adjuncts, such as self-retaining retractors, CUSA, drills, operating microscope, endoscopic equipment and intraoperative monitoring. The need for these should be planned prior to surgery, so that optimal space is made available for them.
- The position of the scrub nurse is also important. It should be such as to make the transfer of instruments easy, safe and unhindered during surgery. The scrub nurse and her table should not be too close. It may interfere with the free movements of the arms of the surgeon. Too far a table hinders the smooth transfer of the instruments.
- Positioning of the patient is a dual responsibility of the surgeon and the anaesthetist. Accessibility to the anaesthetists has to be taken into consideration, while positioning. In any case, the surgeon should himself make sure that the airway is properly secured. It is

imperative to check with the anaesthesiologist that the airway pressures are within normal limits. This should be confirmed after the final positioning of the patient. High airway pressures may result in undue intra-operative complications, such as brain bulge and excessive venous oozing.[6] A reasonable guide to uncompromised airway is a two-finger breadth space between the manubrium and the chin.

- Special precautions to be taken in elderly patients: excessive rotation of the neck should be avoided as they may have spondylotic spines with compromised spinal canals.
- The head can be placed on a head-rest (horse shoe) or can be fixed with skull fixation systems (Sugita or Mayfield-Kees skull fixation systems). The horse shoe should be soft and adequately padded. Special care should be taken while positioning the patient prone to avoid undue pressure on the eyeballs. While using the skull fixation systems with pins, care should be taken to avoid the midline, the frontal sinuses, the squamous temporal bone and temporalis muscle.
- The head and neck position have significant effect on the intracranial pressure. Excessive rotation and flexion of the head and head down position result in significant raised ICP, by increasing the cerebral venous pressure by impeding the cerebral venous drainage. Patients with compromised ICP are more affected during identical manoeuvres than those with normal compliance. Although there are pharmacological means to control or reduce the ICP, proper positioning can itself significantly reduce the raised ICP. Studies have shown significantly higher ICP in the prone than in supine position. A reverse Trendelenburg position by 10 degrees itself reduces the ICP without compromising the CPP.

These are some steps to be followed for every patient. Every neurosurgeon should make his own list of important steps to be followed, while positioning the patient. The operating position for the neurosurgeon should be such that it suits him. The surgeon may prefer to operate in the standing or sitting position. A standing position provides for greater and faster mobility. The entire operative field is under vision and the surgeon may make minor adjustments, swiftly. While this is difficult in the sitting position,[5] it is more ergonomic and less tiring to operate in the sitting position. With the upper limbs supported, the muscle fatigue is less and tremors of the hands are reduced. Keeping in mind these general principles the standard positions have been described and subsequently variations of these have also been mentioned. These are divided into three groups: positioning for cranial, spinal and nerve repair procedures.

Cranial Procedures

Supine Position

The supine position with varying degrees of rotation of the head can provide adequate access to procedures for frontal, pterional, temporal, interhemispheric, trans-sphenoidal and transbasal approaches. This is one of the most commonly used positions. Various craniotomies which can be done in this position are:

- Bifrontal or unilateral frontal craniotomy
- Frontotemporal, pterional and Falconer's craniotomy
- Temporal and temporoparietal craniotomy
- Trans-sphenoidal approaches
- Frontal/frontoparietal parasagittal craniotomies
- Burr hole placements for drainage of chronic subdural haematoma and ventriculoperitoneal shunts.

Additional points to be considered while positioning the patient supine are:

- The patient should be more towards the left or the right side of the operating table, depending upon the side of the craniotomy. This makes access to the field more comfortable.
- The head should be sufficiently out of the upper edge of the operating table. This makes manoeuvrability of the head easy for positioning. This avoids obstacles and provides more working space.
- When planning frontal craniotomy when more extension is required, a sand-bag or a pillow should be placed below the shoulders. The degree of extension varies as per the procedure. Transbasal transfrontal approaches require more extension, as compared to craniotomy for frontal lobe surgery. Contralateral rotation by 10–15 degrees is useful for unilateral procedures, whereas the neutral position is preferred for bifrontal approaches.
- When planning a temporal or pterional craniotomy, the shoulder ipsilateral to the craniotomy should be elevated and supported with a sand bag. This avoids undue traction on the brachial plexus. For a pterional craniotomy, the head is extended to make the maxilla most prominent. The amount of rotation depends upon the trajectory planned. While a more anterior exposure of the Sylvian fissure requires greater rotation, a more posterior exposure of the Sylvian fissure requires more extension and less rotation.
- When planning interhemispheric procedures, the degree of flexion or extension of the head should be such that the planned site of entry should be kept highest. More posteriorly placed lesions require more flexion. The tables can also be broken midway, which further helps in bringing the posteriorly placed lesions into direct trajectory, without excessive flexion of the neck, which may compromise the venous return and complicate surgical procedures.
- For the trans-sphenoidal approach, the head should be mildly flexed and laterally rotated, so that the operating surgeon has the nostrils and the trajectory of the surgery in line with his operating position. This prevents undue bending of the surgeon over the patient and thus avoids undue exertion and discomfort.
- While doing a ventriculoperitoneal shunt through Frazier's point, the ipsilateral shoulder should be mildly elevated and the neck extended and rotated to the opposite side.

- The knees should be gently flexed with a pillow below the knees. The arms are generally placed by the side of the patient.
- Care should be taken to avoid kinking of the endotracheal tube, while putting the craniotomy drapes. As surgeons would be operating from the cranial end, the scrub nurse should not be too far away from the cranial end.

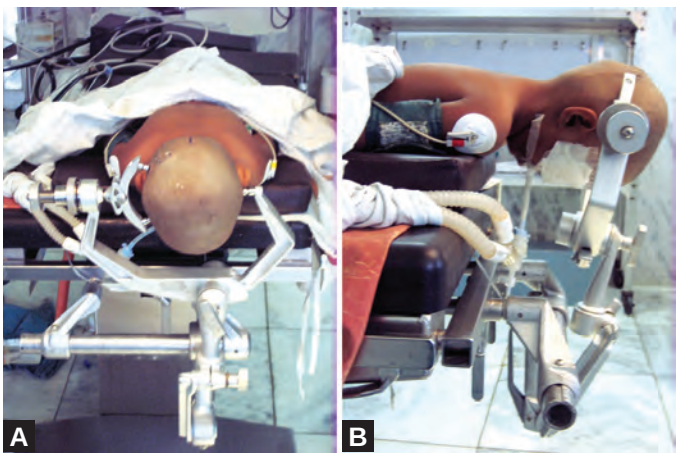
Prone Position

The prone position is used for posterior fossa procedures, such as midline/suboccipital craniectomy, posterior interhemispheric approaches, occipital, parieto-occipital craniotomies, Poppen's and Krause approach (Figs 1A and B). This position requires more care and time for positioning. Various craniotomies done in this position are:

1. Midline/paramedian suboccipital craniectomy/craniotomy.
2. Occipital/parieto-occipital craniotomy.

The patient is anaesthetised on a trolley and subsequently shifted onto the operating table. The following steps are to be followed:

- The anaesthetist usually uses a flexometallic tube for prone positions. This helps maintain better patency of the endotracheal tube and avoids kinking of the tube.
- The patient's head can be placed on a head rest or preferably fixed by three point skull fixation system. If the horse shoe is used, the rim should be soft and adequately padded to avoid a pressure sore over the face. The eyes should be padded and care should be taken to avoid compression of the eyeballs. While using the three point skull fixation, the position of the pins and frame should be such that after the final position, no part of the frame should be in contact with the face ventrally.
- Other areas such as the face, breasts, genitalia and knees should be adequately padded.



Figs 1A and B: Prone position on Mayfield clamps: (A) Patient is more towards the right end of the table. (B) Neck flexed to open the suboccipital space. The shoulders are just out to allow free movement of the neck

- The head should be brought out adequately, so as to increase the working space and avoid the obstacles due to the table and shoulders. This can be done by bringing the shoulders out adequately above the upper end of the operating table. This also helps in flexing the head at the occipitocervical junction, to open the suboccipital space.
- The patient should be more towards the right end of the operating table, to reduce the strain on the surgeon while operating.
- Adequate bolsters/pillows should be placed below the patient, so that the patient is not in direct contact with the operating table. These have to be placed over the shoulders, the thoraco-abdominal region and the pelvis. A small pillow should be placed below the leg to provide mild flexion of the knees. The abdomen should be free and there should be no restrictions in the abdominal movements.
- The extent of rotation depends upon the procedure performed. While the neutral position is maintained for suboccipital craniectomy, for a paramedian craniectomy, the patient should be rotated to the opposite side.
- The patient should be properly secured with belts or straps.

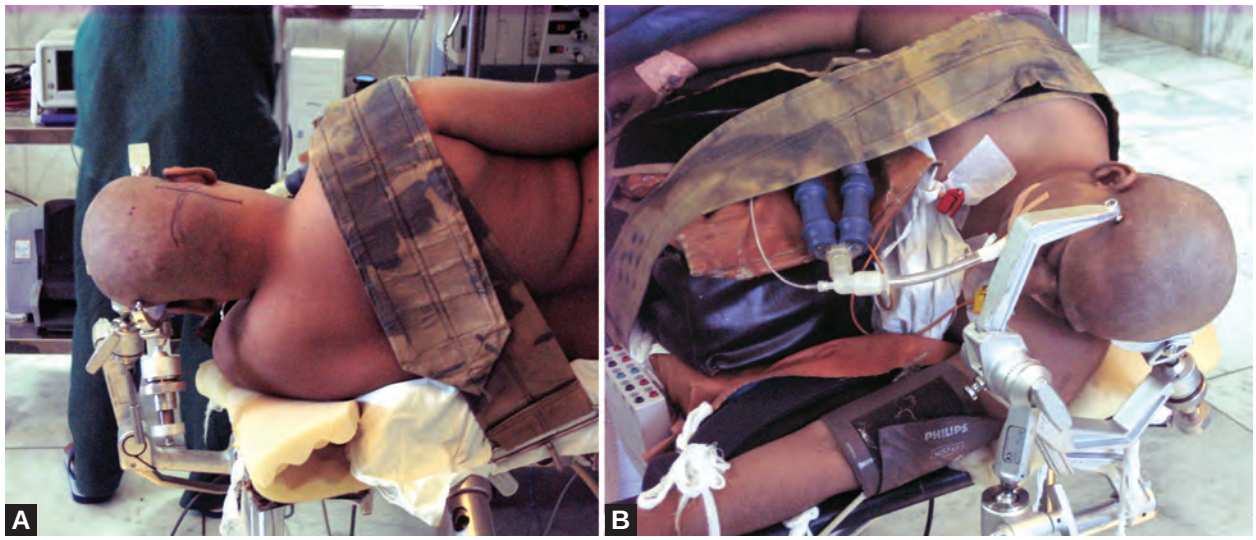
  Some modifications of the prone position are followed, as per the convenience of the surgeon. These are:

  The three-quarter position (3/4th prone): This is used by some surgeons for the parieto-occipital, vermian and supratentorial posterior interhemispheric approaches (Poppen's approach). Here, the left half of the patient is elevated by placing pillows below the bolsters on the left side of the body. This brings the right side of the body to a lower level. During Poppen's approach, this position helps in gravity dependant retraction of the right occipital lobe and the falx keeps the left occipital lobe from falling into the operative field. The upper shoulder is retracted to avoid it from obstructing the operative field. Excessive retraction may result in brachial plexus injury and should be avoided.

  Concorde position: This position is used for the infratentorial supracerebellar approach (Krause's).

Lateral Decubitus Position

This position is used for retromastoid craniectomy for cerebellopontine angle tumours and for far-lateral approaches (Figs 2A and B). Some surgeons are more comfortable in using this position for temporoparietal craniotomy and frontoparietal craniotomy for interhemispheric approaches. The patient is placed in the lateral position with the operating side up. The dependant axilla is adequately padded to avoid compression. The dependant arm is placed on an arm rest. The patient's back is brought to the edge of the operating table. The patient's head is brought out of the upper end of the operating table adequately. The upper shoulder is



Figs 2A and B: Lateral decubitus position: (A) Lateral flexion of the neck. Upper shoulder is retracted and lower shoulder is padded. Patient is towards the edge of the table. (B) Dependant arm on arm board with dependant axilla padded with sand bags and bolsters placed for support

retracted by straps, to avoid its hindering the surgeon while operating. Again, excessive retraction of the shoulders should be avoided to avoid brachial plexus injury. The body is supported by sand-bags and pillows, placed on the abdominal side of the patient and the patient is adequately strapped to secure the patient to the operating table. A pillow should be placed between the two legs with the upper leg flexed. Finally, the head has to be positioned appropriately. The head should be flexed to open the suboccipital space, laterally flexed and rotated to the opposite side, so as to bring the posterior petrous surface parallel to the trajectory of the surgery. Again, proper care of the airway and the airway pressures should be taken. It is preferable to fix the arm of the self-retaining retractor to the side opposite to where the surgeon is standing so that it doesn't interfere with the surgeon's access to the patient.

Sitting Position[2]

There has been significant decline in the use of this position due to risks such as air embolism. The current indication for the sitting position is supracerebellar infratentorial approach to the pineal region. This position gives excellent exposure to midline structures with minimal cerebellar retraction, which is facilitated by gravity. The distinct advantages are bimanual dissection as there is no need of suction because of gravity drainage of CSF and blood. Moreover, as the face is uncovered, it is directly accessible to monitor cranial nerve functions. The complications are hypotension, air embolism, tension pneumocephalus, subdural haematoma and quadriplegia. Other complications are peripheral nerve palsies (common peroneal, sciatic and recurrent laryngeal nerves), macroglossia, and haemarthrosis of the elbow. Varying incidence of air embolism in sitting or semi-sitting position has been cited by various authors. In most of these patients, the air is aspirable through central venous catheters. The tip of the CVP catheter should be at the junction of the superior vena cava and the right atrium. Presence of a patent foramen ovale is an absolute contraindication for using this position. For surgeons it is uncomfortable to operate with raised and extended arms. Monitoring for early detection and treatment of air embolism requires one of the following techniques, like trans-oesophageal Doppler, right heart catheter, fractional nitrogen extraction capnography and continuous capnography. The patient is induced in the supine position and head pins are fixed. Monitoring techniques, as intra-operative somatosensory evoked potentials,[1] have also been used, while positioning the patient to reduce the risk of iatrogenic spinal cord injury. The head end of the table is slowly elevated, over minutes, monitoring heart rate and blood pressure. Hyperventilation should be avoided at this stage, as it will further reduce cerebral blood flow. The table is flexed, the thighs elevated and knees flexed. Hyperflexion of the hips should be avoided to prevent sciatic nerve stretch. The feet should not be allowed to hang and should be secured to prevent Achilles tendon injury. The table is tilted back at the time of flexing the table to reduce haemodynamic response. Once the desirable position is attained the head may be flexed. There should be minimum two finger breadths space available between the lower jaw and the sternum. The arms are positioned in such a way that there should be no drooping of the shoulders to prevent upper trunk injury of the brachial plexus.

Spinal Procedures

Craniovertebral Junction

For transoral approaches, the supine position is used. The patient is more to the right of the operating table. The anaesthetist should be informed regarding the need of fibre-optic assisted intubation, in case there

is significant compromise of the cord and excessive movement of the spine is to be avoided. Following the transoral decompression, most of these patients require posterior fusion. While some surgeons do this as a two stage procedure, others do this at the same sitting. The patient is reversed, shifted onto a trolley and then turned prone using the same principles as followed above. Here the head should be in neutral position, so as to avoid fusion of the spine in an abnormal position. Traction has to be maintained and after final positioning, prior to inducing the patient again, the movements of the limbs should be tested. This provides an assessment of the neurological status of the patient and untoward neurological compromise that may have occurred during the positioning of the patient and decompression of the craniovertebral junction.

Cervical Spine

The supine position is used for the anterior cervical approaches for discectomies, corpectomy and fusion procedures (Fig. 3). The patient is placed supine with adequate extension of the neck. A pillow/sand-bag should be placed between the shoulder blades to extend the neck and to permit the shoulders to fall away from the operative field. The endotracheal tube should be secured properly and the patient should be more to the right edge of the operating table. This is more ergonomical, as it avoids undue bending and straining of the surgeon.

The prone position: It is used following the same principles as described above. This is used for posterior approaches to the cervical spine as for laminectomy, laminoplasty and laminotomy and foraminotomy. Care has to be taken, while turning the patient so that the neck turns along with the body. Excessive flexion or extension of the neck is avoided in an already compromised canal. It is preferable to use skull fixation for laminectomy. This provides a rigid fixation of the head and avoids unnecessary jarring movement while doing the bone work.

Thoracic Spine

The prone position is used for posterior approaches to the thoracic spine, guided by similar principles and indications outlined above.

Thoracotomy is done in the lateral decubitus position. Axillary rolls are placed below the lower axilla. The upper arm is placed on an arm rest. A pillow is placed between the legs with the upper leg flexed and the lower leg kept extended. The patient is tilted forward to about 15 degrees and strapped and secured to the operating table. The table can be flexed/broken to provide better exposure while doing a thoracotomy. However, it must be remembered to bring the table to the neutral position while doing the spinal fusion.

Lumbar and Sacral Spine

The prone position (Fig. 4) is used for posterior approaches, such as laminectomy, fenestration and discectomy, foraminotomy and posterior interbody fusion. The patient can be positioned on pillows, as described earlier or spine frames may be used. Genupectoral position is also used by some surgeons. These frames flex the spine well and the interspinous spaces are opened up, which makes access easier, especially for minimally invasive procedures, such as fenestration or endoscopic discectomies. The arms can be placed on arm boards on either side of the patient's head. Care should be taken to protect and pad the pressure points such as the eyes, breasts, genitalia and knees. The abdomen should hang free so as to decrease the intra-abdominal pressure. This decreases intra-operative venous bleeding.

Thoraco-abdominal approaches give access to D12-L1 level. The patient is positioned in the right or left lateral decubitus position, with precautions to be taken as described above. Transabdominal approaches are used for surgery at L2-L5 level. The table is flexed to open the space between the rib cage and the iliac crest. The upper leg should be flexed to relax the psoas muscle.

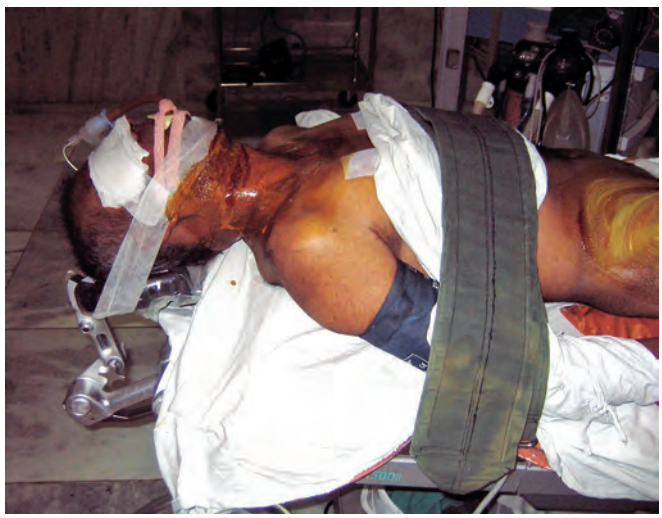


Fig. 3: Position for anterior cervical approach. Patient on horseshoe with neck in extension. Right hip elevated on sand bag for taking the graft

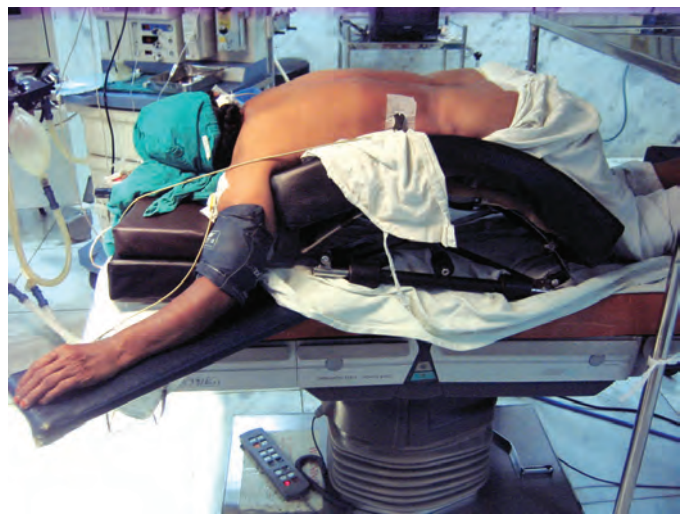


Fig. 4: Patient on Wilson's frame for lumbar discectomy. The arms are placed on an arm support

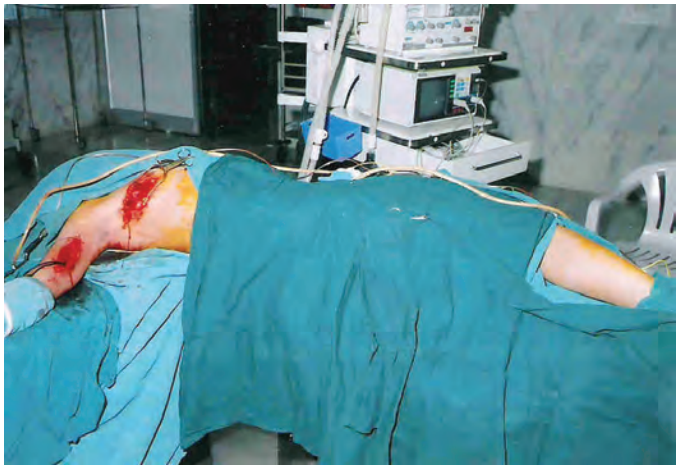


Fig. 5: Positioning for nerve repair. Note the right leg prepared for harvesting the graft. The right forearm and hand are draped for free mobility. Intercostal and musculocutaneous nerves exposed

Again, the side of the approach depends upon the surgeon's preference and the site of the pathology. A left-sided approach is preferred to avoid manipulation of the inferior vena cava and the liver. For L5-S1 access, a direct ventral approach is used. The Trendelenburg position allows the peritoneal contents to move upwards. A pillow or bolster below the sacrum can further improve the exposure.

Peripheral Nerves

Except for sciatic nerve exploration and repair, the patient is placed in the supine position for the majority of nerve repairs (Fig. 5). The involved arm/limb should be free. The site of nerve graft harvesting should also be prepared. The arm should be free for manipulation in the sterile surgical field. For repair of the upper limb nerves, the limb is placed on a side trolley and a large sand bag is placed under the ipsilateral hip, to expose the posterolateral aspect of the calf to harvest the sural nerve for a cable graft. Extent of the chest between the midclavicular line to beyond the axillary line is also prepared for the intercostals nerve harvesting (donor).

Positioning involves a conscious and concentrated effort to optimise the operating conditions for the optimal results. A thorough systemic mental check routinely reduces the chance of mistakes at various steps, thereby improving the surgical results. The importance of this initial step, in neurosurgical procedures cannot be under-estimated by any means.

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207 Operation Theatre for Neurosurgery

Rahmathulla G, Ajaya Nand Jha

"Because the newer methods of treatment are good, it does not follow that the old ones were bad; for if our honourable and worshipful ancestors had not recovered from their ailments, you and I would not be here today." —Confucius

Neurosurgery is a field, which although still in its infancy, has rapidly progressed to its present form. Scientific innovations have been the driving force bringing about this metamorphosis some which initially took millennia, now take decades and in the future may take a only a few years.[14,15]

Several major milestones have marked an evolving operative environment (Fig. 1), which begins with the basic tools to allow intracranial manipulation, development of concepts regarding asepsis in an operating environment, anaesthesia and, along with this, defining the anatomical substrate and design of tools to access various locations in the CNS. The functional concepts of the various cortical areas also began to be elucidated. Subsequent to these developments, the operating theatre being used in the general surgical specialties was specifically modified to accommodate the neurosurgeon's arsenal, ranging from pneumatic instruments, various dissecting tools, electrophysiologic monitors for recording an increasing number of parameters, the operating microscope, which by itself has evolved dramatically and tools for intra-operative neuronavigation.

EVOLUTION OF THE NEUROSURGICAL OPERATING ROOM

Operating rooms have their origin from teaching amphitheatres (Fig. 2), which were used during the Renaissance period. Early pioneers performed neurosurgical procedures in an operating environment, such as Rickman Godlee (1854 to 1920) and Francesco Durante (1844 to 1934). Harvey Cushing and Walter Dandy firmly established neurosurgery as a specialty of its own and organised the operating room accordingly. They assembled combinations of aseptic and anaesthetic protocols, which were customised and laid down.

Anaesthesia was a rapidly developing branch and, as more experience was gained, became highly specialised for neurosurgical procedures. This included continuous monitoring of vital signs and blood gases, along with methods to control intracranial pressure. Development of antisepsis and asepsis brought about dramatic changes in morbidity and mortality due to infections. Mac Ewan established one of the first steam autoclaves in England and went on to perform the first craniotomy in 1879. The neurosurgical operating environment was enhanced with these rapid developments of asepsis and anaesthesia.

In the first half of the 20th century, improvements in operating instruments and better anatomical and physiological knowledge resulted in a more refined and streamlined environment. Surgical minimalism evolved following the use of magnification during surgery with the operating microscope. Theodore Kurze (1922 to 2002) used this first in 1957, many others followed suit

Fig. 1: Evolving operative environment

Fig. 2: Teaching amphitheatres

after seeing the tremendous advantages. Peter Janetta, Robert Rand, and Mahmut Gazi Yasargil established the microneurosurgical revolution.

There has been rapid progress in the past decade in the development of the 21st century operating environment. Concepts in robotics, with complex systems were applied to cardiac surgery and fields such as urology.[8,9,23] Stereotactic surgery makes use of these advances with automatic positioning that has great safety and efficacy, especially with the Leksell Gamma knife. The cyber-knife is a new frameless system, which will change volumetric controlled radiotherapy.[1]

The neurosurgical operating environment encompasses and includes even radiosurgical planning and, thus, has a completely different meaning from the conventional operating rooms, associated with the field of surgery in general. The MRI provides increasing information and we are presently at a point where we have 3T MRI's showing us clear images of the various intracranial structures, including the white matter tracts and combined with spectroscopy. With various isotopes, functional areas can also be well-defined and mapped out. Ultrafast 64-slice scanners with 300 changes per hour have the ability to reconstruct images in three-dimensions. The three-dimension flat panel angiography suite has added to the armamentarium of the surgeon, wherein all the data can be combined and interposed, so as to give the surgeon the maximum information to optimise outcome and results. We are heading to a future where we require increased accuracy, more electrophysiologic data, less invasive techniques, better imaging data and, with nanotechnology, all this may be possible in the near future.

Improved anatomic comprehension, microscopy and microneurosurgical techniques, imaging, computers and ionising radiation, along with biomedical technology and biomolecular science, have entirely reinvented neurosurgery.[2,3]

GENERAL PRINCIPLES OF PRE-OPERATIVE CARE AND OPERATING THEATRE USE-WHO GUIDELINES[12]

Infection Prevention in the Operation Theatre

Prudent use of an aseptic technique should be made to prevent infection. These are:

- Prevent open wound contamination
- Isolate the operative site from the surrounding unsterile environment
- Create and maintain a sterile field in which surgery can be performed safely.

Aseptic technique usually refers to:

- Proper patient preparation for clinical procedures
- Hand washing
- Surgical hand scrub
- Using barriers such as gloves and surgical attire
- Maintaining a sterile field
- Using a good surgical technique
- Maintaining a safe environment in the surgical procedure area.

Pre-Operative Care and Patient Preparation

Pre-Operative Processes

Assessment for infection:

- Whenever possible, identify and treat all possible infections remote to the surgical site prior to elective surgery and postpone surgery, until the remote infection has resolved.
- Adequately control blood sugar prior to surgery and avoid hyperglycaemia.
- Tobacco cessation should be encouraged, with the patient made to abstain for 30 days prior to an elective surgery.

Pre-Operative Showering

Patient to have a shower the night prior to surgery, which is shown to decrease the concentration of skin flora, but not the incidence of surgical site infections.

Pre-Operative Hair Removal

- Shaving is not recommended
- Use hair clippers and remove hair at the incision site, only if it comes in the way.

Patient Skin Preparation in the Operating Theatre

- Wash and clean around the site of the incision to remove gross contamination (Pre-scrub)
- Use an appropriate antiseptic for skin preparation
- Prepare from the operation site outwards, not coming into the area of incision and being adequately extensive, so that a drain can be placed or incision extended.

Antiseptics for Preparation of the Skin and Hands

These are commonly used for surgical hand antisepsis and skin preparation before a surgical procedure. They should never be used to disinfect inanimate objects or surfaces, such as floors or counter tops. Instruments should never be cleaned with them as micro-organisms can gradually live and multiply and cause infection.

The common antiseptics (Table 1) used in the operation theatre (OT) with their advantages and disadvantages are:

1. Alcohol (60–90% *ethyl or isopropyl*): Effective against a broad range of organisms, e.g. bacteria and mycobacteria.

Advantages

- Rapid acting
- Non-staining
- Less expensive
- Effective in reducing vegetative organisms
- Effectiveness only moderately reduced in the presence of blood or other organic material.

Table 1: Antiseptics appropriate for use in clinical procedures

Antiseptic	Uses		
	Surgical Hand Antiseptic	*Preprocedure Skin Preparation*	*Mucous Membranes, e.g. Vagina and Cervix*
Alcohol	Yes	Yes	No
Chlorhexidine gluconate with or without cetrimide	Yes	Yes	Yes, however, products contianing chlorhexidine may not be the best antiseptics to use in antiseptics to use in the genital area because of the small potential for irritation. If an iodophor is not available, product containing chlorhexidine is the best alternative
Hexachlorophene	No	No	No
Iodine, including tincture of iodine (iodine and alcohol)	No	Yes	No
Iodophors	Yes	Yes	Yes

Disadvantages

- Has a drying effect on the skin
- Cannot be used on mucous membranes
- Evaporates rapidly and makes contact time difficult to achieve
- No prolonged activity, but the reduction is so significant that it takes sometime for re-growth.

Comments

- Cannot be used over a dirty area of skin
- The surface must be dried
- 60–90% concentration is the most effective
- Very effective hand antiseptic.

2. *Chlorhexidine gluconate (4%)*: Effective against a broad range of micro-organisms but less so against gram negative bacteria and fungi and minimal against mycobacteria.

Advantage

Has a longer duration of action of 6 hours and is effective even in the presence of blood or other organic material.

Disadvantage

Effectiveness reduced in the presence of hard water, hand creams and soaps. Stains fabric brown in the presence of chlorine based disinfectants.

Comments

- Recommended for surgical hand antisepsis and skin preparation
- Should not be allowed to come in contact with the meninges, brain, eye or middle ear.

3. *Iodine compounds including tincture iodine (iodine and alcohol)*: Effective against a broad range of micro-organisms.
4. *Iodophors (solutions such as povidone iodine, e.g. betadine®)*: Iodine in a complex form making it non-toxic and non-irritating. Effective against a broad range of microbes except mycobacteria.

Advantage

Less irritating than tincture iodine and can be used on the mucous membranes.

Disadvantages

- Effectiveness reduced in the presence of blood or other organic material
- Release of the active iodine takes about 2 minutes and hence needs to be left there for a few minutes prior to the procedure
- Less persistent activity when compared with Chlorhexidine.

Comments

- Recommended for hand antisepsis and skin preparation
- Best for use in the genital area, vagina and cervix
- Need to wait several minutes for it to act optimally
- Should not be diluted.

Principles to Maximise Antibiotic Benefit Pre-Operatively

- An antibiotic to prevent infection does not substitute for good infection control practices and surgical technique.
- Antibiotics should be used in situations where an infection would be catastrophic.
- Should be safe, inexpensive and provide adequate cover against the most probable intra-operative contaminants.
- Administer the initial dose at the time of surgery.
- Maintain therapeutic serum and tissue concentrations till a few hours after surgery.
- Do not prolong antibiotic use, as there is no evidence that this practice offers an advantage. It may promote the growth of resistant bugs.

Pre-Operative Skin Preparation of Operation Theatre Personnel

Surgical hand-washing (Fig. 3) performed prior to surgery is essential and varies from 7 to 9 minutes with older hand scrubs and between 3 and 5 minutes with newer agents (Fig. 4). This prevents the growth of microbes within the warm, moist environment of the gloves. Use of an alcohol hand scrub prior to wearing gloves lowers the quantity of the skin flora so significantly, that they take several hours to grow.

Indications

- Should be done before any invasive procedure from urinary catheterisation, introducing central lines and minor/major surgeries
- All personnel should perform antisepsis.

Tips for Scrubbing

In case of allergies, a hand scrub with plain soap and water can be performed and the hands thoroughly dried. About 5–10 ml of an alcohol scrub can then be applied and the hands allowed to dry before wearing gloves.

Warm water makes antiseptics work better, but hot water damages the skin and removes protective oils.

- Keep finger nails short
- Keep the hands above the elbows before and after scrubbing
- Avoid using a hard brush during scrubbing.

Protective Clothing for Use in the Operation Theatre

These include:

- *Masks*: To be worn covering the mouth and nose
  They should not be re-used
  If moist or stained, replace with a new one
  High efficiency masks for patients with tuberculosis

Fig. 3: Area for hand scrub

- Waterproof aprons and gowns to protect personnel from contamination with blood and fluids
- Sterile drapes (Fig. 5) to create a barrier between the sterile and unsterile areas
- Scrub suits: The OT uniform over which a sterile gown and gloves are used
- Surgical caps/hood: Usually disposable
- Eye protection and face shields: For protection of staff from HIV/HBC/HCV positive patients
- Footwear: Preferably waterproof boots or shoes covering the feet
- Surgical gloves.

Steps for wearing and taking off gloves have to be followed and are available in any introductory surgical text.

Environment and Infrastructure of a Modern Neurosurgical Operating Theatre

The operating rooms have to be designed in such a way, as to minimise any risk of infection, and provide adequate space for equipment and mobility of personnel.

The highest frequency of nosocomial infections has been reported from hospitals of the Eastern Mediterranean and South-East Asian region (11.8% and 10%), respectively[11] The most frequent nosocomial infections are those of surgically infected wounds, urinary tract infections and lower respiratory tract infections. It is estimated that 20% of these infections are contracted in the OT, with irreversible damage to the patient. The economic costs of these infections are tremendous and a WHO study has shown that the overall duration of stay in the hospital for surgical wound infections was 8.2 days and, when these occur deep at the site of the procedure, carries a mortality of 77%.

Every year, in France, about 60,000–100,000 hospitalised patients contract nosocomial infections and corresponds to 6–10% of all admissions.[16] Five to ten thousand people die of hospital acquired infections. In public health terms, these figures are as alarming as those for road traffic accidents (7,800 deaths in 2002). What about India? We have no data, but we should learn from the experience of others.

Factors influencing the development of nosocomial infections are:

- The microbial agent
- Patient susceptibility
- Environmental factors
- Bacterial resistance

The operating theatre for neurosurgery is defined as a level 4 theatre, which is a high-risk zone when one considers the risk factors associated with the procedure, duration and complexity and those with the patient (age, immune status and effectiveness of antibiotic therapy). These operating rooms have to be designed to fulfil the following criteria[11] (Fig. 4):

- Minimum filtration chain
- International standards for particulate classification

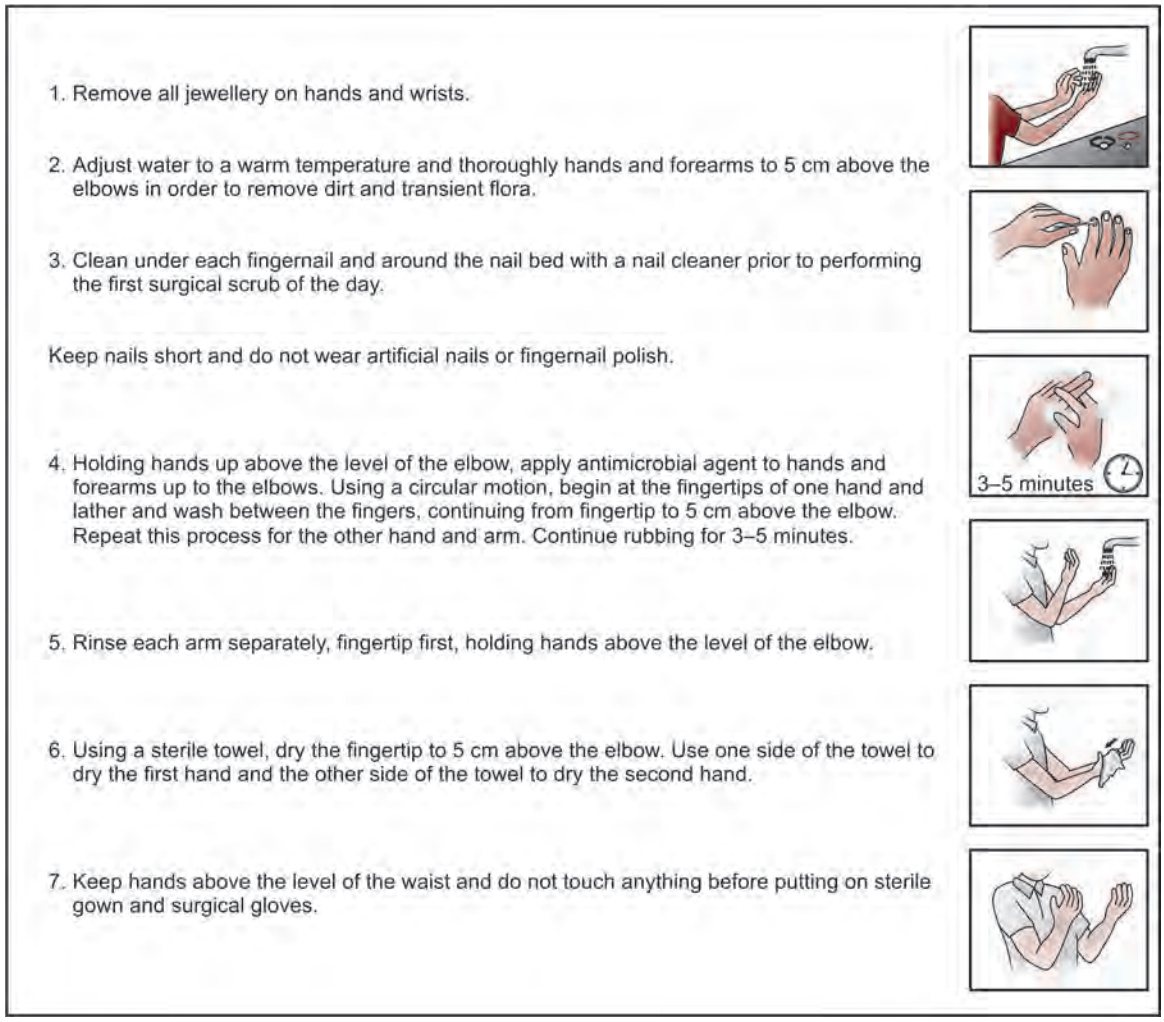

Fig. 4: Steps for a surgical hand-wash

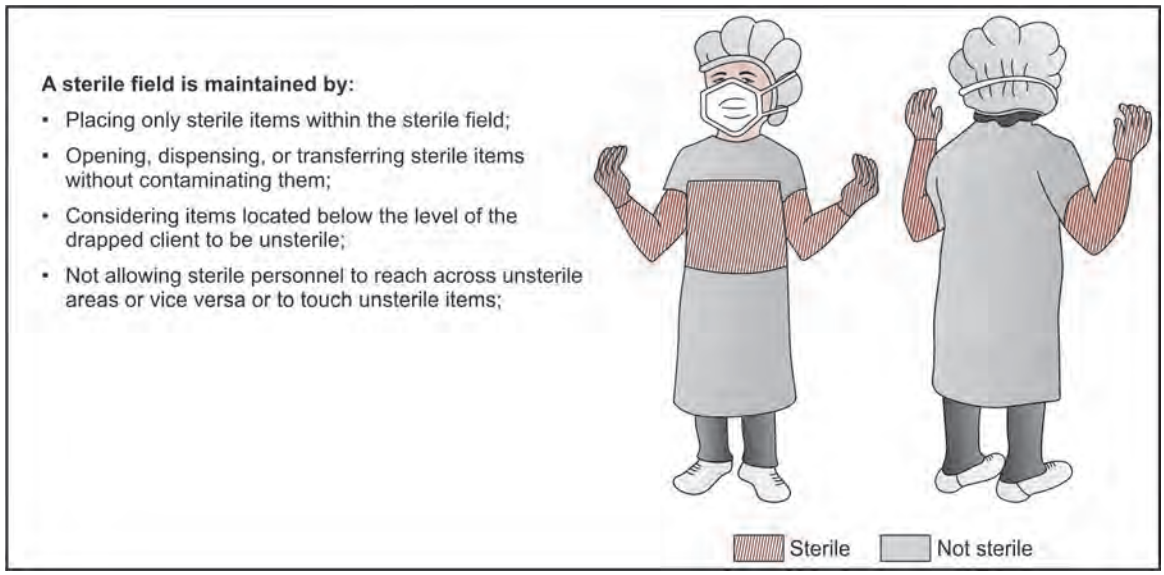

Fig. 5: Establishing and maintaining a sterile field

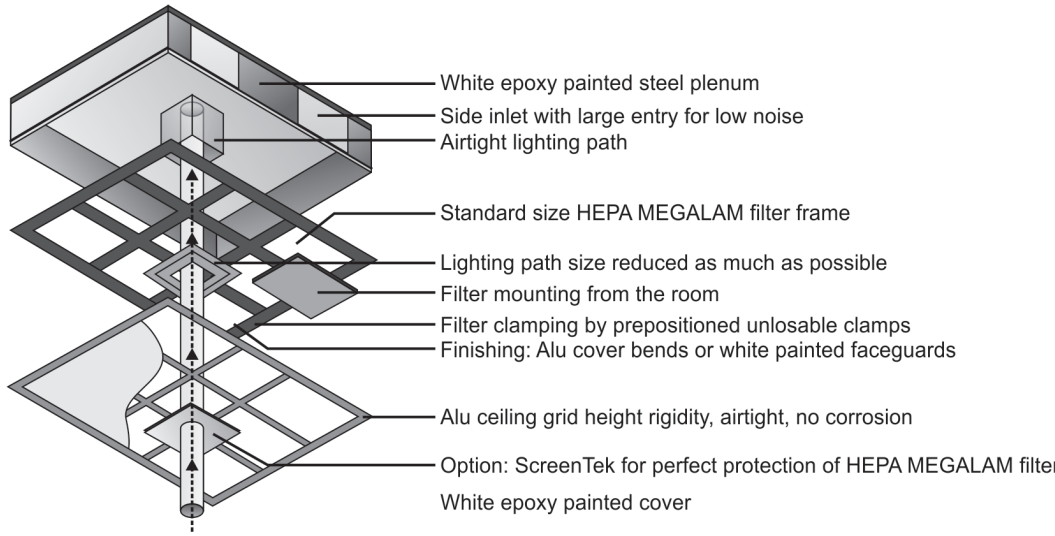

Fig. 6: Ideal ventilation system

- Particulate decontamination kinetic classification
- Use of easily decontaminable material
- Unidirectional flow
- Air exchange of the room more than 50 vol/hr
- Target bacteriological classification.

Ideal ventilation system (Fig. 6) allows frequent and efficient cleaning and disinfection.[11] Figure 7 shows the transmission cycle of infections in the OT.

Layout of the Operation Theatre

Zoned Operation Theatre

The OT should be zoned and access to this should be controlled by trained personnel. Aseptic and clean areas should be separated from the outer areas. Physical barriers may be required in order to restrict access and to maintain unidirectional movement of air in converted theatre units.

The outer zone should contain:

- A main access door
- An accessible area for waste removal
- A sluice
- Storage for medical and surgical supplies
- An entrance to the changing facilities.

The clean or semi-restricted zone:

- The sterile supplies store
- An anaesthetic room
- A recovery area
- A scrub area
- A clean corridor
- Rest rooms for the staff.

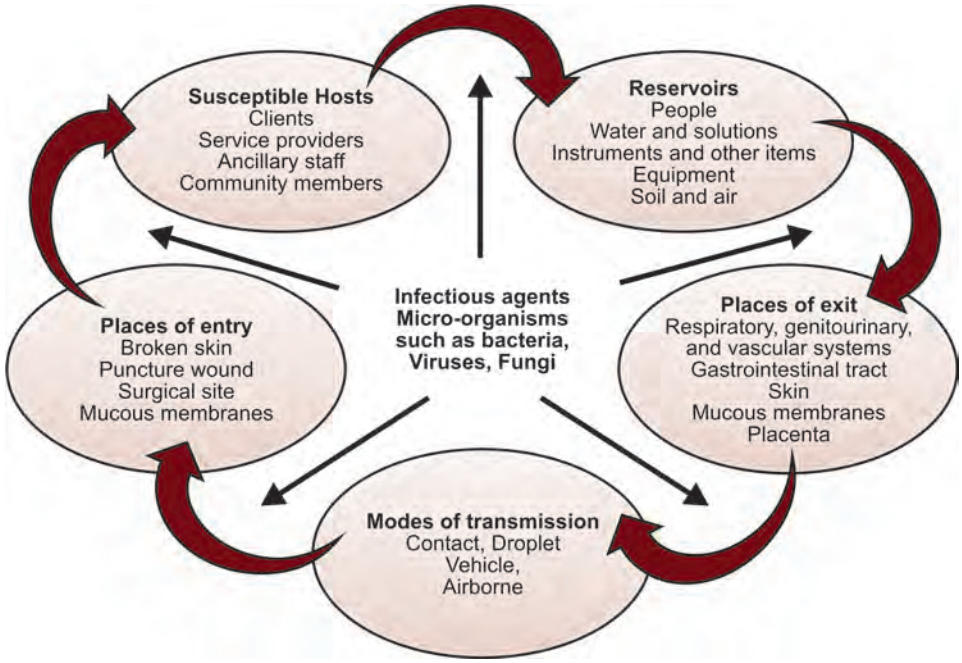

Fig. 7: Transmission cycle of infections in the OT

The staff must change into theatre clothes and shoes before entering this area, but it is not necessary to wear a mask, gloves or gown. Access from this area to the aseptic area (operating room) should be unidirectional, preferably via the scrub area. The clean zone requires exiting through the outer zone.

Aseptic or restricted area (working team only):

- The operating theatre
- The sterile preparation room.

Temperature and Humidity

Temperature and humidity play a very important role in ensuring staff and patient comfort. They must be carefully monitored and regulated. Low humidity increases the risk for electrostatic sparks.

Ideally, the OR should be 1°C cooler than the outer area, which aids in outward air movement as warmer air rises and the cooler air from within the OR moves to replace it.

Ideal Ventilation System: Air Supply and Exhaust

Positive pressure ventilation should be maintained in the corridors and areas to the operating theatre where surgical procedures are to be performed. The number of theatres supplied by air handling units (AHUs) should be consistent with their supply. The AHUs requires routine maintenance and these should not be shut off, unless undergoing servicing.

Design Features

The parameters depending on the available resources should be:

- Air changes: 15–20 air changes/hour, of which at least 3 should be fresh air from outside.
- Filtration: Prefilters with efficiency of 30%, followed by a final filter of 90%. Filters need to be changed at regular intervals.
- Air supply: Entry should be via the ceiling and exit via the floor (avoid placing furniture near the exhaust at floor level, otherwise this will impede flow).
- Doors: Should be closed except during passage of personnel and equipment.
- Traffic: Limit people going in and out of the OR as the microbial load is proportional to the number of people moving about in the theatre.
- Laminar flow and ultraclean air: This is designed to move particulate flow over the operating field in one direction. This can be designed for horizontal or vertical movement with high-efficiency particulate filters (HEPA). HEPA filters remove particles greater than 0.3 microns with 99.97% efficiency. Ultraclean air reduces the risk of surgical site infections. Appropriate use of antibiotics and good OT practices also reduce this risk and should be judiciously used in case resources for the above are not available.

There are various types of air supply:

- Plenum ventilation: Frequently used in general purpose OT's with bacterial counts at the wound site being no more than 50 to 500 CFU.
- Laminar flow ventilation (Ultraflow ventilation): Unidirectional air flow that delivers 300 changes per hour over the operating field. A bacterial count of 10 CFU or less is achieved.
- Wall mounted airconditioners: Used in some tropical countries more for comfort than anything else. The operating table receives no significant air changes and bacterial counts are unaffected.
- Freestanding air conditioners: These do not filter air and do not meet any criteria for being used in the OT.

Waste and Linen

- Minimal handling of soiled linen to avoid transmission of infections
- Body fluids to be disposed of via sluice and staff should use appropriate protective clothing and gloves
- Used linen to be contained in amperes or laundry bags and those soiled with body fluids in waterproof bags
- Other contaminated waste according to hospital and city guidelines, usually colour coded, depending on type of waste.

Environmental Cleaning and Maintenance of the OT

Simple, clear policy and guidelines, which may be set up by the institute.

Microbial Sampling

Depends on the Institute criteria for outbreak of infections and the policy is set in consultation with the Infection Control Committee (ICC). There should be an institutional Infection Control Committee (ICC). In every suite of OTs, a senior nurse should be designated to help the ICC. There should be regular monitoring of the data collected by ICC and a formal warning system established to initiate corrective measures, in the event of any unacceptable degree of contamination observed.

Theatre Sterile Services Unit

- Should have autoclaves and areas for washing and cleaning of instruments
- If available, the only services required would be to rapidly sterilise dropped equipment (134°C for 3–4 min) and for the decontamination of fibre-optics.

Neurosurgical Operating Room

We have covered the basics of operating room design, maintenance of sterility and basic sterile procedures in the operating theatre. From here on, we describe the equipment (Fig. 8) and layout of a neurosurgical operating room, which includes an introduction to the basic equipment used, followed by an introduction to the state of the art operating room (Courtesy, Max Institute of Neurosciences, Saket).

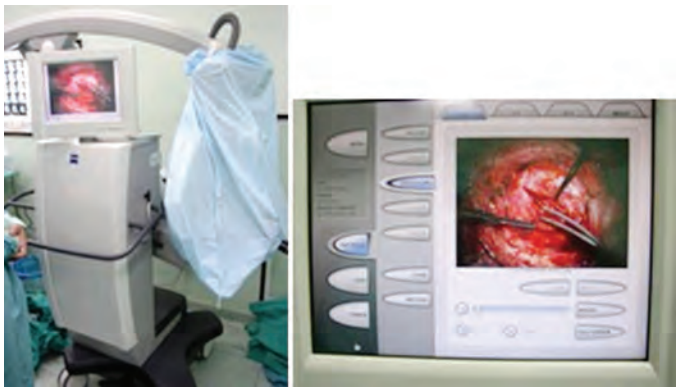

Fig. 8: The Zeiss OPMI PENTERO

Present day OT's are an integration between the neurosurgeon and his requirements, engineers and the technology to bring about best outcomes and business executives without whom this industry would not run (Fig. 9).

Theodore Kurze (1922 to 2002) of the University of South California first used the operating neurosurgical microscope in 1957. The efforts of William House in using the microscope in otological surgery inspired Kurze[13] to use it in neurosurgery. Robert Rand and Charles Drake were introduced to this by Kurze and after an initial resistance it became an invaluable tool in the neurosurgical operating room.[14,15] Peter Jannetta and Robert Rand published their series of posterior circulation aneurysms operated using the microscope and M Gazi Yasargil firmly established the micro-neurosurgical revolution.[13,27,28]

The patient has to be secure at all times, with his head suitably fixed to avoid movement. There should be no damage to the soft tissues and, at the same time, access and surgeon comfort are necessary. The basic 3-pin head holding frame is the Mayfield Kees frame and another 4-pin head holding frame is the Sugita frame.

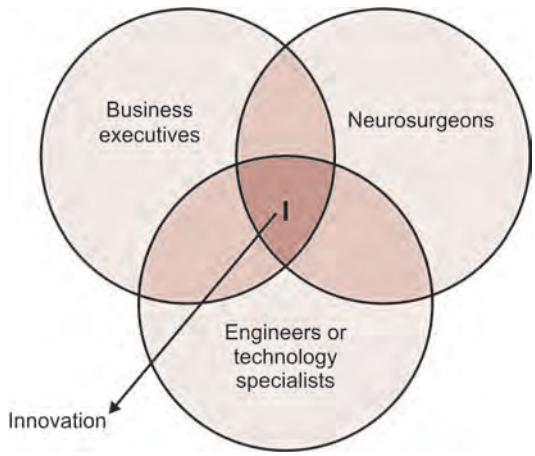

Diagram indicating that innovation is optimized when neurosurgeons, business executives, and engineers or other technology specialists are brought together to work in synergistic ways. It is often the function of venture capitalists to help integrate these individuals at the time of formation of a new venture, in addition to providing capital.

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Fig. 9: Integration required for innovation in the OTs

Mayfield Frame

It is a three pin fixation device, where the head is interposed between the three pins. It should be tightened by about three threads onto an adult skull as each thread is about 20 lb/in^2. The pins should preferably be over areas not covered with muscle. There are different sized pins for adult and paediatric patients.[25]

Sugita Frame

It is a 4–5 pin head holding frame, which we feel is more versatile, less cumbersome, easy to use and provides more stability. It is so designed to enable the neurosurgeon to single handedly perform any microsurgical procedure. It has an attachment for supporting the hands, as well as brain retractors of varying lengths which can be fixed onto the frame. The advantage of all the accessories centred on the frame is that with position changes of the table/head the retractors/accessories do not have to be removed, as the system moves as a unit.

The operating table should be flexible, so as to accommodate varying positions from the supine to prone, the sitting and the lateral along with a place for spine surgeries and the use of fluoroscopy.

An excellent account of positioning, microsurgical instrument (Figs 10 to 14) use and approaches is detailed in the classical 4 volume text of Professor MG Yasargil.[18,25,26] A detailed account of use of instruments and/avoidance of complications is described in Apuzzo's book on avoidance and management of complications.[4]

Brain Suite: (Integrated Operating Room with the Intra-Operative MRI)

The concept of the integrated operating room was first thought of in 1991, as a collaborative effort between GE systems and the Department of radiology and neurosurgery at Harvard. Intra-operative MR imaging is also known as 'MRT' or magnetic resonance therapy. The prototype system was installed in 1994 and was designed to perform real time imaging, while neurosurgical procedures were going on. It was first used in 1995, with the double-doughnut[6] scanner, only for intra-operative use. Just as the microscope changed the scale of dimensions of the operating field, the intra-operative MRI in the operating room has expanded the surgeons view from two-dimensions to three-dimensions. It has given the surgeon an opportunity to look beyond the exposed surface and enable clear visualisation, not only of the operational field but also operational volume.

The Erlangen concept was developed by Robert Fahlbusch with the assistance of Siemens and Carl-Zeiss.[22,24] The operating rooms and the radiofrequency shielded MRI room were different, as MR compatible

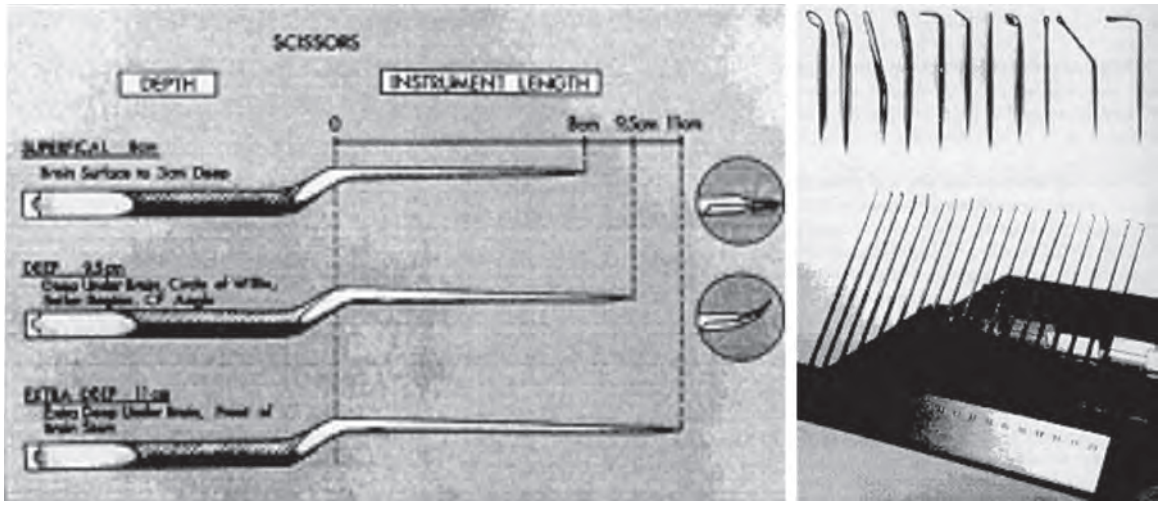

Fig. 10: Basic microsurgical instruments

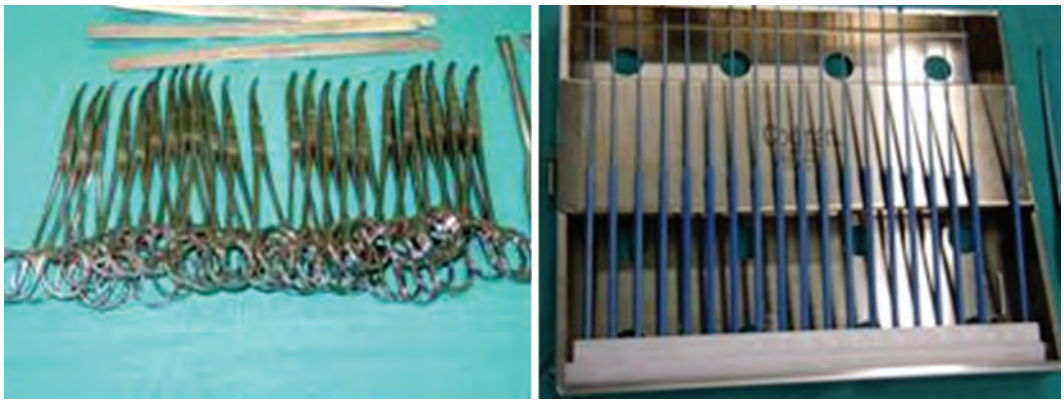

Fig. 11: Microsurgical instruments

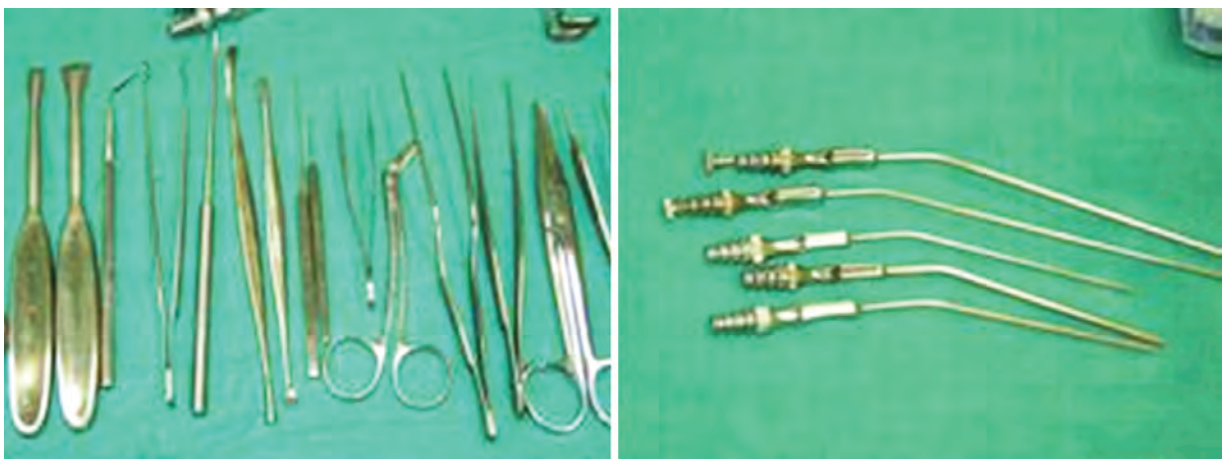

Fig. 12: Microsurgical instruments

Fig. 13: Cavitron ultrasonic surgical asp irator (CUSA)

Fig. 14: Siemens Orbis C-arm

instruments were required for performing all aspects of microneurosurgery. The images from the MRI were transferred to navigation computers and surgery performed. The initial field strengths were 0.5 T and at present 1.5 T magnets are used intra-operatively.

The development of active shielding of superconducting magnets enabled the integration of surgery in the fringe fields with high field MRI.[20] A high field MRI may not only improve the quality of the intra-operative images, but also adds the facility of functional MRI's, diffusion weighted imaging and MR spectroscopy. Operating theatres have to be large enough to accommodate the equipment, which includes all the accessories for navigation, as well as microsurgical work. The use of ferromagnetic materials is to be avoided and non-ferromagnetic materials like aluminium, titanium and cera mics can be used. All equipment has to be compatible with MRI. Anaesthesia and monitoring equipment have also been redesigned for the operative environment.

Equipment and Theatre Set-Up

At the Max Institute of Neurosciences, Delhi, a Siemens 1.5 T MRI scanner is placed in an RF shielded room. The

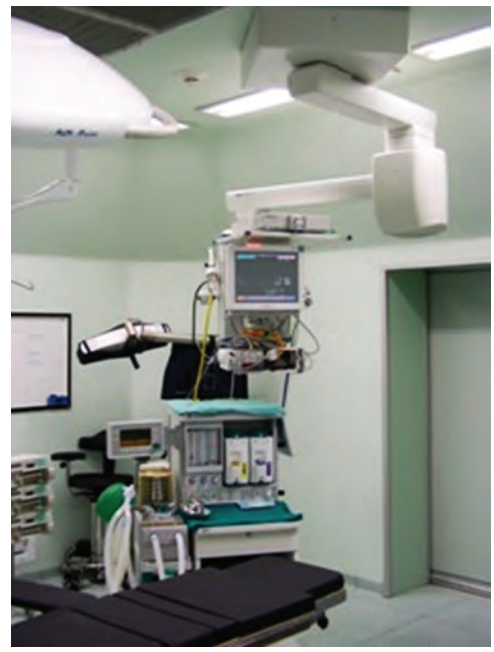

Fig. 15: Anaesthesia equipment in the OT

scanner consists of a superconductive active shielded magnet with a length of 160 cm and an inner bore diameter of 60 cm, equipped with a gradient system with a field strength of up to 40 mT/m. A specially designed rotating surgical MRI table has been adapted to the scanner for intra-operative patient transportation and for imaging. The principal surgical position was at 160° with the patient's head at the 5-Gauss line. Once the rotating mechanism is locked, the height of the table, the angle of tilt, and the lateral tilt can be adjusted by remote control. The rotation of the table axis and turning the table into the axis of the scanner has to be done manually. The ventilator is MRI compatible and MRI-compatible monitoring equipment is used for maintenance of anaesthesia. The monitoring data is transferred to a remote display, which allows continuous monitoring during scanning from outside of the RF-shielded operating room, with a wireless 2.4-GHz connection. Three infusion pumps are shielded in an MRI-compatible carrier for continuous infusion of drugs. This anaesthesia equipment is located outside the 200-Gauss line.[21] Anaesthesia gas inlets and compressed air for surgical drills are integrated in the wall of the RF room (Fig. 15). Service outlets and sockets are connected to different electrical circuits, so that selected lines could be switched off from a switchboard in the MRI control room, to prevent artefacts generated by individual devices. The ceiling outlet for laminar airflow is located above the main operating area. The laminar airflow output is surrounded by a band of fluorescent lamps for optimal illumination. For scanning, the illumination could be turned off from the MRI control room. The entire operating theatre has MRI-compatible spot lighting. Two ceiling-mounted surgical lamps are installed at the main surgical position. Both the 5-Gauss and 200-Gauss lines are marked on the floor. The latter is also marked by a raised stainless steel strip as

a mechanical threshold. All equipment not completely MRI compatible, such as the navigation microscope and the height-adjustable surgeon's chair, are secured to the wall of the RF room mechanically as a safety precaution.

A modern neurosurgical OT has the space to accommodate all the equipment and personnel in a manner that allow ease, access and comfort to the operating surgeon. The instruments should be arranged in an orderly fashion so that it is easy to hand them over to the surgeon in a sequential order, as well as to sterilise them once the surgery is over. The initial requirements are that of a craniotome, with its variety of drill bits, perforators and accessories. These presently could be either pneumatic or can be an electrical craniotome, with the subsequent ones being the macro-instruments, like the dural dissectors, Penfield's instruments, knives, dural hooks, heavy and fine tooth and non-tooth forceps. The micro-instruments are required, depending on the nature of the case and these are shaped in a standard fashion, to provide ease and comfort in accessing almost any intracerebral location. The nurse should be trained and aware of the procedure. Each instrument is designed in a particular way, which is used to provide maximum comfort, steadiness, grip, flexibility and mobility.

A modern neurosurgical OT has all the above and can accommodate tools for neuronavigation such as the intra-operative MRI and the Figures 16 to 18 give us an idea of the arrangement and access with an intra-operative MRI in place.

The arrangement of the entire team is important, so that the surgeon and neuroanaesthetists do not disturb each other, and have adequate room for their monitoring and procedures. The nurses and their instrument trolley should be arranged such that there is easy access.

A trend towards bringing in neurodiagnostic imaging modalities into practice is setting in. The 1970s brought in imaging and opened up new vistas, the 1980s brought in navigation with stereotactic frames and the 1990s brought the scanner and navigation into the OT with further progress being made in the present decade.

Fig. 16: Brain suite iMRI. At Max Superspeciality Hospital, New Delhi (Courtesy: Dr AN Jha)

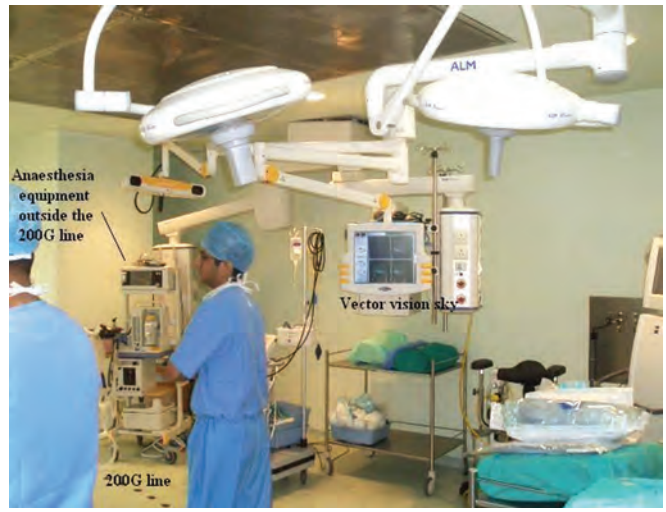

Fig. 17: Arrangement of equipment in the Brain suite

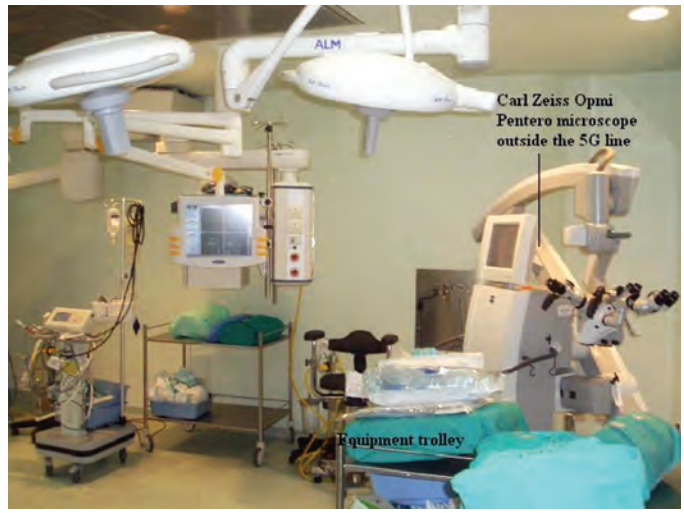

Fig. 18: Equipment set-up in the neurosurgical OT

The Future

Robotics (Fig. 19) and the introduction of more sophisticated devices seem to be incorporated in the OT of the future. The ability to incorporate sensors into operative devices for structural and physiological monitoring, design of visualisation systems for operative needs and high level simulation (rehearsal) systems using holographic and virtual reality based composites are coming.[5]

Trends toward minimalism are evident in the development of robotics such as microelectromechanical systems (MEMS), with products that have diminutive physical dimensions.[19]

Refinements in robotic devices naturally lead to the intriguing prospects of bionic integration. Bionics refers to instruments that are part biological and part machine.[7,17] Bionic devices continue to be an integral part of medical practice. Ventricular assist devices, artificial blood substitutes, and orthopaedic prostheses are all familiar examples. Subretinal implantable chips can

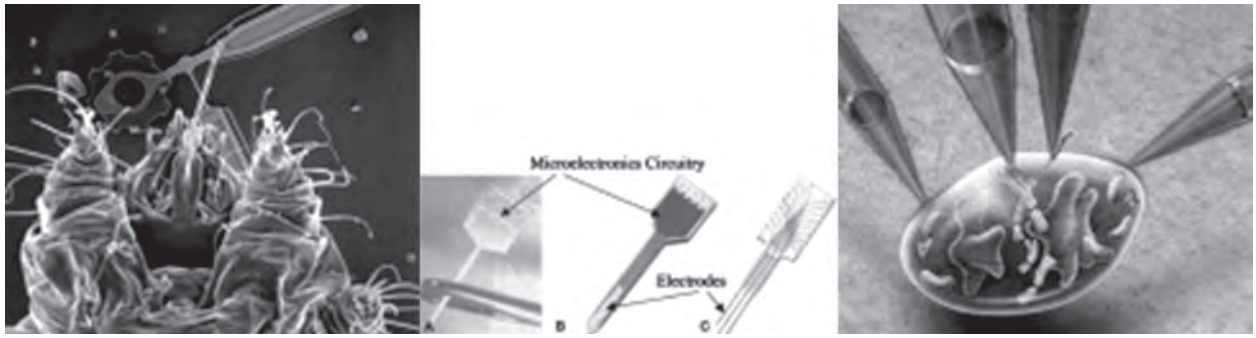

Fig. 19: Microfabrication, micromechanical technology and robotics bring surgery to the cellular level

simulate the function of the photoreceptors.[10] Cochlear implants are also being used with increasing regularity.

The ultimate operating theatre of the future will be functionally complicated with regard to the technology, but simple in use when it comes to the operating surgeon.

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208 Basic Neurosurgical Instruments

Sanjay Behari, Singh RK, Lyngdoh B, Jain S, Chhabra DK

INTRODUCTION

Achieving the desired goals, reducing surgical trauma and increasing intra-operative visualisation are the key features behind every surgical technique. Microneurosurgery reduces the amount of brain retraction required and helps in precisely delineating the neurovascular structures. The use of the operating microscope has substantially improved the illumination and magnification and, consequently, the resolution of the operative field. A variety of microsurgical instruments, retractor systems, operating tables, chairs and nursing stations have been devised to improve the rate of success and reduce the risk to the patient. An adequate knowledge of these instruments and adjuncts as well as their critical properties and performance limitations must be known in order to make the best selection for each procedure.[19,27–29,32,35,41,46] The instrumentation has evolved from the stainless steel-based systems to the titanium based ones, since the latter are lighter and non-ferromagnetic, and therefore, magnetic resonance imaging (MRI) compatible. However, the titanium-based products are more expensive and more susceptible to deformation.

Several ergonomical principals guide the manufacturing of the instruments.[27–29] The instruments should be capable of being held so that the ulnar aspects of the forearm, wrist and hand may be supported. This permits accuracy of handling and prevents hand tremors. The instruments should be held in a pen-holding grip, since this is the most comfortable grip during prolonged surgeries. Straight instruments are the most precise and offer the maximum degree of freedom, but when used for working at the depth, the holding arm obscures the visualisation of their tip. Bayonet-shaped instruments of different lengths are used when operating at a depth. With round-handled instruments the tip of the instruments can be rotated easily.

HEAD FIXATION SYSTEM

Since microneurosurgery involves working with small incisions and narrow-surgical corridors, rigid head fixation is essential in order to maintain the desired head position. Even slight movement of the head during surgery may appear exaggerated when viewed under the operating microscope. Head fixation is commonly achieved using a pin-head-holder. The Mayfield's head-holder (Fig. 1) is a three-pin fixation device and the Sugita head-holder is a four-pin fixation device (Fig. 2).[38,39] These head-holders have a clamp through which sterilised pins are fixed on the skull and the whole assembly is fixed rigidly on to the operating table. Care must be taken to see that the pins are not placed at the thin temporal bones, the venous sinuses, the temporalis muscle (where a rigid fixation is not possible), the skin overlying the tubing and chamber of ventriculoperitoneal shunt systems, and the bones overlying the frontal and the mastoid air sinuses. In children, special paediatric pins are utilised. The advantages of the pin-head-holders are:

Fig. 1: Mayfield head-holder

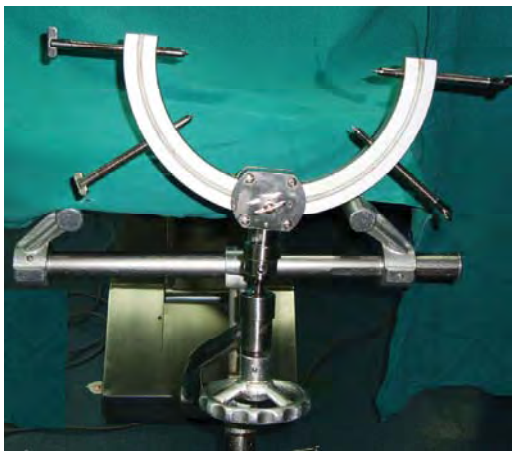

Fig. 2: Sugita head-holder

- Multiple self-retaining retractor systems with flexible arms on them can be fixed
- Arm-rests can be fixed to avoid arm-fatigue and tremors during prolonged operations
- The patient can be positioned in a variety of ways including the park-bench and the sitting positions
- Skin sores that may develop when the face rests on a padded head support for a long period can be prevented
- Electromyography of the facial muscles and somatosensory and auditory evoked potentials can be done since the electrodes may be fitted on the exposed face[28]
- Intra-operative fluoroscopy and angiography is possible with the use of head-holders made of radiolucent materials[16]
- Intra-operative MRI can be performed with the use of non-metallic graphite head-holders[13]
- When the head is rigidly fixed, registration errors while using intra-operative neuronavigation are minimised.[28]

The precautions that must be taken during fixation of the head-holder are:

- Taking care that the pins do not penetrate the inner table of the skull since they may cause cerebrospinal fluid leak, meningitis, osteomyelitis, an intracerebral abscess or, an extradural, subdural or intracerebral haematoma.
- The patient's head should not be in close contact with the head-holder as this may lead to pressure necrosis of the scalp during prolonged surgery.

OPERATING TABLE

Operating tables (Fig. 3) are electrically operated and the patient's position (during initial positioning for surgery and also during the microsurgical procedure) can be altered with ease. Thus, with a subtle change in the table position during surgery, the surgeon gets a different line of sight to the surgical field without changing the microscope's position. It is possible to move the table up and down; head down (Trendelenberg) and up (reverse Trendelenberg); and whole body rotation to the right or left.[35] There are rods on the side of the operating table that provide attachments for body support so that the patient does not move on the table if the position of the table in moved; they also provide attachment for brain retractor support rods and the neuroendoscope holder. The tables are often made of radiolucent material and intra-operative radiographs can be taken. There is a central locking system that prevents the table from inadvertently moving from its position during surgery. The height of the table is usually adjusted to the level of the surgeon's elbow to avoid excessive bending of the surgeon's body and neck.[35,38]

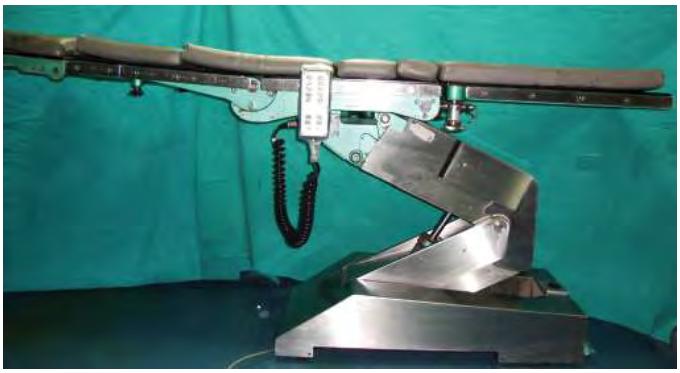

Fig. 3: Operating table

MICROSURGICAL OPERATING CHAIRS

The surgeon generally operates in a sitting position to reduce fatigue during prolonged surgery. The height as well as the position of the operator's position in relation to the operating table can be adjusted in the conventional chairs (Fig. 4). Sugita has devised an operating chair with side arms to support the elbows in order to avoid fatigue and tremors (Fig. 5).[38] It has an up and down movement that can be controlled by a pedal. All joints, other than that for vertical motion, are loosened when another pedal is held down so that the chair can be moved according to the surgeon's desire. The footplates in the chair can control the bipolar cautery, the movements of the operating table and the microscope, the focus of the microscope and the vertical height of the chair. The Sugita operating table, with the chair, is coupled with a remote-controlled microshifter for the horizontal plane. With the aid of this system, an object under the microscope can be kept in the centre of the microscopic field by pedal control.[38] Ohta et al.[24] have devised a freely mobile arm-rest for the microneurosurgical chair that is equipped with a ball-joint which is fixed by mechanical friction and becomes free as it is filled with compressed air after which the frictional force diminishes. As the button below the arm-rest is pressed the mechanical arm can be moved freely to the desired position. The mechanical arm is locked in position as soon as the button is released. These arm-rests can thus be moved freely and can also be fixed in the desired position.

The surgeon should sit comfortably on the electrically-operated surgical chair that has arm-rests. The foot rest is at the same height relative to the seat regardless of the height of the chair.[9] The elbows of the surgeon rest in a comfortable position.[35] Some of the surgical chairs are connected to the operating microscope and the operating table controls and the surgeon can control both the position of the table and the microscope and the magnification of the microscope by manipulating the controls that are situated in the chair close to his feet. This enables the surgeon to continue the surgical procedure without the need of asking for help in manipulating the table and without the need for taking his eyes off the operating field. At the same time, he can keep his arms engaged in the operating procedure.

Fig. 4: Conventional operating chair

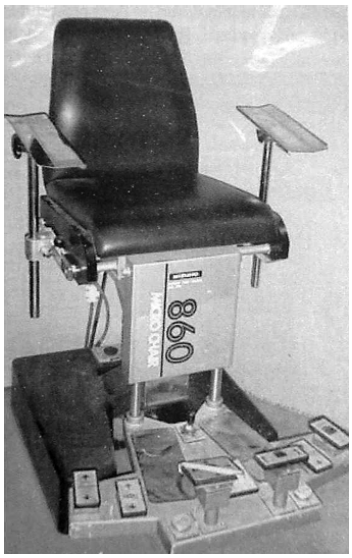

Fig. 5: Sugita operating chair

INSTRUMENT TABLE

For microsurgical procedures, an instruments table has also been devised that has various divisions, where the instruments being utilised for different sections of the operative procedures are kept in separate compartments (Fig. 6).[38] This table over-rides the operating table and is, therefore, more convenient than the one placed on the side of the table. The height of the nurse's platform is electrically changeable depending upon the patient's head position. A moving chair on the platform lessens the fatigue of the scrub nurse.

RETRACTOR SYSTEMS

Self-Retaining Brain Retractor System

A semicircular basal frame is fixed perpendicular to the head holder (Fig. 7). Screws are placed on the frame for holding conventional flexible self-retaining retractors (Leyla-Yasargil). Tapered brain retractors of three sizes (the tips being 2 mm, 4 mm and 6 mm in width) are fixed on the flexible Leyla retractors. Two holes at each end of the frame may be used to fix the hand rests and instrument holders. The angle and height of the hand rests may be adjusted to suit the surgeon. A box may be attached to each end of the basal frame to hold bipolar coagulation forceps, a suction tube or other instruments.[38,39] A smaller semicircular frame fixed on the basal frame is used for retracting the scalp flap; it also supports the plate on which surgical patties may be placed. It may occasionally also hold the self-retaining retractor.[15]

The patient's head is fixed in the desired operating position on the head holder by three or four skull pins. The patient's head may be easily rotated at any time during the operation.

Specific purpose retractor systems may be used for performing specific surgical procedures, for instance, Boyle-Davis mouth gag (Fig. 8) that opens the mouth and simultaneously keeps the tongue retracted may be used for transoral surgery; the Hardy's nasal speculum and trans-sphenoidal retractor systems (Fig. 9) that retract the nasal mucosa during trans-sphenoidal surgery; and the Cloward's self-retaining retractor system (Fig. 10) that retracts the carotid sheath and sternocleidomastoid muscle laterally and the trachea-oesophagus and strap muscles medially may be used for performing anterior cervical discectomy and corpectomy.

Fig. 6: Instrument table

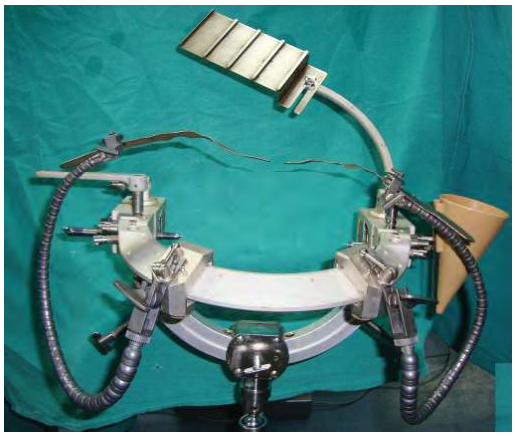

Fig. 7: Self retaining brain retractor system

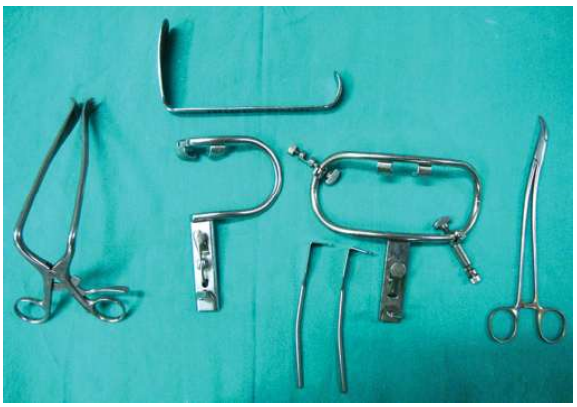

Fig. 8: Boyle Davis mouth gag for transoral surgery

Fig. 9: Hardy's nasal speculum for trans-sphenoidal surgery

FIBRE OPTIC LIGHT SOURCE WITH HEADLIGHT

During the initial part of the exposure where microsurgical dissection is required, illumination may often be provided by a fibre optic headlight[2] (Fig. 11). It is lightweight and facilitates transmission of light with maximal efficiency. Several features contribute to comfort during long procedures. There are no projections, such as rivets, from the headband to obstruct the surgeon's field of view. The headband does not heat up and may be enlarged without removing the harness from the head. The focusing device is maintained in a universal movement friction lock ball joint which is adjustable in all axes. The light beam is directed from the bridge of the nose, thus avoiding shadow in deep operative fields. The fibre optic cable transmits light via fibre optic cables from a remote light source to the headlight. These cables may readily be removed from the harness.[2]

Suction

The suction tip is chosen keeping in mind both the length and the diameter (Fig. 12). For superficial procedures, a length of 8 cm is used; for most of the microsurgical procedures, a length of 10 cm is required; and for deep procedures a length of 13–15 cm is required. The diameter of the suction tube is 3 French (3 French is 1 mm outer diameter) for very small vessel and nerve anastomosis; 5–7 French for most of the neurosurgical procedures and 8 French diameter for heavy bleeding, extradural work and for rapid tumour resection.[30] A wide angle between the handle and the shaft allows the suction tube to be held in a pencil-holding grip so that the ulnar surface of the hand rests comfortably on the border of the wound and thus provides stability to the hand.[28,29,38]

The suction power may be increased by occluding, either completely or partially, the air hole at the base of the suction tube. For microdissection as well as for retraction of microstructures, the minimum power of the suction is used to prevent the entrapping of neurovascular structures. At least two suction apparatuses must be functioning during any microsurgical procedure. They should work at different power and should be colour coded to easily distinguish between the tubing. The simultaneous use of two suctions helps the surgeon in continuing his surgery even when cleaning of suction tips of one of them is taking place in case when its blockage occurs during surgery. The suction tube should be very flexible so that it is not heavy and will not hinder movement.

A malleable suction device is narrow plastic tubing with multiple perforations at one end.[37] The multiple holes allow gentle suction and prevent any tissue from

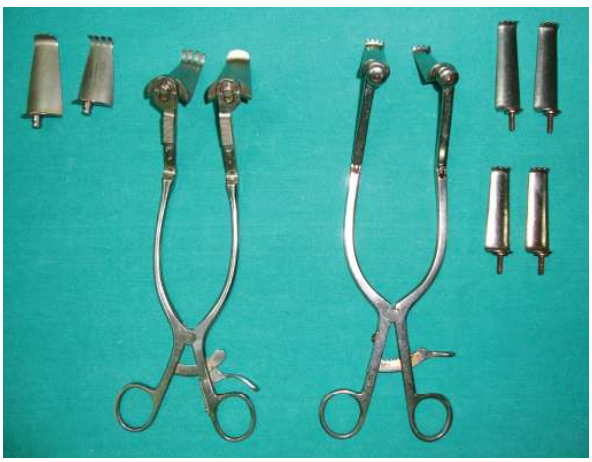

Fig. 10: Cloward self-retaining retractors

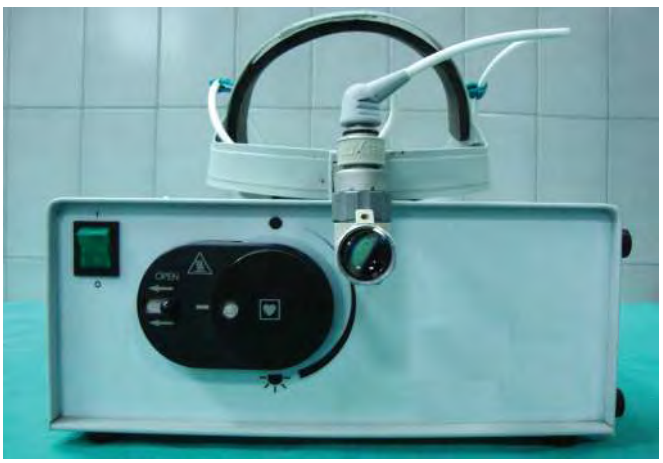

Fig. 11: Fibre optic light source with headlight

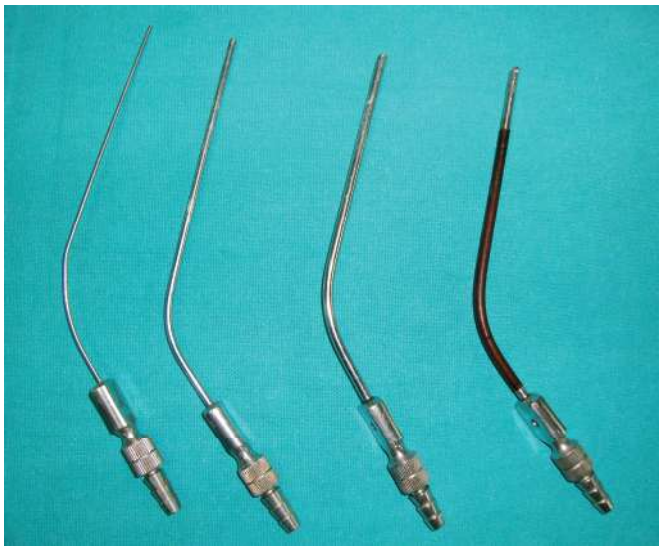

Fig. 12: Suction canula

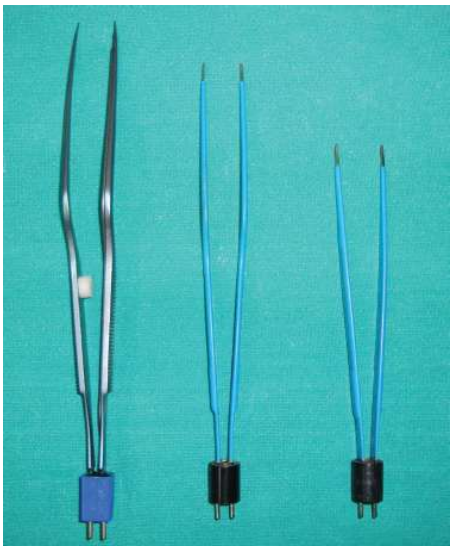

Fig. 13: Bipolar coagulation forceps

being aspirated into the suction tubing. Soft wire that is included into the tubing maintains the suction tip where it is needed. An alternative system that incorporates suction and irrigation allows constant moistening of the immediate area to prevent drying of tissues. The tubing can be fixed at the surgical field to permit microsurgical dissection in a cleaner operative field and without the need to put down an instrument in order to pick up the suction.

COAGULATION FORCEPS

Electric current passing through the tissues produces heat proportional to the distribution of the electrical power used. When heat is applied externally to blood vessels in order to achieve haemostasis, it usually produces a tissue coagulum that proceeds from outside inwards in the vessel; and, also promotes intravascular clotting within the vessel proximal to the point of application of heat. The coagulum may, however, slough off and restart bleeding; and, the heat spread from outside to within may also spread to the surrounding tissues. Thus, there was a need for an instrument that permitted coagulum formation within the vessel; and, the heat generated at the contact point would remain confined to the narrow limits close to the contact points and not spread to the surrounding tissues[18] (Fig. 13). A direct current, as is generated by a battery, introduces heat production in a straight path between the electrodes. This facilitates coagulation from inside-outside as is desired for achieving haemostasis of vessels. The coagulation, however, is poor; the direct current stimulates muscle and nerve tissue that provokes movement; and, electrolysis with marked bubble formation occurs at the negative electrode. Alternating current, as seen in the city light distribution system, further accentuates these effects when low frequency currents are used. However, when the frequency of current is greater than 100 KHz, it provokes little stimulation of muscles and nerves. A high voltage alternating current in the range of 0.5–3 MHz sustains a continuous fine arc between the active electrode and the tissues. The rapid heat produced facilitates cutting of the tissues and is also known as the "cutting current".[18]

Clark devised the first electrosurgical device with a spark generator in 1910 that was used in the operating room.[5] In 1928 Bovie developed an electrosurgical unit with a spark-gap generator that provided an output of damped irregular waveforms in a group of cycles that progressively decreased in amplitude. The multiple interruptions permitted coagulation with little cutting tendency. With a synchronous resonating circuit, it could also provide cutting ability. An electric current requires a return path. In the Bovie's monopolar machine, the current generated by the active electrode returns by the dispersive electrode also known as the ground plate. A higher current per cubic millimetre is achieved as the active electrode is very small compared to the dispersive electrode. The current flow from the active electrode to the ground plate passes through the intervening conductive tissue including blood vessels, muscles, bones, neural structures and body fluids. Heat may be generated at considerable distances from the point of coagulation. Thus, it cannot be used in delicate areas like the brainstem and the spinal cord. The machine output is also not isolated. Thus, the current may also spread to other grounding points of the patient such as metal parts of the table or the monitoring equipment. This system was used by Cushing for achieving haemostasis during his neurosurgical procedures.

Greenwood, in 1940, devised a machine that permitted the return path of the electric flow between the two-point coagulation system that formed the basis of the bipolar system.[14] In this system, the blades of the forceps were insulated from one another. One side of the forceps was attached to the active side of the current generator and the other to the ground generator. Thus, current could flow through the tissues between its blades. The ground plate of the Bovie's system was,

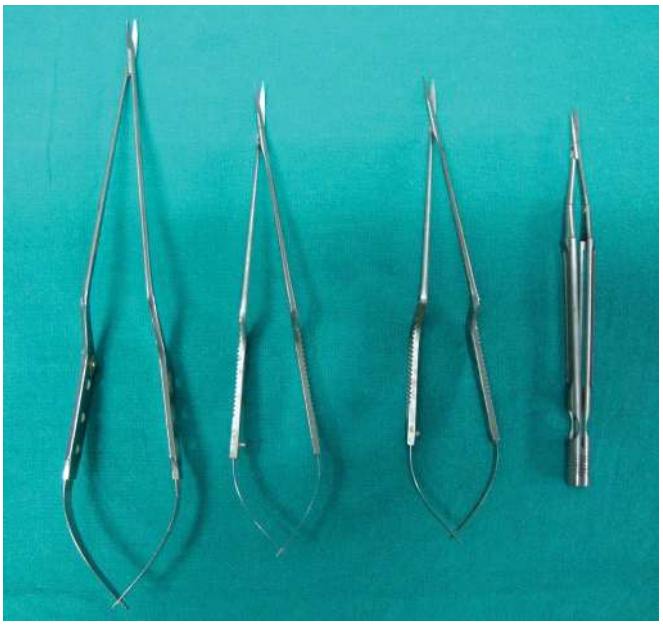

Fig. 14: Microscissors

therefore, not required. While in the monopolar system, the generated current from the active electrode flows to the ground, in the bipolar system, current only flows between the forceps tips. Thus, a bipolar forceps may also be used in delicate regions of the brain. Irrigation of the bipolar forceps cools the area, prevents heat from disseminating to the surrounding normal tissue while further decreasing any chance of the forceps adhering to the tissue. Malis, later on, developed a low power spark gap system that utilised winding coils and transformers to achieve optimum coagulation.[18] The modern microprocessor-controlled solid-state bipolar coagulating and cutting systems rigidly control the voltage generated at the forceps tip and prevents voltage variations with irrigation and with changes in the width of the forceps. They contribute significantly to the performance of major neurosurgical procedures, decreasing operative time and blood loss. According to Malis, the factors required for a superior bipolar generator are:

- Proper waveform
- Lowest possible generator impedance
- Isolated output so that heat does not spread
- Rigidly stabilised voltage output
- Control totally in the hands of the surgeon.[18]

Malis also introduced a self irrigating system for the bipolar forceps. In this system, sterile saline pulsed from a fine channel is added to the bipolar forceps, synchronous with the electrical output, but separately regulated in volume according to the surgeon's preference. This permits the irrigation to reach the desired area without the constant vigilance and skill of a well-trained assistant whose abilities could better be used for other duties.[18] The tip of the bipolar forceps should be clean and absolutely smooth for either coagulation or cutting. A pitted or abraded forceps surface coagulates poorly and tends to build coagulum and produce dangerous sticking. A newly developed tungsten alloy forceps tip material has a surface polish and hardness far better than one made of stainless steel, titanium, or even nickel, as well as a much higher melting point. These new forceps show no wear or change after long testing.

Char formation on the tips of bipolar cautery forceps during neurosurgical procedures is inevitable. Various methods are used to reduce the char. Frequent irrigation with saline or mannitol solution is helpful. Modification for the tips, such as Teflon coating, is available. A simple technique to help reduce char formation and facilitate cleaning during the operation is to bathe the bipolar tips in mannitol. In the instrument pouch, 25 cubic centimetres of 12.5% mannitol-saline solution is placed. When the bipolar device is not in use, the tips are submerged in the mannitol solution. Mannitol reduces the coefficient of surface tension between the char and bipolar tips. In addition, saline dissolves the char by disrupting electrostatic forces within the char. Storing the biopolar tips in a mannitol-saline solution thus reduces char adsorption.[32]

SCISSORS

Different types of scissors are used for different purposes (Fig. 14).[27–29] For excision of large tumours, Metzenbaum scissors are used. In microsurgery, curved or straight stainless steel microscissors are used. For superficial microvascular procedures such as extra-intracranial arterial anastomosis, straight handle scissors are required. For surgery in the deeper planes, the bayoneted scissors are used so that the hand holding the scissors does not obstruct the visualisation of the scissors tip. In deep cavities, it may not be possible to align the straight or curved scissors blades for the desired line of action and so angled blades are used to visualise their tips. Alligator type scissors, with a long shaft, are used for deep and narrow opening such as in trans-sphenoidal surgery. Their blades are oriented in different directions to facilitate cutting in all directions.

Forceps

For superficial operations, the jeweller's forceps may be used, but these are too short for most neurosurgical procedures. The longer straight or bayoneted forceps with a length ranging from 7 cm to 10 cm is ideal for most procedures (Fig. 15).[27] The bayoneted forceps with an angle between the shaft and the handle prevents the surgeon's hand from obscuring the surgical field. Some designs with a rounded shaft permit greater rotational movements of the forceps. The tension of the forceps or the closing force should be minimal to prevent fatigue of the surgeon's hand that may lead to tremors during the prolonged use of the forceps. However, whenever tissue planes and arachnoidal planes require to be developed, and when the bayoneted forceps is used as a dissecting instrument, considerable tension of the forceps is required. The type of tip of the forceps determines its

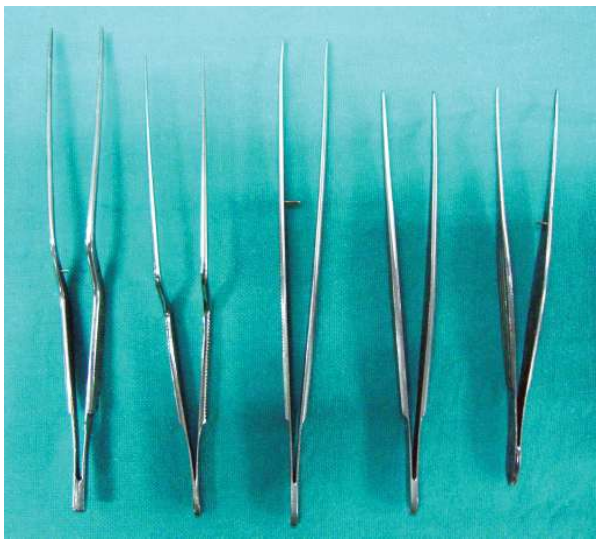

Fig. 15: Bayoneted and tissue forceps

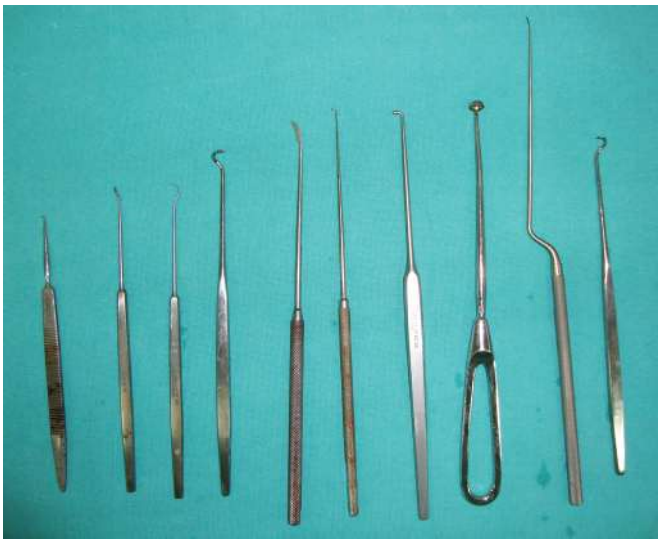

Fig. 16: Microdissectors

usage. For grasping tumour tissues, a ring or a cup is required at the tip. Forceps with teeth, called the tissue forceps are used for grasping tissues including the dura. Forceps with cross serrations, known as the dressing forceps may be used for endarterectomy. Upward and downward angled tips may be used to dissect around the back of an aneurysm.[28,29]

MICRODISSECTORS AND RING CURETTES

The Penfield microdissectors and Rhoton's microdissectors are more frequently used for microneurosurgery (Fig. 16). The straight dissectors are used since rotating them will still keep their tip localised to one place, whereas the tip of a bayoneted dissector rotates through a wide arc.[35] The various microdissectors that may be used are the round, spatula or flat tip dissectors, the right angled nerve hook, the straight needled dissector, the cup shaped micro-curette or the straight or angled tear-drop dissectors. The silver dissector that has a malleable tip that can be moulded to a desired shape is also useful.[38] A hypodermic needle mounted on an artery forceps may also be used for arachnoidal dissection. Developing a cleavage by blunt dissection using a dissector should only be done in cases where only a few and fragile arachnoidal adhesions are present. Usually, sharp dissection using scissors is preferred to avoid tearing the nerves and vessels. The ball-dissector is useful for manipulating nerves and vessels. The angled dissectors are useful for separating tumour from the bone in narrow canals or to develop a plane between the tumour and its capsule.[28,29] For trans-sphenoidal surgery, ring curettes (Fig. 17) with angled handles are preferred as the field of view of the surgeon is not blocked by his hand manipulating the handle of the dissector. The blunt ring may be used to gently ease out the tumour from the lateral margins of the sella and from the supraellar regions. The tips of these curettes may have an angled ring, a straight ring or a loop with a diameter ranging from 3 to 9 mm.[27]

Needle Holders and Sutures

Suturing of blood vessels and nerves[45–47] usually require 8-0 to 10-0 nylon sutures on a variety of needles from 50 microns to 130 microns (Fig. 18). The handle of the

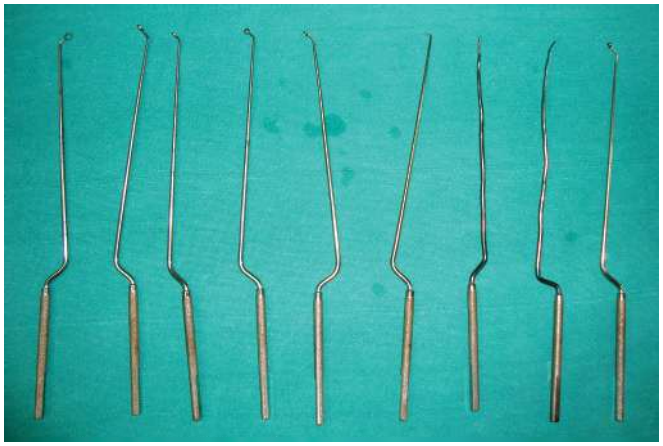

Fig. 17: Ring curettes

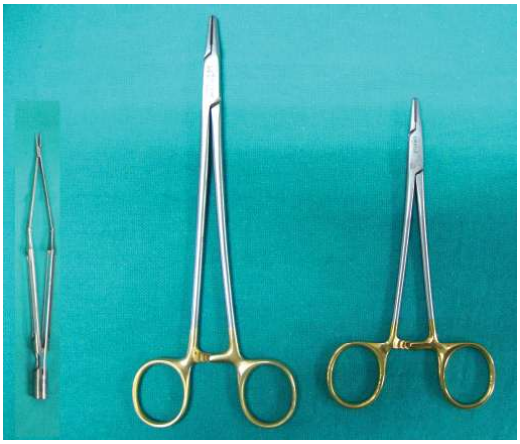

Fig. 18: Needle holders

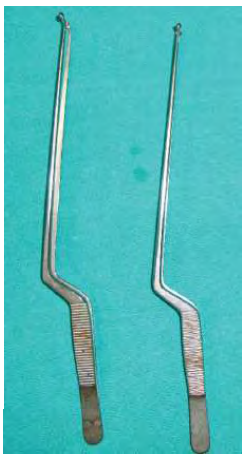

Fig. 19: Cup forceps

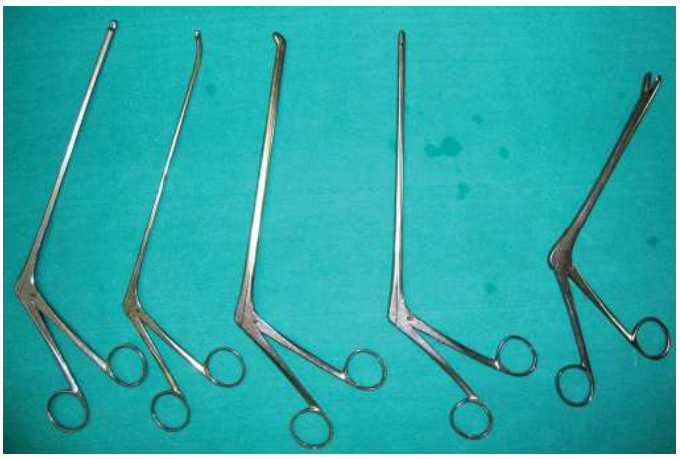

Fig. 20: Biopsy forceps

needle holders should be round so that rotating them between the thumb and the index finger is smooth. A lock or a catch in the needle holder is not preferred. This is because, releasing the lock or catch causes the tip of the needle holder to jump and be misdirected thus causing tissue damage. The straight needle holders are utilised for handling the micro-needle at the cortical surface, while bayoneted needle holders (with the bayonet shaft ranging from 8 to 11 cm) are used while working at the depth.

Cup Forceps and Biopsy Forceps

The fine cup forceps are used for grasping and removing tumours in deep and narrow exposures (Fig. 19). No traction should be applied on the tissues, otherwise the normal structures may be pulled with the tenacious tumour. The cup may be straight or angled upwards or downwards. The cup diameter ranges from 1 to 4 mm for microneurosurgical applications.[28,29] Biopsy forceps have long handles and a cup for grasping tissues at the depth of the surgical field (Fig. 20). They may be used for microsurgery at a depth like trans-sphenoidal surgery.

ANEURYSM CLIPS AND APPLICATORS

In 1910, Cushing introduced the silver clip to occlude vessels that were difficult to ligate.[7] Dandy, in 1937, clipped the neck of an internal carotid artery aneurysm using a modification of the original Cushing clip described by McKenzie.[8,22] In 1966, Scoville described a torsion bar spring aneurysm clip made of stainless steel.[34] In 1971, Mayfield and Kees reviewed the development of their spring clip for the permanent occlusion of aneurysms.[20] The most frequently used aneurysm clips have been designed by Yasargil, Rhoton, Sugita, Sundt, Spetzler and McFadden.[20,21,38,39]

Optimally the aneurysm clips must be designed to satisfy the following criteria:

- Their closing force must be sufficient to obliterate the lumen of the aneurysm against arterial pressure pulsations
- They must be non-corrosive and biocompatible
- They must not produce artifacts on MRI.[31]

The commonly available clips are made of cobalt chrome nickel and/or molybdenum alloys, e.g. Yasargil clips, Sundt clips McFadden clips, Sugita clips and Heifetz clips.[1,17] These materials are durable, biocompatible and non-ferromagnetic, yet they produce artifacts that degrade the quality of MRI scans. The newer titanium clips, while retaining the same design cause less artifacts on MRI.[17]

Dujovny et al. have classified aneurysm clips based on their design.[10,12] The alpha class having the shape of the Greek letter "alpha", have a crossed leg design. The Mayfield, Drake, McFadden, Rhoton, Sundt, Yasargil, Spetzler and Sugita clips have a similar configuration. The clip is usually a single piece except that the Yasargil, Rhoton and Sugita clips have an additional small ringlet as an alignment guide. The blades of pivot clips rotate around a central pivot with a separate coil spring providing the closing force. The Heifetz clip is a prototype of the pivot clip. The mobile fulcrum clip, of which the Scoville clip is an example, consists of an integral spring coil which acts as a fulcrum around which the blades rotate.[26,34]

Temporary clips (Fig. 21)[11,12] are used to achieve temporary vascular occlusion without damaging the vascular endothelium. They are applied to control bleeding from vessels prior to the application of the permanent clips, to isolate the aneurysm during dissection and also to test for the adequacy of occlusion of the aneurysm. The blades of a temporary clip open wider than that of a permanent clip. The permanent clips are of many shapes and sizes and their occlusion force is more than that of the temporary clips (Fig. 22).[26] For large and giant aneurysms, frequently, fenestrated clips that encircle the parent blood vessel harbouring the aneurysm are used (Fig. 23). These obliterate the neck of the aneurysm without occluding the lumen of the parent artery.[38,40] If the parent vessel or neural structures obscure direct access to the aneurysm, a fenestrated clip is especially chosen. Booster clips are often placed in order to augment the

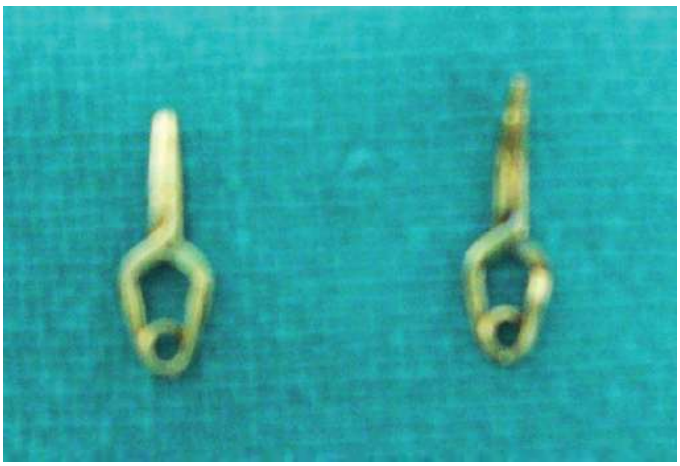

Fig. 21: Temporary aneurysm clips

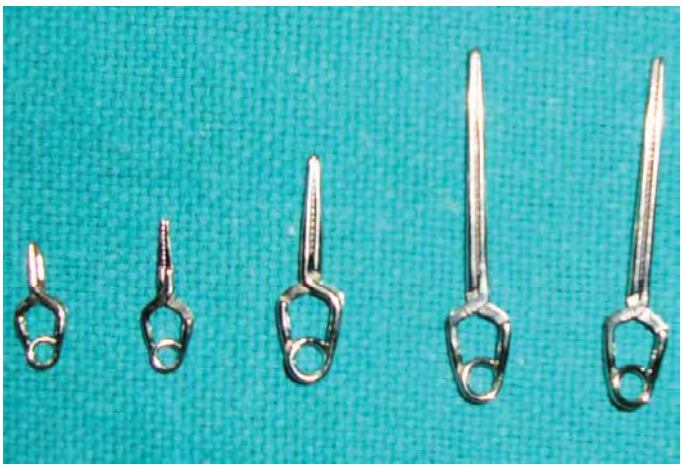

Fig. 22: Permanent aneurysm clips

primary clips. Occasionally, malleable rather than spring clips are used when dealing with broad based or fusiform aneurysms in order to perform an aneurysmorrhaphy.

If the size of the neck of the aneurysm is large compared to the lumen of the parent artery, then the clip blades must be applied parallel to the parent artery to avoid the constriction of the parent vessel or the rupture of the aneurysm base. The mechanical property of the spring clips facilitates application of greater closing force at the bottom of the blades than at the tip.[35] If an aneurysm has a hard wall or is under high pressure, it should be obliterated with the base of the clip rather than its tip.

The closing pressure is the force required to occlude the aneurysm. Besides the clip characteristics like the clip blade width, length and strength, the closing force is also determined by the blood pressure, the diameter of the aneurysms, the stiffness of the vessel wall and the geometric configuration of the aneurysm.[11,12,25] Atkinson et al. in a study of the closing pressure of the various commercially available clips found that the closing force of the aneurysm clips of average size (8–10 mm straight) were consistently satisfactory for each of the clip brands.[1] In order of decreasing strength, the clips were the Sundt, McFadden, Yasargil, Heifetz and the Sugita clips. The closing forces of the larger (20–21 mm) clips were more or less equivalent to each other. However, the closing force was often significantly less in their smaller (8–10 mm) counterparts. Thus, booster clips applied midway along the primary blade length are useful in augmenting the closing force of the larger clips.[35,42] The most important factors determining accidental clip release following its application are the incomplete crossing of the vessel diameter by the clip blades and, the degree of rigidity and thickening of the arterial wall caused by arteriosclerosis.

The clip applicators may be used for ordinary, mini and ultra large clips and may be straight or angled (Fig. 24). The Sano multipurpose clip applicator may be moulded depending upon the trajectory that the surgeon wants to adopt for clip application since it is multijointed. Another variety of Sano applicator has a small rotating socket for the clip head so that the clip may be held at any desired angle.[38,40] With the use of conventional clip applicators there is difficulty in regripping a

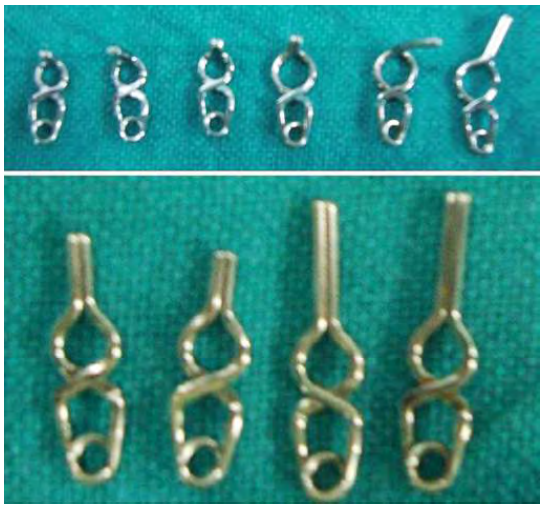

Fig. 23: Fenestrated aneurysm clips

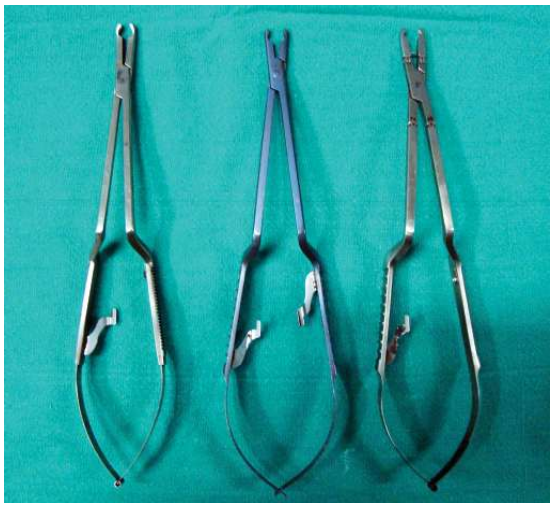

Fig. 24: Aneurysm clip applicators

clip in the narrow surgical field, especially if the vessel is at an awkward angle. If improperly gripped, the clip may jump out. The newer applicators have a wider groove and grip the spring portion of the clip, thus preventing the clip from slipping during its reapplication.[38,40]

NEUROSURGICAL DRILLS

High Speed Drills

The pneumatic microsurgical drills have a vane type of motor (Fig. 25).[44] The motors have a rotor spindle placed eccentrically in its covering. Slots in the rotor spindles have vanes installed in them. These vanes move in and out of their slots to trap air while the rotor rotates within its covering in an eccentric position. A foot operated control regulates the speed of an air driven hand piece that rotates rapidly the cutting or the drilling dissecting tool attached to the end of the hand piece. The flow of compressed air both to and from the hand piece is regulated by the footswitch. Application of an operator's foot pressure on a floor level foot control, simultaneously depresses two valves which control the flow of compressed air. One valve controls the flow of compressed air from its source to the hand piece, and the other valve controls the release into the atmosphere of compressed air from the hand piece. Release of pressure on the foot control returns the two valves, utilising spring forces, to their original position cutting off the flow of compressed air both to and from the hand piece. Air entering the entrance hole pushes the rotor vane. The vane is pushed centrifugally outwards against the inner casing of the rotor housing creating a closed chamber. Thus, a small pressure chamber is created that collects air and holds it until it is released at the exhaust port. This mechanism will permit a rotation of the drill to 75,000–100,000 rpm.[44]

Fig. 25: High speed drill

The electrical drill systems with rotation speeds in the range of 90,000 rpm do not require a pneumatic gas source as the motor is driven by electricity.

The drill systems have two types of dissecting tools. The cutting tools drill the bone fast, but may cause bleeding from the soft tissues and may injure the dura. The diamond tools, on the other hand, require more time and pressure to cut the bone but may be used with much greater safety over the dura and soft neurovascular structures as they resist dissection of the soft tissues. The diamond tools also facilitate haemostasis while drilling the trabecular bone.

The drill systems have the advantage of cutting the bone rapidly and the ability to undercut the bone edge when using a large burr. They operate with virtually no torque. The tendency of the hand piece held in the surgeons hand to shift in position with changes in speed of the drill or its starting and stopping is also minimised. This makes the application of the drill safe in areas where great precision is required. Their disadvantages lie in the risk of direct mechanical and heat injury to nerve, blood vessels, and normal tissue, grabbing of cotton pledgets and in interruption of the operation for frequent irrigation and suction.

Ultrasonic Bone Curette

Ultrasonic surgical aspirators with longitudinal and torsional tip, apart from removing soft tissue tumours, may also be used to cut and scrape bone structures in skull base and spinal surgeries.[3,23] It comprises of a lightweight hand piece which is stable and easy to handle, a power supply unit with irrigation and suction, and a foot switch. Only minimal tip–bone surface pressure is needed to cut the bone. The longitudinal vibration amplitude can be varied from 120 to 365 mm at an ultrasonic frequency of 25 kHz. The tips (1.9 mm and 2.8 mm wide) operate in a scratching motion to resect bone. The irrigation fluid (cool-controlled at 20°C) can be applied from the tip with suction equipment. The ultrasonic curette is a useful instrument for procedures performed near the dura mater or other neural tissue without excessive heat production or mechanical injury. Its advantages include the lightweight of the hand piece, fine motion in scratching and cutting bone tissue, no grabbing of cotton pledgets and an easy preservation of dura and epidural venous plexus at the tips. Its disadvantages lie in less manoeuvreability because of short and fixed tips in a key-hole exposure and the possibility of injuring the neural tissue due to long duration or high energy use.

KERRISON'S PUNCHES AND RONGEURS

The bayoneted osseous punches (Kerrison's punches) (Fig. 26) have been constructed in standard sizes. The 1–5 mm sized punches are especially useful. These have a very thin small foot plate set at either a 90° or a 45° angle. The instrument can easily be slipped under the

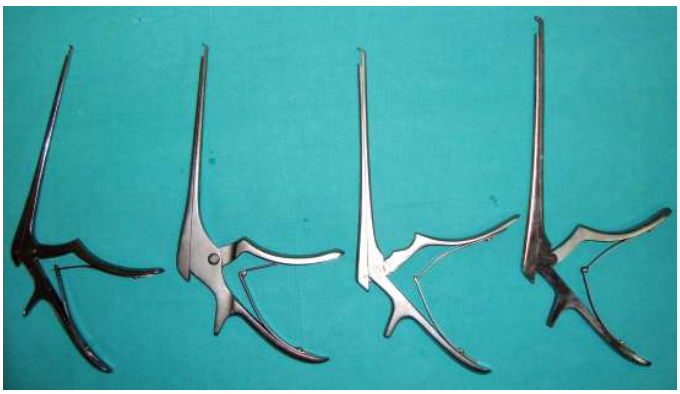

Fig. 26: Kerrison's punches

part of the anterior clinoid process protecting the carotid artery for biting off a portion of the clinoid process. In anterior cervical disc excision, lateral dissection near the nerve root is facilitated by grasping the posterior longitudinal ligament as well as the osteophytic spurs overlying the nerve root with the osseous punch. The bayoneted punch is also helpful in lumbar microdiscectomy. The larger punches can be used to remove the portion of the ligamentum flavum in the lateral recess overlying the nerve root. In trans-sphenoidal hypophysectomy, a longer extension of the distal portion of the instrument is useful in removing the bone from the sphenoid sinus as well as from the anterior portion of the sella. In transoral odontoidectomy the bone edges can be grasped with the small osseous punches while the bayoneted curettes are used to free the odontoid from the underlying connective tissue.

The angled micro-curettes are made with either a 90° or 45° angle. The bayoneted offset allows visualisation of the cutting edges at its end under the operating microscope. These are especially useful while removing a tumour from the sella-suprasellar region in the trans-sphenoidal approach.

The single and double action rongeurs (Fig. 27) may be used to remove bone from the vertebral body and in removing the lamina during a laminectomy; for performing a craniotomy as in removing the lesser wing of the sphenoid during the frontotemporal approach; and, during skull base surgery for nibbling the bone of the calvarium and skull base.

EQUIPMENT FOR ENDOSCOPE ASSISTED MICROSURGERY

Intracranial endoscopy provides a minimal but rapid access to the target via small burr holes without brain retraction. A neuroendoscopic system that includes rigid, semiflexible, and flexible scopes, bright cold light sources, a high-resolution video camera system, effective instruments, and irrigation devices may be combined with microsurgery to improve vision, illumination and minimal invasiveness[33,36] (Figs 28 to 30). The endoscopes are usually introduced via an operating sheath initially inserted with the aid of a trocar, which permits the intra-operative exchange of different scopes without reinserting scopes through brain tissue. This avoids injury to the surrounding healthy brain. Rigid rod-lens scopes have better optical quality and wide-angle view, as well as ease of guidance and orientation and are, therefore, preferred. Rigid scopes have four different angles of view (0°, 30°, 70° and 120°). The 0° and 30° scopes are used for inspection and manipulation; the 70° and 120° scopes are used for inspection only ("looking around a corner").[4]

Instruments such as scissors, biopsy and grasping forceps, hooks and puncture needles have been manufactured that permit surgery through or assisted by an endoscope. The endoscope allows surgery with rigid instruments in a straight line, with a good tactile feedback from the tissue being manipulated and makes easy guidance of the tools possible. Bipolar as well as monopolar diathermy probes and a laser guide are used for haemostasis and dissection. Balloon catheters are used to enlarge ventriculostomies or other fenestrations. For irrigation, an irrigator may be used that controls the flow using a foot switch.[4]

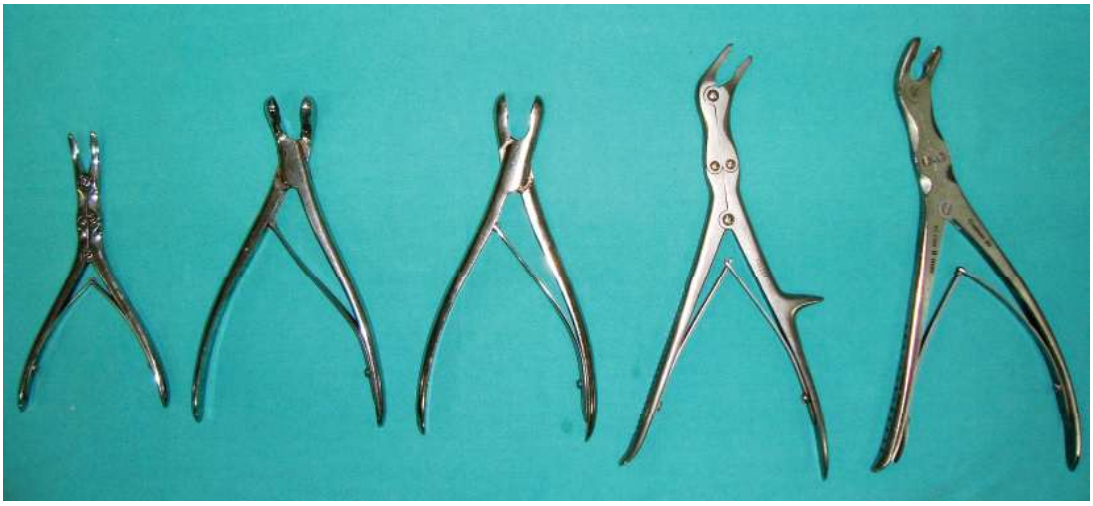

Fig. 27: Rongeurs

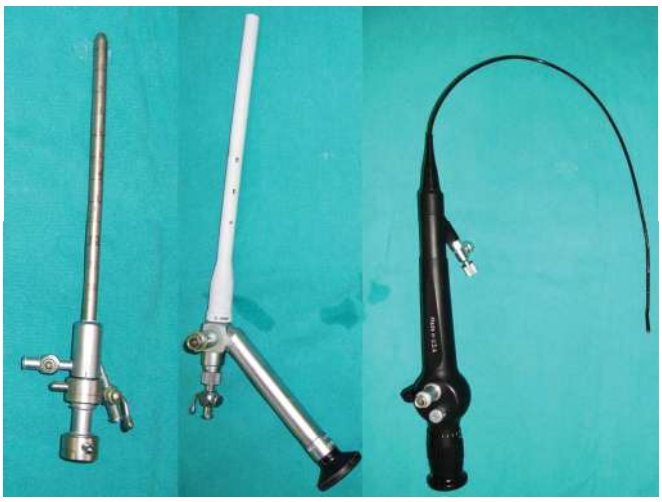

Fig. 28: Rigid and fibre optic endoscope

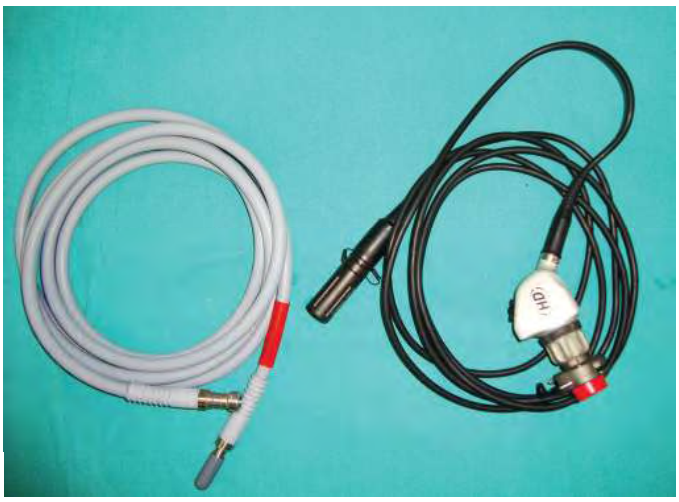

Fig. 29: Light source and camera for endoscope

Lactated Ringer's solution at 36–37°C is preferable to saline as the irrigating fluid as the former prevents post-operative body temperature increase (often observed after profuse irrigation with saline). While introducing irrigating fluid into the brain, it is imperative to keep the outflow channel open to prevent dangerous increases in intracranial pressure. Xenon light sources, transmitted via fibreglass cables from the light to the endoscope provide the best illumination, because the colour temperature of xenon light resembles that of sunlight (6000 K). A mini video camera may also be attached to the endoscope via a sterile optical bridge. The documentation equipment includes a video printer and digital still recorder.

The endoscope is ideal for dealing with pathologies in the ventricular system and subarachnoid spaces; and hydrocephalus, small intraventricular lesions, and arachnoidal and parenchymal cysts may be effectively treated.[33] Even highly vascularised lesions such as cavernomas may be excised with the additional use of lasers and bipolar diathermy. During standard microsurgical procedures, the endoscopic view may provide valuable additional information ("looking around a corner") about the anatomy in the surgical field that is invisible with the microscope. The endoscopic view may be incorporated in the eye piece of the microscopic view to give a "picture in picture" image.[36] The endoscopic image reflects on a mirror in the adaptor and is projected as a part of the unilateral microscopic image by fibre optic cables to the microscope, thus allowing the surgeon to perform endoscope-assisted microsurgery without moving his eyes away from the operative field. This helps the surgeon in getting more detailed information about the neurovascular structures in the shadow of the operating field. In trans-sphenoidal pituitary surgery, the endonasal approach permits a more accurate control of tumour removal in the intrasellar space, especially in the case of larger tumours with parasellar and suprasellar growth. The combined use of endoscopes and computerised neuronavigation systems permits real-time information about the endoscope tip position and approach trajectory while performing a microsurgical procedure. The problem with endoscopic surgery is the lack of appropriate visual cues to orient oneself in three-dimensional space. This makes relatively simple anatomical regions difficult to navigate. To overcome this shortcoming, a neurostereoendoscope, that has a prismatic optical path separator mounted behind the rod-lens and captures stereoscopic three-dimensional images using dual charged-coupled devices, has been developed.

Fig. 30: Monitor for endoscope

COAXIAL MICROSURGICAL INSTRUMENTS

Keyhole microsurgical approaches involve minimal or no brain retraction. The mobility of the conventional microsurgical instruments within such narrow corridors is severely restricted and the surgical field may

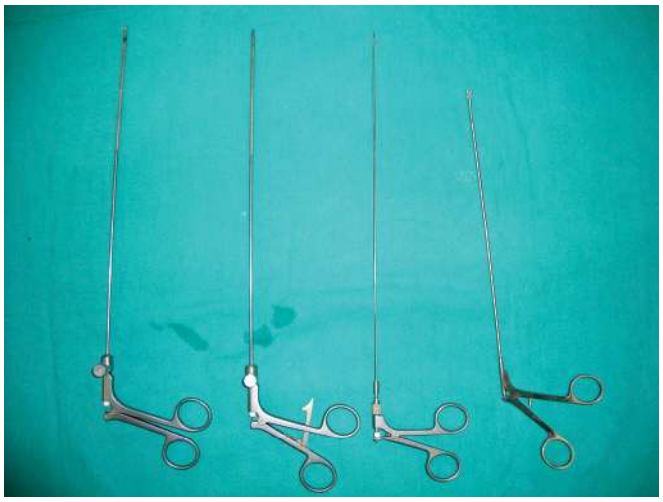

Fig. 31: Coaxial microneurosurgical instruments

Fig. 32: Operating microscope

also be obscured by the relatively large size of these instruments.

The newly designed coaxial instruments contain a coaxial shaft that is made up of a coupled tube and rod rotating in opposite directions along their major axis[6] (Fig. 31) This rotational movement is achieved by compressing and releasing a spring-loaded handle. The tips of the instrument are obtained by flanging the two elements of the shaft. The length of the tips varies between 6 mm and 10 mm and the width between 2 mm and 3 mm. The instrument has all the three variations, the straight and angled tip as well as a variation of the straight one in which the distal third is curved. The instruments include microscissors and micro forceps, tumour grasping forceps as well as aneurysm clip applicators. The diameter of the shaft ranges between 2 mm and 3 mm and the length may be 90 mm, 100 mm and 130 mm. The two elements of the shaft can be disengaged by releasing a catch and be disassembled for cleaning.

The newly designed coaxial instruments possess a low-profile coaxial shaft. They are ergonomically designed with a pencil grip handle and an angled bayonet. Thus they offer a better view of the operative field and can be manipulated through narrow corridors since the bulk of the shaft of the instruments is outside the visual axis.[6]

OPERATING MICROSCOPES

Operating microscopes (Fig. 32) offer a three-dimensional magnified stereoscopic (binocular) vision in a narrow field at depth.[43] The interpupillary distance of the surgeon is maintained by the microscope, so that the images produced by the objective and eyepiece lenses of the two sides respectively are merged into a single three-dimensional image. The microscope provides a good magnification without significant aberrations. Modern microscopes have a motorised zoom system that consists of dual movable lenses which move with respect to one another so that the desired focal length may be adjusted. Field of view is the diameter of the operative field visualised when the microscope is properly focused. Size of the field of view is inversely proportional to magnification (higher the magnification, lesser is the size of field of view). At higher magnifications, the depth of field (that is the distance between proximal and the distal points in focus) also becomes very small. Therefore, at higher magnifications, the operating surgeon has to frequently adjust the microscope to the focal plane of interest to him at any given moment. This challenge may be overcome by an autofocus system that permits him/her to instantaneously focus on the region of interest. Another important feature of the microscope is that it provides good illumination at narrow depths and around corners of the surgical field without producing excessive heat. Fibre optic coaxial illumination is its property of aligning the front surface of mirrors to produce even light distribution and avoiding shadows in the operating field. The illumination, however, decreases at higher magnification. Modern microscopes have incorporated the modification of increasing the illumination in proportion to the magnification used. Automatic light collimation is the property by which an automatic shutter diaphragm increases light at higher magnification to provide appropriate illumination. In the microscopic eyepiece there is a provision for correcting the refractive errors of the surgeon and the assistant. There is a provision of instant stability in six axes without sacrificing operational flexibility. Microscopes are balanced by adjustable counterweights mounted on a stand. Electromagnetic brakes incorporated into various joints of its stand maintain stability in any desired position. Pistolgrip or mouth switch or footswitch controls for releasing the brakes allow all movements in primary axes. The controls for adjusting magnification and focal length can also either be on handles or on a pedal.

The cameras attached to modern microscopes permit recording of high definition surgical procedures. With the appropriate attachments, assistants may visualise the

same surgical field as the primary surgeon and therefore help in his surgery. Microscopes may have the capacity to incorporate neuronavigation that permits the surgeon to determine his actual position during surgery with the previously acquired three-dimensional imaging data set of the patient.[13] It can also display magnetic resonance images, angiograms, and computerised tomography scans simultaneously and combine the information intra-operatively. The simultaneous use of an endoscope with an operating microscope during surgery is facilitated by its "picture in picture" facility that permits the simultaneous display of both the microscopic and endoscopic images on the eyepiece and the microscope display panel. A blue light illumination permits visualisation of malignant gliomas in patients who have been given 5-aminolevulinic acid orally. An intra-operative angiography may be performed by detecting within the focused blood vessels intravenously injected indocyanine green. This real-time access to multiple types of imaging data facilitates spontaneous decision making of the surgeon in the operating room. Thus, a good microscope must have a clear stereoscopic view, ample homogeneous illumination, interchangeable lenses, variable magnification, well-balanced movement, coaxial illumination and provision for add on accessories.

CONCLUSIONS

Though an excellent outcome following a microneurosurgical procedure to a large extent depends on the surgeon's technical skill, an accurate diagnosis and meticulous pre-operative planning, the role of good instrumentation and their proper usage cannot be overemphasised. The microneurosurgical procedures, in an effort to lessen the operative trauma, have evolved into minimally access techniques requiring minimal or no brain retraction. Thus, a thorough knowledge of the proper usage of the newer micro-instruments and their indications and limitations is essential for improving the surgical results.

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Ajaya Nand Jha, Rahmathulla G

INTRODUCTION

'Navigate' defined by the Oxford dictionary means 'to drive a ship'. The Vikings were the earliest to venture beyond their confines without instrumentation and only surface landmarks to guide them to their destinations.[1,32] Development of instruments to measure the altitude of the stars and planets and the discovery of the sextant which made it possible to measure angles, followed by the marine clock in the 18th century determined the progress of land and sea navigation.

Just as these tools were required here, a brain navigation system to reach pathology at difficult locations was developed by the pioneers of stereotaxy. 'Stereotaxic' is derived from Greek roots for 'three dimensional' (stereo) and 'system' or 'arrangement' (taxis). In Latin 'stereo + tactic' means to touch. Lesions that were located at a depth or traversed eloquent cortical areas could be safely reached without causing a permanent neurological sequel. This has been made possible with parallel advances in imaging techniques and instrumentation.

Advances in technology have improved global navigation and these principles have been utilised in parallel, along with modern instrumentation and technology to make brain and spine navigation safe.

HISTORY

Clinical localisation of a brain lesion required the precise analysis of the patient's symptoms and a detailed identification of the signs and these used to be the mainstay of a topological diagnosis. Angiography with the direct and indirect visualisation of the vascular tree[1,32] and deformation of the ventricular system on pneumocephalograms or ventriculograms were the first methods to identify lesions indirectly.[12]

Rene Descartes, a 17th century philosopher and mathematician, developed a system enabling localisation of a point in three-dimensional space using Cartesian coordinates. A few hundred years later, a brain target could be transferred to a stereotactic instrument, which guided probes and even electrodes to specific targets, when the frame was placed on the head. DN Zernov, a Russian surgeon, was the first to demonstrate a device, the encephalometer,[1] that could be fixed onto the patient's head above the sagittal suture in 1889, at the University of Moscow. A number of these instruments were made and forgotten after the Russian revolution. It was Sir Victor Horsley, a British surgeon, and RH Clarke, a British engineer (1908), who came up with a simple and enduring solution and pioneered stereotaxis.[50] They were responsible for coining the term "stereotaxis" and developing the first true frame (Fig. 1).[1] The brain was used as the geometric volume, over which, suitable reference points were defined and specially designed surgical instruments for operating on these targets were made.

In 1918, Aubrey Mussen, a Canadian physiologist, made a study of the vagus nerve in a cat and a monkey, using the Horseley and Clarke system. He later designed one for human use, but this was never used.

The modern era of stereotaxis began in 1947 when EA Spiegel and HT Wycis, in Philadelphia, made the first clinically usable stereotactic (stereoencephalotome) device for humans. This device used hollow threaded screws and could be accurately placed and replaced as necessary[1,14,32,53,54] (Fig. 2). They used positive contrast ventriculography,[11] the foramina of Monro and the pineal body to localise intracranial targets and were the first to consistently use X-rays and ventriculograms to localise the target.

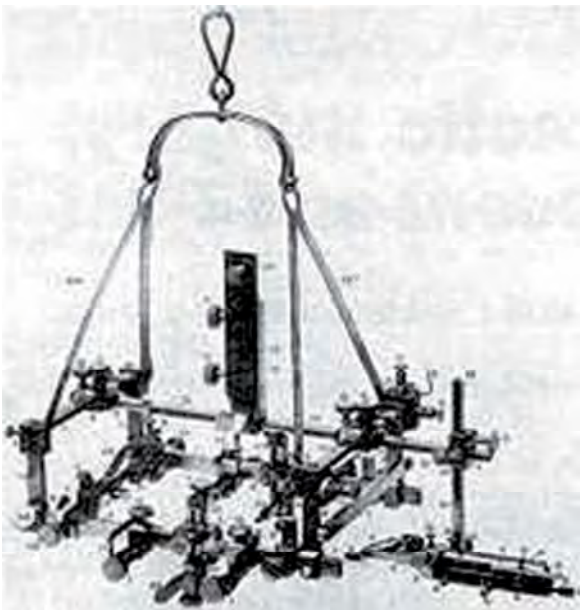


Fig. 1: Horsley and Clarke's original apparatus

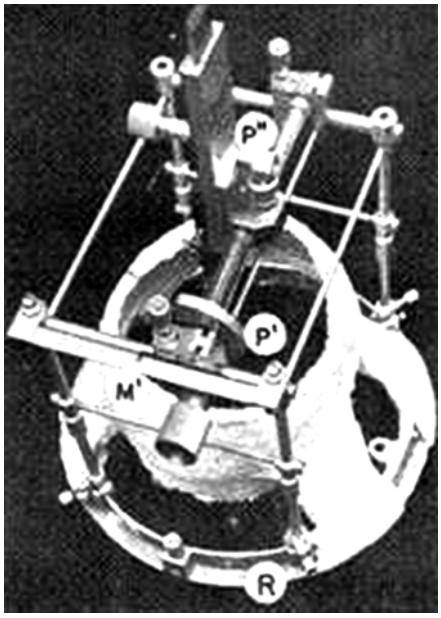


Fig. 2: Original Spiegel and Wycis instrument

Following this, there was an explosion in the number of instruments from various parts of the world: Lars Leksell (1949, Sweden), H Narayabayashi (1951, Japan), T Reichert and Wolf (1951, Germany).

Leksell devised the arc-centred frame system in 1949.[29] The simplicity of this system is the reason for its continued popularity. The fixation device was attached to the patient's skull and the pointer could be moved along the arc-quadrant to localise targets (Fig. 3).

Stereotactic atlases are an important part of the history and development of stereotactic surgery and some of the concepts behind these atlases are described here. It was important to know the distances between various landmarks and the anatomical targets and their variability in the patient population. A series of precise brain sections was made at measured intervals and contained a grid system to relate the coordinates of any point to the intracerebral landmarks. Each human brain has its own variability causing problems for the neurosurgeon and it was Spiegel and Wycis who published the first usable stereotactic atlas in 1952.[1,54] Talairach published an atlas in France with emphasis on the temporal lobes. This was extensively used to treat patients with epilepsy.[1,9,56] He also described a different plane, the anterior commissure (AC), posterior commissure (PC) line, which subsequently became the standard reference for many stereotactic surgeries (Schaltenbrand G Barley P), (Schaltenbrand G and Walker AE). Each page in a stereotactic atlas represents a brain slice taken at a measured position within the brain (Fig. 4).

The rapid development of computer software, along with technological innovations in imaging, has led to a more interactive, real time combination in the use of these atlases. The stereotactic atlas can now be superimposed on the patient's images and various target nuclei specifically located with great accuracy.[8,22] Imaging has

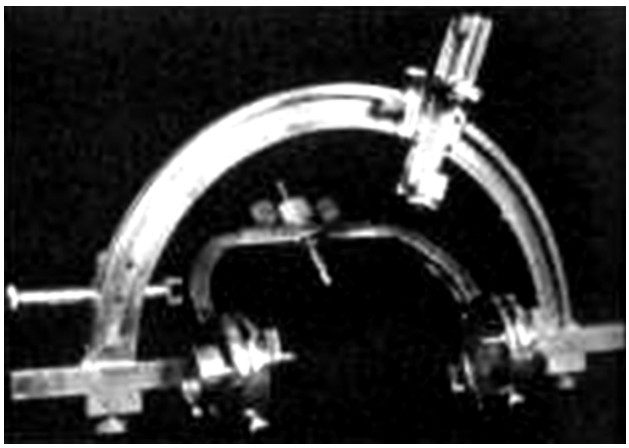


Fig. 3: Leksell's arc centred frame system

been used as a guide to the deeper structures of the nervous system and has evolved from the days of the X-rays and use of the pencil and tape.

The ultrasound was followed by the CT and then the MRI. The introduction of the CT scanner and the MRI created a revolutionary change in the way navigational systems were used. The dependence upon stereotactic atlases, which were based on normal post-mortem specimens, could only be utilised on normal persons with relatively fixed anatomy. Computers further simplified the process of including various data into the scanned images and helped calculate/manipulate the target using the coordinates.[14] This led to a shift from atlas based targeting to directly imaged targets, although not in real time.

Navigation has evolved from frame based systems to interactive image guided surgery. Real time intra-operative imaging utilising an intra-operative MRI (BRAIN SUITE) is now a reality. Using this technology to couple surgical skill with detailed anatomical images, specific targets can be identified and located, avoiding critical areas and maximising the benefits of any neurosurgical procedure. The risk of damage to the adjacent vital structures is minimised, allowing a small craniotomy to be made over the lesion. This reduces operative time, bleeding, infection and damage to vital cortex. The surgeon can maintain three-dimensional orientation of the anatomy and, when differentiation of the pathological lesion from adjacent normal brain is a problem, imaging at surgery is a boon, such as in low-grade gliomas.

GENERAL PRINCIPLES

The principle behind a navigational system is to locate a specific intracranial target point, in relation to a constant external coordinate reference system. Initially, various skull landmarks were used as a guide to locate pathological lesions and craniotomies were performed in relation to these landmarks. Lines connecting various points were used to locate the Sylvian fissure and adjacent structures (Taylor Haughton lines) and these were a guide to the surgeon.

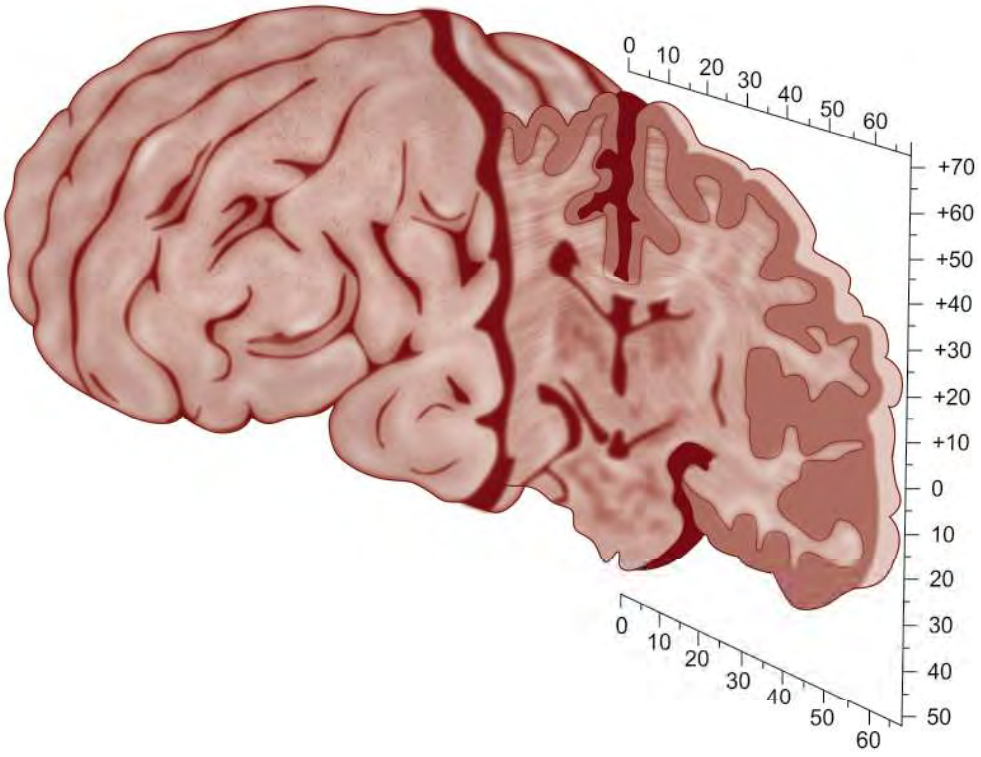


Fig. 4: Page from a stereotactic atlas

Then came the frame based system, where a base ring is attached to the patient's head, and a three-dimensional frame placed over this. The lesion is usually calculated/identified in relation to this external coordinate frame. Each intracranial point is assigned a specific location by the computer, while scanning and for the external coordinate frame as well. The target point is calculated in relation to this using imaging software.

Following this, frameless systems are now used. The external coordinate reference points consist of 'fiducial markers', either placed on the patient or by registration of surface points directly. The imaging sequences are done with the fiducial markers or the scan has to cover the entire face/surface contour, which will be used to register the patient. The location of various targets in relation to this reference system can be plotted out and probes can be used to reach the target along a particular trajectory, making procedures, such as biopsy and lesioning of nuclei in movement disorders, seem like child's play.[21,39]

ELEMENTS OF STEREOTAXIS

Geometry, reference points and surgical instruments[10,46] are the three basic elements which have evolved to produce modern stereotactic surgery.

Brain in a Geometric (Cartesian) System

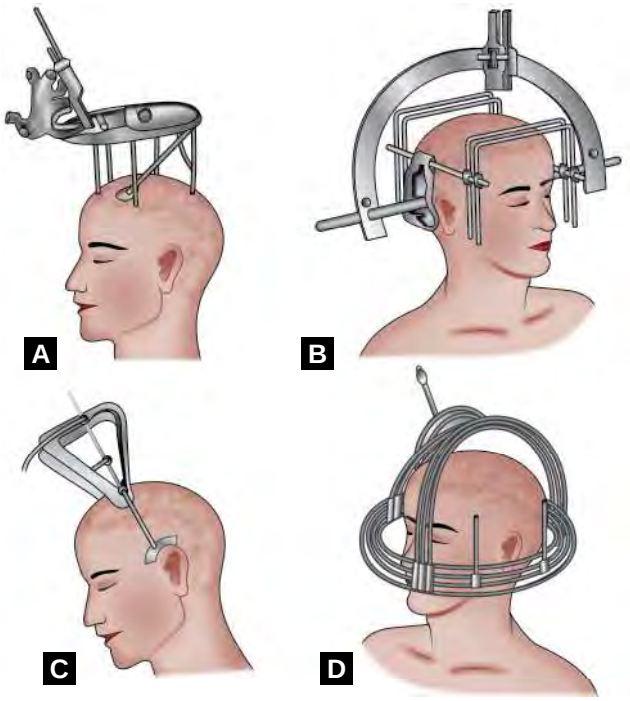
A Cartesian co-ordinate system is a three-dimensional grid with a centre point (origin) that can be used to map locations in space. The position an object occupies in space is determined by its relative position, with respect to a given point which is arbitrarily chosen as the reference point. Adding 3 orthogonal planes to intersect at this reference point which is now taken as zero point, establishes a system of reference axes (x, y, z) (Fig. 4). The location of any point in this system can be measured in relation to the zero point in all 3 axes. This concept, which is intrinsic to geometry, is being used, following the application of the Cartesian system of coordinates by Clarke.

Reference Points

Visible targets, such as tumours, are located by interfacing a stereotactic frame on the patient with CT/MRI. Targets which are not visible, like the ventrolateral thalamic nucleus, can be localised indirectly by using atlases.

Stereotactic Frame

Most frames consist of two elements, the coordinate frame and the aiming device. The frame is a rigid metallic platform attached to the skull by means of head pins, which pierce the outer table of the skull, so that no displacement can occur (Figs 5A to D). The aiming device is usually attached to this and may have a number of moving parts which bear the probe holder. This can usually be moved multi-directionally to point at a specific target in the skull. The stereotactic systems in use are either 'translation rectilinear' systems or 'arc centred' systems. In the former type, both the entry point for the surgical procedure and



Figs 5A to D: Four basic types of apparatus
(A) Translation system; e.g. Horseley and Clarke's, Talairach's and Narabayashi's
(B) Arc system; e.g. Leksell
(C) Burr hole mounted
(D) Interlocking arcs, e.g. Brown-Robert-Well's (BRW) and Cosman-Robert-Well's (CRW) frames

the target are located in relation to an external frame. The stereotactic device is attached to the frame and examples are the Horseley and Clarke system and Speigel and Wycis frames. In the latter variety of frame based systems, the target is located in relation to the frame and is always at the centre of the apparatus.[1] The Leksell and Laitinen frames are examples of such devices.

Along with this, a phantom device can be employed. The phantom reproduces the target and the surgeon can perform a simulation on this, confirming the accuracy of the points taken. The aiming arc is applied and the tip of the probe should accurately touch the target on the phantom. Frame-based systems have their benefits in that they are stable, can hold a trajectory probe and can be used in pre-operative simulation.

The limitations with these systems are that they are temporary, restrictive, sometimes complex to use and bulky, making the patient uncomfortable. Targets are limited to one trajectory at a time. Real time updates are not possible with these systems.

Applications

The various applications are:[1,10,60,62]

A. Functional
   - Movement disorders
     - Parkinson's disease[42,43]
     - Hemiballismus
     - Dystonia[43,45]
     - Choreoathetosis
     - Intention tremors
   - Intractable pain
   - Psychosurgery

B. Anatomical applications
   - Tumour localisation and biopsy[31]
   - Craniotomy guided by stereotaxy
   - Interstitial brachytherapy
   - Radiosurgery
   - Intracranial aneurysms[2,26,33]
   - Stereotactic third ventriculostomy using endoscopy
   - Epilepsy[44]—implantation of depth electrodes

Imaging prior to surgery gives the surgeon a two-dimensional idea of the lesion in relation to various bony and soft tissue landmarks. Earlier, a surgeon would localise a target based on the Taylor-Haughton lines and the corresponding set of images and place his flap in an approximate location. This could lead to a larger craniotomy, damage to vital structures, inability to localise the lesion and define the extent of the resection or the ability to locate deeper structures.

Frame-based Systems

The Cosman-Robert-Well's (CRW) frame is a common, simple and widely used system. It is ideal in situations where only specific target points have to be located, e.g. a thalamic lesion and other target nuclei for movement disorders and deep brain stimulation. The components are, however, common to most of the systems in use (Fig. 6).[41]

- A base ring, which has pins (graphite) with which it is fixed to the skull
- Over this, is fixed a localising unit, which has two vertically and one diagonally placed rod, in an array around the head. These act as the fiducial 'picket fence' pattern
- The base ring has to be fixed onto the gantry table of either the CT or MRI and the operating table. A fixation device does this
- A phantom device on which the target point and the probe should meet concurrently, to confirm the exactness of the coordinates
- During the surgery, a frame attaches to the base ring and is the interface between various instruments
- Software on the computer (stereocalculator) to compute the final target from the set of co-ordinates fed in. Usually, there are nine points starting from X1, Y1 up to X9, Y9 with x being the 9 o'clock position usually The final target is taken as X, Y. Each of these values is fed into the computer, which calculates the final target.

Various instruments are available to work on this platform and the commonly used ones are: Needle coring device, side cutting needles, spiral needle, cup forceps, interfaces for the use of endoscopic instrumentation and a microdrive for implanting deep brain stimulation electrodes.

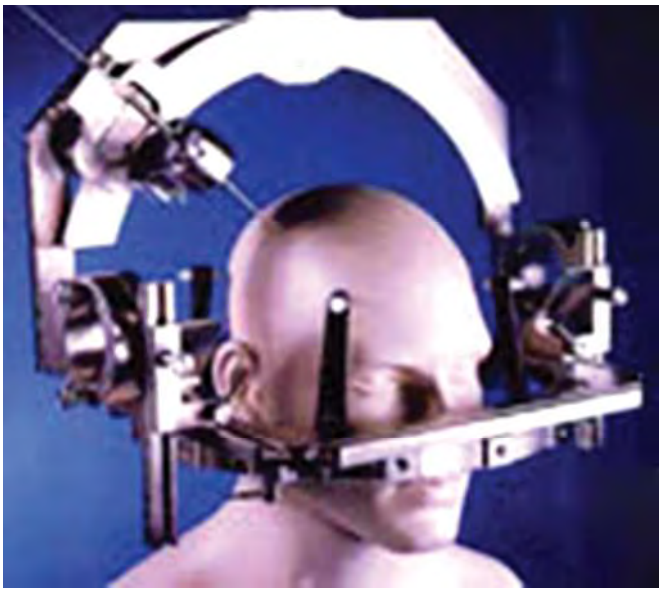


Fig. 6: Cosman-Robert-Well's frame

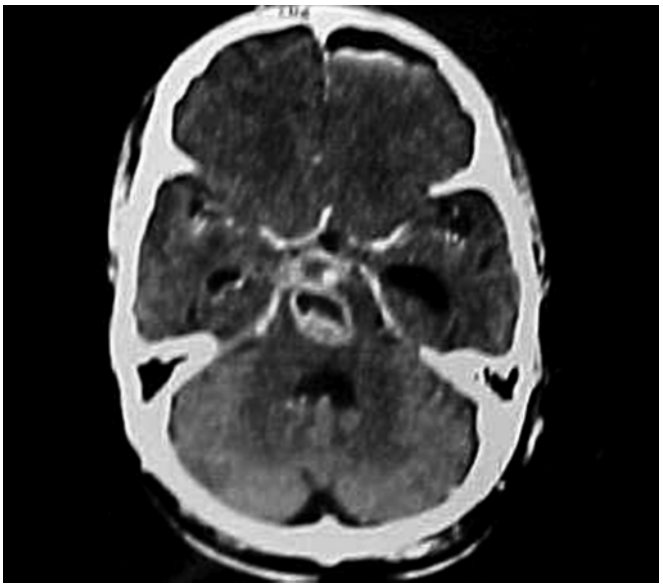


Fig. 8: Post-operative image of an aspirated cyst

The CRW frame can be used for:[43,46]

- Biopsy[31]
- Planning of craniotomy flaps overlying the surgical site
- Aspiration of a colloid cyst along with the endoscopes
- Drainage of deep seated abscesses, cysts (Figs 7 and 8)
- Brachytherapy
- Instilling chemotherapeutic agents in cystic lesions
- Lesioning of nuclei for movement disorders, such as pallidotomy and thalamotomy
- Placement of deep brain stimulating electrodes for movement disorders[43] and pain
- Depth electrode recordings (EEG) for cases of intractable non-localised epileptic foci[46]
- Radiosurgery for small well defined or remnant lesions

The limitations of these systems are that they are cumbersome and require the co-operation of the patient during frame fixation and during local anaesthesia. Fixing the frame and getting the patient scanned is time consuming as there may be other procedures being performed at the same time. The frame is bulky and may come in the way of surgery. At times, more extensive lesion resection and margin targeting may be necessary, which is not possible, unless the margins are retargeted.

Figure 9 shows the Leksell G frame with the multipurpose stereotactic arc in Figure 10. The main components of the frame are seen in Figure 11. The frame is engraved with a rectilinear coordinate scale, graduated in millimetres. The scale conforms to X, Y, Z directions

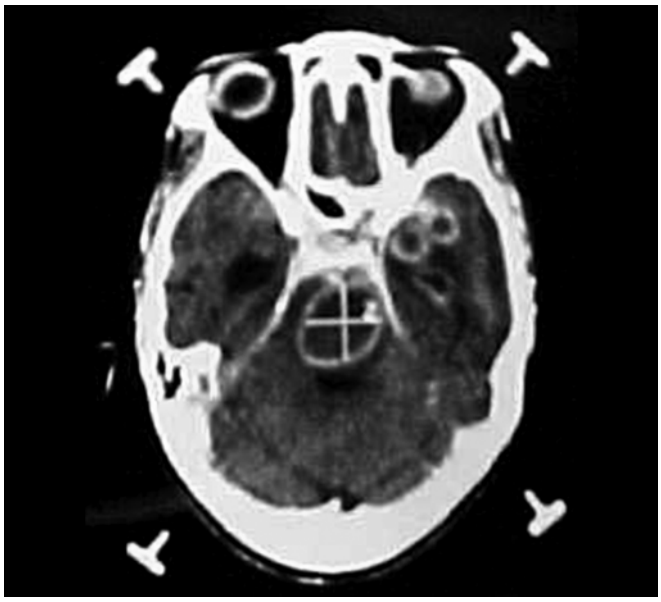


Fig. 7: CRW frame pre-operatively

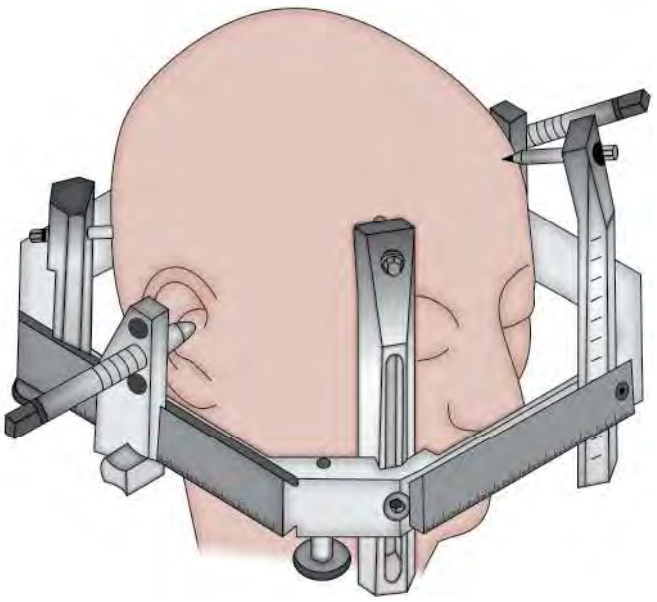


Fig. 9: Leksell stereotactic frame

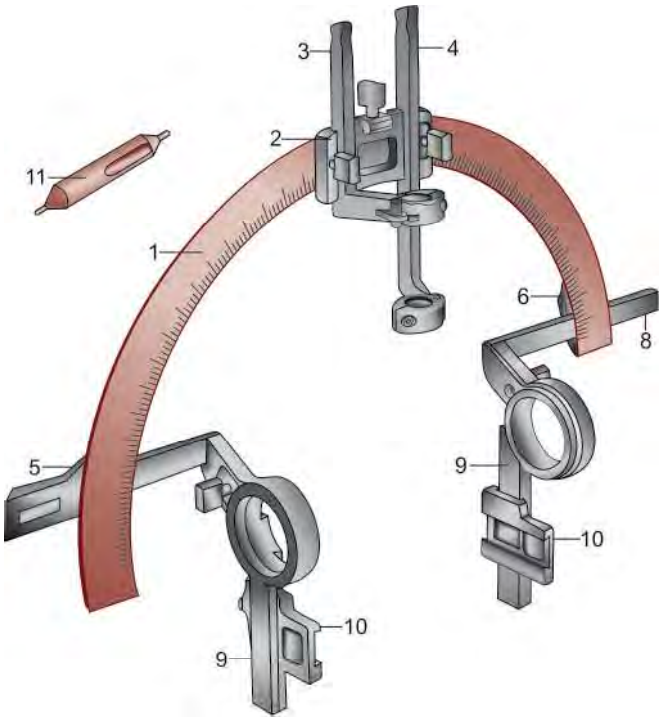


Fig. 10: Multipurpose arc

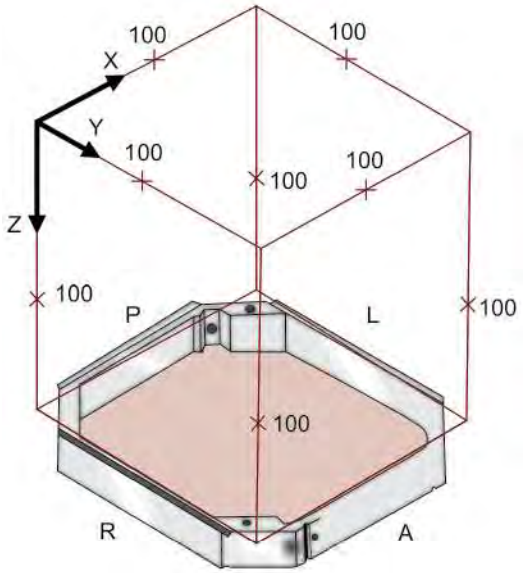


Fig. 12: Coordinate system

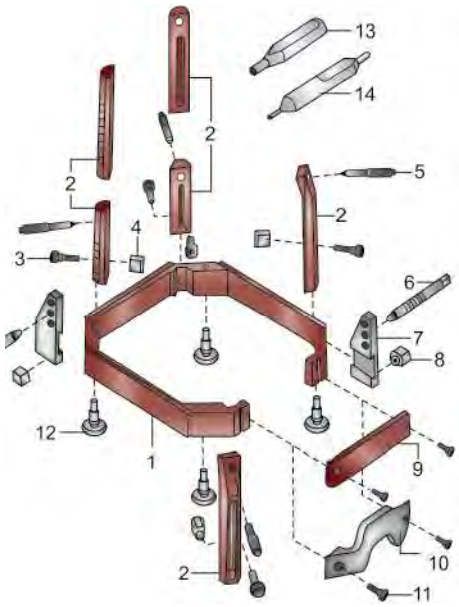


Fig. 11: Main parts of the frame

used in CT and MRI scanning. Origin (X, Y, Z = 0) is located outside the frame at a point superior, posterior and lateral to the frame on the patient's right side (Fig. 12). The frame is versatile and can be used for all stereotactic procedures, as well as target location and planning of gamma knife radiosurgery.

Stereotactic Biopsy

Technique

Stereotactic biopsy (STB) has proven to be highly accurate and safe, with least tissue invasion and proven tissue sampling.[38] The diagnostic yield is over 95%, morbidity less than 5% and mortality close to 0%. STB is often associated with a lower diagnostic yield in non-neoplastic lesions and the yield is much higher for those lesions with clear-cut margins and homogeneous character. It has a role in the diagnosis of a variety of lesions in AIDS, such as toxoplasmosis, lymphomas, focal encephalopathy and is a useful diagnostic tool in tuberculomas[31] and other infections.

Indications[7]

- Multiple intracranial masses, e.g. metastases, inflammatory lesions, lymphomas, multicentric gliomas
- Diffuse ill-defined intra-axial masses
- Deep seated intra-axial lesions which are inaccessible, such as thalamic gliomas, brainstem lesions[47]
- Lesions in eloquent locations, such as the motor or speech areas
- Unresectable invasive lesions
- Potentially radiosensitive lesions, such as germ cell tumours
- Candidates for brachytherapy and radiosurgery

Contraindications

- Suspected vascular lesions. In these cases one can employ frameless or frame based guidance for enhancing open resection

- Large lesions with significant mass effect require an open craniotomy and decompression
- Altered bleeding parameters
- Extra-axial lesions, such as meningioma
- Lesions close to the Sylvian fissure, suprasellar region and the third ventricle and most posterior fossa tumours.

Basic Steps

1. Informed consent is taken.
2. Usually performed under local anaesthesia-2% lignocaine. The scalp is infiltrated at the pin sites, prior to placing the frame. Explaining the procedure step by step is almost always all the analgesia needed.
3. The head ring is fixed onto the region of local anaesthesia with screws penetrating only the outer table of the skull.
4. Ideally, the pins are fixed in the forehead laterally and the mastoids posteriorly, to avoid muscle and the neurovascular pedicles. The target should be located within the limits of the base ring; if the lesion is in the posterior fossa the frame must be fixed at a lower level
5. A CT or MRI is done after mounting the localiser ring. Contrast is given, if required, depending on the type of lesion
6. Calculate the final position of the lesion using a stereo-calculator
7. The target coordinates on the frame system
8. Simulation on the phantom frame after entering the final coordinates and then fix the frame on the patient
9. Fix the arc system on the head frame
10. Make a small skin incision followed by the burr hole. The dura is opened in a cruciate manner and the edges coagulated
11. Adjust the probe tip to its predefined length
12. Perform a biopsy with a pair of forceps or via the needle aspiration technique
13. Send the tissue for a frozen section and paraffin staining
14. Confirm with scan/frozen section report
15. Shift the patient after removing the frame and start on oral diet if the procedure has been done under LA.

Complications

- Haemorrhage
- New neurological deficits
- Seizures
- Infection

Prevention

- Only one trajectory and one plane
- Not for vascular lesions
- Narrow instruments
- Proper choice of probe track

Stereotactic guided craniotomy uses the same principle and the steps are almost similar, except that the patient is under general anaesthesia. A craniotomy flap is marked over the site of the probe, directly overlying the target lesion. It can also be used to map out the location of the eloquent cortex. From the initial days of target localisation with frame-based systems, there has been a shift to more real time interactive imaging.

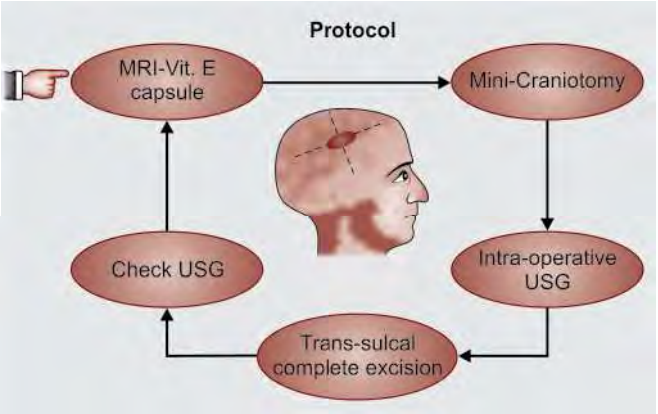


Fig. 13: Initial days of target localisation

Figure 13 depicts the earlier methods of localising targets. A marker object was placed in relation to the lesion and CT/MRI performed (Fig. 14). A mini-craniotomy was performed, based on the relation of this capsule to the underlying lesion. Once this was performed, we would then make use of the ultrasound (Fig. 15), as there would be no barrier from the intervening bone to check our location over the target. If appropriately located, a trans-sulcal approach would ideally place us over the lesion, enabling resection/biopsy, which could again be verified by an ultrasound performed at the end of the procedure.

The advantages of this were that it was accurate, cheap, safe, simple, reproducible and real-time.

The disadvantage of the intra-operative ultrasound is that the bony interface disables its use for planning

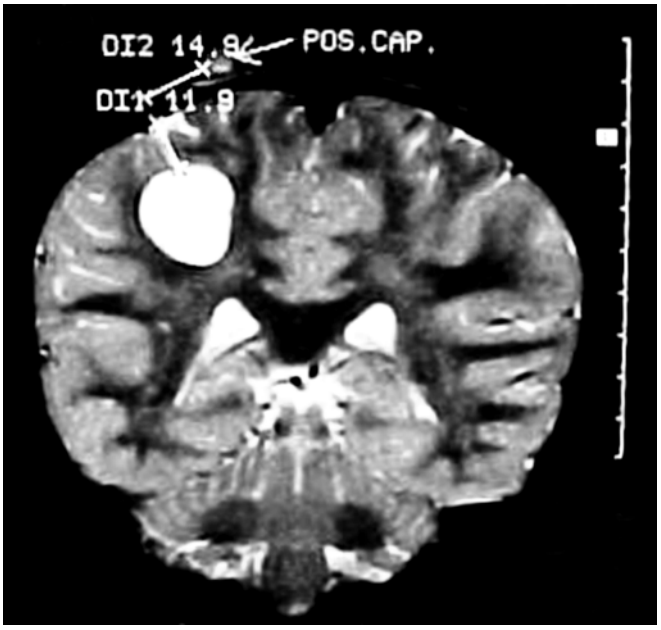


Fig. 14: Pre-operative MRI

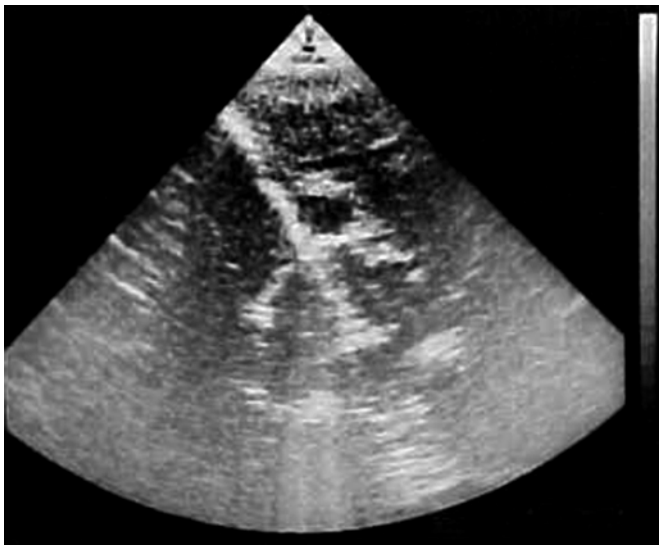


Fig. 15: Intra-operative ultrasonography

specific craniotomy flaps. The lesion consistency should be cystic or solid, to obtain well-defined margins.

Frameless Stereotaxy (Interactive Image Guided Surgery)

Frameless stereotaxy or 'interactive image guided surgery' is a relatively new navigational modality in which there is no frame fixed on the patient's head. The basic principles had already been established in the preceding 50 years, with frame based systems, and technology evolution and implementation to stereotaxy brought about these changes. Neuronavigation is only a tool which is utilised to optimise the approach while minimising morbidity. Technology enables us to identify functional cerebral locations in relation to the lesions and approach and resect these lesions without damaging these eloquent areas.

The technological advances seen in the 1980s led to the ultimate use of these devices. These are:

- Computer software which could be utilised to manipulate data from images from either a CT/MRI
- Spatial accuracy has improved to almost 1 mm, with reasonably good speed
- Low cost equipment, in which three-dimensional digitisers could be used as pointing devices during surgery, is available

The steps in utilising these systems are almost similar:

1. Patient selection
2. Fiducial placement
3. Imaging
4. Data transfer
5. Pre-surgical viewing
6. Identification-registration of markers
7. Planning and intra-operative navigation

How one gets to the lesion, however, does not alter the basic operative technique with which the surgery is performed. These are:

- Relaxed brain—neuroanaesthesia
- Minimal dural opening
- Minimal retraction of normal brain tissue
- Trans-sulcal dissection
- Internal decompression
- Ultrasonic aspirator
- Bipolar coagulation
- Entering into the plane between the tumour and normal tissue
- Haemostasis

Patient selection is an important factor, as all cases do not require the use of navigation to locate the lesion.

Imaging

CT and MRI scans are obtained as three-dimensional volumetric databases, even though they are displayed as two-dimensional slices along an axis. The images contain within themselves a coordinate system conferred by the scanner during the acquisition, which defines a temporary address for each point in that imaging volume. To utilise these medical images, a quantitative relationship has to be established on a point-by-point basis between the information in the images and the physical space.

Surface reference markings that are usually external adhesive markers (called fiducials) are placed at various points to cover a wide area of the scalp and imaging is done with either CT or MRI. Additional contrast-enhanced studies may have to be performed, depending on the type of lesion being delineated. Fine 1–2 mm slices on the CT may also be required to increase the accuracy. These images are recorded on digital media in the DICOM format.

The fiducials are placed so that they cover a wide area, they should also be multiple, not linear and placed in relatively immobile scalp regions. Other imaging modalities such as fMRI and PET scans can also be performed if required. The present generation systems do not require external fiducials and various surface landmarks can be utilised for registration.

Once the imaging has been completed, the data is transferred to the intra-operative guidance computer. Prior to registration, the surgeon analyses the image data to decide the location, size and type of scalp flap, which would be planned. The ideal location for a burr hole and biopsy would be over a gyrus, and away from any vessels. The surgeon's plan can be recorded and used following the registration.

Patient registration is then performed. The patient's head is rigidly fixed on the table with either a Mayfield or a Sugita frame. A reference star is attached and the position of this star cannot be changed throughout the procedure (Figs 16 and 17). Registration involves placing the points in one image volume (patient's fiducials) onto the points of another volume (images taken pre-operatively). The fiducials in principle act like the picket fence target in frame-based systems and these are entered into the operating room space.

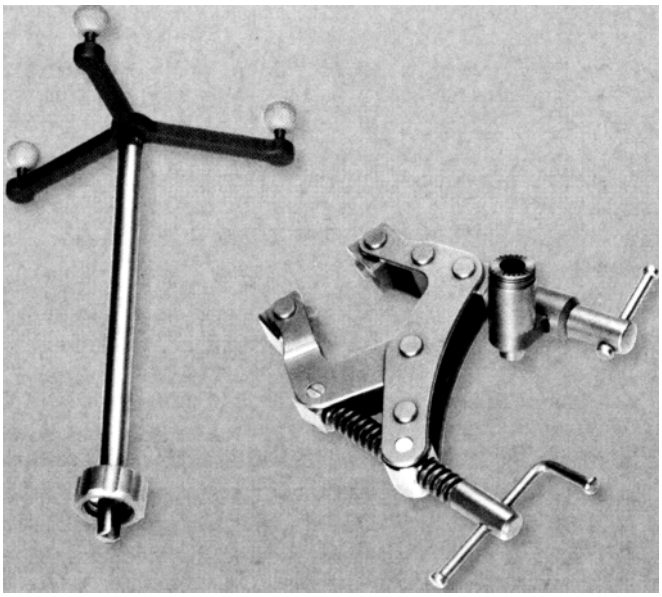


Fig. 16: Mayfield adapter with reference star

Fig. 18: Brain Lab Infrared optic triangulator
(Courtesy: Max Super Specialty Hospital, Delhi)

The different methods of registration include:

- Point-based
  - Intrinsic
  - Extrinsic
  - Non-rigid fiducials
  - Rigid fiducials or a stereotactic frame
- Curve and surface methods
- Moment and principle axis
- Correlation methods
- Interactive
- Atlas

We commonly use the point based systems or the curve and surface methods, as the others are unable to register images in physical space. Either the fiducials are brought into contact with a registration device or, in the newer machines, a laser light scans on the surface contours of various points (Z touch), which is picked up by the light emitting diode detector and correlates these points with the image dataset which has been transferred to the workstation.

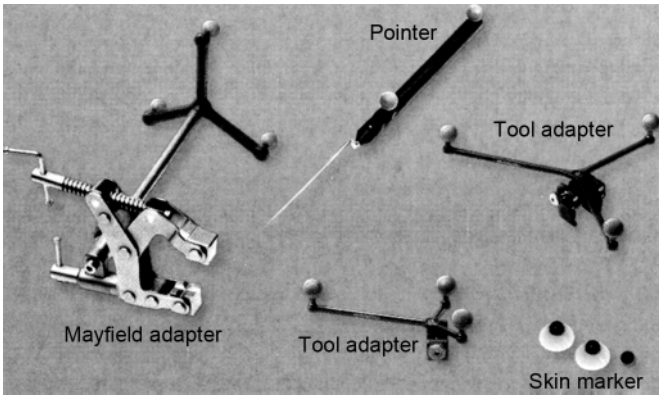


Fig. 17: Mayfield adapter

The device, which enables us to acquire these points, is known as the interactive localising device or the ILD (Fig. 17). These devices may either be linked or non-linked. Linked systems began with the stereotactic aiming arc, active robotic arms, passive articulated arms, intra-operative MRI and CT. Non-linked devices include sonic triangulators, infrared light emitting diode (LED) optic triangulation (Fig. 18), magnetic field deflection and gyroscopes.

Once the registration has been completed, the next step would be to visualise the approach and underlying structures with the help of the navigating pointer. The margins of the lesion can be defined and its relation to the scalp flap delineated. The depth of the lesion can be measured from the surface, using a virtual probe.

Disadvantages

- It is not in real-time
- Inaccuracies may occur due to brain shift
- Increased operating time
- Per-operative (pre-operative?) imaging is mandatory

Uses

- Glioma resection and localisation
- Deep seated tumour localisation
- Drainage of cysts and abscesses
- Placement of a reservoir for chemotherapy
- Surgery for epilepsy[27]
- Guidance to the ventricles

BRAIN SUITE: (INTRA-OPERATIVE MAGNETIC RESONANCE IMAGING AND REAL-TIME NEURO-NAVIGATION)

The concept of the integrated operating room was first thought of in 1991, as a collaborative effort between

GE systems and the Department of Radiology and Neurosurgery at Harvard.[1] Intraoperative MR imaging is also known as 'MRT' or magnetic resonance therapy. The prototype system was installed in 1994 and was designed to perform real time imaging, while neurosurgical procedures were going on. It was first used in 1995, with the double-doughnut scanner,[4] only for intra-operative use. Just as the microscope changed the scale of dimensions of the operating field, the intra-operative MRI in the operating room has expanded the surgeon's view from 2D to 3D. It has given the surgeon an opportunity to look beyond the exposed surface and enabled clear visualisation, not only of the operational field but also operational volume.

The Erlangen concept was developed by Robert Fahlbusch with the assistance of Siemens and Carl-Zeiss.[3,13,17,55,57] The operating room and the radiofrequency shielded MRI room were different, as MR compatible instruments were required for performing all aspects of micro-neurosurgery. The images from the MRI were transferred to navigation computers and surgery performed. The initial field strengths were 0.5 T and at present 1.5 T magnets are used intra-operatively.

The development of active shielding of superconducting magnets enables integration of surgery in the fringe fields with high field MRI.[48] A high field MRI may not only improve the quality of the intra-operative images, but also adds the ability to perform functional MRIs, diffusion weighted imaging and MR spectroscopy.[30] The operating theatre has to be large enough to accommodate the equipment, which includes all the accessories for navigation, as well as microsurgical work. The use of ferromagnetic materials is to be avoided and non-ferromagnetic materials like aluminium, titanium and ceramics can be used. All equipment has to be compatible with MRI. Anaesthesia and monitoring equipment has also been redesigned for the operative environment.[51]

Intra-operative MRI has a wide range of applications for the surgeon:

- Gliomas resection
- Pituitary tumour
- Complicated tumour resection
- Epilepsy surgery
- Intracranial cyst surgery
- Biopsy with and without a frame
- Catheter placement
- Vascular surgery
- Functional imaging
- Diffusion tensor imaging

Equipment and Theatre Set-Up

At the Max Institute of Neurosciences, Delhi, a Siemens 1.5 T MRI scanner is placed in an RF shielded room (Fig. 19). The scanner consists of a superconductive active shielded magnet with a length of 160 cm and an inner bore diameter of 60 cm, equipped with a gradient system with field strength of up to 40 mT/m. A specially designed rotating surgical MRI table has been adapted to the scanner for intra-operative patient transportation and for imaging. The principal surgical position is at 160 degree with the patient's head at the 5-Gauss line. Once the rotating mechanism is locked, the height of the table, the angle of tilt, and the lateral tilt can be adjusted by remote control. The rotation of the table axis and turning the table into the axis of the scanner has to be done manually. The ventilator is MRI compatible and MRI-compatible monitoring equipment is used for maintenance of anaesthesia. The monitoring data is transferred to a remote display, which allows continuous monitoring during scanning from outside of the RF-shielded operating room, with a wireless 2.4 GHz connection. Three infusion pumps are shielded in an MRI-compatible carrier for continuous infusion of drugs. The anaesthesia equipment is located outside the 200 Gauss line.[48] Anaesthesia gas inlets and compressed air for surgical drills are integrated in the wall of the RF room. Service outlets and sockets are connected to different electrical circuits, so that selected circuits could be switched off from a switchboard in the MRI control room, to prevent artefacts generated by individual devices. The ceiling outlet for laminar airflow is located above the main operating table. The laminar airflow output is surrounded by a band of fluorescent lamps for optimal illumination. For scanning, the illumination could be turned off from the MRI control room. The entire operating theatre has MRI-compatible spot lighting. Two ceiling-mounted surgical lamps are installed at the main surgical position. Both the 5 Gauss and 200 Gauss lines are marked on the floor. The latter also is marked by a raised stainless steel strip as a mechanical threshold. All equipment not completely MRI compatible, such as the navigation microscope and the height-adjustable surgeon's chair, are secured to the wall of the RF room mechanically as a safety precaution.

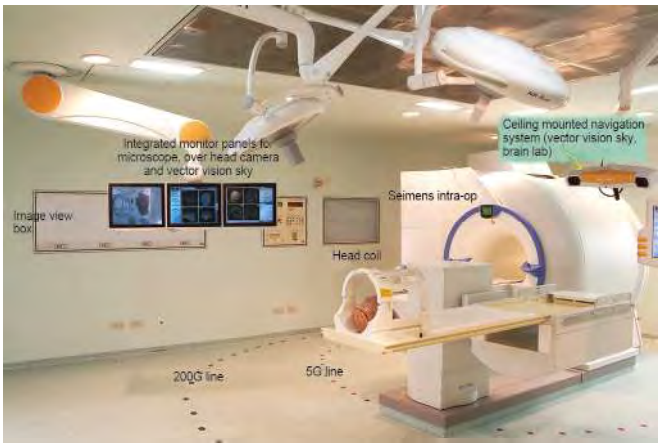


Fig. 19: Brain SUITE iMRI: At Max Institute of Neurosciences, New Delhi (Courtesy: Dr AN Jha)

Benefits of the Intra-Operative Magnetic Resonance Imaging

High field MRI has a number of advantages, such as instant real time feedback in the OR, superior image quality and

acquisition time and advanced MR sequences. Data can be incorporated into decision-making at the time of surgery.

It has the potential for unlimited research and the ability to drive new imaging techniques. Also important are the improved medical outcomes with the use of intra-operative MRI, shorter hospitalisation, and better and faster procedures with fewer complications. Certain economic and practical barriers impede the use of intra-operative MRI, but with increased volumes the cost efficacy barrier can be overcome after looking at the benefits.

MRI guided procedures are a collaborative effort between the neurosurgeons, neuroanaesthetists, radiologists, MR technologists, nurses and engineers and this collaboration is both essential for scientific growth, as well as having no glitches while performing surgery.

Future Developments of Intra-Operative Magnetic Resonance Imaging[23]

- Full patient access during the surgical procedure
- No need to move either the patient or the magnet
- Highest image quality with reduced acquisition time
- Ergonomics that incur no delays for serial or continuous scanning
- Integration of all pre-operative and intra-operative imaging data for interactive navigation
- With the introduction of high field MR systems intra-operative diffusion imaging can demonstrate early ischaemic damage during procedures and can be used to monitor vascular procedures[63]
- Diffusion MRIs can be complemented with perfusion MRIs and surgery and embolisation of AVMs will be made safer by keeping an eye on blood flow, while the blood vessels are being manipulated.
- In aneurysm surgery, 3D visualisation can help identify the position of the clips and their relation to the neck of the aneurysm.[63]

Neuronavigation

The Zeiss Opmi Pentero microscope which is floor mounted on wheels, in combination with a ceiling mounted navigation system (Vector vision sky—Brain lab) which are optimally integrated, are used. The initial sequencing protocol may be standard T1WI, T2WI and other sequences depending on what is specifically required. Functional data and magnetoencephalography, which is obtained a day or two prior to surgery, can be incorporated with the anatomical data registered in the sequences.[16,35,36] fMRI and magnetoencephalography data is used simultaneously to identify eloquent cortical areas.

iMRI Procedure

A four point head holder made of glass fibre with reinforced plastic is integrated into the common system circular head coil used for craniotomy procedures. The upper part of the head coil is sterilised using formalin tablets. Sterile adapters are fixed onto the lower part of the head coil, ensuring sterile draping. This enables variable positioning, except for the sitting position. For imaging during surgery, the head is covered with sterile drapes and the upper head coil is placed on top of the head and imaging done according to the centre protocol and requirements. The surgical strategies that can be employed during the procedure are complete resection and removal in the group of patients whose tumours are to be entirely resected,[37] further but partial removal in the group of patients in whom the tumour was unlikely to have been completely resected and in whom further resection seems to be possible, even though infiltrating and near eloquent areas.

The slice positions of every sequence are recorded to correlate images at various points during the surgery. The data for tumours is analysed to assess residual tumour volume.

Once the patient has been induced and the head fixed onto the frame, the first set of intra-operative MRI images are taken (Fig. 20). Once that is done the patient is manually shifted on the swivel operating table, to the operating position at the 5G line. The reference arc is fixed on the head fixation device and, using the laser pointer (Z-touch), surface landmark registration is performed. Once the system has registered multiple points, it verifies the accuracy and, if this is good, one can proceed with the surgery. Using the navigating pointer, the margins of the tumour can be identified (Figs 21 and 22) and the location of the scalp flap can be marked. The next steps are the routine surgical steps which include the craniotomy and dural opening. The location of the cortical incision and the surgical trajectory can all be planned at the time of surgery, with the help of the navigating tools. Two illustrative cases will be described, in one where navigation has been used during tumour resection and the other for preserving the functional speech cortical area.

Case 1: A 46-year-old male presented to our Institute in May 2006 with symptoms of memory loss for recent events, inability to concentrate on tasks, altered behaviour and inattention for about 6 months, followed by

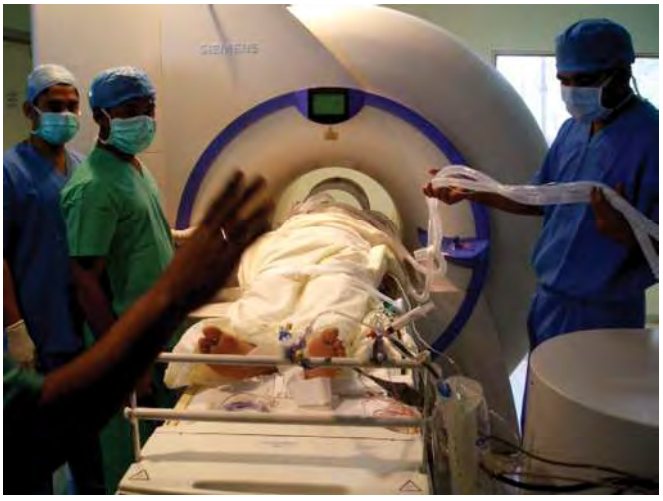


Fig. 20: The patient being positioned in the gantry for the first set of scans.

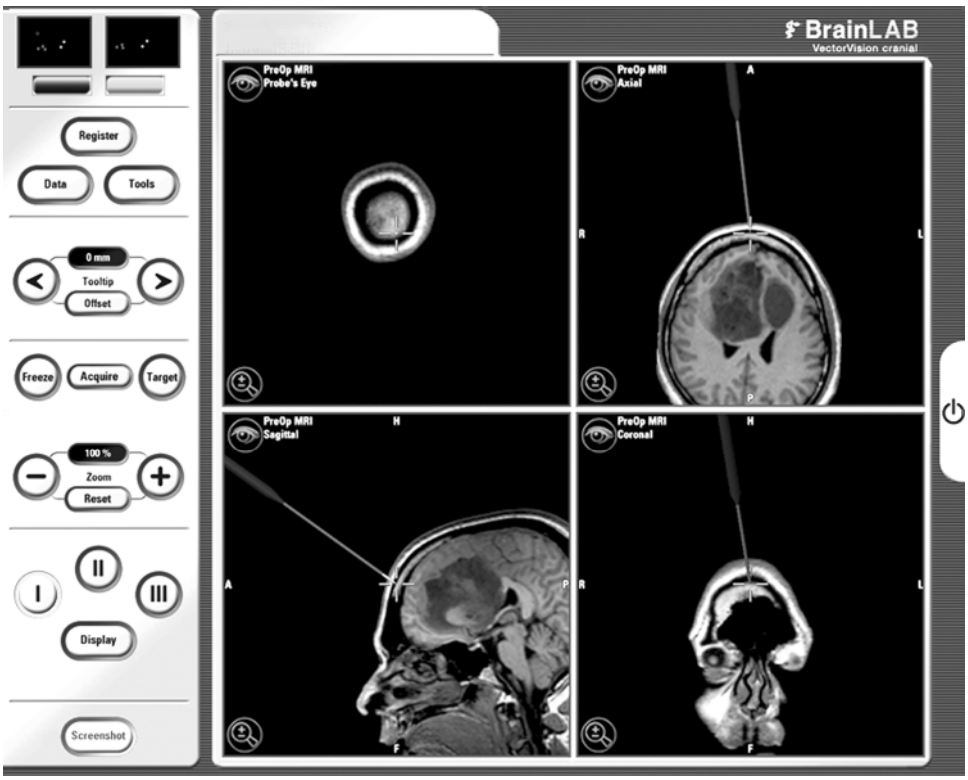


Fig. 21: Locating the margins of the skin and bone flap

urinary incontinence for 2 weeks. An MRI was done which revealed a butterfly corpus callosum glioma with the left side component being cystic and the right being solid. We decided to use intra-operative imaging and navigation to safely and accurately help us in maximising tumour resection with a minimal deficit to the patient.

The patient was induced, his head fixed onto the MRI table and the first set of intra-operative images carried

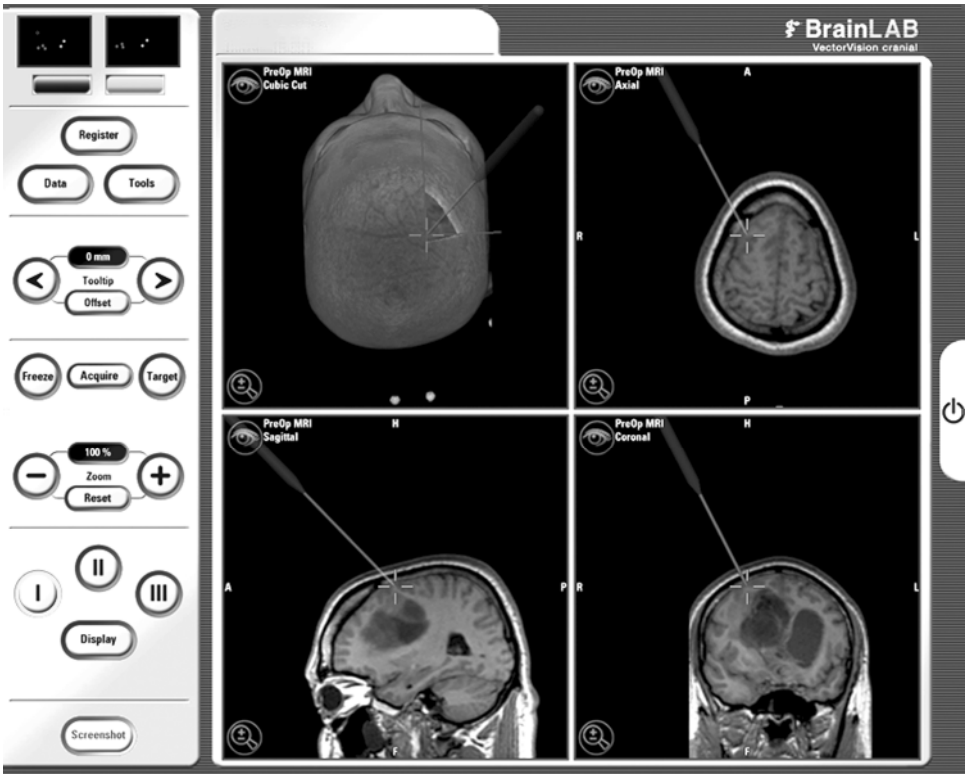


Fig. 22: Locating the margins of the skin and bone flap

out. Surface registration was then performed using the laser pointer (Z-touch) and the limits of the scalp flap marked (Figs 21 and 22). A bifrontal flap and craniotomy was performed and the tumour was approached from the right side, at its closest point to the surface, which was located with the navigation pointer. It did not have a well defined margin. It was greyish white, soft and minimally vascular and following a good decompression, an MRI was done to assess the degree of resection, as well as to acquire new sets of images so as to compensate for brain shift[15,34] (Figs 23 and 24).

The navigation tool was used to identify the trajectory into the cyst cavity and following its decompression, the second MRI revealed residual tumour (Figs 24 to 26). Further resection was then performed and to avoid damage to the ACA's the entire tumour was not chased. Closure was then performed and the final MRI revealing good tumour resection (Fig. 27) in concordance with our pre-operative plan.

Case 2: A 45-year-old gentleman was operated upon in 2000 at a Cancer Hospital for a left frontal oligodendroglioma grade 2, after which he had been followed-up with regular MRI's. His last MRI done in April 2006 revealed an increase in the size of the tumour. He had no symptoms and on examination had no deficits. His speech was intact and we decided to get a functional MRI pre-operatively and utilise these images by integrating them with the intra-operative images in order to protect the speech area during tumour resection. The intra-operative images taken were fused with the pre-operative fMRI, as shown in Figures 28 and 29.

The area in pink (Fig. 28) is the entire tumour volume and the yellow is the speech area, which is marked out by the fMRI done prior to surgery. That is the area which has to be preserved during surgery and it is very easy to get lost in tumour resection and attempt a total resection, giving the patient a permanent speech deficit. Once the images are fused we verify a good fusion by checking the overlap of the margins of the present MRI to the prior one; this is an automated process done by the computer. It selects and matches point to point targets on the images, to fuse them and the accuracy is finally checked manually by the surgeon (Fig. 28).

Once this is done the surgery is started and a craniotomy over the desired limits set out by the surgeon is performed. Using navigation, the tumour resection is begun away from the speech area as seen in Figures 29 and 30. Following a significant resection, we decided to repeat an intra-operative MRI. This was then fused on the previous data sets showing the degree of resection, remaining volume and the relation to the speech area.

The integration of the various components allows the surgeon to view the tumour, as well as speech area margins by the process of image injection. The area on which the surgeon is focusing is calculated by the navigation system and is projected onto their images as the blue circle as seen in Figure 31. Some intra-operative images are shown, as seen in Figures 32 to 36. It is difficult to identify the speech area without the help of navigation. The surgeon may be aggressive in resecting a large quantity of the tumour but cause a permanent speech deficit, making the quality of life of the patient very poor.

Neuronavigation is thus an aid to 3D visualisation of the object, entry and planning of surgical treatment. The ability to identify intra-operative swelling, brain shifts, resection margins and volumes and adjacent functional areas makes intra-operative MRI a useful adjunct to surgery. It contributes to greater tumour volume resection in gliomas.[6,49,52] The ideal treatment for low-grade gliomas is complete resection and this is an ideal modality to achieve a high cure rate.

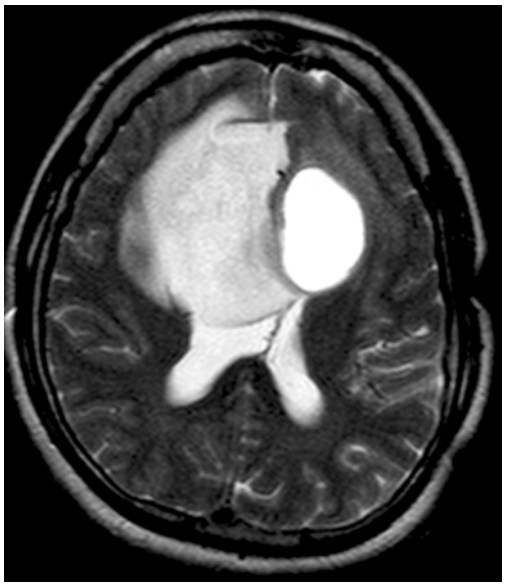


Fig. 23: First intra-operative image

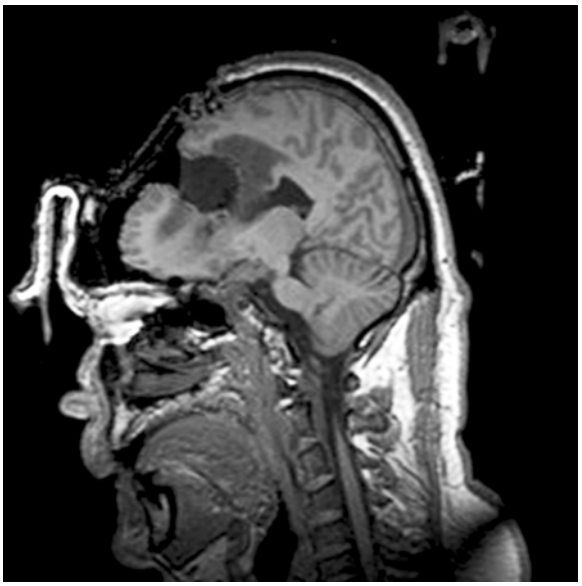
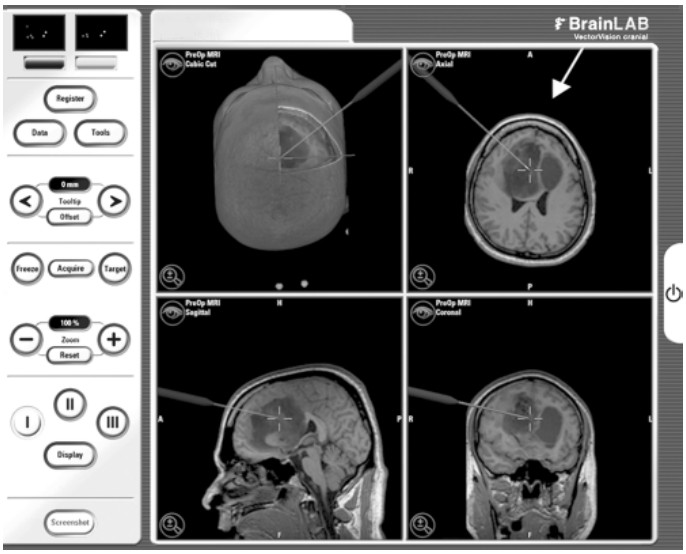
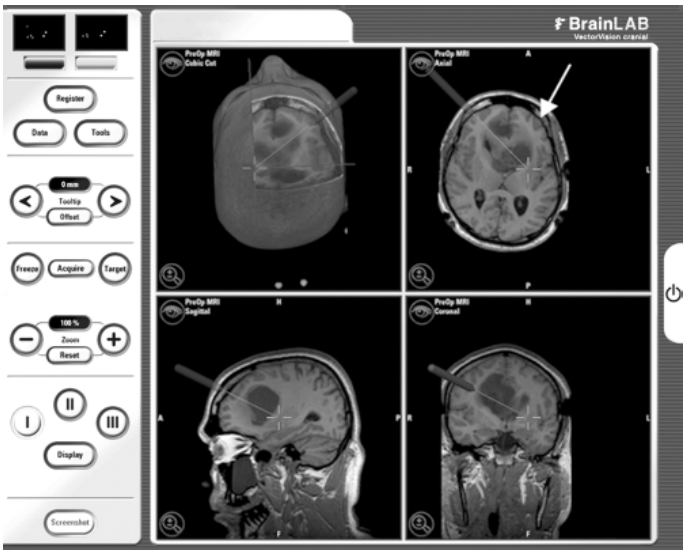


Fig. 24: Second image revealing residual tumour





Figs 25 and 26: Using navigation to guide entry into the cyst and following cyst decompression verifying the margins

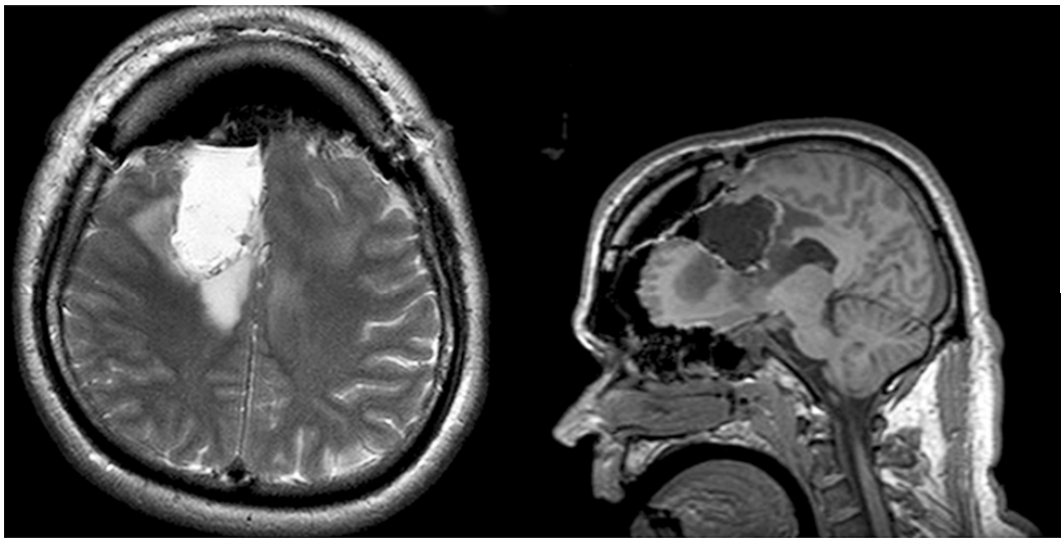


Fig. 27: Final post-operative images showing good tumour resection

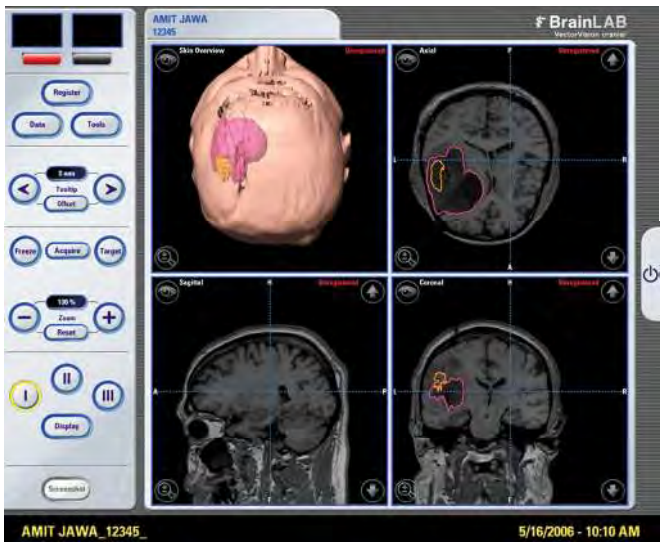


Fig. 28: Tumour volume and speech area fMRI

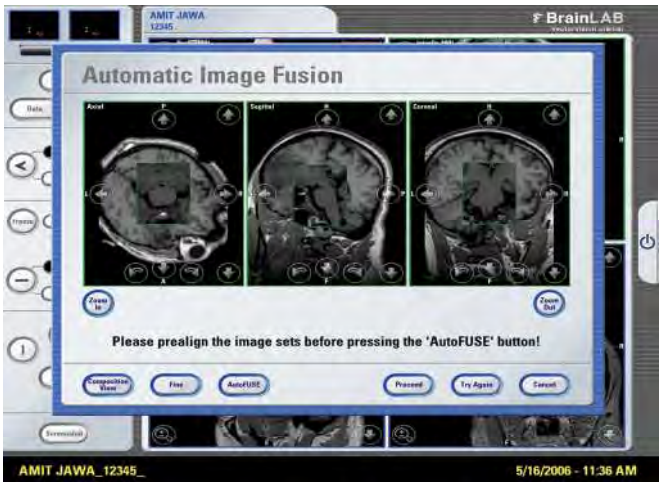


Fig. 29: Automatic image fusion

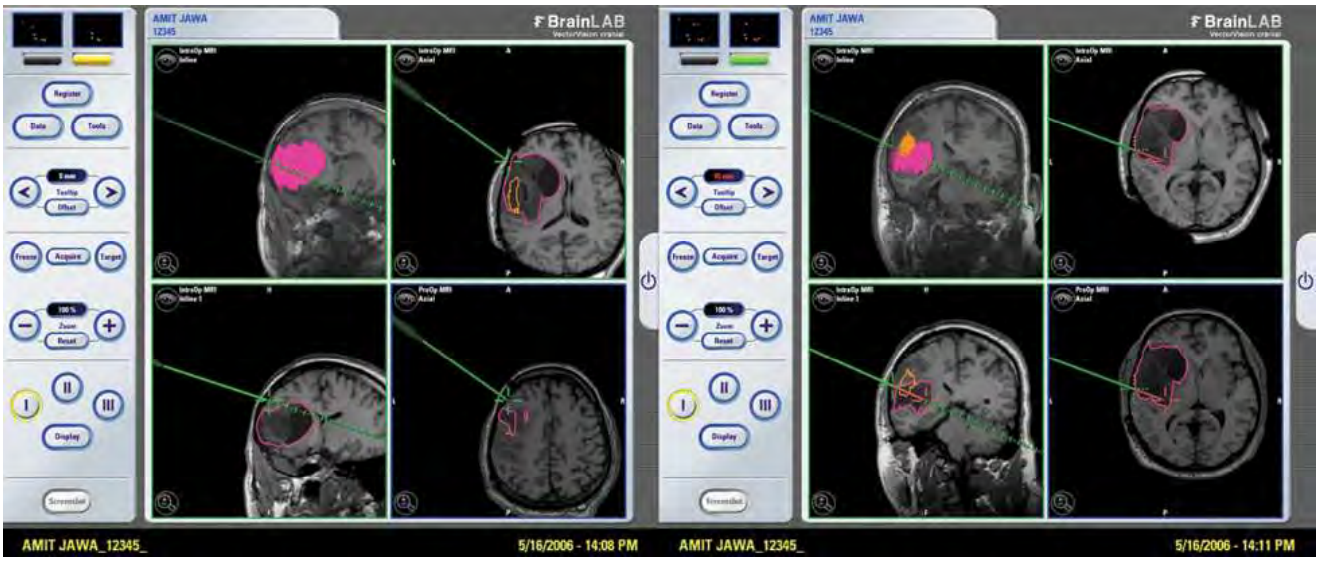


Fig. 30: Resection started at the anterior limit

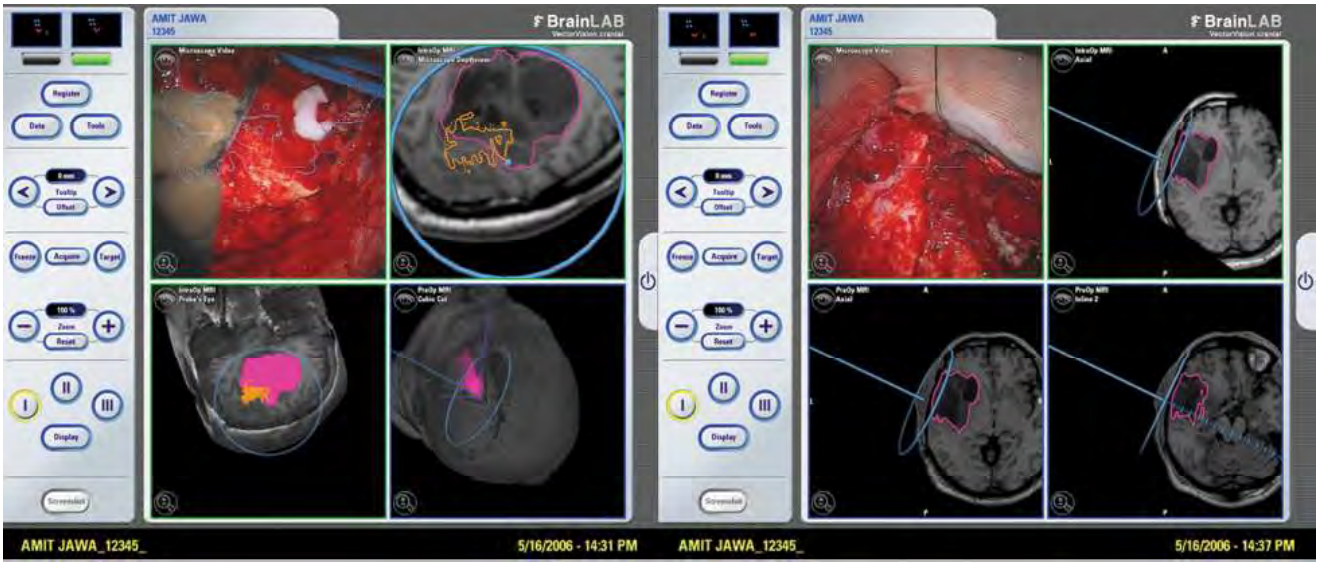


Fig. 31: The microscope has the tumour margins and the speech area injected into the viewers eye piece enabling the surgeon

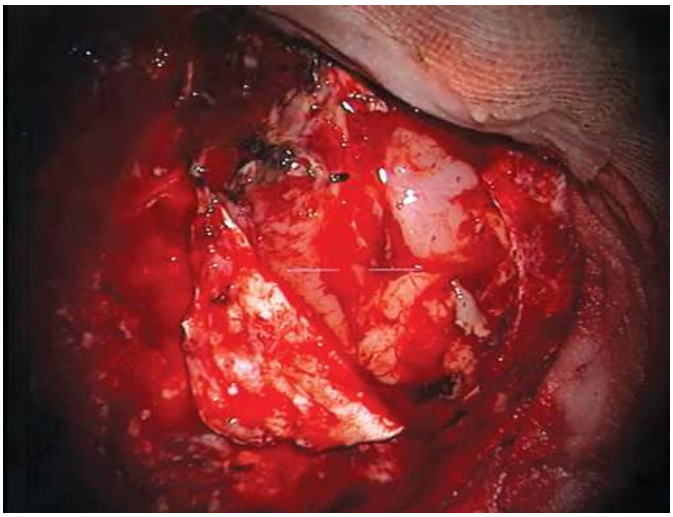


Fig. 32: Dura open and tumour bulging

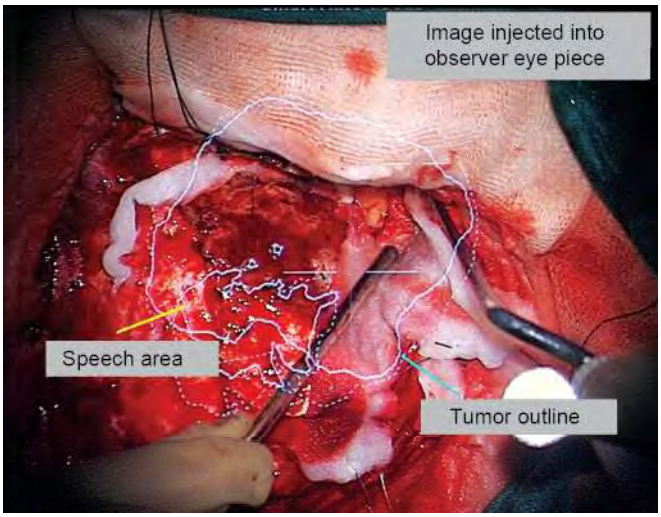


Fig. 33: Image injection into the surgeons eye piece

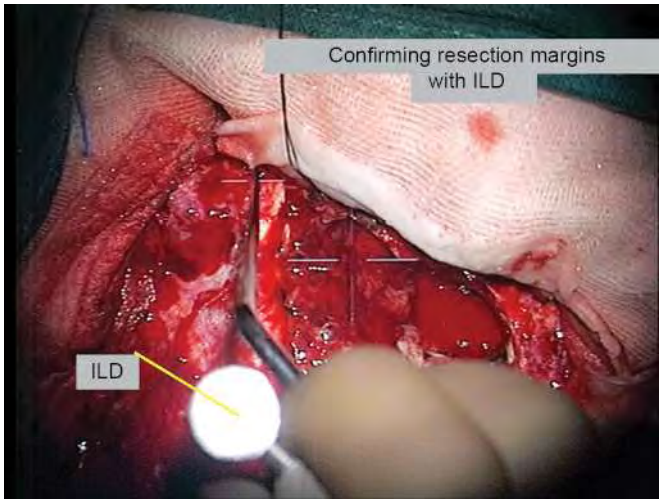


Fig. 34: Confirming resection margins with ILD

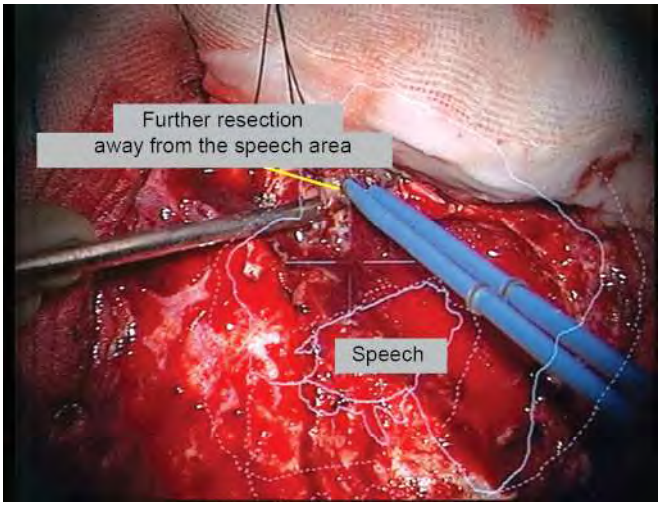


Fig. 35: Preserving the speech area

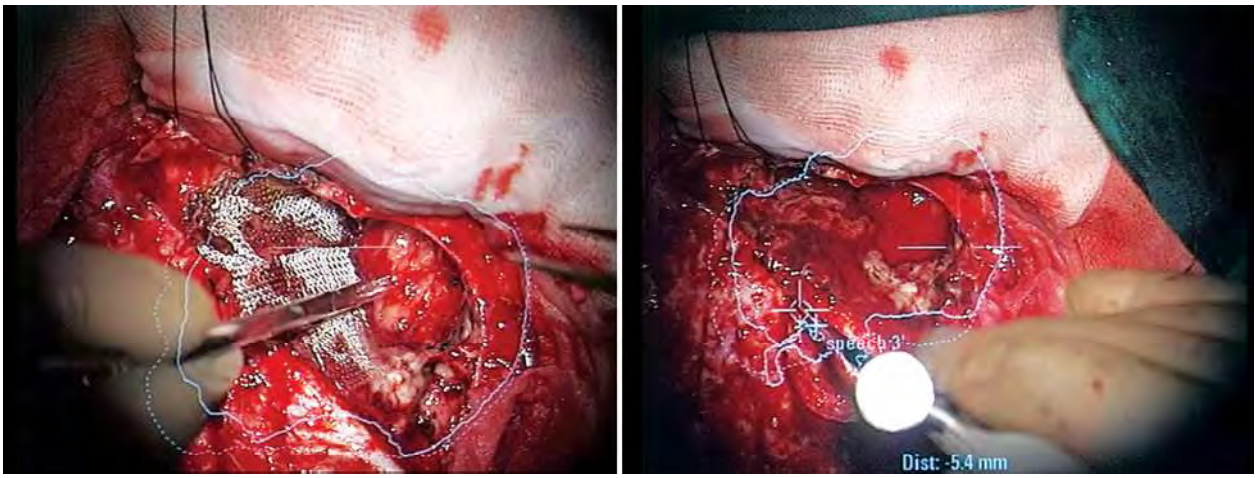


Fig. 36: Confirming resection margins and speech area at end of surgery

One of the advantages of intra-operative MRI in guiding procedures, such as brain biopsy, is that it can definitively show when the biopsy needle is in the lesion, which guarantees success in obtaining a representative specimen. The ability to repeat images at close intervals enables the easy identification of bleeding.

Intra-operative MRI guided surgery is at present superior to any form of neuronavigation system, having the potential to acquire spectroscopic and angiographic data, which could lead to different surgical techniques and surgical goals. It has the ability to compensate for brain shifts, which will occur due to CSF loss, diuretics or tumour/brain being resected and is accurate. The process of updating these images enables a study of these shifts and their continuous monitoring during tumour resection. Mapping of motor and other functional areas helps in avoiding of these areas and prevent permanent neurological deficits.

Debate still exists on the degree of tumour resection necessary for low and high-grade lesions.[5,37] The recurrence of metastatic lesions is most commonly at their resection site. Could extended resections with the help of real-time intra-operative imaging reduce these recurrences? Brain swelling at the time of surgery can be immediately evaluated with immediate scanning and therapy guided towards its correction.

NAVIGATION IN SPINE SURGERY

Spine surgery also has areas where the surgeon is not completely oriented to the complex anatomy of the region and it is here that computer-aided image guidance during surgery plays a big role.[25,28] The spine surgeon's orientation to the non-visualised anatomy has taken a turn-around with crisp three-dimensional images locating the various landmarks.

Many of the surgical techniques, involving spinal surgery, require the precise spatial orientation of structures not in the visual field. In addition to this, the extent of tumour removal and reconstruction, following this by placing pedicle screws at the thoracic, lumbar and sacral spine, needs 'visualisation' of the unexposed structures.

Fluoroscopy has been the conventional guide for the surgeon in these situations, the drawback being that it gives us the trajectories in two dimensions and the surgeon has to extrapolate the third dimension and proceed. Although the lateral view (Fig. 37) may be easy to interpret, the AP view makes it difficult to estimate the depth at which one needs to work. This so called 'dead reckoning' can lead to varying degrees of inaccuracy when doing instrumentation at various spinal levels.[24] Utilising routine radiography to place pedicle screws has been shown to be unreliable at the lumbosacral level with penetration of the cortex ranging from 21% to 31%.[18,19,58]

The principles of image guided navigation for spine surgery remain the same as that for the cranial component, with regards to a number of components. The components which are common to both are the image processing workstation interfaced with an optical infrared localiser. The optical localiser can either be the source of infrared light which is reflected by the instruments back to the camera or can track infrared light, emitted by the LED. The computer workstation then utilises this information to calculate the precise location of the instrument in the surgical field, as well as the location of the specific anatomical target in relation to the instrument resting on it.

Prior to spinal fixation, a pre-operative CT scan of the various levels has to be performed. The images should be a three-dimensional volume acquisition of a continuous dataset with slices 1–2 mm thick. MRI data images may also be used and this data is transferred to the workstation via a CD format.

The application of navigation to spine surgery requires that fixed bony landmarks are utilisded as the fiducial frames of reference. Two separate registration techniques can be harnessed, while using spinal navigation.

The first would be the 'paired point registration' technique where a series of points on the CT or MRI imaging datasets are pre-selected and, on exposing the spine, fixed bony points are selected. Any intra-operative landmarks that can be easily identified, along with its corresponding radiological counterpart, are the reference points for further image-guided navigational projections. The best and easiest would be the tips of the spinous processes and the transverse process, at the levels at which instrumentation is to be performed. Alternatively, other bony landmarks, such as osteophytes or the facet joint can be used. Registration is then performed prior to any surgical decompression or manipulation (Fig. 38), thus preserving the anatomical landmarks and facilitating an easy and accurate registration process.[25] Three separate points are required for registration.

Alternatively, a second technique called 'surface mapping' can be used for registration. Here, multiple non-discreet points on the exposed and debrided surface of the spine, within the surgical field, are selected. No pre-selection of points from the imaging dataset are required and to increase the accuracy of this technique, a greater number of points are required from both the dataset and the surgical field. The positional information of these points is transferred to the workstation and this is used to create a topographic map and match it to the imaging dataset.[40] For this method, about 10–15 mins is required, whereas, for the paired point-based technique only 10–15 sec are required. This can prolong the duration of surgery.

Once the registration has been performed, a spatial relationship has been processed between the surgical space and the image space. Movement of the patient

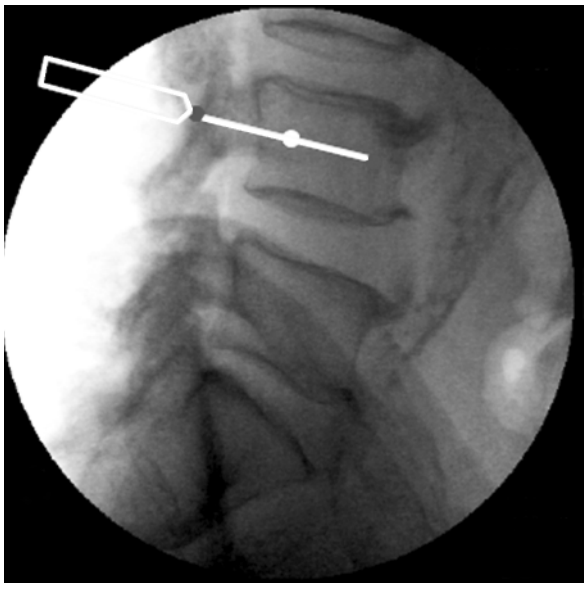


Fig. 37: Lateral view pedicle screw trajectory

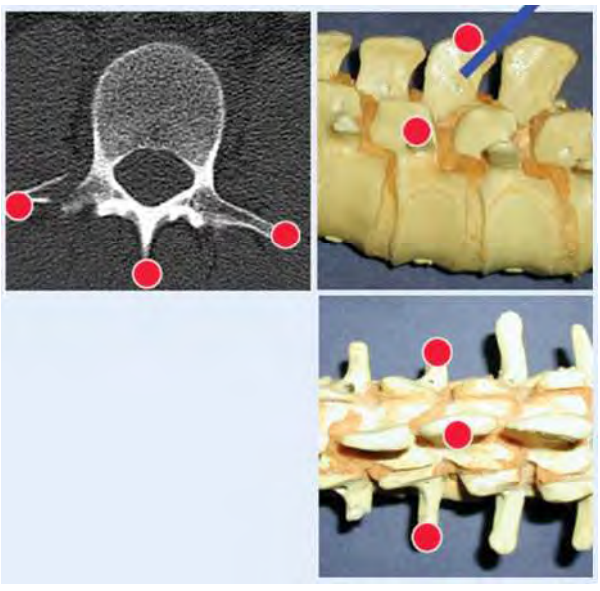


Fig. 38: Registration performed prior to any surgical decompression or manipulation

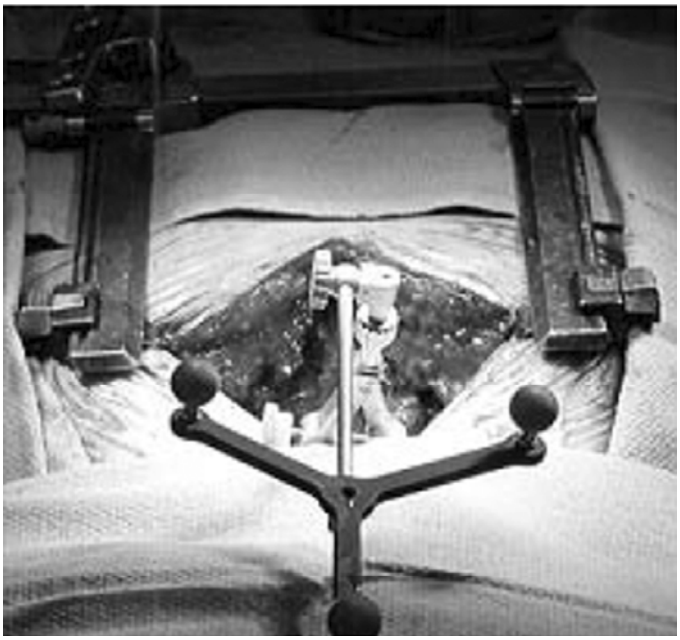


Fig. 39: LED attached to the spine

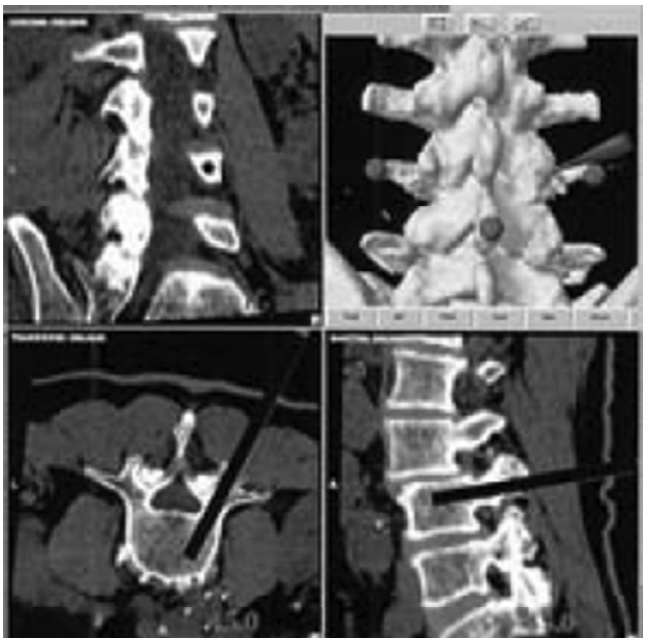


Fig. 40: Pedicle screw fixation and spinal stabilisation

following this will cause spatial distortion and navigation errors. This is usually minimised by using a spinal tracking device, consisting of separate LED or passive reflectors, which are attached to the spine (Fig. 39). This frame can be continuously tracked by the camera and any change in position will alert the navigation system, thus maintaining the accuracy of the registration and eliminating the need for redoing the entire process.

Disadvantages of the tracking device are:

- It comes in the way of the surgical field
- It should always be in the line of site of the camera
- Additional surgical time is needed for its attachment.

Sometimes, the tracking system could be avoided but absolute care has to be taken, to avoid leaning on the patient, changing the position of the table and respiration of the patient.

Clinical Applications of Spinal Navigation

- Metastatic spinal tumours can produce varying degree of spinal instability and cord compression, extending into the paraspinal region and at times encroaching upon the abdominal or thoracic spaces. Approaching the tumour through the posterior or the posterolateral route makes visualisation of its anterior limits and extent difficult and could result in damage to the adjacent soft tissue structures. Optimised excision with a minimum chance of soft tissue damage is aided by navigation
- Pedicle screw fixation and spinal stabilisation,[20, 25] for both tumour and non-neoplastic pathologies, such as spondylolisthesis is another important use (Figs 40 and 41). This prevents the chance of injury to the nerve roots and neurological damage and optimises proper screw placement.

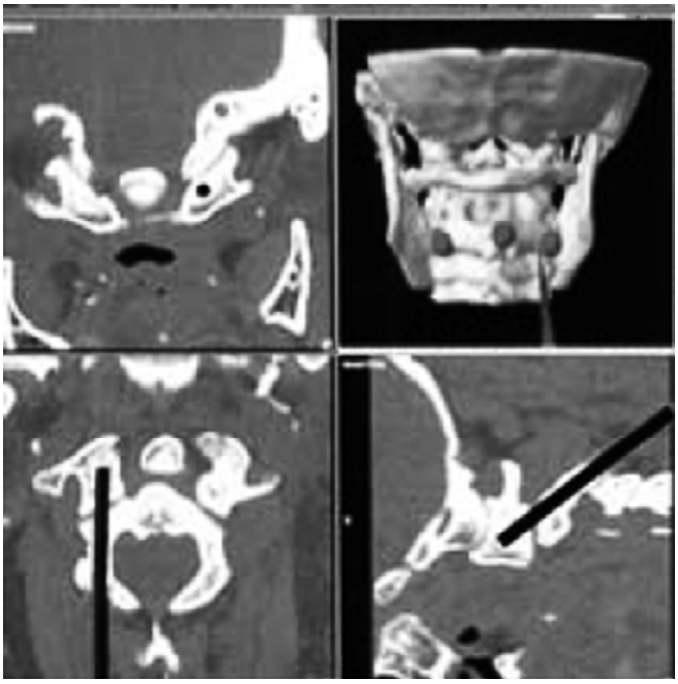


Fig. 41: Pedicle screw fixation and spinal stabilisation

- Transarticular screw fixation at C1 to 2[59] is another very important use, where navigation helps identify the position of the vertebral artery, in relation to the screws being placed and the small space being utilised.
- This can also be used for transoral decompression of the odontoid.[59]
- To fix pedicle screws at the thoracic level.[61]
- Anterior thoracolumbar decompression and fusion procedures
- Anterior screw fixation for odontoid fractures
- Cervical corpectomy and resection of cervical neoplasms via the posterior approach.

Technique

1. Standard exposure of the level to be instrumented is performed and this can be confirmed with the help of conventional fluoroscopy
2. Lateral or AP radiographs can be used to confirm this
3. The computer workstation and the camera have to be appropriately positioned, so that they can be visualised by the surgeon and optimise continuous image input to the camera
4. The infrared camera detector is usually mounted at the foot end of the table and directed rostrally, if surgery is to be performed on the dorsal or lumbosacral spine
5. In case the cervical spine is to be operated on, it would be more rostral or at the side of the table and downwards and rostral to get best image detection
6. Registration by the paired point technique with a minimum of 3 points should be done, prior to any manipulation of the bony anatomy. Pre-selected image points and the corresponding bony landmarks are selected and registered
7. The workstation calculates and gives the accuracy of registration
8. Verify the accuracy by using a probe to check bony landmarks with corresponding images, by watching the location of the cursor, as well as the line of trajectory
9. If this is accurate, proceed with surgery and, if not, re-register the points
10. Depending on the type of procedure, the pedicles, entry point of the screws, trajectory and depth, as well as depth of resection and limits can be accurately localised with the help of navigation and the surgical procedure continued as per standard techniques

For each additional level of instrumentation, re-registration of points can be performed to improve the accuracy; this is called the 'segmental technique'.

Increased precision is a great benefit in the thoracic spine, where the pedicle diameter is small and the risk of neural injury due to malposition greater and more devastating.

Trans-articular screw fixation of C1 to C2 requires passage through the pars interarticularis of C2, across the facet joint and into the C1 lateral mass.

The risks include:

- Vertebral artery injury if the screw is too lateral or anterior
- Spinal cord injury if the screw is placed too medially
- Failure to engage the lateral mass of C1 if the trajectory is too anterior.

Insertion on either side is contraindicated if the pars are too narrow. Selection of the entry site of the screw requires an understanding of the complex atlantoaxial anatomy.

The use of navigation in transoral surgery has its limitations, as readily available registration points are not present and in these cases fiducial markers may be used. Typically, two points on the mastoid processes and two points on the lateral orbital margins are taken for registration. The head is usually fixed on a three-pin head holder.

Pitfalls of Image Guided Surgery

- The registration process is critical for accuracy and best outcomes
- It is not a replacement of the surgeon's own familiarity with spinal anatomy and technique
- It merely serves to confirm estimation of the non-exposed anatomy
- System variations for intra-operative functionality should be factored in
- It takes a longer duration and OT time due to the learning curve and registration process.

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210 Endoscopy in Brain Tumour Surgery

Manas Kumar Panigrahi

INTRODUCTION

Endoscopic techniques have revolutionised the practice of surgery in a number of specialties, which is evident by the impact of endoscopy in otolaryngology, laparoscopy in abdominal surgery, arthroscopy in orthopaedics and thoracoscopy in cardiothoracic surgery. The current popularity of endoscopic neurosurgery is at least in part related to its ability to permit invasive therapy with little disruption of neural structures giving rise to the term "*minimally invasive neurosurgery*".[56,59] Minimally invasive neurosurgery once relegated to the domain of science fiction is now an established discipline with an expanding role paralleling the explosive advances in endoscopic optics and miniaturisation. As the field of neuroendoscopy continues to grow, the indications for this type of intervention are being defined[14] too are its limitations. Endoscopes have been used in neurosurgery since the beginning of this century, primarily within the ventricular system to treat hydrocephalus and assortment of small tumours. Recently, the application of the endoscope outside the ventricle, in the subarachnoid space and spine, is also getting popularised. This chapter reviews the history and evolution of neuroendoscopy from the early part of the 20th century to the current state of art and its increasing utility in the management of brain tumours.

EARLY HISTORY

Max Nitze is credited with designing the first modern endoscope in 1879,[68] which was a crude device, composed of a series of lenses with an illumination source at the tip. L'Espinasse, in 1910, performed the first neurosurgical endoscopic procedure, when he performed fulguration of the choroid plexus in two infants with hydrocephalus using a cystoscope.[72] Twelve years later, in 1922, Walter Dandy described the use of an endoscope to perform choroid plexectomy; however, it was ultimately unsuccessful.

In 1923, Mixter performed the first successful endoscopic third ventriculostomy (ETV) by using a urethroscope in a 9-month-old girl with obstructive hydrocephalus. Mixter's report,[72] however, went largely unnoticed, possibly because of the cumbersome size of his instruments and the poor illumination that they offered.

In 1932, Dandy again reported the use of an endoscope for choroid plexectomy. This time the procedure was successful, but he found the results to be only comparable to those of open choroid plexectomy.[1] After Mixter's paper in 1923, there were no reports of ETV until 1935, when Scarff, described his initial results using a novel endoscope equipped with a mobile cauterising electrode, an irrigation system that prevented collapse of the ventricles, and a movable operating tip that could be used to perforate the floor of the third ventricle. He achieved dramatic results: a 3 cm decrease in head circumference 6 weeks post-operatively. However, the ventriculostomy eventually failed and the patient died. A healed scar over the ventriculostomy site was found at autopsy. Scarff noted, "This case demonstrates clearly the feasibility of the procedure, but points out also the necessity of enlarging the opening beyond a mere puncture wound."

The field of neuroendoscopy began with great promise; this new modality held the potential to allow neurosurgeons to get a magnified view of the anatomical structures within the ventricular system. In reality, however, the technology available to the pioneers of neuroendoscopy was far too primitive for these purposes.[1,72] Illumination and magnification were the major problem. Despite the numerous reports that demonstrated the potential utility of neuroendoscopy, the field never gained favour in general neurosurgical practice because of these technical limitations.

DECLINE OF NEUROENDOSCOPY—ADVENT OF VENTRICULAR SHUNTS AND MICRONEUROSURGERY

Although Fay, Grant, Putnam, Scarff and others continued to perform neuroendoscopic procedures, instrumentation limitations and significantly high morbidity and mortality curbed its use by most neurosurgeons. Furthermore, the report by Nulsen and Spitz[53] in 1952 detailing the treatment of hydrocephalus by using ventricular shunt placement marked the beginning of the era of ventricular cerebrospinal fluid (CSF) shunting and the end of the initial era of neuroendoscopy. In addition, initial success rates for CSF shunts were promising and superior to those of other available treatments.[72] Soon, ventricular shunts became commonplace in the treatment of hydrocephalus and the need for intraventricular endoscopy and ETV lessened even more.

The birth of microneurosurgery in the 1960s[32] pushed endoscopy further into the background. The microscope addressed all of the deficiencies of neuroendoscopy, allowing neurosurgeons to perform operations deep within the brain and at the base of the skull with both adequate illumination and magnification. As microneurosurgery gained popularity, the use of endoscopy waned further.

REDISCOVERY OF NEUROENDOSCOPY

During the 1960s, reports of neuroendoscopic procedures in the literature became sparse. Nevertheless, it was during this period that scientists made a number of key technological advances that would pave the way for modern neuroendoscopy.

New Lens Type

In 1966, Hopkins and Storz developed a rigid endoscope that used a new type of lens, the SELFOC lens. Conventional lenses had a uniform refractive index, so the endoscopes required the careful placement of a series of relay and field lenses to construct an appropriate image, whereas the SELFOC lens used gradient index glass that had a refractive index that varied with the radial dimension of the lens.[44] This new technology essentially obviated the need for the relay lenses while preserving light transmission and creating a wider, effective field of vision.[7]

Invention of Charged Couple Devices

In 1969, George Smith and Willard Boyle invented the first charged couple devices (CCDs) at Bell Laboratories. The CCDs are solid-state devices, usually a silicon chip, which are capable of converting optical data into electrical current. The CCDs are ideal for use in low-light environments and are readily incorporated into the system's apparatus, resulting in both improved quality of the transmitted images and decreased size of the endoscopic systems.

Fibreoptics

Fibreoptic cables were first used in the 1950s and 1960s, and refined further in the 1970s. Fibreoptics allowed the light source to be separated from the rest of the endoscope.[69] Light can be emitted from the tip of the endoscope, without significant heating, through one set of cables, while specialised, coherently arranged cables can conduct images without a loss of luminescence.

These advances, which brought together brighter light sources and cameras with improved resolution, the two key components of any endoscope, were an important part of the rediscovery of neuroendoscopy. As these new technologies were incorporated into the modern endoscope, neurosurgeons began to reconsider the field of neuroendoscopy.

Although CSF shunting procedures had revolutionised the treatment of hydrocephalus, it brought with it the frustration associated with this procedure's complications. Even in modern series, the frequency of shunt malfunction and the long-term morbidity associated with it remains high.[39] The search for a better solution to the problem of hydrocephalus led neurosurgeons to investigate new treatments and to revisit old ones that existed before ventricular shunts. With the improved imaging capability of endoscopes, interest in ETV for the treatment of obstructive hydrocephalus was renewed and currently ETV is primarily used to treat obstructive hydrocephalus caused by benign aqueductal stenosis or compressive periaqueductal mass lesions like pineal tumours and tectal gliomas.

The success of neuroendoscopy in past few decades relied heavily on the success of ETV for the treatment of obstructive hydrocephalus. Now, however, the field of neuroendoscopy has extended itself beyond just ventriculostomy procedures and is being used for the treatment of various types of neurosurgically treatable disorders like intraventricular tumours, skull base tumours, craniosynostosis, degenerative spine disease, intracranial cysts and rare subtypes of hydrocephalus.

USES IN NEURO-ONCOLOGY

The use of endoscopy for the management of brain tumours has evolved from simply treating the associated hydrocephalus, to sampling of tumour tissue, to tumour resection. Fukushima and his colleagues,[25] in 1978, were the first to report the use of neuroendoscope for biopsy procedures in intraventricular tumours. The subsequent technical development, both of endoscopes and of an increasing range of dedicated instruments have expanded the scope of neuroendoscopy in both diagnostic and therapeutic roles.

Instruments

The modern era of neuroendoscopy has been driven by technology and many neurosurgeons have contributed to advances in instruments. Harold Hopkins, an English physicist, deserves greatest credit for laying the groundwork for the modern era of neuroendoscopy by developing optical innovations.[28]

In general, there are two classes of neuroendoscopes: (1) rigid and (2) flexible. Huw Griffith of Bristol, England, pioneered rigid neuroendoscopy in 1970s. Takanori Fukushima is credited with introducing flexible neuroendoscopy.[25] Rigid endoscopes (Fig. 1) have superior optics and working channels, but lack steerability. To overcome lack of manoeuvrability, angled rod lenses (0, 30, 70 and 120 degree) have been developed to look around corners. Flexible endoscopes (Fig. 2) have better manoeuvrability at the expense of a significant reduction in the amount of light transmitted and image clarity. Table 1 enumerates the advantages and disadvantages of both scopes.[69]

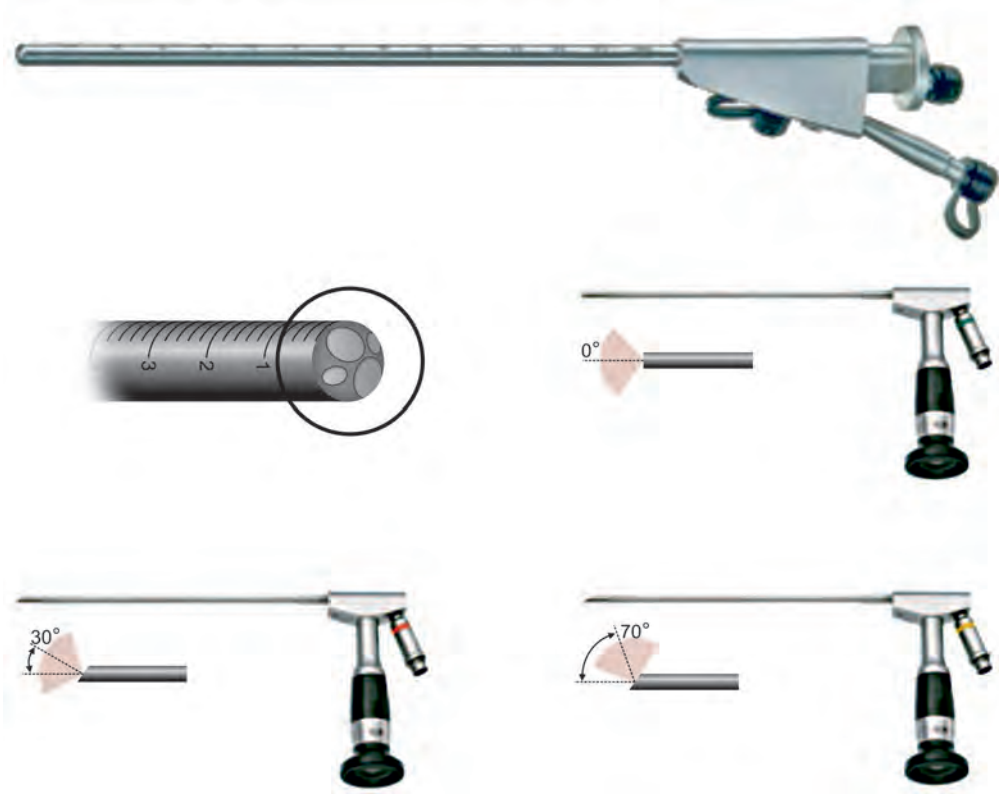


Fig. 1: Rigid endoscope 0, 30 and 70 degree

Although endoscopy can be performed with the operator looking directly through the eyepiece of the lens, it is customary to project the image on to a television monitor. This facilitates manipulation of the various microinstruments, enhances sterility and enables the entire operating team to view the procedure. The optical image is transmitted via a charged couple device microchip camera to a television monitor. Currently, two types of CCDs are in use: (1) single chip camera and (2) three-chip camera. Three chip cameras provide better picture quality; however, camera size is larger and it is expensive. Illumination is provided by a fibreoptic cable connected to a high intensity light source such as xenon. A real time record of the operation can be made on a videocassette and still photographs can be taken with a digitalised camera.

Fig. 2: Flexible endoscope

A variety of miniature instruments are required to perform therapeutic and diagnostic procedures through an endoscope.[55] These instruments can be introduced through working channels in the sheath of the endoscope. Continuous irrigation with warm lactated Ringer's solution can flow through a working channel, which aids in haemostasis in the event of minor venous bleeding and keeps the working field clear. It is essential to provide an escape port for the irrigation fluid

Table 1: Advantages and disadvantages of rigid and flexible scopes

	Rigid scopes	*Flexible scopes*
Advantage	Better image Higher resolution Wider view Better colour Better light transmission	Steerability
Disadvantage	Less manoeuvrable	Poor image Pixel granules Narrower view Less true colour Worse light Small working channel Limited selection of scopes and instruments

to prevent its accumulation in a closed system, which could lead to dangerous enlargement of the ventricles and elevation of the intracranial pressure.

The assortment of microinstruments available for procedures continues to increase. There are ingenious devices for cutting, grasping and sampling tissue. Flexible and rigid probes can be used to fenestrate membranes such as cyst walls, septum pellucidum or the floor of the third ventricle. Balloon catheters can be used to enlarge these fenestrations. Endoscope systems with multiple working channels permit the operator to use more than one instrument at the same time (Figs 3A and B).

Energy sources for endoscopic dissection include monopolar and bipolar coagulators and a number of fibreoptic lasers. Two lasers, which are most commonly used for neuroendoscopic procedures are neodymium doped yttrium aluminium garnet (Nd:YAG) laser and potassium titanyl phosphate (KTP) laser because of their ability to work through water and transmit through the miniature fibreoptic cables. CO_2 laser, commonly used in conjunction with operating microscopes, is not effective in endoscopic ventricular surgery because the CO_2 beam has a very long wavelength and is not transmissible through fluid. As Nd:YAG laser emits invisible light; it is aimed with a visible helium-neon pilot beam. Light emitted by the Nd:YAG laser is absorbed preferentially by pigmented tissue. Tissue that is poorly pigmented, such as ventricular wall and the whitish septum pellucidum, often require a high power setting for fenestration. The KTP laser emits visible green light and, therefore, a pilot-aiming beam is not necessary. The KTP laser produces less thermal injury than the Nd:YAG and can be a useful dissecting tool.

Neuroendoscopy can be done either free hand or using a rigid holder. The most commonly used holders are the pneumatic holder produced by Aesculap or Leyla retractor arms. Table 2 describes the advantages and disadvantages of the scope holder.[69]

Table 2: Advantages and disadvantages of the scope holder

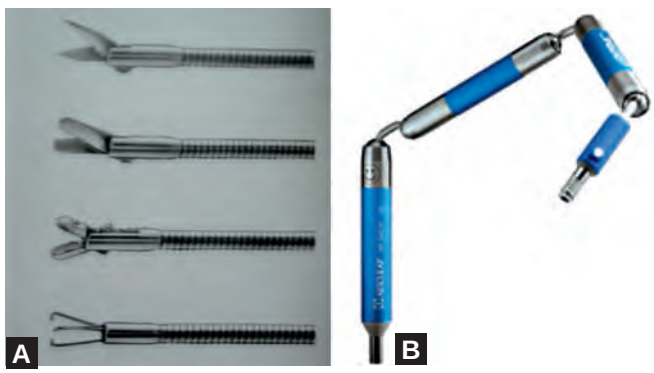
	Free hand	*Rigid holder*
Advantages	(1) More freedom of movement particularly when configuration needs to be frequently or continuously changed, e.g. tumour removal	(1) Surgeon can use both hands (2) Minimises accidental movements and tremor
Disadvantages	(1) More fatigue for surgeon (2) Risk of accidental movements	(1) More static (2) Inconvenient when frequent repositioning is needed

IMAGE-GUIDED ENDOSCOPY

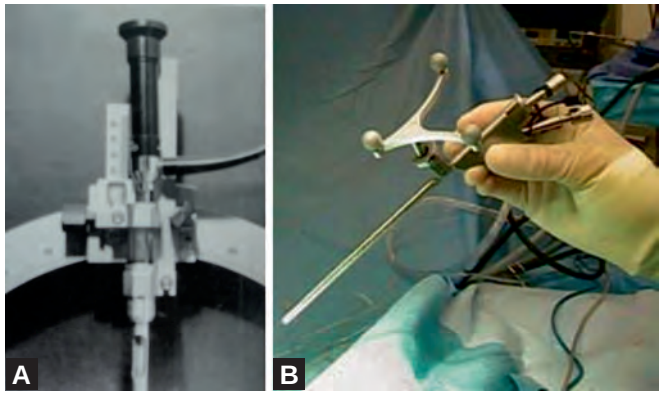
It may be difficult to cannulate the ventricle with freehand techniques to approach an intra-ventricular lesion endoscopically in the absence of hydrocephalus. Similarly, if the ventricles become loculated the endoscopist can easily get lost moving from one cyst compartment to another. In such cases, it is helpful to use the endoscope in combination with some type of guidance system which tracks the endoscope in three dimensions. A guidance system is also worthwhile for some endoscopic procedures conducted in the cerebral parenchyma or at the skull base.

Standard intra-operative C arm fluoroscopy can, on occasion, help to monitor the position of the tip of the endoscope. Ultrasound can provide more information about the location of the endoscope relative to intracranial structures.[42] In infants, an ultrasound probe can be placed directly on the open anterior fontanelle. In older patients, the probe can be placed at a burr hole or a small craniotomy. Small probes have been developed specifically for ultrasound-guided neuroendoscopy.

Stereotactic guidance systems can be combined with both rigid and flexible neuroendoscopes.[5,30] Standard frame based stereotaxy can be used to guide an endoscope to the proximity of a lesion within a small ventricle. The direct view provided by the endoscope lens offers little information as the instrument passes through the substance of the brain. It is helpful only after the ventricle has been entered and one can work within the large CSF space. Stereotaxy guides the endoscope to a ventricle in much the same way that special instruments guide a pilot to a runway in bad weather. Once the pilot gets close enough to the airfield, only he or she can use visual clues to aid in landing the plane. Another advantage of stereotactic guidance is that the frame can serve as a mount to support the endoscope. A limitation is that frame-based stereotaxy is not easily applicable to infants and young children and it is cumbersome and non-intuitive. Furthermore, when the time devoted to frame application and imaging studies is considered, frame stereotaxy may actually lengthen the overall procedure (Figs 4 and B).



Figs 3A and B: (A) Endoscopic microinstruments. (B) Unitrac (Aesculap) pneumatic endoscope holder



Figs 4A and B: (A) Endoscope mounted on stereotactic frame. (B) Frameless stereotaxy guided endoscopy

Recently, frameless stereotaxy has been used to guide the neuroendoscope.[19] The principle of frameless stereotaxy is to define a three-dimensional co-ordinate space for a pre-operative imaging modality and translate this to the three-dimensional co-ordinate space of the operative field. In frameless stereotaxy, a variety of three-dimensional digitisers have been substituted for the frame. These include articulated mechanical arms, sonic or optical digitisers and electromagnetic systems.[62] One limitation is the problem of brain shift, particularly following drainage of significant volumes of CSF or cyst fluid. Moreover, its use is restricted to using rigid endoscopes and the digitiser uses the same working endoscope port so that it must be removed to place instruments into this port.

Management of Ventricular Tumours and Cysts

Endoscopy can be used in tumour management for the following various purposes:

- Ventriculoscopy: inspection of ventricular walls for seedling and CSF sampling
- Relief of tumour associated hydrocephalus by ETV
- Tumour biopsy
- Tumour resection
- Endoscopy-assisted microneurosurgery

Ventriculoscopy

The prognosis of some primary intracranial tumours is dependent on the presence or absence of ependymal spread of tumour. Patients with primitive neuroectodermal tumours, for example, fall into the high-risk group rather than the low-risk group if there is evidence of spinal or ventricular ependymal seedling. Although MRI is reliable in the detection of ependymal tumour spread in most cases, some patients may have ependymal spread without radiological evidence.[22] Ventriculoscopy can be more sensitive than MRI with little added morbidity. Through a frontal or parietal burr hole, one can access the lateral ventricle, examine the surface, document any findings with colour photography, and even biopsy suspicious areas. This takes substantially less time than needed for an MRI examination. Furthermore, if present, definitive treatment of CSF obstruction can be achieved by either third ventriculostomy or tumour resection at the same sitting.

Endoscopic Third Ventriculostomy: Management of Tumour Associated Hydrocephalus

The risk of shunt complications and shunt failure is well documented and shunt-free outcome in management of hydrocephalus is always welcome, especially so in a patient with a tumour, in whom adjuvant therapy is proposed. Chemotherapy and neutropaenia are worrying enough without the additional concerns of the foreign body of a shunt.

An early report of successful ETV in children with posterior fossa tumours was from Chumas et al. in 1995.[16] DC MacArthur et al. (2002) found ETV successful as a long-term means of CSF diversion in 83% cases (55/66 cases) of tumour-related hydrocephalus.[46] Ray et al. (2005) achieved 69.8% (27/43) overall long-term success rate for ETV in similar patients with mean follow-up of 2 years.[60] However, Goh and Abbott (2000) described a similar series of 63 patients undergoing ETV as part of treatment of tumour-related hydrocephalus with rather different results; a disappointing 31 of their 63 (49%) required shunting over a mean follow-up period of 11.4 months. This compared unfavourably with their 15/43 (35%) rate for requirement of shunt following failed ETV in non-tumoural hydrocephalus, the difference just achieving statistical significance.[27]

Success rate of ETV for tumour-related hydrocephalus varies from 23 to 100% depending on the institution, definition of failure (resolution of clinical symptoms and radiological findings or shunt independence), indication and origin of hydrocephalus and follow-up period.[37,58,65]

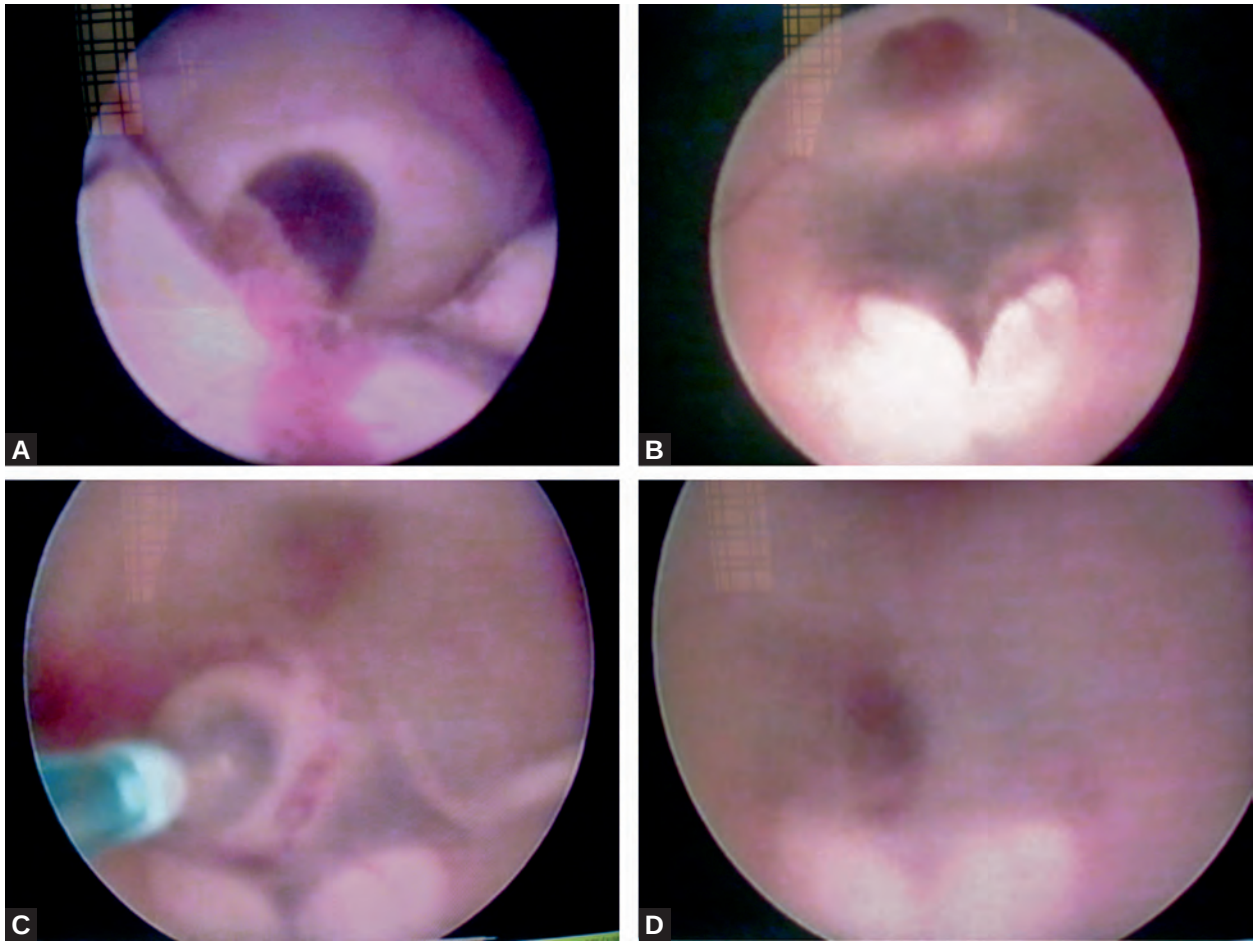
Ray et al.[60] found 100% success rate for ETV, when obstruction was at or around the aqueduct of Sylvius such as midbrain/tectal tumour, pineal region tumours or third ventricular tumour. Table 3 shows the relationship of the level of obstruction and success rate in the series of Ray et al. Hopf et al.[31] and Scarrow et al.[67] also found high success rates with ETV in patients with a space occupying lesion in the midbrain and pineal region. High success rate for such patients is due to open subarachnoid spaces and intact CSF absorption pathways. Despite these outstanding results, in a certain number of patients with ideal indications, the procedure may fail due to undetectable deficiency of CSF absorption at the level of the arachnoid villi or blockade of CSF flow from the third ventricle to the prepontine cistern by Lilliquist's membrane. Buxton et al.[12] stated that in order to achieve successful ETV not only must the floor of the third ventricle be opened but also Liliequist's membrane.

Posterior fossa and thalamic tumour associated hydrocephalus yielded a less favourable outcome following ETV. Other series have also found low success rate (0–63%) for such tumours.[12,31,37,67]

Table 3: Origin of hydrocephalus in 43 patients who underwent ETV[60]

Tumour location	*No. of pts.*	*No. of successful pts.*	*Success (%)*	*No. of procedure failed*	*No. of procedure abandoned*
Midbrain	4	4	100	0	0
Posterior fossa	9	4	44	5	0
Brainstem	14	11	79	3	0
Thalamus	6	4	67	0	2
Pineal	3	3	100	0	0
Third ventricle	2	2	100	0	0
Others	5	4	80	1	0
Total	43	32	74	9	2

Management of hydrocephalus associated with posterior fossa tumours has been a long-standing controversy. In the past, some authors advocated placement of a ventricular shunt before definitive resection because this decreased morbidity and mortality associated with tumour resection.[3,45,61] Currently, however, early surgery and the use of corticosteroids have brought down the morbidity and mortality with no need for pre-craniotomy shunt.[20,23] Use of ETV in patients with posterior fossa tumour has been reported before or after tumour resection and their successful outcome has been between 50% and 85%.[11,65,67] Some authors advocate ETV prior to resection in all cases. However, it was determined that only 15.5% of patients who undergo early and aggressive surgery require CSF diversion. Based on this finding, Ray et al. supported early surgery rather than early ETV followed by surgery and suggested ETV only for symptomatic patients after resection (Figs 5A to D).



Figs 5A to D: Steps of third ventriculostomy

There are a few precautions to be taken when performing ETV for hydrocephalus secondary to a tumour.[15]

1. In patients with tumours localised around the third ventricle, the ETV can be more challenging because of possible deformation of the third ventricle or tumour layering over the third ventricle floor, e.g. a pontine glioma may distort the floor of the third ventricle and displace the basilar artery forward so that the safe zone to penetrate the floor is narrowed. Only the blunt technique to create the stoma should be used in such cases.
2. If hydrocephalus resulting from tumour is of relatively acute onset, then floor of the third ventricle is often opaque and non-attenuated. This makes blind penetration more difficult and hazardous. It invariably requires a sharper technique without visualisation of the underlying neurovascular structures.
3. If ETV is to be performed simultaneously with tumour biopsy or resection, ETV is performed before tumour manipulation because of the expectation of some intraventricular haemorrhage and reduced image resolution after attempted tumour resection. With respect to an entry site, a trajectory is used that approximates a compromise between the two ideal trajectories for each procedure. The trajectory from a pre-coronal burr hole to the floor of the third ventricle is different from the path to the posterior third ventricle, although both must traverse the foramen of Monro. Using a rigid endoscope introduced through a standard pre-coronal burr hole is an ideal trajectory through the foramen of Monro for ETV but may require dangerous stretching of the periforaminal structures to look back at the pineal region. Pre-operative MRI may be used to solve this problem. By moving the burr hole more anteriorly one can gain access to both the anterior and the posterior third ventricle. This entry site is typically located 2–3 cm anterior to the coronal suture on the non-dominant side.

The ETV is a reasonable option to treat the secondary hydrocephalus before definitive treatment of the primary tumour. A CSF sample can be taken at the time of surgery and one can also explore the ventricle and take biopsies, if necessary. Importantly, ETV may be the definitive treatment if the obstruction is caused by a tumour that does not require removal such as a tectal plate tumour. The situations in which bilateral ventricular enlargement exists due to a tumour situated in the anterior third ventricle at the foramen of Monro, an endoscopic septostomy can eliminate the need for biventricular catheters or for CSF shunting altogether.

Secondary ETVs performed to relieve recurrent symptomatic hydrocephalus due to shunt malfunction were also found to be successful by Cinalli et al.[17] It has been suggested, however, that prior radiotherapy might have an adverse effect on outcome following ETV.[38]

Neuroendoscopic Biopsy

Endoscopic biopsy is well recognised as an acceptable or preferred technique for tumour sampling in patients with an intraventricular or paraventricular brain lesion.[25,26,46,50,58,63] There are definite advantages of endoscopic biopsy over stereotactic needle biopsy like:

- Direct visualisation of the tumour allows more accurate and safer sampling. A region for biopsy can be chosen under endoscopic vision, and vessels can be avoided.
- The specimen obtained is larger and not subjected to as much mechanical artefact. It does not need to be sucked through a needle or manipulated.
- Any resultant bleeding can be controlled by either coagulation or packing under direct visualisation.
- If the tumour is relatively avascular, it may be removed totally by endoscopic techniques.
- Other procedures can be performed at the same operation (e.g. ETV, septostomy).

Endoscopic biopsy of third ventricular tumours was first reported by Fukushima in 1973,[25] who used a flexible steerable ventriculofibreoscope that he had designed. Out of 37 patients whom he studied he took biopsy in 11 patients without any serious complications, but he was able to make a successful diagnosis in 6 only. In 4 cases of cystic tumour, he was able to perform endoscopic puncture and evacuation of the cyst. He chose not to take biopsy samples of pineal tumours because of concern about bleeding (Fig. 6).

Subsequently, both rigid and flexible endoscopes have been used to take samples from tumours in and around the third ventricle. Rigid endoscope has the advantage of superior optics of the rod lens system and working channels, which helps in obtaining a larger and better biopsy specimen. The flexible endoscope on the other hand facilitates work at more than one target site within the ventricular system via a single entry point and with less risk of injuring the brain in the course of manipulation. If there is difficulty in reaching the

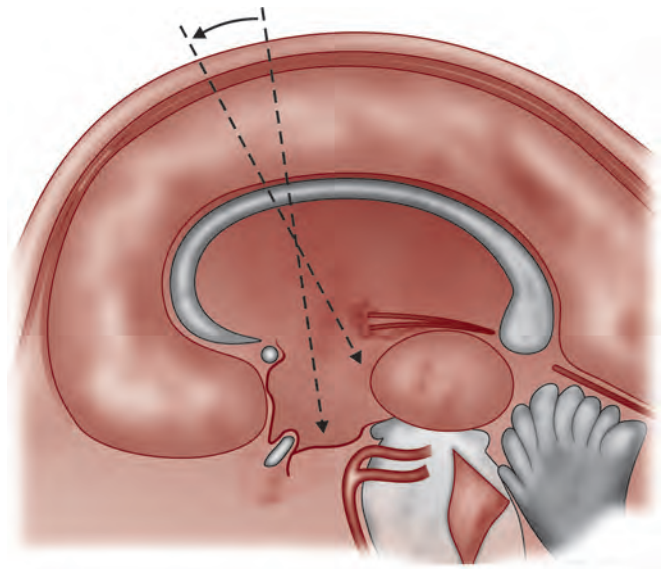


Fig. 6: Entry point for pineal tumour biopsy

posterior third ventricular lesion with a rigid endoscope one can substitute angled lenses or use a flexible endoscope for biopsy. Enrique Ferrer described a mother-daughter technique[4] in which rigid endoscope is used to perform the ETV and then a small flexible endoscope is introduced through either the rigid endoscope sheath or one of the working channels to perform tumour biopsy. Some authors have described use of stereotactic guidance. Apuzzo et al.[15] introduced a rigid endoscope through a stereotactic frame to visualise and sample a third ventricular craniopharyngioma and an ependymoma and to aspirate a colloid cyst without complications. Hellwig et al.[30] have reported using a flexible steerable endoscope in conjunction with a stereotactic frame to take biopsy samples of 22 midline cerebral tumours without any complications and a 100% success rate.

Recently, Veto et al.[24] reported a biportal technique for performing ETV and posterior third ventricle tumour biopsy. This method uses a standard coronal burr hole for ETV and a second anterior forehead burr hole for tumour biopsy. The use of two endoscopes allows independent visual control of each procedure, ensuring safe passage of each endoscope through the foramen of Monro as it is monitored by the other endoscope. A disadvantage of this technique is that it necessitates a second burr hole and corticectomy. Whereas multiple portals have become standard in laparoscopic procedures, they have a different significance in neurosurgery, because each corticectomy carries a small but real risk of injury to neural tissue. It's preferable to use a single high-resolution endoscope to perform both ETV and biopsy through a single burr hole.

Many factors including the surgical technique, the tumour type and the experience of the pathologist can influence the success of a diagnostic tumour biopsy procedure. Earlier series showed a diagnostic yield ranging from 52 to 63%. Recently, however, Pople et al.[58] and Souweidane et al.[50] have achieved a success rate of 90% and 96% respectively with 0% mortality and minimal morbidity. A small working channel and biopsy forceps size obviously significantly limits biopsy size. Paraventricular tumours tend to be subependymal and taking a biopsy not from the surface, but from the deeper tissues after incising the ependyma with the cutting diathermy can increase the yield of very small tissue samples. Diagnostic yield is most dependent on the ability to sample tissue rather than the histological interpretation.[50,63]

Surgical planning is critical for successful endoscopic tumour procedures. The most critical aspect is selecting an entry site that offers the most direct intraventricular, linear route to the target. This principle avoids undue torque on the cortical and intraventricular surface. A relatively anterior entry site with reference to the coronal suture is most important for lesions situated in the posterior third ventricle or pineal region.

With respect to laterality, most entries should be on the non-dominant side. The exceptions to this recommendation are the following: (1) hypothalamic lesions, which are best targeted using a contralateral approach and (2) in a situation in which there is significant ventricular asymmetry in which case the preference is to enter the side with greater ventricular size. Following entry into the ventricular compartment, normal anatomical landmarks including the choroid plexus, venous tributaries and the septum pellucidum are used to establish appropriate orientation. Inspection of the ependymal surface of the ventricle is performed to assess any metastatic components of the disease. Once the lesion is identified, cupped biopsy forceps are used for tissue sampling. The sites for this procedure are chosen based on an avascular pattern and the appearance of the tumour surface. Given the limited sample size, coagulation of the tumour surface prior to tissue sample is intentionally avoided to guard against any thermal artefact. Bleeding of tumour after biopsy can be controlled mostly with irrigation alone. If bipolar and monopolar instruments are available, they can be used, but they are often ineffective. Patience and copious irrigation are the keys. If the tumour appears highly vascular, however, it is recommended that endoscopic biopsy should not be carried out.

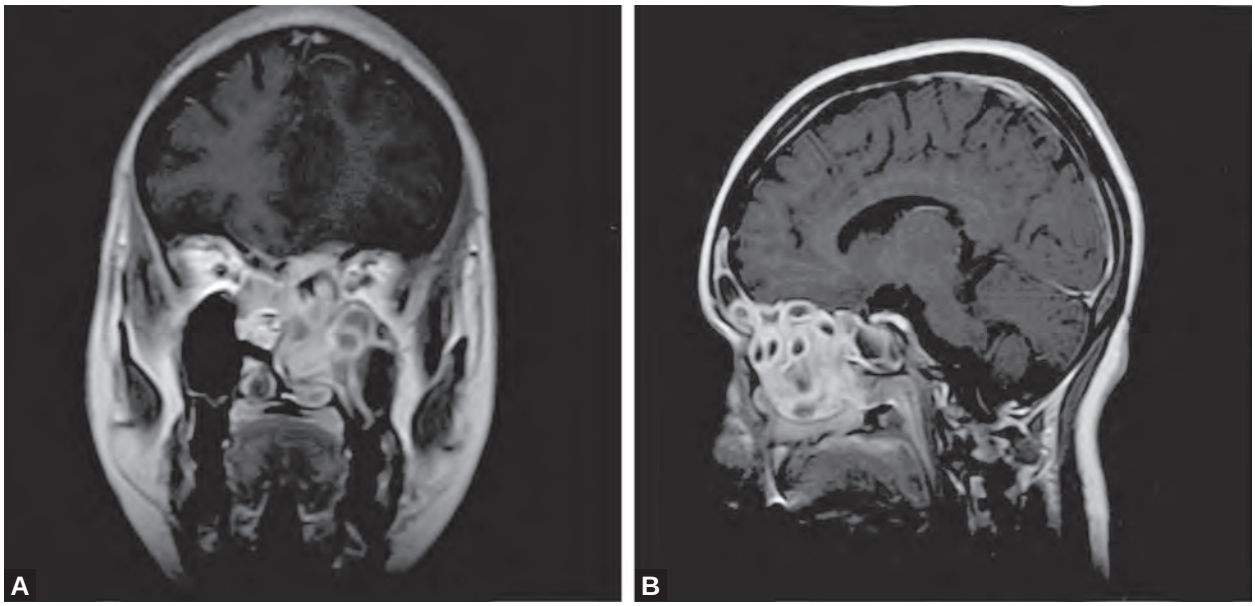
Case: A 19 years female presented with history of repeated blocking of nose and nasal discharge. An MRI was suggestive of enhancing lesion involving sphenoidal, ethmoidal sinus and nasal cavity. Malignant lesion was suspected. Patient underwent endoscopic biopsy and decompression. Histopathology confirmed it to be aspergilloma. Patient was given full course of antifungal and was totally cured (Figs 7A and B).

Endoscopic Fenestrations of Intracranial Cysts

Intracranial cystic lesions, like arachnoid cysts, tumour-associated cysts (craniopharyngioma), porencephalic cysts, multiloculated hydrocephalus,[42] septum pellucidum cysts and pineal cysts, are amenable to endoscopic management.

Arachnoid cysts are intra-arachnoid CSF containing lesions that are not in direct communication with the ventricular system. They constitute 1% of intracranial masses. Arachnoid cysts arise from a gradual expansion of clefts, or duplication in or adjacent to normal arachnoidal cisterns. The cysts expand when CSF pulsation which are concordant with the cardiac cycle become entrapped between the leaflets of the membrane. In contrast to these developmentally acquired cysts, a separate category of acquired arachnoid cysts exists, in which the pathological entity develops secondary to trauma, surgery or infection. Arachnoid cysts occur in multiple locations throughout the intracranial compartment. The commonest site is the middle cranial fossa.

Planning the trajectory is often the most crucial aspect of this surgical procedure. An entry site must be selected that provides a direct, linear route to the cyst to accomplish two distinct goals. One is to minimise any



Figs 7A and B: Lesion involving paranasal sinuses

torque on the cortical or intraventricular neural tissue. The second is to allow direct inline access to the distal edge of the cyst wall; the edge abutting the CSF containing cistern into which the cyst will be fenestrated.[33] After thorough inspection of the cystic space and selection of the target site, bipolar diathermy instrument is used both to attenuate the tissue and to provide a blunt instrument with which to perforate the cyst wall. Fenestration can be further enlarged using a combination of a balloon catheter and sharp scissors. This creation of a fenestration between the cyst and the basal cisterns is called a cystocisternotomy.

Middle Fossa Cyst

This is the most common site for intracranial arachnoid cyst (50–60%). There is still substantial support for the use of open or "Keyhole approach" craniotomy in this particular location compared with other intracranial regions, where endoscopy has been more uniformly adopted. Proponents of craniotomy point to the larger working space it affords leading to better haemostasis; however, in other case series investigators have suggested equal success rates for neuroendoscopic management of middle fossa cysts. A burr hole is made on the coronal suture approximately 5 cm lateral to midline to avoid vessels of the Sylvian fissure and to allow an optimal trajectory to the medial edge of the cyst and the adjacent cistern.

Suprasellar Cysts

These are rare lesions (5–12% of all arachnoid cysts). A variety of interesting symptomatology has been attributed to a large cyst in this region besides hydrocephalus and its associated spectrum of symptoms. Visual impairment, endocrinopathies and head bobbing may all be observed. Several authors have advocated the use of endoscopy for the management of cysts in this region. The first endoscopic fenestration of a suprasellar arachnoid cyst was reported in 1990 by Peirre-Kahn et al. using monopolar coagulation to puncture the cyst.[57] In 1992, Caemert et al. modified the approach using an Nd:YAG laser to open the cyst widely to communicate it with both the lateral ventricle and basal cisterns.[13]

The entry site is roughly at the coronal suture, 1–2 cm off the midline. Through the foramen of Monro, the blue apical dome of the arachnoid cyst with numerous fine vessels on the surface is typically seen. Ventriculocytostomy is done using bipolar diathermy and sharp dissection. Resection of the membrane at this rostral extent is not required. The endoscope is then advanced to the basal cyst membrane, where a cystocisternostomy is performed without the use of any energy source, using blunt biopsy forceps between the cranial nerves exiting the brainstem.

The MRI (T2 weighted and FLAIR sequences) is an excellent tool through which to judge the success of CSF flow through fenestrations and overall cyst volume reduction post-operatively.

Caemaert et al.[13] reported an interesting endoscopic observation about the pathophysiology of suprasellar arachnoid cysts. These investigators noted the presence of a slit valve mechanism between the cyst and the basal cisterns. A similar observation was reported by Schroeder and Gaab, who watched the arachnoid adjacent to the basilar artery open and close with each arterial pulsation, and by Santamarta et al.[66] who demonstrated cine MRI and endoscopic evidence for a slit valve mechanism. This slit valve mechanism may be related to the genesis of cyst enlargement.

Stereotaxy can also be of great help in fenestrations of deep-seated cystic lesions. Abdullah and Caemaert described favourable results in treating three cystic

craniopharyngiomas using stereotactic endoscopic technique.[2] By using frameless stereotaxy systems one moves from navigating by dead reckoning based on surface landmarks to image based navigation where the tip of the scope or a second instrument channel can be seen on CT or MRI.

Endoscopic Resection of Intraventricular Tumours

Tumours with following characteristics are ideally suited for endoscopic resection:

1. Moderate to low vascularity
2. Soft consistency
3. Less than 2 cm in diameter[26]
4. Associated secondary hydrocephalus
5. Histologically low grade
6. Situated in lateral ventricle/third ventricle

Clearly colloid cyst represents the ideal intraventricular tumour that can be completely resected via the endoscopic approach. Most of the experience with endoscopic tumour resection in the literature specifically addresses the removal of colloid cysts. Fourth ventricle tumours are rarely suitable for an endoscopic resection because of the limited space available. Table 4 shows the entry point for tumours in different locations.

Colloid Cyst

Colloid Cysts have been approached endoscopically for longer than 25 years. Successful aspiration and partial resection of colloid cysts were reported by Powell et al. in 1983[59] and Auer et al.[8] in 1988 respectively. In 1994, Lewis et al.[43] compared endoscopic resection of colloid cysts using the flexible endoscope with microsurgical excision. In those patients who were treated endoscopically, they found significantly reduced operative time, duration of hospitalisation and length of time before returning to work.

Endoscopic surgery should be considered as the first line surgical modality for the treatment of colloid cysts as it offers the advantages of direct tumour visualisation while being a minimally invasive technique.[56] Rigid endoscopes are superior to flexible endoscopes in colloid cyst surgery due to high definition image and magnification and availability of multiple viewing angles that allow one to look around the corners and behind obstructions. In most patients, a single portal endoscopic approach is sufficient for tumour removal. The disadvantage is that the surgical instruments are passed in the same line of sight as the endoscope; movement of the instruments is dependent on movement of the video image. Three-dimensional appreciation of the operative field is lost. However, precise three-dimensional clues can be gained by continuously repositioning the endoscope within the ventricle. By incorporating a second adjacent portal the endoscopic instruments can be manipulated independent of the endoscope and consequently one achieves more of a panoramic feel for the surgery gaining additional degrees of freedom with the surgical tools.

The main technical factor that affects colloid cyst removal is the density of the cyst contents. This can best be estimated using non-contrast CT. Hypodense or isodense contents are usually fairly liquid and can be removed through the small apertures of the endoscope without difficulty. A small suction catheter attached to a 10 or 20 ml syringe may help in this regard. Hyperdense cysts may have more tenacious contents, which can prove more difficult to remove with the endoscope. Cup forceps may need to be used to remove the contents of these denser cysts piecemeal. On MRI, high signal on T1-weighted imaging correlated with higher cholesterol content, thicker consistency, and more difficult removal.

The foramen of Monro, in the presence of a colloid cyst, is usually expanded. The cyst is attached to the roof of the anterior third ventricle, and its anterolateral surface usually bulges into or through the visible part of the foramen. The cyst wall can be opened with fibre-optic laser or bipolar coagulation and the cyst contents can be emptied. The cyst wall can be shrunk down with a laser/bipolar and a large portion of cyst wall can be removed with grasping forceps and micro scissors. One must avoid excessive traction on the cyst capsule. Too much traction is unnecessary and dangerous, since bleeding from partially avulsed vessels from the roof of the third ventricle may be difficult to control. Every effort is made to preserve all normal structures in removing a colloid cyst. Generally, this can be accomplished; however, three structures may be sacrificed, if necessary, to provide widened access to the tumour, in descending order of preference: choroid plexus, the thalamostriate vein and the ipsilateral fornix. The first structure is sacrificed with impunity, but sacrifice of the latter two should only be considered if all other options have been exhausted. Total or near total resection of colloid cysts should be the goal for all patients. Only in situations in which a nubbin of tissue cannot be separated from neural or vascular structures should it be coagulated and left *in situ*.[73]

Limitations of the endoscopic approach are the difficulty of working when the foramen of Monro is small and when the cyst is lying posteriorly.[18] Such cases can be recognised pre-operatively on MRI and they should be probably best managed via standard microsurgery.

Table 4: The entry point for tumours in different locations

Tumour location		Entry point
Lateral ventricle—Frontal horn		2–3 cm parasagittal, coronal to 2 cm pre-coronal
	Body	2–3 cm parasagittal, coronal to 2 cm pre-coronal
	Trigone	2–3 cm parasagittal, 4–6 cm pre-coronal
Foramen of Monro		3–5 cm parasagittal, 2–4 cm pre-coronal
Third ventricle—Anterior		1–2 cm parasagittal, coronal
	Posterior	1–2 cm parasagittal, 4–6 cm pre-coronal

Overall complication rate is very low. Reported complications include injury to the fornix, epilepsy and short-term memory problems.

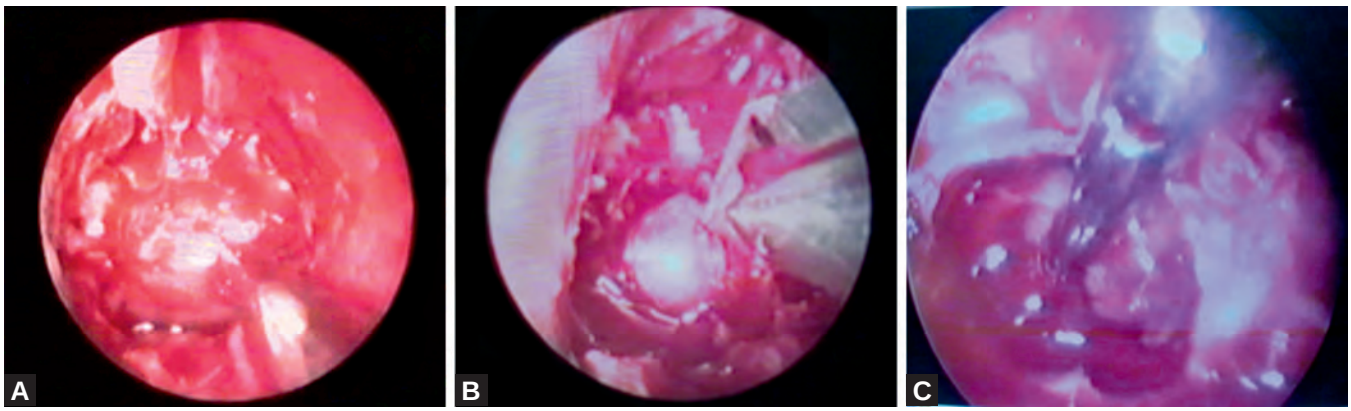
Endoscopy-Assisted Microneurosurgery

During the last century evolution of neurosurgical techniques has occurred with the aim to reduce the pre-, intra- and post-operative traumatisation of patients undergoing diagnostic and therapeutic neurosurgical procedures. The results of this ongoing process can be observed in today's microneurosurgery, which uses sophisticated microscopes, microinstruments, neuronavigation and stereotactic techniques. The improvement in diagnostic imaging enables not only precise localisation of lesions but also the accurate determination of topographical relations of specific lesions to individual anatomic variations of intracranial structures. This parallel improvement in diagnostic and surgical techniques gave rise to concept of "keyhole microneurosurgery".[9] Keyhole surgery does not imply that the craniotomy has the size of a keyhole but that the choice of the correct individual craniotomy has a key function to enter a particular area and to work there with minimum of traumatisation. By choosing the correct keyhole approach to a specific lesion, it becomes possible to dramatically reduce the size of the craniotomy, and the dura opening and less brain retraction that contributes to improved post-operative results.

However, a keyhole approaches have a few shortcomings like narrow viewing angles, reduction of light intensity in the operating field and the necessity for almost coaxial control of the microinstruments. Advantages of endoscopes like increased light intensity while approaching an object, clear depiction of exposed (patho) anatomic structures and extended viewing angle (fisheye effect) to inspect hidden but important anatomical structures without applying additional retraction, can be used to overcome the above mentioned shortcomings of keyhole approaches. This gave rise to the concept of endoscopy-assisted microneurosurgery. Apuzzo et al.[6] were the first to apply neuroendoscopic techniques to craniotomy. In 1977, they reported using side viewing angled rod lenses to assess the adequacy of aneurysm clip placement and assist visualisation during both subfrontal and trans-sphenoidal pituitary surgery.

Depending on the precise location of the lesion, a small craniotomy is fashioned and the initial exposure of the deep structures is done under the operating microscope. The solid rod endoscope lens is introduced into the craniotomy exposure and guided into position under the direction of the operating microscope. Deep structures can be seen through the endoscope with minimal or no brain retraction. The endoscope can be used free-hand or mounted to the operating table and standard microsurgical instruments are introduced into the field adjacent to the lesion. The endoscope and microscope complement one another and can be brought in and out of the field during various stages of the procedure. By alternating the use of endoscope with the operating microscope, one can improve the visualisation of the deep anatomy during craniotomy. It is prudent to inspect the position of the endoscope frequently during the dissection to maintain overview of the entire operative field and avoid complications of injuring the surrounding structures by the endoscope itself. The use of a picture in picture device allows the operator to view both the images on one screen. Taneda et al.[70] developed a display system that permits the surgeon to watch the endoscopic image through one of the ocular lenses of the surgical microscope.

The introduction of the endoscope has to revolutionised the approach to certain tumour types by allowing safe and radical removal. These techniques are particularly applicable to a wide range of troublesome tumours including sellar tumours like pituitary tumours, craniopharyngioma and Rathke's cleft cysts; clival chordomas, pineal tumours, intraparenchymal tumours near the brainstem or cranial base; acoustic neuromas and anteriorly or centrally located posterior fossa tumours (Figs 8A to C).



Figs 8A to C: An endoscopic view showing. (A) Sellar floor. (B) Dura being cut. (C) Tumour removed

The endoscope has allowed a conceptual change in the approach to low grade or benign tumours like craniopharyngioma. In the past some surgeons have discouraged radical debulking of the hypothalamic portion of these tumours because of the unacceptable side effects attended by damage to this vital structure. In fact poor visualisation is what limits adequate and safe removal of tumour. With the endoscope the occult parts of the tumour can be removed under vision making this part of the tumour as accessible as the directly visualised portion. Because the prognosis for a number of tumours depends on the adequacy of tumour removal the use of the endoscope in this fashion to obtain the best removal possible and to document that removal is highly recommended.

Endoscopic Pituitary Surgery

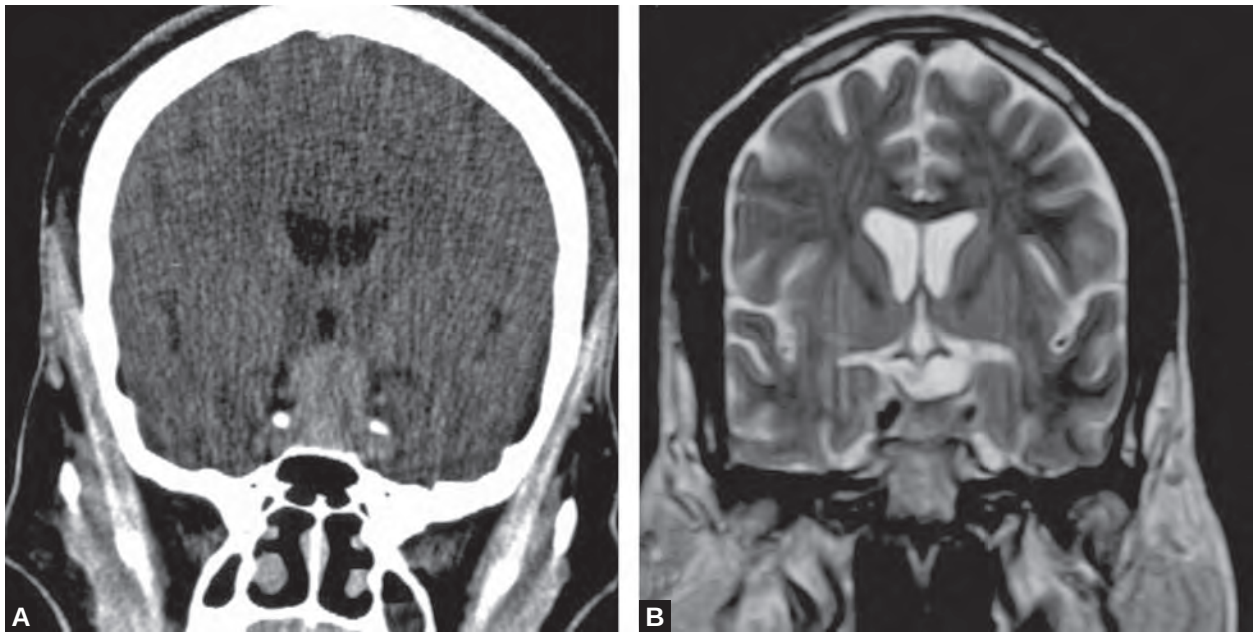
The earliest trans-sphenoidal surgeries by Schloffer, Von Eiselsberg and Kocher required an external rhinotomy incision. Hirsch and Halstead introduced endonasal sublabial approaches in 1920 respectively. These initial procedures were not trans-septal and required some degree of middle or inferior turbinectomy, ethmoidectomy and septectomy. These extensive exposures were required in order to provide both illumination and room for the use of operative instruments[36] (Figs 9A and B).

By 1914, Cushing had reported a less traumatic trans-sphenoidal technique using a sublabial trans-septal approach. The primary obstacle to trans-sphenoidal approach remained illumination and visualisation of the operative field until the later 1960s, when Hardy popularised the use of the operating microscope. Its excellent magnification and illumination capabilities facilitated the effective removal of large and small tumours alike without significant anatomical disruption. Since then, progressive modification of the microscopic approach has been done. Sublabial approach has been largely replaced by pure endonasal microscopic approaches. Endonasal microscopic trans-sphenoidal approach has several variations including the trans-septal submucosal technique, the septal pushover and the direct sphenoidotomy.

More recently, the endoscope has been introduced to trans-sphenoidal surgery and has gained significant popularity. Endoscope assisted trans-sphenoidal operation refers to the microscopic procedure in which the endoscope is used as an adjunct to the microscopic removal of a tumour. The manner in which the endoscope is used adjunctively, however, can vary significantly. The endoscope may simply be used to perform an anterior sphenoidotomy prior to inserting the nasal speculum and using the microscope. It may also be used during the microscopic tumour resection to inspect for areas of tumour residue out of the line of sight of the microscope. Pure endoscopic trans-sphenoidal surgery refers to the removal of tumour without the use of the operative microscope.

Although the endoscope assisted trans-sphenoidal approach had been reported by others, the pure endoscopic trans-sphenoidal approach was introduced and popularised in late 1990s by Jho and Carrau from the University of Pittsburgh Medical Center.[35]

Endoscopic sphenoidotomy is performed by using 0 or 30 degree rigid rod endoscopes. The endoscope is held in the left hand while supporting it superiorly against the soft tissue of the nares. Instruments are passed beside the endoscope and not through a working channel. Learning to work with the endoscope and instruments one above another provides the surgeon



Figs 9 and B: Pre-operative and post-operative images of pituitary tumour

with a significant amount of working space as compared to their side by side use. The safety of the approach described requires that the surgeon identify the posterior middle turbinate and the ostium of the sphenoidal sinus located in the sphenoethmoidal recess between the septum and the superior turbinate. Routine partial middle turbinectomy is not advocated, except for those with an unusually small nose and nasal cavity, because it is mostly unnecessary in the adult patient and leads to crusting and delayed epistaxis. Care must be taken to identify normal intra-sphenoidal anatomical landmarks and to be cognisant of the positions of the optic nerves and carotid arteries at all times. Angled endoscopes allow the surgeon added panoramic visualisation.

Entry to the sphenoid sinus can also be accomplished directly through the anterior wall of the sphenoid or via the ethmoidal bulla and sinus, if the anatomy of the nasal cavity, previous nasal surgery or other limitations hinders access to the sphenoidal ostium. The technique can also be performed trans-septally, analogous to the microscopic approach.

Although surgery can be performed through a single nostril, which acts as a portal for the endoscope and the surgical instruments, the dual-portal technique allows superior manoeuvrability, flexibility and efficiency over a single portal approach. Using the three-hand technique, as advocated by Kassam,[40] the advantages of the endoscope can be realised. This manoeuvre requires co-operation between the endoscopist and the surgeon. The endoscopist can move in during the tumour resection and focus closely on areas of interest. As instruments are moved in and out of the nose, the endoscope operator can follow the instruments, ensuring that they do not injure the nasal mucosa.

The endoscopic approach should be individualised to the patient and assessed pre-operatively by studying the computerised tomography and magnetic resonance imaging and ultimately by endoscopic assessment at the time of operation. The endoscopic approach can also be used as an adjunct to the microscopic approach in inspecting the operative site for residual disease. Using the endoscope in this way can be particularly helpful in advancing surgeons along the learning curve in endoscopy.

The endoscopic pituitary surgery technique has evolved over time due to acquisition of new instruments and a persistent quest for improved exposure and resection. Initially it was tried to recapitulate the microscopic adenomectomy by adopting a mononostril approach with the endoscope holder. However, with experience, it has been found that holder on the contrary tends to negate the advantages of the endoscopes. The surgeon can obtain a pseudo-depth perception from the dynamic movement of the endoscope relative to operative instruments. Placing the endoscope in a fixed position likens the technique of a microscopic adenomectomy during which the surgeon has wide-angle view but has limited depth perception and zoom views. Also if the endoscope becomes occluded by blood beyond the cleaning ability of the irrigation system it must be removed from the holder cleaned and then brought back into the field. These interruptions tend to disrupt flow of the operation significantly and in situation of significant bleeding can be disconcerting. Moreover downward drift of the endoscope because of the weight of the attached camera is a common problem.

De Divitiis et al.[21] have expanded the scope of this approach to include other lesions of the sellar and parasellar region. The bilateral endonasal endoscopic approach now allows for visualisation of tumours at the anterior skull base up to the crista galli and down to the level of C-2.

Microscopic Adenomectomy versus Pure Endoscopic Adenomectomy

Microscopic Adenomectomy

Advantages:

- Familiarity to neurosurgeons
- Three-dimensional view with easily manipulated zoom and focus
- Easy maintenance of the appropriate trajectory to the sella once it is defined
- Nasal speculum used for microscopic surgery protects the nasal mucosa from injury by instruments
- Microscope being out of the surgical field, the view does not suffer from red out when bleeding fills the surgical field and it does not obstruct the entry or manoeuvring of instruments into or out of it.

Disadvantages:

- Field of view is narrow and visualisation is limited by line of sight. The surgeon cannot see around corners wither towards the cavernous sinus or the suprasellar space and optic chiasm.
- Sinonasal complications due to sublabial or trans-septal approaches like anosmia, alveolar numbness, saddle nose deformity and nasal septum perforations. Post-operative nasal packing may cause facial pain and headache. However, minimally invasive approaches of the septal pushover and direct sphenoidotomy do not require nasal packing and are associated with fewer sinonasal complications.

Pure Endoscopic Adenomectomy

Advantages:

- Provides panoramic views of areas outside of a microscopes line of sight and allows dynamic, magnified inspection of areas of interest. Visualisation of the carotid protuberance is rarely possible with the operating microscope, and confirmation of their precise location does at least improve surgeon's comfort. During trans-diaphragmatic dissection, the optic chiasm can be seen and chiasmal decompression, which is often the goal of surgery, can be confirmed

- Wide views of the nasal anatomy allow the surgeon to discern the appropriate level of entry into the sphenoid sinus more easily (either by visualising the sphenoid ostia or the level of superior turbinate. This obviates the use of intra-operative video fluoroscopy
- No nasal packing unless significant CSF leak, which decreases patients discomfort and affects patients satisfaction
- Fewer nasosinal complications like saddle nose deformity, alveolar numbness septal perforations
- No alar incision is required, as in microscopic direct sphenoidotomy.

Disadvantages:

- Less familiar
- A facile endoscopist must stay throughout the entire operation while using three hand technique
- Limited zoom facility: To obtain magnification endoscope is brought closer to the region of interest requiring frequent refocus manoeuvres that are not as easily performed as with the microscope
- Endoscope gives two-dimensional views. Depth perception is provided by the dynamic interaction between surgical instruments and the endoscope. It is possible in the learning phase to dissect into the posterior pituitary, cavernous sinus and diaphragm over aggressively and cause more complications
- Because instruments enter the field out of the line of sight of the endoscope and because no nasal speculum is used the nasal mucosa along the septum and the medial wall of the middle turbinate can be injured in the course of the operation
- Posterior septal branches of the sphenopalatine artery are also at greater risk than during trans-septal microscopic approaches because in trans-septal approach mucosa containing this vessel are elevated from the sphenoid rostrum and are thereby protected. The direct sphenoidotomy places these vessels at greater risk of damage and of early post-operative epistaxis.

It is perhaps an overstatement to assert that the endoscope is less invasive than the microscope. The endoscopic approach may seem so to the patient initially because there is no nasal packing but endoscopic approach disturbs and removes more anatomical structures than the various standard microscopic approaches. The sphenoidotomy is larger so that the endoscope does not impede the necessary manoeuvring of the operative instruments. To achieve the same manoeuvrability for the operative instruments as in the microscopic adenomectomy a binasal technique is used that requires a posterior partial septectomy. Although not routine a partial middle turbinectomy is also performed at times, an action never necessary when performing a microscopic adenomectomy. All these manoeuvres are undertaken in an effort to provide an exposure that allows the surgeon to use both instruments and the endoscope.

Thus, the choice to use the endoscopic in lieu of microscopic technique should not be in the pursuit of a less invasive approach but because of the advantages provided by the endoscopic procedure.

Endoscopy Assisted Surgery for Skull Base Lesions

There has been recent interest in the use of the neuroendoscope to assist with "traditional" skull base microsurgery. Cranial base approaches have resulted in improved surgery at the cranial base by removing or displacing soft tissue and bone. The hope is that in selected situation a less invasive approach combined with the increased visualisation afforded by the endoscope will be an effective surgical alternative or adjunct. Early experiences seem promising in this regard.

The concept of using endoscopes to visualise the anatomy of the posterior fossa is not new. In 1917, Doyen described a technique for trigeminal root neurectomy under endoscopic guidance via an occipital craniotomy. Since then, published experience with posterior fossa endoscopy has been scarce. Isolated reports detailing endoscopic exploration of the posterior fossa for diagnostic purposes and for selective trigeminal nerve root sectioning were published in the 1970s, but only during the past decade has interest in the application of endoscopic imaging to this region been renewed. In 1992, O'Donoghue and O'Flynn described and classified the endoscopic anatomy of the CPA.[54] Since then, a number of neurotologists have presented their experiences with CPA endoscopy, particularly as an imaging modality in acoustic neuroma surgery.[10,34,41,48,49,64,71] A recently published atlas specifically details the endoscopic surgical anatomy of the cranial nerves at the posterior skull base.[47] Grotenhuis has reported techniques for endoscope-assisted craniotomy both supratentorially and in the posterior fossa.[29] The future of neuroendoscopy in skull base surgery will involve its use both as the primary surgical approach and as an adjunct to the microscope.

Cranial base endoscopic surgery presents unique challenges not encountered within the ventricular system, e.g.:

- Unlike with intraventricular endoscopy there is the lack of significant true or expandable space through which one can manipulate multiple instruments
- One must navigate around the lattice of nerves and arteries not present within the ventricles
- Instruments are usually not passed through working channels of the endoscope or portals as they are during intraventricular surgery, but rather must be passed alongside the telescope.

Pre-requisites to make full use of this subarachnoid space are correct positioning of the patient's head to support gravity-related self retraction of the cerebrum or cerebellum, careful release of CSF from the cisterns and, if applicable, from the ventricular system at an early stage of the procedure, and cautious debulking of the tumour. With these simple methods in most cases adequate subarachnoid working space for one endoscope and two additional instruments can be created without

significant application of retraction and traumatisation of surrounding brain substance.

Endoscope is well suited for dealing with deep midline tumours like craniopharyngiomas and epidermoid tumours, lesions of the posterior fossa and cerebellopontine angle (Figs 10A and B, 11A and B). It is a very useful adjunct in surgery of acoustic schwannoma. Other indications include microvascular decompression of the cranial nerves, vestibular neurectomy and an assortment of intrinsic and extrinsic lesion involving the brainstem.

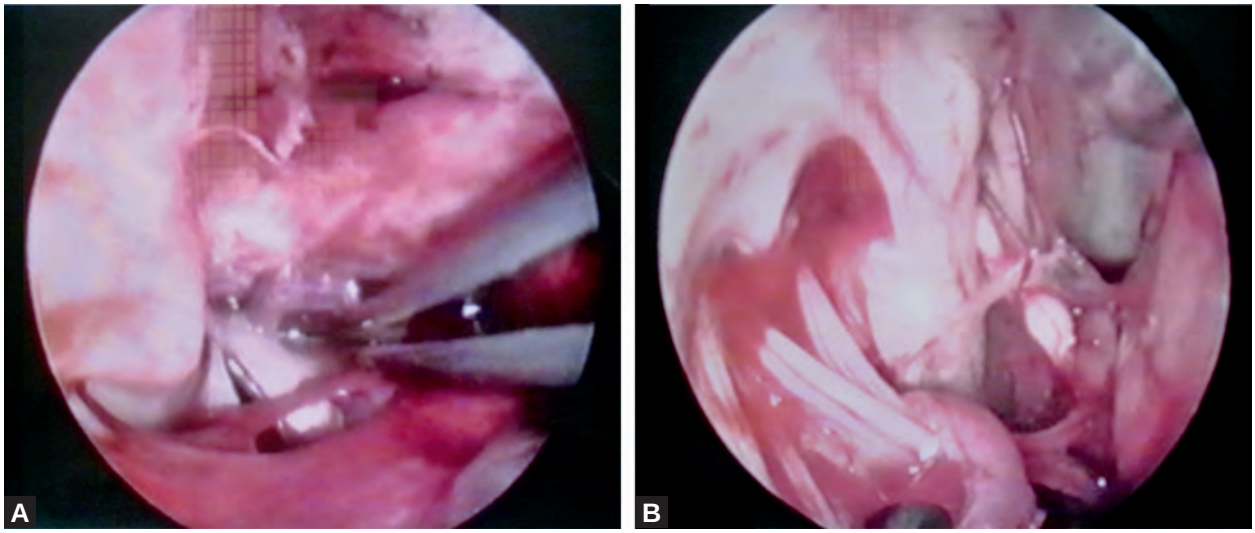
Advantages of endoscopy in surgery for vestibular schwannoma are:

- Improves visualisation of bony, neural and vascular relationships while minimising retraction
- When one is attempting to preserve hearing, it is critical that the intraosseous endolymphatic sac and posterior semicircular canal are not violated when the posterior wall of the IAC is removed. The main use of endoscope is to visualise the lateral end of the IAC, which helps the surgeon to minimise the drilling of the petrous bone with lower risk of entering the posterior semicircular canal and the vestibule
- Inspection of the IAC with angled endoscopes for residual remnants. It can also minimise the bony removal of posterior lip of the canal while achieving excellent visualisation of the fundus
- Angulated endoscope is also very useful when directed into the opposite direction, i.e. towards the brainstem and even anterior to it to the prepontine area. It is particularly useful in patients with far prepontine extension of epidermoid tumours
- Direct identification of violated air cells within the temporal bone. Identifying and sealing these with bone wax may reduce post-operative CSF leakage rate.

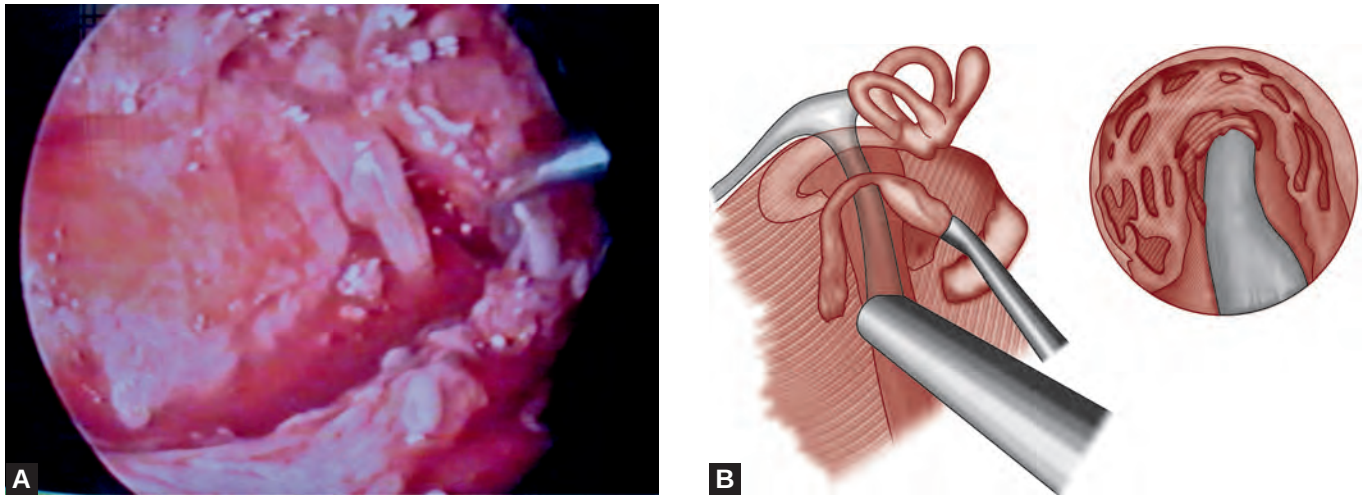
Nebil et al.[52] reported that the use of endoscopes does not appear to increase the hearing preservation rate, but is very helpful in complete tumour removal in the posterior fossa approach.

Robot-Assisted Neuroendoscopy

With the ongoing development of computer assisted surgery the appearance of robotic devices is the next step for precise conversion of the pre-operative surgical plan derived from the navigation system into surgical action. The precision of motion, the submillimetre resolution and the repetitive accuracy of a robotic tool are unavailable with other techniques. In 1992, Benabid et al. reported the first application of robotic device for stereotactic procedures including placement of electrodes for deep brain stimulation. With the Evolution 1 precision robot (Universal Robot Systems, Schwerin, Germany) a new neurosurgical tool has become available for the precise steering of instruments within the cranium.[51] It allows highly precise and reproducible positioning of any rigid instruments with an accuracy of 50 μm. All motion of the robot immediately stops if a deviation between the nominal position and the commanded position of the precision robot is detected. The universal instrument interface allows the flexible attachment of endoscopes, guiding instruments and drill instruments, and permits their exact robotic positioning with six degrees of freedom. Attached to the instrument interface is a force torque sensor, which monitors the forces applied to the patient and presents tissue damage by stopping robotic motion if these forces exceed predefined values. The advantage of using the robot as a holding and positioning device for the endoscope is the possibility of performing very smooth and slow motions in critical regions. Compared with free hand endoscopy targeting of small vessels for coagulation is easier, faster and more precise with the use of a robotic device. Neuronavigation may enhance the accuracy and safety of robot assisted endoscopic procedures particularly among patients with pathological ventricular anatomy, small ventricles or large cystic lesions. However, Robot has few limitations. It has a limited range of



Figs 10A and B: Endoscopic cerebellopontine angle view. (A) Vascular loop in front of VII nerve. (B) Lower cranial nerves and VII-VIII complex entering IAM



Figs 11A and B: (A) Endoscopic view of VII nerve separated from the tumour and entering IAM. (B) Schematic diagram showing exposed air cells

motion. Therefore, robot cannot be used for endoscopic procedures for which a larger range of motion is necessary, e.g. ventriculostomy with fenestration of a cyst, both targets can be reached via a single transcortical approach but the distance exceeds the range of motion of the precision robot.

CONCLUSION

Neuroendoscopy has a rich history that dates back to the early decades of the twentieth century. Applications for neuroendoscopy are rapidly expanding from management of pure intraventricular pathology only to endoscopic assisted microneurosurgery for pathology in the subarachnoid space. In the future, one can expect routine use of the endoscope for management of a multitude of neurosurgically treatable pathological conditions, either as the primary surgical approach or as an adjunct. However, microscope will never replace the headlight and loupes nor will endoscope ever replace the microscope. It will simply move us one step closer in our perpetual quest for minimally invasive and maximally effective surgery, with the ultimate goal of providing better care for our patients. The continued evolution of this modality will rely on new technological advances, improved understanding of endoscopically demonstrated neurosurgical anatomy, discovery of novel applications, and the training of neurosurgeons in neuroendoscopic procedures.

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211 Orthotics

PK Sethi

INTRODUCTION

Galen (131–201 AD) was the first to use the term "scoliosis, kyphosis and lordosis". He advocated chest strapping, breathing exercises and singeing for the scoliosis. Ambrose Pare (1510–1590 AD) is considered the pioneer of the art of brace making and designed metal corsets and leather splints. During the early part of the 18th century Heister is credited with making the first spinal orthosis. The latter half of 20th century saw the development of various types of spinal orthoses. During this period, Schmidt and Blount developed the Milwaukee brace.

FUNCTIONS

Similar to the basic functions of an orthosis, which are correction, protection, stabilisation and immobilisation; spinal orthoses have corrective and protective functions. They support and thus stabilise the spine, as well as immobilise and thus rest the spine. Following surgery or injury, the spinal orthosis protect the cord and nerve roots, and carry out the functions that intrinsic structures of the spine and the muscles normally achieve. Many a time, the orthosis is designed to prevent a particular movement. For scoliosis and kyphosis it has a corrective role.[20]

BIOMECHANICS

The spine can be considered mechanically as a series of semi-rigid bodies (vertebrae) separated by viscoelastic linkages (discs and ligaments).[9]

Movements of the Spine

Measurement of joint motion is of considerable importance in determining the degree of deformity, in prescribing an orthosis and measuring the progress during treatment. This applies to the spine as well. The data on Indian subjects is not available. The average range of motion available from various studies are described below:[2,3]

The *Cervical Spine* is the most mobile part of the spine. It has flexion, extension, lateral flexion, rotation and gliding (translatory) movements (Table 1) at different levels. Females show slightly greater movement than males.[17]

The *Thoracic and Lumbar Spines* have similar movements as that of the cervical spine like flexion, extension, lateral flexion and rotation (Table 1). Above the age of 50 years, the range of motion gradually starts reducing and by the age of 80 years the range reduces by 10 degree.

Balanced Horizontal Forces

Horizontal forces provide efficient bending movement for correction of lateral curvature and immobilisation of the spine. This can be expressed as three-point loading system (Fig. 1), where the arrows represent the magnitude and direction of the forces (Fig. 1).[20]

Three forces are applied along the length of the spine, two in one direction and one in the opposite direction. Since the system is in equilibrium, the sum of the forces and sum of the bending movement they create remains zero. The sum of forces at B and C has to be equal to the

Table 1: Motion of cervical, thoracic and lumbar spine (in degrees)

Movement	*Cervical*	*Thoracic*	*Lumbar*	*Total*
Flexion	60	15	40	55
Extension	80	15	25	40
Lateral Flexion (Rt.)	45	15	20	35
Lateral Flexion (Lt.)	45	15	20	35
Rotation (Rt.)	75	40	5	45
Rotation (Lt.)	75	40	5	45

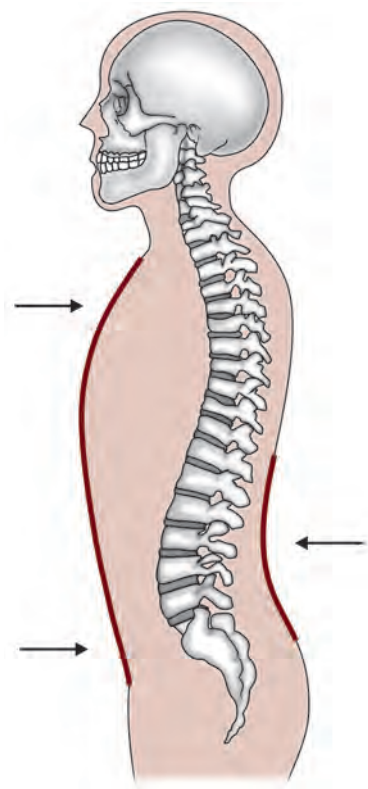


Fig. 1: Three point pressure system in correcting the spine

force at A (B + C = A). In order to have the same skin pressure, the size of the skin pad should be proportional to the pressure applied through it. By placing the force at the apex of the curvature, the correctional efficiency becomes maximal.

Fluid Compression

Pascal's law states that fluids in a closed chamber behave like solids and the pressure applied at any point is transmitted equally in all directions. This principle is utilised in supporting the spine by compressing the abdominal cavity by a tightly applied corset or abdominal support. This increases the intra-abdominal cavity pressure and produces a distracting force, thereby effectively distracting the lumbar spine.

Traction

By applying traction alone it is possible to achieve a certain amount of immobilisation and stability of the spine even if there is lateral instability.

Sleeve Principle

It is caging the patient between two semicircular fixation points, one above and the other below. Between these two semicircular fixation points there are various uprights. The uprights may be in front, at the sides of the patient, posterior or paraspinous. These uprights serve as a sleeve, splint or distracter.[20]

Skeletal Fixation

This is the most effective method of applying reliable control on the spine. Halo traction and halo pelvic fixation devices are the examples.

After the diagnosis is made the clinician decides the specific goals to be achieved, whether to support, immobilise or correct the spine and what degree of freedom is to be controlled, to what extent and in which manner.

NOMENCLATURE

Spinal orthoses can be grouped as orthoses, corsets, belts and braces. They are best described using generic names; referring to the anatomical level they are capable of controlling and treating.[6]

CO = Cervical Orthosis
HCTO = Head Cervico Thoracic Orthosis (SOMI)
TLO = Thoraco-Lumbar Orthosis
LSO = Lumbo-Sacral Orthosis
TLSO = Thoraco-Lumbo-Sacral Orthosis
CTLSO = Cervical Thoraco-Lumbo-Sacral Orthosis

Based on the effectiveness of the control applied by the orthosis, they are also grouped as minimum control, intermediate control and most effective control orthosis.

Corset and Belts

Corsets

Corsets are flexible orthoses made of fabrics with vertical stays (Fig. 2). They are adjustable by means of laces, hooks and elastic abdominal straps. They are effective for management of pain due to muscle strain by relieving the activity of spinal and abdominal muscles. However, long-term use of corsets may lead to atrophy of these muscles. Therefore, corsets should be used only for the duration necessary and not for a long term for psychological support. Corsets have vertical channels where spring steel strips or plastic strips can be placed to stiffen the corset.[16]

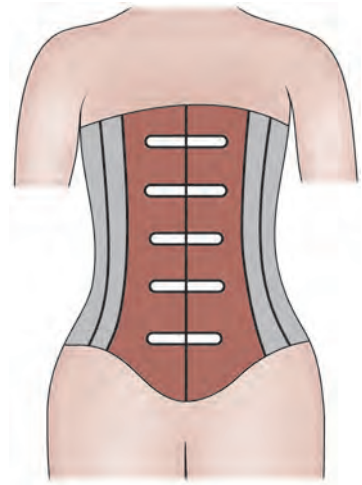


Fig. 2: Corset

Belts

Sacroiliac belt is a 5–10 cm wide belt encircling the pelvis between the iliac crest and the greater trochanter and helps in stabilising the sacroiliac joints. An abdominal belt is a 10 cm wide belt and is worn by weight lifters to prevent collapse of the vertebrae.

Orthoses

Cervical Orthoses

There are three types of cervical orthoses: (1) collars; (2) poster devices and (3) custom made. Collars restrict excessive movements, especially flexion of the cervical spine, through a feedback system and acts as a reminder to restrict movement. They have negligible control on rotation. Poster cervical orthoses provide more control and provide more rigid immobilisation because of mandibular and occipital pads, and sternal and thoracic pads. Custom-made cervical orthoses are made to relieve the weight of the head on the cervical spine.

Soft cervical collars: These are most commonly used collars and are made of foam, wrapped around the neck and are comfortable, although may not be effective in restricting the movements of the cervical spine (Fig. 3). The therapeutic rationale is that it restricts motion, reduces body heat loss and keeps the neck warm and thereby relieves muscle spasm. It maintains the head directly over the centre of gravity and reduces the cervical lordosis, which opens the intervertebral foramen and reduces nerve root pressure.

Philadelphia collar: This is a soft type of collar and provides better support due to the width of the collar that surrounds the neck. It also has anterior and posterior stiffeners to provide additional support (Fig. 4).[10]

Hard cervical collars: These are made of rigid material like low-density polyethylene. They reduce cervical movements better in the sagittal plane than a soft collar. However, they provide little control on lateral flexion and rotation, and may be of fixed or adjustable width (Fig. 5).

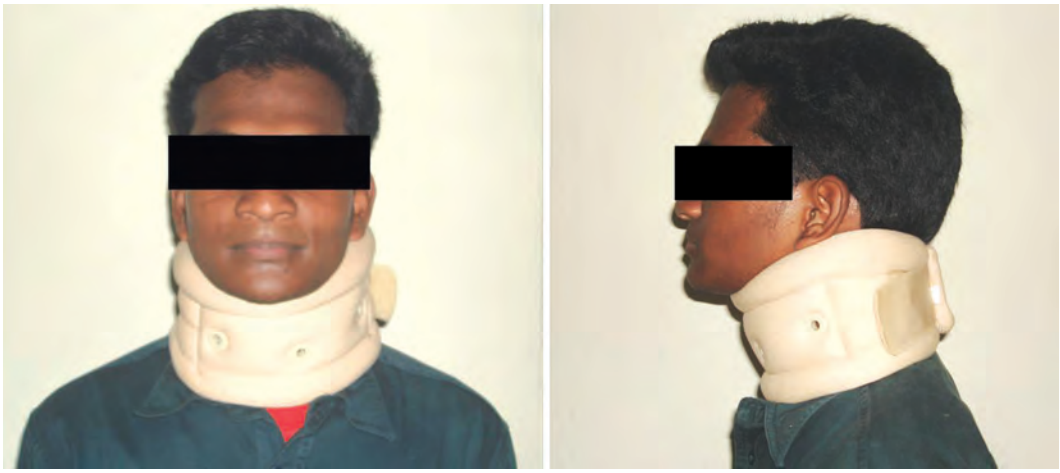


Fig. 3: Soft collar

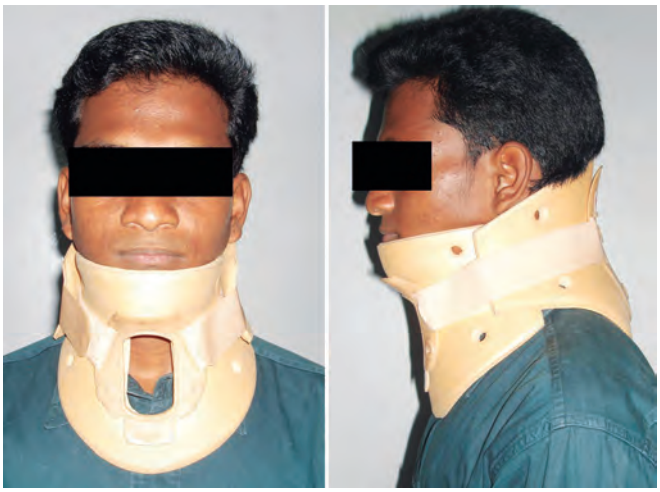


Fig. 4: Philadelphia collar

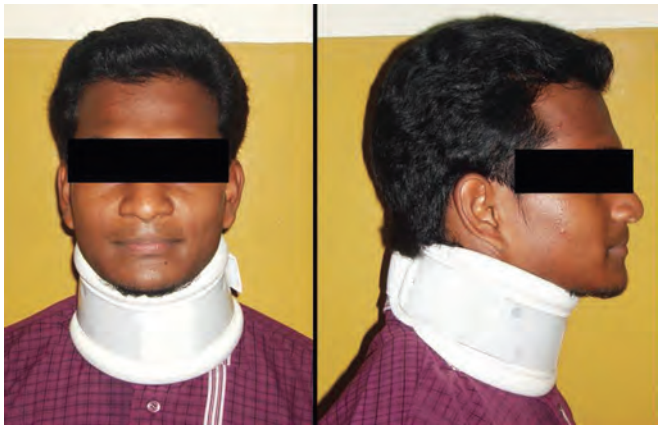


Fig. 5: Hard collar

Four-post cervical collar: This is a flexion extension control orthosis (Fig. 6). Anteriorly there is a chin support and a sternal support and two turnbuckle uprights. Posteriorly there is an occipital support thoracic plate connected together with two turnbuckle uprights. The uprights are adjustable in height and made of aluminium. A traction force is applied between the cervical and the shoulder rings, which restricts flexion and extension and thus maintains the specific position as required. Lateral flexion and rotation are also restricted. The weight of the head is bypassed from the cervical spine. However, since there is no direct support to the spine, inter-segmental movements are possible.[8]

Sternal occipital mandibular immobiliser (SOMI) orthosis [head cervico thoracic orthosis (HCTO)] is commercially available and consists of a sternal plate, shoulder strips, mandibular pad, occipital pads and support bars. It has good control on flexion but allows a little extension and rotation (Fig. 7).

Halo cervico thoracic orthosis: It consists of a halo ring fixed to the skull with pins, chest jacket and connections between them (Fig. 8). This provides the most effective control on cervical movements. It allows inter-segmental movements; still this is the best option for fractures of the cervical spine.[7]

Minerva Jacket provides total control of movements including inter-segmental control. They are individually made moulded appliances and restrict flexion, extension, lateral bending, as well as rotation and, the weight of the head is relieved from the cervical spine (Fig. 9).

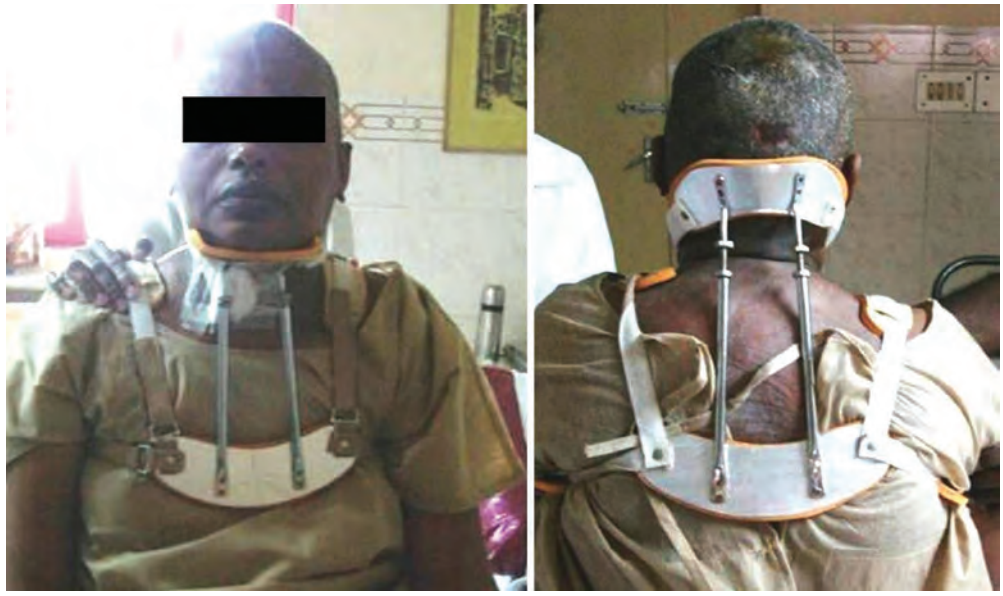


Fig. 6: Four-post cervical collar

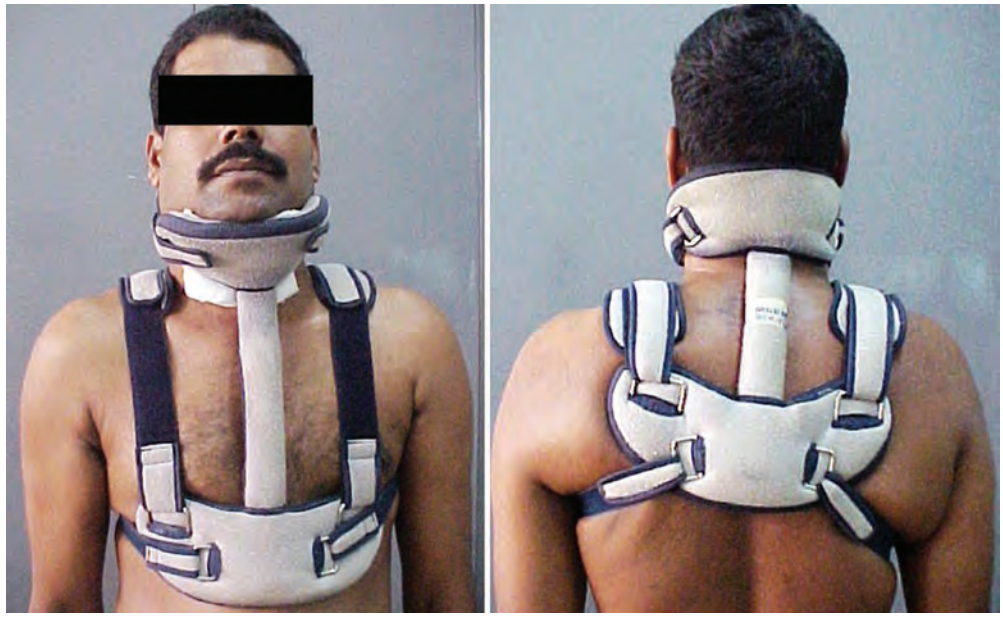


Fig. 7: SOMI brace

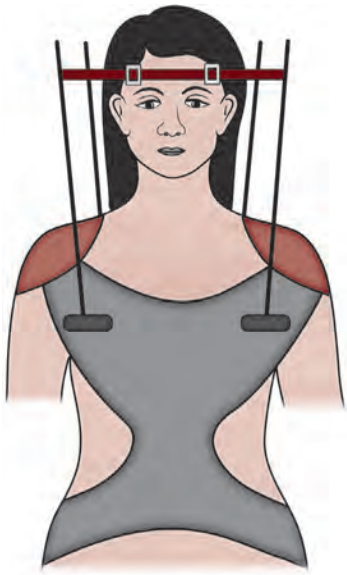


Fig. 8: Halo cervico-thoracic orthosis

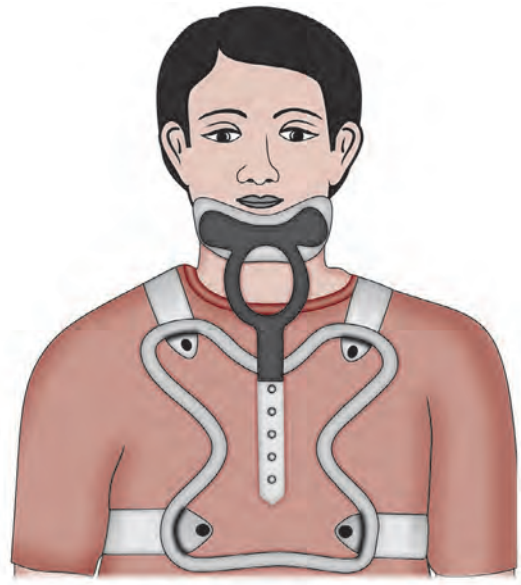


Fig. 9: Minerva jacket

Thoraco-Lumbar Orthoses

The thoraco-lumbar orthosis (TLO) is the most prescribed orthoses covering the dorsal and lumbar spine. It consists of two posterior paraspinal uprights extending up to the interscapular region. Uprights are attached to the full front abdominal corset. An interscapular band holds the uprights and serves as an attachment for axillary straps, which pass under the axilla coming over the shoulder and attached to the upper end of the uprights posteriorly with the help of a buckle or Velcro fasteners (Fig. 10). It controls flexion and extension of the thoraco-lumbar spine, but does not prevent lateral flexion and rotation.[13]

Lumbo-Sacral Orthoses (LSO)

Lumbo-sacral flexion and extension control orthosis (LSO): It consists of two posterior paraspinal uprights attached inferiorly to a pelvic band and superiorly to a thoracic band. It is a three-point pressure system consisting of a posteriorly directed force from the abdominal support and an anteriorly directed force from the pelvic and thoracic bands. This orthosis provides only flexion and extension control.

Lumbo-sacral flexion, extension and lateral control orthosis (LSO): This is one of the most commonly prescribed spinal orthoses. Lateral uprights are incorporated in the above LSO to which the abdominal support is attached as shown in Figure 11. This restricts lateral flexion. Oblique bars, when incorporated, provide structural integrity and may control rotation to some extent.

Thoraco-Lumbo-Sacral Orthoses

Thoraco-lumbo-sacral flexion-extension control orthosis (TLSO) (Taylor): When TLO is extended to the pelvic region it becomes TLSO. It consists of two posterior paraspinal uprights attached inferiorly to a pelvic band. A

Fig. 10: Thoraco-lumbar orthoses

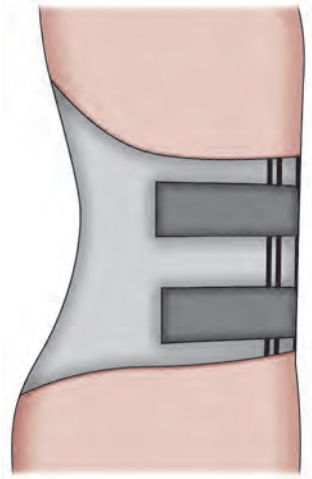


Fig. 11: Lumbo-sacral flexion, extension and lateral control orthoses (LSO)

interscapular band holds the uprights and serves as an attachment for axillary straps. It is a flexion and extension control orthosis, and commonly known as Taylor's brace (Fig. 12). It provides three-point pressure, posteriorly from the axillary pad and pelvic straps, and anteriorly from the posterior uprights at the thoraco-lumbar region.[15]

Jewett's Orthosis is a prefabricated TLSO, available in various sizes and consists of anterior and lateral frames with sternal and pubic pads and a posterior midline thoraco-lumbar pad (Fig. 13). It prevents flexion with the help of posteriorly directed forces at the sternal and pubic pads and anteriorly directed force by the posterior midline pad. Lateral strips help in preventing lateral flexion. It does not support the spine.

Anterior spinal hyperextension orthosis: Anterior spinal hyperextension (ASH) orthosis also known as cruciform anterior spinal hyperextension (CASH) orthosis is also a prefabricated TLSO. This consists of two strips at right angles to each other forming a cruciform frame. The vertical strip has sternal and pubic pads and the two lateral ends of the abdominal strip are connected with a lumbo-sacral belt having a lumbo-sacral pad (Fig. 14). The function of this orthosis is similar to that of Jewett's brace. It allows extension and lateral bending but prevents flexion. It does not support the spine.

Thoraco-lumbo-sacral flexion-extension and lateral control orthosis (TLSO) (Knight- Taylor): Two lateral uprights are added between the lateral margins of the pelvic and the thoracic bands similar to that of lateral control orthoses (LSO). An abdominal corset is fastened from the lateral uprights. These lateral uprights prevent lateral flexion, but do not control rotatory movements.

Thoraco-lumbo-sacral flexion, lateral and rotary control orthosis (TLSO) (Cow Horn): It is similar to that of Thoraco-Lumbo-Sacral Flexion-Extension and Lateral Control Orthoses (TLSO). For rotary control the thoracic band is extended anteriorly and superiorly up to the infra-clavicular region with rounded and well padded ends (Fig. 15).

Cervical Thoraco-Lumbo-Sacral Orthoses

This is a commonly prescribed orthoses for the management of spinal deformities. This can correct the curves up to 40–45 degree during the growth period. However, this is contraindicated where bony maturity has been completed. Spinal curvatures are taken care of by adding the pads over the convexity of the curvatures as well as on humps.

Fig. 12: Thoraco-lumbo-sacral flexion and lateral control orthoses

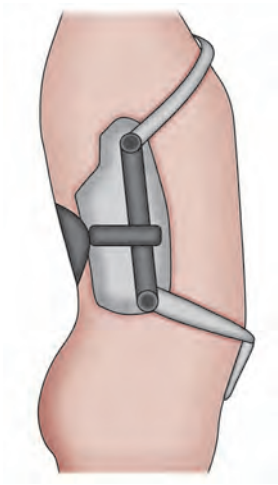


Fig. 13: Jewett's orthosis

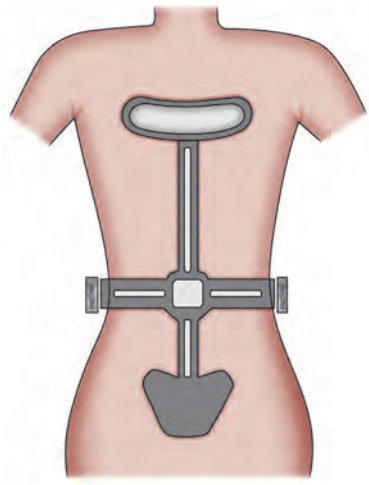


Fig. 14: ASH brace

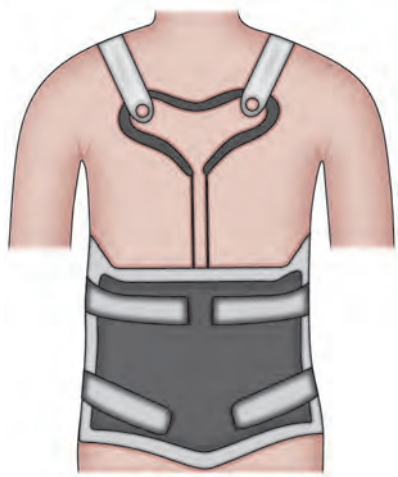


Fig. 15: Thoraco-lumbo-sacral flexion, lateral and rotatory control orthosis (TLSO)

Milwaukee Orthosis (CTLSO): It is a posteriorly open orthosis used to control and correct spinal curvatures like scoliosis and lordosis. It is like an exoskeleton and consists of a pelvic girdle, head support, one anterior and two posterior uprights and corrective pads (Fig. 16).[1]

Pelvic girdle (pelvic support) is a moulded leather construction, which has a posterior opening. It provides the foundation for the entire orthosis and also provides increased intra-abdominal cavity pressure, thus providing a distraction force on the spine.

The head support provides reaction points to encourage distraction and serves as an attachment for the uprights. It consists of a neck ring, throat piece and occipital pads (Fig. 16). The neck ring provides attachment to the throat piece and occipital pads. The throat piece falls short of the mandible and is attached to the anterior upright. The occipital pads are left and right pads and are almost right angled, attached to the posterior uprights. The horizontal portion is well padded and supports the occipital protuberances.

Uprights: The anterior upright extends vertically upwards from the pelvic girdle to the throat support and remains in the midline. The posterior uprights extend from the pelvic girdle upwards to the occipital pads on either side of the midline 8–12 cm away from each other. The uprights are contoured along the body curvatures but remain 1–2 cm away from the body. They are adjustable, transmit forces between the pelvic and the head supports and also serve as attachments for the pads.

Pads are cushioned sheet metal or plastic pieces of size proportional to the forces they have to apply over the apex of the deformities. The thoracic pads apply force directed medially, superiorly and anteriorly to the vertebral column through the ribs. Straps and pads also limit the movements of the patients inside the upright by acting as a reminder to the patient. The patient thus moves inside and stretches to reduce the scoliotic curve. This also reduces the rib hump. The lumbar pads provide an anteriorly directed force towards the transverse process, and thus de-rotate the spine.

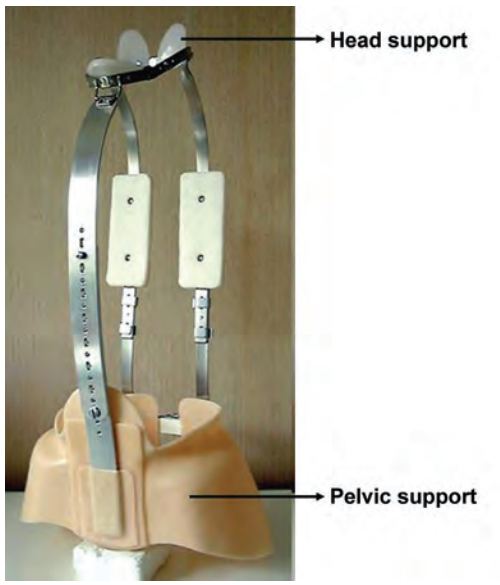


Fig. 16: Milwaukee orthosis

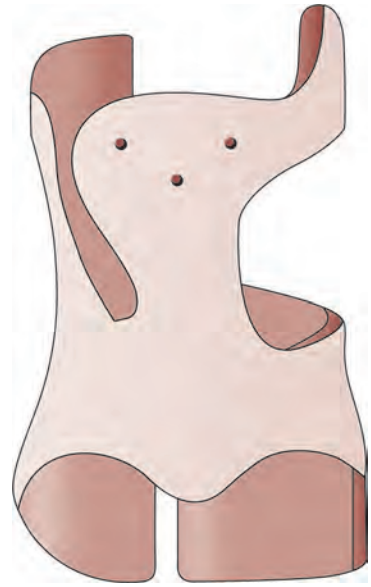


Fig. 17: Boston orthosis

Two kyphosis pads are placed one above and one below the apex of the kyphotic hump from the posterior uprights. The sternal pad is well padded and fixed to the anterior upright below the sternal notch. This encourages voluntary extension of the upper thoracic and cervical spine and also helps in relieving the uncomfortable pressure of the throat piece.

Boston Orthosis, Miami Orthosis and Under Arm Plastic Body Jacket

The TLS metallic uprights are replaced by plastic materials, hence they provide a better cosmetic appearance and therefore, more acceptable to the patients. They are custom fabricated (Fig. 17).

Casts: They are moulded orthosis and can apply force at any level and are used for severe degree of curves. Patients can be ambulatory but it restricts breathing and pressure sores can develop if not managed well.

Turnbuckle and Hinged Orthosis

This is a plastic jacket with a hinge and turnbuckles. When firmly worn, it is effective in correcting scoliosis.

17Halo Head Cervico Thoraco-Lumbo-Orthosis (HCTLO)

This provides the most effective control on cervical movements. It provides a distraction force and is used pre- and post-operatively following cervical spinal surgery.

MECHANISM OF ACTION

The results of wearing a spinal orthosis are due the forces the orthosis applies to the body and the reactionary forces the body applies against the orthosis. The location, direction and magnitude of these forces depend upon the design of the orthoses, the tightness with which it is worn and the patients efforts to move inside the orthoses. All spinal orthoses produce three basic effects: (i) reduce trunk movements; (ii) improve skeletal alignment and (iii) increase intra-cavity pressure.[12]

Reduced trunk movement is essential for bony injury healing and to give rest to the part and, thus improve the healing of the soft tissues. Skeletal alignment is an important factor in improving spinal function. Increase in intra-cavity pressure indirectly applies a distracting force on the spinal column, thus relieving the weight of the body on the vertebrae and improving the alignment.

Effectiveness of the orthoses is based on proper fit, alignment, location, material, and to their relationship with skeletal and other body landmarks. The metallic bands act as a base for the orthosis and keep the orthosis in correct position, whereas the uprights and straps help in applying the corrective forces in the right direction and hold the pads in the right place.

ORTHOTIC MANAGEMENT OF SPECIFIC PROBLEMS

Low Back Pain

Around 80–85% of the population suffers from low back pain at some time or the other in their life. Low backache, lumbo-sacral strain, sciatica, sciatic radiculitis and intervertebral disc prolapse all are included in this group. They can be caused by a number of entities like muscle weakness, skeletal instability, degenerative disc disease, osteoarthritis of facet joints or acute injury.

Muscle weakness enhances instability and encourages disc degeneration, which leads to herniation of the disc and sciatic radiculitis. This may also cause spondylosis or spur formation. Degenerative disc disease also leads to spondylolisthesis and may lead to facet joint arthritis with back pain and may lead to sciatica by root compression.

The orthosis would reduce the pain and encourage healing by trunk support and restricting the movements of the spine. When the spine is in flexion, weight transmission is through the vertebral bodies and thus reduces muscle activity. This changed posture combined with increased intra-cavity pressure relieves the pain. Patients with disc herniation will be more comfortable with LSO which maintains or increases hyperextension (lumbar lordosis) by increasing intervertebral body space and closing the facet joints. Prescription of spinal orthoses is based upon the therapeutic requirement that varies with the severity of the symptoms.

Minimal Symptoms (Mild)

In the absence of physical findings orthosis need not be provided and exercises are the best option. Analgesics may be given. If there is no improvement, a corset should be provided.

Less Severe Symptoms (Sub-acute)

Patients with moderate pain with few physical findings are provided semi-rigid orthosis (corset) to permit ambulation.

Severe Symptoms (Acute)

Spinal muscle spasm, severe sciatica, inability to walk or sit and progressive neurological deficit all need bed rest as well as rigid spinal support.

Corset is indicated in sub-acute patients especially the obese and elderly. It is more acceptable than rigid orthoses. Rigid orthoses are used when a corset does not relieve the symptoms. They are used for a severe long-term deteriorating clinical pattern and are more effective in limiting spinal motion, as also being useful in arthritis and in realigning the spine. However, it should be used for a limited period. An early start of isometric exercises of spinal and abdominal muscles within the orthosis is effective in all disorders.

For discogenic pathologies including herniation, multiple level disc bulging and degenerative disc disease the lumbar spine is set in full extension. In patients with spondylolisthesis, lumbar stenosis or facet syndrome the lumbar spine is immobilised in flexion.

Spinal Deformities

Scoliosis

Scoliosis is defined as an appreciable lateral curvature of the spine usually with rotational elements.[4] This may either be non-structural where the curvature can be corrected by change of posture or structural, which is characterised by asymmetrical side bending, fixed rotation and alterations in vertebral anatomy (Figs 18A to D).[14]

Curve progression is idiopathic and is sometimes explained using Euler's theory of elastic buckling of a slender column. Buckling load of a straight slender elastic column is a function of its flexibility, length and end support system. This relationship is described as:

$$F = C \times A^2 / L^2$$

(F is buckling load; C is constant (Pie x E/4); A is cross-sectional area of column and L is the length)[19]

In a child the weight of the upper trunk and arm may not exceed the buckling force of the spine and therefore any existing curve may not increase. Increase in the child's height greatly increases his capacity to bear the axial load by the spine. A 10% increase in height results in about 20% increase in buckling load.

The mechanism of action of spinal orthosis in correction of deformity is through end point control, transverse loading and curve correction.[11]

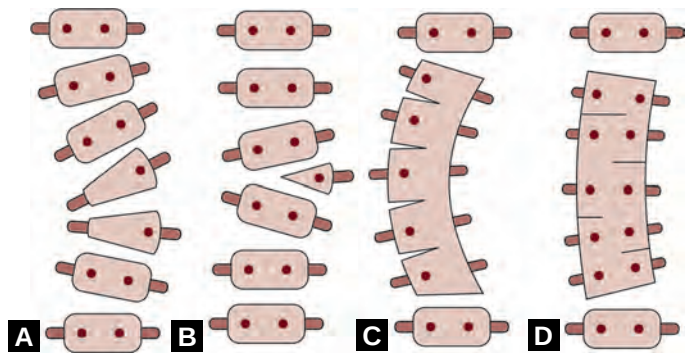
Endpoint Control

This denotes the mechanical constraints provided by an orthosis on the spine. It is done by fixing the orthosis rigidly to the base of the spine and fixing the upper end by means of a hinge. This increases the critical load value to eight times, i.e. it would require a load of 8 times to produce the scoliosis. Similarly, rigid fixation of the upper end will increase the critical load to 16 times.[18]

Transverse control is provided by all orthoses through a transversely directed force to the scoliotic spine. This is done by the load directed at the apex and two forces on either end, directed in opposite directions. However, long-term maintenance is essential.

Curve Correction

This is achieved by a three-point pressure system where one force is applied at the apex to correct the deformity and two forces are applied above and below the apex in opposite directions to produce the counter pressure and stabilisation of the spine. Up to 20 degree of curvature the patient should be kept under observation. If the deformity increases beyond 20 degree, an orthosis is indicated. Surgery followed by orthosis is indicated if the angulation is above 40 degree.



Figs 18A to D: Vertebral structural abnormality in scoliosis. (A) Wedge vertebrae partial unilateral failure of formation. (B) Hemivertebrae complete unilateral failure of formation. (C) Congenital bar unilateral failure of segmentation and (D) Block vertebrae bilateral failure of segmentation

Orthotic management of scoliosis is best done by providing a spinal orthosis TLO, LSO, TLSO or CTLSO (Milwaukee orthosis) depending on the site of the deformity, and degree and flexibility of the deformity. Other factors that should be considered are aetiology, progression of deformity and age of the patient. An elderly patient may not be able to tolerate a rigid orthosis; he should be provided a corset.

Kyphosis

Kyphosis is defined as a sagittal plane curvature of the spine with a posteriorly directed curvature. This can be generalised, angular and knuckle. They are due to deforming spinal arthropathy (Scheuermann's disease), fracture spine or collapse of the vertebrae (Tuberculosis). Kyphosis is managed by treating the cause and by applying the corrective pads below and above the apex of the deformity at an early stage.[5]

Lordosis

One of the commonest causes is obesity, when there is excessive adipose tissue over the lower abdomen. This shifts the centre of gravity anteriorly away from the spine, resulting in lordosis. An abdominal corset will improve the condition.[19]

Spinal Surgery

Pre-Operative

An orthosis, which immobilises the spine like lumbosacral flexion, extension and lateral (F E and L) control orthosis, if provided pre-operatively, can give a clue and predict the role of surgical immobilisation. It means that if such an orthosis relieves the symptoms and symptoms re-appear on removing this orthosis, it is a clear indication that surgical stabilisation would be beneficial and will offer a reasonable chance of success.

Post-Operative

Post-operative spinal support is indicated to prevent stress on the fusion from the normal physiological demand and permits transportation without causing stress over the surgical fusion. However, long-term use produces muscle atrophy and may lead to fibrosis.

Disc Surgery without Fusion

Orthosis for 4–6 weeks following surgery is a common practice to support and distract the spine by increasing the intra-abdominal cavity pressure. Corsets are found to be adequate for this purpose.

Fractures

To classify spinal fractures, the spine has been subdivided into three load bearing columns. (1) The anterior longitudinal ligament, anterior annulus fibrosus and the anterior part of the vertebral body form the anterior column. (2) The middle column is formed by the posterior longitudinal ligament, posterior annulus fibrosus and posterior wall of the vertebral body. (3) The posterior column is formed by the posterior arch, supra and infra spinous ligaments and the ligamentum flavum.

Facet joint injury increases flexion and extension of the spine. In a fully disrupted facet joint, flexion and lateral bending increases twofold, whereas axial rotation increases about ten times. Compression fracture involves failure of the anterior column with the middle column being totally intact. Burst fracture involves both the anterior and the middle column. Seat belt type of injury leads to failure of the middle and posterior columns. Fracture dislocation injury represents failure of all the three columns. Substantial instability appears if two columns are disrupted, whereas three-column injury renders the segment completely unstable.

Mechanisms of Action of Spinal Orthoses

The orthosis for spinal injury protects the spinal cord from loads and stress caused by angulation and translational deformity and provides biomechanical stability. Spinal orthoses either can be used as a substitute for operative treatment or post-operatively to provide stability to the spine.

Orthoses for Thoraco-Lumbar Injury

Anterior column compression and anterior with middle column burst fractures are best treated by bivalve TLSO in hyperextension. It reduces the segmental angle, unloads the fracture and pushes the fractured segments in an anterior direction. This stabilises the injury, reduces the segmental motion and thus allows healing.

For posterior and middle column injury, the same mechanism of action takes place and spinal extension closes the fracture and thus helps bony union. Injuries, like severe burst injury and three-column instabilities, due to fracture dislocation cannot be treated by orthoses alone. Since there is always a risk of progression of injury, surgery is the treatment of choice.

Transverse process fracture is essentially a soft tissue injury and heals quickly. Trunk support similar to that of uncomplicated fracture is the usual orthotic requirement.

Osteoporosis and Multiple Vertebral Compression Fractures

Flexible external support (corset) reduces pain by reducing movements and by increase of intra-thoraco-abdominal pressure, which in turn reduces the vertebral body compressive pressure. A corset also helps in early mobilisation and reduces weakness and disability.

For elderly patients, a flexible orthosis is suitable whereas, in younger patients, a rigid orthosis is more suitable. The deformity resulting from multiple fracture episodes cannot be prevented by bracing, and, on the other hand, excessive pressure by the orthosis to prevent the deformity may cause rib fractures.

Inflammatory Spinal Arthritis

Various inflammatory conditions, like rheumatoid arthritis, ankylosing spondylitis and Still's disease, do need bracing with the aim to relieve pain and prevent deformity. Orthotic management must restrict flexion. The orthoses used are with thoracic band extensions and subclavicular pads for restriction flexion. This does not affect the respiratory function. Extension exercises should be continued.

Juvenile Spinal Osteochondritis (Scheuermann's Disease)

This is a short-term deforming spinal arthropathy. Three-point flexion control spinal orthosis (Lumbo-sacral flexion control) and Milwaukee brace are useful.

Infectious Disorders of Spine

Osteomyelitis and Tuberculosis

Motion control is the major requirement. Large body casts have been replaced with orthosis, which control the movements. Size of the bracing is determined by the spinal level to be immobilised. The TLSO with flexion, extension and lateral control orthosis is the most prescribed orthosis.

Tumours of the Spine

Spinal support is of great benefit as an adjuvant to radiotherapy and chemotherapy. Flexion extension control orthosis are recommended to prevent deformity in children. In adults corsets with flexible stays are adequate. In the presence of neurological deficit or major instability a wider plastic moulded orthosis with an anterior wide fabric corset is given to provide better support and weight distribution. Head and neck supports may also be given.

Paralytic Disorders

Poliomyelitis and Dystrophies Involving the Trunk

Trunk support or regional pressure system applied by control orthosis is required. For the control of deformities, pads are incorporated in the orthosis.

Paraplegia

In paraplegia with absence of pelvic control and balance, spinal orthoses are counterproductive. The spinal brace with HKAFO on both the legs may allow a few paraplegics to move only a short distance. However, a corset will permit the patient to sit in a chair/wheelchair to perform the activities of daily living. In case the diaphragm is also affected, the wheelchair may be provided with special supports to control the spine and prevent collapse, which can be accomplished by ASH (CASH) brace.

Spina Bifida

With a neurological deficit the trunk needs to be supported depending upon the amount and level of weakness, instability and age of the patient. The spinal orthosis is modified for each patient and is used when there is a trunk weakness or paralysis with room to avoid pressure on the posterior mass.

Spondylolisthesis

Congenital (Developmental) Spondylolisthesis

Support is needed to realign the spine by using a three-point pressure system. Lumbo-sacral extension and lateral control orthosis will improve the lumbar lordosis and correct the pelvic tilt.

Degenerative Spondylolisthesis

This may lead to osteoarthritis of the posterior joints. Motion control is essentially required, especially if root compression is present. Lumbo-sacral corset is adequate.

Cervical Conditions

Sprains

A firm collar during the day and soft collar during the night is indicated which reduces neck movements and encourages healing. In severe cases where simple collar is unable to control symptoms, cervical spinal orthosis with posts is provided which controls the position of the spine and also relieves the weight of the head. It must be discarded as early as possible lest weakness and atrophy of muscles ensue.

Torticolis

Post appliance is provided for acute torticolis resulting from injury. This would maintain the corrected position pre-operatively as well as post-operatively.

Cervical Spondylosis and Cervical Spondylitis

They are degenerative disc lesions. Orthotic restrictions of movements improve the symptoms and permit irritative lesions to become quiescent. Soft cervical collar during the night and firm collar during the day will be a good combination. Sometimes, increased motion control and weight relief is required for severe pain by post appliances, which also reduce the shearing force.

Fracture Dislocation

The orthotic requirement is determined by the stability of the fracture, state of the nervous system, and state of cervical spinal fusion (if performed). Cervical spinal orthoses with posts will be useful to control the movements, keep the head in the desired position and relieve the weight of the head.

In unstable fractures or where the fracture or dislocation has been reduced, skeletal traction (Halo) needs to be applied, which can be mounted on a body cast. A moulded cervical collar can replace this. Maximum

support is needed for fusion of the upper cervical and cervico-occipital segments. Posterior and posterolateral fusions also need thorough external support by a moulded Minerva jacket.

Single level anterior fusion and locked interbody fusion following disc excision can be managed by simple hard and soft collars. For complete fusion, complete immobilisation with weight relief is indicated.

Minor injuries which have no or low-risk of progression, or have marginal instability that does not require surgery, do require orthosis to provide stability and prevent further progression of injury and deformity.

Post-Operative Orthosis

The aim of post-operative orthoses stabilisation is to protect the surgical correction from large loads created by movements till bony consolidation takes place. The orthosis must control the motion in which the surgical construction is most vulnerable to failure. Most commonly these motions are flexion and torsion (axial rotation). The TLSO with adequate anterior height up to the sternum resists forward bending and is quite suitable; however, it should not be allowed to provide hyperextension.

Post-Operative TLSO

The post-operative TLSO should provide a firm support at the sacrum. The upper margin should be above the most superior portion of spinal fusion. For lumbar spinal fusion, it should be up to the xiphoid process or below the breast line that can provide the immobilisation up to T11 level. For surgical procedures up to T4 the TLSO should be up to the sternal notch. For procedures up to T2 level the trim line should come up to the shoulders to reduce upper thoracic motion caused by shoulder joint movements. For procedures extending up to T1 or lower or mid cervical region, SOMI brace should be used to prevent cervical movements. In procedures in the cervical region it is motion control that is more important than flexion control alone. For lumbo-sacral fusion the TLSO must have thigh extension to provide support at the lumbo-sacral region.

POSITIVE EFFECTS OF SPINAL ORTHOSES

There are three positive effects of spinal orthosis: (1) trunk support, (2) motion control and (3) realignment. It is not possible to segregate these functions since all the orthoses have all these functions although one may be more than the other. These functions are achieved by increasing the intra-cavity pressure, containment of torso inside the orthosis providing the regional pressure and a three-point pressure system, which specifically improve alignment. These effectively reduce the functional demand on the spinal musculature as well as vertical loading on the spine. One should distinguish between motion control and trunk support by the ASH brace or SOMI (HCTO) brace, which restricts forward flexion of the spine without supporting the spine.

NEGATIVE EFFECTS OF SPINAL ORTHOSES

It is essential to be aware of the negative effects of spinal orthoses and their effects on the management of spinal conditions.

Weakness and Atrophy

Restricted spinal motion due to orthoses reduces muscular activity. Weakness and atrophy can be prevented by exercises, especially isometric, to the extent that the patient can tolerate within the orthosis.

Contracture

Prolonged immobilisation leads to progressive fibrosis of muscles, ligaments and fascia. It is therefore better to prevent this by a rehabilitation programme from the very beginning.

Psychological Dependence

This usually follows after prolonged use of orthosis. The patient feels secure with an orthosis even when it is no more required and may be due to the fear of recurrence. Over treatment must be avoided, especially when a third party is responsible for the cost of treatment.

Aggravation of Symptoms

Spinal orthosis by virtue of providing rest will improve the symptoms even when wrongly diagnosed. Thus the disease may continue to progress and may lead to a difficult situation. Frequent review of the patient will be helpful.

Hazards of orthotic use can be due to various reasons, namely wrong diagnosis, wrong prescription, wrong donning and prolonged use even when not required. Hazards can also be due to wrong manufacturing and poor finish having sharp margins and edges. The effects can be injury, swelling, ulceration, pressure sore or increased symptoms.

An understanding of the pathology and pathophysiology of the disorder and accurate assessment of orthosis both positive and negative is essential to finally select an orthosis most suitable for a patient.

CHECKOUT OF SPINAL ORTHOSIS

Checkout procedure is actually a systematic evaluation of orthosis and to ascertain that the orthosis is satisfactory and to modify it if required. The critical evaluation pertains to fit, comfort, function and appearance. The patient should be able to don and doff the orthosis easily. Check all the components of the orthosis and their function such as rotatory, flexion and extension as well as lateral flexion control. The patient should be

comfortable when sitting and standing while wearing the orthosis. Patients should be examined immediately after doffing the orthosis for signs of any undue pressure or injury, especially over the bony prominences.

PAEDIATRIC SPINAL ORTHOSES

In a child, the weight of the upper trunk and arm should not exceed the buckling force of the spine in order to prevent an increase in the existing curve. With height growth and weight gain, it increases more than the buckling load and this will lead to increase in the scoliosis even if the child does not gain in height. Increase in height of the child greatly increases his capacity to bear the axial load by the spine. Commonest causes of injury in children are falls, road traffic accidents and sports injuries.

Cervical Spine

Cervical spine immobilised with cervico thoracic orthosis (CTO) four-post cervical collar is one of the best choices.

Thoracic Spine

The Milwaukee brace is often used for thoracic injuries especially above T8.

Thoraco-Lumbar injuries from T11 to L2 are generally unstable and are best treated by custom moulded bivalve thoraco-lumbo-sacral orthosis.

Lumbar spinal injuries are not well immobilised by external orthosis. Halo pelvic traction can provide adequate fixation.

LONG-TERM USE OF ORTHOSES

This is aimed to promote bony healing and prevention of deformity, which can occur at or below the level of injury. It improves sitting balance, frees the upper extremities, slows rates of spinal deformity and may avoid the need for surgery in children.

RECENT ADVANCES

With the advent of newer materials, plastic is now replacing the metallic frame of the orthosis. There also have been improvements in reinforcing these orthosis with glass fibre or carbon fibre. Carbon fibre reinforced spinal orthoses are rigid and as strong as steel. The plastic moulded frames are pre-fabricated and provide adequate support even if they are flexible. Their flexibility is useful and can take the shape of the contours of the body.

Pneumatic cervical spinal orthosis is also a new concept where the orthosis is inflated after wrapping it around the neck and is considered to be more useful in transporting patients with a cervical spine injury.

BRACE CARE

DOs:

- The brace should be kept clean and dry with the help of mild soap.
- It should be worn over a vest or T-shirt.
- The instructions must be followed about wearing the brace.
- It should be worn snugly and tightly.

DON'Ts:

- The brace should not be removed or discarded unless advised.
- It should not be adjusted or modified unless advised.
- It should not be cut, filed or damaged.
- No additional padding should be added or removed by the patient himself.
- One should not engage in any physical activity that causes excessive pain.

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212 Principles of Physiotherapy

Sangeetha Ranganath

INTRODUCTION

Neurological rehabilitation has come a long way from passive movements, training of patients in compensatory strategies, and attempting to control secondary dysfunctions due to imbalanced muscle activity, to task specific, well defined, training methods aimed at improving function. This shift in therapeutic methods can be attributed to a better understanding of how the central nervous system is reorganised after injury and training.

Recovery involves changes in synaptic plasticity of the brain in response to motor learning. The basis for learning, memory and retrieval of information in the injured brain is the same as the normal brain, but with a lesser component of intact neural pathways.

Early gains may be got due to resolution of oedema and inflammatory processes. Once this stage has passed, the therapist has to rely on training, skill development, motivation, feedback and working memory systems to induce physiological and morphological plasticity, which can translate into functional recovery. Re-organisation also occurs in bilateral networks and hence the sensorimotor structures of the uninjured hemispheres also adapt and contribute to recovery.

Research has shown that there is a neural proliferative response to injury. This proliferation, migration, and extension of neuronal processes can probably be potentiated by the right approach to rehabilitation.

Neuroplasticity is the ability of the nervous system to modify its structural and functional organisation post-injury or surgery. Collateral sprouting of new synaptic connections, unmasking of previously redundant pathways and release from inhibition facilitate reorganisation of cortical maps. This may account for considerable recovery as this plasticity can be influenced by proper external stimuli.

In learning, the brain records patterns of synaptic connections that define an event or object, related events, the body's exploration of the environment, the body's reaction to the event, etc. in both "motor and perceptual schemas".

Computational neuroscience has enabled us to understand how complex movement and behaviour can emerge from the interaction of the thousands of neurons that are linked together in neural networks and that these form the essential units of cortical function. These networks have an enormous storage capacity of sequential knowledge.

Hence, it is important for the therapist to bear in mind that rehabilitation strategies should be task specific, intensive and progressive in their demands, and repeated at regular intervals to encourage activity-dependant plasticity in the brain.

Physiotherapy administered to patients can be divided into two parts:

1. Physiotherapy in intensive care
2. Functional rehabilitation.

PHYSIOTHERAPY IN INTENSIVE CARE

Physiotherapy should be seen as an integral part of the multidisciplinary team in the intensive care unit (ICU). Care has to be taken while administering physiotherapy for the intubated patient. The haemodynamic and metabolic status of the patient has to be carefully monitored. There can be an increase in the heart rate, blood pressure, intracranial pressure, increased oxygen consumption, increased carbon dioxide output, etc. as part of an exercise like response and an increased sympathetic output during multimodality physiotherapy.

A number of modalities are at the disposal of the therapist. A holistic assessment of pulmonary, neurological and musculoskeletal conditions need to be made by the therapist and appropriate treatment administered.

It is important that the programme of the therapy should be planned in consultation with the other members of the ICU team and the concerned neurosurgeon.

Treatment Techniques

An important component of physiotherapy in the ICU deals with respiration. This entails:

- Positioning: Includes side lying, postural drainage, getting the patient upright, etc.

All this helps to increase lung volumes and reduce the work of breathing; enhances mucociliary clearance, especially if the respiratory system is depressed. Getting the patient upright as soon as he is physiologically stable not only helps the respiratory system but also keeps the skin intact, prevents pressure sores, helps early mobilisation so the patient moves towards functional recovery soon.

- Percussion and vibration: Manually vibrating, clapping, shaking or compressing the chest wall during expiration is believed to increase the clearance of airway secretions
- Suction: To remove secretions by suctioning if a tracheostomy has been done for the patient
- Manual hyperventilation: Involves the use of a manual resuscitator bag. The lungs are inflated with a large tidal volume via the bag. Manual hyperventilation is used to prevent pulmonary collapse, improve oxygenation and lung compliance and increase movement of secretions towards the central airways, in patients on the ventilator or with a tracheostomy
- Mobilisation and limb exercises: Can be passive, active assisted, or active depending on the level of sensorium of the patient. It would include limb exercises, turning, sitting up, standing, transfer from bed to chair, etc.

FUNCTIONAL REHABILITATION

Sensory Stimulation and Arousal Therapy

This should begin as soon as the patient is medically stable. Various sensory modalities can be used like auditory, tactile, visual, olfactory, etc.

- Auditory stimuli like familiar family voices and names, music, ringing bells and so on
- Visual stimuli like family photographs, flash cards, bright colours, etc.
- Olfactory stimuli like fragrances, coffee and food
- Taste of swabs of familiar flavours, sugar, salt, etc.
- Tactile stimuli like temperature (warm and cold), touch (feel of different fabrics), pressure, etc.

Though the efficacy of sensory arousal is not fully clear, care must be taken to administer the stimulus in a way that it benefits the patient. Over stimulation and bombarding the nervous system with too much stimuli at the same time can be disturbing to the patient, and too routine a stimulus can lead to habituation.

A patient's (with head injuries or following major brain surgery) level of arousal could range from no response to confused, agitated, automatic, purposeful and appropriate. A positive approach from the start can contribute greatly to the success of the treatment. It would be wise to remember that the patient is not merely a "head injury" or a "hemiplegic", but a human being and should be treated well, with dignity and respect. The therapist may misjudge the extent of sensorial impairment, and therefore, must always be careful on casual comments about the patient's prognosis, etc. Another important factor is that "brain damage" is a family affair. Hence, all persons at home and in the environment have to be involved if the patient has to integrate back into home and family.

Every patient who has suffered a brain lesion will "feel differently" from the way he did prior to the lesion even if his sensations are seemingly normal. It is not just loss of motor control, altered tone, balance, gait, etc. that have to be assessed, but also a thorough sensory analysis has to be done. The neurological therapist has to deal with various perceptual, cognitive and behavioural issues. Patients can have visuo-spatial defects that involve neglect of certain parts of one side of the body and the world around them. He can also have problems analysing and remembering visual information, recognition of objects, judging form and distances, problems with perception of the environment and with awareness of the body in space and so on.

All this can influence the rehabilitation and recovery, and so have to be considered carefully. After a good sensory and motor assessment (can use motor assessment scale, or stroke rehabilitation assessment of movement) the next step is to move on to motor training.

There are many theories of motor control and motor recovery. Hence there are various approaches to motor training, like the neurodevelopmental theory, motor relearning model by Carr and Shepherd that the neurotherapist can use. Perhaps the various approaches are not mutually exclusive, but can be combined at different stages of recovery.

The activities can be broken down into various components starting with activities in bed, grasping, reaching out, segmental rolling and attempting to sit. The therapist can then progress to sitting balance, active trunk control, weight bearing on arms and activities while sitting. The next step is to train the patient in standing (with full support if needed), balance and walking.

There is mounting evidence to show that we learn what we practice. This has been proven at behavioural, biomechanical and biological levels. Hence, any motor learning model has to be task and context specific. It cannot for example be assumed that successfully flexing and extending the elbow in bed will automatically translate into feeding activity while sitting. This is because any activity involves a sequence of muscle activation patterns, not a muscle contracting in isolation. Hence, there is importance of task oriented activity in training. The same principle holds true for lower limb training, standing, walking or any other activity.

Constraint Induced Therapy

It is found that over a period of time patients develop a learnt non-use of the affected limb in addition to the deficit that they have. So strapping the normal arm for example, for several hours during the day enables, or rather forces the patient to attempt the use of his affected arm for various activities. This has found to produce good results.

Soft Tissue Flexibility

Alteration in tone or spasticity does have its role in causing motor dysfunction. But now there is evidence to show that changes in soft tissue length and muscle itself will limit segmental movement. It is typical for

paralysed limbs to remain motionless for long periods of time in one position. This causes changes in the properties of muscle fibres and connective tissues. Muscles persistently held in the shortened position develop length-associated changes. The clinical resistance to passive stretch is now considered to also be due to a reduced compliance of muscles. Hence, it is critical to start early task oriented mobilisation to maintain a sufficiently flexible musculoskeletal system.

There has been an attempt here to point out a growing shift in rehabilitative strategies, from passive movements and exercises in bed to a more dynamic approach involving activities of daily living. Hence, rehabilitation should be planned to maximise regaining of motor competence and integrate the patient back into his environment as early as possible.

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